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BLOOD RESEARCH

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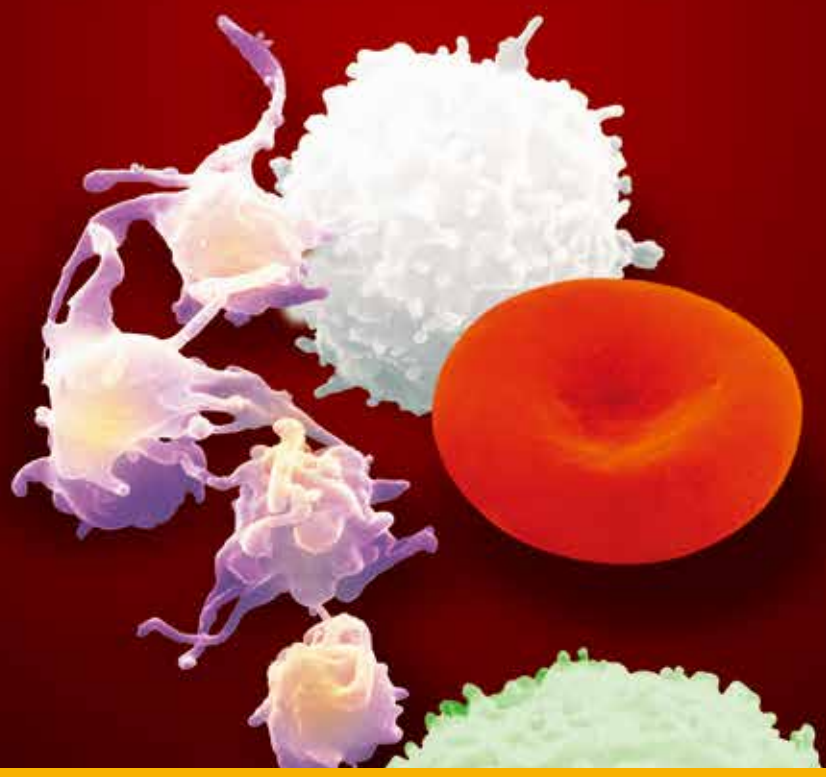
2023 Korean Society of Hematology
International Conference
& 64th Annual Meeting

Date : March 30(Thu.) - April 1(Sat.), 2023
Venue : Grand Walkerhill Hotel, Seoul, Korea




ICKSH 2023

2023 KOREAN SOCIETY OF HEMATOLOGY INTERNATIONAL CONFERENCE
& KSH 65th ANNIVERSARY

ABSTRACT BOOK

MARCH 30 – APRIL 1, 2023

GRAND WALKERHILL HOTEL, SEOUL, KOREA

www.icksh.org

The Korean Society of Hematology

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About Blood Research

Blood Research is a peer-reviewed open-access journal and delivers important clinical, translational and basic study results in hematology and related fields to the readers worldwide. The areas covered by **Blood Research** include topics ranging from basic laboratory research to clinical studies, translational studies and precision medicine in the field of hematology. Any physicians or researchers throughout the world are welcome to submit a manuscript related to topics in hematology written in English. Our readership consists of clinical hematologists, hematopathologists, clinical oncologists, scientists in related fields, laboratory technicians, nurses and students.

All of the submitted manuscripts undergo intensive peer review by at least two independent reviewers and are selected based on the importance of the topic, originality of the work, quality of the content, and the compliance to the journal's format.

Blood Research publishes Original Articles, Review Articles, Editorials, Perspectives, Letters to the Editor, and Images of Hematology. It is published online (http://bloodresearch.or.kr) and in print quarterly (March 31, June 30, September 30, and December 31). All the articles published online are made publicly available in PDF files for free-of-charge. The printed copy of our Journal is distributed without charge to the members of the hematologic Societies. Corresponding author also receives the free copy of the journal in which his/her article was published.

Blood Research is indexed and covered by ESCI, PubMed Central, Scopus, KCI, KoreaMed Synapse, and CrossRef.

As the official journal of the Korean Society of Hematology, **Blood Research** has been published since 1966. As the international journal in the field of hematology, its former journal title, the Korean Journal of Hematology (p-ISSN 1738-7949, e-ISSN 2092-9129), has been changed to **Blood Research** since 2013.

The logo represents three types of cells (red blood cell, nucleated blood cell, and stem cell) in the field of hematology, and the earth, which overall signifies globalization and international scientific forum for blood research.

Open Access Policy

Disclaimer
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WELCOME MESSAGE

Dear Colleagues and Friends,

On behalf of the organizing committee, it is our great pleasure to invite you to participate in the 2023 Korean Society of Hematology (KSH) International Conference & 64th Annual Meeting, hosted by KSH, from March 30 to April 1, 2023.

Held every year since 2018, the ICKSH congress shares up-to-date information and provides a unique opportunity for world class leaders in the field to debate vital and contentious issues in Hematology.

Finally, after two years of the COVID-19, ICKSH 2023 is prepared as a face-to-face meeting and, of course, a virtual meeting for participants who are physically unable to attend.

Our programs will include topics such as benign hematologic diseases, various types of hematologic malignancies, coagulation/thrombosis related disorders and transfusion medicine through plenary lectures, as well as scientific and educational sessions.

In addition, a variety of stimulating social programs has been planned so participants can enjoy the fascinating Korean culture and share our warm spirit of friendship. We are preparing a memorial exhibition of the 65th Anniversary of the Korean Society of Hematology this year as well.

We welcome your support and look forward to seeing you at ICKSH 2023 in Seoul, Korea!

Cheol-Ju Yoo, MD., Ph.D.
Congress Chair
The Korean Society of Hematology

Seongsoo Jang, MD., Ph.D.
President
The Korean Society of Hematology

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PROGRAM AT A GLANCE Thursday, March 30, 2023

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
08:00-09:00	Registration			
08:50-09:00	Opening Remark			
09:00-10:15	**CS01** **Innovative diagnostic technologies**	**SS01** **Challenging issues in childhood blood disorders**	**SS02** **How far has cell therapy developed in Hodgkin lymphoma?**	**ES01** **Different treatment goals for overcoming resistance or functional cure in CML**
	Accelerate breakthroughs in hematology with single cell sequencing (Geoffrey McDermott, USA)	How to diagnosis and treat neutropenia in childhood (Kelly Walkovich, USA)	Pathogenesis of Hodgkin lymphoma (Ralf Küppers, Germany)	Asciminib: the first-in-class allosteric inhibitor of BCR/ABL1 kinase (Eun-Ji Choi, Korea)
	AI technology in the fi eld of blood disease (Tabe Yoko, Japan)	Updates in the treatment of pediatric relapsed/refractory acute myeloid leukemia (Keon Hee Yoo, Korea)	Emerging cellular therapy in Hodgkin lymphoma (Natalie S Grover, USA)	Treatment after failure of frontline therapy of CML-CP including allo-HSCT (Jieun Uhm, Korea)
	Discover the unique power of using droplet digital PCR (ddPCR) for hematology-oncology applications (Gina Sun, USA)			
	Holotomography and artificial intelligence: label-free 3D imaging, classification, and inference (Yongkeun Park, Korea)	Use of chimeric antigen receptor (CAR) expressing T cells for acute lymphoblastic leukemia (ALL) (Michael Verneris, USA)	Novel treatment of relapsed/refractory Hodgkin lymphoma (Hyeon-Seok Eom, Korea)	Update on treatment free remission (Jae Joon Han, Korea)
10:15-10:30	Break			

PROGRAM AT A GLANCE Thursday, March 30, 2023

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
10:30-11:15	**PL01** Regulation of iron metabolism (Martina U. Muckenthaler, Germany)			
11:15-12:00	**PS01** What can Nano do for Medicine? (Taeghwan Hyeon, Korea)			
12:00-12:15	Break			
12:15-13:05	**SY01** Satellite Symposium 01 - CML NOVARTIS ASCIMINIB, new paradigm treatment option in CML for patients who were previously treated with 2 or more TKIs (Andreas Hocchaus, Germany)	**SY02** Satellite Symposium 02 - DLBCL Roche Unmet need in 1L DLBCL and POLARIX trial (Georg Lenz, Germany)	**SY03** Satellite Symposium 03 - MM Bristol Myers Squibb Celgene | A Bristol Myers Squibb Company Maintenance treatment post autotransplant for multiple myeloma (Kevin Song, Canada)	
13:05-13:20	Break			
13:20-14:50	Young Investigator Presentation	**OP01** Acute myeloid leukemia	**OP02** Lymphoma	**OP03** Stem cell transplant and laboratory hematology
14:50-15:05	Break			

PROGRAM AT A GLANCE Thursday, March 30, 2023

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
15:05-16:20	**JS01** **Asian Hematology Session I (JSM & KMMWP)** **- Multiple Myeloma**	**SS03** **Where we are, in the era of new agents for aplastic anemia?**	**SS04** **How can we approach thrombocytopenia?**	**ES02** **How I treat rare lymphomas?**
	POEMS syndrome: advances in molecular pathophysiology and treatment (Chiaki Nakaseko, Japan)	Aplastic Anemia: Current management considerations (Emma M. Groarke, USA)	Diagnosis and treatment of TA-TMA; Current challenge and future strategies (Sandro Rossetti, USA)	Prognostic factors in intravascular large B-cell lymphoma: A comprehensive review (Youngwoo Jeon, Korea)
	Updates on POEMS syndrome in Korea (Jin Seok Kim, Korea)	Clinical and molecular factors of clonal evolution in aplastic anemia (Jaroslaw P. Maciejewski, USA)	Genetics of inherited thrombocytopenia (Kathleen Freson, Belgium)	T-large granular lymphocytic leukemia (Jae-Cheol Jo, Korea)
	Therapeutic approach of Waldenström's macroglobulinemia in Japan (Hiroshi Handa, Japan)			
	Clinical researches on Waldenström's macroglobulinemia in Korea (Hosup Lee, Korea)	Non-transplant therapy for pediatric aplastic anemia (Jae Wook Lee, Korea)	Advances on pathogenesis and diagnosis of TTP (Hyun Kyung Kim, Korea)	Lymphomatoid granulomatosis (Jeong-Ok Lee, Korea)
16:20-16:35	Break			

PROGRAM AT A GLANCE Thursday, March 30, 2023

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
16:35-17:50	**CS02** Innovative therapeutic technologies	**SS05** Artificial intelligence application in hematology	**SS06** Defining and improving survival of high-risk multiple myeloma	**ES03** Rare hematologic malignancies with cutaneous manifestation
	A Phase 1a Study of BR101801, PI3Kγδ and DNA PK triple inhibitor, in adult patients with advanced hematologic malignancies (Bong-Seog Kim, Korea)	Artificial intelligence in hematology: basic concepts (Roni Shouval, USA)	Identification of high-risk multiple myeloma (Niels van de Donk, The Netherlands)	Sezary syndrome and mycosis fungoides (Hyewon Lee, Korea)
	The gut microbiome as a novel predictive biomarker and therapeutic target in lymphoma patients (Woorim Kang, Korea)	How machine learning deepens our understanding of hematologic malignancies (Valeria Visconte, USA)	Updated diagnosis and treatment of plasma cell leukemia (Sung-Hoon Jung, Korea)	Systemic mastocytosis (Hyun Jung Lee, Korea)
	Bispecific antibody : ABL Bio (Jonghwa Won, Korea)			
	KF1601, a novel orally bioavailable inhibitor of Bcr-Abl T315I, without thrombotic microangiopathy (Sung-Min Ahn, Korea)	Pitfalls of AI for medical application (Jongmun Choi, Korea)	Safety and efficacy of locally produced novel BCMA CART cells for relapsed/refractory multiple myeloma and AL amyloidosis (Moshe Gatt, Israel)	Plasmacytoid dendritic cell neoplasm (Yoo Jin Lee, Korea)
17:50-18:30	Break			
18:10-19:30	**Welcome Reception** (VISTA Hall Lobby)			

PROGRAM AT A GLANCE Friday, March 31, 2023

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
08:00-09:00	Registration			
09:00-10:15	**JS02** ASH-KSH Joint Symposium - T Cell Lymphoma	**SS07** What is the direction of the new CAR-T therapy?	**SS08** Comprehensive approaches to understand hemophilia	**ES04** Back to the basic: transfusion support
	NK cells: next generation cell therapies for cancer (Katy Rezvani, USA)	Engineering next-generation T cells for cancer immunotherapy (Yvonne Chen, USA)	Genotyping of hemophilia, why we need it and how we do? (Jill Johnsen, USA)	Transfusion support for HSCT (Dong Wook Jekarl, Korea)
	Treatment of extranodal NK/T-cell lymphoma: Korean Lymphoma Working Party experience (Seok Jin Kim, Korea)	Development of CAR-T therapy for acute lymphoblastic leukemia (Hyoung Jin Kang, Korea)	Value of national cohort registry data of hemophilia (Jung Woo Han, Korea)	Evidence based transfusion threshold (Dae-Hyun Ko, Korea)
	CAR-T for the treatment of T cell malignancies (John DiPersio, USA)			
	Treatment of peripheral T-cell lymphoma: Korean Lymphoma Working Party experience (Deok-Hwan Yang, Korea)	Updates on the latest developments in CAR-T therapies (Hiroshi Fujiwara, Japan)	Essentials of laboratory issues in Emicizumab (Sang Hyuk Park, Korea)	Current status of manufactured blood cells (Eun Jung Baek, Korea)
10:15-10:30	Break			

PROGRAM AT A GLANCE Friday, March 31, 2023

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
10:30-11:15	**PL02** The role of the intestinal microbiome in cancer immunotherapy (Marcel van den Brink, USA)			
11:15-12:00	Poster Viewing (Walker Hall)			
12:00-12:15	Break			
12:15-13:05	**SY04** Satellite Symposium 04 - AA KYOWA KIRIN Recent advances in the pathogenesis and treatment of aplastic anemia (Kohei Hosokawa, Japan)	**SY05** Satellite Symposium 05 - AML HANDOK Value of intensive therapy in high-risk AML (Martin Bornhaeuser, Germany)	**SY06** Satellite Symposium 06 - CLL janssen When and whom to start treatment of CLL patients and how to optimally manage CLL patients with Imbruvica (Ghia Paolo, Italy)	
13:20-14:50	**OP04** Acute leukemia and quality of life	**OP05** Bone marrow failure syndrome and myeloproliferative neoplasm	**OP06** Multiple myeloma	**OP07** Anemia, bleeding and platelet
14:50-15:05	Break			

PROGRAM AT A GLANCE Friday, March 31, 2023

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
15:05-16:20	**JS03** EHA-KSH Joint Symposium - Myelodysplastic Syndrome	**SS09** Which immune therapy is our future weapon against AML?	**SS10** Next-generation molecular genomic and cytogenomic technology in hematology	**ES05** Practical issues in CAR-T KOR
	Novel approaches in MDS (Uwe Platzbecker, Germany)	Immune checkpoint inhibition for AML ; CD47 blockade and beyond (Naval Daver, USA)	A transcriptomic approach to clinical diagnosis, prognosis and therapy selection in AML (Aly Karsan, Canada)	Setting up the facility for CAR T cell therapy (Ja Min Byun, Korea)
	Treatment of MDS: Korean AML/MDS working party experience (June-Won Cheong, Korea)	Determining the barriers to successful CAR T cell therapy for AML (Miriam Y Kim, USA)	Whole genome sequencing of fluorescence in situ hybridized cells in hematologic malignancies using SLACS (Sunghoon Kwon, Korea)	Technical aspect of manufacturing CAR T cell product (Jong-Seo Lee, Korea)
	Standard management of MDS (Lionel Adès, France)			
	Genetic alterations in myelodysplastic neoplasms (Yoo-Jin Kim, Korea)	Adoptive T cell transfer of three universal tumor associated antigens-specific T cells for the treatment of AML (Byung Sik Cho, Korea)	Next generation cytogenetics – optical mapping for comprehensive structural variant detection in hematological malignancies and beyond (Alexander Hoischen, The Netherlands)	Managing adverse events of CAR T cell therapy (Jae Won Yoo, Korea)
16:20-16:35	Break			

PROGRAM AT A GLANCE Friday, March 31, 2023

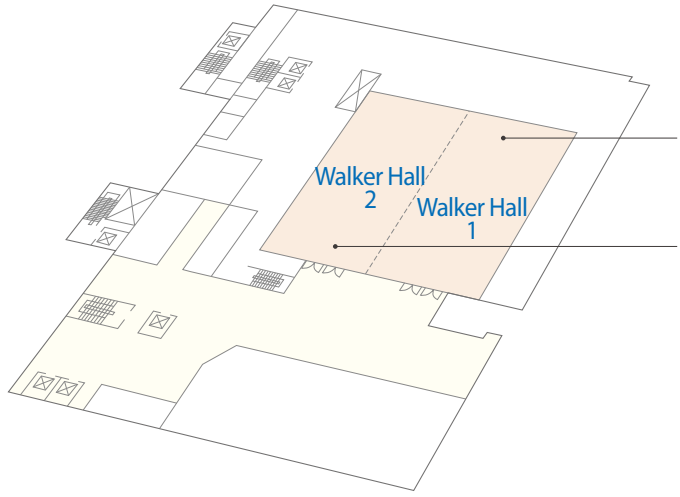
Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
16:35-17:50		**JS04** International Collaborative Session - Aplastic anemia	**SS11** Liquid biopsy application in hematology	**SS12** Up-to-date diagnostic and treatment strategies of adult ALL patients
		Overview of AA diagnosis and treatment in NIHBT, Vietnam (Nguyen Thi Thao, Vietnam)	Cell-free DNA profiling for monitoring of complications of hematopoietic cell transplantation (Iwijn De Vlaminck, USA)	Are we moving towards a chemo- and transplant-free management of Ph-positive adult ALL? (Robin Foa, Italy)
		The incidence and real-world outcome of aplastic anemia in Thailand (Lalita Norasetthada, Thailand)	Towards non-invasive monitoring of disease and microbe invasion in patients with hematologic malignancies (Charles Gawad, USA)	Development of more-effective CAR T-cell therapy for ALL (Saar I Gill, USA)
		Role of TPO receptor agonists in aplastic anemia treatment (Jun Ho Jang, Korea)	Clinical applications of circulating tumor DNA analysis in lymphoma (Seung-Tae Lee, Korea)	Overcoming high-risk features in adult ALL patients (Jae-Ho Yoon, Korea)
17:50-18:30	Break			
18:10-18:40	**Cocktail Reception** (Vista 3)			
18:40-20:00	**Gala dinner** (Vista 1+2)			

PROGRAM AT A GLANCE Saturday, April 1, 2023

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
07:30-08:30				Business Meeting
08:30-09:00	Working party Report			
09:00-10:15	**JS05** Asian Hematology Session II - Red Blood Cell Disorder	**SS13** Current knowledge of human hematopoietic stem cell	**SS14** What's new in chronic lymphocytic leukemia?	**ES06** Novel therapeutics for myeloproliferative neoplasms
	Overview of thalassaemia and hemoglobinopathies in Bangladesh (Mahmood A. Chowdhury, Bangladesh)	Single cell HSPC map (William J. Greenleaf, USA)	Translating scientific advances in CLL (Richard Rosenquist, Sweden)	Prognostication in MPNs (including mutation abnormalities) (Junshik Hong, Korea)
	Current situation of thalassemia care in Cambodia (Chean Sophâl, Cambodia)	Humanized mouse and non-human primate: Animal models for hematopoietic stem cell research (Kyung-Rok Yu, Korea)	Patient selection for time limited versus continued therapy (Jennifer R. Brown, USA)	Novel therapeutics for MF (including cyotpenic myelofibrosis) (Sung-Eun Lee, Korea)
	Epidemiology and diagnosis of hemolytic anemia in Korea (Heewon Chueh, Korea)	What we know about HSC homing? (Xinxin Huang, China)	MRD monitoring in CLL Patients (Ki-Seong Eom, Korea)	Novel therapeutics for ET/PV (Seugyun Yoon, Korea)
10:15-10:30	Break			
10:30-11:15	**PL03** Recent advance in the hematopoietic stem cell research (Toshio Suda, Singapore)			
11:15-11:30	Break			
11:30-12:00	Award Ceremony & Closing			

FLOOR PLAN

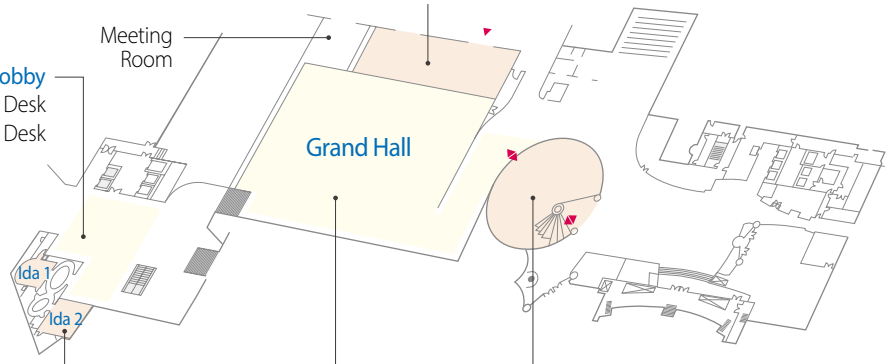
1F



Room 4
- Educational Session
- Business Meeting(April 1)

Posters

B1



Room 3
- Scientific Session

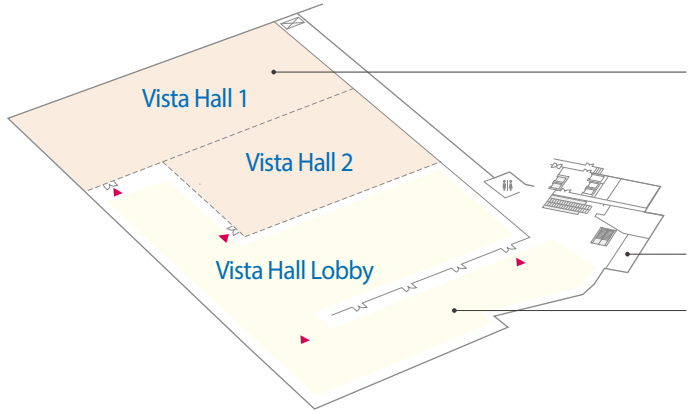
Ida Lobby
- Kit & Cloak Desk
- Event Desk

Ida 2
- Preview Room

Grand Hall Lobby
- Exhibition
- Coffee Break
- Internet Lounge

65th Anniversary Hall
- Memorial Exhibition of KSH
- Event & Photo Zone
- Coffee & Tea

B2



Room 1/Room 2
- Plenary Session
- Scientific Session
- Opening & Closing
- Gala Dinner (March 31)

ICKSH Secretariat

Vista Hall Lobby
- Exhibition
- Coffee Break
- Welcome Reception (March 30)

GENERAL INFORMATION

REGISTRATION

All participants are required to check in at the registration desk to pick up their name badge. Badges must be worn during all scientific sessions and social programs.

>> Location: Vista Lobby (B2)

>> Operation Hours: March 30 (Thu) 08:00 - 18:00
March 31 (Fri) 08:00 - 18:00
April 1 (Sat) 08:00 - 13:00

>> On-Site Registration Fees

Category	On-Site Registration Fees
General	USD 200
Resident/ Trainee/ Nurse/ Student	USD 100

+ Registration fees include: Participation in all scientific sessions, exhibition, satellite symposium including lunch, coffee breaks, conference kit, welcome reception and gala dinner.
+ Conference Kit will be distributed with your name badge at the Kit desk (B1). The kit includes a Program book and Abstract book.

LUNCH

Lunch boxes will be provided during the satellite symposium. Please wear your name badge.

>> Location: Room1 - Room4

>> Operation Hours: March 30(Thu) 12:00 - 13:00
March 31(Fri) 12:00 - 13:00

COFFEE BREAK

Coffee and tea will be served at coffee break times at the Vista Hall Lobby (B2) and Grand Hall Lobby (B1). Barista coffee and tea will be provided during the conference at the Grand Hall Lobby (65th Anniversary Hall of KSH) (B1).

CERTIFICATE OF ATTENDANCE

Participants may receive the certificate of attendance. Please contact the ICKSH 2023 Secretariat after conference via icksh@icksh.org.

USEFUL PHOTO NUMBERS

+ Police 112
+ Fire and ambulance 119
+ Medical Emergency 1339

GENERAL INFORMATION

USEFUL TRAVEL WEBSITE

+ Seoul City Tourism: http://www.visitseoul.net
+ Seoul Metropolitan Government: http://english.seoul.go.kr
+ Korean Tourism Organization: http://kto.visitkorea.or.kr/eng.kto

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SPEAKER INFORMATION

PREVIEW ROOM

All speakers are requested to visit the preview room no later than 2 hours before their session. They will be assisted by our staff who will help upload the presentation file to the server before the session.

>> Location: IDA 2 (B1)

>> Operation Hours: March 30 (Thu) 07:00 - 18:00
March 31 (Fri) 07:00 - 18:00
April 1 (Sat) 07:00 - 12:00

POSTER PRESENTATION

All posters are required to have a presentation time as following schedule.
After onsite reviews, the scientific committee will select Best Posters and the winners should attend the award at Closing Ceremony on April 1 (Sat).

>> Date & Time: March 31(Fri), 11:15-12:00

>> Location: Walker Hall (1F)

SOCIAL PROGRAM

OPENING

With the opening address by Cheol-Ju Yoo, Congress chairman, ICKSH 2023 will begin.

>> Date & Time: March 30 (Thu) 09:00

>> Location: Room1 (B2)

WELCOME RECEPTION

Welcome to ICKSH 2023! The Organizing Committee will prepare welcome reception.

>> Date & Time: March 30 (Thu) 18:10 - 19:30

>> Location: Vista Hall Lobby (B2)

GALA DINNER

Please join us to share an unforgettable evening. Enjoy the climax of ICKSH 2023 with an excellent dinner and exciting performance.

>> Date & Time: March 31 (Fri) 18:10 - 20:00 (Reception: 18:10 - 18:40)

>> Location: Vista Hall (B2)

EVENTS

KSH 65th ANNIVERSARY EVENTS

We are preparing a Memorial Exhibition for the 65th Anniversary of the Korean Society of Hematology this year. Various events and prizes await you, so visit the 65th Anniversary Hall and enjoy the programs!

>> Date & Time: March 30 (Thu) - April 1(Sat)

>> Location: 65th Anniversary Hall (B1)

LUCKY DRAW

Please participate in the KSH General Assembly and do not miss the lucky draw. (Korean participants only)

>> Date & Time: April 1 (Sat) 12:00

>> Location: Vista 1 (B2)

1 Person	1 Person	1 Person	3 Persons
			
LG Stand by me TV	Apple Watch SE (GPS, 44mm)	LG Code Zero	Sinsegae Gift Card

EARLY-BIRD EVENT

Daily gifts will be given to session participants each day up to 100 people on a first come, first served basis.

>> Date & Time: March 30(Thu) - April 1(Sat)

>> Location: Room1 - Room4

BOOTH STAMP EVENT

If you visit exhibition booths and complete the stamp sheet, gifts will be given.

>> Date & Time: March 30 (Thu) - April 1 (Sat)

>> Location: IDA hall Lobby (B1)

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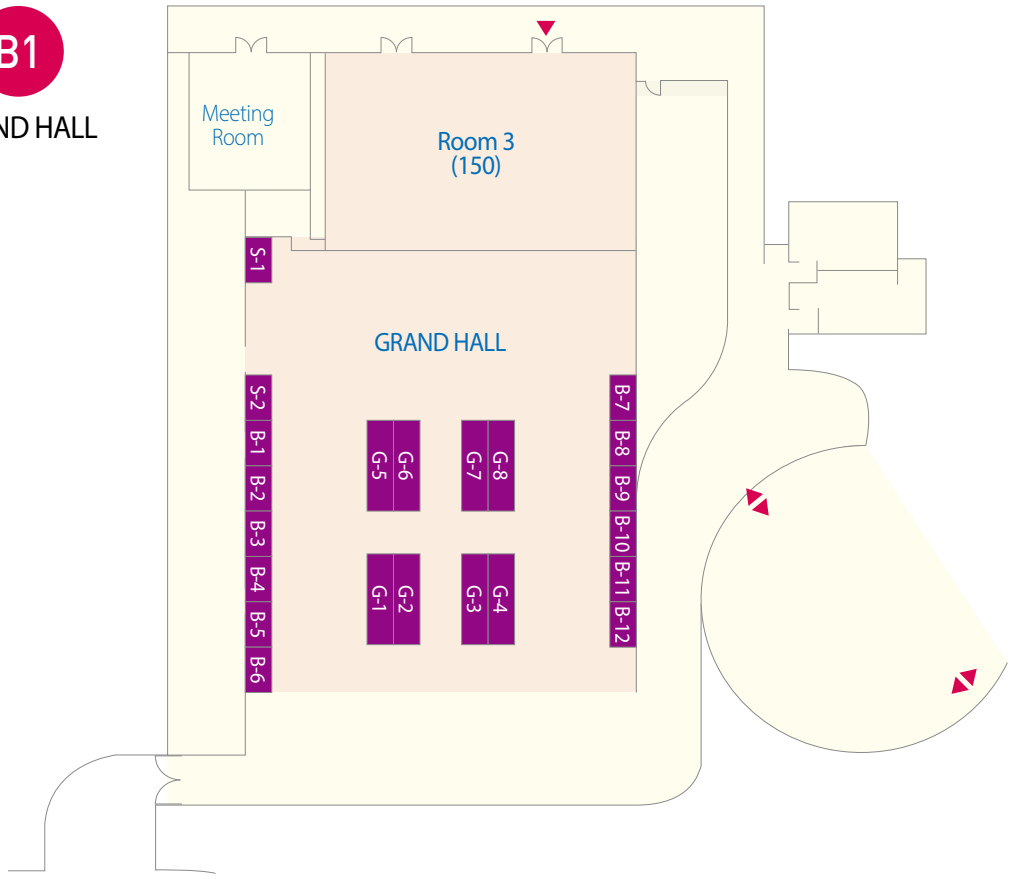
EXHIBITION

B1

GRAND HALL



No.	Company Name
G-1	Antengene Medicine
G-2	Otsuka
G-3	Pfizer Korea
G-4	MSD KOREA
G-5	YUHAN
G-6	Abbvie
G-7	Celltrion Pharm
G-8	Sanofi-Aventis

No.	Company Name
S-1	AstraZeneca Korea
S-2	Roche Diagnostics Korea
B-1	Clinigen Korea
B-2	Bionano genomics & MDxK
B-3	Sysmex Korea
B-4	DIAGENEX
B-5	Samyang Holdings Corp.

No.	Company Name
B-6	PharmaEssentia Korea
B-7	Dong-A ST
B-8	BeiGene
B-9	Recordati Korea
B-10	JW Pharmaceutical
B-11	JW Pharmaceutical
B-12	IL-YANG PHARM

EXHIBITION

No.	Company Name
D-1	Kyowakirin
D-2	Roche Korea
D-3	Celgene/BMS
D-4	Novartis Korea
D-5	Janssen Korea
D-6	Handok Inc.

No.	Company Name
P-1	Takeda Pharmaceuticals Korea
P-2	Amgen Korea
P-3	GC Biopharma
P-4	Astellas Korea

KEY SPEAKERS

MARCH 30 (THU.)

[PL01] Plenary Lecture 01

10:30 - 11:15 | Room 1

Regulation of iron metabolism

Martina U. Muckenthaler
University of Heidelberg, Germany

[PS01] Presidential Symposium

11:15 - 12:00 | Room 1

What can Nano do for Medicine?

Taeghwan Hyeon
Seoul National University, Korea

MARCH 31 (FRI.)

[PL02] Plenary Lecture 02

10:30 - 11:15 | Room 1

The role of the intestinal microbiome in cancer immunotherapy

Marcel van den Brink
Memorial Sloan Kettering Cancer Center, USA

APRIL 1 (SAT.)

[PL03] Plenary Lecture 03

10:30 - 11:15 | Room 1

Recent advance in the hematopoietic stem cell research

Toshio Suda
National University of Singapore, Singapore

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DAILY PROGRAM

DAILY PROGRAM Thursday, March 30

08:50-09:00 **Opening Remark** Room 1

09:00-10:15 **[CS01] Innovative diagnostic technologies** Room 1

Chairs Jin-Yeong Han (Dong-A University College of Medicine, Korea)
In-Suk Kim (Pusan National University School of Medicine, Korea)

CS01-1 Accelerate breakthroughs in hematology with single cell sequencing
Geoffrey McDermott (10x Genomics, Inc., USA)

CS01-2 AI technology in the field of blood disease
Tabe Yoko (Juntendo University, Japan)

CS01-3 Discover the unique power of using droplet digital PCR (ddPCR) for hematology-oncology applications
Gina Sun (Bio-Rad Laboratories, USA)

CS01-4 Holotomography and artificial intelligence: label-free 3D imaging, classification, and inference
Yongkeun Park (Tomocube Inc., Korea)

09:00-10:15 **[SS01] Challenging issues in childhood blood disorders** Room 2

Chairs Hoon Kook (Chonnam National University Medical School, Korea)
Nack-Gyun Chung (College of Medicine, The Catholic University of Korea, Korea)

SS01-1 How to diagnosis and treat neutropenia in childhood
Kelly Walkovich (University of Michigan, USA)

SS01-2 Updates in the treatment of pediatric relapsed/refractory acute myeloid leukemia
Keon Hee Yoo (Sungkyunkwan University School of Medicine, Korea)

SS01-3 Use of chimeric antigen receptor (CAR) expressing T cells for acute lymphoblastic leukemia (ALL)
Michael Verneris (Children's Hospital Colorado, USA)

09:00-10:15 **[SS02] How far has cell therapy developed in Hodgkin lymphoma?** Room 3

Chairs Hyeon-Seok Eom (National Cancer Center, Korea)
Sung Yong Oh (Dong-A University College of Medicine, Korea)

SS02-1 Pathogenesis of Hodgkin lymphoma
Ralf Küppers (University of Duisburg-Essen, Germany)

SS02-2 Emerging cellular therapy in Hodgkin lymphoma
Natalie S Grover (The University of North Carolina at Chapel Hill, USA)

SS02-3 Novel treatment of relapsed/refractory Hodgkin lymphoma
Hyeon-Seok Eom (National Cancer Center, Korea)

09:00-10:15 **[ES01] Different treatment goals for overcoming resistance or functional cure in CML** Room 4

Chair Chul Won Jung (Sungkyunkwan University School of Medicine, Korea)
Hawk Kim (Gachon University College of Medicine, Korea)

DAILY PROGRAM Thursday, March 30

ES01-1 **Asciminib: the first-in-class allosteric inhibitor of BCR/ABL1 kinase**
Eun-Ji Choi (University of Ulsan College of Medicine, Korea)

ES01-2 **Treatment after failure of frontline therapy of CML-CP including allo-HSCT**
Jieun Uhm (Hanyang University College of Medicine, Korea)

ES01-3 **Update on treatment free remission**
Jae Joon Han (Kyung Hee University College of Medicine, Korea)

10:15-10:30 Break

10:30-11:15 **[PL01] Plenary Lecture 01** Room 1+2

Chair Sung-Soo Yoon (Seoul National University College of Medicine, Korea)

Regulation of iron metabolism
Martina U. Muckenthaler (University of Heidelberg, Germany)

11:15-12:00 **[PS01] Presidential Symposium** Room 1+2

Chair Seongsoo Jang (University of Ulsan College of Medicine, Korea)

What can Nano do for Medicine?
Taeghwan Hyeon (Seoul National University, Korea)

12:00-12:15 Break

12:15-13:05 **[SY01] Novartis** Room 1

Chair Dong-Wook Kim (Eulji University School of Medicine, Korea)

ASCIMINIB, new paradigm treatment option in CML for patients who were previously treated with 2 or more TKIs
Andreas Hocchaus (Jena University Hospital, Germany)

12:15-13:05 **[SY02] Roche** Room 2

Chair Seok Jin Kim (Sungkyunkwan University School of Medicine, Korea)

Unmet need in 1L DLBCL and POLARIX trial
Georg Lenz (University Hospital in Münster, Germany)

12:15-13:05 **[SY03] BMS-Celgene** Room 3

Chair Ho Sup Lee (Kosin University College of Medicine, Korea)

Maintenance treatment post autotransplant for multiple myeloma
Kevin Song (Vancouver General Hospital, Canada)

13:05-13:20 Break

DAILY PROGRAM Thursday, March 30

13:20-14:50 **[YI] Young Investigator Presentation** Room 1

Chairs Je-Hwan Lee (University of Ulsan College of Medicine, Korea)
Hyoung Jin Kang (Seoul National University College of Medicine, Korea)

YI-1 Identification of Clonical Significance and Appropriate Diagnostic Tools for Minimal Residual Disease in Acute Myeloid Leukemia Patients Treated with Venetoclax-Based Low-Intensity Chemotherapy
Daehun Kwag (College of Medicine, The Catholic University of Korea, Korea)

YI-2 A study on the discovery of candidates for therapeutic targets using microRNA in T-cell lymphomas and the tracking of minimal residual disease
Youngwoo Jeon (College of Medicine, The Catholic University of Korea, Korea)

YI-3 Monitoring mutational profile and prognosis of multiple myeloma patients with multiple focal lesions in PET/CT using liquid biopsy
Hee Jeong Cho (Kyungpook National University School of Medicine, Korea)

YI-4 Development of cytotoxic T cell therapy against tumor-specific antigen discovered by artificial intelligence
Jeong Suk Koh (Chungnam National University College of Medicine, Korea)

YI-5 Establishment of clinical utility of minimal residual disease assessment using next-generation sequencing
Hye Won Kook (Yonsei University College of Medicine, Korea)

YI-6 Microbiome analysis for anticipating GVHD and predicting clinical outcome in patients received allogeneic hematopoietic stem cell transplantation
Ju Hyung Kim (Kyungpook National University School of Medicine, Korea)

YI-7 A study on machine learning models for early diagnosis of leukemia
Hyunji Kim (Seoul National University College of Medicine, Korea)

YI-8 Establishment of minimal residual disease monitoring strategy for patients B-lymphoblastic leukemia after CD19-targeted therapy and development of standardized protocols through machine learning
Ari Ahn (College of Medicine, The Catholic University of Korea, Korea)

YI-9 Establishment of bortezomib resistant multiple myeloma cell line, and analysis of antioxidant enzymes and autophagy markers
Se Won Lee (Ewha Womans University College of Medicine, Korea)

13:20-14:50 **[OP01] Acute myeloid leukemia** Room 2

Chairs Joon Seong Park (Ajou University School of Medicine, Korea)
Sung Hwa Bae (Daegu Catholic University School of Medicine, Korea)

OP01-1 Prognostic value of genomic clusters using machine learning in older adults with AML
Tong Yoon Kim (College of Medicine, The Catholic University of Korea, Korea)

OP01-2 Validation of the 2022 European LeukemiaNet risk stratification for acute myeloid leukemia in the real world
Ga-young Song (Chonnam National University Hwasun Hospital, Korea)

OP01-3 A paired outcome evaluation of wilms tumor-1 (WT-1) gene mutation and expression in acute myeloid leukemia
Pranay Tanwar (All India Institute of Medical Sciences, India)

OP01-4 CEBPA mutations in 1716 Korean patients with acute myeloid leukemia
Hoon Seok Kim (College of Medicine, The Catholic University of Korea, Korea)

OP01-5 Antileukemic effect of cyclin-dependent kinase 7 inhibitor, YPN-005 combined with FLT3 inhibitor in FMS-tyrosine kinase 3 -mutated acute myeloid leukemia
Bon-Kwan Goo (University of Ulsan College of Medicine, Korea)

DAILY PROGRAM Thursday, March 30

OP01-6 DRP1 inhibition enhances venetoclax-induced mitochondrial apoptosis in TP53-mutated acute myeloid leukemia cells through BAX/BAK activation
June-Won Cheong (Yonsei University College of Medicine, Korea)

13:20-14:50 **[OP02] Lymphoma** Room 3

Chairs Byung-Su Kim (College of Medicine, The Catholic University of Korea, Korea)
Seong Hyun Jeong (Ajou University School of Medicine, Korea)

OP02-1 Classical Hodgkin lymphoma: Clinical features, prognostic factors, and treatment outcomes in a Malaysian tertiary centre
Wei Quan Low (Sultanah Aminah Hospital, Malaysia)

OP02-2 Phase II study of bortezomib/dexamethasone induction and maintenance therapy in relapsed/refractory cutaneous T cell lymphoma (CISL1701 study)
Yoon Seok Choi (Ajou University School of Medicine, Korea)

OP02-3 Odronextamab in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): Phase 2 study (ELM-2) prespecified analysis results
Won Seog Kim (Sungkyunkwan University School of Medicine, Korea)

OP02-4 Novel subgroup analyses of subcutaneous epcoritamab monotherapy in patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL)
Young Rok Do (Keimyung University Dongsan Medical Center, Korea)

OP02-5 The treatment outcome of tisagenlecleucel for the patient with relapsed/refractory B-cell lymphoid malignancies in Samsung Medical Center
Sang Eun Yoon (Sungkyunkwan University School of Medicine, Korea)

OP02-6 How to improve clinical outcomes of tisagenlecleucel treatment in relapsed/refractory diffuse large B cell lymphoma?
Gi June Min (Seoul St. Mary's Hematology Hospital, Korea)

OP02-7 Distribution and sequential patterns of the second malignancies among the lymphoid neoplasm in South Korea
Tong Yoon Kim (College of Medicine, The Catholic University of Korea, Korea)

13:20-14:50 **[OP03] Stem cell transplant and laboratory hematology** Room 4

Chairs Young Kyung Lee (Hallym University College of Medicine, Korea)
Young-Uk Cho (University of Ulsan College of Medicine, Korea)

OP03-1 Genomic alterations in chronic myeloid leukaemia patients who failed second generation tyrosine kinase inhibitor
Siew Lian Chong (Hospital Ampang, Malaysia)

OP03-2 Genome-wide methylation profiling of BCR/ABL1-negative myeloproliferative neoplasms
Miyoung Kim (University of Ulsan College of Medicine, Korea)

OP03-3 Machine learning based predictive classifier for bone marrow failure syndrome using complete blood count and differential cell populations
Hongyul An (Genome Opinion, Korea)

OP03-4 G6PD-independent differentiation of human CD34 positive haematopoietic stem and progenitor cells into mature erythrocytes
Kanyarat Boonpeng (Chulalongkorn University, Thailand)

DAILY PROGRAM Thursday, March 30

DAILY PROGRAM Thursday, March 30

DAILY PROGRAM Thursday, March 30

OP06-5 Antibody targeting of soluble MHC-class-I-related molecule augments natural killer cell function by restoring NKG2D in multiple myeloma
Hyunsoo Cho (Yonsei University College of Medicine, Korea)

OP06-6 Monocytic myeloid-derived suppressor cells expand but lose suppressive activity following stem cell mobilization with G-CSF in multiple myeloma patients
Egor Batorov (Research Institute of Fundamental and Clinical Immunology, Russia)

13:20-14:50 **[OP07] Anemia, bleeding and platelet** Room 4

Chairs Seong Kyu Park (Soonchunhyang University Bucheon Hospital, Korea)
Jaewoo Song (Yonsei University College of Medicine, Korea)

OP07-1 GC1126A, a novel ADAMTS13 mutein that evades autoantibody as a superior therapy for acquired thrombotic thrombocytopenic purpura (aTTP)
Hyun-Ja Nam (GC Biopharma, Korea)

OP07-2 Obesity is associated with poor response to corticosteroid-based therapy in chinese primary immune thrombocytopenia (ITP) patients
Gege Feng (Qilu Hospital of Shandong University, China)

OP07-3 Deciphering transcriptome alterations in bone marrow hematopoiesis at single-cell resolution in immune thrombocytopenia
Xinyi Zuo (Shandong University, China)

OP07-4 A Phase 1 study of the safety, tolerability, pharmacokinetics and pharmacodynamics of MG1113 in healthy subjects and hemophilia patients
Jung Woo Han (Yonsei Cancer Center, Yonsei University Health System, Korea)

OP07-5 Evaluation of safety and efficacy of hbs-sailin®: A potent ingenious anti-sickling agent that reduces pain and improves the quality of life in sickle cell patients
Shruti Bhatt (University of Delhi South Campus, India)

OP07-6 Favorable outcomes of hematopoietic stem cell transplantation after fludarabine-based, radiation-free conditioning in children with inherited bone marrow failure syndrome
Suejung Jo (College of Medicine, The Catholic University of Korea, Korea)

14:50-15:05 Break

15:05-16:20 **[JS03] EHA-KSH Joint Symposium - Myelodysplastic Syndrome** Room 1

Chairs June-Won Cheong (Yonsei University College of Medicine, Korea)
Lionel Adès (Hospital Saint Louis and Paris University, France)

JS03-1 Novel approaches in MDS
Uwe Platzbecker (Leipzig University Hospital, Germany)

JS03-2 Treatment of MDS: Korean AML/MDS working party experience
June-Won Cheong (Yonsei University College of Medicine, Korea)

JS03-3 Standard management of MDS
Lionel Adès (Hospital Saint Louis and Paris University, France)

JS03-4 Genetic alterations in myelodysplastic neoplasms
Yoo-Jin Kim (College of Medicine, The Catholic University of Korea, Korea)

15:05-16:20 **[SS09] Which immune therapy is our future weapon against AML?** Room 2

Chairs Hyeoung-Joon Kim (Chonnam National University Medical School, Korea)
Hee-Je Kim (College of Medicine, The Catholic University of Korea, Korea)

SS09-1 Immune checkpoint inhibition for AML ; CD47 blockade and beyond
Naval Daver (MD Anderson Cancer Center, USA)

SS09-2 Determining the barriers to successful CAR T cell therapy for AML
Miriam Y Kim (University of Washington, USA)

SS09-3 Adoptive T cell transfer of three universal tumor associated antigens-specific T cells for the treatment of AML
Byung Sik Cho (College of Medicine, The Catholic University of Korea, Korea)

15:05-16:20 **[SS10] Next-generation molecular genomic and cytogenomic technology in hematology** Room 3

Chairs Myungshin Kim (College of Medicine, The Catholic University of Korea, Korea)
Yoon Hwan Chang (Seoul National University Hospital, Korea)

SS10-1 A transcriptomic approach to clinical diagnosis, prognosis and therapy selection in AML
Aly Karsan (University of British Columbia, Canada)

SS10-2 Whole genome sequencing of fluorescence in situ hybridized cells in hematologic malignancies using SLACS
Sunghoon Kwon (Seoul National University, Korea)

SS10-3 Next generation cytogenetics – optical mapping for comprehensive structural variant detection in hematological malignancies and beyond
Alexander Hoischen (Radboud University Medical Center, The Netherlands)

15:05-16:20 **[ES05] Practical issue in CAR-T** Room 4

Chairs Jae-Yong Kwak (Jeonbuk National University Hospital, Korea)
Hyoung Jin Kang (Seoul National University College of Medicine, Korea)

ES05-1 Setting up the facility for CAR T cell therapy
Ja Min Byun (Seoul National University College of Medicine, Korea)

ES05-2 Technical aspect of manufacturing CAR T cell product
Jong-Seo Lee (AbClon Inc., Korea)

ES05-3 Managing adverse events of CAR T cell therapy
Jae Won Yoo (College of Medicine, The Catholic University of Korea, Korea)

16:20-16:35 Break

16:35-17:50 **[JS04] International Collaborative Session - Aplastic Anemia** Room 2

Chairs Jun Ho Jang (Sungkyunkwan University School of Medicine, Korea)
Lalita Norasetthada (Chiang Mai University, Thailand)

JS04-1 Overview of AA diagnosis and treatment in NIHBT, Vietnam
Nguyen Thi Thao (National Institute of Hematology and Blood Transfusion, Vietnam)

JS04-2 The incidence and real-world outcome of aplastic anemia in Thailand
Lalita Norasetthada (Chiang Mai University, Thailand)

JS04-3 Role of TPO receptor agonists in aplastic anemia treatment
Jun Ho Jang (Sungkyunkwan University School of Medicine, Korea)

16:35-17:50 **[SS11] Liquid biopsy application in hematology** Room 3

Chairs Myung Geun Shin (Chonnam National University Medical School, Korea)
Seung-Tae Lee (Yonsei University College of Medicine, Korea)

SS11-1 Cell-free DNA profiling for monitoring of complications of hematopoietic cell transplantation
Iwijn De Vlaminck (Cornell University, USA)

SS11-2 Towards non-invasive monitoring of disease and microbe invasion in patients with hematologic malignancies
Charles Gawad (Stanford University, USA)

SS11-3 Clinical applications of circulating tumor DNA analysis in lymphoma
Seung-Tae Lee (Yonsei University College of Medicine, Korea)

16:35-17:50 **[SS12] Up-to-date diagnostic and treatment strategies of adult ALL patients** Room 4

Chairs Ho-Jin Shin (Pusan National University Hospital, Korea)
Seok Lee (College of Medicine, The Catholic University of Korea, Korea)

SS12-1 Are we moving towards a chemo- and transplant-free management of Ph-positive adult ALL?
Robin Foa (Sapienza University of Rome, Italy)

SS12-2 Development of more-effective CAR T-cell therapy for ALL
Saar I Gill (University of Pennsylvania, USA)

SS12-3 Overcoming high-risk features in adult ALL patients
Jae-Ho Yoon (College of Medicine, The Catholic University of Korea, Korea)

17:50-18:10 Break

18:10-18:40 **Cocktail Reception** VISTA 3

18:40-20:00 **Gala Dinner** VISTA 1+2

DAILY PROGRAM Saturday April 1

07:30-08:30 **Business Meeting** Room 4

08:30-09:00 **Working Party Report** Room 1

09:00-10:15 **[JS05] Asian Hematology Session II - Red Blood Cell Disorder** Room 1

Chairs Hye Lim Jung (Sungkyunkwan University School of Medicine, Korea)
Hyoung Soo Choi (Seoul National University College of Medicine, Korea)

JS05-1 Overview of thalassaemia and hemoglobinopathies in Bangladesh
Mahmood A. Chowdhury (Chattogram Maa-O-Shishu Hospital Medical College, Bangladesh)

JS05-2 Current situation of thalassemia care in Cambodia
Chean Sophâl (National Pediatric Hospital, Cambodia)

JS05-3 Epidemiology and diagnosis of hemolytic anemia in Korea
Heewon Chueh (Dong-A University College of Medicine, Korea)

09:00-10:15 **[SS13] Current knowledge of human hematopoietic stem cell** Room 2

Chairs Deog-Yeon Jo (Chungnam National University College of Medicine, Korea)
Byung-Soo Kim (Korea University College of Medicine, Korea)

SS13-1 Single cell HSPC map
William J. Greenleaf (Stanford University, USA)

SS13-2 Humanized mouse and non-human primate: Animal models for hematopoietic stem cell research
Kyung-Rok Yu (Seoul National University, Korea)

SS13-3 What we know about HSC homing?
Xinxin Huang (Fudan University, China)

09:00-10:15 **[SS14] What's new in chronic lymphocytic leukemia?** Room 3

Chairs Young Rok Do (Keimyung University School of Medicine, Korea)
Deok-Hwan Yang (Chonnam National University Medical School, Korea)

SS14-1 Translating scientific advances in CLL
Richard Rosenquist (Karolinska Institute, Sweden)

SS14-2 Patient selection for time limited versus continued therapy
Jennifer R. Brown (Dana-Farber Cancer Institute, USA)

SS14-3 MRD monitoring in CLL Patients
Ki-Seong Eom (College of Medicine, The Catholic University of Korea, Korea)

DAILY PROGRAM Saturday April 1

09:00-10:15 **[ES06] Novel therapeutics for myeloproliferative neoplasms** Room 4

Chairs Sung-Yong Kim (Konkuk University School of Medicine, Korea)
Chul Won Choi (Korea University Guro Hospital, Korea)

ES06-1 Prognostication in MPNs (including mutation abnormalities)
Junshik Hong (Seoul National University Hospital, Korea)

ES06-2 Novel therapeutics for MF (including cyotpenic myelofibrosis)
Sung-Eun Lee (College of Medicine, The Catholic University of Korea, Korea)

ES06-3 Novel therapeutics for ET/PV
Seug Yun Yoon (Soonchunhyang University Seoul Hospital, Korea)

10:30-11:15 **[PL03] Plenary Lecture 03** Room 1+2

Chair Kyung Ha Ryu (Ewha Womans University, Korea)

Recent advance in the hematopoietic stem cell research
Toshio Suda (National University of Singapore, Singapore)

11:15-11:30 Break

11:30-12:00 **Award Ceremony & Closing** Room 1+2

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POSTER LIST

POSTER LIST

PP01-1 **Clinical Significance of bZIP in-frame CEBPA-mutated normal karyotype acute myeloid leukemia**

Seo-Yeon Ahn[1], TaeHyung Kim[2,3], Mihee Kim[1], Ga-Young Song[1], Sung-Hoon Jung[1], Deok-Hwan Yang[1], Je-Jung Lee[1], Mi Yeon Kim[4], Chul Won Jung[5], Jun-Ho Jang[5], Hee Je Kim[6], Joon Ho Moon[7], Sang Kyun Sohn[7], Jong-Ho Won[8], Sung-Hyun Kim[9], Hyeoung-Joon Kim[1,4], Jae-Sook Ahn[1,4*] and Dennis Dong Hwan Kim[10]

[1]*Hematology-Oncology, Chonnam National University Hwasun Hospital, Korea*
[2]*The Donnelly Centre for Cellular and Biomolecular Research, University of Toronto, Canada*
[3]*Computer Science, University of Toronto, Canada*
[4]*Genomic Research Center for Hematopoietic Diseases, Chonnam National University Hwasun Hospital, Korea*
[5]*Hematology-Oncology, Samsung Medical Center, Korea*
[6]*Hematology, Cancer Research Institute, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea*
[7]*Hematology-Oncology, Kyungpook National University Hospital, Korea*
[8]*Hematology-Oncology, Soon Chun Hyang University Hospital, Korea*
[9]*Hematology-Oncology, Dong-A University College of Medicine, Korea*
[10]*Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Canada*

PP01-2 **Candidate drug screening for TP53-mutated AML**

Daehyeon Gwak[1,2], Dong-Yeop Shin[1,2,3*], Dongchan Kim[1,2], Ja Min Byun[1,2,3], Youngil Koh[1,2,3], Junshik Hong[1,2,3] and Sung-Soo Yoon[1,2,3]

[1]*Cancer Research Institute, Seoul National University College of Medicine, Korea*
[2]*Center for Medical Innovation of Biomedical Research Institute, Seoul National University Hospital, Korea*
[3]*Department of Internal Medicine, Seoul National University College of Medicine, Korea*

PP01-3 **Prognostic relevance of MN1 expression in cytogenetically normal adult AML Patients**

Anita Chopra[1*], Aparna Ningombam[1], Deepak Verma[1], Rajive Kumar[1], Jay Singh[1], Shadab Ali[1], Avanish Panday[1], Inder Sigh[4], Sameer Bakhshi[2], Atul Sharma[2], Deepam Pushpam[2], Jayanth Palanichamy[3], Pranay Tanwar[1] and Amar Ranjan Singh[1]

[1]*Laboratory Oncology, Professor, All India Institute Of Medical Science, India*
[2]*Medical Oncology, Professor, All India Institute Of Medical Science, India*
[3]*Biochemistry, Additional professor, All India Institute Of Medical Science, India*
[4]*Neurology, Scientist, All India Institute Of Medical Science, India*

PP01-4 **Antileukemic activity of 1,3,5-Triazine (5-TC) against human leukemic cell via inhibition of EGFR-TK**

Udaya Pratap Singh[1*] and Hans Raj Bhat[2]

[1]*Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, India*
[2]*Department of Pharmaceutical Sciences, Dibrugarh University, India*

PP01-5 **Gilteritinib with chemotherapy in patients with newly diagnosed acute myeloid leukemia**

Masashi Sawa[1], Toshihiro Miyamoto[2], Hee-Je Kim[3], Yasushi Hiramatsu[4], June-Won Cheong[5*], Takayuki Ikezoe[6], Tomoki Naoe[7], Koichi Akashi[8], Satoshi Morita[9], Nahla Hasabou[10], Elizabeth Shima Rich[10], Masanori Kosako[11], Eiichiro Uemura[10], Wataru Terada[11], Takeshi Kadokura[11], Jason Hill[10] and Shuichi Miyawaki[12]

[1]*Department of Hematology and Oncology, Anjo Kosei Hospital, Japan*
[2]*Department of Hematology, Kanazawa University, Japan*
[3]*Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Korea*
[4]*Department of Hematology and Oncology, Japanese Red Cross Society Himeji Hospital, Japan*
[5]*Department of Internal Medicine, Yonsei University College of Medicine, Korea*
[6]*Department of Hematology, Fukushima Medical University Hospital, Japan*
[7]*Department of Hematology and Oncology, National Hospital Organization Nagoya Medical Center, Japan*
[8]*Department of Medicine and Biosystemic Science, Kyushu University Hospital, Japan*
[9]*Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Japan*
[10]*Astellas Pharma US, Inc., USA*
[11]*Astellas Pharma Inc., Japan*
[12]*Division of Hematology, Tokyo Metropolitan Ohtsuka Hospital, Japan*

PP01-10 **Mitochondrial Membrane potential as a metabolic related marker to enrich LSCs in AML**

Pingping Yang[1], Aibin Liang[1*], Wenjun Zhang[1] and Yufeng Shi[2]

[1]*Department of Haematology, Tongji Hospital, Tongji University School of Medicine, 1239 Siping Road, China*
[2]*Tongji University Cancer Center, Shanghai Tenth People's Hospital of Tongji University School of Medicine, China*

POSTER LIST

PP01-11 **Genetic, epigenetic, and clinical significance of Wilms' tumor 1 (WT1) gene in primary acute myeloid leukemia and its influence on prognosis**

Harsh Goel[1], Anita Chopra[1], Amar Ranjan[1], Jagdish Prasad Meena[2], Aditya Kumar Gupta[2], Ganesh Kumar Viswanathan[3], Sameer Bakhshi[4], Maroof Ahmad Khan[5] and Pranay Tanwar[1*]

[1]Laboratory Oncology Unit, Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India
[2] Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India
[3]Department of Hematology, All India Institute of Medical Sciences, New Delhi, India
[4]Department of Medical Oncology, Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India
[5]Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India

PP01-12 **Mutation of NPM1 and FLT3-ITD genes in acute myeloid leukemia and their association with clinico-pathological profile**

Smeeta Gajendra[1*], Nupur Das[1], Ritu Gupta[1], Deepshi Thakral[1], Sanjeev k Gupta[1], Sameer Bakshi[2], Ranjit K Sahoo [2] and Atul Sharma[2]

[1]Laboratory Oncology, BRAIRCH, AIIMS, New Delhi, India
[2]Medical Oncology, BRAIRCH, AIIMS, New Delhi, India

PP01-13 **Pursuing the clonal transition of minimal residual disease clones in patients with relapsed and refractory acute myeloid leukemia**

Dongchan Kim[1], Hyojin Song[2,3], Sung-Soo Yoon[1,4], Hongseok Yun[2,3] and Dong-Yeop Shin[1,4*]

[1]Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea
[2]Center for Precision Medicine, Seoul National University Hospital, Seoul, Korea
[3]Center for Medical Innovation, Seoul National University Hospital, Seoul, Korea
[4]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

PP01-15 **Role of HOTAIRM1/miR-222 Axis in the pathogenesis of paediatric acute myeloid leukaemia**

Christine Wilson[1], Diwakar Sharma[1], Sachin Kumar [1], Jayanth K. Palanichamy[3], Anita Chopra [2], Sampa Ghose[1], Sameer Bakhshi[1] and Surender K. Sharawat[1*]

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PP01-16 **Retrospective analysis of TP53 mutations in acute myeloid leukiemia: A single institute study**

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PP01-17 **Role of LncRNA UCA1 long non-coding RNA in pediatric acute myeloid leukemia**

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PP01-18 **Novel HOXA3-HOXA9 fusion genes in acute myeloid leukaemia: The bride or the bridesmaid?**

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PP01-19 **Not only mutations matter: Deciphering the gene expression profiles of FLT3 and NPM1 in acute myeloid leukaemia-normal karyotype by transcriptome sequencing**

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PP01-20 **Reclassification of acute myeloid leukemia and higher-risk myelodysplastic syndrome based on the new International Consensus Classification**

Hye-Seong Ryu[1], Young-Uk Cho[1*], Daehyun Chu[1], Miyoung Kim[1], Seongsoo Jang[1], Chan-Jeoung Park[1], Eul-Ju Seo[1] and Sang-Hyun Hwang[1]

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PP01-22 **Unveiling of some novel compounds to inhibit the overexpressed genes of acute myeloid leukemia for the new therapeutics discovery**

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PP01-23 **A prospective study to evaluate the prognostic implications of MMP-2 gene in acute myeloid leukemia**

Harsh Goel[1], Anita Chopra[1], Amar Ranjan[1], Aditya Kumar Gupta[2], Jagdish Prasad Meena[2], Ganesh Kumar Viswanathan[3], Sameer Bakhshi[4], Maroof Ahmad Khan[5] and Pranay Tanwar[1*]
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PP01-24 **Azacytidine venetoclax posaconazole combination in the treatment of acute myeloid leukemia in a resource limited setting: A single centre experience**

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PP01-26 **Discovery of neoantigens using artificial intelligence (NEO-ARSTM) in AML: A pilot study**

Suyoung Choi[1,2,3], Joo-Young Kang[4], Hyun-Jin Yang[4], Jeong-Yeon Park[5], Il-Oh Jeong[5], Jong Hui Hong[5], Jongsun Jung[5], Thi Thuy Duong Pham[1,2,3], Bu-Yeon Heo[1,2,3], Jeong Suk Koh[6], Myung-Won Lee[6], Jung-Hyun Park[7], Yunsun Jang[7], Deog-Yeon Jo[6], Jaeyul Kwon[1,2,3,7,8] and Ik-Chan Song[1,3,6*]
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PP01-27 **Effects of venetoclax-based combinations for the treatment of newly diagnosed acute myeloid leukemia in clinical settings**

Young Seob Park[1], Min Kyoung Kim[1*], Sung Hwa Bae[2], Sang Kyun Sohn[3], Joon Ho Moon[3], Hee Jeong Cho[3], Juhyung Kim[3], Young Rok Do[4], Mi Hwa Heo[4] and Jung Min Lee[4]
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PP01-29 **The role of estrogen related receptor alpha (ERRα) as therapeutic target of acute myeloid leukemia**

Wonhyouong Seo[1], Ik-Chan Song [2], Kyung Tae Kim [1], Sang Min Jeon[1], Taylor Roh [1] and Eun-Kyeong Jo[1*]
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PP01-30 **Pharmacological GLUT3 salvage augments the efficacy of vitamin C-induced TET2 restoration in acute myeloid leukemia**

Junshik Hong[1*], Jun Liu[1], Suji Min[1] and Sung-Soo Yoon[1]
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PP01-31 **Differences of categories and their prognosis between the International Consensus Classification 2022 and the 5th World Health Organization classification in acute myeloid leukemia**

Jin Jung[1,2], Daehun Kwag[3], Hoon Seok Kim[1,2], Jong-Mi Lee[1,2], Ari Ahn[1,2], Byung-Sik Cho[3], Hee-Je Kim[3], Yonggoo Kim[1,2], and Myungshin Kim[1,2]

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PP01-32 **Physical function in older adults with acute myeloid leukemia treated with hypomethylating agents with or without venetoclax**

Daehun Kwag[1,2], Su-yeon Bang[1,2], Jong Hyuk Lee[1,2], Gi-June Min[1,2], Sung-Soo Park[1,2], Silvia Park[1,2], Jae-Ho Yoon[1,2], Sung-Eun Lee[1,2], Ki-Seong Eom[1,2], Yoo-Jin Kim[1,2], Seok Lee[1,2], Hee-Je Kim[1,2], Chang-Ki Min[1,2], Seok-Goo Cho[1], Jong Wook Lee[1], and Byung-Sik Cho[1,2]

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PP02-1 **Proerythroblasts as the main erythroid dysplasia in myelodysplastic syndrome**

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PP02-2 **Is MDS really treatable in Pakistan? Gaps and challenge- Single centre experience from Pakistan**

Nida Anwar[1*], Uzma Mahar[1], Aisha Arshad[1], Naveena Fatima[2], Sumaira Sharif[2] and Tahir Shamsi[1]

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PP02-3 **Significance of platelet count at diagnosis and its association with survival in MDS Patients; An experience from Pakistan**

Nida Anwar[1*], Naveena Fatima[2], Aisha Arshad[1], Anum Khalid[2] and Laraib Majeed[2]

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PP02-4 **Impact of transfusion burden in lower-risk MDS**

Jungmin Lee[1], Juhyung Kim[2], Hee Jeong Cho[2], Dong Won Baek[3], Ji Yeon Ham[4], Soon Hee Chang[5], Sang Kyun Sohn[2] and Joon Ho Moon[2*]

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PP02-5 **A rare case of coexisting myelodysplastic syndrome and T-cell lymphoproliferative disorder**

Yuna Choi[1], Miyoung Kim[1*], Young-Uk Cho[1], Sang-Hyun Hwang[1], Seongsoo Jang[1], Eul-Ju Seo[1], Eun-Ji Choi[2], Han-Seung Park[2] and Chan-Jeoung Park[1]

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PP02-6 **Myelodysplastic syndrome occurrence in post-therapeutic systemic lupus erythematosus patients**

Adika Zhulhi Arjana[1] and Umi Solekhah Intansari[1*]

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PP02-7 **Next-generation sequencing as an essential test in addition to conventional cytogenetics for the diagnosis of hypoplastic myelodysplastic neoplasm**

Min-Kyung So[1], Sholhui Park[1], Dong Jin Park[1], Young Hoon Park[2], Yeung-Chul Mun[2] and Jungwon Huh[1*]

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PP02-8 **SF3B1-mutated myeloid neoplasms: pathologic correlation focusing on myelodysplastic syndrome with mutated SF3B1**

Daehyun Chu[1], Young-Uk Cho[1*], Miyoung Kim[1], Sang-Hyun Hwang[1], Seongsoo Jang[1], Eul-Ju Seo[1] and Chan-Jeoung Park[1]

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PP03-1 **The challenges in managing Philadelphia chromosome negative acute lymphoblastic leukemia in adolescents and young adults (AYA) treated with MASPORE**
Yang Liang Boo[1*], Christopher Chin Keong Liam[1], Yih Seong Wong[1], Azizan Sharif[1] and Soo Min Lim[1]
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PP03-6 **B-Lymphoblastic leukemia acquiring BCR::ABL1 rearrangement upon relapse: A Case Report**
Jinho Lee[1], Hongkyung Kim[1], Won Kee Ahn[2], Seungmin Hahn[2] and Saeam Shin[1*]
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PP03-14 **Machine learning-based detection of leukocyte counts in microscopic images of acute lymphoblastic leukemia**
Rifaldy Fajar[1], Nick Nieber[1] and Peter Val[1]
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PP03-16 **Bilateral facial nerve palsy in t-cell acute lymphoblastic leukemia: A case report and review of the literature**
Jhicel Ibañez[1*] and Jeremiah Vallente[1]
[1]*Department of Internal Medicine, Mariano Marcos Memorial Hospital and Medical Center, Philippines*

PP03-18 **Usefulness of immunoglobulin gene rearrangement analysis using next-generation sequencing in adult and pediatric B-lymphoblastic leukemia**
Daehyun Chu[1], Miyoung Kim[1*], Young-Uk Cho[1], Sang-Hyun Hwang[1], Seongsoo Jang[1], Eul-Ju Seo[1], Chan-Jeoung Park[1], Han-Seung Park[2], Jung-Hee Lee[2], Hyery Kim[3] and Ho Joon Im[3]
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PP03-19 **Analysis of marrow infiltrating T cell at 3 months after allogeneic hematopoietic stem cell transplantation in patients with hematologic malignancies**
Thi Thuy Duong Pham[1,2,3], Su-young Choi[1,2,3], Bu-Yeon Heo[1,2,3], Jeong Suk Koh[6], Myung-Won Lee[6], Jung-Hyun Park[4], Yunsun Jang[4], Deog-Yeon Jo[6], Jaeyul Kwon[1,2,5] and Ik-Chan Song[6*]
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PP03-20 **Poor prognosis of IKZF1 and CDKN2 gene deletions in patients with Philadelphia chromosome-negative acute lymphoblastic leukemia**
Jae-Ho Yoon[1], Daehun Kwag[1], Jong-Hyuk Lee[1], Gi June Min[1], Sung-Soo Park[1], Silvia Park[1], Sung-Eun Lee[1], Byung-Sik Cho[1], Ki-Seong Eom[1], Yoo-Jin Kim[1], Hee-Je Kim[1], Chang-Ki Min[1], Seok-Goo Cho[1], Jong Wook Lee[1] and Seok Lee[1*]
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PP03-21 **Real-world experiences of inotuzumab ozogamicin in adult patients with relapsed/refractory acute lymphoblastic leukemia**
Jae-Ho Yoon[1], Daehun Kwag[1], Gi June Min[1], Sung-Soo Park[1], Silvia Park[1], Sung-Eun Lee[1], Byung-Sik Cho[1], Ki-Seong Eom[1], Yoo-Jin Kim[1], Hee-Je Kim[1], Chang-Ki Min[1], Seok-Goo Cho[1], Jong Wook Lee[1] and Seok Lee[1*]
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PP03-22 **A fatal pneumatosis intestinalis after ponatinib treatment on a relapsed Philadephia-positive acute lymphoblastic leukemia patient: A case report**
Jong Hyuk Lee[1], Seok Lee[1*], Jae-Ho Yoon[1], Daehun Kwag[1], Gi-June Min[1], Sung-Soo Park[1], Silvia Park[1], Sung-Eun Lee[1], Ki-Seong Eom[1], Byung-Sik Cho[1], Yoo-Jin Kim[1], Chang-Ki Min[1], Seok-Goo Cho[1], Jong Wook Lee[1] and Hee-Je Kim[1]
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PP04-2 **A rare case of three way Philadelphia variant (9;11;22)(p11.2;q34;q11.2) & del(12) in chronic myeloid leukemia: A case report**
Noorulain Fareed[1], Noor Muhammad Somroo[1], Ghulam Fatima[1] and Saba Aman[1]
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PP04-3 **Retrospective study of subsequent line nilotinib in chronic myeloid leukemia patients**
Ram Kumar Mummoorthy[1*], Jayachandran Perumal Kalaiyarasi[1], Nikita Mehra[1], Parathan Karunakaran[1], Venkatraman Radhakrishnan[1] and Krishnarathinam Kannan[1]
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PP04-4 **Targeting CXCR2 overcome intolerance to ponatinib via AKT/mTOR and MYC signaling in chronic myeloid leukemia cells**
Ji-Hea Kim[1,2], Ji-Hyeon Hong[1,2] and Byung-Soo Kim[3*]
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[2]Biomedial Science, Korea University College of Medicine, Korea
[3]Internal Medicine, Anam Hospital Korea University Medical Center, Korea

PP04-5 **A case of chronic myeloid leukemia with novel X-linked four-way Philadelphia chromosome and molecular unresponsiveness with clonal evolution**
Sooeung Park[1], Hye Jin Kang[2], Ae-Chin Oh[1], Jin Kyung Lee[1], Young Jun Hong[1] and Heyjin Kim[1*]
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PP04-6 **Investigation of the regulatory landscape of transcription modulators in chronic myeloid leukemia for the new biomarker discovery**
Mohammad Uzzal Hossain
Bioinformatics Division, National Institute of Biotechnology, Bangladesh

PP05-1 **Outcome of hematopoietic stem cell transplantation for pediatric lymphoma : A retrospective analysis of a single-center**
Hongbo He
Hematology Center, Beijing Key Laboratory of Pediatric Hematology Oncology, Beijing Children's Hospital, China

PP05-2 **Loss of ccar2 is associated with a better outcome in burkitt lymphoma cells**
Pingping Yang[1], Wenjun Zhang[1], Aibin Liang[1*], Lixin Lv[1] and Jinyuan Lu[1]
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PP05-3 **The iminent role of alk inhibitors in relapsed and refractory ALK positive anaplastic large cell lymphoma**
Jayachandran Perumal Kalaiyarasi[1*], Indhuja Muthiah Vaikundaraja[1], Sivasree Kesana[1], Nikita Mehra[1], Parathan Karunakaran[1], Arun Kumar Rajan[1] and Venkatraman Radhakrishnan[1]
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PP05-4 **Reduced dose rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) therapy for diffuse large b-cell lymphoma (DLBCL); A practical approach for the elderly and frail**
Christopher Chin Keong Liam[1*], Yang Liang Boo[1], Yih Seong Wong[1], Azizan Sharif[1] and Soo Min Lim[1]
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PP05-5 **Subcutaneous panniculitis-like T-cell lymphoma associated with hemophagocytic lymphohistiocytosis: A systematic review of 63 patients reported in the literature**
Wenxin Ou
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PP05-6 **Indolent extranodal NK/T-cell lymphoma of the gastrointestinal tract mimicking indolent T-cell lymphoproliferative disorder of the gastrointestinal tract**

Shih-Sung Chuang
Pathology, Chi-Mei Medical Center, Tainan, Taiwan

PP05-7 **Transcriptomic profiling of double-hit lymphoma patients identifies aberrant ALOX5 captures vulnerability to ferroptosis**

Syahru Agung Setiawan[1,3,5], Chia-Hwa Lee[2], Mardiah Suci Hardianti[3], YunRu Liu[4], Chi-Tai Yeh[5] and Tsu-Yi Chao[6*]
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PP05-8 **Long-term clinical outcomes of follicular lymphoma: A single-center experience of 275 patients in Catholic Hematology Hospital**

Gi June Min[1], Seok-Goo Cho[1*], Su-Yeon Bang[1], Young-Woo Jeon[2], Tong Yoon Kim[2], Byung-Su Kim[3], Joonyeop Lee[3], Daehun Kwag[1], Jong Hyuk Lee[1], Sung-Soo Park[1], Silvia Park[1], Jae-Ho Yoon[1], Sung-Eun Lee[1], Byung-Sik Cho[1], Ki-Seong Eom[1], Yoo-Jin Kim[1], Seok Lee[1], Hee-Je Kim[1], Chang-Ki Min[1] and Jong Wook Lee[1]
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PP05-9 **A case report: primary pulmonary malt lymphoma in Ho Chi Minh City**

Duong Thao Quyen Nguyen[1], Nguyen Phuong Dung Co[2*] and Quoc Thanh Nguyen[3]
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PP05-10 **Prognostic significances of molecular assay in primary central nervous system lymphoma**

Yu Ri Kim
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PP05-11 **PET-adapted approach in advanced Hodgkin lymphoma: A single centre experience**

Yang Liang Boo[1*], Christopher Chin Keong liam[1], Wei Quan Low[1], Yih Seong Wong[1], Azizan Sharif[1] and Soo Min Lim[1]
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PP05-13 **Subcutaneous epcoritamab + rituximab and lenalidomide (R2) vs R2 for relapsed/refractory follicular lymphoma: EPCORE FL-1**

Sang-Hee Kim[10], Lorenzo Falchi[1*], Franck Morschhauser[2], John Gribben[3], Huiqiang Huang[4], Minh Dinh[5], Rebekah Conlon[5], Xiaorong Chen[6], Brian Elliott[7] and John F. Seymour[8,9]
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PP05-14 **Odronextamab in patients with relapsed/refractory (R/R) follicular lymphoma (FL) grade 1–3a: phase 2 Study (ELM-2) prespecified analysis results**

Seok-Goo Cho[3], Tae Min Kim[1*], Michal Taszner[2], Silvana Novelli[4], Steven Le Gouill[5], Michelle Poon[6], Jose C. Villasboas[7], Rebecca Champion[8], Emmanuel Bachy[9], Stephanie Guidez[10], Aranzazu Alonso[11], Deepa Jagadeesh[12], Michele Merli[13], David Tucker[14], Jingxian Cai[15], Carolina Leite de Oliveira[15], Min Zhu[15], Aafia Chaudhry[15], Hesham Mohamed[15], Srikanth Ambati[15] and Stefano Luminari[16]

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PP05-15 **Patterns of nodal and extranodal involvement in diffuse large B-cell lymphoma**

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PP05-16 **MYD88 strongly associated with extranodal involvement in diffuse large B-cell lymphoma**

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PP05-17 **A Novel CD19-directed car t cell therapy (AT101) targeting a pristine membrane-proximal epitope under phase I clinical trial**

Ki Hyun Kim[1], Soohwan Kim[1], Sung-Min Kim[1], Jong-Ho Lee[1], Hyun-Jong Lee[1], Ji-Ho Park[1], LeiGuang Cui[1], Min Yoon[1], Ki-Hyun Kim[2], Soohyun Kim[2], In-Sik Hwang[1], Youngha Lee[1], Jong-Hoon Kim[1], Hyungwoo Cho[3], Jong-Seo Lee[1], Dok Hyun Yoon[3] and Junho Chung[2*]

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[2]*Cancer Research Institute, Seoul National University College of Medicine, Korea*
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PP05-18 **Impact of time-variant variable as cycle threshold with COVID19 infection in patients treated with rituximab and bendamustine for mature B cell lymphomas**

Tong Yoon Kim[1], Gi June Min[2], Sung Soo Park[2], Jung Yeon Lee[2], Byung-Su Kim[3], Chang-Ki Min[2], Seok-Goo Cho[2] and Young-Woo Jeon[1*]

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PP05-19 **Trial in progress: A phase 2 basket trial of nanatinostat in combination with valganciclovir in patients with EBV-Positive (EBV+) relapsed/refractory lymphomas (NAVAL-1)**

Young-Rok Do[1*], Won Sik Lee[2], Jae Hoon Lee[3], Dong Won Baek[4], Seok-Goo Cho[5], Donald Strickland[6] and Lisa Rojkjaer[6]

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PP05-20 **The outcome of hematopoietic stem cell transplantation for pediatric patients with lymphoma: A single-center study**

Wonkee Ahn[1], Seungmin Hahn[1], Jung Woo Han[1] and Chuhl Joo Lyu[1*]
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PP05-21 **A multi-center and non-interventional registry of brentuximab vedotin in patients with relapsed or refractory CD30-positive lymphoma: CISL1803 BRAVO study**

Seok Jin Kim[1*], Young Rok Do[2], Ho-Sup Lee[3], Won-Sik Lee[4], Jee Hyun Kong[5], Deok-Hwan Yang[6], Jae-Yong Kwak[7], Hyeon-Seok Eom[8], Joon Ho Moon[9], Jun Ho Yi[10], Jeong-Ok Lee[11] and Jae-Cheol Jo[12]
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PP05-22 **MicroRNA 340-5p-mediated PD-L1 expression in the etoposide-resistant NK/T-cell lymphoma**

Kyung Ju Ryu[1], Bon Park[1], Sang Eun Yoon[2], Won Seog Kim[1,2], Chaehwa Park[1] and Seok Jin Kim[1,2*]
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PP05-23 **Role of MiR-155-5p in ibrutinib-resistant diffuse large B cell lymphoma cells**

Bon Park[1], Myung Eun Choi[1], Kyung Ju Ryu[1], Jung Yong Hong[2], Won Seog Kim[1,2], Chaehwa Park[1] and Seok Jin Kim[1,2*]
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PP05-24 **Detection of tumor-derived mutations using liquid biopsy of plasma and cerebrospinal fluid in primary central nervous system lymphoma**

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PP05-25 **Exploratory study on circulating tumor DNA characteristics in various lymphomas**

Hongkyung Kim[1], Hyunsoo Cho[2], Haerim Chung[2], Yu Ri Kim[2], Seung-Tae Lee[1], Jong Rak Choi[1], Saeam Shin[1*] and Jin Seok Kim[2]
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PP05-26 **A comprehensive analysis of relapse pattern in patients with DLBCL after chemoimmunotherapy using national health insurance database of South Korea**

Hyun Jung Lee[1], Dong Wook Kim[3], Jae Joon Han[1] and Myung Hee Chang[2*]
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PP05-27 **Whole genome sequencing reveals clinicogenetic characteristics of blastic plamacytoid dendritic cell neoplasms in South Korea: CISL1906 study**

Ji Hyun Lee[1], Sung-Yong Oh[1], Saeam Shin[1], Seung-Tae Lee[1], Namhee Kim[1], Min Kyung Pak[1], Sung-Soo Yoon[2], Youngil Koh[2], Ja Min Byun[2], Cheolwon Suh[2], Dok Hyun Yoon[2], Jae-Cheol Jo[2], Deok-Hwan Yang[3], Seo-Yeon Ahn[3], Hyeon Seok Eom[3], Hyewon Lee[3], Ji Yun Lee[4], Jong Ho Won[4], Ho-Young Yhim[5], Ho Sup Lee[6], Won Seog Kim[7] and Seok Jin Kim[7*]

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PP06-1 **Cladribine combined with cytarabine regimen as a salvage therapy for paediatric refractory/relapsed langerhans cell histiocytosis: A single-armed, single-center study**

Ang Wei[1], Honghao Ma[1], Tianyou Wang[1] and Rui Zhang[1*]

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PP06-2 **Serum cytokine pattern in children with hemophagocytic lymphohistiocytosis**

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PP06-3 **A case of favorable outcome with pembrolizuamb for refractory histiocytic sarcoma**

Hyeon Gyu Yi

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PP07-3 **Immunological features and cytokine regulation in plasma cell neoplasms**

Zhanna Kozich[1], Natalya Klimkovich[2], Victor Martinkov[1] and Janna Pugacheva[1]

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PP07-4 **Prognostic value of serum free light chains measurements in newly diagnosed multiple myeloma patients at the Blood Transfusion Hematology Hospital**

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PP07-5 **Open-labeled, multicenter phase II study of prophylactic administration of pegylated granulocyte colony-stimulating factor in relapsed or refractory multiple myeloma who received pomalidomide/dexamethasone-containing regimens (KMM170)**

Ga-Young Song[1], Sung-Hoon Jung[1], Joon Ho Moon[2], Dajung Kim[3], Min Kyoung Kim[4], Hyo Jung Kim[5], Yeung-Chul Mun[6], Won-Sik Lee[7], Young Rok Do[8], Jae Hoon Lee[9], Je-Jung Lee[1*] and Jin Seok Kim[10]

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PP07-6 **Epidemiological characteristics of multiple myeloma and comorbidity-based model predicting for development of multiple myeloma**
Suein Choi[1], Suenghoon Han[1], Sung-Soo Park[2*] and Chang-Ki Min[2]
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PP07-7 **Development of multiple myeloma treatment using apoptosis multi-protein target tetracyclic triterpene compound**
Hye Ran Kim[1], Young Eun Lee[2,3], Yong Jun Choi[2], Ha Jin Lim[2], Ju Heon Park[2], Jong Hee Shin[2] and Myung Geun Shin[2,3,4*]
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PP07-10 **Naïve B cell as predictor of early and long-term treatment outcome in post-transplant myeloma patients**
Nupur Das[1], Meetu Dahiya[1], Ritu Gupta[1*], Lalit Kumar[2], Atul Sharma[2] and Om Dutt Sharma[1]
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[2]*Medical Oncology, BRAIRCH, AIIMS, New Delhi, India*

PP07-12 **The role of minimal residual disease evaluation for patients with multiple myeloma**
Sang Eun Yoon[1], Hyun-Young Kim[2], Duck Cho[2], Seok Jin Kim[1] and Kihyun Kim[1]
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PP07-14 **Machine learning-based sequential analysis to assist selection of frontline treatment: Bortezomib-melphalan-prednisolone vs lenalidomide-dexamethasone in multiple myeloma**
Sung-Soo Park[1], Jong Cheol Lee[2], Ja Min Byun[3], Kyucheol Choi[4], Kwan Hyun Kim[4], Sungwon Lim[4,5], Young-Woo Jeon[6], Seung-Ah Yahng[7], Seung-Hwan Shin[8], Chang-Ki Min[1] and Jamin Koo[4,5,9*]
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PP07-15 **Multiparameter flow cytometry provides a highly sensitive and informative method for assessment of minimal residual disease in multiple myeloma**
Min-Sun Kwak[1], Jae-Ryong Shim[1], Suji Park[1], Sung-Hyun Kim[2], Ji Hyun Lee[2] and Jin-Yeong Han[1*]
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PP07-16 **Real-world treatment outcomes of carfilzomib plus dexamethasone in patients with relapsed and/or refractory multiple myeloma: Impact of trial-fitness and comparison to alternative regimens**
Seunghwan Shin[1], Seoyoung Koo[2], Sungsoo Park[3], Youngwoo Jeon[4], Seungah Yahng[5], Jaeho Yoon[3], Sungeun Lee[3], Byungsik Cho[3], Kis-eong Eom[3], Yoojin Kim[3], Seok Lee[3], Heeje Kim[3], Seokgoo Cho[3], Jongwook Lee[3] and Changki Min[3*]
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PP07-17 **Insulin signaling-inducible IFITM1 promotes multiple myeloma progression and bortezomib resistance**
Ji-Young Lim[1], Sung-Soo Park[1], Jungyeon Lee[1], Byung-Su Kim[2] and Chang-Ki Min[1*]
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PP07-18 **Inflammatory factor-based staging system in multiple myeloma in the new agent era: KMM176 study**

Ji Hyun Lee[1], Sung-Hyun Kim[1], Dongyeop Shin[2], Sung-Soo Yoon[2], Ja Min Byun[2], Sung-Hoon Jung[3], Je-Jung Lee[3], Chang-Ki Min[4], Young Rok Do[5], Hyo Jung Kim[6], Byeong Seok Sohn[7], Sung Hwa Bae[8], Gyeong-Won Lee[9], Sungwoo Park[9], Hyun Jung Lee[10], Min Kyoung Kim[11] and Ho Sup Lee[12*]

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PP07-19 **Exploration of clinical implication of liquid biopsy targeting circulating tumor DNA in multiple myeloma and its precursor diseases**

Sung-Soo Park[1], Chang-Ki Min[1*], Ji-Young Lim[1] and Seung-Hyun Jung[2]

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PP07-20 **Development of risk model including functional high risk in patients with relapsed/refractory multiple myeloma: Dynamic Risk Model**

Hee Jeong Cho[1], Myung Won Lee[2], Ju-Hyung Kim[1], Dong Won Baek[1], Sang-Kyun Sohn[1], and Joon Ho Moon[1]

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PP08-2 **Myeloproliferative neoplasms with hypereosinophilia and rearrangement PDGFRB gene in children under 2 years old: First case at Vietnam National Children's Hospital**

Huong TM Nguyen[1] and Ha Nguyen[1]

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PP08-3 **Incidental abdominal computed tomography findings of patients newly diagnosed with Philadelphia-negative myeloproliferative neoplasm**

Ik-Chan Song[1], Jeong Suk Koh[1], Sora Kang[1], Myung-Won Lee[1], Hyewon Ryu[1], Hyo-Jin Lee[1], Hwan-Jung Yun[1], Seon Young Kim[2], Jeong Eun Lee[3], Kyung Sook Shin[3] and Deog-Yeon Jo[1*]

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PP08-4 **Acquired von Willebrand disease in patients with Philadelphia-negative myeloproliferative neoplasm**

Ik-Chan Song[1], Jeong Suk Koh[1], Sora Kang[1], Myung-Won Lee[1], Hyewon Ryu[1], Hyo-Jin Lee[1], Hwan-Jung Yun[1] and Deog-Yeon Jo[1*]

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PP08-5 **Detection of JAK2 V617F mutation in polycythemia vera diagnosis first time in Mongolia**

Tsogjargal Burentogtokh[1], Sarantsetseg Jigjidsuren[1*] and Odgerel Tsogbadrakh[2]

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PP08-6 **The value of Neutrophil-to-lymphocyte ratio at the diagnosis of myeloproliferative neoplasm**

Seug Yun Yoon[1], Min Jung Kim[1], Min-Young Lee[1], Kyoung Ha Kim[1], Namsu Lee[1] and Jong-Ho Won[1*]

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PP08-8 **Prognostic value of modified criteria for hydroxyurea resistance or intolerance in patients with high-risk essential thrombocythemia**
Young Hoon Park[1], Sewon Lee[1], Yeung-Chul Mun[1] and Dong Jin Park[2*]
[1]Division of Hematology-Oncology, Department of Internal Medicine, Ewha Womans University Mokdong Hospital, Seoul, Korea
[2]Department of Laboratory Medicine, Ewha Womans University Mokdong Hospital, Seoul, Korea

PP10-1 **Neutrophil - lymphocyte ratio and interferon gamma release assay results**
Pradita Sri Mitasari[1] and Umi Solekhah Intansari[1,2*]
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[2]Integrated Clinical Laboratory, Sardjito General Hospital, Yogyakarta, Indonesia

PP10-2 **The diagnostic value of extended complete blood count parameters for determining infection etiology**
Duyen Nguyen Thi[1] and Nghiem Luong Thi[1]
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PP10-3 **A smartphone-based diagnostic platform for detection of abnormal red blood cell in resource–limited settings**
Duangdao Palasuwan[1*] and Attakorn Palasuwan[1]
[1]Oxidation in Red Cell Disorders Research Unit, Department of Clinical Microscopy, Faculty of Allied Health Sciences, Chulalongkorn University, Bangkok, Thailand

PP10-4 **Chronic active epstein-barr virus infection of T/NK Cell type systemic form mimicking classic Hodgkin lymphoma**
Hoang Thien Dang
Histopathology and Cytology, Blood transfusion and Hematology Hospital, Viet Nam

PP10-5 **The clinical application of RNA sequencing and analysis in hematologic malignancies**
Hongkyung Kim[1], Young Kyu Min[1], Yu Jin Park[1], Saeam Shin[1*], Seung-Tae Lee[1] and Jong Rak Choi[1]
[1]Department of Laboratory Medicine, Yonsei University College of Medicine, Korea

PP10-6 **A prospective analysis about the concordance of current tests used for the diagnosis of BM involvement of B-lineage lymphoma with respect to different lymphoma grade: Focused on the fluorescence in situ hybridization lymphoma panel**
Sang Hyuk Park[1], Seulgi Moon[1], Hyerim Kim[1*] and In-Suk Kim[1]
[1]Laboratory Medicine, University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, Korea

PP10-10 **White blood cell counting of Sysmex XN hematology analyzer in severe leukopenic samples: Comparison between whole blood mode and low white blood cell mode**
Jongho Yi[1], Hanah Kim[1*], Gun-Hyuk Lee[1], Seung-Wan Kim[1] and Mina Hur[1]
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PP10-11 **The first Korean case of transcobalamin II deficiency with a pathogenic variant in the TCN2 Gene**
Ju Hyeong Lee[1], Yoon Hwan Chang[1*], Jee-Soo Lee[1], Kyung Taek Hong[2], Jung Min Ko[2], Hyoung Jin Kang[2], Hyun Kyung Kim[1] and Moon-Woo Seong[1]
[1]Department of Laboratory Medicine, Seoul National University Hospital, Korea
[2]Department of Pediatrics, Seoul National University Children's Hospital, Korea

PP10-12 **Clinical performance of a novel next-generation sequencing-based IGH clonality assay in pediatric B-cell acute lymphoblastic leukemia patients**
Min-Seung Park[1], Hee Young Ju[2], Keon Hee Yoo[2], Hee-Jin Kim[1], Sun-Hee Kim[1], Duck Cho[1] and Hyun-Young Kim[1*]
[1]Department of Laboratory Medicine & Genetics, Samsung Medical Center, Korea
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PP10-13 **Effect of refrigeration storage time delay and RNA extract kit difference in RNA-seq data quality of blood EDTA samples**
Jae Won Yun[1*], Ye Eun Yoon[1], Kwang Woo Lee[1], Jae Sook Han[1], Yoon Jeong Yu[1] and Je Hyun Seo[1]
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PP10-14 **Comparison study of two analysers for routine coagulation tests**
Halimatun Radziah Othman[1], Mohd Zul-fakar Abd Razak[1] and Khoo Bee Ghai Jessy[1]
[1]Department of Clinical Diagnostics Laboratories, Hospital Al Sultan Abdullah UiTM, Malaysia

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PP10-15 **HTLV-1 bZIP factor modulates acetylation-dependent functions in cells via suppression of HDAC6**
Takayuki Ohshima[1*] and Risa Mukai[1]
[1]Faculty of Science and Engineering, Tokushima Bunri University, Japan

PP10-17 **Ribosomal component RPS4X as a novel modulator of MDM2 stability: interfering to E3 ubiquitin ligases for MDM2 and prevention of proteasome-mediated degradation**
Satsuki Ryu[1], Hiroki Nakashima[1], Yuka Tanaka[1], Yasuhiro Ishihara[2], Takashi Tominaga[1] and Takayuki Ohshima[1,3*]
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PP10-20 **Evaluation of monocyte distribution width as an early marker for diagnosis of sepsis**
JooHeon Park[1*], JulKi Kang[1], Young Jun Choi[1], Hyun Woo Choi[2], Seung Jung Kee[2], Jong Hee Shin[2] and Myung Geun Shin[1]
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[2]Department of Laboratory medicine, Chonnam National University Hospital, Korea

PP10-21 **Lower red blood cell distribution width than actual red blood cell anisocytosis from automated hematology analyzer**
Sholhui Park[1], Min-Kyung So[1] and Jungwon Huh[1*]
[1]Department of Laboratory Medicine, Ewha Womans University, College of Medicine, Korea

PP10-22 **A clinical laboratory-oriented targeted RNA-seq system accurately detected various types of gene fusion reported in Philadelphia chromosome-like B-lymphoblastic leukemia**
Yong Jun Choi[1], Ju Heon Park[1], Young Eun Lee[1,2], Ha Jin Lim[1], Ji Hu Jeon[1], Hye Ran Kim[3], Jong Hee Shin[1] and Myung Geun Shin[1,2,4*]
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PP10-23 **Performance evaluation of a digital morphology analyzer for leukocyte differential count**
Sojin Lee[1], Jaewoo Song[1*], Hongkyung Kim[1] and Saeam Shin[1]
[1]Department of Laboratory Medicine, Yonsei University College of Medicine, Korea

PP11-2 **Spectrum of haemoglobinopathies; A tertiary care hospital experience**
Noorulain Fareed[1], Ghulam Fatima[1], Aisha Mahesar[1] and M. Saeed Quraishy[1]
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PP11-4 **microRNA signature in G6PD gene: Novel insight into miRNA based diagnostic approach**
Attakorn Palasuwan
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PP11-5 **Sustained complement C1s inhibition with sutimlimab in patients with cold agglutinin disease results in continued efficacy in part B of CADENZA Study**

Jung Won Shin[21], Alexander Roth[1*], Sigbjørn Berentsen[2], Wilma Barcellini[3], Shirley D'Sa[4], Bernd Jilma[5], Marc Michel[6], Ilene Weitz[7], Masaki Yamaguchi[8], Jun-ichi Nishimura[9], Josephine M.I. Vos[10], Joan Cid[11], Michael Storek[12], Nancy Wong[13], Ronnie Yoo[14], Jenifer Wang[15], Deepthi S Vagge[16], Marek Wardęcki[19], Frank Shafer[17], Michelle Lee[18] and Catherine M Broome[20]

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[9]*Section for Hematology, Department of Medicine, Haukeland University Hospital, Bergen, Norway*
[10]*Associate Professor of Clinical Medicine, Keck School of Medicine of USC, Los Angeles, USA*
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[12]*RCTs Post-Hoc Analyses Team, Sanofi, Cambridge, USA*
[13]*Global Safety, IQVIA, India*
[14]*GPV Rare Diseases, Sanofi, Paris, France*
[15]*Immuno Hematology, Sanofi, Bridgewater, USA*
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[20]*Department of Hematology, Osaka University Graduate School of Medicine, Japan*
[21]*PharmD, RPh. Medical Lead, Rare Blood Disorders, Specialty Care, Sanofi, Korea*

PP11-6 **Inhibition of complement C1s with sutimlimab in patients with cold agglutinin disease (CAD): 2-Year follow-up from the CARDINAL Study**

Jung Won Shin[19], Alexander Röth[1*], Wilma Barcellini[2], Shirley D'Sa[3], Yoshitaka Miyakawa[4], Catherine M Broome[5], Marc Michel[6], David J Kuter[7], Bernd Jilma[8], Tor Henrik Anderson Tvedt[9], Ilene C Weitz[10], Timothee Sourdille[11], Jennifer Wang[12], Deepthi S Vagge[13], Katarina Kralova[14], Frank Shafer[15], Marek Wardecki[16], Michelle Lee[17] and Sigbjørn Berentsen[18]

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[18]*Department of Research and Innovation, Haugesund Hospital, Haugesund, Norway*
[19]*PharmD, RPh. Medical Lead, Rare Blood Disorders, Specialty Care, Sanofi, Korea*

PP11-7 **Unusual type of anemia gravis associated with trilogy of hookworm infection, peptic ulcer, and melena: A rare case**

Winda Atika Sari[1], Maulidi Izzati[1] and Berty Denny Hermawati[1*]

[1]*Department of Internal Medicine, Faculty of Medicine of Universitas Sebelas Maret, Surakarta, Indonesia*

PP11-8 **Assessment of knowledge, attitude and practices on iron-deficiency anemia among Filipino teens in Laguna, Philippines**

Cherry Ann Garcia-Durante[1,2*] and Estrella San Juan[2]

[1]*Nursing, Emilio Aguinaldo College Manila, Philippines*
[2]*Nursing, University of Perpetual Help - Dr Jose G Tamayo Medical University, Philippines*

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PP11-13 **Hereditary pyropoikilocytosis: A rare and severe form of congenital haemolytic anaemia**
Jian An Boo[1,2]
[1]Department of Paediatrics, Hospital Sultanah Bahiyah, Alor Setar, Kedah, Malaysia
[2]Neonatology Unit, Department of Paediatrics, Hospital Sultanah Bahiyah Alor Setar, Malaysia, Hospital Sultanah Bahiyah Alor Setar Kedah, Malaysia

PP11-14 **Classification of anemia level based on fuzzy c-means algorithm**
Rifaldy Fajar[1*], Siti Nadya[2], Tiwul Wulandari[3] and Nana Indri[1]
[1]Mathematical Medicine Laboratory, Karlstad University, Sweden
[2]Data Management, Cendana Clinic Laboratory, Indonesia
[3]Computational Bioloy and Medicine Laboratory, Yogyakarta State University, Indonesia

PP11-16 **Are the prevalence of stunting height, anemia among women pregnant, undernourishment and GDP percapita influence to prevalence of anemia among children in ASEAN 5**
Putri Ayu
Economics, Andalas University, Indonesia

PP11-17 **Diagnostic yield of targeted next-generation sequencing for pediatric hereditary hemolytic anemia**
Yu Jeong Choi[2], Saeam Shin[2] and Seung-min Han[1*]
[1]Department of Pediatrics, Yonsei University College of Medicine, Korea
[2]Department of Laboratory Medicine, Yonsei University College of Medicine, Korea

PP11-20 **A delayed manifestation of autoimmune lymphoproliferative syndrome (ALPS)**
Shi Chyn Lim
[1]Department of Paediatrics, Hospital Sultanah Bahiyah, Alor Setar, Kedah, Malaysia, Hospital Sultanah Bahiyah Alor Setar, Kedah, Malaysia

PP11-24 **TMPRSS6 rs855791 polymorphism and iron deficiency anaemia susceptibility among Asian population: A systematic review and meta-analysis**
Indah Sagitaisna Putri[1*] and Bastomy Eka Rezkita[1]
[1]Faculty of Medicine, Sebelas Maret University, Indonesia

PP12-1 **Association of CD16 158F>V gene polymorphisms with risk of idiopathic thrombocytopenic purpura susceptibility: An updated meta-analysis**
Bastomy Eka Rezkita[1,2*] and Steven Irving[3]
[1]Internal medicine, University of Sebelas Maret, Indonesia
[2]General Medicine, University of Muhammadiyah Jember Hospital, Indonesia
[3]General Medicine, Ciputra Hospital CitraGarden City, Indonesia

PP12-3 **Cannabinoid receptor 2 signaling: Role in megakaryocyte development and neuro-immune regulation**
Ravi Kumar Gutti
Department of Biochemistry, University of Hyderabad, India

PP12-4 **Evaluation the outcome of primary immume thrombocytopenia purpura (ITP) in children under 2 years old at Vietnam Children's Hospital**
Huong TM Nguyen[1] and Manh Tran[1]
[1]Clinical Hematology, National Children's Hospital, Viet Nam

PP12-5 **Bone marrow resident memory T cells suppress megakaryocyte apoptosis and promote humoral immunity in immune thrombocytopenia**
Anli Liu[1], Qiang Liu[1], Shaoqiu Leng[1], Xiaoyu Zhang[1] and Jun Peng[1*]
[1]Department of Hematology, Qilu Hospital, Shandong University, China

PP12-6 **Performance validation of three scoring systems for the prediction of thrombotic microangiopathy due to severe ADAMTS13 deficiency and treatment response to therapeutic plasma exchange: The first study in Korea**
Sang Hyuk Park[1], Hyun-Ki Kim[1], Joseph Jeong[1], Seon-Ho Lee[1], Yoo Jin Lee[2], Yoo Jin Kim[2], Jae-Cheol Jo[2] and Ji-Hun Lim[1*]
[1]Laboratory Medicine, University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, Korea
[2]Hematology and Cellular Therapy, University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, Korea

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PP12-7 **Investigation of the immunomodulatory effect of bitter taste receptor on CD4+ T cells in immune thrombocytopenia**
Xiaoyu Zhang
Department of hematology, Qilu Hospital of Shandong University, China

PP12-9 **Eltrombopag plays an anti-viral role by elevated function of exhausted T cells**
Yuefen Hu[1], Shuqian Xu[1] and Jun Peng[1*]
[1]Department of Hematology, Qilu Hospital of Shandong university, Cheeloo College of Medicine, Jinan, China

PP12-10 **Predictive value of high ICAM-1 level for poor treatment response in corticosteroid-resistant immune thrombocytopenia patients**
Li Chaoyang
Department of Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, China

PP12-11 **Correlation between HDAC3 rs2530223 polymorphism and the susceptibility or severity of ITP**
Ruxia Zhao
Department of Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, 250012, China

PP12-12 **The association between nutritional status and platelet count among pediatric patients with dengue hemorrhagic fever in Pekalongan City, Indonesia**
Nisrina Nabila[1*] and Irena Agustiningtyas[2], Nur Aini Djunet[3]
[1]Medical Student, Universitas Islam Indonesia, Indonesia
[2]Microbiology, Universitas Islam Indonesia, Indonesia
[3]Biochemistry, Universitas Islam Indonesia, Indonesia

PP12-15 **Short chain fatty acid butyrate reprogram macrophage function and phenotype in immune thrombocytopenia via immunoepigenitic pathway**
Qiang Liu[1]
[1]Department of Hematology, Qilu Hospital of Shandong University, Jinan, Shandong, 250012, China

PP12-16 **Management of severe hemophilia A: Low-dose prophylaxis vs on-demand treatment**
Munira Borhany[1*], Rabeea Munawar Ali[1], Madiha Abid[2], Sidra Zafar[2], Rukhshanda Nadeem[3] and Raheel Ahmed[3]
[1]Clinical Hematology, National Institute of Blood Disease and Bone Marrow Transplantation, Pakistan
[2]Research and development, National Institute of Blood Disease and Bone Marrow Transplantation, Pakistan
[3]Haemophilia, Haemophilia Welfare Society, Karachi, Pakistan

PP12-17 **Characteristics of essential thrombocytosis in children-A single institution retrospective study**
Jae Wook Lee[1*], Suejung Jo[1], Jae Won Yoo[1], Seongkoo Kim[1], Pil-Sang Jang[1], Nack-Gyun Chung[1] and Bin Cho[1]
[1]Division of Pediatric Hematology/Oncology, Department of Pediatrics, College of Medicine, The Catholic University of Korea, Korea

PP12-18 **Thrombotic thrombocytopenic purpura treatment at the hematology department of Cho Ray Hospital**
Thao Nguyen Van[1], Nhu Cao Thi Bich[1*], Tung Tran Thanh[1], Suong Pho Phuoc[2], Toan Ho Trong[2], Tung Nguyen Khac[1], San Le Thi[1], Minh Nguyen Ngoc[1], Ut Nguyen Thi Be[1] and Trung Thai Minh[1]
[1]Hematology, Cho Ray Hospital, Viet Nam
[2]Laboratory, Cho Ray Hospital, Viet Nam

PP12-20 **Romiplostim in pediatric immune thrombocytopenia: A meta-analytic synthesis**
Md Azharuddin[1*] and Manju Sharma[2]
[1]Pharmaceutical Medicine, Jamia Hamdard, India
[2]Pharmacology, Jamia Hamdard, India

PP12-21 **Klinefelter syndrome identified by multi-gene panel testing by massive parallel sequencing as a risk factor for venous thromboembolism**
JaeJoon Lee[1], Min-Seung Park[1], Hyun-Young Kim[1], Chang-Hun Park[3], Sung-A Chang[2], Sun-Hee Kim[1] and Hee-Jin Kim[1*]
[1]Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea
[2]Division of Cardiology, Department of Internal Medicine, Imaging Center, Heart Stroke & Vascular Institute, Sungkyunkwan University School of Medicine, Samsung Medical Center, Korea
[3]Department of Laboratory Medicine & Genetics, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Korea

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PP13-1 **Analysis of BK virus infection in children after hematopoietic cell transplantation: A retrospective single-center study**
Ang Wei[1], Yuanfang Jing[1], Maoquan Qin[1*] and Tianyou Wang[1]
[1]*Hematology center, Beijing children's hospital, China*

PP13-2 **High dose etoposide based chemo-mobilization for autologous stem cell transplantation – Revisited**
Jayachandran Perumal Kalaiyarasi[1*], Nadeem Ahmed[1], Parathan Karunakaran[1], Nikita Mehra[1] and Krishnarathinam Kannan[1]
[1]*Medical Oncology, Cancer Institute (WIA), Adyar, Chennai, India*

PP13-3 **Autologous stem cell transplantation in relapsed Hodgkin lymphoma – A single centre experience from India**
Mangai Suseela Murugesan[1*], Jayachandran Perumal Kalaiyarasi [1], Nikita Mehra[1], Parathan Karunakaran[1], Venkatraman Radhakrishnan[1], Gangothri Selvarajan[1], Sivasree Kesana[1], Carthikeyan Subramaniam Murali [1], Krishnarathinam Kannan[1] and Sagar Tenali Gnana [1]
[1]*Medical Oncology, Cancer Institute (WIA), Chennai, India*

PP13-4 **Clinical impact of recipient-derived isoagglutinin levels in ABO-incompatible hematopoietic stem cell transplantation**
Minjeong Nam[1], Mina Hur[2*], Hanah Kim[2], Tae-Hwan Lee[2], Gun-Hyuk Lee[2], Sumi Yoon[3], Sung Yong Kim[4] and Mark Hong Lee[4]
[1]*Department of Laboratory Medicine, Korea University Anam Hospital, Korea*
[2]*Department of Laboratory Medicine, Konkuk University School of Medicine, Korea*
[3]*Department of Laboratory Medicine, Chung-Ang University College of Medicine, Korea*
[4]*Division of Hematology-Oncology, Department of Internal Medicine, Konkuk University School of Medicine, Korea*

PP13-5 **Efficacy and safety of cytokine-induced killer cells infusion after autologous hematopoietic stem cell transplantation: an interim result of investigator's initiated clinical study**
Gi-June Min[1], Seok-Goo Cho[1*], Nayoun Kim[3], Keon-il Im[3], Tong Yoon Kim[2] and Young-Woo Jeon[2]
[1]*Department of Hematology, Seoul St. Mary's Hematology Hospital, Korea*
[2]*Department of Hematology, Yeouido St. Mary's Hematology Hospital, Korea*
[3]*Institute for Translational Research and Molecular Imaging, The Catholic University of Korea, Korea*

PP13-6 **Comparable outcomes of allogeneic peripheral blood versus bone marrow hematopoietic stem cell transplantation from a sibling donor for pediatric patients**
Bo Kyung Kim[1], Kyung Taek Hong[1], Jung Yoon Choi[1], Hyery Kim[2], Hyun Jin Park[1] and Hyoung Jin Kang[1*]
[1]*Department of Pediatrics, Seoul National University College of Medicine, Korea*
[2]*Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Korea*

PP13-7 **Better fitness of body surface area-based dosing of mycophenolate mofetil in pediatric patients undergoing HSCT: A prospective model-informed drug development approach**
Kyung Taek Hong[1], Hyun Jin Park[2], Nayoung Han[3], In-Wha Kim[2], Jung Yoon Choi[1], Jung Mi Oh[2] and Hyoung Jin Kang[1,4*]
[1]*Pediatrics, College of Medicine, Seoul National University, Seoul National University Hospital, Korea*
[2]*College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Korea*
[3]*College of Pharmacy, Jeju National University, Korea*
[4]*Wide River Institute of Immunology, Korea*

PP13-10 **Role of short tandem repeat (STR) in leukemia patients received allogeneic hematopoietic stem cell transplantation**
Juhyung Kim[1], Hee Jeong Cho[1], Joon Ho Moon[2], Sang Kyun Sohn[1] and Dong Won Baek[2*]
[1]*Hematology/Oncology, Kyungpook National University Hospital, Korea*
[2]*Hematology/Oncology, Kyungpook National University Chilgok Hospital, Korea*

PP13-11 **A case report of central nervous system autoimmune demyelinating disease following allogenic hematopoietic stem cell transplantation**
Ye eun Oh[1], Jong Hyuk Lee[1], Daehun Kwag[1], Gi-June Min[1], Sung-Soo Park[1], Silvia Park[1], Jae-Ho Yoon[1], Sung-Eun Lee[1], Ki-Seong Eom[1], Yoo-Jin Kim[1], Seok Lee[1], Hee-Je Kim[1], Chang-Ki Min[1], Seok-Goo Cho[1], Jong Wook Lee[1] and Byung-Sik Cho[1*]
[1]*Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea*

PP13-12 **How the caregiver status could increase the quality of life among elderly after allogeneic-HSCT (allo-HSCT) with dementia status?**
Rosinta Hotmaida Pebrianti Purba
Poverty Alleviation and Community Empowerment, Ministry of National Development Planning, Indonesia

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PP14-1 **Bitter receptor agonist denatonium benzoate promotes hematopoietic reconstitution after hematopoietic stem cell transplantation in mice**
Jing Qin[1] and Jun Peng[1*]
[1]*Department of Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, China*

PP14-2 **Novel mechanism of thrombopoiesis by the human megakaryoblastic leukemia cell lines**
Nuntiporn Nunthanasup[1], Kasem Kulkeaw[2], Attakorn Palasuwan[1] and Duangdao Palasuwan[1*]
[1]*Oxidation in Red Cell Disorders Research Unit, Department of Clinical Microscopy, Faculty of Allied Health Sciences, Chulalongkorn University, Bangkok, Thailand*
[2]*Siriraj Integrative Center for Neglected Parasitic Diseases, Department of Parasitology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand*

PP14-4 **Telomere shortening in survivors of childhood hematologic malignancies**
Meerim Park[1], Hye-Young Jin[1], Jun Ah Lee[1], Myung-Shin Kim[2] and Hyeon Jin Park[1*]
[1]*Department of Pediatrics, Center for Pediatric Cancer, National Cancer Center, Korea*
[2]*Departmant of Laboratory Medicine, Seoul St. Mary's Hospital, College of medicine, The Catholic University of Korea, Korea*

PP14-5 **Clonal hematopoiesis: Somatic mutations in blood cells from patients with acute ischemic stroke**
Jin-Yeong Han[1*], Suji Park[1], Jae-Ryong Shim[1], Min-Sun Kwak[1], Ji-Hyun Lee[2], Sung-Hyun Kim[2] and Dae-Hyun Kim[3]
[1]*Department of Laboratory Medicine, Dong-A University College of Medicine, Korea*
[2]*Department of Hemato-oncology, Dong-A University College of Medicine, Korea*
[3]*Department of Neurology, Dong-A University College of Medicine, Korea*

PP16-1 **Analysis of blood product and laboratory resource wastage due to non-severe allergic transfusion reaction**
Anila Rashid[1*], Hasan Hayat[1], Hareem Alam[1] and Qadeer Ahmed[1]
[1]*Haematology & Transfusion Medicine, Aga Khan University Hospital, Pakistan*

PP16-2 **Platelet transfusion in pediatric intensive care unit patients**
Pradita Sri Mitasari[1], Usi Sukorini[1,2*] and Teguh Triyono[1,3]
[1]*Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Indonesia*
[2]*Integrated Clinical Laboratory, Sardjito General Hospital, Yogyakarta, Indonesia*
[3]*Blood Bank and Transfusion Unit, Sardjito General Hospital, Yogyakarta, Indonesia*

PP16-3 **The effect of premedication in transfusion reaction : Systematic review and meta-analysis**
Steven Irving[1,2*] and Bastomy Eka Rezkita[1,3]
[1]*Faculty of Medicine, University of Sebelas Maret, Indonesia*
[2]*General Medicine, Ciputra Hospital CitraGarden City, Indonesia*
[3]*General Medicine, University of Muhammadiyah Jember Hospital, Indonesia*

PP16-4 **Variables affecting immunogenicity of blood group antigens: reflections on the formula calculating immunogenicity**
Yousun Chung[1], Han Joo Kim[2], Hyungsuk Kim[3], Sang-Hyun Hwang[2], Heung-Bum Oh[2] and Dae-Hyun Ko[2*]
[1]*Department of Laboratory Medicine, Kangdong Sacred Heart Hospital, Korea*
[2]*Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea*
[3]*Department of Laboratory Medicine, Seoul National University Hospital, Korea*

PP16-5 **Assessment of platelet consumption in malignant blood disorders; Can we develop a rationale way to save platelet?**
Nida Anwar[1*], Naveena Fatima[2], Aisha Jamal[1], Qurat-ul-Ain Rizvi[1], Anum Khalid[2], Laraib Majeed[1] and Tahir Shamsi[1]
[1]*Hematology, National Institute of Blood Diseases and Bone Marrow Transplantation, Pakistan*
[2]*Research and Dvelopment, National Institute of Blood Diseases and Bone Marrow Transplantation, Pakistan*

PP16-6 **Quality of life in transfusion-dependent thalassemia patients in Bihar**
Gireesh Dayma[1*] and Sukrat Sinha[2]
[1]*Department of Medicine, Rama Medical College, India*
[2]*Department of Zoology, Nehru Gram Bharati, India*

PP16-11 **Successful plasmapheresis for patients with catastrophic antiphospholipid syndrome**
Ninda Devita[1] and Adika Zhulhi Arjana[2*]
[1]*Biomedical Sciences Programmes, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Indonesia*
[2]*Clinical Pathology and Laboratory Medicine, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Indonesia*

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PP16-13 **Advanced Red Cell Immunohematology for Direct Antiglobulin Test (DAT) In Healthy Blood Donors During COVID-19 Pandemic**
Divya Setya[1] and Ankit Malhotra[2]
[1]*Transfusion Medicine, Manipal Hospital Jaipur, India*
[2]*Hematopathology, Manipal Hospital Jaipur, India*

PP17-1 **Predicting hematologic cancer using artificial intelligence**
Jakir Hossain Bhuiyan Masud
Digital Health, Public Health Informatics Foundation, Bangladesh

PP17-5 **Chemotherapy induced thrombocytopenia and its association with coagulopathy; A single centre experience**
Nida Anwar[1*], Nvaeena Fatima[2], Laraib Majeed[2] and Anum Khalid[2]
[1]*Hematology, National Institute of Blood Diseases and Bone Marrow Transplantation, Pakistan*
[2]*Research and Development, National Institute of Blood Diseases and Bone Marrow Transplantation, Pakistan*

PP17-6 **Secondary hematological malignancies in sarcoma patients: A single-center retrospective study**
Hong Kyu Jeong[1,2], Chang-Bae Kong[3], Won Seok Song[3], Wan Hyeong Cho[3], Dae Geun Jeon[3], Yoon Jung Jang[2], Sung Hyun Yang[2], Im Il Na[2], Hyo-Rak Lee[2] and Hye Jin Kang[2*]
[1]*Hematology and Oncology, Hallym Hospital, Incheon, Korea*
[2]*Hematology and Oncology, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Korea*
[3]*Orthopedic Surgery, Korea Institute of Radiological and Medical Sciences, Korea*

PP17-10 **Study of agricultural vulnerability to organic compound fungides and herbicides and myeloproliferative neoplasms incidence in rural population in India**
Ankush Kumar[1] and Prachi Mishra[1]
[1]*Basic Sciences, DAV, A State University, India*

PP17-15 **Treatment, outcomes and prognostic factors of patients with prolymphocytic leukemia**
Su-Yeon Bang[1], Daehun Kwag[1], Jong Hyuk Lee[1], Gi-June Min[1], Sung-Soo Park[1], Silvia Park[1], Jae-Ho Yoon[1], Sung-Eun Lee[1], Byung-Sik Cho[1], Yoo-Jin Kim[1], Seok Lee[1], Hee-Je Kim[1], Chang-Ki Min[1], Seok-Goo Cho[1], Jong Wook Lee[1] and Ki-Seong Eom[1*]
[1]*Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea*

PP17-16 **Combination of red cell distribution width and serum human epididymis secretory protein 4 levels as a predictor of malignant ovarian tumors**
Wankyu Eo[1] and Ki Hyung Kim[2*]
[1]*Department of Internal Medicine, Kyung Hee University, Korea*
[2]*Department of Obstetrics and Gynecology, Pusan National University, Korea*

PP17-19 **Empowering communities for anemia prevention: Lesson learnt from Indonesian government program**
Mahyuddin Mahyuddin[1] and Kadriah Kadriah[2]
[1]*Sociology, Institute Agama Islam Negeri Parepare, Indonesia*
[2]*Public Health, Al Asyariah Mandar University, Indonesia*

PP17-22 **A meta-analysis of emergency hospital admissions among hematological malignancies**
Meenakshi Mourya
Department of Anesthesia, Safdarjung Hospital, New Delhi, India

PP17-24 **Risks of surgical treatment when appendicitis is diagnosed in hematologic patients**
Ho Seok Seo Seo[1*], Sung-Soo Park[2], Kyoung IL Min[2] and Seung Hyun Lee[1]
[1]*Department of Surgery, College of Medicine, The Catholic University of Korea, Seoul, Korea*
[2]*Department of Hematology, College of Medicine, The Catholic University of Korea, Seoul, Korea*

PP18-3 **Assessment of the quality of life by the SF-36 questionnaire in patients with chronic myeloid leukemia in chronic phase after treatment with imatinib mesylate achieved complete cytogenetic response**
Anh Chau Hong[1], Dung Co Nguyen Phuong[1*], Quyen Nguyen Duong Thao[2] and Hoa Nguyen Thi My[1]
[1]*Blood Transfusion Hematology Hospital and Pham Ngoc Thach University of Medicine, Hematologist, Viet Nam*
[2]*Blood Transfusion Hematology Hospital, Hematologist, Viet Nam*

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PP18-6 **Study of reality and perspectives factors for blood donating motivation among urban population of Delhi, India**
Pardeep Kumar[1*], Ranbir Singh[1] and Vinod Sharma[1]
[1]*Basic and applied sciences, Shri Maha Maya Vaishnav Devi Mandir Research Institute, India*

PP18-8 **Quality of life matters in hematopoietic stem-cell transplantation (HSCT)**
Mega Dwi Septivani
Business Administration, Politeknik Negeri Padang, Indonesia

PP18-9 **Spirituality as an alternative to reduce depression in leukemia patients**
Kadriah Kadriah[1*] and Mahyuddin Mahyuddin[2]
[1]*Public Health, Al Asyariah Mandar University, Indonesia*
[2]*Sociology Department, Institute Agama Islam Negeri Parepare, Indonesia*

PLENARY LECTURE & PRESIDENTIAL SYMPOSIUM

PL01

Regulation of iron metabolism

Martina Muckenthaler
University of Heidelberg, Germany

Imbalances of iron homeostasis account for some of the most common human diseases. Iron deficiency that is frequently caused by malnutrition, chronic inflammation or blood loss, and less commonly as a consequence of genetic mutations affects critical cellular processes such as oxygen transport, DNA synthesis and energy production. Likewise, iron overload due to Hereditary Hemochromatosis or ineffective erythropoiesis (e.g. in Thalassemia) will result in the generation of reactive oxygen species (ROS) that damage proteins, DNA, and lipids and cause organ dysfunction. Iron overload shows toxic effects already at a transferrin saturation of 60%–70%, when the iron binding capacity of transferrin is exceeded and "non-transferrin-bound iron" (NTBI) is formed.
In my presentation I will present state-of-the art knowledge about major pathways involved in cellular and systemic iron handling and explain control mechanisms that maintain iron homeostasis. Moreover, I will elaborate on how dysregulation of iron homeostasis causes diseases of iron overload and deficiency.

PL02

The role of the intestinal microbiome in cancer immunotherapy

Marcel van den Brink
Memorial Sloan Kettering Cancer Center, USA

Intestinal microbiomes and their mammalian hosts have co-evolved, resulting in mutualistic interactions that affect health and disease. A role for the gut microbiota in the development of graft-versus-host disease (GVHD) after Allogeneic Hematopoietic Cell Transplantation (allo-HCT) was first described in the 1970s by van Bekkum, who demonstrated that mice kept under germ-free (GF) conditions exhibited less mortality from acute GVHD than conventionally housed animals. In recent years several studies have demonstrated that the intestinal microbiome can modulate cancer immunotherapy, especially check poinwzt inhibition. We began our investigation into the role of the intestinal microbiome in alloin 2009 using next-generation sequencing. We have demonstrated a relationship between microbiota composition and clinical outcomes, including acute GVHD, chronic GVHD, infection, engraftment, relapse, and immune reconstitution. We will briefly highlight some of the main findings of a few of these studies.

In a study of 8,767 fecal samples obtained from 1,362 patients from four centers we found that patterns of microbiota disruption, characterized by loss of α-diversity during allo-HCT were similar across transplantation centers and geographic locations. Higher diversity of intestinal microbiota both before transplantation and at the time of neutrophil engraftment was associated with a lower risk of death in independent cohorts. After allo-HCT, almost all patients incur a period of microbial domination by certain bacteria, most frequently Enterococcus, which is associated with higher risk of acute GVHD-related mortality and shortened overall survival (OS). We found similar expansion of Enterococcus in GVHD mouse models and demonstrated in gnotobiotic models that Enterococcus administration aggravates acute GVHD. We observed a) enterocyte damage resulting in less expression of lactase and the anti-microbial protein Reg3γ/β (which controls Enterococcus) and b) dysbiosis characterized by contraction of salutary commensal flora, all contributing to alloreactivity. Enterococcus growth is dependent on the disaccharide lactose, and we demonstrated that withholding dietary lactose attenuates Enterococcus outgrowth and reduces the severity of GVHD in mice. Finally, allo-HCT patients with a lactase-deficiency genotype showed compromised clearance of post-antibiotic Enterococcus domination.

We also analyzed 1,161 fecal samples collected from 534 autologous HCT recipients at two transplantation centers and found that, similar to allo-HCT, high fecal intestinal diversity in the peri-engraftment period was associated with longer progression-free and overall survival.

We expanded our analyses of microbiome to outcomes after therapy with chimeric antigen receptor (CAR) T cells. We found in a retrospective cohort of 228 patients from two centers that exposure to broad-spectrum antibiotics within the 4 weeks prior to anti-CD19 CAR T cell infusion was associated with shorter overall survival and increased risk of neurotoxicity. Importantly, we also identified species within the class Clostridia that were associated with day-100 complete response.

In our recent unpublished studies in mouse and man we have found relationships between diet, drugs (also non-antibiotic drugs) and bile acids and the composition of the intestinal microbiome and clinically relevant outcomes after allo-HCT.

In conclusion, the concordance of microbiota disruption patterns and their associations with clinical outcomes suggests that approaches to manipulate the intestinal microbiota could improve cancer immunotherapy, such as allo-HCT and CART cell therapy.interactions that affect health and disease. A role for the gut microbiota in the development of graft-versus-host disease (GVHD) after Allogeneic Hematopoietic Cell Transplantation (allo-HCT) was first described in the 1970s by van Bekkum, who demonstrated that mice kept under germ-free (GF) conditions exhibited less mortality from acute GVHD than conventionally housed animals. In recent years several studies have demonstrated that the intestinal microbiome can modulate cancer immunotherapy, especially check point inhibition. We began our investigation into the role of the intestinal microbiome in alloin 2009 using next-generation sequencing. We have demonstrated a relationship between microbiota composition and clinical outcomes, including acute GVHD, chronic GVHD, infection, engraftment, relapse, and immune reconstitution. We will briefly highlight some of the main findings of a few of these studies.

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PL02

contraction of salutary commensal flora, all contributing to alloreactivity. Enterococcus growth is dependent on the disaccharide lactose, and we demonstrated that withholding dietary lactose attenuates Enterococcus outgrowth and reduces the severity of GVHD in mice. Finally, allo-HCT patients with a lactase-deficiency genotype showed compromised clearance of post-antibiotic Enterococcus domination.
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In our recent unpublished studies in mouse and man we have found relationships between diet, drugs (also non-antibiotic drugs) and bile acids and the composition of the intestinal microbiome and clinically relevant outcomes after allo-HCT.
In conclusion, the concordance of microbiota disruption patterns and their associations with clinical outcomes suggests that approaches to manipulate the intestinal microbiota could improve cancer immunotherapy, such as allo-HCT and CART cell therapy.

PL03

Recent advance in the hematopoietic stem cell research

Toshio Suda
National University of Singapore, Singapore

Tissue stem cells are capable of self-renewal and multi-lineage differentiation. The fate of hematopoietic stem cells (HSCs) is determined by the intrinsic cell program and the extrinsic microenvironment (niche) effect. Although self-renewal is essential for maintaining HSCs, the mechanism of the process has not been well elucidated.
Very recently, we have clarified that in the period of HSC formation, they show the predominant self-renewal capacity more than differentiation capacity to mature cells by using in vivo genetic tracing (Yokomizo T et al. Nature, 2022). From now, it will be possible to dissect how these two seemingly opposite tasks; self-renew and differentiation are regulated in normal and leukemic stem cells.
On the other hand, we can see a significant advance in the research of hematopoietic stem cell niche by introducing the advanced technology single cell RNA seq. We have previously delineated that oxidative stress (ROS) limits the self-renewal activity of HSCs and that the metabolic state is quite different between quiescent (self-renewing) HSCs and cycling HSCs. Especially, we are now analyzing the mitochondria metabolism in stem cells.
In this meeting, I would like to talk about recent advance in the stem cell research, especially development and metabolism of HSCs. On the basis of the basic research,
I will refer to the clonal hematopoiesis and blood diseases.

PS01

What can Nano do for Medicine?

Taeghwan Hyeon
Seoul National University, Korea

Over the last 20 years, our laboratory has focused on the designed chemical synthesis, assembly and medical applications of uniform-sized nanocrystals. We reported that uniform 2 nm iron oxide nanoclusters can be successfully used as T1 MRI contrast agent for high-resolution MR angiography of monkeys.1 We demonstrated that ceria nanoparticles and ceria–zirconia nanoparticles can work as therapeutic antioxidants to treat various nasty diseases, including ischemic stroke, Alzheimer's disease, sepsis, and Parkinson's disease, and radioprotectants.2 We developed a click reaction-assisted immune cell targeting (CRAIT) strategy to deliver drug-loaded nanoparticles deep into tumor interiors, reducing tumor burden in an aggressive 4T1 breast cancer model without any systemic toxicity.3 We synthesized $MnFe_2O_4$-anchored mesoporous silica nanoparticles to overcome hypoxia, and consequently enhancing the therapeutic efficiency of photodynamic therapy.4 We synthesized manganese ferrite and ceria nanoparticle-anchored mesoporous silica nanoparticles (MFC-MSNs) that can synergistically scavenge ROS and produce O_2 for reducing M1 macrophage levels and inducing M2 macrophages for rheumatoid arthritis treatment.5 We reported a heterogeneous chemodynamic therapy system based on copper-iron peroxide nanoparticles for tumor microenvironment-mediated synergistic therapy. CFp NPs degrade under the mildly acidic condition of TME, and the released Cu and Fe ions, with their larger portions at lower oxidation states, cooperatively facilitate the hydroxyl radical production through a highly efficient catalytic loop to achieve an excellent tumor therapeutic efficacy.6 We report a highly sensitive and selective K+ nanosensor that can quantitatively monitor extracellular K+ concentration changes in the brains of freely moving mice experiencing epileptic seizures.7

We fabricated ultraflexible and/or stretchable soft-electronic and optoelectronic devices integrated with various functional nanomaterials and their applications to wearable and implantable medical and healthcare devices.8 We introduced electromechanical cardioplasty using an epicardial mesh made of electrically conductive and elastic Ag/Au nanowire-rubber composite material to resemble the innate cardiac tissue and confer cardiac conduction system function.9 We fabricated highly conductive and elastic nanomembrane for skin electronics.10 We synthesized a flexible, sticky, and biodegradable electronic patch for controlled drug delivery for GBM treatment.11 We developed a microneedle-based delivery method of theranostic NPs and high-energy photons to treat two types of brain tumors.12 Recently, we synthesized an injectable hydrogel nanocomposite for intracortical drug delivery to treat deep-seated brain tumors.\

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JOINT SYMPOSIUM

JS01-1

POEMS syndrome: advances in molecular pathophysiology and treatment

Chiaki Nakaseko
International University of Health and Welfare School of Medicine, Japan

POEMS syndrome is a rare plasma cell disorder characterized by multiple symptoms, λ-type M-protein, and serum VEGF elevation. A favorable prognosis has been reported by suppressing underlying monoclonal plasma cell proliferation with novel agents for multiple myeloma (MM) such as proteasome inhibitors and immunomodulatory drugs and autologous stem cell transplantation. In contrast to the clinical advances, the pathogenesis of POEMS syndrome has not been fully understood. In our previous studies, variable regions of the clonal immunoglobulin λ light chain (IGL) (IGLV) were found to be restricted to IGLV1-44 or IGLV1-40 germline sequences, suggesting that clonal plasma cells lack diversity in the immunoglobulin repertoire. Our recent genome sequencing of BM plasma cells in POEMS syndrome identified 7 recurrently mutated genes. Importantly, none of the driver gene mutations frequently found in MM were identified. Then, we performed single cell RNA sequencing of bone marrow plasma cells from patients with POEMS syndrome and identified POEMS clones that had Ig λ light chain (IGL) sequences (IGLV1-36, -40, -44, and -47) with amino acid changes specific to POEMS syndrome. The proportions of POEMS clones in plasma cells were markedly smaller than in patients with multiple myeloma (MM) and patients with monoclonal gammopathy of undetermined significance (MGUS). Single-cell transcriptomes revealed that POEMS clones were CD19+, CD138+, and MHC class IIlo, which allowed for their prospective isolation. POEMS clones expressed significantly lower levels of c-MYC and CCND1 than MM clones, accounting for their small size. VEGF mRNA was not upregulated in POEMS clones, directly indicating that VEGF is not produced by POEMS clones. These results reveal unique features of POEMS clones and enhance our understanding of the pathogenesis of POEMS syndrome.

JS01-2

Updates on POEMS syndrome in Korea

Jin Seok Kim
Yonsei University College of Medicine, Korea

POEMS syndrome is a paraneoplastic syndrome due to an underlying plasma cell neoplasm. Distinctive presenting characteristics of the syndrome that differentiate POEMS syndrome from standard multiple myeloma (MM). We retrospectively reviewed patients diagnosed with POEMS syndrome at 8 institutions in South Korea, between January 2,000 to October 2,022.

A total of 84 patients were included with a median follow-up time of 40.7 months (range, 1–207). The median age was 53 (range 26–77) and 63.1% (n=53) were male.

The median time from neurologic symptom presentation to the diagnosis of POEMS syndrome was 173 days (range, 0–3,969). Peripheral neuropathy was present in all patients (100.0%) and monoclonal plasma cell proliferation was shown in 96.4% (n=81). Bone lesions were documented in 70 patients (sclerotic bone lesions in 68 patients). The Castleman disease was found in 18.3% (n=15) and plasma VEGF levels were available in 32 patients with a median of 821 pg/mL (range, 26–12,900). Organomegaly was observed in 72.6% (n=61) and endocrinopathy was observed in 69.1% (n=56). Skin changes were detected in 54.2% (n=45) of patients and extravascular volume overload was observed in 71.4% (n=60).

Seventy-five patients received treatment. The first-line treatments were local radiotherapy only in 6 (8.0%) patients, chemotherapy ± radiotherapy in 26, and autologous stem cell transplant (ASCT) in 43 (57.3%) (without induction chemotherapy in 12 patients and with induction chemotherapy in 31 patients).

The median OS was not reached (78% of 5-year OS and 65% of 10-year OS) and the median EFS was 5.95 years (55% of 5-year EFS and 37% of 10-year EFS). The patients who received frontline ASCT (n=43) showed 85% of 5-year OS and 59% of 5-year EFS.

This nationwide study demonstrated the current status of POEMS syndrome in Korea and the demographics and clinical characteristics were similar to the previous studies reported by the Japanese, UK, and US groups. Because the patients with initial extravascular volume overload were relatively higher in our cohort, early suspicion and initiation of diagnostic approach should be emphasized. In addition, the satisfied EFS was not observed in our cohort because of the rarely available new target agents based on the therapeutic agents of multiple myeloma. Therefore, new treatment strategies with several target agents according to the risk group should be incorporated into the treatment of POEMS syndrome in Korea.

JS01-3

Therapeutic approach of Waldenström's macroglobulinemia in Japan

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Gunma University, Japan

Waldenström's macroglobulinemia or lymphoplasmacytic lymphoma (WM/LPL) is a rare subtype of indolent B-cell lymphoma with plasmacytic differentiation. Owing to its rarity, the pathogenesis, biology, and standard of care have not been established. In 2012 the MYD88 L265P mutation is proven as the major oncogenesis in WM/LPL.

Although population-based cancer registries have reported lower incidence of WM in East Asia than in Western countries, previous retrospective analyses have found the clinical features of WM to be similar in these two populations. Our recent retrospective analysis demonstrated that symptomatic WM was found in 73 (78.5%) and asymptomatic WM in 20 (21.5%) of cases examined. The median overall survival (OS) was similar to that in reports from Western countries. Treatment regimens such as DRC, VDR and R-CHOP were preferably used and the patients receiving those regimens including rituximab exhibited significantly better survival.

Tirabrutinib is a second-generation Bruton's tyrosine kinase inhibitor with greater selectivity than ibrutinib. We conducted a multicenter, phase II study of tirabrutinib in patients with treatment-naïve (Cohort A) or with relapsed/refractory (Cohort B) Waldenström's macroglobulinemia (WM). MRR and ORR were 88.9% and 96.3%, respectively. The progression-free and overall survival rates at 24 months were 92.6% and 100%, respectively. Serum IgM levels in all patients except one declined and were maintained at low levels, although transient increases occurred after temporal interruption of the study drug. There was no flare unlike rituximab. Tirabrutinib is now approved for LPL not only WM in Japan and is broadly applied to the treatment of those patients.

In this session, I will present recent treatment approaches in Japan and discuss about some rare complications and/or subtypes of this disease i.e., Bing Neel syndromes, amyloidosis, and peripheral neuropathy with anti MAG antibody.

JS01-4

Clinical researches on Waldenström's macroglobulinemia in Korea

Hosup Lee
Kosin University College of Medicine, Korea

Waldenström's macroglobulinemia (WM) is a B-cell proliferative malignancy characterized by immunoglobulin M monoclonal gammopathy and bone marrow infiltration by lymphoplasmacytic cells. Clinical features and cytogenetics of WM in Asia including Republic of Korea remain unclear. The epidemiological features of WM have seldom been investigated at a national level, particularly in East Asia. The goal of our study is to present the incidence, prevalence, mortality, survival with competing risks, and causes of death of patients with WM. The sensitivity of MEMO-PCR was estimated to be approximately 10-16.7%. MYD88 L265P was detected in 21 of 28 LPL cases (75%) and only three of 69 B cell NHL cases (4.3%). 45% patients showed cytogenetic aberrations using FISH: 6q deletion in eight (37%) and IGH rearrangement in four (18%). 69% patients presented with the MYD88 L265P mutation. MYD88 mutations were significantly associated with the presence of 6q deletions. Patients with the 6q deletion for whom sequencing was possible were found to harbor MYD88 mutations. The MYD88 L265P mutation was also associated with increased lymphocyte burden in BM biopsy. This is the first report of high frequency MYD88 L265P mutations in Korean WM patients. Use of novel agents produced higher ORR but survival benefit was not apparent due to the small number of patients and short follow-up duration. Further studies are needed to confirm the efficacy of novel agents in patients with WM. The national incidence of WM in Korea, a racially homogeneous country in Asia, was lower than that in previous reports from other countries, reflecting ethnic disparities. However, the incidence increased, and mortality was the highest ever reported. The main cause of death was WM in itself. This study reflects the need for greater awareness of WM, particularly in Asian countries. At now, a multicenter Phase II study of Rituximab combined bortezomib, lenalidomide plus dexamethasone followed by maintenance lenalidomide in patients with newly diagnosed WM is ongoing in order to estimate the efficacy and safety of the chemotherapy in south Korea.

JS02-1

NK cells: next generation cell therapies for cancer

Katy Rezvani
The University of Texas MD Anderson Cancer Center, USA

Dr. Rezvani will discuss a new frontier in NK cell therapeutics: engineering NK cells with chimeric antigen receptors. She will discuss the opportunities and challenges of NK cell CAR engineering, and present pre-clinical and early phase clinical data on cord blood-derived NK cells expressing CD19 CAR and IL-15 to enhance their in vivo persistence in patients with relapsed or refractory blood cancers. In addition, she will discuss novel strategies for the gene editing of CAR NK cells to enhance their function by targeting immune checkpoints. Finally, she will discuss the approach of precomplexing NK cells with an anti-CD16 bispecific antibody targeting CD30 to redirect their specificity, and updates on a clinical trial using this approach in patients with CD30-expressing lymphoma.

JS02-2

Treatment of extranodal NK/T-cell lymphoma: KSH Lymphoma Working Party experience

Seok Jin Kim
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The Korean Society of Hematology (KSH) Lymphoma Working Party (KLWP) has conducted many prospective and retrospective studies since KLWP was started in 2006. The KLWP has the research consortium for clinical and translational studies for lymphoma that was named as CISL (Consortium for Improving Survival of Lymphoma). The KLWP/CISL produced outstanding research outcomes through various subtypes of lymphomas. Among them, extranodal natural killer (NK)/T-cell lymphoma (ENKTL) is the main study topic of the KLWP because ENKTL is relatively more common in East Asian countries than Western countries. ENKTL is a rare but fatal subtype of non-Hodgkin lymphoma. The treatment outcomes for ENKTL was improved by the development of non-anthracycline-based chemotherapy regimens incorporating etoposide and L-asparaginase. However, a substantial number of patients, especially those with advanced disease, experience disease relapse or progression, and these patients have extremely poor survival outcomes. Thus, effective treatment strategies to prevent relapse are required. Currently recommended treatments for localized ENKTL are based mainly on the results of phase II studies and retrospective analyses. Because the previous outcomes of anthracycline-containing chemotherapy were poor, nonanthracycline-based chemotherapy regimens, including etoposide and L-asparaginase, have been used mainly for patients with localized nasal ENKTL. Radiotherapy also has been used as a main component of treatment because it can produce a rapid response. Accordingly, the combined approach of nonanthracycline-based chemotherapy with radiotherapy is currently recommended as a first-line treatment for localized nasal ENKTL. However, there is no consensus regarding the optimal therapy for advanced disease of ENKTL because there are little data about randomized studies. Intensified nonanthracycline-based chemotherapy regimens, including etoposide and L-asparaginase such as SMILE are recommended as primary treatment for patients with advanced disease of ENKTL. Autologous or allogeneic stem cell transplantation (SCT) could be done as frontline consolidation for disseminated NK/T-cell lymphoma and as salvage consolidation for relapsed–sensitive disease. However, the outcome of autologous and allogeneic SCT is still not satisfactory. The novel agents with different mode of action such as immune checkpoint inhibitors could be used for relapsed or refractory patients, but the efficacy of those drugs is still limited. This lecture summarizes the use of nonanthracycline-based chemotherapy with radiotherapy, which have been proposed as a first-line treatment for newly diagnosed patients with localized nasal ENKTL, as well as the management of advanced disease of ENKTL including relapsed or refractory disease.

Keywords: NK/T-cell lymphoma, Chemotherapy, Radiotherapy, Transplantation, Prognosis

JS02-3

CAR-T for the treatment of T cell malignancies

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The overarching goal of this work is to improve chimeric antigen receptor T cell (CAR-T) therapy for patients with T-cell Acute Lymphoblastic Leukemia (T-ALL) and T-NHL via the use of 'off-the- shelf' universal allogeneic CAR-T (UCART) cells. Several challenges have limited the clinical development of CAR-T cells against T cell malignancies. First, the shared expression of target antigens between T effector cells and T cell malignancies results in fratricide, or self-killing, of CAR-T cells. Second, harvesting adequate numbers of autologous T cells, without contamination by malignant cells, is technically challenging and prohibitively expensive. Third, the use of genetically modified CAR-T cells from allogeneic donors may result in life-threatening graft-versus-host disease (GvHD) when infused into immune-compromised HLA-matched or mismatched recipients. Thus, development of an 'off-the-shelf' fratricide-resistant CAR-T product would allow the use of allogeneic donor T cells for the treatment of T cell hematologic malignancies without inducing life-threatening GvHD represents a significant unmet medical need. Previously, we generated allogeneic 'off-the-shelf' UCART targeting CD7 (UCART7) using multiplexed CRISPR/Cas9 gene editing to delete CD7 and the T cell receptor alpha chain (TRAC). These UCART7 cells prevented fratricide and efficiently killed human T-ALL cell lines and patient-derived primary T-ALL in vitro and in vivo without resulting in xenogeneic GvHD. We hypothesize that the administration of allogeneic UCART7 cells to patients with relapse/refractory T-ALL will be safe, tolerable, and provide anti-tumor activity resulting in improved clinical outcomes. We plan to test this hypothesis via the following specific aim:

In general, three barriers to effective CAR-T cell therapy, including potentially UCART7, for hematologic malignancies are (1) the development of life-threatening cytokine release syndrome (CRS), (2) suboptimal CAR-T cell cytotoxicity and persistence that allows target antigen-positive tumor escape and disease relapse, and (3) relapse due to antigen escape via downregulation or mutation of the target antigen. IL-7 is a main regulator of peripheral homeostatic expansion of CD4 and CD8 T cells. It binds to the IL-7 receptor which consists, in part with the common gamma chain to signal through JAK/STAT- pathways to stimulate the differentiation, proliferation, and survival of T cells. NT-I7 (efineptakin alfa, NeoImmuneTech) is a long-acting cytokine, consisting of a genetically modified recombinant human IL-7 fused to a hybrid Fc region of a human antibody (half-life of ~63 hours vs. <2 hours for IL-7). NT- I7 is safe and well tolerated in mice and man. Furthermore, preclinical work by others and us suggests that duvelisib, a dual phosphoinositide 3-kinase delta/gamma (PI3Kdg) inhibitor, may provide effective prophylaxis against CRS while enhancing the persistence and efficacy of CAR-T cells. Finally, multi- antigen-targeted CAR-T cells are a promising direction to overcome single antigen relapse issues following CAR-T cell therapy. We plan to address these three barriers to CAR-T cell therapy in the following specific aim:

This work will further the development of a viable 'off-the-shelf therapy' for the treatment of T-ALL and potentially other malignancies expressing CD7 or CD2 such as NK and NKT lymphomas, T-NHLs and AML. Additionally, the work proposed here may provide a strategy to treat relapse after UCART7 and prevent life-threatening CRS, a major limitation of CAR-T cell therapy, applicable across the field of adoptive T cell therapy.

JS02-4

Treatment of peripheral T-cell lymphoma: Korean Lymphoma Working Party experience

Deok-Hwan Yang
Chonnam National University Medical School, Korea

It has been well known that peripheral T cell lymphomas (PTCLs) has undergone poor prognosis compared with B-cell phenotype lymphomas. However, significant advances were recently made to overcome these obstacles based on well conducted prospective studies with combined novel agents. Pralatrexate, a unique antifolate, romidepsin, a histone deacetylase inhibitor, and brentuximab vedotin, an immunoconjugate of anti-CD30 improved the prognosis and survivals in PTCLs. Furthermore, new understanding of the biology and molecular pathogenesis using next-generation sequencing (NGS) assessment could enable the selective targeted therapy and have demonstrated the clinical efficacy and tolerability in both frontline or relapsed clinical settings. This presentation will summarize the clinical outcomes of PTCLs based on Korean studies and discuss wide-ranging novel agents which mainly targeting intracellular pathway or hypomethylating agents in the treatment of PTCLs.

JS03-1

Novel approaches in MDS

Uwe Platzbecker
Leipzig University Hospital, Germany

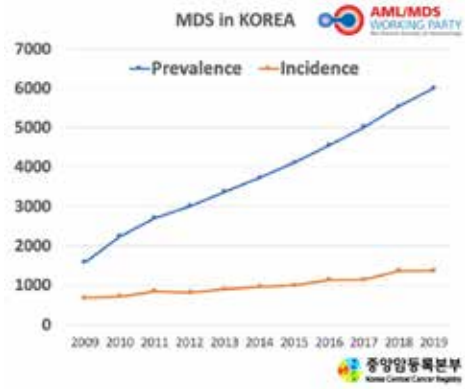
Myelodysplastic syndromes (MDS) represent a heterogeneous group of myeloid neoplasms that are characterized by ineffective hematopoiesis, variable cytopenias, and a risk of progression to acute myeloid leukemia. Most patients with MDS are affected by anemia and anemia-related symptoms, which negatively impact their quality of life. While many patients with MDS have lower-risk disease and are managed by existing treatments, there currently is no clear standard of care for many patients. For patients with higher-risk disease, the treatment priority is changing the natural history of the disease by delaying disease progression to acute myeloid leukemia and improving overall survival. However, existing treatments for MDS are generally not curative and many patients experience relapse or resistance to first-line treatment. Thus, there remains an unmet need for new, more effective but tolerable strategies to manage MDS. Recent advances in molecular diagnostics have improved our understanding of the pathogenesis of MDS, and it is becoming clear that the diverse nature of genetic abnormalities that drive MDS demands a complex and personalized treatment approach.

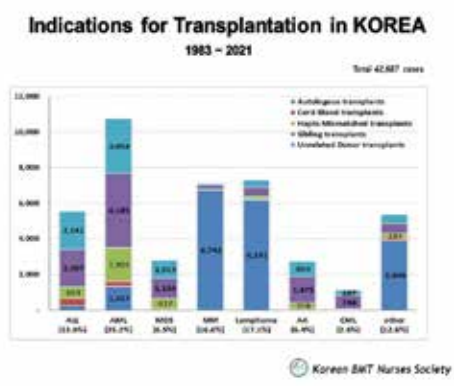
JS03-2

Treatment of MDS: Korean AML/MDS working party experience

June-Won Cheong
Yonsei University College of Medicine, Korea

Although myelodysplastic syndrome (MDS) is not the most common myeloid neoplasm in Korea, the clinical significance of MDS is increasingly growing due to the aging of Korean population. According to the Korea Central Cancer Registry, the incidence (680 in 2009 vs. 1,371 in 2019) and the prevalence (1,584 in 2009 vs. 6,010 in 2019) has been increased by approximately two-fold and four-fold in the last decade, respectively. Prior to the introduction of the epigenetic treatment in 2006 in Korea, MDS patients had no choice but to be treated with supportive treatment or conventional chemotherapy for myeloid neoplasms. With the availability of azacytidine since 2006 and decitabine since 2009, the main treatment strategy for the lower-risk MDS patients requiring disease modifying treatment has become based on the hypomethylating agents. Since various working parties were established within the Korean Society of Hematology in the latter half of 2005, the AML/MDS working party was fortunate to begin its clinical and research activities in a situation where the epigenetic treatment was available for use. Lenalidomide was available for MDS with 5q deletion since 2019, and luspatercept was also available since last year. In the management of higher risk MDS patients, allogeneic hematopoietic stem cell transplantation (HSCT) is still the treatment of choice for transplant candidate. Since the first HSCT in Korea in 1981 until 2021, more than forty-two thousand patients had received HSCT, and MDS patients accounted for 6.5% (2,734 patients). Recently, about 300 patients receive HSCT every year. For MDS patients in Korea, lack of flexibility of National Health Insurance System as well as incomplete understanding about disease and the goal of treatment remain obstacles to keep the treatment guideline for patients. Since the establishment, AML/MDS working party has conducted numerous retrospective and prospective studies and made every effort to establish treatment guidelines to provide patients with high-quality care. We hope that through these efforts, patients suffering from AML or MDS can live longer and enjoy a better quality of life.





JS03-3

Standard management of MDS

Lionel Adès
Hospital Saint Louis and Paris University, France

Myelodysplastic syndromes (MDS) are clonal stem cell disorders (HSC) predominating in the elderly, characterized by ineffective haematopoiesis leading to blood cytopenias and by progression to acute myeloid leukaemia (AML) in 1/3 cases. Their pathophysiology is a multistep process involving cytogenetic changes and/or or gene mutations and widespread gene hypermethylation at advanced stages.
Diagnosis of MDS is still based on the blood and marrow examination, showing blood cytopenias, hypercellular marrow with dysplasia, with or without excess of marrow immature cells (blasts) . Prognosis is largely based on the marrow blast percentage, number and extent of cytopenias and cytogenetic abnormalities, including mutations. Treatment of MDS remains challenging but has recently improved. The therapeutic strategy remains largely based on the IPSS/IPSS-R classification. In patients with Higher risk MDS, with a median survival of only about 12 months, treatment should aim whenever possible at modifying the disease course, ie avoiding progression to AML, and improving survival. On the contrary, patients with Lower risk MDS have more prolonged survival and often die from causes other than MDS. Therefore, their treatment mainly aims at reverting the consequences of cytopenias and transfusions, and improving quality of life. However, some lower risk patients may benefit from treatments generally applied to higher risk MDS.
Allogeneic SCT remains, with few exceptions, the only curative treatment of higher risk MDS, with prolonged disease free survival in 35-50% of the patients . However, it can generally be offered only to younger patients for myeloablative allogeneic SCT and elderly patients up to 70 years (or even more in very "fit" patients) for reduced-intensity SCT with an HLA identical donor (familial or unrelated) ie to a small minority of MDS.
Hypomethylating agents have become the first line treatment in most higher risk MDS, after clinical trials establishing a survival benefit with azacytidine over conventional care regimens (CCR), with a median survival of 24.4 months vs 15 months. Nevetleless, the median survival of 2 years achieved with AZA in high-risk MDS remains modest, and many groups evaluated combination of drugs with AZA. While results of some phase II trials combining AZA and another drug, including Histone deacetylase (HDAC) inhibitors, Lenalidomide, Thalidomide, gemtuzumab ozogamicin, Pevonedistat, Sabatolimab have shown promising response rates, no randomized trial has so far demonstrated any response or survival advantage of those combinations over AZA alone.
Treatment of low-risk smd aims at limiting the transfusion burden and improthe ving quality of life. It is based on ESAs as the first line therapy and lenalidomide as second line in case of 5q deletion and Luspatercept in the presence of a SF3B1 mutation.

JS03-4

Genetic alterations in myelodysplastic neoplasms

Yoo-Jin Kim
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Mutations in various genes can contribute to the development of myelodysplastic neoplasms (MDS), and specific gene mutations can influence the course of the disease. Research on gene alteration in MDS has been extensively conducted for more than 10 years since the introduction of next-generation sequencing (NGS). Starting with the collection of basic data such as the types and frequencies of mutated genes in MDS, elucidating roles of genetic alterations in the pathogenesis of MDS, prediction and monitoring of treatment response, survival prediction, and discovery of therapeutic targets were the main research topics. As a result of the efforts, various results have been achieved, such as the classification of new subtypes or precursor conditions, improvement of the prognostic scoring system, and discovery of treatments for specific genes. These various contents will be delivered through lectures by other speakers of this joint symposium.

Although typical de novo MDS are predominantly sporadic diseases affecting older adults due to the acquisition of age-related somatic mutations, inherited forms of MDS are increasingly recognized following the advent of genetic screening. Several inherited mutations predisposing to myeloid neoplasms have been identified, with DEAD box helicase 41 (DDX41) the most commonly mutated gene. Since the first report of DDX41 mutations, both germline and acquired somatic DDX41 mutations have been identified and found to define a significant disease entity characterized by late-onset and unique clinical features. The frequency of DDX41 mutations is high in Korean MDS patients and there are also differences in mutational alleles. It is an important task to study the molecular mechanisms underlying the effects of DDX41 mutations on MDS biology. In this lecture, I will present the experimental results of the role of DDX41 in R-loop physiology and their contribution to MDS. Additionally, R-loop-induced DNA damage by splicing factor mutation will also be touched on in the lecture. Further understanding of molecular mechanisms underlying the contribution of R-loops and m6A methylation to the pathogenesis of MDS may expand the therapeutic options for cases of MDS with DDX41 or splicing factor mutations.

JS04-1

Overview of AA diagnosis and treatment in NIHBT, Vietnam

Nguyen Thi Thao
National Institute of Hematology and Blood Transfusion, Vietnam

From 2011 to 2020, National Institute of Hematology and Blood Transfusion (NIHBT), Viet Nam has developed in the diagnosis and treatment of Aplastic anemia (AA). There are an average of 1,300 AA inpatient visits per year [698-1910], including an average of 240 new AA patients per year [73-345]. Diagnosis of AA has based on clinical evidences, peripheral blood cell tests and bone marrow biopsy, diagnosed according to the Camitta criteria.

The clinical data of 60 AA patients were treated with horse anti thymocyte globulin (hATG) plus cyscloporin A (CSA) regimens from 2011 to 2020 showed that the overall response (OR) and complete response (CR) were 65.1% and 32.6%. The response of the transfution dependent non severe AA (TD-NSAA) group was the highest, OR was 71.4%; CR was 42.9%; the lowest was very severe AA (VSAA) group with OR 55% and CR 22.9%. The response rate in the group lower than 18 years old was statistically significantly higher than the group older than 18 years old. The 3-year overall survival (OS) was 93.8%. Clonal evolution of 2.6% in all treated patient at 3 years, relapse rate after achieving response was 5.3%.

Study of 47 patients with SAA (7-41 years old) were treated with peripheral blood stem cell transplantation (PBSCT) from sibling donor at NIHBT, Hanoi, Vietnam between 2010 and 2022. The conditioning regimen were Cy/Flu/with or without hATG. Regarding the GVHD prophylaxis, all patients were used CSA and short course of MTX. Results: The incidence of engraftment at day 30 was 100%. The estimated 5-year overall survival (OS) and disease-free survival (DFS) were 84.8% and 91%. The incidence of acute graft-versus-host disease (aGVHD) and chronic GVHD (cGVHD) were 17% and 40.5%, respectively; Severity of acute and chronic GVHD was only 2.1%. CMV reactivation was observed in 96.7% of patients. The incidence of two-year transplant related mortality was 12.7%.

Allo-HSCT and immunosupression hATG+CSA are the effective first line treatment of SAA.

JS04-2

The incidence and real-world outcome of aplastic anemia in Thailand

Lalita Norasetthada
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The incidence of aplastic anemia (AA) varied worldwide, with the estimated annual incidence of AA in Western countries of 1.5–2.3 per million inhabitants per year, while the incidence was 2-3 times higher in Asia (3.0-7.5 per million). From a prospective multi-center nationwide population- based observational study of patients with AA in Thailand aged over 15, the annual incidence was 4.6 per million inhabitants. There was a higher annual incidence of severe (SAA) and very severe aplastic anemia (VSAA) (3.8 per million) than non-severe aplastic anemia (NSAA) (0.8 per million). The peak incidence was in patients from 80-89 years old (14.4 per million).

Due to the lack of matched donor and transplantation eligibility, only 3.6% of patients aged < 50 years with SAA/VSAA underwent hematopoietic stem cell transplantation (HSCT) in Thailand. Immunosuppressive therapy (IST) is recommended for patients with severe AA who are not eligible for HSCT. Horse ATG (hATG) is recommended over rabbit ATG (rATG) as first-line therapy. Due to the unavailability of hATG, rATG is widely used as an initial treatment in Europe and Asia. Among Thai patients with SAA/VSAA (n = 280), the overall response rate (ORR) for patients treated with rATG & cyclosporin A (rATG±CsA) was superior to those treated with CsA and anabolic steroids (44.4% vs. 36.4% and 31.2%, respectively, P < 0.001). The 2-year OS among SAA/VSAA patients treated with rATG±CsA, CsA, and anabolic steroids were 54.8%, 54.5%, and 37.6% (P = 0.037), respectively.

Conclusion: The incidence rate of AA in Asia, as well as in Thailand, is higher than in western countries and even higher among the elderly. rATG & CsA provided a better response than anabolic steroids, which translated into superior survival among patients with SAA/VSAA treated with IST.

JS04-3

Role of TPO receptor agonists in aplastic anemia treatment

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Aplastic anemia (AA) in its severe form has historically been associated with high mortality. With limited supportive care and no effective strategy to reverse marrow failure, most patients diagnosed with severe AA (SAA) died of pancytopenia complications.
In recent phase II/III, multicenter, open-label study, romiplastim was effective to AA patients who are refractory to IST. Hematological response at week 27 was 84%. Trilineage response was 39% at week 53. The most common treatment-related adverse events (AEs) were headache and muscle spasms.
Other study showed high dose romiplostim was highly effective in AA patients refractory to eltrombopag. Sequential therapy with eltrombopag followed by romiplastim may further improve the prognosis of AA patients refractory to conventional therapy.
High-dose romiplostim is effective and well tolerated in the treatment of patients with AA refractory to IST.
Eltrombopag (EPAG), a thrombopoietin receptor agonist, has recently emerged as a novel therapeutic agent for AA. EPAG directly acts on HSCs and stimulates proliferation, thereby achieving remission in approximately 40% AA patients refractory to IST.
When eltrombopag was combined with IST as upfront therapy, overall (about 90%) and complete responses (about 50%) were higher than observed extensively with IST alone of 65% and 10%, respectively. Not surprisingly, given the strong correlation between hematologic response rates and survival in SAA, most (>90%) were alive after a median follow-up of 18 months.

JS05-1

Overview of thalassaemia and hemoglobinopathies in Bangladesh

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Bangladesh is a country with a population of 160 million with a gross national income per capita of US$1580.00. The major health problems in Bangladesh include acute respiratory infection, pneumonia, dengue fever, malaria, and water-borne diseases. The health care system in Bangladesh is divided into primary secondary and tertiary levels, with each level having its breakdown of available hospital beds and other treatment facilities. Thalassemia is a major health problem in Bangladesh. There are two types of Thalassemia in Bangladesh: β-Thalassemia (b-thal) and Hb E (HBB: c.79G>A)/β-thal, with the prevalence rate of the β-thal trait being 4.1% and Hb E trait 6.1%. This study discusses spectrum types of Thalassemia and hemoglobinopathies in Bangladesh and the types of carrier detection. The distribution of common mutations of Thalassemia is also discussed and the distribution frequencies of genotypes and alleles of β-thal and Hb E patients are also compared. Additionally, we also conducted a study of the spectrum of Thalassemia using high-performance liquid chromatography (HPLC) of the tribal populations and analyzed the findings in our discussion. The results of these studies show that the phenotypic and genotypic presentation in Bangladesh is highly diverse. To properly understand this, we have to conduct an epidemiological survey of the population. There is no coordinated thalassaemia prevention program. Prenatal diagnosis does not exist. Safe blood transfusion is cost-effective and present in teaching hospitals only. Iron overload control is difficult as chelating agents are also costly. Furthermore, there also has to be an improvement in the awareness of Thalassemia among the population to properly equip themselves to survive this disease.

JS05-2

Current situation of thalassemia care in Cambodia

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One of the South-East Asia countries, the population of Cambodia was approximately 16 million (2019) with an annual growth rate of 1.4% in which the prevalence of hemoglobinopathies was estimated at about 40.0% (range 30.0–50.0%) to be carriers, and 2240 annual births for β-thalassemia major (β-TM).
The overall prevalence of β-thalassemia (β-thal) and α-thalassemia (α-thal) were 40.9 and 39.6%, respectively. Currently, the specific epidemiological data regarding the abnormal gene frequency/mutations among different ethnic groups is unknown. Thalassemia is currently diagnosed by Hb electrophoresis using the Capillary Minicap Analyzer (Sebia, Lisses, France). In 2011, national guidelines for the Clinical Management of Patients with Thalassemia in Cambodia were developed and published by the Ministry of Health (MoH).
Transfusion Leukocyte-depleted packed red cells (LDPRC) are not available, only Packed red cells (PRCs) are available at most referral hospitals (provincial hospitals). Blood group phenotyping and antibody screening are not available. Oral iron chelators [deferiprone (DFP) and deferasirox (DFX)] are only available from a private pharmaceutical company. Hydroxyurea (HU) is available at some private pharmacies.
The future needs for Cambodia are to develop a national policy on the prevention or control of β-thal and α-thal, and a national registry of patients with thalassemia, to determine the gene frequency of α- and β-thal in different regions of the country, and to place the iron chelators on the list of essential medicines.

Keywords: Cambodia, Prevalence, Diagnosis, Treatment, Thalassemia

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JS05-3

Epidemiology and diagnosis of hemolytic anemia in Korea

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Hereditary hemolytic anemia (HHA) is known to be rare in Korea, due to its ethnic characteristics or its difficulties in diagnosis. RBC disorder Working party of KSH have made lot of efforts on revealing status and epidemiology of HHA in Korea, which lead to set a proper public health policy. And we also tried to settle guidelines on diagnosis of HHA for clinicians easy to reach in clinics. According to recent studies, its epidemiology has been changed over decades by several reasons. Epidemiologic study which the RBC disorder Working party of KSH reported on 2019 revealed that thalassemia trait has been increased over recent 10 years may be due to increase of international marriage. And the effect of increased diagnosis of enzymopathies owe to advances in diagnostic techniques also contributed to the changes in epidemiology in Korea. We also expect that the epidemiology would change because Korea has become Super-aging society, and many public policies to overcome the problems of low-birth and super-aging society will eventually affect epidemiology of Korea. We also expect the widespread of use of molecular genetic studies in diagnosis of HHA. RBC disorder working party had proposed multi-gene panels for Korean patients who suspect HHA, which are available as Next generation sequencing. We have encouraged to use this panel for patients whose diagnosis are not sure or ambiguous. We expect if the cost of the NGS go down for the sake for technical development, or changes in insurance coverage, the rate of diagnosis will be more increase. In this lecture, I'll introduce the studies on epidemiologic studies and molecular diagnosis of HHA conducted in Korea, and future studies of RBC disorder working party.

COLLABORATIVE SESSION

CS01-1

Accelerate breakthroughs in hematology with single cell sequencing

Geoffrey McDermott
10x Genomics, Inc., USA

Join us to learn how single cell, spatial, and in situ technologies from 10x Genomics can help you push the boundaries of your translational and clinical research. Discover novel therapeutic targets, explore how therapeutics modulate disease-associated cell populations and states, gain insights into mechanisms governing therapeutic toxicity, and understand resistance mechanisms governed by transcriptomic and epigenetic remodeling. Enabling deeper insight into cancer, immunology, neuroscience, and immuno-oncology, 10x Genomics gives researchers the ability to see biology in new ways.

CS01-2

AI technology in the field of blood disease

Tabe Yoko
Juntendo University, Japan

As an aging society progresses, the uneven distribution and shortage of medical professionals is becoming an issue. In this context, the pandemic of SARS-CoV-2 has underscored the need for Internet of Things (IoT) and Artificial Intelligence (AI) systems in the medical field. AI image analysis capabilities have made great strides in the development of DNN (Deep Convolutional Neural Network) based deep learning technology and is being increasingly adopted in the area of diagnosis.

In blood morphology testing, the shortage of skilled laboratory technicians and hematopathologists has become a problem. Establishing an automated AI blood image analysis technology and building an AI diagnostic support system are critical issues. Integration of AI technology with basic laboratory information to provide diagnostic support is a realistic goal for the near future. In the research phase, an AI-DNN analysis system for cell classification and morphological abnormality detection has been constructed using about 700,000 digital images, which demonstrated high accuracy in differentiating myelodysplastic syndrome and aplastic anemia (sensitivity: 96.2%, specificity: 100.0%). (Reference [1]) In addition, the "Integrated AI Analysis System", combinational analysis of the morphological automated AI results and blood cell parameters measured by an automated hematology analyzer, showed good differential performance for the identification of Ph-negative myeloproliferative neoplasms. (Reference [2])

Taken together, AI image analysis technology is a promising tool in the automation and standardization of morphology testing, which has been a longstanding issue in blood testing. It is hoped that the practical application of such medical AI technologies will support initial medical examinations.

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CS01-3

Discover the unique power of using droplet digital PCR (ddPCR) for hematology-oncology applications

Gina Sun
Bio-Rad Laboratories, USA

Monitoring minimal or measurable residual disease (MRD) is an important step in managing treatment in cancer patients. Droplet Digital PCR (ddPCR) is a powerful technology that enables expansion of MRD testing capabilities and personalized patient care. ddPCR based hematology-oncology solutions provide results with industry-leading sensitivity, accuracy, and unmatched precision, without the need for standard curves and extensive interpretation. Utilizing ddPCR for detecting BCR-ABL fusion transcripts in clinical studies has demonstrated the potential for a better classification of patients and elevated CML monitoring to a new level of precision. ddPCR's other applications include direct clinical sample monitoring via various mutation detection as well as liquid biopsy and personalized cancer recurrence surveillance for precision oncology beyond hematological malignancies.

CS01-4

Holotomography and artificial intelligence: label-free 3D imaging, classification, and inference

Yongkeun Park
Tomocube Inc., Korea

Holotomography is a label-free high-resolution three-dimensional quantitative phase imaging (QPI) techniques1-3. QPI uses refractive index (RI) distributions as intrinsic imaging contrast for label-free imaging1. HT is optical analogous to X-ray computed tomography; multiple 2-D holograms of a sample are measured with various illumination angles, from which a 3-D RI distribution of the sample is reconstructed by inversely solving the wave equation.
When label-free and quantitative 3D imaging capability of ODT is combined with machine learning approaches, it can provide synergistic capability in bioimaging and clinical diagnosis. We will discuss the potentials and challenges of combining QPI and artificial intelligence in terms of various aspects of imaging and analysis, including segmentation, classification, and imaging inference3-6. In particular, various hematological applications will be discussed, including label-free classification of lymphocyte subtypes, label-free blood analysis, and the interactions of chimeric antigen receptor (CAR) T cells and target leukemic cells.

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CS02-1

A Phase 1a Study of BR101801, PI3Kγδ and DNA PK Triple Inhibitor, in Adult Patients with Advanced Hematologic Malignancies

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Boryung Co. Ltd., Korea

Background: Peripheral T-cell lymphoma (PTCL) is a rare and heterogeneous subset of aggressive Non-Hodgkin Lymphoma and patients with PTCL, especially those who are with relapsed or are refractory to conventional treatments such as CHOP regimen have shown poor prognosis. PI3K/AKT pathway is known to be in association with the occurrence of tumor and it also plays a major role in response to cancer treatment. In recent clinical studies, Phosphoinositide 3-kinase (PI3K) inhibitors showed good clinical outcomes, and the therapeutic approach via PI3K/AKT pathway are considered to be alternative therapeutic options for advanced hematologic malignancies such as PTCL. BR101801, as a PI3Kγ/δ and DNA PK inhibitor, blocks not only the signal affecting cell growth caused by PI3K but also efficiently induces cell cycle arrest and apoptosis through inhibition of DNA-PK activation, and finally decrease the stability of oncogenic protein, c-Myc(AACR2020 abstract #655).
Methods: This is a phase 1a, multi-center, open-label, first-in-human study in adult patients with advanced hematologic malignancies including PTCL. BR101801 was administered orally QD in 28-day cycles.
Results: As of July 31, 2022, 12 patients (8 PTCL, 2 DLBCL, 1MF and 1 MZL) with advanced hematologic malignancies were enrolled and treated with 50-325mg of BR101801. In 11 evaluable patients, the median age was 63 years (range 30-76 years). Histological subtypes include AITL (n=4, 36.4%), PTCL-NOS (n=3, 27.3%), DLBCL (n=2, 18.2%), MZL (n=1, 9.1%) and MF (n=1, 9.1%).
Efficacy analysis was performed in evaluable 11 patients. Objective response was evaluated in 3 patients (ORR 27.3%) and clinical benefit was observed in 6 patients (CBR 54.5%). Median survivor follow-up duration was 19.9 months (range 3.4-27.7months) and median progression free survival (mPFS) was 11.1 months. Of 7 patients with PTCL (PTCL-NOS and AITL), ORR was 42.8% (1 CR and 2 PRs), CBR was 85.7%, mPFS was 22.2 months (range 3.57-22.2) and median overall survival has not yet reached. Duration of response of the 3 responders were 9.2, 14.1+ and 20.7+ months, respectively.
Safety was analyzed in 12 patients. 10 patients (83.3%) experienced ≥1 treatment-emergent adverse event (TEAE). The most common (≥ 10%) TEAEs were ALT increased (33.3%), AST increased (25.0%), Rash (16.7%) and Diarrhea (16.7%). Grade 3 TEAEs occurred in 6 patients (50.0%) and the most common (≥ 10%) Grade 3 TEAEs were ALT increased (25.0%), AST increased (16.7%). There were no Grade 4 or 5 TEAEs and no treatment related death observed.
Conclusions: In phase 1a clinical study, 200mg QD of BR101801 was shown to provide target exposure for clinical efficacy with the tolerable and safe profiles. BR101801 showed signs of preliminary activity, especially in relapsed or refractory(R/R) PTCL patients. Hence we expect BR101801 would become a promising therapeutic option for R/R PTCL patients. Now, we are conducting phase 1b-II clinical study in patients with PTCL-NOS and AITL (NCT 04018248).

CS02-2

The gut microbiome as a novel predictive biomarker and therapeutic target in lymphoma patients

Woorim Kang
CJ Bioscience Inc., Korea

The role of the gut microbiome in regulating host metabolism and immunity has been the subject of extensive research in recent years. This research has opened up new possibilities for investigating the relationship between the gut microbiome and disease, leading to the development of innovative diagnostic and therapeutic approaches that leverage the power of gut microbes.
Our study focuses on Diffuse Large B-Cell Lymphoma (DLBCL) and aims to evaluate the impact of the gut microbiome on the safety and efficacy of R-CHOP chemotherapy in DLBCL patients. We obtained stool samples from newly diagnosed, treatment-naive patients and analyzed using 16S rRNA gene and whole-genome shotgun metagenomics method.
The results showed that alpha diversity was significantly lower in DLBCL patients compared to healthy controls ($P < 0.001$) and that there was a significant difference in microbial composition between the two groups ($P < 0.001$). The abundance of the Enterobacteriaceae was significantly higher in DLBCL patients. The functional analysis revealed that type 1 pili expression, biofilm formation, and antibiotic resistance genes were associated with DLBCL. Patients who experienced febrile neutropenia and relapse or progression had a significant enrichment of Enterobacteriaceae ($P < 0.001$). Additionally, higher abundance of Enterobacteriaceae was correlated with shorter progression-free survival ($P = 0.007$). Cytokine profiles of patients with an Enterobacteriaceae-enriched microbiome showed significant associations with interleukin 6 ($P = 0.035$) and interferon-g ($P = 0.045$) levels.
In conclusion, the results of this study demonstrate the presence of gut microbial dysbiosis in patients with DLBCL. The abundance of the Enterobacteriaceae family was found to be associated with treatment outcomes and febrile neutropenia. Given these observations, it is anticipated that the efficacy of R-CHOP treatment in DLBCL patients could be predicted through analysis of the gut microbiome and further improved through modulation of the abundance of Enterobacteriaceae.

CS02-3

Bispecific antibody: ABL Bio

Jonghwa Won
ABL Bio Inc., Korea

Taming T cells has been a long-cherished projects to provide the protective immunity in patients with cancers, however, mostly ended with unsuccessful clinical outcomes with serious side effects. Innovative designing of bispecific antibodies made these old wishes come true by triggering target-specific T cell activation. In our study, asymmetric CD3 T cell engager and Grabody T assets resulted in tumor-associated antigen-dependent T cell activation and cytotoxicity. With promising efficacy and safety data, CD3 and 4-1BB T cell engagers warrant further clinical studies.

CS02-4

KF1601, a novel orally bioavailable inhibitor of Bcr-Abl T315I, without thrombotic microangiopathy

Sung-Min Ahn
ImmunoForge Inc., Korea

Targeting Bcr-Abl with tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of chronic myeloid leukemia (CML) by significantly improving patients' survival. However, the gatekeeper mutation T315I confers resistance to TKIs targeting Bcr-Abl, presenting a formidable task in CML's clinical management. Ponatinib is the most widely used drug for Bcr-AblT315I, but often accompanies severe, life-threatening side effects. Herein, we report KF1601, a novel orally bioavailable TKI. 1) It inhibited kinase functions of both Bcr-AblWT and Bcr-AblT315I with nanomolar IC50 values; 2) In orthotopic in vivo models using Ba/F3 Bcr-AblT315I cell line, it showed promising in vivo antitumor efficacy, comparable to that of ponatinib; 3) In animal models, it did not cause thrombotic microangiopathy, a major mechanism of ponatinib's toxicity. In summary, KF1601 is a promising drug candidate for safely treating CML patients with drug-resistant Bcr-AblT315I mutation.

ICKSH 2023

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SCIENTIFIC SESSION

SS01-1

How to diagnosis and treat neutropenia in childhood

Kelly Walkovich
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Neutropenia, defined as an absolute decrease of segmented neutrophils and bands in the peripheral blood, is a common laboratory finding in childhood. Classically, the degree of neutropenia is divided into mild (ANC 1000-1499 cells/μL), moderate (ANC 500-999 cells/μL) and severe (ANC < 500 cells/μL). However, these subdivisions are only applicable for children greater than 1 year of age and fail to account for ethnic differences in ANC normal ranges, e.g. Duffy null associated neutrophil counts. Importantly, this historical neutropenia classification system is also limited in that the ANC only reflects the 3-5% of neutrophils in circulation within the peripheral blood pool without consideration of the reserve and proliferative pools found in the bone marrow. Thus, while it is helpful in predicting the infectious risk of patients with compromised reserve/proliferative pools, it does not have the same instructive utility for other etiologies of neutropenia.

In pediatrics, the most likely causes of neutropenia are driven by age, underscoring the importance of an age-specific history and approach to evaluation. For neonates, appreciating the impact of gestational age, maternal health and delivery complications on neutrophils is of critical importance to deducing the etiology of neutropenia. For infants and children, eliciting post-infectious, nutritional, and medication-related contributors is most useful as these are common, often reversible, drivers of neutropenia within this age group. For adolescents, screening like that for infants/children should be obtained and supplemented with additional queries for rheumatologic conditions, eating disorders and recreational drug/substance exposures to inform the differential diagnosis. Regardless of age, maintaining a high index of suspicion for rare diagnoses, particularly inborn errors of hematopoiesis (IEH) and inborn errors of immunity (IEI), is valuable as neutropenia may be the first presenting sign and serve as a diagnostic clue for the underlying disorder.

The physical exam for the neutropenic patient is best focused on the oral cavity where clinically significant neutropenia is often evidenced by oral ulcers, gingivitis, periodontitis, or other dental abnormalities. Assessing for exam features, e.g. skeletal anomalies, integumentary changes or lymphoproliferation, supportive of specific underlying IEH/IEI is also recommended.

While all patients benefit from review of a complete blood count with differential and peripheral smear, the remainder of the diagnostic evaluation should be tailored to the patient age and presenting clinical features. If a satisfactory etiology of neutropenia is not elucidated upfront, then a bone marrow aspirate/biopsy should be considered. Recognizing children with an insufficient neutrophil reserve pool or limited capacity to augment myelopoiesis is critical as these patients are most at risk for serious infectious complications and benefit from rapid institution of supportive measures during infectious episodes. Germline genetic testing and functional immune assays may also be warranted to secure a definitive diagnosis. Leveraging the diagnostic algorithm to identify children with an underlying IEH/IEI is valuable as it facilitates personalized prognostication for the risk for bone marrow failure, malignancy or additional organ dysfunction while also providing insights to the utility of granulocyte colony stimulating factor, molecular targeted therapies, hematopoietic stem cell transplant and prenatal counseling.

SS01-2

Updates in the treatment of pediatric relapsed/refractory acute myeloid leukemia

Keon Hee Yoo
Sungkyunkwan University School of Medicine, Korea

Although the treatment outcome of patients with pediatric acute myeloid leukemia (AML) has improved over the last several decades, the overall survival remains suboptimal reaching up to 70% with contemporary chemotherapy protocols with or without hematopoietic stem cell transplantation (HSCT). Besides, the outcome is much more disappointing in those with relapsed or refractory (R/R) AML, and HSCT is considered the only curative option for these patients. With FLAG (fludarabine, cytarabine, G-CSF) regimen with or without anthracyclines having been most widely used in real world practice as a reinduction regimen, various combinations of intensive chemotherapy, epigenetic agents, antibody-drug conjugates, and cell-based immunotherapy have been tested for the purpose of proving their safety and efficacy in pediatric R/R AML. Given the heterogeneity of R/R AML, understanding the genomic landscapes and individualized approach may also pave the way to further improvement in their outcomes. In this context, recent updates on the progress for the treatment of pediatric R/R AML will be reviewed and discussed.

SS01-3

Use of chimeric antigen receptor (CAR) expressing T cells for acute lymphoblastic leukemia (ALL)

Michael Verneris
Children's Hospital Colorado, USA

CAR T cells have revolutionized the care of patients with relapsed and refractory B cell malignancies. In this presentation, I will be discussing the biology of CAR T cells and the clinical outcomes in ALL. In particular, the Eliana Trial ("Study of Efficacy and Safety of CTL019 in Pediatric ALL Patients" (ELIANA) NCT02435849) lead to the licensing of Tisagenlecleucel in the U.S. I will address the post-marketing reproducibility of this study using data from the "Real World" Consortium. As well, I will address the challenges of when to collect CAR T cells in patients with ALL, the use of CAR T cells in "special patient" populations (infants, Down syndrome and obesity) and the tracking of residual disease (flow cytometry and next generation sequencing) and speculate on whether CAR T cells should be used as a bridge to allogeneic transplantation or as a "stand alone" therapy. Lastly, I will share data on the response to re-infusion of CAR T cells and the immunogenicity of CD19 directed CARs.

SS02-1

Pathogenesis of Hodgkin lymphoma

Ralf Küppers
University of Duisburg-Essen, Germany

Various key aspects of the pathogenesis of Hodgkin lymphoma (HL) are currently under intensive investigation. This presentation aims to highlight recent developments in the field. Our understanding of the mutational landscape of Hodgkin and Reed/Sternberg (HRS) cells is evolving, based on exome and whole genome sequencing studies of isolated HRS cells. For lymphocyte predominant HL, a recent study provided evidence for a role of combined antigenic and superantigenic triggering of the lymphoma cells and/or their precursors by bacterial antigens in lymphoma pathogenesis. Gene expression studies of HRS cells point to a close relationship of these cells to the rare normal CD30+ B cells. HRS cells indeed highly and consistently express CD30 on their cell surface, which is used for its diagnosis and also for targeted therapy with drug-conjugated CD30-specific antibodies. However, the role of CD30 in the pathogenesis of classic HL is not well understood and controversially discussed. We characterized CD30-depleted HL cell lines and identified a growth disadvantage under competitive growth conditions and increased cell death. Furthermore, contribution of CD30 signaling to the high MYC activation signature of cHL cell lines was identified. These results point to an important role of CD30 expression by HRS cells for the pathobiology of cHL.

SS02-2

Emerging cellular therapy in Hodgkin lymphoma

Natalie S Grover
The University of North Carolina at Chapel Hill, USA

Although the majority of patients with classical Hodgkin lymphoma (cHL) are cured after initial therapy, about 20-30% of patients have relapsed or refractory disease. cHL is characterized by a small number of malignant cells that universally express CD30 in in an inhibitory tumor microenvironment. Therefore, there has been interest in targeted and immune based therapy to treat this disease. The introduction of novel therapies such as the anti-CD30 antibody drug conjugate, brentuximab vedotin, and checkpoint inhibitors has greatly changed the treatment paradigm of cHL with these treatments being moved to earlier lines. However, treatment options for patients who are refractory or have progressed after BV and checkpoint inhibitors are limited. Given the success of chimeric antigen receptor (CAR) T cells in B-cell non-Hodgkin lymphoma, there has been significant interest in investigating this approach in cHL. This talk will review the current results of clinical trials of CD30 directed CAR-T cells in cHL. We will also review approaches of improving the efficacy of this therapy including increasing trafficking to the tumor site with CAR-T cells co-expressing CCR4 and combination therapies with checkpoint inhibitors. Finally, we will discuss future directions of cellular therapies in cHL and where CAR-T cells may fit in the treatment landscape.

SS02-3

Novel treatment of relapsed/refractory Hodgkin lymphoma

Hyeon-Seok Eom
National Cancer Center, Korea

About a quarter of patients relapse after a frontline chemotherapy and these patients can be treated with salvage chemotherapy regimen. Transplant-eligible patients undergo high-dose chemotherapy and autologous hematopoietic stem cell transplantation (auto-SCT). Recent studies have been done to see whether the addition of new agents such as brentuximab vedotin or checkpoint inhibitors (CPIs) including anti-PD-1 antibodies to salvage therapy might increase the response rates and increase the number of patients who can get an auto-SCT subsequently. For those patients who relapse following auto-SCT, multiple treatment options are available, including single-agent chemotherapy, combination chemotherapy strategies, radiotherapy, antibody-drug conjugates (ADCs) brentuximab vedotin, checkpoint inhibitors (CPIs) nivolumab and pembrolizumab, lenalidomide, everolimus, or observation in selected patients. Recent improvements in outcomes in patients with early relapse after auto-SCT are mainly attributable to the use of novel agents, including ADCs and PD-1 blocking antibodies.
In patients with an available transplant donor, allogeneic SCT (allo-SCT) could be considered. Brentuximab vedotin followed by allo-SCT can be an option. Because allo-SCT still have a role, haploidentical transplantation with post-transplant cyclophosphamide (PT-Cy) in patients without HLA-matched donors should be considered. However, allo-SCT is still associated with substantial morbidity and mortality. In this novel agent's era, some patients can be cured without transplant. Optimal timing of allo-SCT is not clearly determined in the era of new drugs. Safety concerns with CPIs are exist in pre- and post-allo-SCT.
Other promising approaches are combination therapy of Brentuximab vedotin with CPIs such as nivolumab and ipilimumab, chimeric antigen receptor (CAR) T-cell therapy, and novel ADCs. Although CAR T cell therapy in Hodgkin lymphoma is still in its early stage of development, it has been shown to be safe with very promising clinical activity. The new ADCs, ADCT-301 (camidanlumab tesirine) is an ADC targeting CD25 and conjugated to a pyrrolobenzodiazepine dimer toxin and highly effective. With the advent of new drugs in the field of treatment, changes in treatment patterns and improved clinical outcomes are expected.

SS03-1

Aplastic anemia: Current management considerations

Emma M. Groarke
National Institutes of Health, USA

Aplastic anemia (AA) is a blood rare disorder characterized by pancytopenia and marrow hypocellularity. The commonest etiology is immune, and the underlying pathophysiology includes stem cell destruction by activated CD8+ T lymphocytes leading to increase in inflammatory cytokines and cell apoptosis.

Current management strategies for treatment naïve severe AA (SAA) include immunosuppressive therapy (IST) or bone marrow transplant (BMT). Treatment algorithms depend on the patients age and donor availability, with transplant being increasingly favored in younger patients due to improved outcomes. Bone marrow transplant is the only curative therapy for SAA but carries risks of treatment related mortality, graft versus host disease (GVHD), and graft failure. Immunosuppressive therapy carries less upfront risk, but patients have a long-term risk of clonal evolution to myeloid malignancy and relapse.

In children, matched unrelated donor transplant is increasingly being used for upfront SAA therapy due to superior event free survival and similar overall survival (OS) compared to IST. In contrast, OS for adults >40 years transplanted for SAA continues to be poorer, favoring IST as upfront therapy. Haploidentical BMT is increasingly being used in SAA and recent studies have shown favorable OS, and low rates of acute and chronic GVHD can be attained.

Despite many attempts to improve hATG and cyclosporine combination therapy developed in the 1980s, it was not until 2017 that the addition eltrombopag was shown to improve hematologic response rates. Now with ~5 year median follow up, relapse remains an issue with hATG/CSA/EPAG therapy, and ongoing research is required to mitigate this risk; sirolimus is currently being studied in an NIH clinical trial. Romiplostim has recently shown promise in relapsed and refractory AA patients, and recently published data using JAK inhibition in a murine AA model is also currently being developed into a clinical trial.

Clonal evolution is one of the most feared complications after IST; it can be broken down into "high" risk (chromosome 7 abnormality, complex karyotype, or morphologic dysplasia) or "low" risk (isolated non-7 non-complex abnormal karyotype in the absence of dysplasia). Low-risk evolution confers a similar OS to non-evolvers, while high-risk evolution confers s poor OS which may only be mitigated by BMT. Age is the strongest predictor of high-risk clonal evolution; recently somatic mutations in myeloid cancer genes RUNX1, splicing factors, and ASXL1 have also been shown to predict for clonal evolution when detected at 6 months after IST. Eltrombopag may increase clonal evolution in the refractory setting but has not been shown to predict for high-risk evolution when used in combination with cyclosporine and hATG in the upfront setting, though long term follow up is still required.

SS03-2

Clinical and molecular factors of clonal evolution in aplastic anemia

Jaroslaw P. Maciejewski
Cleveland Clinic, USA

Clonal evolution to either paroxysmal nocturnal hemoglobinuria (PNH) or myeloid neoplasia (post-AA MN) constitute medically important complications of idiopathic aplastic anemia (AA). Among them, post-AA myelodydplastic syndrome (MDS) and acute myelogenous leukemia (AML) are particularly serious and require hematopoietic stem cells transplantation for cure. Post-AA MNs are characterized by a distinct pattern of associated somatic mutations and a high prevalence of 7q deletion or monosomy-7 (-7del7q), which could point towards existence of specific germ line predisposition in selected patients. According to one possible theory, clonal evolution may correspond to somatic gene rescue (SGR) in the context of deficient function of hematopoietic stem cells impaired by the AA immune attack. While clonal hematopoiesis may represent adaptive SGR, only in the context of genetic specific hits it can initiate post-AA MN (maladaptive SGR). Such hits may precede -7del7q. It is possible that founder clones for post-AA MN are present early in the course of disease and may serve as triggers for immune attack directed toward elimination of genetically aberrant cells. Such a reaction could cause bystander damage and ultimately lead to clonal escape. Finally, immune selection via acquisition of PIGA or HLA mutations also correspond to a special type of SRG. We explore here the molecular mechanisms of most possible mechanisms of clonal evolution, describe clinical features of the most common presentations, risk factors and clinical management.

SS03-3

Non-transplant therapy for pediatric aplastic anemia

Jae Wook Lee
College of Medicine, The Catholic University of Korea, Korea

A key non-transplant treatment for pediatric severe aplastic anemia is immunosuppressive therapy (IST) with anti-thymocyte globulin and cyclosporine. IST may result in an overall response rate of 70% and complete response (CR) rate of 23-60% in children with SAA. However, disease relapse and clonal evolution may limit long-term event-free survival to 50-60%. Eltrombopag is an oral thrombopoietin-receptor agonist that may improve the blood counts of SAA patients by stimulating hematopoietic stem cell expansion. Studies based mostly on adult patients have shown that eltrombopag monotherapy may result in multi-lineage responses in patients who have failed previous IST. Furthermore, eltrombopag combined with standard IST (horse ATG and cyclosporine) may result in higher response rates than found in historical cohorts treated with IST only. The results of eltrombopag combined with IST in pediatric SAA patients have been conflicting. A subgroup analysis of a National Institutes of Health trial of eltrombopag with IST showed that the addition of eltrombopag did not improve the outcomes of children with treatment-naïve SAA compared with a historical IST only cohort. In contrast, a recent randomized clinical trial found that treatment with eltrombopag and IST resulted in a higher CR rate overall, and a higher overall response rate specifically for SAA patients. Higher pre-treatment reticulocyte count, higher neutrophil count, and reduced thrombopoietin levels may predispose to better response to eltrombopag with IST.
Genetic abnormalities in telomere maintenance may also result in bone marrow failure. Treatment with danazol, a synthetic sex hormone, results in telomere elongation which translates into hematologic response.
Overall, although a human leukocyte antigen matched donor hematopoietic stem cell transplantation remains the first-line treatment for pediatric SAA, the recent introduction of novel drugs for therapy has allowed for improvement in the cytopenia of pediatric SAA.

SS04-1

Diagnosis and treatment of TA-TMA; Current challenge and future strategies

Sandro Rossetti
Alexion Pharmaceuticals, Inc., USA

SS04-2

Genetics of inherited thrombocytopenia

Kathleen Freson
University of Leuven, Belgium

Inherited thrombocytopenia is characterized by marked genetic heterogeneity. Most patients have spontaneous or trauma-related bleeding problems, but they can also present with clinical symptoms outside the blood system. The classification of inherited thrombocytopenia in diagnostic algorithms was typically driven by the presence or absence of other clinical features besides a platelet defect (syndromic versus non-syndromic), the mode of inheritance (recessive, dominant and X-linked) and the platelet size (macro, micro and normal size platelets). Applying such algorithm was very useful since the numbers of genes implicated in inherited thrombocytopenia was less than half of the genes we know today. At this moment, already 38 diagnostic-grade genes have already been found to cause inherited thrombocytopenia. Since the discovery of many novel genes for inherited thrombocytopenia using next generation sequencing approaches over the last decade, phenotype-genotype associations for this disorder have become very complex. In addition, the mode of inheritance has expanded for well-known genes. To date, multigene panel testing is typically used to diagnose inherited thrombocytopenia by investigating all diagnostic-grade genes involved in this pathology in a single analysis. A diagnostic rate of 50-60% can be expected from such test, depending on prescreening for immune thrombocytopenia. The major drawback of performing a multigene panel test for inherited thrombocytopenia is the detection of many variants of unknown significance and unsolicited findings. On the other hand, genetic data can influence the clinical management of patients with inherited thrombocytopenia and examples will be discussed.

SS04-3

Advances on pathogenesis and diagnosis of TTP

Hyun Kyung Kim
Seoul National University College of Medicine, Korea

Thrombotic thrombocytopenic purpura (TTP) is a fatal thrombotic microangiopathy, characterized by a severe thrombocytopenia, microangiopathic hemolytic anemia and organ ischemia caused by disseminated microvascular platelet-rich thrombi. It is caused by a severe deficiency of the enzyme ADAMTS13, which is mainly resulted from autoantibodies targeting ADAMTS13 (immune TTP), but rarely from mutation in the ADAMTS13 gene (congenital TTP, Upshw-Schulman syndrome). Recent advances in fundamental and translation research on ADAMTS13 and TTP have improved the understanding of diagnosis and management for TTP, though still lots of questions remain unanswered. This presentation will deal with current advances of pathogenesis and diagnosis for TTP.

SS05-1

Artificial intelligence in hematology: basic concepts

Roni Shouval
Memorial Sloan Kettering Cancer Center, USA

The digitalization of data has transformed almost every aspect of health care. Each interaction with a patient generates vast quantities of electronic data. Free text describing the patient's encounter, vital signs, labs, pathology results, and imaging are just some examples of data integrated into the electronic medical record. More recently, patient-generated health data includes multi-omics data (e.g., genomics, proteomics, metabolomics), amounting to unprecedented data complexity. Based on their training, experience, and intuition, clinicians formulate a working hypothesis and act upon it. However, the human mind is limited by its perceptions and biases. Artificial intelligence (AI) and machine learning offer tools to meaningfully process volumes of data exceeding the capacity of the human brain's comprehension. There is both much hope and hype surrounding their application in medicine. In the presentation, I aim to expose clinicians and investigators to basic concepts in AI and machine learning and discuss potential implications. In addition, I will provide guidance on the design and appraisal of machine learning studies.

SS05-2

How machine learning deepens our understanding of hematologic malignancies

Valeria Visconte
Cleveland Clinic, USA

Machine learning (ML) has allowed the recognition of genomic patterns in high dimensional space. Common lists of ML algorithms span from linear and logistic regression, decision tree and random forest, to gradient boosting in order to increase robustness of prediction. The advent of several ML approaches has motivated the hematology field to investigate the pro and contra of using them. Applicability of ML has been shown in a variety of contexts including cytogenetics and molecular analyses to detect malignant cell populations and medical imaging to surpass limitations and challenges due to diagnostic ambiguity.

Given the heterogeneity and complexity of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) classifications, clinical prognostication does not often reflect disease pathogenesis and new strategies may be needed to deconvolute the molecular diversity. Beside the current practicability of classification schemes according to clinical features (cytogenetics, molecular mutations), ML algorithms can be helpful in improving the resolution of prognostication models by integrating complex genomic interactions at a high dimensional level. Potential applications are the generation of automated diagnostics of morphologic features, multiparameter flow cytometry and personalized therapeutic models.

This lecture will discuss the use of ML analytic methods to resolve critical matters in myeloid neoplasia and elaborate on the following aspects:

- o ML-based tools to identify relevant sub-entities between primary and secondary AML.
- o The development of clinically viable algorithms to improve prognostic precision in clinical settings by resolving TP53 allelic configurations in MDS.
- o The integration of multi-omics data combining gene mutations, clonal architecture, and transcriptomic profiles (gene expression and RNA-splicing) to inform new therapeutics in MDS.

SS05-3

Pitfalls of AI for medical application

Jongmun Choi
Seegene Medical Foundation, Korea

In the near future, the introduction of artificial intelligence in the medical field will proceed rapidly. Hematology is an especially promising field for the use of artificial intelligence, such as digital pathology, and cancer genetics for hematologic cancer. Recently, artificial intelligence, especially deep learning, has developed remarkably. However, if we want to develop or introduce medical artificial intelligence, we need to consider serious problems that may arise.

First, we don't have a transparent way to look into why deep learning-based algorithms make such decisions. This infamous "block-box problem" will be one of the biggest obstacles to the adoption of medical AI. Second, we must address the inevitable data shortage and imbalance problem in the medical AI development. Third, we will have to solve the practical problems about big data management, like data generation, storing, and processing.

These problems can't be solved by technology alone. We need to understand the incompleteness of medical AI and prepare workflows that can compensate for it. In addition, cooperation between researchers and capital investment for big data management would be required.

SS06-1

Identification of high-risk multiple myeloma

Niels van de Donk
Amsterdam University Medical Center, The Netherlands

The identification of newly diagnosed multiple myeloma (MM) patients with a poor survival is important for the initiation of risk-adapted therapy, such as double autologous stem cell transplant or for inclusion of such patients in specific studies for high-risk disease aiming at improving their prognosis. At the time of diagnosis cytogenetic abnormalities (t(4;14); t(14;16); del(17p); and gain/amp1q) are used to assess survival, whereby patients with two or more abnormalities (double hit MM) have very poor outcomes. Next to cytogenetic abnormalities, also the presence of certain mutations (e.g. p53 mutation) gene, circulating tumor cells, and specific gene expression profile have prognostic value. Functional high-risk is defined as early relapse after transplant or optimal induction therapy. Although the identification of patients has substantially improved over time, there is still a subgroup of patients who develops early first relapse without being classified as high risk at diagnosis. Patients with early relapse may benefit from access to novel therapies, especially T-cell immunotherapies (bispecific antibodies and CAR T-cell therapies).

SS06-2

Updated diagnosis and treatment of plasma cell leukemia

Sung-Hoon Jung
Chonnam National University Hwasun Hospital, Korea

Plasma cell leukemia (PCL) is a rare plasma cell dyscrasia with a dismal prognosis. In 1974, Kyle developed diagnostic criteria of PCL, which required both more than 20% circulating plasma cells and an absolute count greater than 2 x 109/l plasma cells in peripheral blood. Diagnostic criteria of PCL proposed by Kyle were not based on the results of prospective studies, and the cutoff peripheral plasma cell level was thus artificial. Two recent retrospective studies explored the optimal peripheral plasma cell cutoff number. A study of 482 Spanish patients evaluated survival outcomes by the percentages of circulating plasma cells; thus 0, 1-4, 5-20, and more than 20%. A Mayo Clinic study reviewed the survival outcomes of 176 patients with circulating plasm cell proportions of 1-4, 5-19, and ≥20%. The survival outcomes of patients with ≥5 and ≥20% circulating cells were similar in both study, and patients with ≥5% had inferior survival than those with less than 5%. Thus, the IMWG recently revised the diagnostic criterion of primary PCL to 5% or more circulating plasma cells in peripheral blood smears. Recently, the Korean Multiple Myeloma Working Party performed the multicenter retrospective study and showed that the revised criterion of CPCs ≥ 5% in a peripheral blood smear is appropriate for PCL diagnosis. The median overall survival (OS) of patients with CPCs ≥ 5% and ≥ 20% was similar, but had significantly inferior median progression-free survival and median OS than those with CPCs < 5%. Primary PCL diagnosed using the revised criteria presented with higher total calcium levels and serum creatinine levels, lower platelet counts and frequent organomegaly and plasmacytoma at diagnosis. As primary PCL is rare, only a few studies have explored appropriate treatments; most were both small and retrospective. The therapeutic recommendations are similar to those for multiple myeloma. In general, primary PCL requires prompt intensive therapy with novel agents to decrease early mortality and disease-related complications. In transplant-eligible patients, autologous stem cell transplantation (ASCT) followed by maintenance therapy is recommended. Maintenance with lenalidomide may reduce early relapse after ASCT. Immunotherapies using monoclonal antibodies, CAR-T cells, bispecific T-cell engagers, or antibody-drug conjugates may further improve the prognosis of primary PCL

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SS06-3

Safety and efficacy of locally produced novel BCMA CART cells for relapsed/refractory multiple myeloma and al amyloidosis

Moshe Gatt
The Hebrew University of Jerusalem, Israel

Excellent response achieved by Chimeric Antigen Receptor T (CART) cell therapy targeting B-Cell Maturation Antigen (BCMA) in multiple myeloma (MM) makes this treatment a great promise. To advance the treatment of MM in Israel, we have developed a novel CAR molecule for BCMA targeting (i.e. HBI0101) and assessed its activity both in vitro and in vivo. Based on our results, we obtained approval from the Israeli Ministry of Health to carry out a clinical trial using HBI0101 for the treatment of relapsed refractory (R/R) MM (NCT04720313). At the beginning of 2021, a phase Ia/Ib clinical trial, aimed at evaluating HBI0101 safety and efficacy was initiated. Thirty-six heavily pretreated R/R MM patients and 5 AL amyloidosis patients were administrated with HBI0101 at Hadassah Medical Center. The median age was 62 with a median of five previous treatment lines. Six patients were infused with 150-million HBI0101 cells, seven with 450-million, and 28 with 800-million cells. Two patient had grade 3 cytokine release syndrome (CRS). No grade 4 CRS was recorded and none of the patient had immune effector cell-associated neurotoxicity syndrome, confirming that HBI0101 is well tolerated. Overall response rate was 50%, 85% and 91% for 150-, 450- and 800-million cells, respectively. At the dose of 800-million cells, 39% achieved complete response, 48% achieved very good partial response and 4% achieved partial response. Most of these achieved minimal residual disease negativity. The median follow up of patients treated with 800-million cells was 132 days and at this time both the median progression free survival and median overall survival were not reached. Altogether, HBI0101 therapy for R/R MM and for the first time reported- AL Amyloidosis patients, proves safe with manageable toxicities and promising responses.

SS07-1

Engineering next-generation T cells for cancer immunotherapy

Yvonne Chen
University of California, USA

The adoptive transfer of T cells expressing chimeric antigen receptors (CARs) has demonstrated clinical efficacy in the treatment of advanced cancers, with anti-CD19 CAR-T cells achieving up to 90% complete remission among patients with relapsed B-cell malignancies. However, challenges such as antigen escape and immunosuppression limit the long-term efficacy of adoptive T-cell therapy. Here, I will discuss the development of and clinical data on next-generation T cells that can target multiple cancer antigens and resist antigen escape. I will also present recent work on tuning CAR signaling activities via rational protein design to achieve greater in vivo anti-tumor efficacy. This presentation will highlight the potential of synthetic biology in generating novel mammalian cell systems with multifunctional outputs for therapeutic applications.

SS07-2

Development of CAR-T therapy for acute lymphoblastic leukemia

Hyoung Jin Kang
Seoul National University College of Medicine, Korea

The cure rate of acute lymphoblastic leukemia (ALL) in children dramatically improved over past 5 decades from zero to about 80-90%. The main cause of improvement was owing to the development of chemotherapy by multicenter clinical trial of large study groups with the understanding of leukemia biology. Despite the improvement of outcomes in pediatric ALL, there were some remained problems and the outcome of relapsed/refractory patients remained very poor. To overcome this problem, anti-CD19 chimeric antigen receptor introduced T cells (CAR-T) had been developed and approved by US FDA as a breakthrough therapy for relapsed/refractory pediatric ALL with promising results. Although CAR-T therapy showed dramatic effect, it is not perfect yet and need modification of development in terms of efficacy and safety. Also the complexity and variability of manufacture process and high prices are remaining hurdles. The development of CAR-T and current direction of its use will be presented in this talk.

SS07-3

Updates on the latest developments in CAR-T therapies

Hiroshi Fujiwara
Mie University, Japan

Facilitated by commercial availability of CAR-T products, CD19 CAR-T therapy has currently emerged as a potent therapeutic option for the treatment of relapsed/refractory (r/r) B-lymphoid blood cancers in daily practice. And now, B cell maturation antigen (BCMA) specific CAR-T therapy against r/r multiple myeloma (MM) is chasing after. Accumulated lines of clinical evidence have revealed challenges to derive desired level of its effectiveness, which include design and manufacturing of CAR-T cells, management of CAR-T therapy itself (lymphodepleting, bridging therapy, combination strategy, and so on) and management of patients' condition (achieving desired physical status for infusion of CAR-T cells, and mitigating toxicities, such as CRS and ICANS). Consequently, huge efforts to address those challenges and to maximize the potential of CAR-T therapy have been being made at this very instant.

Design of CAR-T cells largely being engaging the construction of those efforts, includes engineering of CAR gene and manipulating immune cells being CAR gene-transduced. CAR gene engineering is currently aiming at improving functional persistence (e.g., endowing the resistance to exhaustion) and mitigating adverse events including CRS/ICANS, expanding array of target molecules for CAR-T cells and clinical accessibility of CAR-T therapy. Manufacturing is aiming at expanding spectrum of immune cells transduced with CAR-gene, and also clinical availability.

Here, in this talk, I am going to focus on the design and manufacturing of CAR-T cells to address current challenges with some of our own on-going attempts.

SS08-1

Genotyping of hemophilia, why we need it and how we do?

Jill Johnsen
University of Washington, USA

Brief Summary. Hemophilia gene sequencing is clinically useful for diagnosis, risk of developing neutralizing antibodies against the affected coagulation factor (inhibitors), pregnancy and neonatal management, and family counseling. New genomic technologies can detect multiple kinds of DNA changes with high sensitivity. Systematic collection of genotype-phenotype data is important to better understand the genetics of hemophilia.

Hemophilia background. Hemophilia A and hemophilia B are rare inherited X-linked bleeding disorders caused by deficiencies in coagulation factor VIII (FVIII) or factor IX (FIX), respectively. FVIII is encoded by the F8 gene, and FIX is encoded by the F9 gene. In males, the most common patterns of bleeding involve joints, soft tissue, and provoked bleeding. Females can also have excessive mucocutaneous bleeding and reproductive tract bleeding. Hemophilia severity is defined by coagulation factor activity levels: severe hemophilia is defined as < 1% activity, moderate hemophilia is defined as 1% to < 5% activity, and mild hemophilia is defined by levels 5–40% activity. In males, coagulation factor activity levels generally correlate with bleeding. Females can have excessive bleeding even with factor activity levels in the normal range.

Hemophilia genotyping. Hemophilia genotyping is a high yield test. Clinically reportable DNA variants are detected in nearly all (>98%) males with hemophilia A or B. Genotyping is particularly useful in females where factor levels can be normal and are not well correlated with bleeding severity.

The most common types DNA changes found in individuals with severe hemophilia are DNA variants predicted to disrupt gene expression (e.g. gain-of-stop, frameshift, or large structural DNA variants). Missense DNA variants predominate in mild and moderate hemophilia. In severe hemophilia A, recurring F8 intron 1 and intron 22 inversions are associated with intermediate risk of inhibitor formation (~20–36%), while large gene deletions are associated with high risk (~50%). Complex F8 intron 1 and intron 22 inversions have high inhibitor risk similar to deletions. Similarly, in severe hemophilia B, large gene deletions are associated with high rates of inhibitor formation (57%).

Care needs to be taken when interpreting the significance of variation in these genes. Many DNA variants lack sufficient evidence to classify as pathogenic or benign with a high degree of certainty. These are classified as DNA variants of Uncertain Significance until more evidence can be gathered to support accurate interpretation.

When there is no DNA variant found (NVF) in individuals with severe hemophilia A, the rate of inhibitor formation is high, suggesting that there is a causative DNA variant disrupting the gene that has been missed by current genotyping methods. Alternately, some individuals with non-severe hemophilia and NVF genotypes may have been incorrectly diagnosed. Misdiagnosis of hemophilia A can occur with von Willebrand disease or combined deficiency of coagulation factor V and VIII. Vitamin K-dependent coagulation factor deficiency can be misdiagnosed as hemophilia B.

Comprehensive, unbiased DNA sequencing methods have become a necessity in hemophilia genotyping. Novel (previously unknown) DNA variants are still commonly found, and some individuals may have more than one causative DNA variant. New technologies are being adopted in the clinic, including next generation DNA sequencing and long-read DNA sequencing. These methods hold the promise to systematically capture the genetic variation of the whole loci of F8 and F9, including the noncoding regions. Knowledge of the genetic basis of hemophilia is critical to advancing research into the disease, developing new treatments, and for clinical care.

SS08-2

Value of national cohort registry data of hemophilia

Jung Woo Han
Yonsei University College of Medicine, Korea

Hemophilia, a genetic bleeding disorder that affects over 1.2 million patients worldwide, requires life-long treatment and management that can be costly. To help healthcare professionals better understand and manage this condition, hemophilia registries have been established as databases containing patient information such as demographics, bleeding history, treatment, and outcomes. The data is gathered by healthcare providers and stored centrally for tracking incidence and prevalence trends, monitoring treatment outcomes, and identifying research gaps.
One major benefit of hemophilia registries is that they help healthcare providers identify patterns and trends that can inform treatment decisions. By analyzing bleeding history and treatment outcomes data, providers can improve patient outcomes and quality of life. Hemophilia registries also help identify patients at risk of complications, including inhibitor development.
World federation of hemophilia published the guideline for developing a national patient registry. In this article the process of establishing patient registry is explained and the collection forms of data items are listed. In addition, some examples of registries are introduced; a patient organization registry, a medical registry, a government registry and a form of combined registry. In 2018, world bleeding disorders registry (WBDR) was established and the effort is being made to collect the data worldwide.
In Korea, the Korean Hemophilia Foundation (KHF) has developed a registry that has helped patients and families access better treatment. While registration is not mandatory, and nationwide data is limited, the KHF registry has had a positive impact. However, to improve the accuracy and scope of data, the first nationwide hemophilia registry is being developed in Korea. This registry will help healthcare providers better understand hemophilia, leading to better treatment options for patients and improved quality of life.

SS08-3

Essentials of Laboratory Issues in Emicizumab

Sang Hyuk Park
University of Ulsan College of Medicine, Korea

The recent development of emicizumab (Hemlibra, also previously referred to as ACE910; Hoffman-la Roche) extends treatment options for haemophilia A patients, with and without anti-Factor (F) VIII inhibitors, and provides an alternative to FVIII replacement therapy for patients with severe haemophilia A. The novel nature and mode of action of the molecule have implications for the laboratory testing of coagulation parameters in patients receiving this treatment. Emicizumab is an engineered IgG4 bispecific antibody that binds both factor IXa (FIXa) and its substrate factor X (FX). This interaction colocalises the components of the intrinsic tenase complex and improves the ability of FIXa to activate FX in the absence of FVIIIa. It therefore is a FVIII mimetic, in that it acts as a cofactor for FIXa activation of FX. Recently published study has provided some information on the influence of emicizumab on certain coagulation tests, measurement of FVIII in the presence of emicizumab and measurement of emicizumab levels. In this presentation, the issues of laboratory testing in hemophilia A patients who is receiving emicizumab were summarized.

SS09-1

Immune checkpoint inhibition for AML ; CD47 blockade and beyond

Naval Daver
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SS09-2

Determining the barriers to successful CAR T cell therapy for AML

Miriam Y Kim
University of Washington, USA

Acute myeloid leukemia (AML) has thus far proven fairly resistant to T cell redirecting therapies such as bispecific T cell engagers or chimeric antigen receptor (CAR) T cells. We hypothesize that indiscriminate targeting of normal myeloid cells with AML reduces the anti-leukemic effect of CAR T cells. Conversely, removing the target antigen from myeloid cells can improve the efficacy of CAR T cells against AML by permitting sustained myeloid cell support of CAR T cell activity. For example, removing CD33 expression from normal myeloid cells improves CD33-targeting CAR T cell expansion and disease control. By interrogating the mechanisms of these interactions, we aim to achieve a better understanding of how CAR T cells operate, and illuminate methods to intervene within these interactions to improve the outcomes of therapy for AML.

SS09-3

Adoptive T cell transfer of three universal tumor associated antigens-specific T cells for the treatment of AML

Byung Sik Cho
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Relapse is the most frequent cause of death after allogeneic hematopoietic stem cell transplantation (HSCT) for acute myeloid leukemia (AML). Current strategies to treat post-HSCT relapse (chemotherapy and donor lymphocyte infusions) have low efficacy and are associated with graft-versus-host disease. Second allogeneic HSCT is effective in some patients, but not in patients who relapse early after HSCT. New immunotherapeutic strategies, notably transgenic chimeric antigen receptor (CAR) T cells, have shown minimal efficacy in AML to date, whereas encouraging success in patients with lymphoid malignancies with a risk for significant toxicities. Moreover, the shared expression of CAR-targeted AML surface antigens on normal myeloid precursors can incur myelotoxicity.

An alternative strategy to boost the graft-versus-leukemia effect is to infuse donor-derived T cells targeting tumor-associated antigen (TAA) peptides. TAA-specific CD8 and CD4 T cells play a pivotal role in anti-tumor immunity. However, immune surveillance system can be circumvented by leukemic cells that have developed a variety of immune evasion mechanisms. Most tumor cells express high levels of multiple TAA, which accounts for the significantly lower surveillance efficiency of single antigen specific T cells compared with multiple antigen-specific lymphocytes. Thus, cytotoxic T lymphocytes specific to multiple TAAs have a greater ability than single-T cells to effectively kill leukemic cells because they can compensate if one antigen is lost or edited.

In this lecture, I will introduce a novel, multitargeted T-cell therapeutic in an attempt to decrease relapse after allogeneic HSCT in AML. T cells capable of recognizing the three universal antigens are generated to overcome the limitations of known HLA-restricted epitopes. These triple antigens-specific T cells produce anti-leukemia immune responses, and data of early clinical trials will be shared.

SS10-1

A transcriptomic approach to clinical diagnosis, prognosis and therapy selection in AML

Aly Karsan
University of British Columbia, Canada

Clinical genetic testing in the myeloid malignancies is undergoing a rapid transition from the era of cytogenetics and single-gene testing to an era dominated by next-generation sequencing (NGS). This transition promises to better reveal the genetic alterations underlying disease, but there are distinct risks and benefits associated with different NGS testing platforms. NGS offers the potential benefit of being able to survey alterations across a broader set of genes, but analytic and clinical challenges associated with incidental findings, germline variation, turnaround time, and limits of detection must be addressed. Additionally, transcriptome-based testing may offer several distinct benefits beyond traditional DNA-based methods. This presentation will examine the potential for genome-scale testing in the clinic with a particular focus on RNA-Seq as a diagnostic, and its potential role in revealing mechanisms of therapy resistance.

SS10-2

Whole genome sequencing of fluorescence in situ hybridized cells in hematologic malignancies using SLACS

Sunghoon Kwon
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Cancer is spatially heterogeneous in terms of genetic molecules. Revealing genomic, epigenomic, transcriptomic, and epitranscriptomic features that are unique to the malignant cell populations within cancer lead to cancer biomarker discoveries that can be translated into diagnostic or therapeutic tools. Here, we introduce spatially-resolved laser-activated cell sorting (SLACS) technology coupled to next generation sequencing that analyzes genetic molecules from regions of interest within spatial and phenotypical context. Specifically, we demonstrate application of SLACS in a case of simultaneous occurrence of multiple myeloma and leukemia. Co-occurrence of plasma cell myeloma and acute myelogenous leukaemia is extremely rare, so that five cases are reported globally. Neoplastic plasma cells and myeloblasts commonly originate from multi-potent hematopoietic stem cell, but depending on the clonal acquisition or loss at lower level, they delineate from each other. We identified the clonal changes in heterogeneous hematopoietic lineages by integrating whole genome sequencing, cell morphology, and cytogenetic aberrations at single cell level. We selected each single cell from Wright-Giemsa stained slide or fluorescence in situ hybridised slide, with subsequent whole genome sequencing, using novel Hema-seq technique. By integrating results in each cell lineage, we inferred the sequential clonal changes along the hematopoietic tree, revealing the decisive changes leading to myeloma cell and leukemic cell. Furthermore, examples of discovering cancer biomarker and their mechanism of action within spatial context are provided. Bridging spatial technologies to omics technologies, the discovery of specific markers within spatial context will provide insights into the next generation diagnostics and cancer therapeutics such as cancer vaccines.

SS10-3

Next generation cytogenetics – optical mapping for comprehensive structural variant detection in hematological malignancies and beyond

Alexander Hoischen
Radboud University Medical Center, The Netherlands

Structural variants (SVs) are an important source of genetic variation in the human genome and they are involved in a multitude of human diseases as well as cancer. SVs are enriched in repeat-rich regions of the human genome, and several remain undetected by conventional short-read sequencing technologies.
We now applied Bionano Genomics' high-resolution optical mapping to comprehensively identify SVs in a clinical research setting.
We previously performed two proof-of-concept studies for clinical use: 1.) to show 100% concordance in 85 samples with 99 clinically relevant constitutional aberrations [1] ; 2.) to comprehensively detect somatic SVs on 52 leukemia samples, and allowed the 100% concordance for all aberrations with >10% variant allele fraction that previously required a combination of karyotyping, FISH and/or CNV-microarray [2]. The latter is now confirmed with a prospective clinically utility with >50 AML samples – demonstrating that OGM is ready for clinical use.
In addition, optical mapping allowed the identification of SVs that remained refractory to detection by classical methods including MLPA, Sanger sequencing, exome and/or genome sequencing. This allowed the identification of likely disease causing SVs in several previously undiagnosed rare disease cases.
In summary, the full concordance with diagnostic standard assays for hematological malignancies and constitutional aberrations demonstrates the potential to replace classical cytogenetic tests. We furthermore show how the complementary use of mapping rather than sequencing approaches can unmask hidden SVs in rare disease research.

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SS11-1

Cell-free DNA profiling for monitoring of complications of hematopoietic cell transplantation

Iwijn De Vlaminck
Cornell University, USA

This presentation will focus on the potential of cell-free DNA as a versatile analyte for monitoring post-transplant complications after hematopoietic cell transplantation (HCT), the gold standard treatment for many blood disorders, including blood cancers. Frequent complications such as Graft-Versus-Host Disease, infection, graft failure, and disease relapse limit the long-term benefit of HCT. Our recent work demonstrated that a single cell-free DNA sequencing assay followed by disease-specific bioinformatic analyses can inform on these therapeutic complications. The test only requires low coverage DNA sequencing and small blood volumes. Cell-free DNA has the potential to improve care for allogeneic HCT recipients by enabling earlier detection and better prediction of post-transplant complications.

SS11-2

Towards non-invasive monitoring of disease and microbe invasion in patients with hematologic malignancies

Charles Gawad
Stanford University, USA

The high cures rates of children with acute lymphoblastic leukemia (ALL) requires the use of ten or more antineoplastic drugs in various combinations over two to three years, resulting in significant short and long-term morbidity and mortality. In addition to disease recurrence, one of the most important complications of ALL treatment is the development of invasive infections as a result of immunosuppression from the therapies. Sequencing DNA circulating in plasma has recently been developed as a powerful tool for monitoring cancer formation and treatment response, organ health or rejection, and infectious microbes. I will first discuss our use of microbial plasma DNA sequencing to predict impending bloodstream infections in pediatric patients with recurrent cancer. I will then present a more sensitive plasma DNA sequencing strategy we recently developed to monitor disease status, viral reactivation, and invasive infections in childhood ALL patients as they undergo induction therapy. Finally, I will conclude by discussing our recent development of biochemical and computational tools for sequencing the genomes of single minimal residual disease cells from ALL patients, where our work has uncovered novel mutations that correlate with positive clonal selection and treatment resistance. In summary, this presentation will highlight the technical advances that are enabling us to interrogate the blood of patients with hematologic malignancies in new ways and at higher levels of sensitivity and precision, which could ultimately result in better disease and health monitoring tools that improve the outcomes of our patients.

SS11-3

Clinical applications of circulating tumor DNA analysis in lymphoma

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Circulating tumor-derived DNA (ctDNA) has recently emerged as a promising biomarker in the field of oncology to identify tumor-specific genetic aberrations using peripheral blood testing. Several technical precautions are needed at the pre-analytic stage, and numerous techniques are available to identify these molecular aberrations, ranging from the detection of single point mutations to extended genetic screening panels. Testing ctDNA can sometimes complement pathology results or serve as a proxy approach for particular lymphoma presentations where biopsies are sometimes difficult to perform. Moreover, ctDNA testing can characterize, at diagnosis or during treatment, mutations that may contribute to the choice of an optimal targeted therapy or detect the emergence of resistance to those therapies. Monitoring ctDNA levels during therapy in several lymphoma subtypes (diffuse large B-cell and Hodgkin lymphomas) has been explored. Preliminary studies have demonstrated that this monitoring technique can predict clinical outcomes and that this approach may complement the information provided by metabolic imaging assessments. Also in Extranodal NK/T cell lymphoma, we found that ctDNA analysis can be used to genotype at diagnosis and estimate the tumor burden, and furthermore, monitor therapeutic responses. Technical standardization and careful prospective evaluation of the role of ctDNA monitoring in clinical studies represent current important challenges to allowing its application in routine practice.

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SS12-1

Are we moving towards a chemo- and transplant-free management of Ph-positive adult ALL?

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Ph+ acute lymphoblastic leukemia (ALL) is the most frequent genetic subgroup in adult ALL and its frequency increases progressively with age, accounting for about 50% (or more) of B-lineage ALL in the older patients. Ph+ ALL represents the most illuminating example of how the management and outcome have profoundly changed over the years in ALL. From being the hematologic malignancy with the worse prognostic likelihood, the scenario has changed to such an extent that many patients can be managed without systemic chemotherapy and transplant. Indeed, prior to the advent of tyrosine kinase inhibitors (TKIs), the only possibility of cure was represented by an allogeneic stem cell transplant, doable only in a limited proportion of patients due to the lack of response to conventional treatment and age. Many elderly patients were in fact managed only by palliative treatment.

The scenario has changed when the use of TKIs, that have modified the natural history of chronic myeloid leukemia (CML), was extended also to Ph+ ALL. Initially, TKIs were added to the backbone of the ongoing schemes of multi-agent chemotherapy. This increased the rates of response but was invariably associated with notable toxicity and deaths in induction. This led to the association of a TKI with de-intensified chemotherapy, that proved equally effective with less toxicity. In Italy, over the last 20 years we took a different approach based on the use in induction of only a TKI plus steroids (and CNS prophylaxis) without systemic chemotherapy. The first GIMEMA study was carried out with imatinib in patients older than 60 years and with no upper age limit. The observation that all elderly patients could obtain a hematologic complete remission (CR) led to the subsequent studies with 2nd and 3rd generation TKIs in induction, always without systemic chemotherapy. This approach was associated with hematologic CR rates of 94-100%, with virtually no deaths in induction. A proportion of patients could obtain a molecular response with a TKI alone. Some elderly patients treated only with TKIs remained alive and well after many years from diagnosis.

Two other factors have emerged as key players in the management of Ph+ ALL. The first - which impacts across all forms of ALL - is the knowledge that the primary endpoint of frontline treatment is/should be the achievement of a status of sustained minimal/measurable residual disease (MRD) negativity. The second, specific to Ph+ ALL, is the genetic landscape at presentation. The presence of the so-called IKZF1plus profile has been associated with an unfavorable prognosis.

The results obtained clearly indicated that the induction treatment for adult Ph+ ALL patients of all ages could be based on a TKI alone (plus steroids) without systemic chemotherapy. Induction needed, however, to be consolidated with systemic chemotherapy and/or transplant to improve the deepness of the response and the possibility of cure. Our group again took a different approach and designed a study - GIMEMA LAL 2116, D-ALBA - in which all adult Ph+ ALL patients (with no upper age limit) were treated in induction with the 2nd generation TKI dasatinib followed by a consolidation with a minimum of 2 (up to a maximum of 5) cycles with the bispecific monoclonal antibody blinatumomab. Thus, a targeted treatment in induction followed by immunotherapy with blinatumomab as consolidation. The post-consolidation treatment was left open to the treating physicians. The results, published in October 2020 in the NEJM, showed that this chemo-free induction/consolidation strategy was feasible, associated with very high rates of CR (98%), 60% of molecular responses at the primary endpoint (after 2 cycles of blinatumomab) and rates of overall survival (OS) and disease-free survival (DFS) at 18 months of 95% and 88%, respectively. The rates of molecular responses increased further with additional cycles of blinatumomab. These very positive results have been confirmed at a 3-year and 4-year follow-up analysis. Patients in complete molecular response have so far not relapsed. The unfavorable impact of the IKZF1plus is confirmed at a longer follow-up. Most patients have not undergone systemic chemotherapy nor transplant and remain MRD-negative in CR. In patients who underwent a transplant the transplant-related mortality has been low, presumably because they did not undergo systemic chemotherapy. It should be underlined that in patients treated with dasatinib followed by blinatumomab we could document a marked modulation of the host immune system, more evident after repeated cycles of blinatumomab. The references to the above studies are detailed below. The possibility of omitting chemotherapy is also confirmed by the preliminary data of a study conducted at the MD Anderson Cancer Center with ponatinib plus blinatumomab for patients with newly diagnosis and relapsed Ph+ ALL and CML in blast crisis (Jabbour E et al. Lancet Haematol, 2022; Nov 16).

SS12-1

Based on these results, the new ongoing GIMEMA study (LAL 2820) is the first phase 3 randomized study designed for adult Ph+ ALL patients. The experimental arm is based on the 3rd generation TKI ponatinib followed by blinatumomab. Only patients with an unfavorable genetic profile at presentation and/or evidence of MRD will undergo a transplant. The aim is to conclusively document that a large proportion of adult Ph+ ALL patients can be managed without systemic chemotherapy and transplant.

All the above is doable only if i) Ph+ ALL patients are identified within one week from diagnosis (which usually corresponds to the steroid pre-phase); ii) the presence (or absence) of IKZF1plus can be defined on the diagnostic material; iii) MRD can be adequately investigated on bone marrow samples (ideally by RQ-PCR); iv) the presence (or absence) of ABL1 mutations can be investigated, particularly if 1st and 2nd generation TKIs are used; v) drugs are available. It should also be underlined that such an approach should be extended to ALL patients of all ages. Elderly/old patients with Ph+ ALL - if identified (too many elderly/old ALL patients are not tested) - can be managed with a TKI given orally and largely at home, with little/limited hospitalization. This is also a cost-saving approach.

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SS12-2

Development of more-effective CAR T-cell therapy for ALL

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Chimeric antigen receptor (CAR) T cell therapy has revolutionized the treatment of relapsed/refractory B-cell malignancies, exemplified by B-cell acute lymphoid leukemia (B-ALL). However, depth and duration of remission are limited by leukemia-related factors (e.g. antigen loss or down-regulation) and T cell related factors (such as exhaustion). Antigen density is an important factor modulating CAR T cell response, since antigen expression below a certain threshold fails to trigger the full range of T cell functions. Given that signal strength induced upon antigen encounter determines CAR T cell activity, the simultaneous targeting of two dimly expressed antigens by T cells that co-express two full-length CARs with different specificities results in enhanced CAR T cell function: Compared to monospecific CAR19 or CAR22 T cells, bispecific CAR19/22 T cells exhibit improved cytotoxicity, cytokine production and immunological synapse (IS) quality, as well as superior therapeutic efficacy in vivo against low antigen density (LAD) patient-derived B-cell acute lymphoid leukemia xenograft models. This bispecific design is superior to other means of achieving dual antigen specificity, such as tandem or loop CAR designs. Thus, multi-specific CAR T cells are a promising strategy to improve efficacy against LAD tumors, in addition to the recognized benefit of reducing antigen-negative escape.

SS12-3

Overcoming high-risk features in adult ALL patients

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High-risk features of adult acute lymphoblastic leukemia (ALL) were suggested as various disease-related and patients-specific factors. Conventionally, old age, hyperleukocytosis, central nervous system (CNS) involvement, T-ALL, Philadelphia chromosome (Ph)-positive ALL, and poor response to initial induction chemotherapy have been known as important adverse-risk features for survival outcomes. Among the Ph-negative population, MRC UKALL/ECOG suggested that patients could be categorized as low risk (no risk factors based on age or WBC count), intermediate risk (either age >35 years or elevated WBC count), or high risk (both age >35 years and elevated WBC count). The 5-year overall survivor (OS) rates based on these risk categories were 55%, 34%, and 5%, respectively, suggesting that patients with Ph-negative ALL in the high-risk subgroup showed poorer survival outcomes compared to patients with Ph-positive ALL. Now we still have more high-risk features in the context of poor immunophenotypic or poor cytogenetic characteristics that can further divide ALL patients into specific disease subgroups.

Ph-positive ALL is an already well-known poor prognostic subgroup even after introduction of tyrosine kinase inhibitors (TKI). Intensive chemotherapy combined with imatinib or dasatinib showed improved survival outcomes of Ph-positive ALL, but still large number of patients relapse even after allogeneic hematopoietic cell transplantation (allo-HCT). Interestingly, several Working Groups tried to introduce chemo-free induction regimens which consisted of TKI and steroid, suggesting there might be a possible responding group which may benefit from chemo-free regimen. Furthermore, recent data showed the beneficial role of ponatinib as a frontline therapy combined with attenuated chemotherapy or steroid alone that were significantly superior to the other TKI-based regimens although allo-HCT was not performed in MRD-negative subgroup.

Other than Ph-positive ALL, we also identified that there are several poor cytogenetic abnormalities such as complex karyotype with 3 or more aberrations, monosomal karyotype, hypodiploidy, t(4;11) KMT2A translocation, 7 abnormalities, and t(8;14) translocation. Among them, Burkitt leukemia with t(8;14) translocation is now successfully treated with rituximab combined hyper-CVAD and HDMTX/ARA alternative regimens. Except for Burkitt leukemia, we still should be vigilant to induce remission and conduct post-remission therapy for other poor cytogenetic abnormalities.

Next to these poor recurrent cytogenetic abnormalities, BCR-ABL1-like or Ph-like ALL was identified as a high-risk subtype of BCP-ALL which has a gene expression profile like Ph-positive ALL but lacks the BCR-ABL1 fusion protein. Subsequent studies have unveiled its characteristic genetic abnormalities including CRLF2 rearrangements, ABL-class rearrangements, JAK2 or EPOR rearrangements, mutations activating JAK-STAT signaling and RAS signaling, and uncommon kinase alterations. This subtype is known as having high MRD level after remission induction chemotherapy and associated with inferior survival outcomes. However, our recent analysis revealed that allo-HCT-based post-remission therapy may have contributed to non-inferior outcomes of adult Ph-like ALL. IKZF1 alteration is also suggested as poor prognostic marker but there are not enough data in Korean population yet.

Although T-ALL is known as high-risk subtype due to poor remission rate and poor survival outcome, some pediatric-inspired L-asparaginase containing regimens showed improved survival outcomes with or without allo-HCT as a post-remission treatment. However, early T-cell precursor (ETP)-ALL that has a specific immunophenotypic marker – absence of CD1a/CD8, weak expression of CD5 (<75% positive lymphoblasts), and presence of 1 or more stem cell or myeloid markers (CD34, HLA-DR, CD117, CD13, CD33, CD11b, or CD65) – showed worse survival outcomes even after the pediatric-inspired regimens. For now, the worse survival outcome of ETP-ALL is partly overcame only with allo-HCT-based post-remission therapy. Recent trials showed possible application of novel agents such as nelarabine, daratumumab, and venetoclax concomitant with conventional regimens.

Post-induction or pre-HCT MRD-positive status is a very high-risk of subsequent relapse after post-remission therapy. At present, blinatumomab is approved due to its efficacy in patients with positive MRD in both Ph-positive and Ph-negative B-ALL and allo-HCT is recommended for long-term remission achievement. In Ph-positive ALL, preemptive TKI can be considered in this high-risk subgroup. For relapsed or refractory ALL, there are still many clinical trials using many novel drugs. At present, application sequence considering leukemia-related factors and regimen-related factors are still challenging between blinatumomab, inotuzumab ozogamicin, and CAR-T therapy.

We are now in the era of precision medicine with a lot of genetic information and variable treatment strategies including many novel agents. ALL also should be precisely managed from diagnosis to treatment initiation followed by post-remission period, and many relapsed or refractory cases should be focused into translational research. We will review those topics in this session.

SS13-1

Single cell HSPC map

William J. Greenleaf
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Identifying the causes of human diseases requires deconvolution of abnormal molecular phenotypes spanning DNA accessibility, gene expression and protein abundance. We present a single-cell framework that integrates highly multiplexed protein quantification, transcriptome profiling and analysis of chromatin accessibility. Using this approach, we establish a normal epigenetic baseline for healthy blood development, which we then use to deconvolve aberrant molecular features within blood from patients with mixed-phenotype acute leukemia. Despite widespread epigenetic heterogeneity within the patient cohort, we observe common malignant signatures across patients as well as patient-specific regulatory features that are shared across phenotypic compartments of individual patients. Integrative analysis of transcriptomic and chromatin-accessibility maps identified 91,601 putative peak-to-gene linkages and transcription factors that regulate leukemia specific genes, such as RUNX1-linked regulatory elements proximal to the marker gene CD69. These results demonstrate how integrative, multiomic analysis of single cells within the framework of normal development can reveal both distinct and shared molecular mechanisms of disease from patient samples.

SS13-2

Humanized mouse and non-human primate: Animal models for hematopoietic stem cell research

Kyung-Rok Yu
Seoul National University, Korea

A lot of important knowledge about human biological processes has been obtained from studying unique animal models. To study pathophysiology of human hematologic disease, humanized mouse or non-human primate model has been established. Humanized mouse is immunodeficient in nature and are created by engrafting with human hematopoietic cells to support human immune system. Humanized mouse with the efficient engraftment of human hematopoietic stem cells or peripheral blood-derived mononuclear cells recapitulates the interactions between immune components of human origin, allowing evaluation of immunotherapeutic modalities. Non-human primate is a robust model to study clinically relevant aspects of human hematopoietic system due to its similar physiology, lifespan, inferred hematopoietic stem cell dynamics, and aging phenotype. Recent research adapted CRISPR/Cas9 editing of non-human primate hematopoietic stem cells followed by autologous transplantation to created the engineered large animal model of a hematologic disease. In this talk, I will introduce the translational hematology research for therapeutic interventions using humanized mouse and non-human primate model.

SS13-3

What we know about HSC homing?

Xinxin Huang
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Hematopoietic stem cells (HSCs) are multipotent stem cells that are at the apex of hematopoietic lineage and give rise to all blood cell types throughout the lifespan. Hematopoietic stem cell transplantation (HSCT) is an effective and widely used treatment for many malignant and non-malignant blood disorders. After infusion into the peripheral blood circulation, HSCs home to the bone marrow (BM) microenvironment through sensing and migrating directionally along external chemical gradients of chemoattractants. The BM microenvironment provides a unique matrix bedding and conducive signaling environment supporting long-term engraftment and balances HSC proliferation and differentiation.

HSC homing is an initial critical step for HSC transplantations. The interaction between CXCL12/stromal cell-derived factor (SDF)-1 and its receptor CXCR4 play an important role during HSC homing. CXCL12/CXCR4 interactions are involved in chemotaxis, the process of directed cell movement in response to a chemical concentration gradient, and their intracellular signaling has been considered as a promising target for enhancing HSC transplantations. Recent studies have identified new approaches to potentially improve HSC homing and engraftment, including neutralizing negative epigenetic regulation by histone deacetylase 5 (HDAC5), short-term treatment of HSCs with glucocorticoids, pharmacological stabilization of hypoxia-inducible factor (HIF)-1A, activation of nitric oxide signaling, increasing membrane lipid raft aggregation, and inhibition of dipeptidyl peptidase 4 (DPP4) etc. Besides, adhension molecules, like P-sellectin, CD44 and integrin VLA4, are also involved in HSC homing to the BM.

Successful clinical outcomes after HSCT rely on adequate HSC numbers and the homing and subsequent short-term and long-term engraftment of these cells in the bone marrow. Enhancing the homing capability of HSCs could have a great impact on improving HSCT procedures and patient survival. Further explore the mechanisms of HSC homing process, identify regulators involved in HSC homing and develop new approaches to enhance HSC homing are future directions to expand our understanding of HSC biology and improve HSC based therapy.

SS14-1

Translating scientific advances in CLL

Richard Rosenquist
Karolinska Institute, Sweden

Genetic diagnostics of hematological malignancies has over the years evolved from cytogenetics to high-throughput sequencing and is an integral part of routine diagnostics since decades. In CLL diagnostics today, we apply fluorescence in situ hybridization (FISH) analysis to detect recurrent chromosomal aberrations [i.e., del(11q), del(13q), trisomy 12 and del(17p)] as well as targeted sequencing (IGHV and TP53) for risk-stratifying purposes. In addition, some of these markers may assist in clinical decision-making and therapy selection including targeted therapy. In this lecture, I will present the current view on the molecular landscape of CLL and give an update on the latest advances in CLL research with translational potential. I will also discuss different state-of-the-art technologies that are applied in CLL diagnostics and highlight important genetic markers with prognostic and/or predictive impact that are clinically relevant to assess (TP53 aberrations and IGHV mutational status) or may become relevant (e.g., complex karyotype, B cell receptor stereotypy and recurrent gene mutations). In the coming years, it will be important to develop more comprehensive gene panels that can capture all types of clinically relevant genetic aberrations, preferably as a single test, but also to develop highly sensitive assays to detect mutations effecting therapy response or resistance to targeted therapies.

SS14-2

Patient selection for time limited versus continued therapy

Jennifer R. Brown
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Development of CLL targeted therapy began with the approval of the B cell receptor pathway inhibitors, in particular the BTK inhibitors, which were developed largely as single agents to be given as continuous therapy. As these regimens moved to earlier lines of therapy, it became increasingly clear that continuous therapy over years had potentially undesirable consequences, including the accumulation over time of toxicity and cost, as well as the risk of selecting resistant clones. Therefore, clinical development efforts shifted to focus more on time-limited targeted therapy, beginning with the one year venetoclax obinutuzumab (VO) regimen developed in the CLL14 study, and since then moving on to combined BTK inhibitor (BTKi) – venetoclax regimens that have been studied as fixed duration or minimal residual disease (MRD) guided regimens. With longer follow-up of all of these studies, some themes have begun to emerge. The first is that, after time-limited therapy, disease with higher risk biology tends to relapse earlier, just as we saw in the era of FCR chemoimmunotherapy. Hence in CLL14, patients with 17p deletion relapse with the shortest median PFS (49 mos), while those with unmutated IGHV have also reached a median PFS at 64.2 months. In contrast, the patients with mutated IGHV have very prolonged remissions that are ongoing. Again, similar to what we saw with FCR, achievement of undetectable MRD is very predictive of outcome after time-limited VO. In contrast, continuous therapy with BTK inhibitors – if the patient is able to remain on the BTK inhibitor -- appears to be effective in substantially reducing the excess risk associated with IGHV unmutated or 11q deleted disease. Even TP53 aberrant disease can have prolonged remissions on continuous BTK inhibitors – although these remissions still appear shortened compared to patients without TP53 aberrancy. Data are only starting to emerge on the BTK inhibitor-venetoclax combinations, but so far it appears that, when truly fixed duration, the biologic prognostic factors again predict durability of response, although achieving undetectable MRD may not be quite as predictive of progression-free survival as it is after venetoclax obinutuzumab. Interestingly, rates of undetectable MRD in patients with mutated IGHV are lower after BTKi-venetoclax combinations than they are after venetoclax obinutuzumab, although implications for progression-free survival are not yet clear. Many outstanding questions remain, and include patient selection for the different types of time-limited therapies, optimizing the duration of time-limited therapies, and understanding the potential benefit of re-treatment with the same time-limited therapy at relapse.

SS14-3

MRD monitoring in CLL Patients

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The introduction of chemoimmunotherapy and more recently the implementation of novel agents into first-line and relapse treatment have substantially improved treatment outcomes in patients with chronic lymphocytic leukemia (CLL). With longer progression-free survival (PFS) and more frequently observed deep remissions there is an emerging need for sensitive methods quantitating residual disease after therapy. Over the last decade, assessment of minimal residual disease (MRD) has increasingly been implemented in CLL trials. MRD in CLL is defined as the number of leukemic cells that can be detected in peripheral blood (PB) or bone marrow (BM) following treatment. Undetectable MRD (uMRD) is currently defined as the presence of less than 1 CLL cells in 10,000 leukocytes (<10–4). The predictive value of MRD status on survival outcomes has repeatedly been proven in the context of chemoimmunotherapy, cellular therapies, and recently Bcl-2 inhibitor-based therapy. While the relevance of MRD assessment as a surrogate endpoint in clinical trials is largely undisputed, its role in routine clinical practice has not yet been well defined.
The established MRD detection level of <10–4 can currently be achieved by 3 different methods: multi-color flow cytometry, real-time quantitative polymerase chain reaction and high-throughput sequencing (HTS), each with their specific advantages.
Several clinical trial using chemotherapy or chemoimmunotherapy demonstrated uMRD is associated with better PFS. While complete response rate increases gradually during the course of chemotherapy with BTK inhibitor, they remain low and uMRD is only achieved by a minority of patients. PFS in patients with low MRD (<10–2) and high MRD (≥10–4) after 3 years of ibrutinib was not different statistically. Combination of venetoclax with monoclonal antibodies have yielded high rate of uMRD. The MURANO study that investigated the use of rituximab and venetoclax in relapsed or refractory CLL, showed uMRD in PB in 62% of all patients after the end of combination treatment with uMRD translating into considerably longer PFS.
Because of the concordance result of residual disease between PB and BM is variable, if MRD is not detectable in PB, it is recommended to confirm uMRD status in BM. Furthermore, even in absence of residual disease in the BM, patients may have significant residual disease in unassessed sites.
New MRD-guided treatment approaches will probably soon find their way into clinical practice, allowing for a more individualized therapy, possibly leading to less treatment related toxicities and better outcomes. Until this has become reality, it is necessary to eliminate the remaining weaknesses of current MRD assessment approaches and develop more sensitive methods to also detect residual disease beyond the BM and PB compartment.

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EDUACATION SESSION

ES01-1

Asciminib: the first-in-class allosteric inhibitor of BCR/ABL1 kinase

Eun-Ji Choi
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The prognosis of the patients with chronic phase chronic myeloid leukemia (CML) has significantly improved owing to the development of potent BCR-ABL1 tyrosine kinase inhibitors (TKIs). However, approximately 5–15% of the patients still experience treatment failure including resistance or intolerance to TKI therapy. As the prognosis of the patients failing multiple TKIs is known to be poor, an optimal therapeutic approach is required for patients with CML with treatment failure. Asciminib, an allosteric inhibitor targeting ABL1 myristoyl pocket, has been approved by the Food and Drug Administration for patients with chronic phase CML with resistance or intolerance to 2 or more prior TKIs and those with T315I mutation. Through the phase 1 trial, asciminib monotherapy showed a relatively favorable safety profile and potent efficacy in both cohorts with or without T315I mutation. In the subsequent phase 3 trial, ASCEMBL, the efficacy and safety of asciminb was compared with those of bosutinib in the patients with chronic phase CML without T315I or V229L mutations and failed 2 or more prior TKIs. The primary endpoint, major molecular response at week 24, was significantly higher in asciminib arm than bosutinib arm. Asciminib was well tolerated with a lower rate of discontinuation with manageable toxicities. Several clinical trials for asciminib are ongoing in various clinical settings including frontline for newly diagnosed chronic phase CML as a single agent or combination with other TKIs and adjunctive to other TKIs for chronic phase CML who have not achieved a deep molecular response. The choice of drug for the patients with chronic phase CML with treatment failure should be based on comorbidities, disease biology including mutation profiles, and response to prior therapy, and asciminb can be an option for beyond third-line treatment for these patients.

ES01-2

Treatment after failure of frontline therapy of CML-CP including allo-HSCT

Jieun Uhm
Hanyang University College of Medicine, Korea

The treatment outcomes of chronic myeloid leukemia in chronic phase (CML-CP) have dramatically improved with comparable life-expectancy to average of general population in tyrosine kinase inhibitor (TKI) era. However, less than a half of patients who started with TKI can remain on frontline TKI. The reasons of switching TKI can be either intolerance or the lack of efficacy. Although a kinase domain (KD) mutation can guide to select salvage TKI from the point of view on the efficacy of TKIs, many factors need to be considered before choosing next-line TKI such as the high-risk features of CML, the adverse events with prior TKI, and the comorbidities of patients. The therapeutic options for CML-CP after failing frontline TKI due to treatment failure or suboptimal responses will be reviewed including allogeneic hematopoietic stem cell transplantation.

Keywords: chronic myeloid leukemia, tyrosine kinase inhibitors, ponatinib, asciminib, allogeneic hematopoietic stem cell transplantation

ES01-3

Update on treatment free remission

Jae Joon Han
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Chronic myeloid leukemia (CML) has been a successful model of targeted therapies. Today, we could expect the overall survival of CML patients very similar to the healthy population by using tyrosine kinase inhibitors (TKIs). A new goal in CML treatment is achieving treatment free remission (TFR) maintaining a stable response after discontinuation of TKIs.
In 2007, the French group published a pilot trial of 12 patients who stopped imatinib after 24-46 months of negative BCR-ABL transcripts by RTQ-PCR. After a median follow-up of 18 months, 50% of them remained in molecular remission. This study proved a concept that imatinib discontinuation is feasible and safe in selected patients.
In this lecture, I would like to review the next topics to understand the current practice of stopping TKIs
1. Selection of the patients who can stop TKI successfully
2. Clinical issues after stopping TKI; side effects of stopping TKI and monitoring disease
3. Treatment of relapse and second attempt of TFR

ES02-1

Prognostic factors in intravascular large B-cell lymphoma: A comprehensive review

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Intravascular large B-cell lymphoma (IVLBCL) is a rare and aggressive subtype of non-Hodgkin lymphoma that primarily affects small vessels in various organs, leading to a broad range of clinical manifestations. Due to its non-specific symptoms and lack of reliable diagnostic criteria, IVLBCL often remains undiagnosed until autopsy. Therefore, early recognition of the disease is essential for the initiation of prompt treatment and improving patient outcomes.

Prognostication in IVLBCL has been challenging due to the rarity of the disease and its variable clinical presentation. The International Prognostic Index (IPI) is a widely used prognostic tool that helps clinicians predict the outcome of aggressive NHL lymphomas. It identifies several negative prognostic factors such as age over 60, advanced stage disease, elevated LDH levels, poor performance status, and multiple extranodal sites of disease. In addition, a prognostic model focusing on elderly patients with large B-cell lymphoma treated with R-CHOP identified age over 75, low serum albumin levels, and a high Charlson Comorbidity Index (CCI) as independent predictors of worse overall and progression-free survival.

Interestingly, several studies have consistently shown that cutaneous involvement is associated with a significant increase in overall survival in IVLBCL patients. This finding suggests that cutaneous symptoms should be included in future prognostic models to more accurately estimate prognosis. However, previous classifications have only differentiated between the categories of "cutaneous involvement" and "no cutaneous involvement," which overlooks the fact that many patients have both visceral and skin manifestations. Therefore, a differentiation into three categories, i.e., "cutaneous involvement only," "cutaneous and further visceral involvement," and "no cutaneous involvement," could be beneficial.

Advances in molecular technologies, such as genome sequencing of cell-free DNA and testing for tumour cell expression of PD-L1, are being investigated to improve early diagnosis, prognostic accuracy, and therapy. These technologies may be particularly helpful in cases where clinical indicators are inconclusive, such as in patients with multiple negative prognostic factors but with cutaneous involvement. Additionally, PD-L1 expression testing could represent a rationale for immunotherapy using checkpoint inhibitors in refractory cases.

In conclusion, IVLBCL is a challenging disease with a broad range of clinical manifestations, making early recognition essential for improved patient outcomes. Prognostication in IVLBCL is complex and requires consideration of multiple negative prognostic factors. Cutaneous involvement appears to be a positive prognostic factor in IVLBCL, and its integration into future prognostic models is warranted. Advances in molecular technologies may also provide useful tools for early diagnosis, prognostic accuracy, and targeted therapies.

Keywords: ntravascular large B-cell lymphoma, Prognosis, Cutaneous involvement, PD-L1 expression,

ES02-2

T-large granular lymphocytic leukemia

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T-cell large granular lymphocyte (T-LGL) leukemia is characterized by clonal expansion of cytotoxic T cells resulting in cytopenia. The proliferation of clonal LGLs is caused by prolonged antigenic stimulation, which leads to apoptotic dysregulation owing mainly to the constitutive activation of survival pathways, notably the JAK/STAT pathway. Understanding how leukemic T-LGL persists can aid in the development of future immunosuppressive therapies, as opposed to existing immunosuppressive strategies. In this review, we summarize the diagnosis and current standard of therapy for T-LGL leukemia, as well as recent advances in clinical trials.

ES02-3

Lymphomatoid granulomatosis

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ES03-1

Sezary syndrome and mycosis fungoides

Hyewon Lee
National Cancer Center, Korea

Mycosis fungoides (MF) and Sézary syndrome (SS) are a distinct disease entity of cutaneous T-cell lymphoma with heterogenous clinical features and prognosis. MF mainly involves skin and usually shows an indolent and favorable clinical course. In patients with advanced-stage disease, extracutaneous involvement including lymph nodes, viscera, and blood, or large cell transformation may be observed. SS is a leukemic form of advanced-stage MF, characterized by generalized erythroderma. Early-stage MF can be treated with skin-directed therapy. However, patients with refractory or advanced-stage disease are associated with severe symptoms or poor prognosis, requiring systemic therapy. Recent progress in understanding the pathogenesis of MF/SS has contributed to advances in the management of these rare diseases. This review aims to describe the clinical manifestations, diagnosis, risk stratification, and treatment strategy of MF/SS, focusing on the recent updates in the management of these diseases.

ES03-2

Systemic mastocytosis

Hyun Jung Lee
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Mastocytosis is a heterogeneuous neoplasms characterized by accumulation of neoplastic mast cells in various organs. Including bone marrow, skin, the gastrointestinal tract, the liver, and/or the spleen. There are 3 main types of mastocytosis; cutaneous mastocytosis (CM), systemic mastocytosis (SM) and mast cell sarcoma (MCS). CM mainly affect children and is confined to the skin, while the SM usually affect adults and is characterized by extracutaneous involvement with or without evidence of cutaneous involvement. While most of the SM usually presented with indolent clinical course, some types of SM are associated with aggressive behavior and patients with these types have dismal clinical outcome. Recent advances in diagnosis and understanding about molecular changes in SM have changed the diagnostic and therapeutic landscape for aggressive and advanced SM subtype of patients. The International Consensus Classification (ICC) has refined the diagnostic criteria and classification of SM with accumulation of clinical experience and development of diagnostic tools to define biologic and molecular features of SM. Somatic mutations in the KIT gene, most frequently KIT D816V, are detected in 90% of patients with SM. Expression of CD30 and any KIT mutation are introduced as minor diagnostic criteria with the introduction of highly sensitive screening methods. SM has wide spectrum of clinical features and only a few drugs have shown efficacy in advanced SM. Current mainstay of SM treatment was only limited in management of chronic symptoms related to mast cell mediator release. Small molecular kinase inhibitors targeting KIT-downstream pathway and KIT-independent pathways were approved for advanced SM in US recently. Clinical update of the diagnosis, classification, and management of SM will be reviewed.

ES03-3

Plasmacytoid dendritic cell neoplasm

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Plasmacytoid dendritic cells are type I interferon-producing cells that modulate immune responses. There were two types of plasmacytoid dendritic cell neoplasm: 1) mature plasmacytoid dendritic cell proliferation (MPDCP) associated with myeloid neoplasm and 2) blastic plasmacytoid dendritic cell neoplasm (BPDCN). MPDCP is clonal expansion of mature plasmacytoid dendritic cells, and predominantly associated with chronic myelomonocytic leukemia. BPDCN, on the other hand, is a clinically aggressive myeloid malignancy that involves skin, bone marrow, lymphatic organs and the central nervous system. There are various types of skin lesions, ranging from solitary brown or violaceous lesions to disseminated cutaneous lesions, which often spread throughout the body. The expression of CD4, CD56, CD123, and pDC markers (TCL-1, TCF4, CD303 and CD304) is a typical immunophenotype of BPDCN. Historically, BPDCN treatments were based on acute leukemia regimens and allogeneic hematopoietic cell transplantation for selected patients. Recent advances in molecular biology and genetics have led to the development of targeted agents such as tagraxofusp (recombinant fusion protein targeting CD123), anti-CD123 CAR-T cells, XmAb14045 and IMGN632. This review provides a comprehensive overview of plasmacytoid dendritic cells neoplasm.

ES04-1

Transfusion support for HSCT

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Transfusion support is a critical supportive method for the patient before, during and after hematopoietic stem cell transplantation (HSCT). The general principle for transfusion is to transfuse cells or plasma that exactly matches between donor and recipient. However, these circumstances are usually unmet for patients undergoing HSCT. Therefore, an additional principle is required for safe transfusion. If exact matching is unavailable, transfusion should be performed to the recipient using a product expressing lesser antigen and antibody. For example, packed red blood cells (PRBC) with blood group O could be transfused into a recipient with AB blood group. As antibodies are an important factor for transfusion with abundant plasma components, platelet, fresh frozen plasma, or cryoprecipitate with blood group AB could be transfused to A recipient. Determination of ABO and Rh typing is important for transfusion. Cell typing and serum typing results both should be considered for the determination of the blood group.

Packed RBC, leukocyte-reduced RBC, packed platelet, single donor-derived platelet, fresh frozen plasma, cryoprecipitate and granulocytes are one of the most commonly transfused products. Most of the products are irradiation with gamma rays or X-ray irradiators (25-50 Gy) to prevent graft versus host disease (GVHD) and leukoreduction (leukocyte < 1x106/unit) except for granulocyte products. Usually, life time use of irradiated blood is administered as immunological reconstitution status is difficult to confirm.

In HSCT, ABO incompatibility could be classified as either major, minor, or bidirectional. Major incompatibility could be defined as the recipient having preformed antibodies or isoagglutinin to donor RBC or graft. This occurs in recipients with O blood type and donors with non-O blood type and recipients with A or B blood group and donors with AB blood group. Minor incompatibility could be defined as the donor having antibodies or isoagglutinin to the recipient RBC. This occurs in the recipient with A, B, or AB blood group and donor with O blood group or recipient with AB and donor with A or B blood group. donor with O blood type and recipient with A blood type). Bidirectional incompatibility could be defined as the recipient having A or B and the donor having B or A, respectively.

A restrictive RBC transfusion threshold of 7-8g/dL of hemoglobin is recommended for hemodynamically stable adult. Hg threshold of 8g/dL is recommended for underlying cardiovascular diseases. Platelets should be transfused to nonbleeding, nonfebrile adult patient at platelet count ≤10x109/L. Active bleeding, febrile adult patients might be transfused at platelet count ≤20x109/L or even at higher concentration depending on patient status.

Clinical complications of major incompatibility are hemolysis, delayed RBC engraftment, pure red cell aplasia (PRCA) and delayed granulocyte or platelet engraftment. Clinical complications of minor incompatibility are hemolysis or passenger lymphocyte syndrome causing delayed hemolysis. Bidirectional incompatibility could have features of a combination of both major or minor incompatibilities.

Prevention of clinical features for major incompatible cases could be performed by decreasing isoagglutinin either by plasma exchange or by immunoadsorption. Prevention of clinical features for minor incompatible cases includes alleviating passenger lymphocyte syndrome by a selection of graft from peripheral blood stem cells, administration of calcineurin inhibitors or exchange of donor RBC before HSCT. Prevention or treatment of sinusoidal obstruction syndrome or veno-occlusive syndrome could be performed by ursodeoxycholic acid or defibrotide, respectively.

Transfusion support is requested for not uncommon clinical situations. Cord blood cell HSCT in adults requires 2 donors and often donor and recipient ABO groups could show incompatible ABO blood group features. A patient undergoing 2nd HSCT with an incompatible ABO blood group from the 1st donor could also happen. In these complicated cases, RBC of the O blood group and platelet, plasma with AB blood group are usually selected.

RhD incompatibilities should also be considered. RhD-negative blood is recommended for transfusion unless both donor and recipient are RhD-positive. As RhD negative blood are rare in some region, alternative strategy should be considered. For RhD-positive recipients and RhD-negative donors, RhD-positive blood could be transfused until RhD antigens are weakened. For RhD-negative recipients and RhD-positive donors, RhD-negative blood should be selected until the RhD antigen appears to some degree and then, RhD-positive blood could be selected. In case of platelets, anti-RhD should be administerd before RhD incompatible transfusion.

Granulocyte transfusion (GT) could be administered for patients undergoing chemotherapy or HSCT. GT could cause logistic problems and difficulties in recruiting designated donors. As decreased granulocyte could provoke or sustain the microbial infection, GT could be a therapeutic option as a bridging therapy until the recovery of white blood cells. However, as the efficacy of GT was not evident, further studies along with risk stratification of patients could provide an impact of GT undergoing HSCT.

ES04-1

Transfusion support for HSCT patients should be determined based on the patient's cell typing and serum typing results for in vivo survival of RBC or grafts and to alleviate potential clinical complications.

			Phase I	Phase II				Phase III
ABO incompatibility	Recipient	Donor	Donor All Product	RBC	PLT 1st	PLT 2nd	Plasma	All Product
Major	O	A	Recipient	O	A	AB	A	Donor
	O	B	Recipient	O	B	AB	B	Donor
	O	AB	Recipient	O	AB	A	AB	Donor
	A	AB	Recipient	A	AB	A	AB	Donor
	B	AB	Recipient	B	AB	B	AB	Donor
Minor	A	O	Recipient	O	A	AB	A	Donor
	B	O	Recipient	O	B	AB	B	Donor
	AB	O	Recipient	O	AB	A	AB	Donor
	AB	A	Recipient	A	AB	A	AB	Donor
	BB	B	Recipient	B	AB	B	AB	Donor
Bidirectional	A	B	Recipient	O	AB	B	AB	Donor
	B	A	Recipient	O	AB	A	AB	Donor

ES04-2

Evidence based transfusion threshold

Dae-Hyun Ko
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The transfusion threshold is one of the key concepts of patient blood management. There have been many studies and reports about the advantage of a restrictive transfusion threshold over a liberal transfusion threshold. However, these studies are usually based on data from acute blood loss such as surgical patients or critical care settings. Patients who are suffering from chronic anemia such as myelodysplastic syndrome or aplastic anemia usually need transfusion regularly, especially in the outpatient clinic. For this reason, some researchers have claimed that patients with myelodysplastic syndrome or aplastic anemia need different transfusion strategies, especially in reference to the quality of life, rather than survival. In this presentation, I will briefly look over current evidence for transfusion threshold for various clinical settings and discuss what is a more desirable option for better patient care.

ES04-3

Current status of manufactured blood cells

Eun Jung Baek
Hanyang University College of Medicine, Korea

Blood shortage has been a serious problem around the world due to donor-dependent issues such as population aging and unpredictable pandemics. In vitro production of red blood cells (RBC) and platelet is a promising substitute for clinical-quality blood, especially for patients with rare blood group phenotypes. Although autologous transfusion of cultured RBCs (cRBCc) was demonstrated safe in the first-in-human clinical trial in 2011, its limited production quantity makes it difficult to be used in clinics. To scale-up the lab culture systems, various methods such as hollow fiber bioreactors, microcarriers, and porous scaffolds, and stirred tank reactors (STRs) have been applied. Recently, allogenic transfusions of mini-dose cRBCs generated from primary hematopoietic stem cells were applied to multiple volunteers in the UK. Still, there remain many challenges to manufacture blood cells on a large scale. Recently, the first-in-human clinical trial using induced pluripotent stem cell-derived platelet product was announced in Japan and demonstrated its quality, safety, and efficacy. They developed a vertical reciprocal motion liquid culture bioreactor (VerMES) for platelet production efficiency. Since manufacturing processes that use bioreactors are critical in cRBC and platelet production, here we review recent advances in manufacturing processes as well as medium, and various cell sources.

ES05-1

Setting up the facility for CAR T cell therapy

Ja Min Byun
Seoul National University College of Medicine, Korea

Chimeric antigen receptor (CAR) T-cell therapy represents a revolutionary advancement in personalized cancer treatment. During this treatment, a patient's own T cells are genetically engineered to express a synthetic receptor that binds a tumor antigen. CAR T-cells are then expanded for clinical use and infused back into the patient's body to attack cancer. CAR T-cells have produced remarkable clinical responses with B-cell malignancies. However, CAR T-cell therapy is not without faults: barriers to effective CAR-T cell therapy include severe life-threatening toxicities and modest anti-tumor activity. Also, setting up CAR-T cell therapy comes with hurdles with newly implemented policies and regulations. In this review, I introduce the concept of CAR T-cell therapy, currently available CAR T-cell therapy options, how to deal with adverse events and most importantly how to set up cell therapy at each institution.

ES05-2

Technical aspect of manufacturing CAR T cell product

Jong-Seo Lee
AbClon Inc., Korea

ES05-3

Managing adverse events of CAR T cell therapy

Jae Won Yoo
College of Medicine, The Catholic University of Korea, Korea

Immunotherapy using CD19-targeted chimeric antigen receptor (CAR)-engineered T cells is a promising approach for the treatment of refractory B cell malignancies. In pediatric B cell acute lymphoblastic leukemia (ALL), complete remission rates have been improved to ~60-90% of patients who receiving CAR T cell therapy. Although CAR T cell therapy is a durable and an effective treatment, it is also associated with characteristic acute toxicities represented as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and hemophagocytic lymphohistiocytosis-like toxicity after CAR T cell therapy (carHLH). The severity of these toxicities can range from low-grade physical symptoms to a high-grade syndrome linked with life-threatening multiple organ failure. In rare cases, severe CRS can progress to fulminant hyperinflammatory syndrome known as hemophagocytic lymphohistiocytosis with poor prognosis and a challenging diagnosis. The traditional treatment options for CRS are tocilizumab and corticosteroids as front-line agents per expert guidelines. However, when severe CAR T-cell toxicities are refractory to front-line treatment, alternative options such as anakinra (IL-1 receptor antagonist), siltuximab (IL-6 receptor antagonist), and ruxolitinib (JAK1/2 inhibitor) to treat ongoing inflammatory toxicities are needed. Beyond treatment, risk-adapted preemptive or prophylactic use of tocilizumab to mitigate severe CRS has been under investigated in recent studies, and the optimal timing for starting CRS management should be determined.
In my talk, I will briefly review current guidelines of CRS/ICANS management and discuss several novel agents which are under investigating to manage severe form of CRS (e.g., carHLH). I will also share our institution's experiences of management CRS/ICANS after Tisagenlecleucel in pediatric B cell ALL.

ES06-1

Prognostication in MPNs (including mutation abnormalities)

Junshik Hong
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Increasing knowledge of the molecular features of myeloproliferative neoplasms (MPNs) is being combined with existing prognostic models based on clinical, laboratory, and cytogenetic information. Mutation-enhanced international prognostic systems (MIPSS) for polycythemia vera (PV) and essential thrombocythemia (ET) have improved prognostic assessments. In the case of overt primary myelofibrosis (PMF), the MIPSS70 and its later revisions (MIPSS70+ and MIPSS70+ version 2.0) effectively predicted the overall survival (OS) of patients. Because post-PV and post-ET myelofibrosis have different biological and clinical courses compared to overt PMF, the myelofibrosis secondary to PV and ET-prognostic model was developed. Although these molecular-inspired prognostic models need to be further validated in future studies, they are expected to improve the prognostic power in patients with MPNs in the molecular era. Efforts are being made to predict survival after the use of specific drugs or allogeneic hematopoietic stem cell transplantation. These treatment outcome prediction models enable the establishment of personalized treatment strategies, thereby improving the OS of patients with MPNs.

ES06-2

Novel therapeutics for MF (including cyotpenic myelofibrosis)

Sung-Eun Lee
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Myelofibrosis (MF), including primary MF (PMF), post-essential thrombocythemia MF (post-ET/MF), and post-polycythemia MF (post-PV/MF), is a progressive myeloid neoplasm characterized by clonal ineffective hematopoiesis, extramedullary hematopoiesis, a reactive bone marrow environment resulting in reticulin deposition ad fibrosis, and a propensity toward leukemia transformation. Although the identification of driver mutations in JAK2, CALR, and MPL has contributed to a better understanding of disease pathogenesis, implicating near-universal upregulation of JAK-STAT signaling, and has led to the development of the targeted therapy for MF, the JAK2 inhibitors. Although the clinical development and approval of ruxolitinib and fedratinib have been achieved, use of these medication is limited by their side effects including anemia and thrombocytopenia. Recently, for thrombocytopenic patients who were a group of patients with a significant unment clinical need, pacritinib was approved for patients with thrombocytopenia (baseline platelet count <50x109/L). Momelotinib showed significant improvements in anemia measures as well as MF-associated symptoms and spleen size compared with danazol in symptomatic and anemic patients with prior JAK inhibitor exposure. Although the remarkable development for JAK inhibitors, medical needs to modify the natural course of the disease remain. Therefore, many novel treatments are in clinical development. Agents targeting BET protein, anti-apoptotic protein Bcl-xL, and phosphatidylinositol-3-kinase delta have been studied as combination with a JAK inhibitor in the frontline and 'add-on' approaches to a JAK inhibitor in the second line. In addition, several investigational agents are being studied as monotherapies in ruxolitinib-resistant or ineligible patients.
Herein, I review several new MF treatments in advanced stages of clinical development and treatment options for cytopenic patients.

ES06-3

Novel Therapeutics for ET/PV

Seug Yun Yoon
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Myeloproliferative neoplasms (MPNs) are clonal disorders of hematopoietic stem cells, which include polycythemic vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). MPNs are inflammatory cancers in which the malignant clone generates inflammatory cytokines, which sustain the inflammatory drive in a self-perpetuating vicious cycle. The course of MPNs follows a biological continuum from the early cancer stages (ET/PV) to the advanced "burnt-out" myelofibrosis and impending leukemic transformation. MPN-related symptoms, including fatigue, general weakness, and itching occur due to inflammatory cytokines. In addition, it is known that thrombosis and bleeding are increased by inflammatory cytokines in patients with MPN. Until recently, the primary objective of therapy for ET and PV was to increase the survival rate by preventing thrombosis. However, several medications have lately shown the ability to modify the course of the disease, and patients are anticipated to actively relieve their symptoms. This review will focus on the emerging therapeutic agents in clinical development for ET/PV.

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SATELLITE SYMPOSIUM

SY01

ASCIMINIB, new paradigm treatment option in CML for patients who were previously treated with 2 or more TKIs

Andreas Hocchaus
Jena University Hospital, Germany

Adenosine triphosphate (ATP)–competitive tyrosine kinase inhibitors (TKIs) have transformed chronic myeloid leukemia (CML) from a fatal disease to one associated with near-normal life expectancy. However, some patients do not respond to TKI therapy (primary resistance), lose response (secondary resistance), or experience intolerance. Available therapies for patients with resistance to or intolerance of 2 or more TKIs are often limited by modest efficacy, safety concerns, or both. Following the failure of second-generation TKI (2G-TKI), use of alternative 2G-TKIs rarely results in optimal or durable responses. Ponatinib, a third-generation TKI, is effective in patients who received prior therapies, but it is associated with high iatrogenic cardiovascular risk. All approved TKIs for CML bind to the ATP site of the BCR::ABL1 oncoprotein to inhibit aberrant kinase activity. Asciminib is a novel, first-in-class Specifically Targeting the ABL Myristoyl Pocket (STAMP) inhibitor that potently inhibits the kinase activity of BCR::ABL1 via allosteric binding. It has potential to maintain activity against most ABL1 kinase domain mutations (eg, T315I) that confer resistance to approved TKIs.
Asciminib achieved its primary endpoint in ASCEMBL, an open-label, randomized, phase 3 trial comparing asciminib with bosutinib in patients with CML in chronic phase (CML-CP) previously treated with 2 or more TKIs its pivotal phase 3 clinical trial. The MMR rate at week 24 was 25.5% with asciminib and 13.2% with bosutinib and MMR rate at week 96 was 37.6% and 15.8% respectively in asciminib arm and bosutinib arm. And safety profile of asciminib has shown favorable safety and toxicity profile.
Studies are ongoing testing asciminib in the first line indication.

SY02

Unmet need in 1L DLBCL and POLARIX trial

Georg Lenz
University Hospital in Münster, Germany

Rituximab in combination with CHOP chemotherapy (R-CHOP) has been the standard therapeutic approach for the vast majority of patients diagnosed with diffuse large B-cell lymphoma (DLBCL) for many years. Using R-CHOP, depending on the prognostic subgroup of patients, approximately 65% of treated patients can be cured. Patients that are refractory to R-CHOP or who relapse after an initial response are characterized by adverse survival. Thus, novel therapeutic strategies to improve front-line therapy for DLBCL patients are urgently warranted.
While many randomized trials in the past failed to show an improvement of outcome compared to R-CHOP the recently completed POLARIX phase 3 study showed a significant improvement of progression-free survival (PFS) for patients treated with the combination of polatuzumab vedotin and R-CHP (pola-R-CHP) chemoimmunotherapy compared to R-CHOP treated patients. In this trial DLBCL patients with an international prognostic index (IPI) of 2-5 were included. After three years, PFS was improved by 7.7% using pola-R-CHP compared to R-CHOP. In contrast, no improvement of overall survival (OS) was detectable. Adverse events occurred similarly frequent in R-CHOP and pola-R-CHP treated patients.
In summary, pola-R-CHP significantly improved PFS in DLBCL patients with an IPI 2-5. Despite the fact that OS was not prolonged this finding is clinically meaningful, as relapses are prevented and subsequent therapies can be avoided to achieve long-term remissions compared to R-CHOP. Therefore, pola-R-CHP can be considered as a novel therapeutic standard approach for subgroups of DLBCL patients.

SY03

Maintenance treatment post autotransplant for multiple myeloma

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Treatment of patients with Multiple Myeloma has evolved over the past 25 years with an increased number of novel drugs becoming available, resulting in improved response and survival. Effective use of these drugs is of paramount importance to improve patient outcomes and quality of life. An important component of first-line treatment of transplant eligible patients has been maintenance treatment post autotransplant. Maintenance treatments studied include drugs such as interferon, thalidomide, bortezomib and more recently lenalidomide. Bortezomib maintenance, primarily used in patients with high-risk cytogenetics, is based on data from the HOVON-65/GMMG-HD4 randomized trial. Studies including the IFM 2005-02 and CALGB 100104 randomized trials have found lenalidomide maintenance (LM) to be effective, convenient and relatively well tolerated for which reason the use of LM is more pervasive. A meta-analysis of these LM studies demonstrated improved overall survival resulting in the general acceptance and establishment of LM. In Canada, funding for LM has been available for the past decade. Data from the Canadian Myeloma Research Group (CMRG) National Database supports this approach by demonstrating improved survival. Analysis of 1,256 patients of whom 723 (57.6%) receive LM and 533 (42.4%) who did not post autotransplant was performed. With median follow-up of 45.3 months in the non-LM group and 49.1 months in the LM group, the median PFS was 34.6 month versus 58.2 months respectively. The Median OS was 98.3 months in the non-LM cohort (95%CI: 83.5) but not reached (>124 months) in the LM group ($P<0.0001$). Given these results, LM post autotransplant is the standard approach upon which future post remission strategies are measured against and built upon.

SY04

Recent advances in the pathogenesis and treatment of aplastic anemia

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Aplastic anemia (AA) is an acquired bone marrow (BM) failure characterized by marrow hypoplasia, a paucity of hematopoietic stem and progenitor cells, and pancytopenia of the peripheral blood, due to immune attack on the BM. Once an immune attack against hematopoietic stem cells (HSCs) occurs, HSCs that undergo somatic mutations survive the immune attack and continue to produce their progenies. Thus, the presence of mature blood cells derived from mutated HSCs in the peripheral blood serves as evidence of the immune-mediated destruction of HSCs. Glycosylphosphatidylinositol-anchored protein-deficient (GPI[-]) blood cells and HLA class I allele-lacking (HLA[-]) leukocytes are two major aberrant cells that represent the immune mechanism underlying BM failure. I will briefly summarize the importance of identifying immune mechanisms using laboratory markers, such as GPI(-) cells and HLA(-) leukocytes in the management of AA patients, and help physicians to choose appropriate therapy.
Eltrompopag (EPAG), a TPO-RA, has been shown to induce hematologic recovery in about 50% of patients with AA refractory to immunosuppressive therapy. Moreover, EPAG was reported to increase response rates when added to ATG/CsA in treatment-naive SAA patients compared with a historical cohort. Although EPAG has changed the paradigm of AA treatment, novel therapies are still needed to rescue EPAG-refractory patients. A recent clinical trial showed that another TPO-RA, ROMI, was effective in EPAG-naïve refractory AA patients. The effectiveness of 20 μg/kg ROMI (the maximum dose approved for use in AA patients in Japan) in EPAG-refractory cases has not been closely examined. Our recent retrospective study showed that high-dose ROMI was highly effective in AA patients refractory to EPAG. I will update our recent experience of sequential therapy with EPAG followed by ROMI in refractory AA patients.

SY05

Value of intensive therapy in high-risk AML

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Until a few years ago, the improvements in outcome for patients with AML occurred only in small incremental steps. In the recent years, optimized supportive care and the addition of novel targeted compounds as well as the introduction of novel drug formulations, like CPX-351 (Vyxeos) have lead to further optimization of treatment outcomes in selected patient subgroup

Choice of initial treatment regimen for AML is typically based on both patient and disease characteristics. Although younger adults are commonly treated with intensive chemotherapy, his-torically there has been a tendency to view older patients as universally ineligible for intensive chemotherapy , and clinical trials of intensive chemotherapy have often excluded older patients and those with clinically significant comorbidities. However, an increasing number of registry studies have demonstrated that many older patients benefit from receiving intensive induction therapy versus lower-intensity therapy or best supportive care.

Given these outcomes in older patients, eligibility for intensive treatment must be assessed with a more holistic approach, taking into account each patient's comorbidities, cognitive status, preferences, and treatment goals in addition to age and performance status. Importantly the potential tolerability of allogeneic hematopoietic cell transplantation is an important assessment which has to be achieved throughout the initial work-up, ideally.

Conventional chemotherapy, such as the '7 + 3 ' induction regimen of cytarabine (100 to 200 mg/m2 continuous infusion for 7 days) plus 3 days of an anthracycline (daunorubicin or idarubicin), has been a standard of care for several decades. However, CR rates with 7 + 3 vary according to patient subgroups. CR is achieved in 45% to 65% of patients aged <65 years compared with 30% to 40% in those aged >65 years; younger patients also tend to have correspondingly longer OS. Still. 3+7 regimens remain the standard of care in intermediate-risk AML without FLT3 aberrations. Patients with FLT3-ITD or TKD mutations should receive midostaurin in addition to 3+7. In case of core-binding factor aberrations or a NPM1 mutation, the addition of gemtuzumab ozogamicin to 3+7 is recommended in several countries.

CPX-351 (Vyxeos® in the United States; Vyxeos® Liposomal in Europe) is a nanoscale liposomal dual-drug encapsulation of daunorubicin and cytarabine at a synergistic 1:5 molar drug ratio and is approved by the U.S. Food and Drug Administration and the European Medicines Agency as induc-tion and consolidation therapy for adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes (AML-MRC; e.g., AML with antecedent myelodysplastic syndromes [MDS] or MDS/myeloproliferative neoplasms, de novo AML with certain MDS-related changes, and multilineage dysplasia in the absence of NPM1 or biallelic CEBPA mutations); current management guidelines for AML also recommend CPX-351 for patients with these AML subtypes. CPX-351 allows the maintenance of a synergistic drug ratio in plasma following administration, and prolongs drug exposure relative to the free drugs. Further, the CPX-351 liposome is preferentially taken up by leukemia cells versus normal cells in the bone marrow, followed by intracellular release of the encapsulated drugs.

In a randomized, open-label, phase 3 trial, CPX-351 induction followed by consolidation was compared with 7 + 3 in 309 patients aged ≥60 years with high-risk/secondary AML. CR was achieved by significantly more patients in the CPX-351 group relative to the 7 + 3 group (37.3% vs 25.6%; P = 0.04). The primary endpoint analysis, which included a median follow-up of 20.7 months, found significantly longer median OS with CPX-351 versus 7 + 3 (9.56 vs 5.95 months; hazard ratio [HR] = 0.69 [95% confidence interval (CI): 0.52, 0.90]; 1-sided P = 0.003). A final analysis of the study, which included up to 5 years of follow-up, confirmed the improvement in OS observed with CPX-351 versus 7 + 3, with an HR that was consistent with the primary endpoint analysis and Kaplan-Meier–estimated 5-year survival rates of 18% versus 8%. Several real-world analyses in Europe suggest that patients who receive allogeneic HCT do benefit most from induction therapy with Vyxeos.

Ongoing trials will answer the question whether Vyxeos will also be beneficial for younger patients with intermediate-or low-risk AML.
In summary, patients with AML at initial diagnosis should be carefully assessed for the tolerability of intensive therapy as no comparative treatment with similar efficacy has been developed, so far. Biological risk and eligibility for allogeneic HCT are major factors for further treatment algorithms.

SY05

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SY06

When and whom to start treatment of CLL patients and how to optimally manage CLL patients with Imbruvica

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The treatment landscape for chronic lymphocytic leukemia (CLL) has dramatically changed due to the introduction more than a decade ago of the first BTK inhibitor. Together with BCL-2 inhibitor, this has allowed to progressively move away from immunochemotherapy to chemo-free treatments for most if not all patients. The impressive efficacy of BTK inhibition with rapid and prolonged responses has led to a subsequent quest for improvements in this class of drugs with the production of second and third generation of BTK inhibitors that confirm and extend the great efficacy and overall tolerability of this mechanism of action.

BTK inhibitors are typically characterized by a broad efficacy in all subgroups of patients with CLL including those once considered at high risk, due to the presence of TP53 aberrations and/or unmutated IGHV genes. Response are prolonged and durable, with more than 5-8 years of follow-up in front-line but achieving rarely complete clinical responses, though this does not affect the long-term outcome of patients. Due to this, all these drugs need to be administered continuously until progression or intolerance. In terms of safety, BTK inhibitors show a cardiovascular toxicity such as an increase of the blood pressure, occurrence of atrial fibrillation/flutter and of minor and major bleeding that may lead to discontinuation if not properly managed.

The need of continuous treatment with the related risk of adverse events with time, the possibility of clonal evolution/drug resistance and the overall financial burden, has recently led the investigators to test combinations with Venetoclax (for 1 or 2 years) to allow for fixed-duration strategy that now start being used at least in some parts of the world.

The path to cure of CLL remains still open, but thanks to the use of continuous BTK inhibition our patients >65 years of age have now a life expectancy that is similar to that of unaffected individuals of the same age.

ICKSH 2023

2023 KOREAN SOCIETY OF HEMATOLOGY INTERNATIONAL CONFERENCE
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ORAL PRESENTATION

OP01-1

Prognostic value of genomic clusters using machine learning in older adults with AML

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Background : Older adults with AML have a decline in performance statues and acquired comorbidities compared to younger patients. Treatment intensity and outcomes were varied according to those factors. Various studies tried to classify genetic landscapes to predict outcomes in AML patients. However, those were mostly for younger patients treated with intensive chemotherapy. Machine learning (ML) is useful for classifying large data by calculating each data and subtracting characteristics. Given the limited data of genomic classification for older adults with AML, we analyzed genetic landscapes using ML in the context of treatment intensity.

Method : Unsupervised hierarchical clustering method was used to determine the most likely set of clusters according to cytogenetic/mutation properties at AML diagnosis. Patient selection criterion for this analysis were set as follows; (a) elderly (60 years or older) AML patients who were diagnosed in Seoul St. Mary's Hospital between Jul 2017 and Oct 2021, (b) having available information on chromosome and gene mutation at diagnosis and (c) treated with either intensive chemotherapy (IC), hypomethylating agents (HMA), or HMA plus Venetoclax (HMA/VEN). Patients who received best supportive care only were not included in this study.

Results : A total of 279 patients who met inclusion criteria were selected and their median age at diagnosis was 68 years (range 60-84). As first-line treatment, 131 patients received IC (47.0%), 76 patients received HMA only (27.2%), and 72 patients were treated with HMA/VEN (25.8%). After a median follow up of 22.5 months, the median overall survival (OS) in the three groups were 22.7, 8.8, and 12.0 months, respectively (p<0.001). We applied the ELN2022 risk stratification to these 3 different treatment groups. For IC group, there was no survival difference between favorable, intermediate, and adverse groups (p=0.069). In addition, HMA groups (p-value =0.926) and HMA/VEN group (p-value = 0.498) did not showed survival differences according to risk groups by ELN2022. Next, we conducted hierarchical clustering analysis in a total cohort, which was found to be best classified into 9 clusters by indices for determining the number of clusters. The dominant cytogenetic features of each cluster are demonstrated as follows. The cluster 1(C1) was a group that there were no dominant genomic alteration; C2 was a group that monoalleic CEBPA and FLT3-ITD mutations were mostly proportioned; C3 was ASXL1 and RUNX1 dominant; C4 was RUNX1-RUNX1T1 or CBFB-MYH11 fusion dominant; C5 was BCOR and DNMT3A dominant; C6 was NPM1 dominant with FLT3-ITD wild type, bZIP in-frame CEBPA, NRAS, and PTPN11; C7 was abnormal karyotype [-5 or del(5q); -7;-17/abn(17p)] dominant; C8 was SRSF2 and TET2 dominant ; C9 was complex karyotype dominant. Thereafter, we linked these genomic clusters with survival outcomes of each treatment arm. Among the 131 patients in the IC group, C3 and C4 were identified as favorable groups while C2, C7, and C8 were classified as adverse groups. On the other hand, in the HMA group, C1, C3, and C7 were allocated to favorable groups and C2 and C4 as adverse. In the HMA/VEN group, C1, C3, and C5 showed favorable survival outcomes while C6 and C8 showed poorer outcomes. Interestingly, we found that an allocation of each genomic cluster to three distinguished (favorable, intermediate, adverse) prognostic groups was changed by the treatment types and survival outcomes of each cluster was substantially different according to different treatment arms. The groups of C7 and C9 showed no differences in OS between IC, HMA and HMA/VEN groups (HMA vs HMA/VEN vs IC, 8.6 vs 9.5 vs 9.4 months, p=0.904). While among C4, C6, and C8, IC showed better outcomes than HMA/VEN groups (HMA/VEN vs IC, 7 vs 23.6 months, p=0.009). The HMA/VEN arm showed better outcomes than HMA only (HMA vs HMA/VEN, 9.2 vs 31.4 months, p=0.002) in the rest of clusters.

Conclusion : This study suggests that genomic clustering by unsupervised ML could identify genomic groups by co-occurrence patterns having different survival outcomes according to each treatment modality, thus potentially guiding treatment selection in older adults with AML.

Keyword : AML, Machine learning, NGS, Clustering

OP01-2

Validation of the 2022 European LeukemiaNet risk stratification for acute myeloid leukemia in the real world

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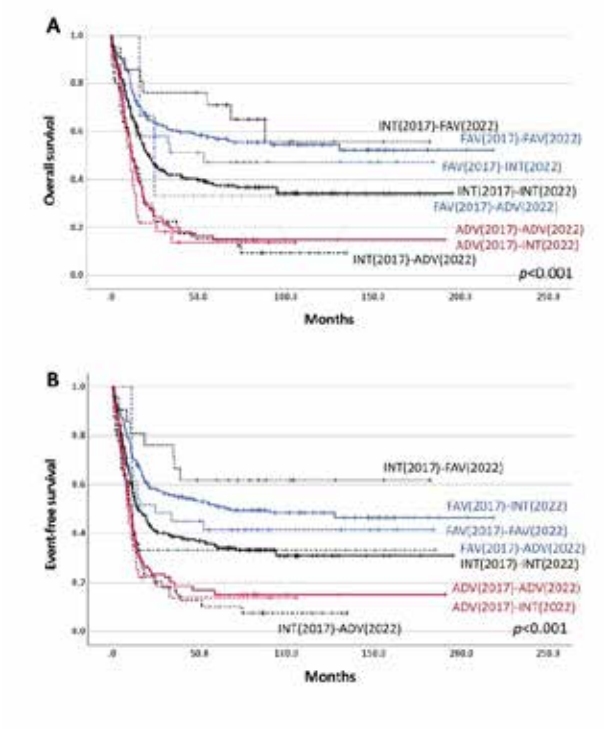
Background : The European LeukemiaNet (ELN) reported 2022 guideline of the recommendation for diagnosis and management of acute myeloid leukemia (AML). Compared to 2017, ELN 2022 recommendation has some significant changes in risk classification. First, an exclusion of the FLT3-ITD allelic ratio in the risk classification, and FLT-ITD without NPM1 mutation is no longer classified as adverse risk because of the incorporation of FLT3 inhibitor. Next, in-frame mutations affecting the basic leucine zipper region (bZIP) of CEBPA regardless of monoallelic or biallelic is classified as favorable risk group. Another important change is the inclusion of myelodysplasia-related gene mutations, and patients with these gene mutations are now categorized as adverse risk group. The purpose of this study was to verify and compare the prognostic predictability between previous and new recommendation in the real world.

Method : A total of 624 patients who were newly diagnosed with AML from October 1998 to October 2014 in seven institutions were included in this study. Patients who achieved complete remission (CR) received consolidation chemotherapy with or without allogeneic hematopoietic stem cell transplantation (HCT), depending on the availability of a matched donor. Genetic factors were not considered while considering allogeneic HCT. Cryopreserved bone marrow or peripheral blood samples obtained at diagnosis were archived. Genomic DNA was extracted using QIAamp DNA blood mini-kits (Qiagen, Valencia, CA, USA) according to the manufacturer's protocol. Genetic profiling included the targeted deep sequencing of 45 genes, which had been selected based on recurrent driver mutations from previous studies. Agilent custom probes were designed to cover the entire exon regions of targeted genes and sequenced using an Illumina HiSeq 2000 sequencer. The threshold of mutation positivity was defined as a variant allele frequency≥2%.

Results : All of the 624 patients were older than 18 years and age with median age was 51 years (range 18-84). All patients were treated with induction chemotherapy using a standard 3+7 protocol, and 523 patients (83.8%) achieved CR. Among them, 235 patients (44.9%) proceeded to allogeneic HCT. After median follow-up of 84.4 months, median overall survival (OS) was 22.0 months and median event-free survival (EFS) was 16.2 months in all patients. By applying the 2022 ELN risk classification, each risk groups showed significant prognostic difference with Kaplan-Meier analysis of OS (P<0.001) and EFS (P<0.001) in all patients. According to ELN 2017 risk stratification, 218 patients (34.9%) were in favorable risk group, 298 patients (47.8%) were in intermediate risk group, and 108 patients (17.3%) were in adverse risk group. Among the previously favorable group, 31 patients were reclassified as intermediate risk group and 3 patients as adverse risk group, and there was no significant prognostic difference in OS (P=0.289) and EFS (P=0.279) between patients newly classified as favorable risk group and those reclassified as intermediate or adverse risk groups. But in patients without allogeneic HCT, favorable group by 2022 edition showed significantly longer OS (P=0.003) and EFS (P<0.000) than intermediate or adverse groups. Among the previously intermediate risk group patients, 21 patients were reclassified as favorable group and 46 patients as adverse risk group, and each group showed significant difference of OS (P<0.001) and EFS (P<0.001). Also, in adverse risk group patients by the 2017 edition, 33 patients were reclassified as intermediate risk group. Because the anti-FLT3 inhibitor therapy was not available at that times, patients who reclassified as intermediate group showed no survival difference compared to the patients remaining in the adverse group. The survival analyses comparing ELN 2017 and ELN 2022 are described in figure 1.

Conclusion : ELN 2022 guideline is superior to the ELN 2017 for risk stratification and better predicts the prognosis of patients with AML in the real world.



OP01-3

A paired outcome evaluation of Wilms Tumor-1 (WT-1) gene mutation and expression in acute myeloid leukemia

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Background : Acute myeloid leukemia (AML) is a complex hematopoietic neoplastic disorder characterized by uncontrolled blast cell proliferation and bone marrow failure. Wilms Tumor 1(WT-1) gene is primarily considered a tumor suppressor gene and is located at 11p13.7, which, encodes a transcription factor. It is involved in biological processes such as cell growth, proliferation, differentiation, and apoptosis. There has been limited data available on the impact of the WT1 gene on the biology of AML. In this study, we aim to evaluate the association of Mutation and expression of WT1 gene mutation in newly diagnosed primary cases of AML and its correlation with clinical features and disease outcome

Method : Bone marrow (BM) and Peripheral blood (PB) samples having blast count of ≥20%, were collected from 100 newly diagnosed cases of AML. The genomic DNA and RNA were extracted, quantified by spectrophotometry, and their quality was checked by agarose gel electrophoresis. In addition, genomic DNA was amplified for the coding region and intron-exon flanking of exons 7 & 9 of the WT-1 gene using PCR, and amplified PCR products were sequenced with the help of Sanger sequencing to confirm WT-1 mutations. The extracted RNA was reverse transcribed into cDNA, followed by a real-time PCR-based quantitative assessment of WT-1gene expression. The statistical data analysis was done using (SPSS 16.0 and Graph Prism Software).

Results : Of the 100 subjects studied, 60 cases were male (60%), and 40 were females (40%) with a median age of 17.5 years (range-3 months - 69 years). 2 out of 100 cases (2%) showed point mutation, i.e., single base substitution was found only in exon 9. We have reported two novel mutations on exon 9 of the WT-1 gene due to the single base substitution of nucleotide (1373 G>C), resulting change in the amino acid sequence of the protein (p.R432P and R458P) and among all analyzed AMLs 12 cases (12%) had synonymous single nucleotide polymorphism (SNP) exclusively on exon seven which has been previously reported in SNP database (rs16754). Eighty-one cases (81%) showed overexpression of the WT-1 gene at the time of diagnosis as compared with control samples (p= <0.001). In all AML patients, WT-1 expression was positively associated with high marrow blast counts, M4 subtype, and adverse risk cytogenetic compared to patients with low WT-1 expression levels. While there were no statistically significant differences in clinical parameters like hemoglobin levels, white blood cells count (WBCs), platelets count, & blast cell percentage at primary diagnosis between wild-type and mutant-type cases. In Survival Analysis, poorer overall survival was seen in patients with WT1 mutation and higher WT-1 gene expression than in the lower expression group.

Conclusion : The overexpression and mutation of the WT-1 gene were positively associated with inferior outcomes suggesting a role of WT1 in AML. Thus, this gene can be considered a promising molecular marker for prognosis, improved risk stratification, and MRD monitoring in AML.

Keyword : AML, WT1 Gene Expression, WT1 gene Mutation, Prognosis

OP01-4

CEBPA mutations in 1716 Korean patients with acute myeloid leukemia

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Background : CCAAT/enhancer binding protein alpha (CEBPA) is a major myeloid transcription factor encoded by the CEBPA gene, which is mutated in 5-15% of adult acute myeloid leukemia (AML). CEBPA mutations (CEBPAmu) can be divided into two groups based on their location and type: an N-terminal frameshift mutation in transcription activation domains (TAD) causing a 42-kDa isoform truncation and 30-kDa isoform overproduction and a C-terminal in-frame mutation in the basic leucine zipper (bZIP) region disrupting the DNA binding and dimerization of CEBPA. Previous studies have shown that patients with biallelic CEBPA mutations (CEBPAdm) have a more favorable outcome. As a result, CEBPAdm has been recognized as an independent entity in the 2016 World Health Organization (WHO) classification as well as ELN2017 recommendations. However, the impact of monoallelic CEBPA mutations (CEBPAsm) on prognosis has been less clear. Very recently, a report of 240 CEBPA-mutated patients in 4708 AML cases showed that CEBPA mutations in the in-frame bZIP domain are associated with favorable clinical outcomes regardless of mono- or biallelic mutation status. In this study, we aimed to investigate the characteristics of Korean CEBPA-mutated AML patients and find out the association between CEBPA mutation status and clinical outcomes.

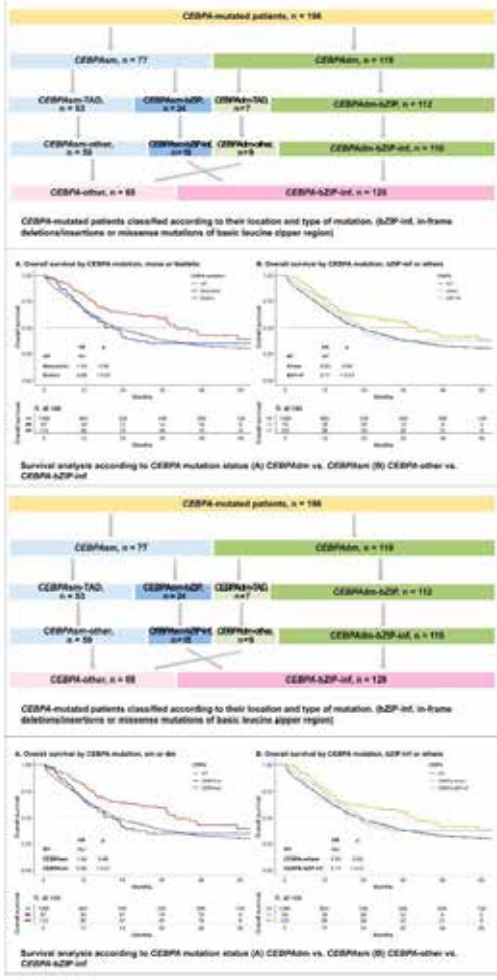
Method : This study includes 1716 adult patients with newly diagnosed AML in the Seoul St. Mary's Hospital from December 2013 to December 2021. Patients were diagnosed according to the WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues based on morphology, immunophenotyping, cytogenetics, and molecular genetics. Next-generation sequencing (NGS) was performed on initial bone marrow (BM) samples using St. Mary's customized panel for acute leukemia covering 67 genes (Thermo Fisher Scientific, Waltham, MA, USA). Sanger sequencing was used to confirm mutations of CEBPA and NPM1, and fragment length analysis was used to identify FLT3 internal tandem duplication (FLT3-ITD). Conventional BM karyotyping was performed on G-banded metaphase chromosomes using a routine laboratory protocol. All available patients regardless of treatment regimen (intensive 7+3 chemotherapy, hypomethylating agent with or without venetoclax, and best supportive care) were included. To investigate the prognostic impact of CEBPA mutation status in AML patients, clinical outcomes were analyzed through a retrospective review of medical records. Overall survival (OS) curves were estimated using the Kaplan-Meier method and analyzed with the log-rank test.

Results : A total of 315 individual CEBPA mutations were identified in 196 (11.4%) of 1716 patients, which were 119 patients (60.7%) with CEBPAdm and 77 patients (39.3%) with a CEBPAsm. Of the CEBPAdm patients, 110 (92.4%) of 119 patients harbored at least one in-frame mutation in the bZIP domain (CEBPAmubZIP-inf), comprising 100 in-frame deletions/insertions and 10 missense mutations. These patients included 105 patients with both CEBPAmubZIP and CEBPAmuTAD and 5 patients with two CEBPAmubZIP. Other CEBPAdm patients included 7 patients (5.9%) with 2 CEBPAmuTAD and 2 patients (1.7%) with CEBPAmuTAD and out-of-frame mutation in the bZIP domain (CEBPAmubZIP-other)(1 frameshift and 1 nonsense mutation). Three patients had mutations (2 CEBPAmubZIP-inf and 1 CEBPAmuTAD) with high variant allele frequencies indicating a homozygous status. Of the CEBPAsm patients, 18 (23.4%) of 77 patients carried CEBPAmubZIP-inf, consisting of 12 in-frame deletions/insertions and 6 missense mutations. The remaining CEBPAsm patients were 53 patients (68.8%) with CEBPAmuTAD (43 frameshift and 10 nonsense mutations) and 6 patients (7.8%) with CEBPAmubZIP-other (6 frameshift mutations). Additional mutations were identified in 93 (83.0%) of 112 patients with CEBPA-mutated AML through targeted NGS. The most frequently mutated genes were TET2 (19.6%; 22 of 112), WT1 (17.0%; 19 of 112), NRAS (15.2%; 17 of 112), CSF3R (11.6%; 13 of 112), GATA2 (10.7%; 12 of 112), NPM1 (10.3%; 20 of 195), DNMT3A (8.9%; 10 of 112), RUNX1 (8.0%; 9 of 112), and IDH2 (7.1%; 8 of 112). Furthermore, we investigated the correlation of CEBPA mutation status with characteristics of other genetic alterations. Of the 1703 patients (99.2%) whose cytogenetic data were available, patients with CEBPA mutations were more likely to have a normal karyotype compared to CEBPA-wild type (CEBPA-WT) (CEBPA-WT, 36.0%; CEBPAsm, 53.2%; CEBPAdm, 74.8%; CEBPA-bZIP, 69.9%; CEBPA-bZIP-inf, 72.7%). NPM1 and FLT3-ITD results were available in 1703 (99.2%) and 1653 (96.3%) patients, respectively. NPM1 was mutated in 17.4% of CEBPA-WT, 25.0% of CEBPAsm (5.6% of CEBPAsm-bZIP-inf and 31.0% of CEBPAsm-other), 0.8% of CEBPAdm (0% of CEBPAdm-bZIP-inf and 11.1% of CEBPAdm-other), 2.9% of CEBPA-bZIP, and 0.8% of CEBPA-bZIP-inf. FLT3-ITD was detected in 18.9% of CEBPA-WT, 31.6% of CEBPAsm (11.1% of CEBPAsm-bZIP-inf and 37.9% of CEBPAsm-other), 9.2% of CEBPAdm (9.1% of CEBPAdm-bZIP-inf and 11.1% of CEBPAdm-other), 10.3% of CEBPA-bZIP, and 9.4% of CEBPA-bZIP-inf. Survival data for 1547 out of 1716 patients were available, and we compared OS in these patients according to the CEBPA mutation status. As well known, we could verify a significantly superior survival in CEBPAdm patients than in CEBPAsm or WT patients (median OS; WT vs. CEBPAsm vs. CEBPAdm: 22.6 months vs. 21.0 months vs. 40.3 months, hazard ratio (HR) to WT in Cox model; CEBPAsm vs. CEBPAdm: 1.00 vs. 0.66, p; 0.99 vs. < 0.01, respectively). Additionally, we found a significant difference in OS according to the

CEBPAmubZIP-inf (median OS; WT vs. CEBPA-others vs. CEBPA-bZIP-inf: 22.6 months vs. 23.2 months vs. 40.1 months, HR to WT in Cox model; CEBPA-others vs. CEBPA-bZIP-inf: 0.93 vs. 0.71, p; 0.68 vs. < 0.01, respectively).

Conclusion : Our study suggests that in-frame mutation of CEBPA in the bZIP domain may be a valuable prognostic marker in AML, with the potential to inform treatment decisions and improve patient outcomes. However, we could not clearly confirm that the classification according to CEBPAmubZIP-inf showed a more demarcating difference in OS prediction than the previous classification according to mono- or biallelic mutation. Additional subgroup analysis on prognosis according to other genetic alterations is needed to fully elucidate the implication of these findings. Further research is also needed to better understand the biological mechanisms underlying the observed associations.

Keyword : Acute myeloid leukemia, CCAAT-Enhancer-Binding Protein-alpha, Basic-Leucine Zipper Transcription Factors, In-frame mutation, Korean



OP01-5

Antileukemic effect of cyclin-dependent kinase 7 inhibitor, YPN-005 combined with FLT3 inhibitor in FMS-tyrosine kinase 3 -mutated acute myeloid leukemia

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Background : FMS-like tyrosine kinase-3 (FLT3) mutation which is found in approximately 25% of acute myeloid leukemia (AML) is associated with a poor prognosis. Although several tyrosine kinase inhibitors (TKIs) have been introduced for treating FLT3-mutated AML, single agent FLT3-TKI showed limited clinical outcomes. Cyclin-dependent kinase 7 (CDK7) has a critical role in transcription regulation and cell cycle transition, and CDK7 inhibition showed antitumor activities in various cancers including AML. We previously identified an antileukemic effect of YPN-005, a CDK7 inhibitor, in AML cells, especially in those harboring FLT3-ITD mutation. In this study, we investigated the efficacy of YPN-005 in combination with FLT3 inhibitors in AML cell lines and primary AML cells with FLT3-ITD mutation.

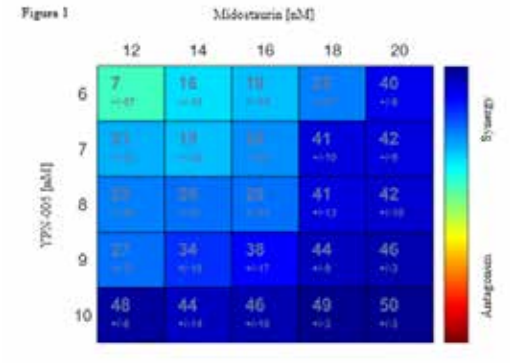
Method : The synergistic effect of YPN-005 and FLT3-TKI combination therapy was assessed based on the cell viability assay and Bliss independence model using FLT3-mutated AML cell lines (MOLM-13, MOLM-14, and MV4-11) and FLT3-ITD-expressing BaF3 cells (BaF3/ITD). FLT3-TKIs include midostaurin, gilteritinib, and quizartinib. The level of apoptosis was measured by Annexin V-FITC/propidium iodide staining. Protein levels of cleaved poly PARP, caspase 3, c-MYC, and MCL1 were evaluated by western blot analysis. Changes in mitochondrial membrane potential (MMP) were detected by flow cytometry analysis of fluorescent TMRE (tetramethylrhodamine, ethyl ester) staining, and damaged mitochondria were indicated by electron microscope. We performed a colony-forming unit (CFU) assay to evaluate combination effects in primary AML cells which were obtained from bone marrow samples of patients with FLT3-ITD mutated AML. Leukemic orthotopic mouse model was established with pGFP-transduced MOLM-13 cells in NOG (CIEA Inc., japan) and NRG (JA BIO, Inc., Korea) mice.

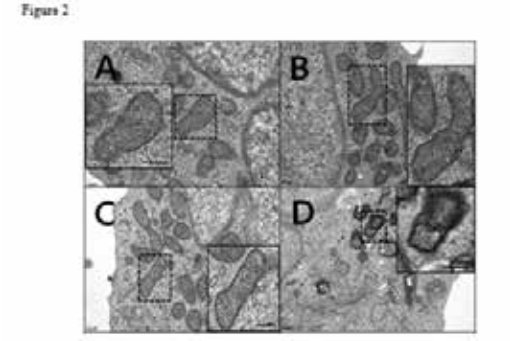
Results : The combined treatment with YPN-005 and FLT3 inhibitors significantly inhibited cell growth in FLT3-mutated AML and BaF3/ITD cell lines with strong synergistic effects (Figure 1). This

antileukemic effect was related to apoptotic cell death with an increased proportion of annexin-V-positive cells and upregulated cleaved PARP and caspase 3. The western blotting assays also showed that co-inhibition of CDK7 and FLT3 reduced the expression of phosphorylated FLT3 and STAT5, c-MYC, and MCL1 protein. As decreased MMP is known to be associated with earlier apoptosis, we assessed MMP before and after combined treatment with YPN-005 and FLT3 inhibitors to further evaluate the mechanism of apoptosis. The FLT3 and CDK7 inhibition significantly induced loss of MMP and mitochondrial damage which was revealed by flow cytometry with TMRE staining and electron microscope, respectively (Figure 2). We next evaluated CFU production in primary AML cells with FLT3-ITD mutation ex vivo after treatment with YPN-005 and FLT3 inhibitors. The result showed that FLT3 and CDK7 co-inhibition more suppressed colony formation compared to the treatment with each single agent. In addition, YPN-005 and quizartinib combination treatment showed superior survival outcomes compared to YPN-005 or quizartinib monotherapy in an orthotopic mouse model.

Conclusion : In conclusion, our study identified that YPN-005, a CDK7 inhibitor combined with FLT3 inhibitors exerted a synergistic antileukemic effect by inducing apoptosis and suppressing FLT3/STAT5 and anti-apoptotic proteins through disruption of mitochondrial function in FLT3-ITD mutated AML cells. These results provide preclinical evidence of combined treatment of YPN-005 and FLT3 inhibitor for therapeutic strategies for FLT3-mutated AML.

Keyword : FLT3-ITD, CDK7 inhibitor, Mitochondrial dysfunction, Apoptosis





OP01-6

DRP1 inhibition enhances venetoclax-induced mitochondrial apoptosis in TP53-mutated acute myeloid leukemia cells through BAX/BAK activation

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Background : Although TP53 mutations in acute myeloid leukemia (AML) are associated with poor response to venetoclax, the resistance mechanism is unclear. TP53 is suggested to be involved in mitochondrial dynamics, which could regulate drug resistance in various cancer cells. dynamin-related protein 1 (DRP1) is the key protein that induces mitochondrial fission and increasing evidence shows the pivotal role of mitochondrial fission in chemoresistance. However, the influence of TP53 on mitochondrial dynamics and the role of DRP1 in the chemoresisgance are yet to be investigated in AML. In the present study, we investigated the functional role of DRP1 in venetoclax sensitivity in AML cells with respect to TP53 mutation status.

Method : The effects of DRP1 inhibition on venetoclax-induced cell death were compared in TP53-mutated and TP53 wild-type leukemia cell lines as well as in primary leukemic blasts obtained from patients with TP53-mutated AML.

Results : In contrast to TP53 wild-type AML cell lines (MOLM-13 and MV4-11), the extent of venetoclax-induced apoptosis was markedly lower in TP53-mutated AML cell lines (THP-1 and Kasumi-1). MMP disruption was markedly lower in TP53-mutated AML cells compared to that in TP53 wild-type AML cells after venetoclax treatment. The protein levels of DRP1 and phosphorylated-DRP1 at S616 reduced in TP53 wild-type AML cells after venetoclax treatment, but was not affected in TP53-mutated AML cells. Combined treatment of TP53-mutated AML cells with venetoclax and a TP53 activator NSC59984 led to suppression of DRP1 together with increased apoptosis. Combination treatment of DRP1 inhibitor, Mdivi-1, and venetoclax significantly increased the level of apoptosis in TP53-mutated AML cell lines and primary leukemic blasts obtained from patients with TP53-mutated AML. Addition of Mdivi-1 to venetoclax led to a significant increase in the extent of intracellular ROS

generation and disruption of the MMP compared to that observed with venetoclax alone in TP53mut AML cells. These findings were consistent with the results of Drp1 knockdown experiments using anti-Drp1 siRNA. Moreover, combined Mdivi-1 treatment or Drp1-silencing with venetoclax considerably increased the extent of cytosolic cytochrome C release from the mitochondria in TP53-mutated AML cells. When we examined changes in the expression of several BCL-2 family proteins after treatment of TP53-mutated AML cells with venetoclax in the presence or absence of DRP1 inhibition, BCL-2 protein levels were not altered by venetoclax and/or Mdivi-1 treatment. MCL-1 and phosphorylated MCL-1 at T163 were upregulated by venetoclax treatment alone, however, combination treatment of Mdivi-1 and venetoclax markedly decreased the protein levels of MCL-1 and phosphorylated MCL-1 at T163. Downregulation of BCL-xL was also observed with combination treatment of Mdivi-1 and venetoclax. These findings were accompanied with upregulation of NOXA, PUMA, BAK, and BAX.

Conclusion : These results suggest that targeting DRP1 in TP53-mutated AML cells may represent a novel strategy to overcome chemoresistance. Hence, combination therapy with DRP1 inhibitors and venetoclax may be a useful approach for the treatment of patients with TP53-mutated AML. Our findings may provide valuable insights into the molecular mechanism underlying venetoclax resistance in TP53-mutated AML cells as well as potential therapeutic targets.

Keyword : TP53 mutation, DRP1 inhibition, Venetoclax resistance, Mitochondrial apoptosis, Acute myeloid leukemia

OP02-1

Classical Hodgkin lymphoma: Clinical features, prognostic factors, and treatment outcomes in a Malaysian tertiary centre

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Background : Classical Hodgkin lymphoma (cHL) is a clinicopathologically unique, aggressive B cell lymphoma. It remains one of the most curable of all haematological malignancies. This study aimed to determine the clinical characteristics, prognostic factors, treatment regimens, response rates, and survival data of patients diagnosed with cHL in a tertiary centre in Malaysia.

Method : A retrospective review was conducted to include patients with the diagnosis of cHL from 2013 till 2021. Demographic data, clinical characteristics, treatment regimes, and outcomes were collected and analysed using SPSS version 26.0.

Results : A total of 204 patients were recruited with the median age of 27 (range 13-75) years old. Majority of the patients were male (55.9%) with 75% of them were Malay. Nodular sclerosing remained the most common subtype and accounted for 67.6%, followed by mixed cellularity (9.8%), and others (22.6%). One hundred and forty-six (71.6%) patients presented with advanced-stage disease, and among these, 24.5% had International Prognostic Score (IPS) ≥4. All the patients received chemotherapy and ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) was the most common used chemotherapeutic combination followed by escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone). Eighty-nine patients with advanced-stage disease (61.0%) received PET-adapted therapy. Following treatment, 71.1% achieved complete remission (CR), 14.2% had partial remission, and 11.8% had progressive disease. Twenty-four patients had progressive disease, and 6 patients had relapsed disease. Among these, 25 of them underwent salvage therapy and autologous stem cell transplantation, and 14 patients achieved second CR. A total of 45 patients received radiotherapy as consolidation, of which 27 were from advanced stage and 18 from early stage disease. With a median follow-up of 36 (range 1-118) months, the 3-year and 5-year overall survival (OS) of the entire cohort were both 91.6%. The 3-year and 5-year progression-free survival (PFS) were 73% and 72%, respectively. The 5-year OS and PFS in advanced-stage disease were 89.2% and 66.9%, compared to 96.6% and 83.4% in early-stage disease. Presence of extra nodal involvement (p=0.001) and disease stage (p=0.046) had significant impact on the 5-year PFS, but only extra nodal involvement was linked to 5-year OS (p=0.019). Extra nodal involvement remained an independent prognostic factor for poorer PFS under the multivariate cox proportional hazards model.

Conclusion : The treatment outcomes from our centre are comparable to the published data. Longer follow-up will be beneficial to assess the long-term complications such as secondary malignancy.

Keyword : Hodgkin Lymphoma, Outcome, Malaysia

OP02-2

Phase II study of bortezomib/dexamethasone induction and maintenance therapy in relapsed/refractory cutaneous T cell lymphoma (CISL1701 study)

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Background : Cutaneous T cell lymphoma (CTCL) is a heterogenous group of extranodal lymphoproliferative disorders with primary skin involvement, originating from tissue resident T cells in skin. Typically, the disease has a chronic relapsing course. Although novel monoclonal antibody-based agents have recently introduced, currently available treatment options rarely lead to durable remissions and patients often require multiple lines of therapy for control of disease. It has been reported that the activity of NF-κB plays a critical role in the proliferation and survival of tumor cells in CTCL. A constitutive increase in NF-κB activity was known to be associated with an active mutation of TNFR2 in patients with CTCL. In this context, in vitro treatment with bortezomib resulted in decreased survival and migration of CTCL cells. Herein, we performed a multicenter prospective phase II trial to investigate the efficacy and safety of bortezomib in combination with dexamethasone in patients with relapsed/refractory CTCL.

Method : In this phase II study, patients with CTCL (including mycosis fungoides, Sezary syndrome, primary cutaneous CD30+ lymphoproliferative disorders and primary cutaneous peripheral T-cell lymphoma, unspecified) were treated with bortezomib 1.6 mg/m2 and dexamethasone 40mg on D1/8/15 of 28-day cycle for 8 cycles. Thereafter, maintenance therapy with bortezomib 1.6 mg/m2 and dexamethasone 40mg every 4 weeks was followed for maximum of 1 year. The primary end point was overall response rate assessed by investigators according to ISCL-USCLC-EORTC consensus criteria. Secondary end points included objective global response lasting at least 4 months (ORR4), progression-free survival, overall survival and toxicity profiles.

Results : From 14 institutions in the republic of Korea, 29 patients were recruited in this trial. Most common histologic subtype was mycosis fungoides and median number of previous systemic therapies was 2 lines. Overall response was observed in 13 (44.8%) of 29 patient including 2 patients showing complete response. ORR4 was seen in 34.5%, indicating that most responders had response duration longer than 4 months. At medical follow-up duration of 18 months, median progression-free survival was 5.8 months (95% CI, 2.46 to 9.14) and median overall survival was not reached. Of note, median progression-free survival of responders was 14.0 months (95% CI, 6.85 to 21.15). Treatment-emergent adverse events were generally mild with relatively low incidence of peripheral neuropathy and hematologic toxicities.

Conclusion : Bortezomib in combination with dexamethasone has significant and sustainable activity and an acceptable safety profile in treatment of relapsed/refractory CTCL.

Keyword : Cutaneous T cell lymphoma; Mycosis fungoides, Bortezomib

OP02-3

Odronextamab in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): Phase 2 study (ELM-2) prespecified analysis results

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Background : Odronextamab is a hinge-stabilized, human IgG4-based CD20×CD3 bispecific antibody (Ab) that binds CD20 on B cells and CD3 on T cells, triggering T-cell-mediated cytotoxicity of malignant B cells. In ELM-1 (Ph1, NCT02290951), odronextamab demonstrated encouraging activity in pts with DLBCL receiving ≥2 prior lines of therapy (LOT), including a cohort of patients post-CAR T therapy (Bannerji R. et al. Lancet Haematol. 2022). The R2PD for R/R DLBCL was determined as 160 mg weekly. Here, we present for the first time, results from a prespecified analysis of the 160 mg DLBCL cohort from the ELM-2 study (Ph2, NCT03888105), which incorporated an optimized step-up regimen designed to maintain efficacy while minimizing acute toxicity including cytokine release syndrome (CRS).

Method : ELM-2 is a global, multicenter study enrolling pts at 91 sites in 13 countries. Adult pts with DLBCL who had relapsed or were refractory to ≥2 prior LOT including an anti-CD20 Ab and an alkylator were enrolled. IV odronextamab was administered in 21-day cycles with steroid prophylaxis and weekly step-up dosing during Cycle (C) 1 to mitigate risk of acute toxicity. The initial step-up regimen was 1 mg split over C1 Day (D) 1 and C1D2, and 20 mg split over C1D8 and C1D9, followed by the 160 mg full dose on C1D15 (1/20 regimen). The 1/20 regimen was revised during the study to further mitigate CRS risk. The modified regimen consisted of 0.7 mg split over C1D1 (0.2 mg) and C1D2 (0.5 mg), 4 mg split over C1D8 and C1D9, and 20 mg split over C1D15 and C1D16, followed by the 160 mg full dose on C2D1 (0.7/4/20 regimen). 160 mg weekly continued until the end of C4. After C4, maintenance treatment was 320 mg odronextamab every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint was ORR assessed by independent central review (ICR) according to Lugano 2014 criteria. CRS was assessed using 2019 ASTCT criteria.

Results : As of April 20, 2022, 121 pts with DLBCL were evaluable for safety; 90 for efficacy. Median age 67 y (range 24–88), 60% male, 80% Ann Arbor stage III–IV, 58% IPI score ≥3, median prior LOT 2 (range 2–8), 56% primary refractory and 65% double refractory to anti-CD20 Ab and alkylator in any LOT. Median duration of study follow-up was 17.1 mos. ORR and CR rate by ICR were 53% and 37%, respectively. CRs were durable; median duration of CR was not reached (95% CI: 10.2 mos–not estimable). TEAEs occurred in 117 (97%) pts, considered treatment related in 102 (84%). In the overall safety-evaluable population, the most common TEAEs (>30% all grades) were CRS (53%), pyrexia (41%), and anemia (34%). The 0.7/4/20 step-up regimen reduced the incidence of grade 2 and grade 3 CRS. All CRS events resolved with supportive measures; 20% of pts received tocilizumab and none required vasopressors or mechanical ventilation for CRS management. ICANS was reported in only 2 pts (4%) following revisions to step-up dosing, and both were low grade; ICANS occurred in 6% of pts with the 1/20 regimen. Treatment-related Grade 5 AEs occurred in 2 pts (2%), and treatment-related AEs led to odronextamab discontinuation in 8 pts (7%).

Conclusion : In the first results from a Ph 2 trial, odronextamab demonstrated clinically meaningful efficacy, durable CRs, and manageable safety. With the 0.7/4/20 regimen, the risk of high-grade CRS was mitigated, and ICANS were rare and of low grade. Updated safety and efficacy data will be presented.

Keyword : DLBCL, Bispecific antibody, Phase 2, B-NHL, Clinical trial

OP02-4

Novel subgroup analyses of subcutaneous epcoritamab monotherapy in patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL)

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Background : Epcoritamab, a subcutaneous (SC) bispecific CD3x-CD20 antibody, has demonstrated compelling, clinically meaningful efficacy across a highly refractory population in the EPCORE NHL-1 LBCL expansion cohort, as well as a manageable safety profile consistent with prior findings. Presented here are additional subgroup analyses of the efficacy and safety of epcoritamab in the LBCL expansion cohort of the EPCORE NHL-1 phase 2 trial (NCT03625037).

Method : Patients (pts) with R/R CD20+ LBCL received SC epcoritamab in 28-d cycles (QW: cycles 1–3; Q2W: cycles 4–9; Q4W: cycles ≥10). To mitigate CRS, step-up dosing and corticosteroid prophylaxis were administered in cycle 1. Subanalyses were performed for prespecified and exploratory subgroups.

Results : As of Jan 31, 2022, 157 pts with LBCL, including double/triple-hit (DH/TH) lymphoma, were treated (median age, 64 y). Pts had a median of 3 prior lines of therapy (range, 2–11); 39% had received prior CAR T. Most (61%) had primary refractory disease. Central FISH confirmed DH/TH lymphoma in 14% of pts with diffuse LBCL (DLBCL; 12/88 tested). Median follow-up was 10.7 mo. Overall response rates (ORRs)/complete response (CR) rates (by independent review committee) were 63%/39% overall and similar across subgroups: 55%/30%, primary refractory; 54%/34%, prior CAR T; 69%/42%, CAR T–naive; 50%/33%, DH/TH; and 63%/41%, non-DH/TH. Responses were seen early (median time to response, 1.4 mo). Median duration of response (mDOR) was: 12.0 mo, overall; not reached (NR), primary refractory; 9.7 mo, prior CAR T; 12.0 mo, CAR T–naive; 12.0 mo, DH/TH; and NR, non-DH/TH. Among those who achieved CR, mDOR was 12.0 mo for DH/TH pts and NR in other subgroups. Of 112 pts evaluable for minimal residual disease (MRD), 52 (46%) were negative at any time point on treatment (by ctDNA NGS assay). MRD negativity was reached early (median for complete responders, 8 wk). High MRD-negativity rates were observed across all subgroups: 43%, primary refractory; 50%, prior CAR T; 44%, CAR T–naive; 33%, DH/TH; and 49%, non-DH/TH. Responses with MRD negativity were durable and correlated with PFS. In the dose-escalation portion of this trial with longer follow-up (median, 21.1 mo; longest follow-up, 26.7 mo), durability of CR was shown in a cohort of pts with DLBCL, of which 6 pts (at ≥12 mg) remain in CR with Q4W treatment (median duration of CR, NR). After wk 12, incidence of AEs declined; only 1 pt experienced any related serious treatment-emergent AE after wk 12 (CRS grade [G] 1/2). CRS occurred in 78 pts (49.7%), events were primarily low grade (47.1% G1–2, 2.5% G3), and all but 1 resolved. Timing of CRS was predictable (most common after first full dose; median time to onset after first full dose, 20 h). ICANS was reported in 10 pts. All but 1 ICANS event occurred in cycle 1; 9 events were G1–2, and 1 event was G5 (the only treatment-related death; multiple confounding factors). Eight pts (5%) had CRS and ICANS. G3 or G4 neutropenia occurred in 33 pts (21.0%; 10.8% G3, 10.2% G4). G3 anemia occurred in 16 pts (10.2%). Few pts (n=11) discontinued epcoritamab treatment due to AEs. None discontinued treatment due to neutropenia or anemia.

Conclusion : Epcoritamab is a convenient, off-the-shelf SC therapy that has yielded deep, durable responses, including high MRD-negativity rates, across subgroups of pts with R/R LBCL. The safety profile was manageable; CRS events were mostly low grade with predictable timing. These results show consistent, clinically meaningful activity of epcoritamab in this highly refractory population.

Keyword : Clinical trials, Non-Hodgkin lymphoma, B-cell lymphoma, Aggressive lymphoma, Bispecific antibody therapy

OP02-5

The treatment outcome of tisageneucel for the patient with relapsed/refractory B-cell lymphoid malignancies in Samsung Medical Center

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Background : Although patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) have achieved more than a 60% of cure rate through immunochemotherapy, 30-40% still are in relapse or refractory situations. Among various salvage therapeutic options, CD19-positive Chimeric antigen receptor (CAR) T-cell therapy has dramatically changed the therapeutic strategies for RR-B-cell lymphoid malignancies based on superior efficacy and safety. As a result, three types of autologous CD19 CAR-T cells such as, axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel approved by the FDA as second or third-line therapeutic options for RR-B-cell lymphoid malignancies from 2019. Among them, the clinical use of tisa-cel for adult patients with RR-DLBCL or patients under 25 years with RR B-cell acute lymphoblastic leukemia (RR-B-ALL) has been allowed as the third-line treatment in Korea. Herein, we analyzed the treatment outcomes of patients who received tisa-cel tracked since 2019 and discussed those who could get benefit from actual CAR-T cell therapy in the future.

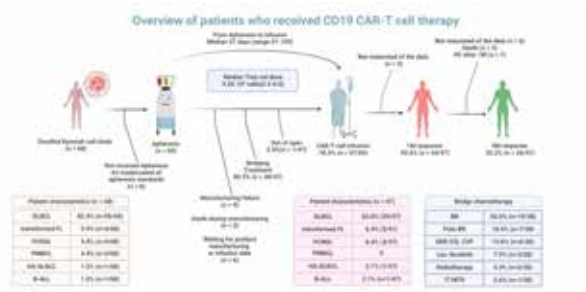
Method : A total of 68 patients registered in the Kymriah cell chain to manufacture CAR-T cells between April 2021 and November 2022. The baseline evaluation was conducted for patients who planned to receive tisa-cel therapy before apheresis, and the therapeutic response evaluation was conducted one month and three months after CAR-T cell infusion (D0) with computed tomography (CT) and positron emission tomography (PET) based on the Lugano recommendation for response assessment. In addition, the grading of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) was measured and managed through the American Society for Transplantation and Cellular Therapy (ASTCT) criteria. CARTOX-level II criteria were calculated with baseline platelet and ferritin levels. Moreover, we defined the early rituximab failure patients who received rituximab-based first-line chemo-immunotherapies and then relapsed within 12 months of initial diagnosis. Time to progression (TTP) was defined from the tisa-cel infusion date until the disease worsened. Progression-free survival (PFS) was calculated from the starting date of front-line chemotherapy to disease progression, death related to any cause, or last follow-up. The data cutoff date was December 2022, and this study was approved by the Institutional Review Board of Samsung Medical Center (approval number. 2016-11-040-019). Statistical analyses were performed using an IBM PASW version 25.0 software program (IBM SPSS Inc., Armonk, NY).

Results : Among 68 patients, 47 (69.1%) received tisa-cel infusion. 11.8% (n = 8) of patients did not undergo apheresis for manufacturing tisa-cel due to inadequate apheresis standards. In addition, 19.1% (n = 13) of patients did not receive tisa-cel finished version due to manufacturing failure (n = 4), death during manufacturing (n = 3), and ongoing manufacturing of tisa-cel or waiting for infusion date (n = 6). A total of 47 patients received the final product of tisa-cel, which took a median of 37 days (range 31-105 days). The median cell dose accounted for 3.2 x 108 cells (range 0.3-6.0 cells). During manufacturing time, 38 patients received bridge therapy, such as BR (n = 19, 50.0%), pola-BR (n = 7, 18.4%), and other cytotoxic chemotherapies (n = 6, 15.8%). The median age of patients treated with tisa-cel was 65 (range 24-77). Of 47 patients, 83.0% (n = 39) had RR-DLBCL, 6.4% (n = 3) had transformed follicular lymphoma, and 6.4% (n = 3) showed RR-PCNSL or secondary CNS lymphoma. Moreover, a patient had been diagnosed with RR-B-ALL and received allogeneic stem cell transplantation (allo-SCT) twice. The median prior lines of therapy were 3 (range 2-6), and 23.4% (n = 11) underwent autologous stem cell transplantation (auto-SCT). During the median 4.5-month follow-up (95% CI 2.7-6.3), a 1-month response evaluation could perform for 44 patients (n = 44/47, 93.6%), and a 3-months response evaluation was able to undergo 26 patients (n = 26/47, 53.2%). The response rate at one month was 72.7% (n =32/44), including 19 CR (43.2%), 1MRD-negative (2.3%), and 12 PR (27.3%). Moreover, the three-month response rate was 46.2%, including 10 CR (38.5%), 1MRD-negative (3.8%), and

1PR (3.8%). There were no patients who converted from PR to CR. The median TTP was 3.7 months (95% CI 0.4-4.7), and the median PFS was 3.4 months (95% CI 2.6-4.2) for 44 patients who were available for response assessment. The patients who experienced early rituximab failure within 12 months seemed to show inferior TTP (5.1 vs. 12.8 months, p-value = 0.115) and PFS (3.1 vs. 4.0, p-value = 0.220) than those who did not. Moreover, the patients with high CARTOX scores (ferritin≥ 2,000 ng/dL and platelet < 75,000/ul) did not show extended TTP (p-value = 0.038) and PFS(p-value = 0.001) statistically compared to those who did not. The patients who experienced grade 3 or 4 novel immunotherapy toxicities such as CRS and ICANS presented poor TTP (p-value=0.022) and PFS (p-value=0.012) Regarding safety issues, grade 3 or 4 neutropenia, anemia, and thrombocytopenia were documented in about 89.4% (n = 42/47), 47.7% (n=21/47), and 10.6% (n = 5/47). Moreover, 70.2% (n =33/47) showed all grade CRS, and 10.6% (n = 5/47) presented grade 3/4 CRS. Furthermore, grade 3/4 ICANS were identified in 4.2% (n = 2/47) among 25.5% (n = 12/47) representing all grade ICANS. Uncontrolled CRS and ICANS were the cause in 3 patients of the seven transfers to the intensive care unit (ICU), and disease exacerbation was the cause in the remaining 4 cases. 70 % of patients received tocilizumab, and 27 % were administered steroids for CRS and ICANS control according to ASTCT guidelines. 23.4% (n = 11/47) of patients needed to treat with antibiotics during the administration period after the infusion date. During follow-up duration, the number of patients with hypogammaglobulinemia or COVID-19 infection was counted at about seven (n = 7/40, 17.5%) or eleven (n = 11/47, 23.4%).

Conclusion : Although our data was analyzed based on short-term follow-up duration than the JULIET phase II study (4.5 vs. 17.8 months), the response rate seemed to be consistently well maintained, and all safety issues were well managed through anti-IL-6 antagonists and steroids. According to our analysis, inferior TTP and PFS seemed to relate to early rituximab failure within 12 months, high CARTOX scores (higher ferritin levels ≥ 2,000 ng/dL and lowered platelet, < 75,000/ul), and grade 3/4 CRS or ICANS values. However, based on our results, it was challenging to conclude the definite clinical biomarkers for early discovering the patients who expected to get superior response rates and extended survival outcomes with CD19 CAR-T cell therapy. Therefore, tisa-cel has currently considered a treatment that has secured good treatment results and safety, but continuous efforts are needed to select candidates through accumulated experience and interest.

Keyword : Diffuse large B-cell lymphoma, B lymphoblastic leukemia/lymphoma, Tisagenleucel, Chimeric antigen receptor T cell



OP02-6

How to improve clinical outcomes of tisagenlecleucel treatment in relapsed/ refractory diffuse large B cell lymphoma?

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Background : The chimeric antigen receptor (CAR) T-cell therapy is an attractive option for relapsed/ refractory (R/R) diffuse large B cell lymphoma (DLBCL) and is associated with favorable clinical outcomes even in the elderly and unhealthy populations. In Korea, Tisagenlecleucel (Tisa-cel) is the only second-generation CAR T-cell therapy approved by the Korean Ministry of Food and Drug Safety in 2021 and it was covered by National Health Insurance in April 2022. Approval was based on the phase II JULIET trial result, with a best overall response rate (ORR) of 52% and a complete response rate (CR) of 40%. We hereby present the outcome of Tisa-cel treatment and clinical application strategies.

Method : In this study, we enrolled 22 patients with R/R DLBCL treated with Tisa-cel treatment between April and September 2022 at the Catholic Hematology Hospital. All patients were initially diagnosed with de novo DLBCL and underwent at least 2 lines of che-

motherapies. As in the JULIET trial, we used bridging chemotherapy in patients with rapid disease progression. Toxicities and treatment responses were graded following the ASTCT (American Society for Transplantation and Cellular Therapy) criteria and Lugano 2014 classification, respectively.

Results : Of the 22 patients included, two did not undergo apheresis due to the rapid progression of the disease, and 20 patients underwent apheresis. Fourteen of the 20 patients (70%) received Tisa-cel, including one case of out-of-specification by CD3 cell viability of less than 70%, and among them, 11 patients underwent bridging therapy before Tisa-cel infusion. The remaining 6 patients (30%) could not receive Tisa-cel, with one case of a manufacturing failure, because disease progression drove patients to death. There were no significant differences in the clinical characteristics of the two groups except for frequent persistent grades 3-4 thrombocytopenia (100% vs. 28.6%, p=0.002) and bone marrow involvement (50.0% vs. 0%, p=0.010) in patients who could not receive Tisa-cel. Grade 3 or higher cytokine release syndrome and neurotoxicity occurred in 21.4% and 7.1% of patients, respectively; 64.3% of patients received tocilizumab, 28.5% received high-dose steroid infusion, and 35.7% underwent intensive care unit management. Among the infused patients, the best ORR and CR were 71.4% and 51.7% in the one-month response evaluation. However, with a median follow-up of 126 days (range, 41 – 175) from Tisa-cel infusion, CR decreased to 35.7% (n=5) and 64.3% (n=9) of patients eventually showed disease progression with the median progression-free survival of 97 days (95% confidence interval, 27 – 152). All patients with Myc overexpression (n=5) and persistent grades 3-4 thrombocytopenia (n=4) showed disease progression.

Conclusion : Based on real-world data with relatively poor clinical outcomes, assessing the risk of post-CAR T-cell failure and careful patient selection are crucial factors for successful CAR T-cell therapy. Elevated lactate dehydrogenase level, Myc overexpression, thrombocytopenia grade 3-4, multiple lines of treatments, lower performance status, primary refractory status, and bridging therapy before CAR-T cell infusion led to poor prognostic factors. In conclusion, the early treatment decision soon after second-line treatment failure and selecting patients with a limited burden of disease who did not require bridging therapy would become better candidates for Tisa-cel therapy.

Keyword : Tisagenlecleucel, Chimeric antigen receptor T cell, Relapsed, Refractory, Diffuse large B cell lymphoma

OP02-7

Distribution and sequential patterns of the second malignancies among the lymphoid neoplasm in South Korea

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Background : The development of the treatment of lymphoma increased the number of patients with long-term survival. Since radiotherapy and transplant are included in the treatment options, there is an increased risk of secondary cancer among patients. Furthermore, as the diagnosis at older age increased, there was a higher risk of comorbidities and histories of solid cancers. However, there are few studies to evaluate the impact of co-occurred cancers in mature lymphoid malignancies in South Korea.

Method : A total of 4187 adult patients diagnosed with lymphoid neoplasms between January 2000 and April 2021 at Seoul and Yeoido St. Mary's Hospital were included in this study. Lymphomas were classified according to the 2016 World Health Organization system.

Results : The median age who were diagnosed with Mature lymphoid neoplasm was 59(18-96) years. Patients who were Initially diagnosed with Mature-B cell neoplasm were 3455 (82.5%) and 672 (16.0%) with mature T and NK cell neoplasm. Among the B cell neoplasm, 1775 (51.4%) diffuse large B cell lymphomas (DLBCL) were the most common form of lymphoma, followed by follicular lymphoma (FL), and marginal zone lymphoma. PTCL NOS was the most dominant 215 (31.9%) in the T cell neoplasm, followed by Extranodal NK/T cell lymphoma and angioimmunoblastic T cell lymphoma. Hodgkin lymphoma was composed of 244 (5.8%) cases. Two hundred one(4.8%) patients had historic or newly diagnosed solid cancer cases, and the median diagnosed age was 64 (27-92) years. In solid cancer, lung cancer was dominant, followed by the thyroid and colorectal cancer. Among lymphoma patients with other cancers, the median time to secondary cancer after lymphoma diagnosis is 13 years. Among the 163 patients with Mature B cell lymphoma, 38 lung cancers are associated with inferior overall survival (p-value =0.023). In the DLBCL, patients with other cancers, accompanied by eight prostate cancer, impact poorer survival. (Hazard ratio 2.84, 95% Confident interval, 1.22- 6.61, p-values =0.011). By association analysis, FL followed by DLBCL or DLBCL followed by FL were the most common forms of overlapped hematologic malignancies. DLBCL, followed by lung cancer, showed the highest support and confidence in secondary cancer.

Conclusion : Solid cancers in patients with lymphoma showed similar trends with the Korean population. Secondary cancer could influence the treatment timeline and increase treatment-related mortality in patients with lymphoma. This study suggested awareness of secondary malignancies in mature lymphoid neoplasms.

Keyword : Secondary cancer, Association analysis, Non Hodgkin lymphoma

OP03-1

Genomic alterations in chronic myeloid leukaemia patients who failed second generation tyrosine kinase inhibitor

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Background : The practice of prescribing Chronic Myeloid Leukaemia (CML) patients with indefinite tyrosine kinase inhibitors (TKIs) has gone uncontested, and the capacity of TKIs to eliminate the CML clone is also still unknown. Although the vast majority of CML patients do respond to TKIs, nonetheless, resistance may develop either de novo or during treatment. TKI resistance pathways are commonly classified as BCR-ABL1-dependent or BCR-ABL1-independent. The molecular evolution causal for this subset of individuals to lose molecular remission is still unknown. In this study, our goal was to explore the molecular mechanisms involved in resistance to TKI in patients who failed second-generation TKIs in order to identify potential genetic signatures and pathways that lead to TKI resistance.

Method : At the time of analysis, a total of 34 samples (2 responder and 32 non-responder) were subjected to whole-transcriptomic analysis. mRNA gene expression, gene fusion and single nucleotide variation (SNV) were determined using Illumina DRAGEN Bio-IT Platform pipeline.

Results : A preliminary results for a total of 386 differentially regulated genes (DEGs) were identified, with 148 genes up-regulated and 238 genes down-regulated in the non-responder group. The DEGs were enriched in histone acetylation/deacetlylation (HDACs/HATs), DNA methylation, and RNA polymerase regulation pathway. Further analyses demonstrated that CCCDC32-CBX3 fusion is significantly associated with non-responder.

Conclusion : Techniques with enhanced sensitivity such as next-generation sequencing and the use of artificial intelligence techniques coupled with the development of mathematical modelling and computational prediction methods could reveal the underlying mechanism of drug resistance and facilitate the design of more effective treatment strategies for improving drug efficacy in CML patients. This preliminary analysis found that individuals who failed second-generation TKIs express a potentially unique genetic signature. Analysis using larger sample size is necessary to validate these findings.

Keyword : CML, TKI, Second generation TKI, 2GTKI, NGS

OP03-2

Genome-wide methylation profiling of BCR/ABL1-negative myeloproliferative neoplasms

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Background : Even though Philadelphia chromosome (Ph)-negative myeloproliferative neoplasms (MPNs) have common driver mutations such as JAK2, CALR, or MPL mutations, they vary in terms of the severity of symptoms and the progression to marrow fibrosis or acute leukemia, suggesting the role of epigenetic machinery in the pathogenesis and the progression of Ph-negative MPNs. In this study, we performed genome-wide DNA methylation arrays on Korean patients with Ph-negative MPNs for the first time.

Method : The study included 6 patients with polycythemia vera (PV) with JAK2 V617F mutation, 8 essential thrombocythemia (ET) patients with JAK2 V617F mutation, 9 ET patients with CALR mutation,

6 patients with primary myelofibrosis (PMF) with JAK2 V617F mutation and 7 patients with lymphomas without bone marrow (BM) involvement who served as controls. Genomic DNA was extracted from BM aspirates. Genome-wide methylation profiling was done by Infinium MethylationEPIC BeadChip. The raw methylation signal was inputted into the minfi R package. Then, a series of data filtering was done, namely, excluding the data from probes with bad detection, probes with SNPs and cross-hybridization, probes in sex chromosomes, and probes with infinite M values. Then, the filtered methylation signal was normalized by noob (normal-exponential using out-of-band probes) method. Differential methylation analysis on the normalized methylation signal was done next to identify differently methylated probes (DMPs) between two groups of patient cases. The probes with less than a false discovery rate (FDR) of 0.01 were deemed differentially methylated. To identify prevalent biological themes among the DMPs, functional enrichment analysis with respect to pathways in the KEGG database was done. The pathways with less than FDR 0.05 were deemed significantly enriched.

Results : We compared methylation between a pair of three groups of patients: (i) a highly severe group that consists of PMF patients; (ii) a less severe group (n=19) that consists of PV or ET patients with JAK2 V617F or CALR mutations; and (iii) a control group. There were thus a total of three pairwise comparisons, namely, highly vs less, highly vs normal, and less vs normal. From these comparisons, the following number of DMPs were identified: 66,348 DMPs from the highly vs less comparison, 42,675 DMPs from the highly vs normal comparison, and 126 from the less vs normal comparisons. A considerable number of DMPs were identified from the first two comparisons whereas only very few DMPs were obtained from the last comparison. Therefore, the highly severe group has a highly distinctive methylation pattern when compared to either the less severe group or the normal group, whereas the less severe group and the normal group are indiscernible with respect to methylation. Functional enrichment analysis of the DMPs from the first two comparisons identified a number of biological pathways. There were 76 such pathways from the highly vs less comparison, and 41 such pathways from the highly vs normal comparison. By literature search, we found that 38 (50%) out of the 76 pathways and 16 (39%) out of the 41 pathways were those which are relevant to MPN.

Conclusion : Our results showed that DNA methylation differs depending on the disease categories among Ph-negative MPNs, suggesting that alterations in the DNA methylation landscape should play an important role in the pathogenesis of Ph-negative MPNs and it could serve as a putative target of treatment.

Keyword : Myeloproliferative neoplasms, Methylation

OP03-3

Machine learning based predictive classifier for bone marrow failure syndrome using complete blood count and differential cell populations

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Background : Bone marrow failure syndrome (BMFS) is a heterogenous collection of non-malignant hematologic diseases defined by cytopenia in one or more lineages. Aplastic anemia (AA), myelodysplastic syndrome (MDS), and paroxysmal nocturnal hemoglobinuria (PNH) are the three primary diseases that comprise acquired BMFS. For prompt diagnosis and treatment initiation, it is essential that primary care physicians identify BMFS early and refer patients to specialists. Complete blood count (CBC) profiles like MCV or RDW offer additional diagnostic information, but they are difficult to comprehend without hematologic expertise. Our goal was to create a machine learning-based classifier that would identify CBC profiles indicative with BMFS and prompt confirmative tests such as bone marrow (BM) exam.

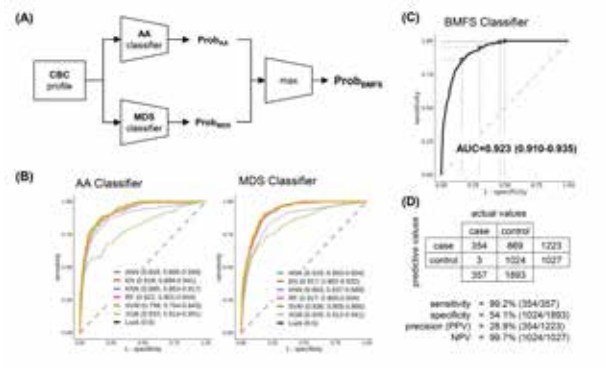
Method : Data from patients who had BM exams between January 2010 and May 2021 at Seoul National University Hospital in South Korea were collected retrospectively. Patients were eligible if their CBC results were available within one month of their BM exam. Diagnosis was determined based on ICD-10 codes and concordant results of BM exam. Case group included cases diagnosed with AA, MDS, and PNH, while control group included all the other cases. Age, sex, and CBC profiles were used. We selected 17 CBC features that were commonly tested: hemoglobin, hematocrit, RBC, RDW, MCH, MCHC, MCV, MPV, PCT, PDW, PLT, WBC, ANC, lymphocyte, monocyte, basophil, and eosinophil. Patients who were missing more than 20% of these features were excluded. Then, missing values were imputed with MissForest algorithm. Cases before 2019 were set as training set (75% of the total), and the remaining 25% were placed as test set. We developed a BMFS classifier that combines two separate binary classifiers for AA and MDS. To develop these two classifiers, we applied six machine learning models:

artificial neural network, elastic net, k-nearest neighbor, random forest, support vector machine, and XGBoost. For each model, hyperparameter tuning was conducted on the training set using 10-fold cross-validation. The final BMFS probability was provided by the maximum of the output probabilities from AA and MDS classifiers.

Results : We collected data of 9,056 patients. Among them, there were 1,286 BMFS cases (AA, 591 cases; MDS, 685; PNH, 10) and 7,770 controls. For both AA and MDS classifier, the XGBoost model showed the best performance. Under the cutoff that offered 99% sensitivity, the AUC of classifiers for AA and MDS were 0.933 and 0.926, respectively. The features with highest variable importance were WBC, platelet, and age for AA, as well as RDW, WBC, and PDW for MDS. The AUC of the BMFS classifier was 0.923. The cutoff probability for 99% sensitivity resulted in 54.1% specificity and 28.9% precision. The BMFS classifier succeeded in predicting all nine PNH cases.

Conclusion : We developed a machine-learning based classifier that can predict the diagnosis of BMFS with age, sex, and common CBC profiles. It can aid primary care physicians to decide when to refer their patients to hematologists for further work up.

Keyword : Bone marrow failure syndrome, Complete blood count, Machine learning, Predictive classifier



(A) The architecture of BMFS classifier. AA and MDS classifiers calculate the probabilities for AA and MDS using CBC profiles. Afterward, the final BMFS probability is determined as the maximum of the two.
(B) ROC curve and AUC of candidate machine learning models for AA and MDS classifiers. In both, XGBoost model outperformed the others. ANN: artificial neural network, EN: elastic net, KNN: k-nearest neighbor, RF: random forest, SVM: support vector machine, XGB: XGBoost.
(C) ROC curve and AUC of BMFS classifier. Four dashed lines represent cutoff probabilities that offered 100%, 99%, and 95% sensitivities and Youden's index.
(D) Confusion matrix of BMFS classifier. A probability cutoff was set to result in a sensitivity of 99%.

OP03-4

G6PD-independent differentiation of human CD34 positive haematopoietic stem and progenitor cells into mature erythrocytes

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Background : The deficiency of glucose-6-phosphate dehydrogenase (G6PD) impairs cellular processes under oxidative stress. Individuals with severe G6PD deficiency still produce sufficient numbers of erythrocytes. Nevertheless, the G6PD independence of erythropoiesis remains questionable. Alternative to this hypothesis, the bone marrow microenvironment may provide low oxidative stress, allowing normal erythropoiesis in the G6PD-deficient population. This study aims to elucidate the role of G6PD in erythroid differentiation of human HSPCs in a niche-free context. Human CD34-positive HSPCs were used as a model of erythropoiesis in bone marrow.

Method : Peripheral blood-derived CD34-positive hematopoietic stem and progenitor cells (HSPCs) of the human subjects, whose G6PD activities were normal, moderate G6PD Viangchan (487G>A) variants, and severe G6PD Viangchan (487G>A) variants, were cultured in two distinct phases: erythroid commitment and terminal differentiation. Cell morphology was observed at days 7, 14, and 21 by May-Grunwald-Giemsa staining. The cell surface phenotypes were examined using flow cytometry on days 7, 14, and 21. A total of 1 x 105 cells was labelled with APC-conjugated anti-CD34 antibody, PE-conjugated anti-CD71 antibody, and FITC-conjugated anti-CD235a antibody. The erythroid-specific transcription factors for GATA1 and GATA2 regulating terminal differentiation and erythrocyte-specific globin (α-globin and β-globin) were examined.

Results : In the presence of cell proliferation-promoting SCF, the human CD34-positive HSPCs were highly proliferative regardless of G6PD deficiency. There was a 36-fold increase in the viable cell number of the normal subjects, while an 34-35-fold increase was observed in the moderate and severe G6PD deficiency. These data show that G6PD Viangchan HSPCs were capable of committing to erythroid lineage at an extent similar to wildtype G6PD HSPCs. On day 7 of cell differentiation, there was no significant difference in the levels of GATA1 transcript between the normal G6PD and moderate G6PD-deficient groups. In contrast, the levels of the GATA1 transcript in individuals with severe G6PD deficiency were downregulated, implying delayed expression of erythroid genes. Consistent with the GATA1 expression pattern, transcripts encoding hemoglobin subunit alpha (HBA) and beta (HBB) of severe G6PD

deficiency were relatively decreased on day 14. The results indicated that G6PD deficiency likely impaired globin gene expression via the delayed expression of GATA1.

Conclusion : The evidence firmly indicates that the population with the G6PD variant could produce erythrocytes to an extent similar to healthy individuals.

Keyword : Haematopoietic stem and progenitor cells, CD34, Glucose-6-phosphate dehydrogenase, Erythropoiesis

OP03-5

LeGO vector labeling of stem cells and non-stem cells in ectopic foci formation model

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Background : Transplantation of bone marrow (BM) or adherent cell layer (ACL) of long-term bone marrow culture (LTBMC) under the kidney capsule of syngeneic recipient lead to hematopoietic ectopic focus formation (HEF). It provides a convenient model for studying formation and functioning of BM hematopoietic territory in conditions close to native. It is considered that HEF forms de novo from mesenchymal stem cells (MSCs), while differentiated progeny does not survive the procedure. It was also mentioned earlier that transduction of LTBMC by lentiviral vectors effectively marks MSCs. We used this method in attempt to study clonal activity of BM-MSCs.

Method : ACL of each LTBMC (n = 10) from mouse BM were transduced with a self-inactivating LeGO lentiviral vector based on HIV-1. Random site of integration (SI) of a provirus provided genetically inherited marker unique for each initial integration. Transduced ACLs were implanted under the kidney capsule in syngeneic recipients for 42 days. To evaluate labeling efficiency of stromal cells, 15000 cells/well (n = 540) were seeded in 96-well plates from each HEF inner cell mass (ICM). Two weeks later, DNA was isolated from each well and provirus-containing wells were determined by traditional nested PCR (tnPCR) and digital droplet PCR (ddPCR). Libraries for SIs sequencing on Illumina MiSeq (NGS) were prepared from DNA of HEF using PCR. Bioinformatics analysis was performed using the original algorithm in the Python, SI mapping was performed using the NCBI BLAST.

Results : Despite high efficiency of ACLs transduction, only 33/309 wells were labeled out of 309 wells with marked cell growth according to tnPCR. Only 8/33 of those samples contained 0.4-7.1% marked cells (1-3 marker molecules) according to ddPCR: totally, there were 12 provirus DNA molecules registered for 10389 of genomic Gapdh molecules. NGS analysis showed that only 15 out of 2165 analyzed clones among all samples consisted of ≥ 6 cells. Therefore, cells with high proliferative potential were not effectively transduced. Consequently, the majority of registered labeled cells were non-stem stromal cells that survived implantation. Mapping SI showed that they were distributed throughout the mouse genome, with slight preferences to genes. Index-hopping or formation of chimeric molecules is a serious obstacle to the analysis requiring a counting of individual molecules from amplified libraries. Chimeric molecules recombinantly provide false unique molecular identifiers (UMIs), which should be recognized during bioinformatic analysis for proper clustering.

Conclusion : tnPCR measurement provide false positive results from single molecules and cannot be considered as a proper tool for determining marked cell colonies. Non-stem cells of a transplanted stroma contributed to the HEF's ICM stroma. In the ACL of LTBMC, the efficiency of MSC infection is noticeably lower than that of more differentiated stromal cells. This may be due to a combination of molecular processes that determine the stem status of a cell. This implies that the efficacy of gene therapy based on such lentiviral vectors may be limited and is determined mainly by the lifetime of infected non-stem cells. On the other hand, this means a reduced risk of stem cell dysfunction. Proper single-cell methods or methods targeting definite subpopulations are required to study stem cells presenting only small subpopulation of cells (10-4-10-6) to evade wrong aggregating conclusions. While short-time effects from small subpopulation of stem cells could be hard to detect, a long-term effects are may be shaped by stem cells.

OP03-6

Outcome analysis and of BKPyV-associated hemorrhagic cystitis in paedriatric allogenic stem cell transplant recipients for benign hematological disorders in Pakistan

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Background : BKV Hemorrhagic Cystitis remains one of the most significant late onset bleeding complication after allogeneic stem cell transplant (ASCT), leading to substantial morbidity and increase health burden with a reported incidence of 8 to 25 % in pediatric population. Several predisposing factors have been reported in various retrospective studies which contribute to the etiology of BKV-HC such as type and intensity of conditioning regimen, advanced age, male gender, HLA antigen mismatch, concomitant CMV viremia and acute Gvhd.

Method : A retrospective analysis of 225 recipients of ASCT was conducted at the National Institute of Blood Diseases and Bone Marrow transplantation from January 2017 till December 2021. Patients with benign hematological disorders and age less than 18 years were recruited in this study. Both Full matched and haplo matched transplant recipients were included in this study. Data was analyzed by using SPSS version 24. Risk factors for the development of BKV were evaluated in univariate and multivariate analysis using a Fine and Gray model. A value of $p<0.05$ was considered statistically significant.

Results : Among 225 patients, plasma BKPyV was detected in (n=42) 18.6% patients in post-transplant phase. Univariate and multivariate analyses were performed to identify the factors associated with BKPyV. The factors reactivation significantly associated with BKPyV-reactivation in multivariate analysis were age (p=0.014), GVHD (p=0.041) and CMV viremia (p<0.001.The distribution of BKPyV. The Kaplan-Meier curves showed the overall survival and relapse free survival was 84.00%

Conclusion : Presence of CMV antigenimia and haplo identical transplant and GvHD were significantly associated risk factors for the development and severity of HC. Although presence of BKPyV didn't adversely affect the overall survival but demanded frequent and prolonged hospitalization and amplified financial burden. Lack of resources and financial limitation of patients makes BKPyV HC difficult to manage especially in countries like Pakistan and warrants the need of cost effective and potent antiviral therapy.

Keyword : Hemorrhagic cystitis, BKV viremia, Benign disorders

OP04-1

A study on heterogeneity and early response to chemotherapy in children with ETV6-RUNX1 positive acute lymphoblastic leukemia by RNA-seq expression profile

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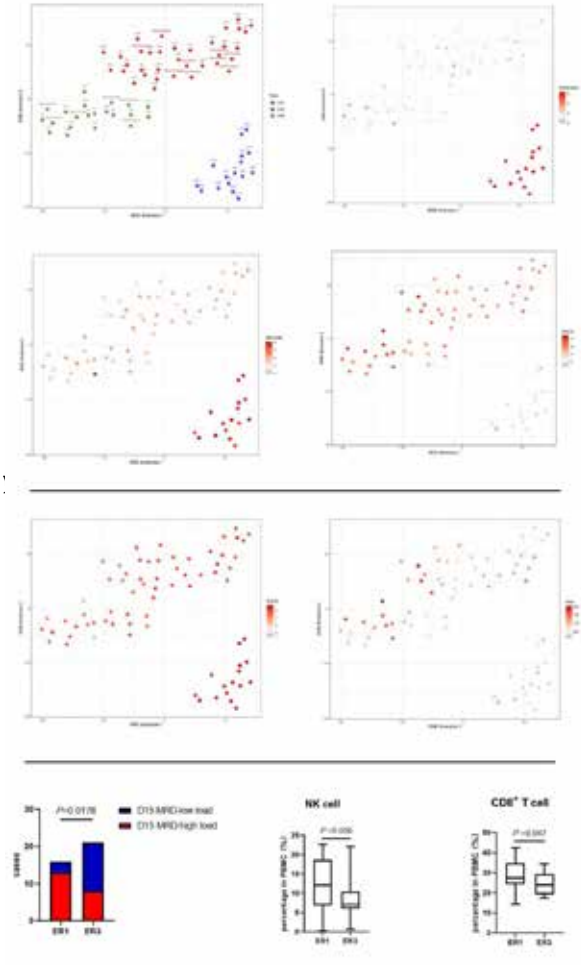
Background : ETV6-RUNX1 positive ALL is the most common type in childhood acute lymphoblastic leukemia(ALL), and it is also a type with good prognosis. However, there are still recurrent or refractory cases in this type, and there is still heterogeneity among individuals. In this research, we investigate the heterogeneity of ETV6-RUNX1 positive ALL in children by RNA-seq expression profile, and to explore the early response to chemotherapy and microenvironment characteristics of different clusters, so as to provide evidences for the exploration of genetic high-risk factors and clinical personalized diagnosis and treatment of such children.

Method : From September 2019 to June 2021, 72 children with newly diagnosed ETV6-RUNX1 positive ALL in standard risk group were enrolled and treated with CCLG-ALL-2018 chemotherapy protocol, which were all detected by RNA-seq technology. The sequencing results were analyzed by cluster analysis and bioinformatics analysis. We explored the early response to chemotherapy and microenvironment characteristics of the different clusters.

Results : ETV6-RUNX1 positive ALL were divided into three groups according to the RNA-seq expression profile including 16 cases (22.2%) in ER1 group, 35 cases (48.6%) in ER2 group and 21 cases (29.2%) in ER3 group. The number of patients with co-negative minimal residual disease (MRD) by flow cytometry (MRD-FCM) and next-generation sequencing (MRD-Gene) on the 15th day of chemotherapy in ER1 and ER3 groups was significantly different (3/16 vs. 13/21, P=0.0178), while there were 17 cases (17/35) with co-negative MRD in ER2 group after fifteen-day chemotherapy. It showed that the proportion of NK cells (P=0.056) and CD8+ T cells (P=0.047) in peripheral blood in ER1 group were both higher than those in ER3 group. Compared with ER3 group, ER1 group showed low expression of RPL41 and high expression of MRPS28 and SERPIND1, which were mainly involved in stress, proliferation and drug resistance of cells and the differentiation of hematopoietic stem cell. In addition, ER1 group showed lower expression of ribosome-related genes and higher activation of mTOR pathway than ER3 group.

Conclusion : The heterogeneity in gene expression profile were presented in children with ETV6-RUNX1 positive ALL. Compared with ER3 group, patients in ER1 group may have a poorer early response to chemotherapy with a relatively higher risk due to the stronger proliferation and drug resistance of leukemic cells probably. For patients in ER1 group, even if MRD is negative on the 15th day of themotherapy, it may be necessary to strengthen the observation of early response and consider the treatment for escalated risk in time.

Keyword : Pediatrics, Acute lymphoblastic leukemia, Heterogene-



OP04-2

Quality of sample is important for measurable residual disease with multiparameter flow cytometry in pediatric B acute lymphoblastic leukemia in direct comparison to next generation sequencing

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Background : Measurable residual disease (MRD) measurement is the standard of practice in B-lymphoblastic leukemia (B-ALL). Multiparametric flow cytometry (MFC) and next generation sequencing (NGS) of immunoglobulin gene (IGH) rearrangements are widely used. Since NGS are shown to have higher sensitivity compared to MFC, we have evaluated a commercial NGS panel, LymphoTrack and compared the results with 8-color 2 tube MFC in pediatric B-ALL. We aimed to compare the MFC and NGS data and explore the discrepant cases to enhance the MRD assessment with MFC in pediatric B-ALL.

Method : Pediatric B-ALL patients who had both undergone MFC and NGS-MRD during February through August 2022 were included. Two independent bone marrow aspirate pulls were obtained and subsequently processed to perform MRD. Antibodies used were anti-CD34, CD19, CD10, CD20, CD38, CD81, C73, CD66c/CD123 (Becton Dickson, USA) in all cases and CD58, CD22, CD24, CD66b in selected cases. Bulk-lysis was performed according to the EuroFlow guidelines. The events from the two tubes were merged with Infinicyt software 2.0.5 (Cytognos, Salamanca, Spain). The limit of detection (LOD) was defined as identifying more than 60 events/total nucleated cells (TNC) *100 and lower limit of quantitation (LLOQ) as 100 events/TNC*100. IGH rearrangement and clones were assessed using LymphoTrack assay (InvivoScribe). Samples was considered positive for MRD when at least two identical clonotypic reads were detected.

Results : In total 84 cases from 41 pediatric B-ALL patients, median age of 12 (1 – 18), were assessed with both MFC and NGS. MRD positivity was detected in 21 (25%) cases with MFC with median 0.017% (0.0013 – 5.9%) and 28 (33.3%) cases by NGS with median 0.0069% (0.001-44.9%). With MFC-MRD, median TNC of 6,803,166 (916,235 – 9302,173) events were analyzed with median LOD of 0.00088 % (0.00065 – 0.00655%) and median LLOQ of 0.0015% (0.0011 – 0.0109%). We found significant correlation between two methods ($r = 0.601$, $P < 0.001$) and concordance of 78.6%, with 14 (16.7%) showing positive MRD with NGS and 4 (4.8%) cases only with MFC. MFC–/NGS+MRD cases showed median 0.0012% (0.0001-0.0263%) of MRD, while 57.1% of the MFC–/NGS+MRD cases showed MRD level below LLOQ of MFC-MRD. MFC+/NGS–MRD cases showed

median 0.0025% (0.0025-0.015%) of MRD. MFC and NGS-MRD discrepant cases showed lower number of hematogones with MFC-MRD compared to the concordant cases (P < 0.001) and the percentages of hematogones not detected by MFC were higher in the discordant cases (P = 0.0047).

Conclusion : MFC and NGS-MRD showed relatively high concordance and correlation for MRD results in pediatric B-ALL. The hemodilution of the BM sample, assessed by the number of hematogones acquired with MFC, was higher in discordant cases, suggesting poor quality of the sample. Underestimation of MFC-MRD should be considered with hemodiluted samples, determined by number of hematogones and may give false negative MRD with MFC.

Keyword : Measurable residual disease, B-lymphoblastic leukemia, Next generation sequencing, Multiparameter flow cytometry

OP04-3

Evaluation of FTO polymorphisms in 6-mercaptopurine related intolerance in children with acute lymphoblastic leukemia

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Background : Thiopurine drugs like 6-Mercaptopurine (6-MP) are the cornerstone of maintenance therapy in acute lymphoblastic leukaemia (ALL). A number of variants in thiopurine metabolism related genes have been implicated in inter-patient variability in adverse effects related to 6-MP. A recently described variants of alpha-ketoglutarate dependent dioxygenase (FTO) have been reported to play an important role in thiopurine induced myelosuppression in IBD patients. However, the available evidence of association of such toxicities with FTO gene polymorphisms is scarce and contradictory. In the present study we genotyped a coding variant (p.Ala134Thr, rs79206939) and an intronic variant (rs16952570) of FTO gene in Indian children with ALL on maintenance phase chemotherapy and identified associations, if any, between the presence of these polymorphisms and the risk of thiopurine induced myelosuppression and hepatic toxicity.

Method : We recruited 174 cases (age <12 years) entering maintenance therapy and evaluated for the presence of FTO polymorphisms viz. rs79206939 {p.Ala134Thr (c.400G>A)} and rs16952570 (c.751+5327T>C) by Real-Time PCR and confirmed by Sanger sequencing. Haematological parameters and hepatotoxicity was monitored for 36 weeks of treatment. Associations if any, between the presence of these polymorphisms and the risk of myelosuppression and hepatic toxicity was analysed.

Results : Out of 174 children enrolled in our study, the prevalence of FTO rs16952570 polymorphism (intronic variant) was 18.4% (n=32) with 142 (82%) cases with TT genotype, 26 (15%) with TC genotype and 6 (3.4%) CC genotype. FTO rs79206939 (coding variant) was absent and non-polymorphic in our study group. Correlation between FTO polymorphic (rs16952570) cases was analysed with 6-MP induced toxicities. The mean dose of 6-MP during 36 weeks of maintenance of TT, TC and CC carriers was 53.7, 53.6 and 54.1 mg/m2/day, respectively. Number of patients tolerating starting dose of 60 mg/m2/day or higher was significantly higher in CC (50%) than TT/TC (14%) genotype carrying cases (P=0.014). However, higher nadir white blood cell (WBC) and absolute neutrophil count (ANC) levels were observed in patients harboring FTO rs16952570 TT genotype (wild type) compared with TC/CC carriers at 4, 8, 12 and 36 weeks after start of thiopurine therapy. However, no significant correlation was noted between number of weeks of chemotherapy interruptions or episodes of febrile neutropenia. The cases evaluated for any hepatotoxicity (n=120), also did not show any correlation with the genotype studied.

Conclusion : Our study suggests that FTO rs79206939 variant is non polymorphic in Indian population compared to 5.1.% reported in Korean population. Further, polymorphism in rs16952570 has no role in thiopurine related toxicity in ALL patients as reported previously. However, further validation in other independent cohorts, as well as functional investigation are needed to establish the role of FTO in thiopurine related toxicities.

Keyword : Thiopurine, Myelosupression, FTO polymorphism, 6-mercaptopurine, Thiopurine

OP04-4

Risk stratification for early mortality in newly diagnosed acute promyelocytic leukemia; A multicenter, non-selected, retrospective cohort study

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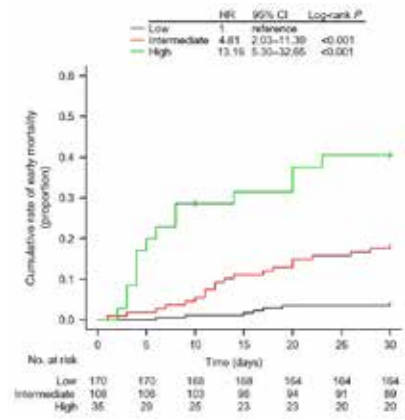
Background : Despites the current effective treatment for acute promyelocytic leukemia (APL), early mortality (EM) is the main challenge to long-term survival. In this study, we aimed to evaluate the incidence and characteristics of EM in patients with newly diagnosed APL in a multicenter, non-selected cohort, and also to develop risk model integrating clinical risk factors.

Method : We consecutively enrolled adult patients with newly diagnosed APL from Jan 2000 to Dec 2021 from 5 tertiary hospitals in Korea. The diagnosis of APL was confirmed by either cytogenetics, fluorescence in situ hybridization or reverse transcriptase polymerase chain reaction for the PML-RARA fusion as well as standard morphologic and immunophenotypic criteria. EM was defined as death within 30 days of presentation. The primary endpoint was the cumulative rate of EM, which was estimated using the Kaplan-Meier method. A receiver operating characteristic analysis was used to determine the optimal cutoff of the continuous variables.

Results : A total of 313 patients were included. The median age was 50 years (range, 19-94) and 63 (20.1%) were ≥65 years. Approximately half of patients were male (n=154). Median baseline white blood cell (WBC) counts was 2,300/μL, and 79 (25.2%) had ≥8,000/μL. Median fibrinogen level was 152.5 mg/dL (39.6-637.0), and median PT and aPTT were 15.9 sec (8.1-35.9) and 35.6 sec (13.3-67.6), respectively. Based on the Sanz score, 71 (22.7%) patients were categorized into high-risk group. The first dose of oral ATRA was administered within 24 hours of presentation in 274 (87.5%) patients, and most (n=293, 93.6%) received 4 alternative days IV infusion of idarubicin (8-12 mg/m2) and oral ATRA (45mg/m2) until complete remission as an induction therapy. EM occurred in 41 patients, and the cumulative rate of EM was 13.1% (95% CI, 9.3-16.7). The major cause of EM was intracranial hemorrhage (ICH) in 22 (53.6%), and median time to ICH occurrence was 2 days (0-25). Other causes of EM included infections/sepsis in 7 (17.1%) and APL differentiation syndrome-related organ failure and thrombosis/bleeding other than ICH in each 5 (12.2%). Most events (31/41) related to EM occurred within first 7 days of APL presentation. In univariable analysis, cumulative rate of EM was significantly higher in patients with age ≥65 years (HR 3.49, p<0.001) and WBC counts ≥8,000/μL (HR, 3.15, p<0.001). In addition, PT ≥17.5 sec, aPTT ≥41.5 sec, intermediate or high Sanz score, and delayed ATRA administration (>24 hours of presentation) were significantly associated with EM. In the multivariable Cox analysis, age, WBC counts, and timing of ATRA administration were independent factors for EM (for age ≥65 years, HR 3.05 [95%CI 1.59-5.87]: for WBC counts ≥8,000/μL, HR 3.50 [95%CI 1.89-6.49]: for delayed ATRA administration, HR 2.2 [95%CI 1.09-4.71]). Thus, the risk stratification model consists of 3 risk factors: age ≥65 years, WBC ≥8,000/μL, and delayed ATRA administration. Based on the number of risk factors, patients were stratified into 3 distinctive groups for EM: low-risk (no risk factor, n=170, 54.3%), intermediate-risk (1 risk factor, n=108, 34.5%), and high-risk (2 or 3 risk factors, n=35, 11.2%), with cumulative rate of EM of 4.1%, 18.5%, and 40.5%, respectively (Fig 1).

Conclusion : We propose a risk stratification model integrating age, WBC counts, and timing of ATRA administration, which predict EM in adult patients with newly diagnosed APL. The model enables us identify patients at high risk for EM who need most urgent and aggressive treatments for preventing EM.

Keyword : Acute promyelocytic leukemia, Risk stratification, Early mortality, Retrospective cohort study, Multicenter, Leukemia



OP04-5

Methods for analyzes and monitor of physiological data and quality of life in relation to chronic myeloid leukemia patients via wearable technology in Jai-

pur City, India

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Background : Cancer survivors are the least physically active of all cancer survivor groups but lifestyle interventions can result in improved health outcomes. New wearable sensor networks together with smartphone applications are being examined and tested for their potential to monitor and manage for track chronic myeloid leukemia patients' symptoms in real time and on a more continuous basis. To develop methods for analyzes and monitor of map the intersection(s) of physiological data in relation to chronic myeloid leukemia via wearable technology (MI band 6) in patients.

Method : Total of 86 chronic myeloid leukemia patients were taken as subject with an equal ratio of male and female. Wearable monitoring devices (MI band 6) were put on the wrist of patients for 30 days and a questionnaire was filled out by each patient. In all subjects, blood glucose was measured on daily basis with day to day data of their monitoring of step count , sleep monitoring (deep sleep, light sleep, wake up time), blood pressure, calorie burnt, stress level, motion time, monitoring heart rate, cardiac arrhythmias to know daily routines and recording them for health purpose.

Results : Results shown that (MI band 6) wearable device reading showed there was a normal heart rate, more calorie burnt with better control of sugar control and average good sleep count in more physically workout, include walking in chronic myeloid leukemia patients compared to less physically workout chronic myeloid leukemia patients, identified by professional physiotherapists. Wearable device reading showed that after changing lifestyle routine among less physically active cancer patients, their post- cancer events normalize with less requirement of medicine and provide effective, intensive, home-based rehabilitation.

Conclusion : With this study we show that , by using, wearable device ensured online assistive feedback for chronic myeloid leukemia patients, it is possible with their health awareness, exercising and motivate further studies.

Keyword : Wearable device, Chronic myeloid leukemia, Physically workout, Quality of life

OP05-1

Clinical and genetic characteristics of myelodysplastic syndrome in young age

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Background : Myelodysplastic syndrome (MDS) is a group of heterogeneous hematologic malignancies derived from clonal hematopoiesis predominantly occurring in elderly over 70 years of age. A substantial portion of patients is diagnosed with MDS at a relatively younger age which may be partly related to germline predisposition. Identification of the clinical and genetic features of young-age MDS compared to elderly patients has a role in understanding pathobiology and providing therapeutic directions. In this study, we compared the clinical and genetic characteristics of young-age MDS with those of the elderly, reviewed the molecular profiles in terms of inherited germline mutations, and identified the risk factors of leukemic progression.

Method : The 1438 patients who were diagnosed or treated with MDS at Asan Medical center between Sep 1989 and Nov 2022 were enrolled in this retrospective study. Young age MDS was defined as the patients aged 50 years or younger at the time of MDS diagnosis. For the mutational analysis, targeted deep sequencing including 61 myeloid neoplasm-related genes was performed with a MiSeqDx sequencer (Illumina) using bone marrow (BM) samples obtained from 421 patients between May 2009 and June 2022. The cut-off level of variant allele frequency (VAF) was set to 2.0% of mutant allele reads.

Results : We compared the clinical and molecular characteristics of young-age MDS (n=463) with those of elderly patients (n=975). The young-age group showed a higher proportion of female patients (44.9% vs. 32.2%, P <0.001), lower platelet counts (median 58.5 × 109/L vs. 77 × 109/L, P <0.001), lower BM blasts (median 2.5% vs. 4.8%, P <0.001), and less genetic mutation (median 1 vs. 2, P <0.001) at the time of diagnosis compared to elderly patients. There was no significant difference between the two groups in terms of white blood cell counts, neutrophil counts, hemoglobin, BM cellularity, and proportion of secondary MDS. The international prognostic scoring system (IPSS) and revised IPSS (IPSS-R) score was significantly lower in young-age MDS which was mainly associated with the different cytogenetic risk distribution between the two groups. The frequency of ASXL1, DDX41, DNMT3A, RUNX1, SF3B1, SRSF2, TET2, TP53, and ZRSR2 mutations was significantly lower in patients with young-age MDS. In univariate analysis, lower hemoglobin (<8 g/dL),

higher IPSS and IPSS-R score, the presence of genetic mutation, and DNMT3A and TP53 mutations were associated with inferior overall and leukemia-free survival in young-age MDS. We evaluated the incidence of germline mutations of DDX41, TP53, RUNX1, GATA2, ETV6, and ANKRD26 genes in young-age MDS patients which were presumed based on VAFs and previously reported mutation types. Of 27 mutations of 6 genes that are listed in myeloid neoplasms with germline predisposition, 9 were confirmed or presumed to be germline origin (3 of 3 DDX41, 3 of 5 GATA2, 2 of 4 ETV6, 1 of 6 RUNX1, 0 of 8 TP53, and 0 of 1 ANKRD26 mutation).

Conclusion : Patients with MDS diagnosed at a young age showed different clinical features and genetic profiles compared to elderly patients. Although mutations related to myeloid neoplasms were less frequently observed in young-age MDS than elderly patients, approximately one-third of young-age patients harbored presumed germline mutations at diagnosis, and DNMT3A and TP53 mutations were associated with worse survival outcomes. Disease-modifying treatment including allogeneic hematopoietic cell transplantation could be beneficial for patients with high-risk features and active surveillance of germline mutations should be considered in young-age MDS.

Keyword : Myelodysplastic syndrome, Young age, Germline predisposition

OP05-2

Reclassification of myelodysplastic neoplasm according to the 5th edition of the World Health Organization classification

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Background : Myelodysplastic neoplasm (MDS) is a category of clonal hematopoietic stem cell neoplasms, defined by cytopenias and morphologic dysplasia, characterized by progressively ineffective hematopoiesis and increased risk of acute myeloid leukemia (AML). The 5th edition of the World Health Organization (WHO) classification grouped MDS entities into two families: those having defining genetic abnormalities and those that are morphologically defined. The former newly included biallelic TP53 inactivation (MDS-biTP53) and SF3B1 mutation, meanwhile the latter newly included hypoplastic MDS (h-MDS) and MDS with fibrosis (MDS-F). Herein, we described the redistribution of the MDS according to new WHO classification and evaluated their significance to predict patient's outcome.

Method : This study was included a total of 595 patients who were diagnosed as MDS based on 4th edition of WHO classification in Seoul St. Mary's hospital from 2016 to 2022. All patients were reclassified according to 5th edition of WHO classification through comprehensive review of bone marrow aspiration and biopsy as well as whole genetic study results including cytogenetic, fluorescence in situ hybridization, and targeted panel next-generation sequencing.

Results : Among the 595 patients, 14 patients were classified as AML with NPM1 mutation. Seven patients were classified as clonal cytopenia of undetermined significance. Of 574 newly defined MDS patients, genetically defined MDS were 13.1% (n=75) and morphologically defined MDS were 86.9% (n=499). Regarding new categories, MDS-biTP53 and MDS-SF3B1 accounted for 5.4% (n=31) and 6.6% (n=38), respectively. h-MDS and MDS-F were 12.0% (n=69) and 2.1% (n=12), respectively. The median survival of the 574 patients were 86 months (95% confidence interval (CI): 65-211). By subgroups, MDS-5q showed the longest survival duration (111 months, 95% CI: 11-111), followed by MDS-SF3B1 (68 months, 95% CI: 40-117), MDS with increased blasts-1 (IB1) (65 months, 95% CI: 45-211) and MDS-IB2 (33 months, 95% CI: 19-50). The median survival of MDS-F (11 months, 95% CI: 8-48) and MDS-biTP53 (12 months, 95% CI: 6-58) were significantly short. The new classification showed meaningful prognostic discrimination by diagnosis subtype ($P<0.001$). MDS-biTP53 showed the worst outcome (hazard ratio (HR): 6.71, 95% CI: 2.67 to 16.87), followed by MDS-F (HR: 5.92, 95% CI: 1.61 to 21.83) and MDS-IB-2 (HR: 2.90, 95% CI: 1.80 to 4.67), compare to MDS with low blasts.

Conclusion : The results validated the clinical relevance of updated WHO classification for MDS and indicated that the newly defined categories such as MDS-biTP53 and MDS-F are unique disease types evidenced by their particular prognostic significance.

Keyword : 5th WHO classification, Myelodysplastic neoplasm, Biallelic TP53 inactivation, Fibrosis

Table 1. Redistribution matrix of the number of MDS patients classified by WHO 2016 and 2022 classification

WHO: World Health Organization, MDS: myelodysplastic syndromes(neoplasms), SLD: single lineage dysplasia, MLD: multilineage dysplasia, RS-SLD: ring sideroblasts with SLD, RS-MLD: ring sideroblasts with MLD, EB1: excess blasts type 1, EB2: excess blasts type 2, 5q: isolated 5q deletion, MDS-U: MDS unclassifiable, MDS-SF3B1: MDS with low blasts and SF3B1 mutation, biTP53: biallelic TP53 inactivation, LB: low blasts, MDS-h: MDS hypoplastic, MDS-f MDS with fibrosis, IB1: increased blasts type1, IB2: increased blasts type2

discharge and then monthly for at least 6 months.

Results : A total of 158 patients (males-85 , females- 73) received IST (Thymogam plus cyclosporine).Most of the patients had non severe AA(58%) followed by severe (28%) and very severe AA(14%). At 6 months post IST, the overall response rate (ORR) was 66% (complete response- 2% and partial response -64%) while the mortality rate was 13%.The ORR was 64% at 12 months and 61% at 24 months after IST. (Table 1) Age, Gender and severity at presentation did not influence response rates.

Conclusion : The ORR of 66 % is comparable to previous studies which have used ATGAM. This is the largest study on Thymogam from India.

Keyword : Aplastic anemia, Immunosuppressive therapy, Thymogam, India

OP05-3

Response to immunosuppressive therapy in aplastic anemia patients - A single centre prospective study of 158 patients from a tertiary care centre in Southern India

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Background : Immunosuppressive therapy (IST) with Antithymocyte globulin (ATG) and cyclosporine is the therapy of choice in aplastic anemia (AA) patients who are more than 40 years of age and younger patients who do not have matched sibling donor for stem cell transplant (SCT). The overall response rate to IST is approximately 65%. The two preparations of ATG that are available in India are Atgam (Pfizer) and Thymogam (Bharat serum, India). Most of the published studies, from India, have used ATGAM. We present the largest study on IST (with Thymogam) from India.

Method : This is a single centre prospective study conducted in a tertiary care institute in southern India, from July 2016 to 2022. All patients of age more than 13 years with diagnosis of aplastic anemia were included. Those with inherited bone marrow failure syndromes were excluded. Severity of AA and response rate was classified based on standard criteria. ATG was given at a dose of 4mg/kg for 4 days and cyclosporine was given at a dose of 5 mg/kg daily at least for 1 year. Patients also received Prednisolone for serum sickness prophylaxis for 2 weeks and then tapered and stopped in the next 2 weeks. Filgrastim and Eltrombopag were not administered. Patients were followed up till

OP05-4

Mutational pattern of T-cell large granular lymphocyte leukemia (T-LGL): Low mutational burden of STAT3 in T-LGL combined with pure red cell aplasia

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Background : T-cell large granular lymphocyte leukemia (T-LGL) is a rare mature T-cell neoplasm induced by clonal expansion of large granular T lymphocyte, usually presented with neutropenia. The autoimmune diseases are often associated with T-LGL in Western country, whereas pure red cell aplasia (PRCA) is more often in Asian country. PRCA develops with various underlying diseases such as thymoma, T-LGL and autoimmune diseases. Bone marrow failure syndromes (BMFS) is characterized by immune attack towards stem cells via T-cell mediated immune mechanism and the T cell

expansion in BM has substantively been detected. It is unclear until now whether the T cell expansion is either just response to immune attack or clonal selection. The discovery of somatic STAT3 mutations has a bright outlook to the genetic basis of T-LGL pathogenesis. Although STAT3 mutations has been reported to be specific for T-LGL, it has been also reported in other conditions showing T cell expansion such as PRCA, aplastic anemia, MDS and other autoimmune disorders. Since clonal hematopoiesis-related genes including TET2, DNMT3A and BCOR are often mutated in BMFS such as PRCA and aplastic anemia and a subset of T-LGL concomitantly occurs with the BMFS, the mutational patterns of T-LGL is thought to be different according to the concomitant disorders.

Method : Patients diagnosed with T-LGL (n=41) or isolated PRCA (n=3) were enrolled. Patients with T-LGL were divided into two groups; T-LGL alone (n=25) and T-LGL combined with PRCA (T-LGL+PRCA, n=16). In addition, we investigated 591 hematologic patients who were requested for NGS panel of hematologic malignancies in Seoul National University Hospital to identify STAT3 and STAT5B mutation frequencies in hematologic diseases without T-LGL. Two custom targeted NGS panels were used. First, for T-LGL and/or PRCA patients, 84 genes included genes reported to be mutated in PRCA or aplastic anemia, recurrently mutated genes in myeloid hematologic malignancy and STAT3 and STAT5B. Sequencing was performed by NovaSeq6000 (Illumina, United States). Second, for hematologic diseases without T-LGL, hematologic malignancies-related 103 gene panel including STAT3 and STAT5B was used. Sequencing was performed by NextSeq550Dx (Illumina, United States). Average depth of coverage for all samples was >200 x and the cut-off value was set to ≥2% VAF.

Results : The patients with PRCA (n=3) did not show any mutation. Of 41 patients with T-LGL or T-LGL+PRCA, 17 patients (41.5%) showed STAT3 mutation, 9 (36.0%) of 25 in T-LGL and 8 (50.0%) of 16 in T-LGL+PRCA. When aligning with STAT3 VAF level, only 2 patients with T-LGL (22.2%, 2/9) showed low VAF (<10.0%) compared with those with T-LGL+PRCA (87.5%, 7/8, P=0.015). STAT5B mutations were found in 2 patients with STAT3 wild type. After excluding STAT3 mutations, the next frequent mutated genes were KMT2D (17.1%), TERT (12.2%), SUZ12 (9.8%), BCOR (7.3%), DNMT3A (7.3%) and RUNX1 (7.3%). Among 17 STAT3 mutations, 16 mutations were localized in SH2 domain where Y640F (n=6), D661Y/V (n=5), N647I (n=3) and G618R (n=2) were discovered. The most frequent mutation, Y640F was mostly observed in low VAF (<10%) level and prevalent in T-LGL+PRCA (62.5%, 5/8), which was significantly different from the prevalence in T-LGL (11.1%, 1/9, P=0.043). Through a retrospective analysis in 591 hematologic patients without T-LGL, we identified 3 patients having STAT3 (n=1, 0.17%) or STAT5B (n=2, 0.34%) mutations. One patient with STAT3 mutation (G618R, VAF 7.6%) was already diagnosed of therapy-related MDS. After reexamination of BM slides with additional CD3, CD4 and CD8 staining, the increased interstitial infiltration of CD3 and CD8 positive T cells were found, revealing co-existence of T-LGL (ALC, 2.3 x 109/L). 2 patients with STAT5B mutation were MDS-excess blasts-1 (N642H, VAF 4.8%) and idiopathic hypereosinophilia (V712E, VAF 7.9%) with no evidence of T cell infiltration.

Conclusion : According to our results, patients with T-LGL combined with PRCA showed a low level of VAF in STAT3, providing further evidence that mutation of STAT3 may emerge as a second event in cases of already existing PRCA rather than as a primary event. This suggests that T-LGL combined with PRCA is a unique disease entity that can be classified as a subtype of T-LGL. Further, routine utilization of high depth NGS testing is important for detection of low mutant clones.

Keyword : T-cell large granular lymphocyte leukemia, Pure red cell aplasia, Mutational profiles, STAT3, Myelodysplastic syndrome

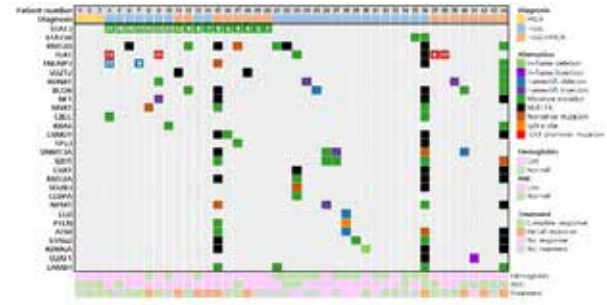

Figure. 1. Oncoplot of targeted gene mutations in pure red cell aplasia (PRCA, n=3), T-large granular lymphocyte leukemia (T-LGL, n=25) and T-LGL combined with PRCA (T-LGL+PRCA, n=16). Among 84 genes tested, 28 genes in which one or more potential somatic mutations were detected were shown. In STAT3 mutation, variant allele fraction (VAF) percentage was shown in numbers and arranged in order of VAF (%). In some other mutations, the VAF was shown in numbers. Bottom annotations represent clinical parameters at diagnosis and treatment responses. Lower than 10 g/dL of hemoglobin marked as "Low" and if it was higher than 10 g/dL, marked as "Normal". Absolute neutrophil count (ANC) cut-off value was 1.8 x 10^9/L. Conventional cytogenetic results were normal karyotype in 42 patients, except 2 patients (Y chromosome loss, 26.1% in patient number 9 & 20.0% in patient number 17).

OP05-5

Abdominal aortic calcification in patients newly diagnosed with Philadelphia-negative myeloproliferative neoplasm

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Background : Although atherosclerosis is likely to be involved in the development of arterial thrombotic events in patients with Philadelphia chromosome-negative myeloproliferative neoplasm (Ph MPN), studies on the prevalence and severity of atherosclerosis in these patients are scarce. Arterial calcification is the end stage of stabilized atherosclerotic plaques, and abdominal aortic calcification (AAC) is a predictor of vascular morbidity and mortality. However, AAC has seldom been evaluated in Ph MPN patients. We retrospectively evaluated the presence and clinical relevance of AAC using abdominal computed tomography (CT) performed at the time of diagnosis of Ph MPN.

Method : We enrolled patients with essential thrombocythemia (ET), polycythemia vera (PV), or prefibrotic/early primary myelofibrosis (pre-PMF) who underwent abdominal CT at the time of diagnosis between January 2002 and December 2021 at Chungnam National University Hospital, Daejeon, Korea. The abdominal CT images were reviewed and an Agatston score was assigned.

Results : Of the 334 patients newly diagnosed with Ph MPN (150, 48, and 136 with ET, pre-PMF, and PV, respectively) during the study period, 198 (59.3%), including 94 with ET (median age: 62 years; range: 1890), 24 with pre-PMF (median age: 67.5 years; range: 3188), and 80 with PV (median age: 64.5 years; range: 1866) were enrolled. The patients were followed up for a median of 3.4 years (range: 0.120.2 years). AAC was detected in 139 (70.2%) of the 198 Ph MPN patients. The prevalence of AAC in ET patients was 66%, which did not differ from that in pre-PMF (70.8%; p = 0.534) and PV (75.0%; p = 0.223) patients. Old age (odds ratio [OR] = 34.7; 95% confidence interval [CI] = 12.3295.91; p < 0.001), male sex (OR = 2.46; 95% CI = 1.348.95; p = 0.010), leukocytosis (OR = 3.07; 95% CI = 1.217.80; p = 0.010), and dyslipidemia (OR = 3.58; 95% CI = 1.0212.55; p = 0.046) were independent risk factors for the presence of AAC at the time of MPN diagnosis. The Agatston score was positively correlated with age (r = 0.435, p < 0.001), white blood cell count (r = 0.186, p = 0.009), neutrophil-to-lymphocyte ratio (r = 0.189, p = 0.008), monocyte count (r = 0.218, p = 0.002), and lactate dehydrogenase level (r = 0.209, p = 0.003). AAC was an independent risk factor for arterial thrombotic events that occurred before or at the time of diagnosis (OR = 2.62; 95% CI = 1.066.46; p = 0.037). AAC was an independent risk factor for arterial thrombotic events in ET patients (OR = 4.12; 95% CI = 1.1115.85; p = 0.034) but not in PV patients. The overall survival (OS) of Ph MPN patients with AAC was significantly worse than that in Ph MPN patients without AAC (15-year OS: 91.7% vs. 47.3%, respectively; p < 0.001). The presence of AAC was an independent risk factor for OS of Ph MPN patients (HR = 11.22; 95% CI = 1.4088.89; p = 0.023).

Conclusion : AAC is common in Ph MPN patients and is associated with the development of arterial thrombotic events and poor survival in these patients.

Keyword : Myeloproliferative neoplasm, Essential thrombocythemia, Polycythemia vera, Prefibrotic/early primary myelofibrosi, Abdominal aortic calcification, Arterial thrombosis, Survival

OP05-6

A single-arm, open-label, multicenter study to assess molecular response of P1101 therapy in patients with polycythemia vera and elevated hematocrit

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Background : Polycythemia Vera (PV) is the commonest myeloproliferative neoplasm, characterized by clonal stem cell proliferation of the erythroid, myeloid, and megakaryocytic lines, and risk for thrombotic events and transformation into post-PV myelofibrosis and acute myeloid leukemia. The excessive myeloproliferation in PV is driven by JAK2 somatic driver mutations. Although hydroxyurea (HU) remains the myelosuppressive agent of first choice, HU treatment can be associated with cytopenia and often unsatisfactory hematological control over time, aphthous and leg ulcers, and concern for the second primary malignancy. Recently, ropeginterferon alfa-2b was developed and an open-label, randomised phase III study (PROUD-PV and CONTINUATION-PV) showed it was more effective in achieving durable hematological and molecular remissions than hydroxyurea and well tolerated during long-term application. However, there are limited data on the clinical relevance of molecular response during ropeginterferon alfa-2b and the efficacy and safety of ropeginterferon alfa-2b in Eastern Asian patients. Therefore, we evaluated clinical and molecular responses, and the association between efficacy and molecular response as assessed by reduction in JAK2 Val617Phe allele burden in Korean patients with polycythemia vera and elevated hematocrit. In addition, the safety and tolerability of ropeginterferon alfa-2b were also collected.

Method : This single-arm, open-label, multicenter study has been performed in 16 hospitals in Korea. Patients were eligible if 19 years or older with PV diagnosed by WHO's 2016 criteria, requiring cytoreductive therapy and elevated hematocrit (hematocrit >45%). Patients were treated with ropeginterferon alfa-2b, subcutaneously every 2 weeks, at a starting dose of 250 μg, followed by 350 μg at week 2, 500 μg at week 4, and thereafter until week 48. The quantitative JAK2 Val617Phe allele burden was assessed every 3 months.

Results : With a data cut-off date of 13 Oct 2022, a total of 96 patients were enrolled and these analyses were performed in 93 full analysis set including 51 (54.8%) patients in HU naïve and 42 (45.2%) patients in HU-resistance/intolerance. The median age was 58 years (range, 26-81) and 51% were male. The percentages of patients with low and high risk were 55.9% and 44.1%, respectively. Until cut-off date, 74, 44, 21, and 6 patients were evaluable at 3, 6, 9, and 12 months, respectively. During the dose escalation period, no specific adverse event was reported. At baseline, mean hematocrit (%) was 50.30 ± 4.15, which significantly decreased to 47.63 ± 5.16, 44.05 ± 6.72, 41.90 ± 5.31, and 37.8 ± 4.13 at 3, 6, 9, and 12 months, respectively. WBC and PLT also decreased steadily over time. Complete hematologic response was in 20 (27%) of 74, 21 (48%) of 44 patients, 14 (67%) of 21 patients, and 6 (100%) of 6 patients at 3, 6, 9, and 12 months, respectively. The JAK2 Val617Phe allele burden changes, which were analyzed with available samples so far, showed a trend for rapid decreasing pattern; at baseline, mean JAK2 Val617Phe allele burden (%) was 63.25 ± 24.47 (n=92), which significantly decreased to 50.57 ± 24.17 (n=71), 47.29 ± 27.00 (n=44), 41.86 ± 28.71 (n=19), and 20.46 ± 15.48 (n=5) at 3, 6, 9 and 12 months, respectively. In terms of safety, although grade 1 & 2 (27%) and grade 3 (6%) treatment emergent adverse events (TEAE) were reported, all reported TEAE was within labeled of Ropeginterferon alfa-2b and there was no unexpected TEAE. Two serious adverse effect (1 hepatotoxicity and 1 bipolar disorder) were assessed related to therapeutic drug.

Conclusion : Our data demonstrated that ropeginterferon alfa-2b therapy with rapid dose optimization induced hematological response and reduction of JAK2 Val617Phe allele burden, and was well tolerated in Korean patients with polycythemia vera and elevated hematocrit. Moreover, rapid dose optimization resulted in achieving adequate hematologic response rapidly without specific adverse reaction during dose escalation, suggesting that this method may be feasible for the patients with polycythemia vera and elevated hematocrit.

Keyword : Polycythemia vera, Ropeginterferon alfa-2b, Complete hematologic response, Molecular response, JAK2 Val617Phe allele burden

OP06-1

Outcome of multiple myeloma patients with Hepatitis B surface antigen: Korean Multiple myeloma working party 2103 study

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Background : Globally, approximately 300 million people have chronic hepatitis B virus (HBV) infection, who are defined as positive for hepatitis B surface antigen (HBsAg) positive, and the prevalence is high in East Asia and Africa. These patients are at higher risk of HBV reactivation (HBVr) compared to patients with resolved HBV infection. HBVr is most commonly reported in patients receiving cancer chemotherapy for hematological malignancies and those receiving stem cell transplantation (SCT). Multiple myeloma (MM) is a malignant neoplasm originated from plasma cells and one of the major hallmarks of the disease is immune dysfunction. Impairment of humoral immunity is accompanied by impaired cellular immunity which is a consequence of the dysregulated tumor microenvironment and anti-myeloma treatment, as well. While MM patients have been often treated with various chemotherapeutic agents, corticosteroids, and SCT, it is still unclear how often these treatments trigger HBVr especially in the era of novel agents. As the incidence of MM is rapidly increasing in Asia [6], MM and chronic HBV infection are often comorbid. In addition, patients with HBsAg are mostly excluded in the clinical trials due to worrisome of HBVr, However, we do not know exact rate of HBVr or the impact of the chronic HBV infection to the outcome of the MM patients. In addition, currently prophylactic use of antiviral agent is a standard procedure especially for the HBsAg positive patients. To further elucidate the nature of HBVr and the role of prophylactic anti-viral agents in this population, we have carried out a multicenter study in Korea.

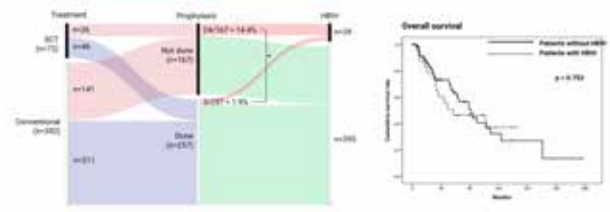
Method : The inclusion criteria were as follows, 1) diagnosis of symptomatic MM based on the International Myeloma Working Group diagnostic criteria; 2) HBV surface antigen (HBsAg)-positive at the time of MM diagnosis; 3) available medical records. Characteristics including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, MM features (stage, high-risk cytogenetics by FISH (Fluorescence in situ hybridization), subtype, anti-myeloma treatment, and receipt of stem cell transplantation), HBV features (baseline HBV deoxyribonucleic acid (DNA) quantity, administration of anti-viral prophylaxis including lamivudine, telbivudine, adefovir, entecavir, or tenofovir, presence of liver cirrhosis, HBVr, and HBV acute exacerbation), and survival data were collected. HBVr was defined as one of the followings, 1) ≥2 log increase from baseline levels or a new appearance of HBV DNA to a level of ≥100 IU/ml; 2) detection of HBV DNA with level ≥100,000IU/ml in a person with no baseline HBV DNA. The primary objective of the study was to evaluate the incidence of HBVr in HBsAg-positive MM patients who had received various anti-myeloma therapy. The subgroup comparisons were performed using Pearson's λ2 tests. Overall survival (OS) was calculated from the date of diagnosis to the date of death by any cause. Cumulative incidence of HBVr and OS were calculated using the Kaplan-Meier method, and subgroup comparisons were performed using a log-rank test. A stepwise logistic regression analysis was performed for multivariate analysis to find predictive factors of HBVr. HBVr during or within 6 months of last drug administration was defined as treatment-related HBVr (TR-HBVr) while HBVr after 6 months of last drug administration was defined as HBVr during drug holiday.

Results : From 2002 to 2021, a total of 123 cases were eligible for analysis. The median age at MM diagnosis was 59 (range 26 – 87), and 72 patients (58.5%) were male. The total number of conventional anti-myeloma treatments was 352 and the total number of SCT treatment was 72 (69 autologous SCT and 3 allogeneic SCT). The median number of treatments for each patient was 3 (range 1 – 11). Bortezomib was the most frequently exposed agent (n=115) followed by thalidomide (n=88), cyclophosphamide (n=81), lenalidomide (n=71), melphalan (n=48), and carfilzomib (n=34). At the time of MM diagnosis, 22 patients (17.9%) had chronic active HBV infection who had already been taking anti-viral agents among which seventeen patients (13.8%) had liver cirrhosis. The other 101 patient (82.1%) were inactive carriers. Baseline HBV DNA level was 370 IU/mL (range 0.0 – 4,588,000). With the median follow-up duration of 41.4 months (95% CI 33.7 – 49.1), 43 cases of HBVr occurred in 35 patients (28.5%), and the estimated 1-year cumulative incidence was 7.5%. Among the 35 patients, 24 patients experienced TR-HBVr, and 14 patients experienced HBVr during drug holiday after a median duration of 15.5 months (95% confidence interval (CI) 12.1 – 18.9). In patients who had experienced HBVr during drug holiday, 2 patients also experienced one episode of TR-HBVr and 1 patient also experienced 2 episodes of TR-HBVr. During 424 treatments, 29 events (6.8%) of TR-HBVr, including 23, 5, and 1 event during conventional anti-myeloma treatment, autologous SCT, and allogeneic SCT, respectively. During the 352 conventional anti-myeloma treatments, prophylactic anti-viral agents were administered in 211 treatments (59.9%) while it was not treated in 141 treatments (40.1%). Taking prophylactic anti-viral agents during treatment was significantly associated with lower chance to experience HBVr compared to treatment without anti-viral agents (4/211 (1.9%) vs. 19/141 (13.5%), $p < 0.001$). After a multivariate analysis, anti-viral prophylaxis (OR 0.153, $p < 0.001$) and treatment with cyclophosphamide (OR 4.732, $p = 0.002$) were risk factors for HBVr while treatment with bortezomib and SCT were not. Treatment with doxorubicin (OR 4.355, $p = 0.053$) showed trends for higher risk of HBVr.

The median OS was 75.4 months (95% CI 58.1 – 92.7). With the 55 cases of death had been documented, MM was the most common cause of the death (N=35). In 11 patients, the cause of death was related neither MM nor HBV-related. The HBV-related death was documented in only 1 case. OS was not significantly different between patients who had experienced HBVr (median OS 97.7 months, 95% CI 70.2 – 125.2) and patients who had not (median OS 68.0, 95% CI 0.0 – 145.1, p = 0.753).

Conclusion : This is the first study to report incidence and risk factors for HBVr in HBsAg-positive MM patients. Rate of HBVr was significantly mitigated by anti-viral prophylaxis. Although 28.5% of patient experienced HBVr, their survival was not inferior, and MM was the dominant cause of death. Therefore, considering very low incidence of HBVr in MM patients who had prophylactic anti-viral agent, HBsAg-positivity should not preclude patients from receiving optimal anti-myeloma treatment or participating clinical trials.

Keyword : Multiple myeloma, Hepatitis B virus, Anti-viral prophylaxis



OP06-2

Genetic alterations in multiple myeloma with extramedullary disease

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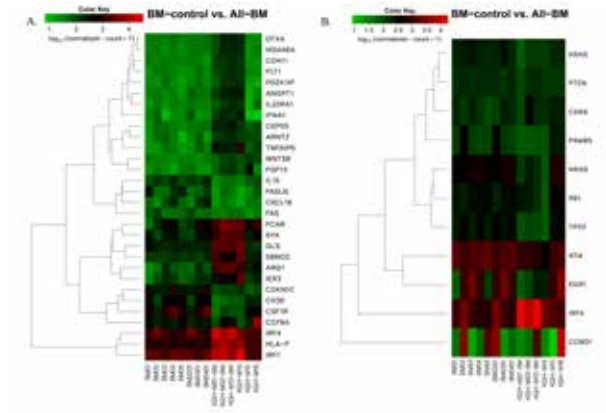
Background : Multiple myeloma (MM) is hematologic malignancy characterized by growth and proliferation of clonal plasma cells in the bone marrow (BM). Extramedullary disease (EM) is aggressive form of MM in which clonal plasma cells exist outside the BM. EM may be found in up to 30% of MM patients. The genetic pathogenesis of EM have not yet been precisely elucidated.

Method : From 2005 to 2020, among patients diagnosed with MM and EM confirmed by CT, MRI, and/or PET-CT, a total of 12 patients who could obtain tumor tissue or BM specimens were enrolled. We defined both bone-ralated EM (EM-B) and soft tissue-related EM (EM-S) as EM. We performed whole-exome sequencing (WES) and NanoString nCounter assay to investigate the genetic alterations in MM with EM (EMM) patients. A total of 9 formalin-fixed paraffin-embeded (FFPE) tumor tissues and 6 BM specimen from 12 EMM patients were sequenced. To clarify the genetic difference between MM and EMM, 8 BM samples of 5 MM patients were analyzed as controls. In addition, 4 buccal swabs from one EMM patient were sequenced for germline control.

Results : The median age was 57 years (range 50-65). Except for one patient, all other patients had EM at the time of diagnosis. WES was performed on 12 EMM cases (BM=6, FFPE=8). In WES, at least one oncogenic or possible oncogenic variant was found in all patients. Mutations were observed in the order of MAP2K3, AHNAK2, CDC27, MUC4, and NBPF1 genes in both BM and FFPE. In particular, variants of the CDC27 gene were observed only in FFPE. We performed RNA analysis by NanoString in 9 EMM patients (BM=6, FFPE=6, buccal swab=4 in one patients) and 5 MM patients. Compared with MM, ARG1, IRF4, and CEP55 were up-regulated and CDKN1C, IL15, and CD3E were down-regulated in the BM of EMM. Comparison of BM specimens from MM and plasmacytoma from EMM showed IRF4 up-regulation in EMM. In plasmacytoma, chemokine and chemokine receptor related genes such as CXCL8, S100A9, S100A8, CCR4, CXCR2, and CXCR4 were down-regulated. Up-regulation of IRF4 was also observed in EMM when comparing normal buccal swab and EMM specimens.

Conclusion : In our study, several common genetic alterations have been identified. Especillay compared with MM, IRF4 was up-regulated all EMM samples. Even in such a small sample, significant differences in expression could be identified, IRF4 could be a candidate for therapeutic target in EMM patients.

Keyword : Multiple Myeloma, Extramedullary disease, Plasmacytoma, Whole exome sequencing, RNA analysis



OP06-3

Epigenetic alteration in key genes and drug resistance in multiple myeloma

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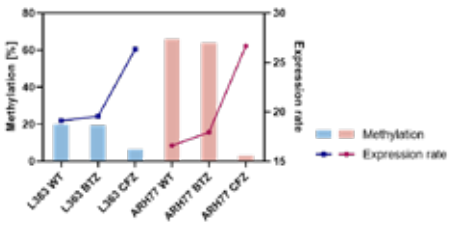
Background : Multiple Myeloma (MM) is the second most common hematologic malignancy, characterized by the presence of clonal plasma cells in the bone marrow. Approved Proteasome inhibitors (PIs), such as bortezomib (BTZ), carfilzomib (CFZ,) and ixazomib demonstrate high anti-MM-activity as a cornerstone of treatment. But for all that, nearly all treated patients relapse developing resistance against one or more drugs with poorly understood underlying mechanisms. DNA methyltransferase inhibitors e.g., decitabine and azacytidine have been approved for treating myelodysplastic syndrome and leukemia, implying the importance of epigenetics in treatments. Considering the lack of studies examining the effect of epigenetic aberration in MM, our current studies investigated the correlation between epigenetic changes and drug resistance (DR) in MM and were able to disclose the role of DNA methylation in the development of DR (Haertle et al., 2021, Blood., 2022, Clin Cancer Res.). In this study, we present the first insight into the impact of the altered methylation profile of MDR1/ABCB1, a drug efflux pump, on CFZ resistance.

Method : First, we confirmed the regulatory impact of DNA methylation in the targeted ABCB1 promoter region using a CpG-free vector-based dual luciferase reporter assay. The methylation level of the same region was then assessed via Deep Bisulfite Sequencing (DBS) in the four PI-sensitive MM cell lines ARH77, L363, AMO1, and RPMI8226 along with their respective CFZ-resistant derivatives. In addition, we screened 15 newly diagnosed MM (NDMM), 50 relapsed/refractory MM (RRMM), and 25 plasma cell leukemia (PCL) patients. Finally, the Proteomes of MM cell lines were measured by micro-LC-Orbitrp MS/MS and searched against human Swiss-Prot database by MaxQuant.

Results : Two out of four CFZ-resistant MM cell lines showed a dramatically decreased ABCB1 promoter methylation rate compared to their parental CFZ-sensitive cells (methylation rate: ARH77 WT 66% / ARH77 CFZ 2,9%, L363 WT 19,6% / L363 CFZ 6,2%). Of note, our proteomic screen revealed the ABCB1 expression level of the CFZ-resistant ARH77 and L363 models to be significantly increased, escalating from 16,5 to 26,6 (log2 fold) in ARH77 and 19,1 to 26,3 (log2 fold) in L363, demonstrating a negative correlation with the obtained promoter methylation level (Figure 1). In addition, hypomethylation of the target region in AMO1 and SH-SY5Y increased the luciferase activity by 27- and 130-fold, confirming that the methylation of the investigated target region downregulates the gene expression. In patients, the ABCB1 promoter methylation rate increased from NDMM (mean: 1.32% ± 0.67%,) to RRMM patients (mean: 2.66% ± 3.21%). PCL patients (mean: 10.24 % ± 15.10%) showed significantly higher methylation levels compared to RRMM ($p \leq 0.01$). Of note, there were no significant differences between primary and secondary PCLs ($p = .8151$) but a tendency for decreased methylation in samples derived from peripheral blood compared to samples obtained from the bone marrow ($p = .0728$).

Conclusion : Based on our dual luciferase assay and DBS, we are the first to confirm the regulatory effects of ABCB1 promoter hypomethylation on the expression of ABCB1 in two MM cell line models, which may underlie their CFZ resistance. In patients, we observed an increasing methylation rate of the ABCB1 promoter region from NDMM to RRMM and a significantly increased methylation in PCL. To elucidate this observation, further experiments e.g., functional validations using targeted (de-)methylation are planned.

Keyword : Multiple myeloma, Drug resistance, ABCB1, Epigenetic, Proteomics, Methylation



OP06-4

Impaired death receptor signalling mediates cross-resistance to immunotherapy in MM

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Background : Genotoxic treatment regiments are being replaced by immunotherapy such as monoclonal antibodies, immunoconjugates, T-cell engaging antibodies (TCE) or CAR T-cells (CARTs) in various cancers. The situation is not particularly different in case of multiple myeloma, in which unprecedented treatment efficiencies are induced by these novel therapies, however, patients continue to relapse, and a subset even faces primary resistance, with the underlying mechanisms poorly understood. It has been shown that the death receptor signaling proteins FADD and BID mediate resistance to CARTs in Acute Lymphocytic Leukemia (ALL) but their impact on MM resistance towards immunotherapy is yet to be explored.

Method : We first generated FADD and BID CRISPR-Cas9 knock out (KO) models in two independent MM cell lines, AMO1 and L363. We confirmed the functional impact of the KO genes on the apoptotic activity using apoptosis inducing, CD95 activating antibody (anti-FAS Ab). Apoptotic differences were monitored via Annexin-V PI staining and measurement of Caspases. Cell models were challenged with immunotherapeutic agents such as Daratumumab and BCMA directed CARTs and their killing efficacy was measured using luciferase and flow cytometry-based methods. Furthermore, functional profiling of CARTs was performed, and clinical relevance of findings was determined by screening expression of these genes in healthy donors and immunotherapy resistant patients.

Results : As expected, treatment with anti-FAS antibody did not induce apoptosis in FADD KO clones compared to 50 % increased apoptosis in WT cells. An increase of 3-4 folds in Caspase 3/7 and 8 was observed in WT cells, whereas minimal increase in KO clones. No detection of cleaved PARP in KO clones further validated the inactivation of the apoptotic pathways. Daratumumab showed significant reduction in killing efficacy in KO clones in contrast to WT cells (22% to 47% surviving cells) after 24 hours of treatment. Similarly, a dramatic reduction in efficacy of BCMA-CARTs was observed with 58% survival in KO models compared to 10% survival in WT cells. Of note, no differences in IC50 of Bortezomib, Lenalidomide, Doxorubicin, Melphalan and Blentamab mafodotin were observed. We performed commercially available cytokine quantification assay to determine the functional profile of CARTs and found no differences in IL-2 and IFN-γ production in response to antigen stimulation with WT and KO cells. In addition, CD38 or BCMA antigen loss was excluded in our KO model by Direct Stochastic Optical Reconstruction Microscopy (dSTORM) which also depicted no significant differences in receptor density /µm2 or antigen surface distribution between the WT and the KO cells. The clinical relevance of our findings was determined by screening for decreased FADD and BID expression levels in a pilot cohort of 24 newly diagnosed (NDMM) and 54 relapsed refractory MM (RRMM) patients and normalized expression levels with 26 CD138+ bone marrow plasma cell samples from healthy donors. No significant expression differences were found among cohorts (that did not include patients post TCE or CARTs). However, when the patients were ranked according to their gene expression of FADD and BID the ten patients with the lowest values were predominantly Daratumumab resistant (7/10 and 9/10, respectively), whereas in the patients with highest FADD BID expression Daratumumab resistance was less pronounced (3/10 and 4/10 respectively).

Conclusion : In conclusion, our study highlights induction of apoptosis as the main mode of action of T-cell based immunotherapies in MM. Furthermore, we provide first evidence, that gene expression of FADD and BID is essential for the action of Daratumumab and BCMA CARTs but may be dispensable for the anti-tumor effects in MM of ADC, IMiD, PI or chemotherapeutic agents. In our in vivo

screen, we identified patients with low expression of FADD and BID being resistant to Daratumumab, suggesting a potential resistance mechanism.

Keyword : Multiple myeloma, Death receptor singling, Apoptosis, Immunotherapy, Resistance

OP06-5

Antibody targeting of soluble MHC-class-I-related molecule augments natural killer cell function by restoring NKG2D in multiple myeloma

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Background : The human tumor-derived soluble MHC-class-I-related molecule (sMIC) impair lymphocyte cytotoxicity by downregulating NKG2D, which is one of the major activating receptor on natural killer (NK) cells. In this regard, sMIC-neutralizing nonblocking anti-MIC mAb (B10G5) was developed as a strategy to restore NKG2D-mediated antitumor immunity. However, the therapeutic effect of targeting sMIC has not been described in patients with multiple myeloma (MM).

Method : The level of sMIC was examined by ELISA in peripheral blood (PB) and bone marrow (BM) of healthy donor, patients with monoclonal gammopathy of undetermined significance (MGUS), smoldering MM, and MM. The proportion and the immuophenotype of NK cells were analyzed by multicolor flow cytometry in patient-derived BM mononuclear cells (BMMCs). MM and NK cell-lines were employed for analyzing immunophenotype, cytokine secretion, degranulation, and cytotoxicity in the presence or absence of B10G5.

Results : The level of sMIC was higher in MM patients compared with healthy, MGUS, and SMM. Indeed, sMICA was higher in BM compared with PB of MM patients. There was a correlation between the level of sMICA and the percentage of plasma cells in BM of MM patients at diagnosis determined by morphology and flow cytometry. Of note, the level of sMICA inversely correlated with the NKG2D+ NK cells among CD56dimCD16+ NK cells in BM of MM patients. The addition of MICA protein in culture of patient-derived BMMCs downregulated expression of NKG2D on NK cells, while the addition of patient-derived BM plasma did not alter NKG2D expression on NK cells. The expression of NKG2D on NK cells was enhanced in the presence of both patient-derived BM plasma and B10G5, while minor changes were observed in other NK activating receptors such as CD226, NKp46, NKp30 and NK inhibitory receptors such as KIR, NKG2A, and TIGIT. The changes in the level of NKG2D expression on CD8+ and CD4+ T cells in BMMCs of MM patients in the presence or absence of plasma and B10G5 were not significant. In vitro, MM cell-lines (RPMI 8226, U226B1, SKO-007) highly and distinctly expressed MICA, while leukemia (IM-9, HS 602) and lymphoma (Jiyoye, Daudi, RPMI 6666, H9, HuT 78) cell-lines did not express MICA. As we were unable to detect endogenous sMIC in the culture soup of MM cell-line, we transduced MICA into the SKO-007 cell-line and generated SKO-007_MICA cell-line to model culture system with sMICA. Co-culture of NK-92_mIL15_CD16 cell-line with SKO-007_MICA in the presence of B10G5 augmented NK cell function compared with the IgG control in terms of cytokine secretion (TNF-α, IFN-g), secretion of perforin, granzyme B, degranulation (CD107a), and apoptosis of MM cells.

Conclusion : The clinical utility of B10G5 may hold promise as a new strategy for myeloma cellular immunotherapy by augmenting NKG2D on NK cells.

Keyword : Multiple myeloma, Natural killer cells, Soluble MHC-class-I-related molecule

Table 1. Result of red blood cell (RBC) classification

	TP	FP	TN	FN	Precision (%)	Recall (%)
Normal cell	2968	10	2584	54	99.66	98.21
Microcyte	126	0	5472	19	100.00	86.81
Spherocyte	81	17	5518	0	82.65	100.00
Macrocyte	147	11	5485	3	93.04	98.00
Ovalocyte	486	15	5105	10	97.62	9487
Target cell	43	2	5567	4	95.56	91.48
Stomatocyte	198	64	5352	2	75.57	99.00
Teardrop cell	25	13	5576	2	65.79	92.60
Burr cell	111	32	5467	6	77.62	94.87
Schistocyte	179	2	5426	9	98.90	95.21
Uncategorized	272	6	5310	28	97.84	90.67

TP=True positive
FP=false positive
TN=True negative
FN=false negative

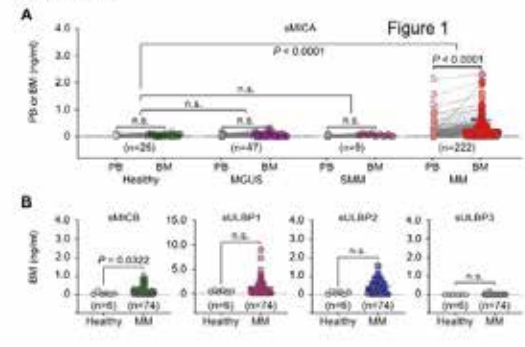
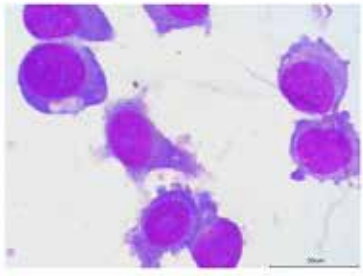


Figure 1. Soluble MICA and soluble MICB are elevated in BM plasma of MM patients and the level of sMICA is higher in BM compared with PB.



OP06-6

Monocytic myeloid-derived suppressor cells expand but lose suppressive activity following stem cell mobilization with G-CSF in multiple myeloma patients

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Background : Hematopoietic stem cell (HSC) mobilization with high-dose cyclophosphamide (HDCy) and granulocyte colony-stimulating factor (G-CSF) is an indispensable step for a subsequent autologous HSC transplantation, a standard of care for multiple myeloma (MM) patients. Simultaneously, G-CSF itself can expand myeloid-derived suppressor cells (MDSCs), a heterogenous immunoregulatory and tumor-promoting population, which may contribute to tumour growth. We comparatively studied frequencies and suppressive potential of granulocytic (G-) and monocytic (M-) MDSCs in MM patients before and following mobilization with HDCy and G-CSF.

Method : Thirty-eight MM patients underwent HSC mobilization with HDCy (2—4 g/m2) and G-CSF (5 µg/kg/day). The relative number of circulating Lin–HLA-DR–CD33+CD66b+ G-MDSCs and CD14+HLA-DRlow/- M-MDSCs, as well as the surface expression of PD-L1 and intracellular production of arginase-1 (Arg-1) and indoleamine-2,3-dioxygenase (IDO) in MDSC subsets were assessed with flow cytometry before HDCy, at the day of graft collection, and three months later. To evaluate suppressive activity, autologous M-MDSCs and G-MDSCs were magnetically selected from the peripheral blood of MM patients before and after G-CSF treatment and co-cultured for 5 days with IL-2/anti-CD3-stimulated CFSE labeled mononuclear cells.

Results : Stimulation with G-CSF led to a significant increase in both G-MDSCs and M-MDSCs comparing to pre-mobilization values. Following 3 months the studied MDSC populations were gradually decreased. The mobilization regimen led to a significant decrease in the frequencies of Arg-1+ and IDO+ G-MDSCs and PD-L1-expressing M-MDSCs. These functional changes in MDSCs also were transient. Co-cultivation of IL-2/anti-CD3-stimulated MNCs with M-MDSCs obtained from MM patients before G-CSF stimulation led to a pronounced suppression of MNC proliferation (according to CFSE, median suppression indices were 76 and 80% for CD4+ and CD8+ T cells, respectively). After stimulation of G-CSF in vivo, the suppressive potential of M-MDSCs significantly decreased (median suppression indices were 3 and 7.6% for CD4+ and CD8+ T cells, respectively), possibly due to the mediated "maturating" effect of G-CSF on immature M-MDSCs. For G-MDSCs, no suppressive activity was detected regardless of G-CSF stimulation in vivo; this may indicate a significant contamination of the pool of cells with G-MDSC phenotype

with granulocytes with a low density (for example, degranulated).

Conclusion : The transient stimulating effect of G-CSF on both G-MDSC and M-MDSC frequencies in vivo was shown. Simultaneously, the expression of inhibitory molecules in the studied MDSC populations was decreased following G-CSF treatment. Monocytic MDSCs of MM patients efficiently suppressed MNC proliferation while treatment with G-CSF abrogated suppressive capacity of M-MDSCs. This work is supported by the Russian Science Foundation under grant № 20-75-10132.

Keyword : Multiple myeloma, HSC mobolization, G-CSF, G-MDSC, M-MDSC, Suppression

OP07-1

GC1126A, a novel ADAMTS13 mutein that evades autoantibody as a superior therapy for acquired thrombotic thrombocytopenic purpura (aTTP)

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Background : Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare blood disorder that forms blood clots in small blood vessels throughout the body, leading to death if not treated immediately. aTTP occurs when the body starts producing antibodies that block an enzyme called ADAMTS13, which plays a role in the cleavage of von Willebrand factor (vWF). ADAMTS13 autoantibodies in plasma from aTTP patients recognize epitopes in all ADAMTS13 domains and most patients have autoantibodies against the cysteine-rich (C) and spacer (S) domains. Protein therapeutics that avoid autoantibodies in aTTP patients and exhibit rapid recovery of ADAMTS13 activity may be an effective way to treat aTTP patients. Here, we developed GC1126A, a novel engineered recombinant protein that consists of MDTCS domains of ADAMTS13 which has muteins, and the Fc domain of an immunoglobulin. We showed GC1126A is resistant to autoantibodies against ADAMTS13 while retaining sufficient proteolytic activity in an aTTP mouse model.

Method : We designed mutein panels using an ADAMTS13 crystal structure by Molecular Dynamics (MD) simulation, 3D point cloud scanning and directed evolution method to identify the ADAMTS13 muteins that are resistant to ADAMTS13 autoantibodies while retaining vWF cleavage activity. We performed a comparative analysis of the half-life extension in C57BL/6 mice receiving single intravenous injection of GC1126A, MDTCS fragment and full-length ADAMTS13, and measured ADAMTS13 activity to determine whether Fc domain conjugation could improve the pharmacokinetic properties. Fianlly, we performed in vivo Proof-of-Concept (PoC) study in an aTTP-mimicking mouse model to determine whether GC1126A improves the recovery of pathophysiological biomarkers shown in aTTP patients such as platelet counts and Lactate Dehydrogenase (LDH) levels.

Results : About one thousand variants were screened by measuring ADAMTS13 autoantibody binding and vWF cleavage activity. The top 5 selected candidates (1C03, 2B02, 5C09, 7A02, and GC1126A) showed the improvement of escaping neutralizing antibodies and vWF cleavage activity compared to full-length ADAMTS13. Among these candidates, GC1126A was the most effective one after rounds of selections. Then GC1126A was additionally engineered, so that C-terminus was deleted to avoid a decrement in half-life by ADAMTS13 autoantibodies in aTTP patients, leaving only the MDTCS domains that is essential for vWF cleavage activity. On behalf of the deletion, the Fc domain was conjugated to increase its molecular weight, thereby improving renal clearance and extending half-life through FcRn-mediated recycling. GC1126A showed approximately 2-fold longer half-life than MDTCS fragment and full-length ADAMTS13. . The aTTP-mimicking mouse model was pretreated with 9 different neutralizing antibodies recognizing different regions of ADAMTS13 and exhibited antibody titers of approximately 3 Bethesda Units (BU), showing decreased platelet counts and increased LDH levels. Thereafter, the GC1126A-treated group showed a dramatic recovery of platelet counts and LDH levels with higher residual activity of ADAMTS13 compared to that of control group (MDTCS-Fc). In addition, mice showing death or hematuria thought to be caused by thrombosis were seen in the vehicle and control group, but not in the GC1126A-treated group.

Conclusion : Our data showed that a novel recombinant protein GC1126A recovers biomarkers by evading ADAMTS13 neutralizing antibodies through in vitro and in vivo PoC studies. GC1126A could be a potential new therapeutic treatment option for aTTP patients.

Keyword : ADAMTS13, Acquired thrombotic thrombocytopenic purpura, von Willebrand factor, GC1126A

OP07-2

Obesity is associated with poor response to corticosteroid-based therapy in chinese primary immune thrombocytopenia (ITP) patients

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Background : Emerging evidence has indicated a strong link between obesity and a range of autoimmune diseases, in which obese patients present progressive disease courses and impaired treatment responses. However, the association of obesity with primary immune thrombocytopenia (ITP) is unclear. Here, we aimed to investigate the impact of obesity on clinical outcomes in a population-based cohort of Chinese adult ITP patients.

Method : A total of 410 newly diagnosed ITP patients (within 3 months from diagnosis) between January 2015 and March 2022 were retrospectively analyzed. 103 patients (25.1%) had received prior ITP-specific therapies. We recorded the weight and height of individuals at admission and calculated body mass index (BMI). According to the recommended BMI cut-offs for Chinese adults, patients were classified as normal BMI (BMI 18.5 - 23.9 kg/m2), overweight (BMI 24.0 - 27.9 kg/m2), and obese (BMI ≥ 28 kg/m2). Patients with BMI < 18.5 kg/m2 were excluded due to rarely seen and the possibility of underlying disease. The primary endpoints were initial and sustained responses. The second endpoint was the duration of response.

Results : Among the whole cohort, significantly lower bleeding scores (p = 0.020) and a higher burden of HBP comorbidities (p = 0.006) were observed in obese patients. Individuals with overweight were older when compared to those with obesity and normal BMI (p = 0.026). A total of 316 subjects received corticosteroid-based therapies after admission, of whom 45.3% (n = 143) were treated with corticosteroid alone, and 54.7% (n = 173) received combination treatments (Table 1). Accompanying agents or none were similar among the three BMI groups. When comparing initial responses, we found significantly elevated no response (NR, p < 0.001) as well as reduced complete response (CR, p < 0.001) rates with BMI categories increasing (Table 1). As to the 6-month sustained response (SR), similarly, along with BMI status increasing, statistically higher NR (p = 0.016) and lower CR (p = 0.004) rates were observed. Elevated rates of relapse were also significantly associated with higher BMI levels (p = 0.021). In univariate analysis, there was a trend towards a higher risk of relapse in the obese population when compared with their normal or overweight counterparts (p = 0.001). Moreover, this trend remained in the subgroups treated with corticosteroid alone (p = 0.028) and in combination (p = 0.024). Further, we performed a multivariate Cox regression model including BMI status, age, gender, platelets, bleeding score, and therapy whether in combination. BMI status (Obese: HR, 2.154; 95%CI 1.385 - 3.350; overweight: HR, 1.228; 95%CI 0.831 - 1.814; p = 0.003) and age (HR, 1.522; 95%CI 1.014 - 2.283; p = 0.042) remained independently prognostic factors. In subgroup analyses, the advanced BMI status provided an increased risk for relapse in the following subgroups: age ≤ 60, female, platelet count ≤ 10×10^9/L, bleeding score ≤ 2, bleeding score > 2, therapy with steroid alone and in combination. Besides, obesity appeared to particularly damage female patients in terms of duration of response due to the significant interactive effect of BMI status and gender (p-interaction = 0.017). Considering the non-significant trend in the interaction of BMI status and therapy whether in combination (p = 0.807), we suggested the negative prognostic implication of obesity in patients treated with corticosteroids, whether alone or combined with other drugs.

Conclusion : Our study reveals the distribution of clinical variables stratified by BMI status and identifies the negative implication of obesity in outcomes following corticosteroid-based treatment. To date, this is the first large cohort study focusing on the association between obesity and treatment outcomes in ITP. External prospective studies are needed to define these associations more clearly.

Keyword : ITP, Obesity, Corticosteroid, Treatment response, Relapse

Table 1. Initial and sustained responses in patients treated with corticosteroid-based therapy according to BMI at baseline.

	Normal (18.5-23.9 kg/m²) n=126	Overweight (24-27.9 kg/m²) n=119	Obese (≥28 kg/m²) n=71	P-value	Total
Corticosteroid, %(n)				0.436	
DXM	72.2 (91)	67.2 (80)	67.6 (48)		69.3 (219)
PDN/MP	27.8 (35)	32.8 (39)	32.4 (23)		30.7 (97)
Accompanying agents					
rhTPO, %(n)	38.9 (49)	41.2 (49)	42.3 (30)	0.883	40.5 (128)
IVIg, %(n)	14.3 (18)	18.5 (22)	16.9 (12)	0.671	16.5 (52)
Eltrombopag, %(n)	4.0 (5)	5.9 (7)	1.4 (1)	0.342	4.1 (13)
Rituximab, %(n)	3.2 (4)	3.4 (4)	0	0.378	2.5 (8)
Decitabine, %(n)	4.0 (5)	5.0 (6)	7.0 (5)	0.640	5.1 (16)
Therapy				0.963	
combination therapy	55.6 (70)	53.8 (64)	54.9 (39)		54.7 (173)
steroid alone	44.4 (56)	46.2 (55)	45.1 (32)		45.3 (143)
Initial response					
NR, %(n)	11.9 (15)	27.7 (33)	42.3 (30)	<0.001	24.7 (78)
R, %(n)	88.1 (111)	72.3 (86)	57.7 (41)	<0.001	75.3 (238)
CR, %(n)	73.8 (93)	53.8 (64)	29.6 (21)	<0.001	56.3 (178)
Sustained response a					
Month 6					
NR, %(n)	45.7 (48)	57.9 (44)	71.8 (28)	0.016	54.5 (120)
SR, %(n)	54.3 (57)	42.1 (32)	28.2 (11)	0.016	45.5 (100)
Sustained CR, %(n)	41.0 (43)	27.6 (21)	12.8 (5)	0.004	31.4 (69)
Relapse, %(n) a	54.3 (57)	63.2 (48)	79.5 (31)	0.021	61.8 (136)

a. Proportion was calculated in patients with initial response and available for follow-up (Normal n=105, Overweight n=76, Obese n=39).

OP07-3

Deciphering transcriptome alterations in bone marrow hematopoiesis at single-cell resolution in immune thrombocytopenia

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Background : Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by reduction in platelet count and increase in the risk of bleeding. Its pathogenesis has been extensively studied, with immune-mediated increase in destruction and decrease in the production of platelets as the accepted mechanisms. Platelet production is a complex biological process that involves hematopoietic stem cell commitment to the megakaryocytic lineage, megakaryocyte (Mk) maturation, and platelet release. Previously, our group and others have demonstrated that antiplatelet autoantibodies, bone marrow (BM) CD8+ T cells, and tumor necrosis factor-related apoptosis-inducing ligand in BM plasma and megakaryocytes impair megakaryopoiesis in ITP. Recent studies have reported selective activations of hematopoietic stem and progenitor cells (HSPCs) in a murine model of ITP or acute thrombocytopenia. However, whether and how hematopoietic differentiation contributes to the pathogenesis of ITP in humans remain unclear

Method : We performed single-cell RNA sequencing (scRNA-seq) of BM CD34+ HSPCs from 4 newly diagnosed ITP patients and 4 healthy controls (HC) on the 10X Chromium platform. CellRanger, the Seurat R package, Monocle2, pySCENIC, and CellPhoneDB were used for bioinformatic analysis. Flow cytometry was used to assess the counts of CD9+ and HES1+ cells from Lin-CD34+CD45RA- HSPCs in ITP and HC. Immune cell progenitors were co-cultured with CD9+Lin-CD34+CD45RA- HSPCs to confirm the interaction between immune cell progenitors and the Mk-biased HSPCs.

Results : Gene expression, cell-cell interactions, and transcriptional regulatory networks varied in HSPCs of ITP, particularly in a pre-B cell subset, highlighting the selective immune aberration associated with defective megakaryopoiesis in ITP (Figure 1). Differentially expressed gene (DEG) analysis indicated there was a bias toward erythrocytes in megakaryopoiesis of ITP. Flow cytometry confirmed that the number of CD9+ and HES1+ cells from Lin-CD34+CD45RA- HSPCs decreased in ITP. Liquid culture assays demonstrated that CD9+Lin-CD34+CD45RA- HSPCs tended to differentiate into megakaryocytes; however, this tendency was not observed in ITP patients and more erythrocytes were produced. The percentage of megakaryocytes differentiated from CD9+Lin-CD34+CD45RA- HSPCs was 3-fold higher than that of the CD9- counterparts from healthy controls, whereas in ITP patients, the percentage decreased to only 1/4th of that in the healthy controls and was comparable to that from the CD9- HSPCs. Additionally, when co-cultured with pre-B cells from ITP patients, the differentiation of CD9+Lin-CD34+CD45RA- HSPCs toward the megakaryopoietic lineage was impaired. Further analysis revealed that megakaryocytic progenitors (MkP) can be divided into seven subclusters with different gene expression patterns and functions. The ITP-associated DEGs were MkP subtype-specific, with most DEGs concentrated in the subcluster possessing dual functions of immunomodulation and platelet generation.

Conclusion : Here, we investigated and compared the transcriptomes of CD34+ HSPCs in ITP and HC using scRNA-seq to reveal the overall transcriptome alterations in HSPCs in ITP. Our results comprehensively dissect defective hematopoiesis and provide new insights regarding the cellular and molecular basis of ITP pathogenesis.

Keyword : Immune thrombocytopenia, Single-cell RNA sequencing, Hematopoiesis, Megakaryopoiesis

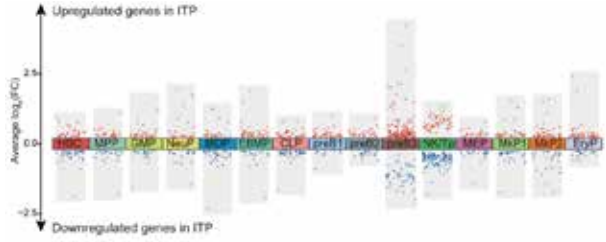

Figure 1. Differential gene expression analysis showing up- (red) and down- (blue) regulated genes in ITP across the 15 HSPC clusters.

OP07-4

A Phase 1 study of the safety, tolerability, pharmacokinetics and pharmacodynamics of MG1113 in healthy subjects and hemophilia patients

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Background : MG1113, developed for the treatment of hemophilia, is a human monoclonal IgG4 antibody with high affinity for tissue factor pathway inhibitor (TFPI), which inhibits the binding of TFPI and activated factor X (FXa) and induces the activation of FX in the extrinsic pathway of blood coagulation. A first-in-human phase 1 study was conducted to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of MG1113 in healthy subjects and hemophilia patients. (NCT03855696)

Method : A randomized, double-blind, placebo-controlled, ascending dose phase 1 study of MG1113 was conducted. A single ascending dose of 0.5, 1.7, or 3.3 mg/kg subcutaneously (SC) or 3.3 mg/kg intravenously (IV) was administered to cohorts of eight healthy volunteers. In hemophilia patients, a single dose of 1.7 or 3.3 mg/kg was administered subcutaneously (N = 9). Plasma levels of MG1113 were determined for pharmacokinetic analysis. Pharmacodynamic evaluations were assessed using blood levels of free TFPI, diluted prothrombin time (PT), residual TFPI activity, thrombin generation assay (TGA), D-dimer, fibrinogen levels, and prothrombin fragment 1+2. Safety and tolerability were assessed during the study period.

Results : A dose-dependent systemic exposure of MG1113 in the SC group was observed in both healthy and hemophilia participant. After MG1113 treatment, free TFPI and FXa (residual TFPI) activity were decreased and both diluted PT and lag time (TGA) were shortened. However, peak height (TGA), ETP (endogenous thrombin potential, TGA), D-dimer, and prothrombin fragment 1+2 increased compared to the baseline. Fibrinogen levels were consistent irrespective of treatment. This pattern is consistent with the expected result considering the mechanism of MG1113 and the coagulation cascade. The most frequent adverse drug reaction (ADR) in healthy volunteers was venous thrombosis (five events). Three events were mild requiring no treatment, but two events were moderate in severity. In hemophilia patients, muscle twitching and pain in extremity that occurred in one subject were initially reported as suspected unexpected serious adverse reactions (SUSARs) considering the aspect of patient safety. However, it was not considered an event related with thrombosis and was finally assessed as not being related to the MG1113. Two healthy volunteers (one subject in the placebo group and one subject in the 3.3 mg/kg IV cohort) exhibited a positive anti-drug antibody (ADA) test after treatment. However, we could not find any positive ADA results in hemophilia patients. Further studies are needed to detect ADAs exerting neutralizing effects on long-term clinical outcome.

Conclusion : MG1113 had a favorable safety profile and was well tolerated in healthy subjects and hemophilia patients receiving a single dose up to 3.3 mg/kg (SC). MG1113 also exhibited a desirable PK profile showing a dose-dependent systemic exposure.

Keyword : Antibodies, Monoclonal, Hemophilia, Pharmacokinetics, Pharmacodynamics, Safety

OP07-5

Evaluation of safety and efficacy of hbs-sail-in®: A potent ingenious anti-sickling agent that reduces pain and improves the quality of life in sickle cell patients

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Background : WHO and the UN have recognized Sickle cell disease (SCD) as a global health pandemic, with approximately 2/3 of 300,000 children born annually in Africa and India, projected to climb to 400,000 by 2050. Inadequate healthcare, poor nutrition, and infections aggravate the disease burden, resulting in 30% of morbidity in the under-five age group. Current medication is insuf-

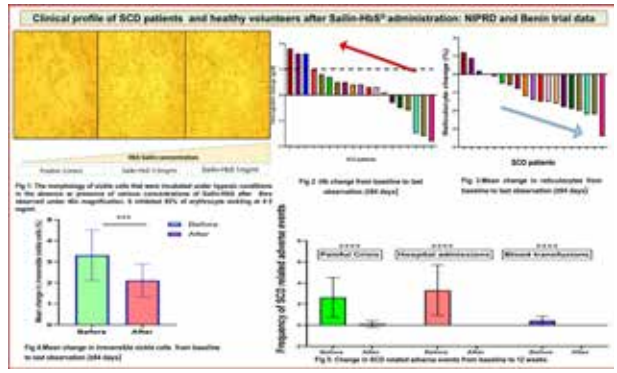
ficient, expensive, or inflicts one with lasting toxicity. The present study investigates the anti-sickling effect of HbS-Sailin® (PatentApplication: WO/2017/125791A1).

Method : We evaluated the in-vitro anti-sickling efficacy of HbS-Sailin® in SCD patient-derived RBCs. Subsequently, animal toxicological studies were carried out in compliance with OECD-GLP (Principles of Good Laboratory Practice) guidelines at the Shriram Institute for Industrial Research (CPCSEA Registration no. 148/PO/RcBi/S/99/CPCSEA,dt. 21/07/2017). A two-site open-labeled, non-randomized clinical observation trial (NCT) of HbS-Sailin® for a 12-week period was undertaken at National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria (Africa) and at the University of Benin Teaching Hospital, Benin (Africa) to determine its safety, efficacy, and tolerability in SCD patients of the Nigerian population.

Results : HbS-Sailin® inhibited the 85% of sickling at 0·5 mg/ml, decreased the polymerization rate of HbS molecules by 75% and reduced osmotic fragility of sickle RBCs making them more resistant to lysis. It did not cause any in-vitro hemolysis and methemoglobinemia. Further, acute, sub-acute and chronic toxicity analysis was performed in swiss mice and wistar rats. All the animals administered were administered with the graded doses of 200, 500, 1000, and 2000mg/kg did not show any toxic signs and mortality. Hence, the MTD, MLD, LD10, and LD50 of the 'Sailin-Hbs 'is ≥2000 mg/kg b.wt which qualifies as category 5 under the Globally Harmonized System of Classification of Chemicals (GHS) of OECD. Oral administration of HbS-Sailin® in 44 patients with SCD in a 12-week study increased hemoglobin levels, remarkable decrease reticulocytes, and irreversible sickle cell population which suggests less hemolysis. A drastic reduction in bone pain crises, SCD-related adverse events, hospital admissions, blood transfusions and enhanced the perception of QOL.

Conclusion : Affordable therapeutic and management strategies for SCD have evolved very slowly, and the treatment of SCD remains a severe unmet medical need. Given the outcome of this study, HbS-Sailin® may be a promising option for the treatment and management of patients with SCD.

Keyword : Sickle cell disease, Antisickling, Animal toxicity, Safety and efficacy, Clinical trials, OECD-GLP guidelines



OP07-6

Favorable outcomes of hematopoietic stem cell transplantation after fludarabine-based, radiation-free conditioning in children with inherited bone marrow failure syndrome

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Background : Inherited bone marrow failure syndromes (IBMFS) are rare genetic disorders characterized by bone marrow failure (BMF), varying degrees of congenital anomalies and cancer predisposition. Hematopoietic stem cell transplantation (HSCT) is the only curative treatment option for hematologic aspects of IBFMS, but it also was associated with significant comorbidities including transplant-related mortality and secondary malignancies. Optimal conditioning regimen based on diseases characteristics is important to improve the outcomes in IBMFS patients. Here, we report the outcomes of HSCT following uniform conditioning regimen for patients with IBMFS in our institution.

Method : We analyzed 34 pediatric patients with Fanconi anemia (FA, n=28), Diamond-Blackfan anemia (DBA, n=3), dyskeratosis congenita (DC, n=2), severe congenital neutropenia (SCN, n=1) who underwent HSCT between Apr. 2007 to Nov. 2022. Most of the patients (31 of 34 patients) received the uniform radiation-free, reduced-intensity conditioning consisted of fludarabine (150 mg/m2), cyclophosphamide (20 mg/kg) and rabbit-antithymocyte globulin (r-ATG, 7.5 mg/kg) regardless of donor type or stem cell source. The type of donors included matched sibling donor (MSD) in 8 (23%),

unrelated donor (UD) in 23 (68%), and haploidentical family donor (HD) in 3 (9%) patients. Stem cell sources were bone marrow (BM) in 6 (18%), peripheral blood stem cells (PBSC) in 21 (62%), and cord blood (CB) in 7 (20%) patients. Graft versus host disease (GVHD) prophylaxis consisted of cyclosporin A with or without methotrexate.

Results : Of 34 patients, IBMFS-related genes were found in 24 (68%) patients (19 FA, 2 DBA, 2 DC, and 1 SCN). Nineteen (68%) out of 28 FA patients had gene mutations (10 FANCA, 8 FANCG, and 1 FANCC). The median age at HSCT was 9.0 years (range, 1.6-27.5). The cumulative incidences (CIs) of neutrophil and platelet engraftment by 1 month were 88.2% and 82.4%, respectively. Five (15%) out of 34 patients experienced primary graft failure. The CIs of grade II to IV and III to IV acute GVHD were 38.2% and 0%, respectively. In particular, no patient experienced any grade of acute GVHD in MSD-HSCT, and the CIs of grade II to IV acute GVHD according to donor types were 52% in UD and 33.3% in HD (P=0.057). By stem cell source, BM presented lower CI of acute GVHD than other sources without statistical significance (BM 16.7% vs. PB 55.0% vs. CB 14.3%, P=0.120). The CI of extensive chronic GVHD was 6.9%, and no differences were found according to donor type. At a median follow-up of 9.1 years (range, 1.3-15.1), the 5-year event free survival (EFS) and overall survival (OS) were 71.3% and 97.1%, respectively. Two FA patients experienced secondary malignancy (1 squamous cell carcinoma of tongue and 1 spindle cell sarcoma of lung) after 5 years post-HSCT. The survival outcomes according to transplant characteristics were presented as below; 5-year EFS and OS were significantly higher in MSD-HSCT compared to other donor types (5-year EFS: MSD 100% vs. UD 67.8% vs. HD 33.3%, P=0.003; 5-year OS: MSD 100% vs. UD 87.5% vs. HD 66.7%, P=0.006), and comparable survival outcomes were found regardless of stem cell sources (5-year EFS: BM 83.3% vs. PB 73.8% vs. CB 57.1% P=0.364; 5-year OS: BM 100% vs. PB 79.2% vs. CB 100% P=0.563).

Conclusion : We showed favorable survival outcomes in patients with IBMFS who underwent HSCT following uniform fludarabine-based, radiation-free conditioning. MSD-HSCT demonstrated excellent outcomes without any transplantation-related complications regardless of stem cell source. However, HD-HSCT still showed inferior outcomes compared to matched donors. Our results highlight the need for intensifying the conditioning regimen for alternative donor transplantation settings.

Keyword : Inherited bone marrow failure syndromes, Hematopoietic Stem Cell Transplantation, Reduced-intensity conditioning, Fludarabine-based conditioning, Radiation-free conditioning


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POSTERS

PP01-1

Clinical Significance of bZIP in-frame CEBPA-mutated normal karyotype acute myeloid leukemia

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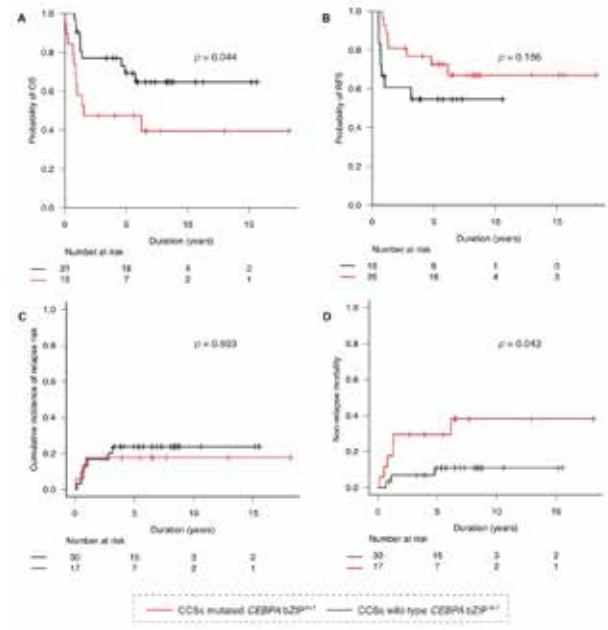
Background : We evaluated the characteristics of CEBPA mutations and the significance of a basic leucine zipper in-frame mutation (bZIPin-f) of CEBPA in patients with acute myeloid leukemia with a normal karyotype.

Method : Based on updated knowledge of CCAAT/enhancer-binding protein α (CEBPA) mutations, we conducted next-generation sequencing analyses in a previously established real-world cohort.

Results : Among 78 of a total of 395 patients (19.7%), 50 had bZIPin-f CEBPA, and 28 had non-bZIPin-f CEBPA. In the multivariate analysis, patients with NPM1mut, those with bZIPin-f CEBPA, and those who underwent allogeneic hematopoietic cell transplantation (allo-HCT) had favorable overall survival (OS), but FLT3-ITDmut was a poor prognostic indicator. For relapse-free survival (RFS) and cumulative incidence of relapse, bZIPin-f CEBPA, and allo-HCT were associated with favorable outcome; FLT3-ITDpos was associated with worse outcomes. In the CEBPA double-mutated group (CEBPAdm), bZIPin-f CEBPA was associated with superior outcomes in terms of OS (p=0.007) and RFS (p=0.007) compared with non-bZIPin-f CEBPA. Of 50 patients with bZIPin-f CEBPA, 36 patients had at least one mutation. When grouped by the presence of mutations in chromatic/DNA modifiers (C), cohesion complex (C), and splicing genes (S) (CCS mutations), CCS-mutated bZIPin-f CEBPA was associated with poor OS (p=0.020, hazard ratio (HR):2.775) and a trend in inferior RFS (p=0.106, HR:2.106).

Conclusion : Only bZIPin-f CEBPA was associated with favorable outcomes in patients with CEBPAdm. However, some mutations accompanying bZIPin-f CEBPA showed inferior OS; thus, further studies with larger numbers of patients are required for clear conclusions of the significance of bZIPin-f CEBPA.

Keyword : Acute myeloid leukemia, CEBPA, NGS, Allogeneic transplantation



PP01-2

Candidate drug screening for TP53-mutated AML

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Background : Acute myeloid leukemia (AML) is a clonal blood malignancy characterized by arrested maturation and abnormal proliferation of hematopoietic precursor cells. This paralysis of normal bone marrow function leads to severe decreased immune function and bleeding tendency, and if not treated, it is an acute disease that dies within a few months due to rapid progression of AML. TP53 mutations occur in 5% to 10% of patients with de-novo acute myeloid leukemia (AML), with higher frequency in patients with relapsed/refractory AML. The treatment approach for many years has used combination chemotherapy, with usually an anthracycline and cytarabine as the foundation. These induction therapy's complete response is achieved in 60 to 85% of adults who are 60 years of age or younger. In patients who are older than 60 years of age, complete response rates are inferior 40 to 60%. TP53 mutated acute myeloid leukemia (AML) responds poorly to the conventional induction therapy and has a short overall survival rate with a median of 5-9 months. Poor outcomes in TP53 mutated AML following chemotherapy have been observed and treatment options remain limited.

Method : In silico analysis- Differentially expressed genes (DEGs) analysis between TP53-Mutated and TP53-Wildtype was performed using genetic data from patients with acute myeloid leukemia of TCGA. After aligning the RNA-seq data of TCGA-LAML to the GRCh37 version of the human standard gene using STAR (Splicated Transcripts Alignment to Reference), expression amount for each gene was calculated using RSEM (RNA-Seq by Expectation-Maximization). Drug candidates were extracted from Connectivity map (CMAP), using the DEGs analysis results. In addition, through a literature search, drugs that can target TP53 and drugs that target leukemia stem cells were selected as candidate groups. In vitro study- In order to produce Drug Tolerant Persister Cells (DTPCs), the kasumi-1 cell line was treated with cytarabine and Idarubicin in combination for 72h. The cell viability was assessed by MTT assay. To confirm the DTPCs phenotype, the changes of cell cycle (PI staining) was detected by flow cytometry. To confirm DTPC's resistance, DTPCs were treated with re-combination treatment. The cell viability was assessed by MTT assay. For drug screening, DTPCs were isolated surviving cells using Ficoll-Paque centrifugation. And DTPCs were treated with 10uM drugs or 1uM drugs. The effect of a 72h treatment on the cell viability was evaluated using the MTT assay.

Results : The kasumi-1 cell, a TP53-mutated AML line, was treated with the AML standard treatments cytarabine and Idarubicin in combination for 72 hours. As a result, 60% of kasumi-1 cell was removed when cytarabine 40nM and Idarubicin 10nM were combined for 72 hours. Similar to DTPCs phenotype the DTPCs that survive cytarabine and Idarubicin combi-treatment displayed G2/M phase cell-cycle arrest and resistance to further cytarabine and Idarubicin combi-treatment. Using in vitro Cytotoxicity assay, we screened 46 candidate compounds at 10uM or 1uM dose and confirmed several drugs that effectively eliminate DTPCs. Drugs that effectively eliminate DTPCs contained several cell cycle checkpoint inhibitors.

Conclusion : Collectively, our study indicates that the cell cycle checkpoint inhibitors has the potential to eliminate DTPCs and therefore prevent minimal residual disease, mutational drug resistance, and relapse in TP53-mutated AML. However, the relationship between cell cycle checkpoint inhibitors and TP53 mutations requires further study.

Keyword : TP53 mutation, Acute Myeloid Leukemia(AML), Drug Tolerant Persister Cells(DTPCs)

PP01-3

Prognostic relevance of MN1 expression in cytogenetically normal adult AML Patients

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Background : Cytogenetically normal AML (CN-AML) represent the largest subgroup of adult AML and are heterogeneous, showing a broad spectrum of genetic mutations. In this prospective study, we evaluated the expression of MN1 in CN-AML adult patients and correlated it with their prognosis and with various laboratory and clinical parameters.

Method : One-hundred sixty three adult patients (≥18 years) with de-novo AML were recruited from April 2014 to April 2018. RNA was extracted from 163 bone marrow (BM) samples using TRIzol reagent following the manufacturer's instructions. MN1 copy numbers normalized to ABL copy numbers were measured in BM samples by real-time reverse-transcriptase PCR quantification. Probes and primers used were as follows: MN1 probe (5′ -FAM- AACAGCAAAGAAGCCCACGACCTCC-TAMRA); MN1 primer forward (5′ -GAAGGCCAAACCCCAGAAC), Primer reverse (5′ -GATGCTGAGGCCTTGTTTGC). In all cases, samples were run in triplicates. Ct values

were normalized with the housekeeping gene. The presence or absence of additional molecular markers such as FLT3, NPM1, and CEBPA was assessed centrally. All patients were treated with a uniform protocol and followed until December 2020. Descriptive statistics were used to summarize baseline characteristics. Mann-Whitney-U test was used to compare continuous, while Fisher's test was used to compare categorical variables. Probability of EFS and OS was calculated using Kaplan-Meier method, with the differences being compared using a two-sided log-rank test.

Results : The median age of the patients was 35 years. Higher MN1 copy numbers were associated with NPM1 wild-type ($p< 0.001$), CD34 positivity ($p=0.006$), and lower clinical remission rate ($p=0.027$). FLT3 and CEBPA mutation had no association with MN1. A high MN1 copy number on survival analysis was associated with poor EFS (HR 2.63, 95% CI 1.36-5.1, $p=0.004$) and OS (HR 3.57, 95% CI 1.56-8.21, $p=0.003$). On multivariate analysis, the MN1 copy number emerged as a predictor of EFS ($p< 0.0001$) and OS ($p< 0.0001$).

Conclusion : MN1expression independently predicts outcome in CN-AML. It can be exploited, especially as a therapeutic target in CN-AML.

Keyword : MN1, AML

PP01-4

Antileukemic activity of 1,3,5-Triazine (5-TC) against human leukemic cell via inhibition of EGFR-TK

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Background : Despite immense advancement in diagnostics and therapeutics, AML is still unmanageable, and usually gets worse quickly if it is not treated adequately. However, current drugs to treat AML face resistance which compromise their clinical utility. The inhibitors of epidermal growth factor receptor (EGFR) have proved its efficacy because of selective targeting of leukemic cells and potent inhibitory activity. Thus, in the present study, a novel series of 1,3,5-triazine conjugates were developed as anti-leukemic agent and mechanistic evaluation.

Method : The molecules were synthesized in excellent yield. The compounds were tested for determination of anticancer activity against human leukemic cells (HL-60). The effect of compound on the cell cycle phase and apoptosis was also studied. The docking study was also carried out on the 3D crystal structure of EGFR-TK (PDB ID: 1M17) to enumerate key contacts for bioactivity.

Results : The compounds showed considerable inhibition against HL-60 with greatest potency in compound 5-TC with IC50 of 1.20 µM. Compound 5-TC causes inhibition of HL-60 cells by inducing apoptosis and arresting the cell cycle at G2/M phase. The compound 5-TC causes induction of PARP, caspase-3 and caspase-9 to stimulate caspase-3 mediated apoptosis in a concentration dependent way. Compound 5-TC also showed to interact predominantly in the active site lined by Arg470, Glu-472 and Asn-473 of EGFR.

Conclusion : As a concluding remark, 1,3,5-triazine conjugates (5-TC) have shown promising anti-leukemic activity via induction of apoptosis and inhibition of EGFR-TK in leukemic cells.

Keyword : 1, 3, 5-triazine, Apoptosis, Synthesis, Docking, AML

PP01-5

Gilteritinib with chemotherapy in patients with newly diagnosed acute myeloid leukemia

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Background : Adding gilteritinib, an FMS-like tyrosine kinase 3 (FLT3) inhibitor active against FLT3 tyrosine kinase domain mutations, to frontline chemotherapy may improve outcomes for patients (pts) with FLT3-mutated acute myeloid leukemia (AML). We assessed safety and efficacy of gilteriti</sup>nib with chemotherapy in adults with newly diagnosed FLT3-mutated AML.

Method : In this Phase 2 part of a Phase 1/2, open-label, single-arm study in the Asia-Pacific region, pts received induction therapy (≤2 cycles): idarubicin 12mg/m²/d (Days [D] 1–3), cytarabine 100mg/m²/d (D1–7) and gilteritinib 120mg/d (D8–21); consolidation therapy (≤4 cycles): cytarabine 1.5g/m²/12h (D1, 3, 5) and gilteritinib 120mg/d (D1–14); and maintenance therapy (≤26 cycles): gilteritinib 120mg/d. The primary endpoint was complete remission (CR) rate after induction; the lower limit of the 2-sided 90% confidence interval (CI) was compared with benchmark CR rate of 55%, based on the placebo arm of RATIFY (Stone et al. 2017). Secondary endpoints included: composite CR (CRc) rate, overall survival (OS), and safety. The primary analysis was conducted after all pts completed induction; and the final analysis is not yet complete.

Results : The full analysis set included 82 pts. After induction, the CR rate was 50.0% (90% CI: 40.4%, 59.6%; the lower limit did not exceed the 55% benchmark) and the CRc rate was 86.6% (95% CI: 77.3%, 93.1%). The OS rate at Month 12 was 86.6% (n=84; 95% CI: 73.9%, 93.4%). There were no new safety findings.

Conclusion : The CR rate after induction with gilteritinib and chemotherapy did not exceed the benchmark. The CRc rate after induction was similar to that previously reported in the Phase 1 2215-CL-0103 study.

Keyword : Open-label, Acute myeloid leukemia, Asia-Pacific, FLT3-mutated, FLT3 inhibitor, Gilteritinib

PP01-10

Mitochondrial membrane potential as a metabolic related marker to enrich LSCs in AML

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Background : Acute leukemias are clonal disorders of hematopoiesis wherein a leukemic stem cell (LSC) acquires mutations that confer the capacity for unlimited self-renewal, impaired hematopoietic differentiation, and enhanced proliferation to the leukemic clone. To date, major research effort has been aimed at identifying and eradicating LSC population. The metabolism heterogeneity of mitochondria in LSCs and non-LSC cancer cells as well as their counterparts in non-malignant cells shows a big promise for cancer research. This reflects an urgent need for a greater understanding of the diversity of tumor biology to propel the development of effective therapeutic tools or combinations of currently existing medicines to target cancer in novel ways. Increased understanding and appreciation for leukemic stem cell biology are paramount to the development of new therapeutic regimens that aim to destroy this population of cells and to eradicate tumors in a manner that minimizes risk of future relapse.

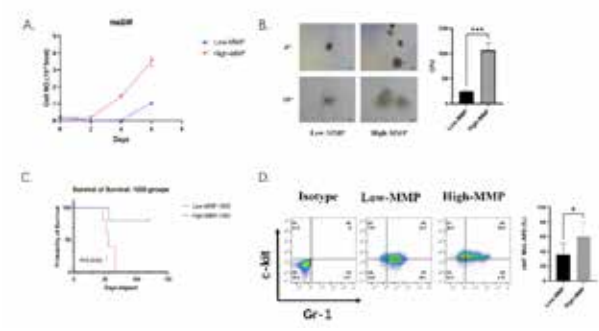
Method : For a better understanding of LSC biology, we must know further unique properties of these cells. Here, we describe a feasible method to enrich LSCs based on a single metabolic parameter: mitochondrial membrane potential (MMP). Mitochondria produce energy by establishing an electrochemical proton motive force across their inner cell membrane, which in turn fuels the synthesis of ATP by driving the proton turbine F0F1 ATPase. Mitochondrial function, a key indicator of cell health, can be assessed through using cationic fluorescent dyes, and MMP reflecting the functional status of the mitochondrion is proved to be highly related to cancer malignancy. Here we utilized a lipophilic cationic dye tetramethylrhodamine methyl ester (TMRM) to identify and isolate tumorigenic robust AML cells based on their MMP. Such as in vitro clonogenic assays ,transplantation and limiting dilution assays were used to assess the renewal and differentiation potential of Low/High-MMP-AML cells.

Results : Specifically, LSCs was characterized by high mmp. However, we found that stem cell-like characteristics were associated with high MMP in AML cell lines and in vivo AML mouse model(driven by MLL-AF9). Here we demonstrate that mouse AML cells sorted for low and high resting mitochondrial membrane potential are indistinguishable in the expression of pluripotency markers(c-kit/CD117), whereas markedly differing in metabolic rates. Interestingly, High-MMP cells are highly efficient at in vitro colony formation and further efficiently form AML in vivo. Here, we propose that the differences of MMP in the mitochondria of AML subpopulations could be as the new potential targets for cancer therapy.

Conclusion : Compared to normal cells, bulk leukemic cells and LSCs would be more hyperpolarised in MMP, we speculates that

the more aggressive and dangerous the cell,the more hyperpolarised MMP they have.Mitochondrial membrane potential (MMP) media a coupling between intrinsic metabolic parameters and stem cell fate in mouse AML Formation Capacity.It is optimistic that selective targeting of LSCs involved MMP with mitochondrial targeted agents is likely to attract great interest. We have found that more hyperpolarised MMP make them vulnerable to compounds that inhibit the OXPHOS system(data not shown), especially due to the more intake of MMP dependent chemicals,which may influence the pathogenesis and treatment of AML. Together, our results suggest a coupling between intrinsic metabolic parameters and stem cell fate that might form a basis for novel enrichment strategies and therapeutic options.

Keyword : Oxidative phosphorylation (OXPHOS), Acute myeloid leukemia (AML), Mitochondrial membrane potential (MMP), Leukemic stem cell (LSC),



PP01-11

Genetic, epigenetic, and clinical significance of Wilms' tumor 1 (WT1) gene in primary acute myeloid leukemia and its influence on prognosis

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Background : Acute myeloid leukemia is a genetically complex hematologic malignancy characterized by abnormal differentiation and clonal proliferation of myeloid progenitor cells in the bone marrow with diverse genetic and epigenetic alterations. Wilms tumor 1 (WT-1) gene is a critical regulator of malignant hematopoiesis, which encodes a zinc-finger transcription factor that can either activate or repress genes to regulate cell growth, apoptosis, and differentiation. Although underlying epigenetic alterations, the biological role of the WT-1 gene and their clinical relevance have not been fully addressed in AML. In the present study, we aim to investigate the RNA expression, methylation levels, and molecular functions of the WT-1 gene in AML cases.

Method : Bone Marrow (BM) and Peripheral Blood (PB) samples were collected from 74 AML cases (74 at diagnosis [day 0] and 67 after completion of induction chemotherapy [day 28] and 20 non-malignant samples were recruited as controls. WT-1 gene expression and promoter methylation status were assessed during both intervals (day-0 & day-28) by performing real-time polymerase chain reaction (RT-PCR) and methylation-specific polymerase chain reaction (MS-PCR). Further, we explore the molecular and biological functions of WT-1 by performing Gene set enrichment analysis (GSEA) and the relationship of WT-1 expression with immune checkpoint analysis using the Sangerbox 3.0 database. Kaplan–Meier survival investigation was performed to estimate the prognostic significance of WT-1 gene in AML.

Results : Of the 27 subjects studied, 51 were male (68.9%) and 23 were females (31.1%), out of these 61 (82.43%) cases showed overexpression of WT-1 gene at the time of diagnosis as compared with cases in complete remission (CR) remission or control samples (p= <0.001). Moreover, Robust hypermethylation of WT1 promoter was observed in 56 (75.67%) AML cases at the time of diagnosis as compared with patients in complete remission (CR) remission or control samples (p= <0.001). In all AML patients, WT-1 expression and methylation levels were inversely correlated with normal hematopoiesis and positively associated with age, high marrow blast counts, M4 subtype, adverse risk cytogenetic, and inferior outcome compared to patients with low WT-1 methylation and expression levels. In Gene set enrichment analysis (GSEA) we found WT-1 gene plays an important role in transcription misregulation of cancer by different molecular functions such as DNA-binding transcription factor activity, RNA binding, protein binding, and methylated DNA binding as well as in multiple molecular functions including negative regulation of cell growth, cell population proliferation, apoptotic process while positive regulation of DNA methylation. In immune checkpoint analysis WT-1 gene expression was positively correlated with CD28, CD40, CD44, CD48, CD80, CD70, CD27, CD86 etc. In

Survival Analysis poorer overall survival was seen in patients having higher WT-1 gene expression as compared with the lower expression group.

Conclusion : Overexpression and Hypermethylation of the WT-1 gene positively associates with the leukemic burden in most cases of AML. Thus, this gene can be considered a promising molecular marker for early diagnosis, and MRD detection, and a target for developing novel therapeutic approaches against AML.

Keyword : Methylation

PP01-12

Mutation of NPM1 and FLT3-ITD genes in acute myeloid leukemia and their association with clinico-pathological profile

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Background : Diagnosis of Acute myeloid leukaemia (AML) has shifted from a primarily clinico-pathological assessment to an integrated approach, including morphology, immunophenotyping, cytogenetics, and molecular genetics. The most frequent acquired molecular alterations as well as the most important diagnostic and prognostic indicators in patients with AML are fms-like tyrosine kinase-3 gene (FLT3) and nucleophosmin-1 (NPM1) mutations. Aim of this study is to investigate the prevalence and clinico-pathological characteristics of NPM1 and FLT3-ITD mutations in AML (excluding acute promyelocytic leukemia/APL).

Method : A total of 490 newly diagnosed cases of AML were included in this study. Mutations of tetranucleotide insertion in exon 12 of NPM1-A and FLT3-ITD were detected by fragment analysis in a multiplex assay. AML cases were dividing into 4 groups based on NPM1 and FLT3-ITD mutation status: NPM1 mutated, FLT3-ITD mutated, both mutations and no mutation; and different clinico-pathological characteristics were compared. Among the total 490 newly diagnosed case of non-APL AML (median age 20yrs; age range: 5 months to 69 years; M:F ratio: 1.45:1), NPM1 mutations were detected in 81 (16.5%), FLT3-ITD in 79 (16.1%) and double mutations of NPM1 and FLT3-ITD in 37 cases(7.6%).

Results : NPM1 and/or FLT3-ITD mutation were prevalent in older age group than unmutated wild group (p<0.001). Females more often had FLT3-ITD and/or NPM1mutation (p<0.001), and more males were double negative(p<0.001). Patients with NPM1and/or FLT3-ITD mutation had higher total leucocyte count(p<0.05)), peripheral blood blast% (p <0.001), and bone marrow blast% (<0.001).These parameters were also higher in AML with co-occurring mutation than in other 3 groups(p <0.001). NPM1 was associated with lack of CD34(p< 0.001) and HLD-DR expression(p < 0.001), while FLT3/ITD mutation with expression of CD7(p 0.003) and co-occurring mutation with presence of CD7(p 0.003),CD123(p<0.001) and CD11b(p<0.001). FLT3 ITD associated more with abnormal karyotype, whereas NPM1 and co-occuring group is with normal karyotype(p<0.001). Patients with isolated NPM1 mutation had highest CR rate (93.3%), followed by cases with co-occuring mutation (73.9%), double negative (69.4%) and isolated FLT3-ITD mutation (61.8%).

Conclusion : About 16% of the non-APL patients with AML have NPM1 and FLT3-ITD mutations each with around 7.6% with a co-occurrence of both the mutations. These mutations were more prevalent in older age group with female predominance in comparison to double negative group which is common in younger age group with male predominance. Patients with NPM1and/or FLT3-ITD mutation had higher total leucocyte count, PB and BM blast%. FLT3 ITD associated more with abnormal karyotype, whereas NPM1 and co-occuring group is associated more with normal karyotype. Isolated NPM1 mutation has the strongest positive effect, whereas isolated FLT3-ITD mutation has a strongest negative effect on CR rate in AML.

Keyword : AML, NPM1, FLT3-ITD

PP01-13

Pursuing the clonal transition of minimal residual disease clones in patients with relapsed and refractory acute myeloid leukemia

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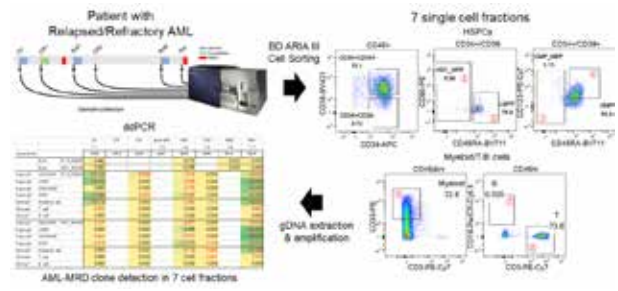
Background : Acute Myeloid Leukemia (AML) is a myelogenous malignancy that frequently relapses despite complete remission (CR) and elicits non-responsiveness (refractory) to treatment. Recent studies have emphasized that acquiring resistance to treatment and/or residual subclones bearing drug such as Cancer stem cells (CSCs) or Minimal residual disease (MRD) clones can lead to relapse and treatment-refractory in AML. Drug persistent AML-MRD having leukemogenic properties and its clinical relevance have not been fully explained due to the AML's cytogenetic clonal heterogeneity. In this study, we pursue the clonal transition of AML-MRD cells in the Bone Marrow (BM) niche of AML patients via genotype/phenotype analysis throughout patient treatment procedure.

Method : To investigate clonal transition, we collected longitudinal BM samples at diagnosis (Dx), remission (CR), relapse (Rel), and treatment-refractory (Per) from relapsed/refractory AML patient. From the serially collected samples, variant allele frequency (VAF) values of somatic variants that frequently occurred in malignant cells were analyzed by performing Whole Exome Sequencing (WES). Two (FLT3_D835E, WT1_R375Pfs) out of five variants were validated their oncogenicity (OncoKB DB), and used to analyzed LSC clones in AML patient BM cells. To identify LSCs in AML BM cells, AML BM cells were separated into seven single cell fractions (4 HSPCs, Hematopoietic Stem and Progenitors: HSC/MPP, LMPP, CMP/MEP, GMP; 3 Mature leukocytes: Myeloid cells, T/B Lymphocytes) according to their surface antigens (BD ARIA III FACS). Using ddPCR assay probes designated to detect selected two oncogenic variants, leukemogenic clones were detected among 7 sorted cell fractions.

Results : In the AML patient BM, we found that the clones with an oncogenic variant that was likely to indicate AML-MRD cells were distributed in not only primitive cell populations with the HSPC (LSC-like) phenotype, but also mature (differentiated) cell populations such as leukocytes. These clones were not completely disappeared even after intense AML chemotherapy, and remained in minimal quantities despite CR. In our sequential analysis, some residual clones distributed in HSPCs (LSC-like) populations exhibited the traditionally well-known MRD's character, such as repopulating leukemic populations. In addition, some other residual clones only in mature populations also seemed to be played a role in functional MRD resulting in the repopulation of leukemic populations. However, whether these residual clones resided in HSPCs (LSC-like) populations or mature populations, repopulating of LSCs continued to be induced during AML relapses, and was significantly aggravated, especially in secondary relapses right before the end point (around 30%, based on the VAF values).

Conclusion : This result indicates that the variant clones in mature cell populations may play role as the temporal salvages of AML-MRD clones (functional MRD) to survive against chemotherapy, and clones in HSPCs (LSC-like) population are likely to be the AML-MRDs practically contributing to AML recurrence and treatment-refractory. This approach suggests the methodology for specifying AML-MRD clones and pursuing its clonal evolution throughout the treatment progress. This will help to improve risk stratification and the diagnostic paradigm of AML, enabling the preemptive detection of AML-MRD at the initial diagnosis time point.

Keyword : Acute myeloid leukemia, Minimal residual disease, Clonal evolution, Leukemic stem cells, Oncogenic variant



PP01-15

Role of HOTAIRM1/miR-222 Axis in the pathogenesis of paediatric acute myeloid leukaemia

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Background : HOTAIRM1 is a long non-coding RNA (lncRNA) that regulates myelopoiesis and we hypothesize that its dysregulated expression has significance in the pathogenesis of acute myeloid leukemia (AML).

Method : Six AML cell lines (Kasumi-1, THP1, HL-60, KG1, MOLM-13, MOLM-14) were cultured in 10% FBS supplemented RPMI-1640 media. Bone-marrow samples from 26 paediatric AML patients and

10 normal marrows were included. Additionally, 45 peripheral blood (PB) samples from paediatric patients and 10 PB samples from healthy controls were also included in the study. The expression of HOTAIRM1 was quantified using qPCR. Downstream microRNA targets of HOTAIRM1 were predicted using DIANA-LncBase and RNA-Hybrid. The microRNA binding region on HOTAIRM1 was cloned into the pmirGLO vector (i.e pmirHM1), and interaction was studied using the dual-luciferase assay. Cell cycle analysis was performed by quantifying 7-AAD, apoptosis by the annexin-PI method and myeloid differentiation by quantifying CD11b expression using flow cytometry.

Results : Expression of HOTAIRM1 transcript variant 1 (HM1V1) was downregulated in HL-60, MOLM-13, and MOLM-14 cell lines ($p<0.05$), whereas transcript variant 2 (HM1V2) was downregulated in all cell lines (KG1, Kasumi-1, THP1, MOLM-13 $p<0.01$ and HL-60, MOLM14 $p<0.001$). In marrow samples from AML patients, both variants were downregulated more than two-fold (HM1V1 $p=0.0007$, HM1V2 $p=0.0023$). Contrarily, the expression of predicted HOTAIRM1 microRNA targets were upregulated in AML cell lines (miR-221 $p<0.001$, miR-222 $p<0.001$), marrow samples (miR-222 $p<0.0001$; miR-221 $p=0.0345$) and peripheral blood samples (miR-222, $p=0.0005$; miR-221 $p=0.431$). Co-transfection of pmirHM1 and miR-222 mimic in HEK293T cells decreased luciferase activity ($p<0.01$) demonstrating an in vitro interaction. Additionally, inhibition of miR-222 in a pediatric AML cell line (THP1) led to cell cycle arrest ($p<0.01$) and increased apoptosis ($p<0.01$), along with a decrease in the level of anti-apoptotic protein BCL-2 and increase in levels of CD11b, an indicator of myeloid differentiation.

Conclusion : The in-vitro experiments elucidate an inverse expression of HOTAIRM1 and its predicted target (miR-222) which indicated a potential regulatory interaction. The HOTAIRM1 and miR-222 interaction was validated by the dual luciferase assay. MiR-222 acts downstream of HOTAIRM1 to promote cell cycle turnover of myeloblasts while inhibiting apoptosis and differentiation. The inverse expression of HOTAIRM1/miR-222 in pediatric AML samples and in vitro experiments established the involvement of HOTAIRM1-miR222 in pediatric AML disease pathology.

Keyword : Pediatric AML, THP1, HOTAIRM1, miR222

PP01-16

Retrospective analysis of TP53 mutations in acute myeloid leukiemia: A single institute study

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Background : Somatic mutations in the TP53 gene are the most common mutations found in human cancers. In acute leukemia, TP53 mutations suggest higher recurrence and lower survival rates. As a system for simultaneously testing multiple genes and evaluating prognosis has been established with the development of technology, the aspects found in patients with TP53 mutations were compared and analyzed with previous literature.

Method : Between November 2018 and October 2022, 136 patients newly diagnosed with AML(Acute myeloid leukemia) or MDS-EB(Myelodysplastic syndromes-Excess blasts) at Dong-A University Hospital were included in the study(106 AML and 30 MDS). We retrospectively analyzed the collected data from chromosomal analysis, FISH(Fluorescence In Situ Hybridization) and targeted gene panel sequencing.

Results : Mutations were detected in 119 (87.5%) of 136 newly diagnosed patients (76 males, 60 females) through panel sequencing, and TP53 mutations were found in 26 (19.1%). An average of the variant allele frequency values was 46.16. A high proportion of complex karyotypes were observed when TP53 mutations were present. 19 out of 26 (73.0%) had a complex karyotype, a high percentage difference compared to the group without TP53 mutation (21 out of 110, 16.7%). Del(5) was most commonly observed in 15 patients. In bone marrow aspiration, the average blast rate was 47.0%, and there was no difference with or without TP53 mutation. The probability of gene aberrations observed in FISH results was twice as high in the presence of TP53 mutations.

Conclusion : The results were found to be generally consistent with the results of previous studies. Detection of mutations such as TP53 will help predict patient treatment and prognosis.

Keyword : Acute myeloid leukiemia, TP53, Next generation sequencing

PP01-17

Role of LncRNA UCA1 long non-coding RNA in pediatric acute myeloid leukemia

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Background : Acute Myeloid Leukemia (AML) is a heterogeneous disease of hematopoietic stem cells, characterized by rationalized premature/unfledged neoplasm. With the advent of next-generation sequencing, long non-coding RNAs (LncRNA) emerged as regulators of the genome. LncRNA UCA1 (Urothelial Cancer Associated-1) is a 1.4kb long transcript found on chromosome 19p13.12 that is known to play roles in proliferation, apoptosis, invasion, and migration in various cancers however its role in AML is unknown.

Method : In the current study, six cell lines (THP1, MOLM13, MOLM14, KG1, Kasumi-1, HL60) and peripheral blood (PB) samples from AML (N=67) with controls (N=10) were studied for UCA1 expression. Dim CD45 expressing myeloblasts were sorted using flow cytometry. The cells were cultured in 10% RPMI for differentiation and MTT assay. A total of 1 microgram RNA was used for the expression study of UCA1 using real-time PCR.

Results : UCA1 expression was downregulated when 67 AML peripheral blood (PB) samples were compared with healthy PB controls($p=0.0425$). Similar expression pattern was observed in Bloodspot database and in five AML (THP1, MOLM13, MOLM14, KG1, Kasumi-1) and one APML (HL60) cell lines ($p<0.0001$). UCA1 expression was additionally compared to sorted granulocytes as myeloid cells control. Furthermore, THP1 cells were treated with 10ng/mL of phorbol 12-myristate 13-acetate (PMA) to induce differentiation (differentiation was validated by flow cytometry and light microscopy), UCA1 expression was overexpressed in differentiated THP1 cells as compared to control ($p=0.0001$. Furthermore, 196.26-fold increased expression UCA1 of ($p<0.01$) was observed in Daunorubicin treated THP1 cells (IC50 was analysed by MTT and Annexin-V FITC PI Apoptosis assay).

Conclusion : The current study depicts the potential role of LncRNA UCA1 in myeloid differentiation and chemoresistance of AML.

Keyword : Pediatric AML, THP1, UCA1, Differentiation, Chemoresistance

PP01-18

Novel HOXA3-HOXA9 Fusion Genes in acute myeloid leukaemia: The bride or the bridesmaid?

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Background : The dysregulations of HOXA genes in acute myeloid leukaemia (AML) are evident in the immortalisation of leukaemic cells. Hitherto, little is known about fusion occurring among the HOXA genes and their clinical relevance in AML. In this study, the role of novel cryptic fusion genes HOXA3-HOXA9, which involves HOXA9 activation region detected using transcriptomic sequencing in the prognostication of AML-normal karyotype (AML-NK), was elucidated.

Method : 51 AML-NK subjects were subjected to high throughput deep transcriptomic sequencing using NovaSeq 6000 (200M reads per sample, 150bp paired-end). Customised transcriptomic pipelines were utilised to detect HOXA fusions and their expression profiles. HOXA3-HOXA9 fusions were correlated with their DEG profiles. In-silico validation and Sanger sequencing were performed on novel chimeric genes and DEGs. The prognostic significance of the HOXA3-HOXA9 fusion in quadrochotomised AML-NK patients based on NPM1 mutation (NPM1mut) and FLT3-internal tandem duplication (FLT3-ITD) or wildtype (FLT3wt) status was scrutinised. The Kaplan-Meier curve analysis and log-rank test were used in univariate analysis to assess potential prognostic factors in predicting patient survival. A prognostic scoring model was developed based on HOXA3-HOXA9/FLT3-ITD/NPM1 genotype, age groups below and above 60 years, and stem cell transplantation (SCT) using Cox-regression multivariate analysis.

Results : The novel HOXA3-HOXA9 fusion was detected in 16% (8/51) of the AML-NK patients, present with coexisting FLT3-ITD/NPM1mut and FLT3wt/NPM1mut in 50% of the cases, respectively. 50% of the AML-NK patients with HOXA3-HOXA9 fusion had poor overall survival (OS<5 years). Patients with genotype negative for HOXA3-HOXA9/ FLT3wt/ NPM1mut were assigned scores as prognostication predictors. Our prognostic scoring model designed for negative HOXA3-HOXA9/FLT3wtand NPM1mut showed that scores ≥ 2 with age <60 as a confounding factor yielded to OS>5 years. However, an in-depth analysis of the HOXA3-HOXA9/FLT3-ITD/NPM1 genotype and the DEG profiles did not show any statistical or

clinical association.

Conclusion : The scoring model based on HOXA3-HOXA9/FLT3/NPM1 genotype developed in this study is applicable for AML-NK prognostication. We deduce that the novel HOXA3-HOXA9 fusion is a veiled bride on the aisle of AML-NK's dismal prognosis altar, necessitating the larger prospective cohort validation.

Keyword : Acute myeloid leukaemia, Transcriptome sequencing, HOXA

PP01-19

Not only mutations matter: Deciphering the gene expression profiles of FLT3 And NPM1 in acute myeloid leukaemia-normal karyotype by transcriptome sequencing

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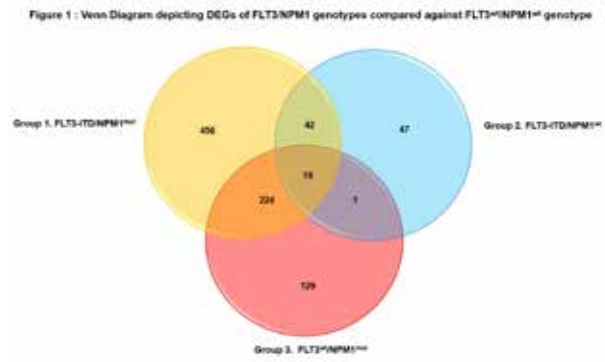
Background : NPM1 mutation and FLT3-internal tandem duplication (FLT3-ITD) are known to have prognostic importance in acute myeloid leukaemia-normal karyotype (AML-NK) patients, but little is known about their gene expression profiles. This study explicated the gene expression profiles of AML-NK patients quadrochotomised based on their NPM1 mutation (NPM1mut) and FLT3-ITD detection.

Method : High throughput deep transcriptome sequencing was performed on 46 AML-NK patients using NovaSeq 6000 (200M reads per sample, 150bp paired-end). Unsupervised clustering method was utilised to group AML-NK patients into 4 groups: FLT3-ITD/ NPM1mut, FLT3-ITD/NPM1 wildtype (NPM1wt), FLT3wt/NPM1mut and FLT3wt/NPM1wt. Customised differentially expressed gene (DEG) pipeline was utilised for quality control (QC), data cleaning, alignment, quantification and normalisation of the sequencing reads. At sample-level QC, multidimensional principal component analysis (PCA) was constructed to identify potential outliers, followed by pairwise comparison of each group against the FLT3wt/NPM1wt group. DEseq2 was used to perform DEGs with the following filters: p-adjusted value (padj) <0.01, log fold change (lfc) >1 and <-1, and basemean >100. Mutually exclusive and inclusive DEGs were discovered, and gene set enrichment analysis (GSEA) was performed to compare the pathways that were enriched among the four AML-NK groups using the WebGelstalt tool for gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment.

Results : Unsupervised clustering of the four groups based on the FLT3/NPM1 genotype revealed distinct gene expression in each group. Compared with the FLT3wt/NPM1wt group, only 18 genes overlapped between the four groups, and the number of mutually exclusive DEGs discovered are as follows: 466 in FLT3-ITD/NPM1mut, 47 in FLT3-ITD/NPM1wt and 129 DEGs in FLT3wt/NPM1mut groups. Although FLT3wt/NPM1wt is classified as an intermediate prognosis, 16/22 (73%) of the patients had poor overall survival, indicating that DEGs are useful in elucidating the expression heterogeneity between the groups.

Conclusion : DEGs based on the genotypes of FLT3/NPM1 yielded unique clusters with novel distinct expression signatures that harness the prognostication of AML-NK patients in this study. This is the first study from Malaysia that explored high throughput deep sequencing of the AML-NK transcriptomes based on FLT3/NPM1 mutational status to illustrate that not only mutations matter in AML-NK, but transcriptomics sequencing sheds light on underlying gene expression of this rather heterogeneous disorder.

Keyword : Gene expression , FLT3-ITD, NPM1, AML



PP01-20

Reclassification of acute myeloid leukemia and higher-risk myelodysplastic syndrome based on the new International Consensus Classification

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Background : The accumulation of data on the biology of myeloid neoplasms have indicated the need for further updating classification system. To meet this need, a professional body recently issued blue book of new classification system, the International Consensus Classification (ICC) of myeloid neoplasms. Application of this new criteria for classification of acute myeloid leukemia (AML) and higher-risk myelodysplastic syndrome (MDS) expected to reveal discrepancies from the present classification system, revised 4th edition of WHO criteria. We thus analyzed the frequency, reclassification patterns and features of discrepant cases resulting from major changes of the new criteria.

Method : We searched genetic mutation-characterized collection of an in-house myeloid neoplasms patients from January 2018 to December 2021. We subsequently classified patients with AML and MDS with excess blasts 2 (MDS-EB-2) into corresponding subtypes according to the ICC criterion.

Results : We reviewed a total of 484 cases for which samples collected at initial diagnosis were available (416 for AML and 68 for MDS-EB-2). In patients with AML, AML with myelodysplasia-related gene mutations (MRG) was the most common subtype (n = 98, 23.6%), followed by AML wit mutated NPM1 (n = 76, 18.3%), AML not otherwise specified (NOS) and AML with mutated TP53 (n = 42, 10.1% each), acute promyelocytic leukemia with PML::RARA (n = 29, 7.0%), AML with RUNX1::RUNX1T1 (n = 28, 6.7%), AML with myelodysplasia-related cytogenetic abnormalities (MRC; n = 23, 5.5%), AML with in-frame bZIP CEBPA mutation (n = 22, 5.3%), AML with CBFB::MYH11 (n = 18, 4.3%), AML with KMT2A rearrangement (n = 17, 4.1%), AML with MECOM rearrangement (n= 8, 1.9%), AML with DEK::NUP214 (n = 4, 1.0%), myeloid sarcoma (n = 3, 0.7%), and AML with BCR-ABL1 (n = 1, 0.2%). Five cases (1.2%) with rare recurring translocations included FUS::ERG (n = 2), NUP98 rearrangement (n = 2) and RBM15::MRTFA (n = 1). The concordance rate in classification between the present WHO criteria and ICC criteria was 76.7% (319/416) in patients with AML. Among 97 discrepant cases, the most common pattern (56.7%, 55/97) was for NOS to MRG or MRC, due to the introduction of mutation-based definition of AML with myelodysplasia-related. The second most common pattern (13.4%, 13/97) was for therapy-related AML to other subtypes, due to the identification of prior cytotoxic therapy as a qualifier. The third most common pattern (9.3%, 9/97) was for AML with biallelic mutation of CEBPA to NOS or MRG, due to the changing definition of AML with CEBPA mutation. The fourth most common pattern (7.2%, 7/97) was for AML with myelodysplasia-related changes to other subtypes, due to the changes of defining genetic abnormalities. In patients with MDS-EB-2, there were two cases (2.9%) harboring NPM1 mutation, for whom reclassification into AML was justified. Almost half of patients were classified as MDS/AML with MRG (n = 32, 47.1%). Other subtypes included MDS/AML NOS (n = 14, 20.6%), MDS/AML with mutated TP53 (n = 12, 17.6%) and MDS/AML with MRC (n = 8, 11.8%).

Conclusion : This study revealed that 24% of patients with AML were reclassified into a different category due to the critical changes of new criteria. Moreover, more than half of MDS-EB-2 were reclassified as MDS/AML with myelodysplasia-related. The refined diagnosis and prognostication of AML and MDS-EB-2 by using new criteria can lead to improve treatment outcomes and facilitate participation of promising clinical trials.

Keyword : Acute myeloid leukemia, Myelodysplastic syndrome, 4th WHO classification, ICC

PP01-22

Unveiling of some novel compounds to inhibit the overexpressed genes of acute myeloid leukemia for the new therapeutics discovery

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Background : Immature myeloid cell growth and bone marrow failure are two features of the heterogeneous clonal illness known as acute myeloid leukemia (AML). A crucial prognostic tool for post-induction treatment is cytogenetics and mutation testing. AML treatment has remained unchanged for the past three decades despite fast breakthroughs in the area, including novel therapeutic targets

and a better knowledge of the biology, with the majority of patients eventually relapsing and passing away from the disease. Consequently, the gene level analysis may have a progressive impact for the flourishing insights for the development of AML and the identification of innovative treatments. A better option for the genetics of AML and its treatment may therefore be transcription profiling and identification of important genes. The important genetic studies that have improved prognosis and innovative treatments will be covered in this study.

Method : The Gene Expression Omnibus (GEO) database provided the RNA sequencing datasets for 151 AML cases. The R platform's edgeR was used to find differentially expressed genes (DEGs). ClusterONE was used to assess PPI network clustering modules, and pathway enrichment analyses for modules were run using the KEGG (Kyoto Encyclopedia of Genes and Genomes) database. Later, Molecular Docking and Molecular dynamics were used to identify some novel compounds that could inhibit the expression of upregulated genes.

Results : We identified genes that are overexpressed in AML patients, including INPP5D, IRS2, JUNB, METTL3, MME, MT1H, NUP98, PHB2, PPIF, PRG2, RAF1, RHOH, SLC25A1, and SLC7A5. These genes are essential for maintaining the homeostasis of the human body, according to the pathway analysis. The investigation of gene interactions also indicated that these genes interact strongly with other genes that are involved in the development of various diseases. Additionally, we selected four compounds through virtual screening to see whether they may suppress these genes' expression. Strong binding affinities between -10.5 Kcal/mol and -13.7 Kcal/mol were demonstrated by these compounds. The Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties of these compounds provided the anticipation for being expected as drug compounds for the treatment of AML. Later, molecular dynamics and simulations study on Root Mean Square Deviation (RMSD), Root Mean Structural Fluctuations (RMSF), Solvent-accessible surface area (SASA) and Radius of Gyration (Rg) confirmed the stability in protein-drug complex at 120ns.

Conclusion : The present study found that multiple genes are involved in the disease of AML from RNA- seq analysis which are crucial for body growth and survival. However, four compounds were also identified to inhibit the upregulated genes of AML. Finally, the results of this study will offer a valuable perspective on the development of novel therapies for the treatment of AML disease.

Keyword : AML, RNA Sequencing, Novel Compounds, ADMET, Novel therapy

PP01-23

A prospective study to evaluate the prognostic implications of MMP-2 gene in acute myeloid leukemia

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Background : Acute myeloid leukemia (AML) is a complex hematologic malignancy characterized by the uncontrolled proliferation of immature myeloid cells in the bone marrow. Matrix metalloproteinase-2 (MMP-2) gene has been involved in tumor invasion and trafficking of normal hematopoietic cells. However, the molecular mechanism of MMP-2 and their molecular interaction in AML remains unknown. Therefore, this study aimed to characterize the molecular functions, clinical and prognostic value of MMP-2 gene in AML.

Method : In this study, first, we investigated the expression level of the MMP-2 gene in AML (n=173) and normal (n=70) cases. Second, we did correlation analysis to find the potentially associated gene linked with the MMP-2 gene based on their expression levels using GEPIA2 database. Kaplan–Meier survival estimation was performed to evaluate the prognostic significance of MMP-2 using UALCAN platforms. In addition, we assess the DNA methylation status of MMP-2 gene using UCSC Xena browser and MEXPRESS database. Third, we explore the molecular mechanisms of MMP-2 in AML, their correlation, and biological function analysis by performing Gene set enrichment analysis (GSEA) and Linked Omics database. Finally, the relationship of MMP-2 expression with different functional states was studied using SANGER Box 3.0 database.

Results : In our analyses, MMP-2 mRNA was significantly overexpressed in AML (n=173) cohorts as compared with normal cases (n=70) and closely associated with poor overall survival ($P < 0.05$). Based on FAB classification higher MMP-2 expression was observed in M7 subtype, followed by M2 and M4. In correlation analysis MMP-2 gene was positively correlated with the WT-1 gene, followed by

CPA3, IGFBP2, FGFRL1, RABL5, ATP1B1 genes with (PCC <0.65) and negatively associated with SERPINB6 gene, followed by RGS10, IL-12RB1, KIAA1949, VCL genes with (PCC >-0.5) in our cohort. Furthermore, a lower methylation level of MMP-2 gene was observed in AML compared to normal cases, which were negatively associated with MMP-2 gene expression. Gene Enrichment analysis revealed MMP-2 gene and its positively associated gene were involved in biological processes such as angiogenesis, blood vessel maturation, regulation of innate immune response, and leukocyte transendothelial migration pathway. Notably, the MMP-2 mRNA expression was negatively linked with cell cycle and proliferation while positively associated with differentiation invasion and metastasis in AML.

Conclusion : In this study, we found that MMP-2 plays a significant role in AML progression and may serve as a potential prognostic biomarker and therapeutic target for the effective management of AML.

Keyword : Methylation

PP01-24

Azacytidine venetoclax posaconazole combination in the treatment of acute myeloid leukemia in a resource limited setting: A single centre experience

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Background : Venetoclax with Azacytidine has become the standard treatment for acute myeloid leukemia patients who are not fit for intensive chemotherapy with complete remission rates of 70-80%. Coadministration of azole antifungal results in elevated Voriconazole levels in blood and it is recommended to reduce the dose of Venetoclax by 75% when used in combination. This interaction is of potential use in a resource limited setting as in India to significantly reduce the treatment cost. We hereby present our experience of successful use of this interaction in induction and consolidation therapy of acute myeloid leukemia

Method : A retrospective review of AML patients treated with venetoclax and Azacytidine from January 2020 to December 2022 was done. Clinical profile, laboratory parameters, treatment outcome and follow up data was evaluated.

Results : Fifteen patients were treated: 8 males and 7 females, median age 65years (61-89). Nine were positive for NPM1 mutation while 3 were FLT3 ITD positive. Aza-Ven was well tolerated except mild nausea and abdominal discomfort in 60% of patients. Twelve out of 15 (80%) patients achieved complete remission while 3 patients did not respond. Neutropenic fever occurred in 9/15 (60%) of patients during cycle one but none developed neutropenic fever during consolidation. All but one patient responded in first cycle. In Two patients of relapsed AML, Aza Ven was able to achieve second complete remission and subsequent allogenic bone marrow transplantation. Median survival has not been reached after 9 months of follow up.

Conclusion : Combination of Azacytidine Venetoclax and posaconazole is highly effective and safe. Posaconazole coadministration results in reduction in dose of Venetoclax and is highly cost effective which is very relevant in resource limited settings.

Keyword : AML, Venetoclax, Posaconazole

PP01-26

Discovery of neoantigens using artificial intelligence (NEO-ARSTM) in AML: A pilot study

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Background : Neoantigens caused by somatic mutations in tumors are attractive therapeutic targets for cancer immunotherapy. However, research on neoantigens in acute myeloid leukemia (AML) is still lacking.

Method : Leukemic blast DNA from bone marrow mononuclear cells (BMMC) at diagnosis was compared with Germline DNA from BMMC at time of complete remission (CR) using whole exome sequencing (WES) for the identification of patient-specific tumor mutations and MHC alleles. In addition, RNA sequencing (RNAseq) was performed to determine the level of expression of the genes with leukemic-specific mutations. Of all possible neopeptides-MHC class I (pMHC) combinations, neoantigen candidates were identified using a physics-informed deep learning algorithm NEO-ARSTM. Briefly, 3D structural modeling and molecular dynamics simulations of pMHCs were conducted and followed by computation of solvent-accessible surface areas of neopeptides for T cell recognition. Neopeptides with low predicted binding energy (i.e., high predicted affinity) were selected as neoantigen candidates and prioritized using solvent-accessible surface areas. For the peptides assumed to be neoantigen, IFN-γ ELIspot experiments were performed using peripheral blood mononuclear cells from human leukocyte antigen (HLA)-matched donor of allogeneic hematopoietic stem cell transplantation.

Results : With this approach, we prioritized a list of 6 neoantigen peptide-HLA candidates from 2 AML patients each (peptide lengths of 9 amino acids) across the available HLA class I alleles for that patient. In one patient (54 years old male with HLA-A*02:01), 90 peptides derived from 15 somatic mutations were designed, and 6 of them were predicted as neoantigen candidates by NEO-ARSTM. In the other patient (55 years old male with HLA-A*11:01), 198 peptides derived from 33 somatic mutations were designed, and 6 of them were predicted as neoantigen candidates by NEO-ARSTM. We synthesized 6 predicted neo-peptides in each patient. In IFN-γ ELISpot assay, the first patient, peptide #1(2068.3), #2(2163.3), #4(2006.6) and #6(1886.6) had higher spot forming units (SFU) than DMSO (1393.3) alone (in the all peptide, $P<0.0001$). In the second patient, peptide #3(1165, $P<0.01$), #4(1043.3, $P<0.05$) and #5(1813.3, $P<0.001$) had higher spot forming units (SFU) than DMSO (653.3) alone.

Conclusion : The neoantigens predicted by NEO-ARSTM showed a good immunogenicity against T cells in ELIspot assay. Thus, the neoantigens predicted by this AI algorithm have the potential to be used efficiently in novel therapies such as customized cancer vaccines or T cell receptor (TCR) T cell therapy for the patients with AML in the future.

Keyword : Acute myeloid leukemia (AML), Immunogenicity, Neoantigens, MHC binding, ELISpot assay

PP01-27

Effects of venetoclax-based combinations for the treatment of newly diagnosed acute myeloid leukemia in clinical settings

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Background : Recently, several therapeutic agents have been developed for the treatment of older adults or medically unfit patients with acute myeloid leukemia (AML). In such patients, venetoclax plus azacitidine combination therapy has shown superior overall survival (OS) and complete response (CR) rate over azacitidine alone. In addition, because its toxicity is tolerable, venetoclax has become one of the main therapeutic agents for AML. In this study, we aimed to evaluate the treatment outcomes and toxicity of venetoclax-based combinations in newly diagnosed elderly or unfit patients with AML in a clinical setting and compared the treatment response when using azacitidine and decitabine in combination. In addition, we compared the OS of patients given a reduced dose of venetoclax with CYP3A inhibitors with that of patients given the original dose of venetoclax(400 mg) without CYP3A inhibitors.

Method : We retrospectively reviewed the clinical data of 22 untreated AML patients who were ineligible for intensive chemotherapy and received venetoclax plus hypomethylating agent/low dose cytarabine as a frontline treatment at four medical centers between March 2020 and December 2022. The primary end point of this study was the rate of composite CR (CR and CR with incomplete hematologic recovery [CRi]). The other end points were overall response

(CR, CRi, morphologic leukemia-free state [MLFS], and partial remission [PR]), OS, toxicities and 30-day mortality. Response to therapy was evaluated according to European leukemia net (ELN)-2017 Criteria.

Results : Of the 22 patients enrolled, azacytidine (Aza) was used in 10 patients (45.5%), decitabine (Dec) in 11 patients (50%), and LDAC in 1 patient (4.5%). 12 of the 22 patients (54.5%) were female. The median age of all patients was 75.5 years (range 51-86). According to 2017 ELN Catergories, 36.4% (n=8) were at adverse risk and 18.2% (n=4) were at favorable risk. Patients received a median of two cycles of chemotherapy (range, 1–18). Among 15 assessable patients, best responses were CR (n=3), CRi (n=4), MLFS (n=3), and PR (n=2), and two patients showed progressive disease. The composite CR rate was 46.7%, and the overall response rate was 80%. Median time to response was 0.92 months (range, 0.82–3.84). During a median follow-up of 3.1 months (range 0.8-23.7), the median OS was 5.29 months (95% confidence interval, 0.8 to 9.8) for all patients. There was no difference in OS between the patients receiving Aza and Dec (6.1 months vs 5.3 months, respectively, p=0.406). There was no significant difference in the OS of patients receiving reduced dose+CYP3A inhibitor (n=13) and original dose of venetoclax (n=9) (Not reached vs 5.3 months, respectively, p=0.782). The most frequently reported hematologic adverse events of Grade 3 or higher included febrile neutropenia (72.7%), neutropenia (86.4%), and thrombocytopenia (86.4%). Notable infectious adverse events were sepsis (22.7%) and pneumonia (31.8%). The percentages of patients who discontinued chemotherapy owing to adverse event was 31.8% (n=7). Of these seven patients, only one patient discontinued the drug due to a hematologic adverse event. Mortality at 30 days was 4.5% (n=1) in this study.

Conclusion : This is a real-world study in which very elderly, frail patients were enrolled, compared to the VIALE-A trial. Through the composite CR rate (46.7%) and overall response rate (80%), deep hematological responses and manageable toxicities were shown despite the use of venetoclax for these patients. Although the number of enrolled patients was small, there was no significant difference in OS on administrating concomitant HMAs (Aza vs Dec) and OS on administrating venetoclax (reduced dose vs full dose).

Keyword : Acute myeloid leukemia, Elderly, Venetoclax, CYP3A inhibitor, Azacitidine, Decitabine

PP01-29

The role of estrogen related receptor alpha (ERRα) as therapeutic target of acute myeloid leukemia

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Background : Acute myeloid leukemia (AML) is a hematologic malignancy with a poor clinical outcome (5-year survival rate of 30%). Many studies have been conducted to overcome their worse prognosis and understand their chemoresistance, and it has been suggested that mitochondria are central to AML tumorigenesis, progression, and relapse. Estrogen-related receptor-α(ERRα; NR3B1) is the orphan nuclear receptor of which no ligand has been identified. ERRα has been reported to regulate mitochondrial biogenesis and function, leading to tumorigenesis, drug resistance, and tumor progression in many solid cancers. But its role in AML regarding mitochondria is still not clear.

Method : We used multiple and independent in silico, in vitro, and in vivo experiments in this study to better understand the role of ERRαin AML. First, the levels of ERRαexpression in hematopoietic cells and AML cells were compared. Then, using multiple genomic data, ERRα target genes were identified and their prognostic values and molecular functions in AML were assessed. The effects of ERRαinhibition on AML cells were analyzed either using an inverse agonist (XCT-790) or genetic silencing. Finally, we evaluated the anti-leukemic effect of XCT-790 using in xenograft mouse models

Results : ERRα transcriptionally regulates mitochondrial oxidative phosphorylation (mtOXPHOS) and mitochondria-related gene sets in AML cells. Patient survival was found to be significantly related to ERRα expression. ERRα inhibition suppressed mtOXPHOS, resulting in apoptotic cell death, and proved therapeutic effects against AML in the animal model.

Conclusion : These findings establish ERRα as a promising therapeutic target to suppress AML tumorigenesis and progression through inhibition of mtOXPHOS.

Keyword : AML, ERRα, Oxidative phosphorylation

PP01-30

Pharmacological GLUT3 salvage augments the efficacy of vitamin C-induced TET2 restoration in acute myeloid leukemia

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Background : Vitamin C has been demonstrated to regulate hematopoietic stem cell frequencies and leukemogenesis by augmenting and restoring Ten-Eleven Translocation-2 (TET2) function, potentially acting as a novel therapeutic agent for acute myeloid leukemia (AML). However, in our previous work, we found that glucose transporter 3 (GLUT3) deficiency in AML cells impeded vitamin C uptake and thus abolished the clinical benefit of vitamin C in (Liu J et al. British J Cancer 2020). In the current study, we investigated the therapeutic potential of GLUT3 salvage in human AML cells.

Method : GLUT3 salvage was conducted in GLUT3-deficient AML cell line OCI-AML3. Cell were transduced with lentiviruses delivering SLC2A3 (which encodes GLUT3) or empty vector (as a control). In addition, pharmacological overexpression of GLUT3 in AML cells was tried with 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), which is known for upregulating GLUT3 by stimulating AMP-activated protein kinase (AMPK) activity in colorectal cancer cells. The effect of pharmacological GLUT3 salvage using AICAR was further confirmed in GLUT3 deficient patient-derived primary AML blast cells.

Results : GLUT3 overexpressing OCI-AML3 cells showed a significantly increased intracellular vitamin C concentration, more 5mC to 5hmC conversion, and effectivel suppression of the cell viability, colony growth, migration, and invasion activity of AML cells upon vitamin C treatment, compared to empty vector OCI-AML3 cells. Transcriptomic analysis showed that genes related to vitamin transmembrane transport were upregulated in the SLC2A3-overexpressing OCI-AML3 cell line, but gene sets related to glycolysis or the tricarboxylic acid (TCA) cycle were not significantly enriched, suggesting that GLUT3 overexpression had no significant effect on the metabolic energy pathway in AML. AICAR pharmacologically turned on the GLUT3 expression in AML cells. The pharmacological GLUT3 salvage using 0.5 mM AICAR for 48 hours augmented TET2 activity and the efficacy of vitamin C treatment. AICAR effectively salvaged GLUT3 expression in patient-derived primary AML blast cells.

Conclusion : GLUT3 represents a potential biomarker to predict the effect of vitamin C-containing treatments, and pharmacological GLUT3 salvage has the potential to overcome GLUT3 deficiency and improve the antileukemic effect of vitamin C treatments in AML.

Keyword : Acute myeloid leukemia, Vitamin C, Ascorbic acid, TET2, GLUT3

PP01-31

Differences of categories and their prognosis between the International Consensus Classification 2022 and the 5th World Health Organization classification in acute myeloid leukemia

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Background : The diagnosis of acute myeloid leukemia (AML) had been classified by the 3rd (2001), the 4th (2008), and the revised 4th editions (2016) of the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues which continued as the single accepted classification scheme for over two decades. However, in 2022, the WHO, the European Association for Haematopathology (EAHP), and the Society for Hematopathology (SH) no longer cooperated and published two competing hematolymphoid classifications, the 5th edition of the WHO classification of haematolymphoid neoplasms by the WHO/IARC and the International consensus classification (ICC) of myeloid neoplasms and acute leukemias co-sponsored by the EAHP/SH. In this background, we classified the AML patients into the 5th WHO classification and ICC, estimated the data distribution and positional change according to the new classification, and compared the prognosis between the two classifications.

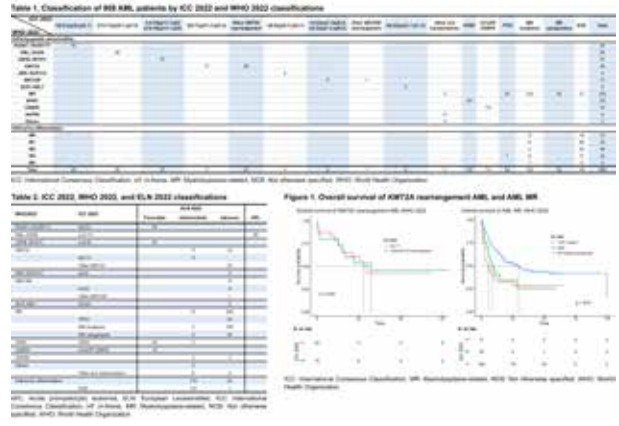
Method : Patients diagnosed with AML at Seoul St. Mary's Hospital from Oct. 2017 to Oct. 2021 were included in this study. All data of

available patients, regardless of the treatment regimen, were analyzed. In the initial bone marrow aspirate of each case, karyotype analysis of at least 20 metaphase cells and the next-generation sequencing (NGS) using St. Mary's customized NGS panel for acute leukemia ("SM Acute leukemia panel") or myeloid panel ("SM MDS/MPN panel") were performed. The "SM Acute leukemia panel" covers 67 genes frequently found mutated in patients with acute leukemia and The "SM MDS/MPN panel" contains 87 genes frequently found mutated in patients with myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN). Variants with more than 20 reads and 5% variant allele frequencies were considered mutated. FLT3-internal tandem duplication mutations were analyzed using fragment analysis and recurrent gene fusions were analyzed by multiplex reverse transcriptase PCR (Bio-Rad Laboratories, Hercules, CA, USA). From these results, we identified the AML category according to the ICC (ICC 2022) and the 5th WHO classification (WHO 2022) for each case, and analyzed the difference in distribution. We also inspected how these categories are distributed on the 2022 European LeukemiaNet risk classification (ELN 2022). In the groups with a large discrepancy between the WHO 2022 and the ICC 2022, we analyzed the overall survival (OS) of the patients to see how the difference in prognosis appears in these groups. Overall survival (OS) curves were plotted using the Kaplan–Meier method and were analyzed with the log-rank test.

Results : A total of 908 patients, including 496 males and 412 females, with a median age of 58 years were analyzed in this study. The results of classifying the patients according to the WHO 2022 and ICC 2022 are presented in Table 1. The difference between the WHO 2022 and the ICC 2022 was noticeable in the KMT2A gene rearrangement group. WHO 2022 classifies 'AML with KMT2A gene rearrangement' into only one group, whereas ICC 2022 classifies it into 't(9;11)(p21.3;q23.3)' or 'other KMT2A rearrangement' groups according to the fusion partner of KMT2A. Of our patients, 40 (4.4%) were in the KMT2A rearrangement group according to the WHO 2022, and among them, 23 (57.5%) and 17 (42.5%) were classified to 't(9;11)(21.3;q23.3)' and 'other KMT2A rearrangements' group by ICC 2022, respectively. The other group in which the difference between the WHO 2022 and the ICC 2022 showed remarkable was the 'AML myelodysplasia-related (MR)' group. WHO 2022 suggests one category of AML MR, but ICC classifies it as 'AML with mutated TP53', 'AML with MR gene mutation', and 'AML with MR cytogenetic abnormality'. Also, somatic RUNX1 mutation is not recognized as a distinct disease type in WHO 2022, but ICC considers RUNX1 as one of the MR-defining genetic mutations. In addition, in WHO 2022, if a patient has a history of MDS or MDS/MPN, then the patient can be classified as 'AML MR', whereas, in ICC, the previous history of MDS/MPN is required to be presented separately from AML type as diagnostic qualifiers (e.g. 'AML with MR gene mutation, progressed from MDS'). These facts caused a discrepancy in MR patients' classification between the WHO 2022 and the ICC 2022. Of our patients, 252 (27.8%) were 'AML MR' on WHO 2022. However, they were separated into 33 (13.1%), 143 (56.8%), 52 (20.6%), and 21 (8.3%) as 'AML with mutated TP53', 'AML with MR gene mutations', 'AML with MR cytogenetics', and AML not otherwise specified (NOS), respectively. These criteria of ICC 2022 were close to the criteria of ELN 2022, and because of this, one ICC 2022 category tended to belong to one ELN 2022 risk group more uniformly than one category of WHO 2022 (Table 2). We examined whether the OS of patients by ICC group differed significantly in the WHO 2022 'KMT2A rearrangement' group and the 'AML MR' group (Figure 1). In our patient, no significant difference in OS was seen by the KMT2A fusion partner (median OS; 't(9;11)' vs. 'Other KMT2A rearrangement': 22.3 months vs. 22.8 months, $p = 0.91$), whereas in the patients ICC 2022 'AML with MR mutation/cytogenetics' in the WHO 2022 'AML MR' group showed superior OS than the 'AML with mutated TP53 ' and 'AML NOS' (median OS; 'AML with MR mutations/cytogenetics' vs. 'AML NOS' vs. 'AML with mutated TP53': 29.3 months vs. 9.2 months vs. 5.6 months, $p < 0.01$).

Conclusion : In AML, both the WHO 2022 and the ICC 2022 are based on recurrent genetic abnormalities. Although there are many similarities, there are also several differences. The difference between the WHO 2022 and the ICC 2022 seemed the most striking in the KMT2A gene rearrangement and MR groups. The ICC 2022 tended to be more consistent with the ELN 2022, which is one of the most established prognostic criteria in practice. In OS, survival differences among ICC groups (TP53 mutated, NOS, and MR mutations and cytogenetics) in AML MR by WHO 2022 were demarcating. Further research is warranted to elucidate the validity of the two classifications.

Keyword : International Consensus Classification, World Health Organization, Acute myeloid leukemia, European LeukemiaNet



PP01-32

Physical function in older adults with acute myeloid leukemia treated with hypomethylating agents with or without venetoclax

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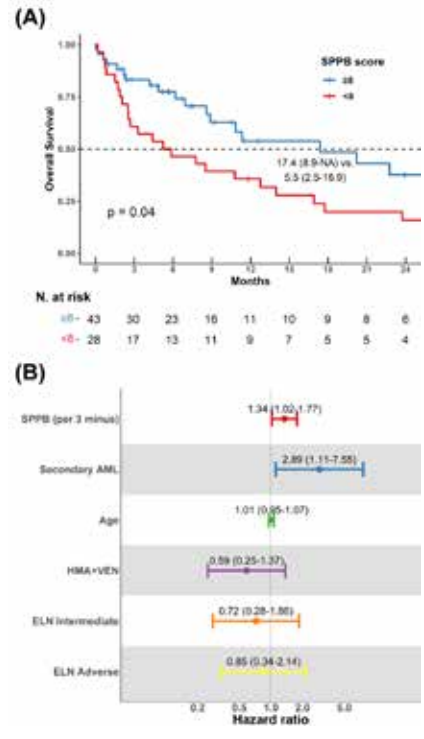
Background : Several prognostic models have been developed to identify patients at high risk of death, treatment resistance, or poor survival after conventional intensive chemotherapy in older adults with acute myeloid leukemia (AML). There are growing evidence that geriatric assessment can detect unrecognized vulnerabilities in patients with hematological malignancies to help predict treatment tolerance and survival. We prospectively demonstrated the prognostic value of physical function for survival outcomes in intensively treated older adults with AML (Min et al. Blood 2022). However, there are limited evidence for prognostic value of physical function in older adults with AML who were treated with low-intensity therapy, such as hypomethylating agents (HMA) with or without venetoclax (VEN). Thus, we evaluated the prognostic role of physical function scores in older adults with AML treated with low-intensity treatment in a prospective observation cohort (CRIS number; KCT0002261).

Method : We have measured physical function by the Short Physical Performance Battery (SPPB) since 2018 in older adults with AML treated with low-intensity treatment. Between 2018 Jan and 2022 May, 71 newly diagnosed AML patients who were aged ≥ 65 years and received low-intensity treatment were examined with SPPB at a median of 3 days prior to the initiation of treatment. The prognostic role of SPPB score on overall survival (OS) was analyzed by the Kaplan-Meier estimates and the log-rank test, and a multivariable Cox hazard model.

Results : The median age of 71 patients was 75 years (interquartile range: 70-78). Males were 59.2%, and patients with an Eastern Cooperative Oncology Group (ECOG) score of 2 or higher was 19.7%. Secondary AML patients were 12.7%. Genetic risk stratification by European Leukemia Net (ELN) 2017 classified 23.9%, 36.6%, and 39.4% as favorable, intermediate, and adverse risk, respectively. Patients were treated with HMA alone (azacitidine or decitabine; 59.2%) or HMA and VEN combination (40.8%). Seventy percent of patients were classified as unfavorable group by Wheatley index, which is a validated prognostic model for low-intensity treatment. There were no differences between HMA alone and HMA and VEN combination in terms of Wheatley index. The median SPPB score of patients was 8 (range, 6-11). The SPPB score had a significant association with OS. In univariable analysis, the hazard ratio (HR) for a 3-point decrease in SPPB was 1.11 (95% confidence interval [CI], 1.02-1.20]. The cut-off of SPPB at which the difference in OS was most pronounced was 8. Patients with an SPPB score of 8 or higher had a median OS of 20.2 months (95% CI: 11.3-Not achieved), whereas that of patients with an SPPB less than 8 was 6.9 months (95% CI: 3.3-16.9, p=0.04, Figure A). In a multivariable Cox model of SPPB with other genetic, etiologic variables, the impact of SPPB on OS was still significant (HR for 3-point decrease in SPPB: 1.35 [95% CI: 1.03-1.78], Figure B).

Conclusion : Our data show that physical function measured by SPPB is a significant prognostic factor for survival in older adults with AML treated with low-intensity treatment, contrasting limited value of 2017 ELN. This suggests that specified prognostic models including diverse geriatric assessment domains should be studied in these elderly population treated with low-intensity treatment.

Keyword : Acute myeloid leukemia, Physical function, Hypomethylating agent, Venetoclax



PP02-1

Proerythroblasts as the main erythroid dysplasia in myelodysplastic syndrome

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Background : We report a rare case of myelodysplastic syndrome (MDS) in which proerythroblasts appeared as the main component of erythroid dysplasia.

Method : A 74-year-old man visited our hospital with general weakness and dizziness for several months. Work up revealed pancytopenia (hemoglobin 5.3 g/dL, white blood cell count 2.4 x 103/μL with an absolute neutrophil count 1.6 x 103/μL, and platelet count 24 x 103/μL). A bone marrow examination revealed 60% cellularity with a myeloid:erythroid ratio of 1.4:1. The immature cells with fine chromatin and vacuolization were about 37% in all nucleated cells (ANC). The immunohistochemical stain revealed negative reactions to CD34, CD31, CD3, CD20, CD10, and CD117. They reveal positive reaction as a granular pattern to periodic acid-Schiff (PAS) stain and E-cadherin immunohistochemical stain. E-cadherin is expressed on early erythroblasts and decreases gradually during cellular maturation. In the present case, the immature cells were identified as erythroid dysplasia, arrested in the proerythroblasts stage. In this case, the total erythroid precursors were about 42% of ANC and blasts were less than 1% of ANC. The typical erythroid dysplasia, such as multi-nuclearity and lobulated nuclei, were not found in this case, except nuclear chromatin clumping. By the diagnostic criteria, this case was diagnosed as MDS with multilineage dysplasia.

Results : Proerythroblasts are not usually described as a type of erythroid dysplasia in MDS. In this case, the majority of erythroid precursors are immature proerythroblasts, suggesting the possibility of a preleukemic state of PEL In cases where myeloid neoplasm with erythroid precursors are > 50% of ANC, there has been considerable interest and reports for the diagnosis. In the present case, proerythroblasts (37% of ANC) appear as the main erythroid component (total erythroid precursors are about 42% of ANC). Before cells were identified through staining, the erythroid component could not be accurately calculated. This can be mistaken as lymphoid malignancy or other immature cells because there is no other typical erythroid dysplasia, and reports of MDS are very rare. The cytogenetic analysis showed complex chromosomal abnormalities of 46~47,XY,del(5)(q13),+8,15,inv(17)(p13q11.2),der(19)hsr(19)(p13.3)add(19)(p13.3),-22,+1~2mar[cp8]. A cancer mutation panel by next-generation sequencing revealed TP53 (p.Met426Val, missense) and AXSL1 (p.Glu635fs, frameshift) mutations, known mutations in MDS. These mutations were also reported in PEL. He experienced no adverse events related to decitabine therapy except myelosuppression, and he continued to receive chemotherapy.

Conclusion : Erythroid dysplasia with maturation arrest at the proerythroblastic stage without other typical dysplastic changes is rare in MDS. If typical dysplasia is absent, such cases can be confused with lymphoblasts or other immature cells. To address this, PAS or other immunohistochemical stains are helpful for rapid differentiation. Clinical and molecular data should be collected to identify the characteristics of this phenotype.

Keyword : Proerythroblast, Myelodysplastic syndrome, Acute proerythroblastic leukemia

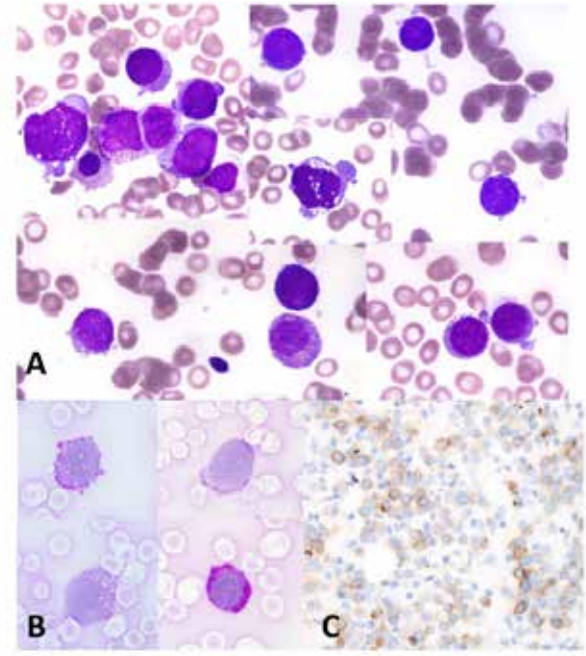

Figure 1. Morphologic findings from bone marrow aspirates (A-B) and clot section (C-G). (A) H & E stain (×1000). Small-to-large immature erythroid precursors with fine chromatin and vacuoles. Some of them seemed like lymphoblasts with a scant amount of cytoplasm, and some of them had light-blue-grey cytoplasm and nucleoli. These cells reveal a fine or punctate granular pattern with periodic acid-Schiff (PAS) stain (B) (×1000) and positivity for E-cadherin

PP02-2

Is MDS really treatable in Pakistan? Gaps and challenge - Single centre ex-

perience from Pakistan

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Background : Myelodysplastic syndromes (MDS) are heterogenous group of clonal hematopoietic stem cell disorders characterized by cytopenia(s), ineffective hematopoeisis and tendency to evolve into acute myeloid leukemia (AML). In west, disease presentation is in advanced age and primary aim of therapy is to improve quality of life however, in our part of the world it presents at an early age where curative treatment i.e. allogenic stem cell transplant can be offered. Majority of patients conventionally being treated by only blood transfusion support are unable to avail standard treatment options. The aim of study was to evaluate challenges in disease management and highlight the gaps in order to improve delivery of standard treatment.

Method : It was an observational cross-sectional study conducted at National Institute of Blood Diseases and Bone Marrow Transplantation (NIBD & BMT), Karachi Pakistan from June 2010 to January 2018. Ethical approval from the institutional ethics committee was obtained prior to the study. After taking informed consent from the patients, their data were used for the study. Baseline lab investigations included complete blood counts (CBC), bone marrow biopsy and cytogenetics. Clinical parameters of all patients were recorded. Patients were classified according to World Health Organization (WHO) 2016 classification and revised international prognostic scoring system (IPSSR) was calculated. Variables were expressed as percentages. Descriptive statistics in which frequency, percentages, mean (standard deviation) and overall survival rate were computed by using social package for statistical science (SPSS) version 23.

Results : A total of 186 patients were included and mean age was 55 years. Cytogenetic data was available for 104 patients and 46(44%) patients had abnormal karyotype. All patients were risk stratified as per revised international prognostic scoring system (IPSSR) and 110(59%), 52(28%) and 24(13%) had low, high and intermediate risk respectively. Our study revealed that around 67% patients enrolled chose supportive care as blood transfusion and hematinics over standard treatment offered after risk stratification. In challenges, transfusion dependency was mostly observed in 112 (60%). Transplant was offered to 80 patients and it was considered by only 01 (1.2%) patient. In treatment, recombinant erythropoietin was received by 25(13%), 19 (10%) received lenalidomide, 11(6%), 6(3%) and 4(2%) patients received thalidomide, hypomethylating agents and growth factors respectively.

Conclusion : Our study revealed that inspite of favorable factors like young mean age, normal karyotype and lower mean IPSSR at diagnosis, our population did not opt for standard treatment offered to them. Disease counseling and motivation of the patients and general physicians, prospective studies to assess treatment response and financial assistance by health insurance or government support are some possible ways to standardize and support treatment.

Keyword : MDS, Treatment, Pakistan, Gaps, Challenges

PP02-3

Significance of platelet count at diagnosis and its association with survival in MDS Patients; An experience from Pakistan

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Background : Myelodysplastic syndromes (MDS) are heterogeneous group of clonal hematopoietic disorder characterized by dysplastic progenitors, peripheral cytopenias and tendency to evolve into acute myeloid leukaemia. Thrombocytopenia is a significant consequence of ineffective hematopoiesis with decreased overall survival. However, there is a scarcity of data with none of the study reported in our country. The study was conducted to observe the association of overall survival of MDS patients presenting with or without thrombocytopenia at diagnosis.

Method : A retrospective cohort study was conducted at NIBD PECHS campus where MDS patients were recruited from 2018-2021. Kruskal Wallis test was applied to observe the difference in survival days and Kaplan Meier Survival analysis was performed to observe the overall survival in each platelet category. P-value of <0.05 was considered to be statistically significant.

Results : A total of 65 patients were analyzed. Median age (IQR) of patients was 60 (37) years with male predominance 41(63%). 18(28%) patients were MDS-EB1 and majority of patients were Intermediate risk IPSS. Overall median (IQR) hemoglobin (Hb) g/dl, total leucocyte count x109/L and platelet count (PLT) x109/L at di-

agnosis was 8(3.1), 4.2 (4.0) and 44 (101) respectively. Overall survival in patients with PLT <25 and with PLT 51-100 was 57%, with PLT 25-50 was 70% and with PLT > 100 was 91%. Median (IQR) survival days with <25 PLT was 79 (331), with 25-50 PLT was 66(577), 51-100 was 210 (301) and with > 100 it was 343 (498) days. The difference in mortality and survival days was not found significant between platelet categories (P-value >0.05).

Conclusion : The median difference in survival days was higher in patients who were not presented with thrombocytopenia at diagnosis however it was not found significant. Further studies with large sample size are needed to evaluate the significance of thrombocytopenia presentation at baseline and its impact on survival in our patients.

Keyword : Platelet Count, MDS, Survival

PP02-4

Impact of transfusion burden in lower-risk MDS

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Background : Myelodysplastic syndrome (MDS) is a heterogenous group of clonal myeloid neoplasms characterized by defective bone marrow (BM) hematopoiesis with peripheral blood cytopenias and a risk of progression to acute myeloid leukemia (AML). Accurate classification of MDS and risk scoring are critical in selecting the appropriate therapy and predicting the prognosis of patients with MDS. The most commonly used prognostic scoring system in MDS has been the International Prognostic Scoring System (IPSS), which has been recently revised to IPSS-R for improved prognostication. Lower-risk (LR) patients are those in the IPSS low to intermediate-1 group, comprised of IPSS-R very low, low, or intermediate scores of up to 3.5 points. The treatment goals in LR-MDS are hematologic improvement to prevent complications related with cytopenias, reduce the transfusion burden, and improve the quality of life. However, some patients with LR-MDS show high-risk features, such as early progression to AML and a shorter overall survival (OS). To improve cytopenias, anabolic steroids, erythroid stimulating agents (ESAs), and immunosuppressive therapy are primarily used. Patients who do not respond to these therapies could be treated with hypomethylating agents (HMAs), the standard treatment option for higher risk MDS. HMAs are also used to treat patients with LR-MDS who initially present cytopenias in more than two blood lineages. The transfusion burden differs among patients with LR-MDS, and those receiving red blood cell (RBC) transfusions are at risk of iron overload. In such cases, the binding capacity of transferrin for iron is surpassed, resulting in non–transferrin-bound iron circulating in the blood and subsequent deposition of free iron in tissues, which can cause significant organ damage and is an important cause of morbidity and mortality. Although new agent such as luspatercept showed a notable response in transfusion-dependent patients with LR-MDS, many patients still need RBC transfusions. Therefore, determining the clinical outcomes of transfusion burden and optimizing treatment for patients with MDS with transfusion dependencies are important. Recently, the MDS International Working Group (IWG) has established criteria for transfusion dependence and defined three categories: non-transfusion-dependent (NTD), low transfusion burden (LTB), and high transfusion burden (HTB). This study retrospectively analyzed the prognostic impact of transfusion burden in patients with LR-MDS and the outcomes of each treatment option. Furthermore, we determined whether transfusion burden manifested high-risk features of LR-MDS.

Method : Data collection Data on 401 patients with MDS from Kyungpook National University Hospital between July 2011 and April 2020 were retrospectively reviewed (Figure S1). Those with LR-MDS, defined as having an IPSS-R very low to intermediate score of up to 3.5, were included in the current study. Patients with uncontrolled infection and uncontrolled illnesses and those treated with investigational agents were excluded. To evaluate the clinical significance of transfusion burden, baseline characteristics and transfusion history of the patients were collected. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Kyungpook National University Hospital (IRB No: 2022-03-002). Treatments and supportive care RBC transfusions were performed for symptomatic anemia or in patients with a hemoglobin level lower than 7–8 g/dL, and platelets were transfused for thrombocytopenic bleeding or in patients with platelet count <2.0 × 109/L. Antibiotics and antifungal agents were used for prophylaxis in patients with recurrent infections. If the serum erythropoietin (EPO) level was lower than 500 mU/mL, ESAs, such as recombinant human EPO or long-acting darbepoetin, were considered to improve anemia. EPO was administered at a dose of

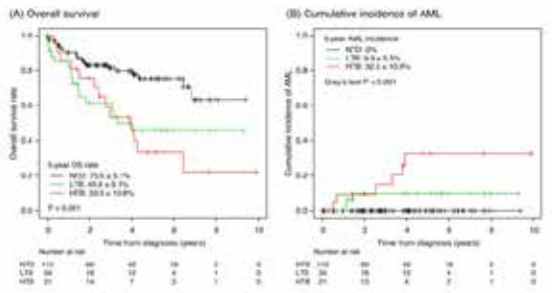
40,000–60,000 units subcutaneously once to twice per week. Darbepoetin alfa was used at the dose of 150–300 mcg subcutaneously per week. HMAs were administered to symptomatic and/or growth factor-unresponsive patients. For patients treated with HMAs, azacitidine was given subcutaneously at a dose of 75 mg/m2 per day for 7 days every 28 days. Treatment with ESA or HMA was continued until progression for the patients who showed responses within 4–6 months. Patients who were not considered for ESA or HMA were treated with anabolic steroids (e.g., danazol or oxymetholone). Definition of transfusion dependency Transfusion burden was defined according to the IWG 2018 guidelines. The NTD category included patients who received no transfusion in a period of 16 weeks. LTB was defined as receiving 3–7 RBC units in a period of 16 weeks in at least two transfusion episodes. High transfusion burden (HTB) was defined as receiving ≥ 8 RBC units in a period of 16 weeks in at least two transfusion episodes. Response evaluation Blood counts were performed every 4 weeks, and BM examination was repeated 4 to 6 months after treatment. The treatment response was observed over 4–6 months after treatment. Responses were evaluated using the IWG response criteria for MDS. For example, hematological improvements were defined as follows: For patients with pretreatment Hb <11 g/dL, >2 g/dL increase in Hb; for RBC transfusion-dependent patients, transfusion independence. Minor erythroid response (HI-E minor) was defined as follows: For patients with pretreatment Hb <11 g/dL, a 1–2 g/dL increase in Hb; for RBC transfusion-dependent patients, 50% decrease in transfusion requirement. Overall response rate (ORR) included the complete response (CR), partial responses (PR) and hematologic improvements (HI), and clinical benefit rate consisted of CR, PR, HI, and stable disease. Statistical analysis Baseline characteristics were analyzed by descriptive methods. Categorical variables were analyzed using the chi-square test and continuous data by ANOVA. OS was defined as the time of diagnosis until death from any cause or until lost to follow-up. The patients who received allogeneic hematopoietic cell transplantation were censored at the time of transplantation. OS values were plotted using the Kaplan–Meier method, and differences between curves were evaluated using the log-rank test. The cumulative incidence of AML was calculated using Gray's method using the "cmprsk" package, considering death without leukemic transformation as a competing event. The significances of covariates affecting OS were determined using the Cox proportional hazards model. Covariates with p-value <0.1 in the univariate analysis were included in the multivariate model. Factors with p-value <0.05 were considered significant. For the statistical analyses, the R statistical software 4.0.3 and SPSS software version 20 (SPSS Inc., Chicago, IL, USA) was used.

Results : Patient characteristics Among 401 patients with MDS, 168 (42.0%) diagnosed with LR-MDS on the IPSS-R were included in the study. The median age was 63 years (range, 20–92 years) at the time of diagnosis, and 94 patients (56.0%) were male. Most patients had multilineage dysplasia (69.0%) or single lineage dysplasia (17.3%), and 7 (4.2%) were excess blast 1 on the WHO classification. IPSS-R risk group classification was very low, low, and intermediate for 26 patients (15.5%), 99 (58.9%), and 43 patients (25.6%), respectively. One-hundred thirteen patients (67.3%) had no transfusion episodes, whereas 34 (20.2%) and 21 patients (12.5%) showed LTB and HTB, respectively. The patient characteristics are summarized in Table 1. Treatment response Of the 168 patients with LR-MDS, 105 (62.5%) received treatments: ESA for 12 patients (7.1%), HMA for 28 (16.7%), and anabolic steroids for 65 (38.7%) (Table S1). Azacitidine and decitabine were administered in 27 patients and 1 patient, respectively. HMA was administered for a median of 5 cycles (range, 1–26 cycles). ORR was achieved in 56 patients (53.3%), with complete response in 1 (1.0%), partial response in 2 (1.9%), and hematologic improvement in 53 patients (50.5%). Including 26 patients with stable disease (24.8%), the clinical benefit rate was 78.1% in treated patients (Table 2). ORR according to treatment option was 47.7% in anabolic steroids (31/65), 41.7% in ESA (5/12), and 71.4% in HMA (20/28) (Table 2). The clinical benefit rate was also similar among treatments: 78.1% in anabolic steroids (51/65), 75.0% in ESA (9/12), and 78.6% in HMA (22/28) (Table 2). Nine patients (5.4%) progressed to AML, and 52 deaths (31.0%) occurred. Survival outcomes The median follow-up duration of treated patients was 36 months (range, 0.6–119 months). OS varied with transfusion burden (Figure 1A). The 5-year OS rate was 75.5 ± 5.1% in NTD, 45.8 ± 9.1% in LTB, and 33.3 ± 10.8% in HTB (p = 0.001). Progression to AML occurred in 9 patients, 3 with LTB and 6 with HTB. The 5-year cumulative incidence of AML also differed according to the transfusion burden (Figure 1B) at 0%, 9.9 ± 5.5% and 32.5 ± 10.9% for NTD, LTB, and HTB, respectively (p < 0.001). The treatment options did not affect OS rate; the 5-year OS rate was 71.9 ± 6.7% in the no treatment group, 55.2 ± 7.7% with anabolic steroids, 82.5 ± 12.6% with ESA, and 51.3 ± 11.1% with HMA (p = 0.413) (Figure S2). However, the patients with treatment response showed improved OS (Figure 2), especially hemoglobin responders, with a 5-year OS rate of 67.0 ± 8.8% for hemoglobin responders and 52.0 ± 7.4% for hemoglobin non-responders (Figure 2B). Neutrophil and platelet responses were not significantly related to OS (Figures 2C and 2D). Factors affecting overall survival In the univariate analyses, age (HR [hazard ratio] 1.04, p = 0.003), sex (female vs. male; HR 0.49, p = 0.015), hemoglobin (<8 vs. ≥10; HR 1.85, p = 0.072), good risk cytogenetics (HR 0.35, p = 0.006), transfusion burden, and hemoglobin response (HR 0.50, p = 0.060) were significant factors and were thus included in the multivariate analysis (Table 3). In the multivariate analysis, age (HR 1.04, 95% confidence interval [CI] 1.02–1.08, p = 0 009), LTB (HR 3.77, 95% CI 1.65–8.61, p = 0.002), HTB (HR 4.59, 95% CI 2.01–10.5, p < 0.001), and hemoglobin response (HR 0.45, 95% CI 0.22–0.95, p = 0.036) were significant factors for OS (Table 3).

Conclusion : This study retrospectively analyzed the prognostic impact of transfusion burden in patients with LR-MDS. Our findings showed that transfusion burden was an adverse prognostic factor for patients with LR-MDS, with a high transfusion burden presenting an increased risk of leukemic transformation. The treatment options did not affect the treatment response and survival outcomes, but a survival benefit was observed for responders to anemia.

In the current study, patients with RBC transfusion dependency showed a poorer OS rate compared with patients with NTD. The severity of anemia in patients may be a risk factor for early mortality. In a retrospective analysis of 840 patients with MDS, the degree of anemia was a significant predictor of cardiovascular death ($p < 0.001$), independent of transfusion status and IPSS risk. In patients with NTD with LR MDS and del(5q), the 5-year OS rates were 65.4% for patients with Hb levels <10g/dL vs. 81.6% for patients with Hb levels ≥ 10.5 g/dL. However, an increased risk was also apparent for moderately transfused patients; therefore, direct toxicity from transfusions, such as toxic iron radicals, even at a relatively low iron load, may adversely impact survival. Recent treatment options for anemia have shortcomings. The use of ESAs is dependent on serum EPO level, and not all patients have a durable response to ESAs. With new agents that became recently available for patients with transfusion-dependent MDS, such as luspatercept, optimizing treatment and defining valuable groups for transfusion-dependent MDS is crucial in managing LR-MDS. Some of the patients with LR-MDS show high-risk features, such as leukemic transformation. Identifying the patients who would progress or not is important because those patients should be treated differently. The results of our study imply that HTB could be a surrogate marker for increased risk of leukemic transformation. Louise et al. reported that progression-free survival (PFS) in patients with LR-MDS treated with RBC transfusions was usually reduced, but whether transfusion dose density is an independent prognostic factor is unclear. The overall PFS of the three groups of patients, stratified according to the dose density at the third visit differed significantly. The HRs for patients in the low and high density groups were 1.85 (95% CI: 1.24–2.76) and 3.79 (95% CI: 2.65–5.42) relative to the non-transfused group, respectively. In the current study, the patients with HTB received more HMAs (66.7%, 14/21) than LTB (11.8%, 4/34) or NTD (8.8%, 10/113) (Table S2). The patients treated with HMA had multiple and severe cytopenias or adverse disease status. Nevertheless, HMA treatment produced ORR and hematologic improvements. Our study suggests that HMA is effective for symptomatic patients with LR-MDS. However, the long-term survival outcomes need to be elucidated to ensure accurate treatment with HMA. Baseline genetic profiling may be useful to find candidates for HMA among patients with LR-MDS. Regarding the therapeutic options for patients with LR-MDS, recent guidelines suggest stratifying patients into several groups with regards to clinically significant cytopenia. Our study showed that the treatment options did not affect the response rates and survival outcomes. However, survival benefit was observed for responders to anemia (Figures 2 and S1). The goals of LR-MDS treatment include improving cytopenia and quality of life. ESA and growth factors are recommended as initial therapy for patients with LR-MDS with symptomatic or transfusion-dependent anemia. The high-risk of leukemic transformation in patients with HTB and an inferior OS rate in hemoglobin non-responders were not supported by clinical parameters. In previous studies, transfusion burden was related to a significantly higher risk of progression to AML. AML progression at 2 years was reported in 16.3% of transfusion-dependent (TD) patients compared with 6.6% of transfusion-independent (TI) patients, which was increased to 17.9% and 11.4% at 5 years in TD and TI patients, respectively. Therefore, patients with LR-MDS who have HTB could be regarded as a higher risk group, and allo-HCT may be considered for transplant-eligible patients. However, the optimal timing of allo-HCT for patients with LR-MDS with HTB, as well as other high-risk features, should be elucidated in the following studies. Although the present data identified RBC transfusion dependence as a prognostic factor in LR-MDS, the study has some limitations. First, the sample size was too small to make meaningful comparisons between AML progression groups. Second, only a small number of patients were treated with ESA. Third, the current study was a retrospective evaluation, and recent genetic information was not evaluated. In conclusion, our findings showed that transfusion dependency was an adverse prognostic factor for patients with LR-MDS. Specifically, HTB indicated a higher risk of leukemic transformation, which suggests that transfusion burden is a high-risk feature in LR-MDS.

Keyword : Transfusion dependency, Transfusion burden, Lower-risk myelodysplastic syndrome



Abbreviations: NTD, no transfusion dependency; LTB, low transfusion burden; HTB, high transfusion burden; AML, acute myeloid leukemia

FIGURE 1
Survival outcomes according to the transfusion dependency

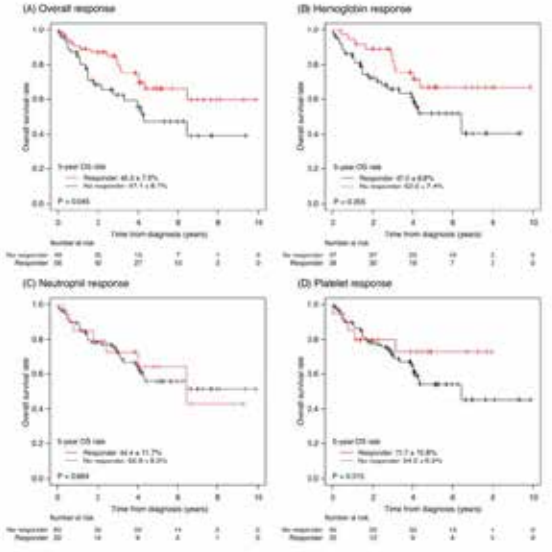


FIGURE 2
Overall survival according to response

PP02-5

A rare case of coexisting myelodysplastic syndrome and T-cell lymphoproliferative disorder

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Background : Myelodysplastic syndrome (MDS) is a group of heterogeneous diseases that is characterized by peripheral cytopenia and paradoxical bone marrow hypercellularity. The phenomenon is caused by ineffective hematopoiesis which is represented by dysplastic features. It is usually considered as a disease of myeloid lineage and combined lymphoid malignancy is very rare. Herein, we report a case of coexisting MDS with ring sideroblasts and single lineage dysplasia (MDS-RS-SLD) and clonal T-cell lymphoproliferative disorder demonstrated by flow cytometry and next-generation sequencing (NGS).

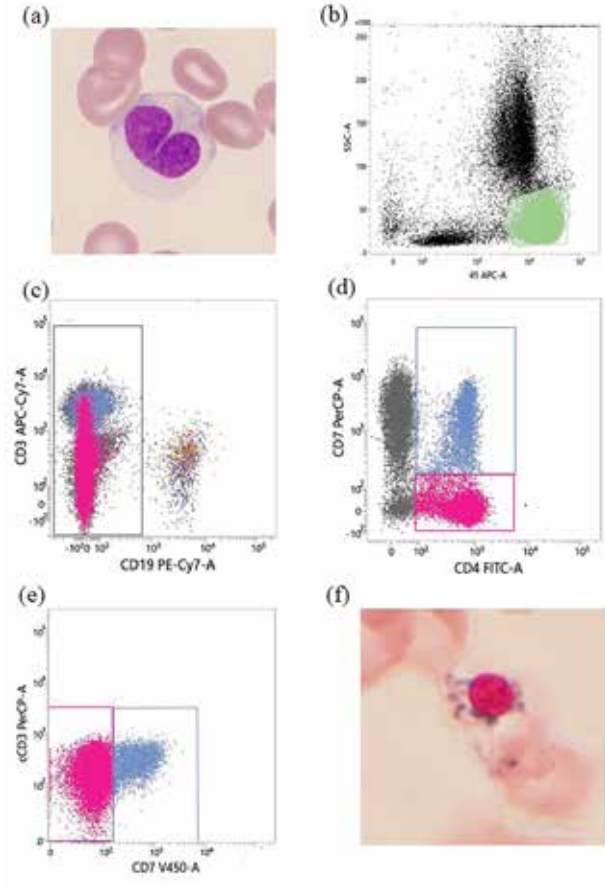
Method : A 74-year-old Korean man was referred from a local clinic for anemia and lymphocytosis with atypical lymphocytes. His complete blood count (CBC) was 8.8 g/dL of hemoglobin with 113.5fL of mean corpuscular volume, 10.0 × 103/μL of white blood cell (WBC), and 277 × 103/μL of platelets. The differential count of WBCs was as follows: band neutrophil, 2%; segmented neutrophil, 38%; lymphocyte, 22%; atypical lymphocytes, 33%; and monocyte, 5%. Peripheral blood smear showed mild RBCs poikilocytosis including target cells, teardrop cells, ovalocytes, and fragmented RBCs. The atypical lymphocytes were medium to large, with cleavaged or bilobated nuclei with condensed chromatin patterns and moderate amount of clear cytoplasm (Figure 1-a). Flow cytometric immunophenotyping on peripheral blood showed that 96.8% of the lymphocytes were cytoplasmic CD3-positive T-cells (Figure 1-b). Among them, 70.3% were CD4-positive T-cells with 59.4% of CD4, CD2, and CD5-positive but surface CD3 and CD7-negative aberrant CD4-positive T-cell population (Figure 1-c, d and e). NGS for T-cell receptor (TCR) genes showed clonal TCR gene rearrangements. Bone marrow (BM) aspiration showed increased erythropoiesis and relatively decreased granulopoiesis with a myeloid to erythroid ratio of 0.4. Megakaryopoiesis was adequate. Dyserythropoietic features such as cytoplasmic vacuolization, karyorrhexis, nuclear budding, and multinucleation were observed in more than 10% of erythroid precursors. Iron staining showed adequate amount of hemosiderin particles with increased sideroblasts and ring sideroblasts (32% and 16% of BM erythroid precursors, respectively) (Figure 1-f). BM biopsy showed normo- to slightly hypercellular marrow for his age with cellularity of 40%. Immunohistochemical (IHC) staining for CD3 showed increased scattered and aggregated T lymphoid cells. IHC staining for CD34, CD117, CD61, and CD20 showed no remarkable finding. Reticulin fibrosis was not observed.

Results : His BM karyotype was 45,X,-Y[20]. NGS with a 165-gene panel for hematologic malignancies showed SF3B1 K700E (variant allele frequency [VAF]: 39.4%), TET2 splicing variant (VAF: 36.4%), and STAT3 N647I (VAF: 2.0%), supporting the diagnosis of concurrent MDS with RS and clonal T-cell disorder. Based on these findings, he was diagnosed with (MDS-RS-SLD) and clonal T-cell lymphoproliferative disorder. The patient is under conservative treatment and

workup for T-cell malignancy.

Conclusion : To our knowledge, this is the first case report of coexisting MDS-RS-SLD with clonal CD4-positive T-cell lymphoproliferative disorder.

Keyword : Myelodysplastic syndrome, Clonal T-cell lymphoproliferative disorder



PP02-6

Myelodysplastic syndrome occurrence in post-therapeutic systemic lupus erythematosus patients

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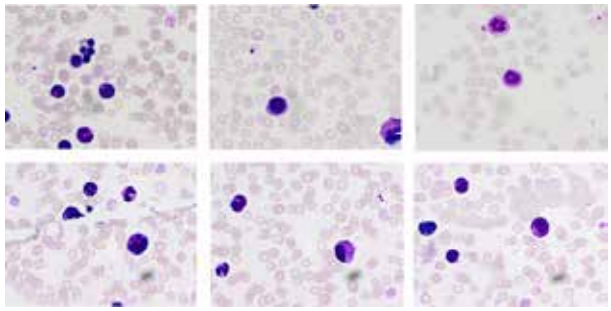
Background : Myelodysplastic syndrome (MDS) is a heterogeneous group of myeloid clonal disorders caused by a failure of blood cell maturation. Most patients with MDS have no apparent cause or idiopathy. However, the iatrogenic cause was not documented yet. This case showed the MDS occurrence in patients with Systematic Lupus Erythematosus after treatment.

Method : A 4-year-old boy comes to the hospital complaining of shortness of breath. He is a Systemic Lupus Erythematosus (SLE) patient with ongoing treatment. The history of the ANA IF examination results revealed a nuclear-speckled pattern. Previously, the patient received Methylprednisolone 8-8-4 mg, Mycophenolate Mofetil 360-0-360, and Hydroxychloroquine 100 mg/day. Physical examination revealed rhonchi on both lungs. A complete blood count revealed pancytopenia with a leukocyte count of 1.31 x 10^3 cells/uL, Hb 6.7 g/dL, and platelets 7 x 10^3 cells/uL. Follow-up examination with bone marrow aspiration revealed an increase in thrombopoiesis, erythropoiesis, and granulopoiesis accompanied by dysplasia in all three lineages showing the picture of Myelodysplastic Syndrome-Multilineage Dysplasia. The patient was then managed with the Myelodysplastic Syndrome protocol while continuing MP 8-8-4 mg therapy and discontinuing Hydroxychloroquine. Clinical improvement was found at the follow-up 1 month after.

Results : Systemic Lupus Erythematosus is a complex autoimmune disease, with many clinical features. Organ involvement in SLE cases often impacts the emergence of other diseases that have a picture of organ involvement. SLE therapy given is immunosuppressive to relieve the symptoms that arise. The incidence of Myelodysplastic Syndrome can be associated with this patient's primary condition, which is suspected to involve the bone marrow organ. However, it is undeniable that some immunosuppressive medications can trigger dysplasia. Cellular apoptosis that occurs because of treatment can trigger the development of other lineages not affected by the drug and eventually become dysplastic. In this case, it is not known with certainty the cause of MDS whether it is related to the pathophysiology of SLE or the impact of treatment.

Conclusion : This case demonstrates the need for clinician vigilance in providing SLE treatment protocols and more attention to the risk of MDS development

Keyword : MDS, SLE, Iatrogenic



PP02-7

Next-generation sequencing as an essential test in addition to conventional cytogenetics for the diagnosis of hypoplastic myelodysplastic neoplasm

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Background : In the 5th edition of the World Health Organization classification of hematolymphoid tumors (2022), hypoplastic myelodysplastic neoplasm (MDS) is proposed as a distinct subtype of MDS. Although the presence of dysplasia is an important morphological feature of MDS in patients with hypocellular marrow, hypoplastic MDS can be difficult to differentiate from other hypoplastic bone marrow failure disorders, such as aplastic anemia, paroxysmal nocturnal hemoglobinuria, inherited bone marrow failure, and marrow changes due to drugs, infections, or rheumatologic causes, et al. This study aimed to investigate the usefulness of next-generation sequencing (NGS) for the diagnosis of hypoplastic MDS in patients with hypocellular marrow.

Method : From March 2021 to November 2022, 24 patients who were identified as having hypocellular marrow (age-adjusted, less than 25%) and cytopenia in the peripheral blood were analyzed. The diagnostic sensitivity and specificity of next-generation sequencing (NGS), chromosomal analysis, and fluorescence in situ hybridization (FISH) results were calculated based on whether the final diagnosis was hypoplastic MDS.

Results : Of the 24 patients with hypocellular marrow, 11 were confirmed to have MDS and 13 patients were confirmed to have hypocellular marrow related to other causes at the final clinical diagnosis. The diagnostic sensitivity and specificity of NGS were 63.6% and 92.3%, respectively, and NGS showed a higher diagnostic sensitivity than chromosomal analysis (36.4%) and FISH (40.0%). However, the diagnostic specificity of NGS was lower than that of chromosomal studies, which showed a 100% diagnostic specificity. Moreover, NGS exhibited a diagnostic specificity (92.3 %), similar to that of FISH. In the NGS results of patients with hypocellular, tier 1-2 mutations were observed in TET2, BCOR, TP53, DNMT3A, ASXL1, and GATA2. In one of the non-MDS cases, a TET2 gene variant, which is frequently found in clonal hematopoiesis of indeterminate potential, was observed. High diagnostic sensitivity (90.9%) and specificity (84.6%) were demonstrated when the three test methods (NGS, FISH, and chromosomal analysis) were used simultaneously.

Conclusion : NGS, in addition to conventional cytogenetics and FISH, may be useful for diagnosing newly classified hypoplastic MDS and providing insights, such as identifying inherited bone marrow failures and confirming clonality.

Keyword : Next-generation sequencing, Hypoplastic MDS, Hypocellular marrow, FISH, Chromosome

Table 1. Diagnostic performance of the genetic tests for distinguishing MDS from other causes in patients with hypocellular marrow and cytopenia

	MDS		Cytopenia with other causes		Diagnostic sensitivity % (95% CI)	Diagnostic specificity % (95% CI)
Test	Positive	Negative	Positive	Negative		
NGS	7	4	1	12	63.6 (30.8 - 89.1)	92.3 (63.3 - 99.8)
Chromosome	4	7	0	13	36.4 (10.9 - 69.2)	100.0 (75.3 - 100.0)
FISH	4	6	1	12	40.0 (12.2 - 73.8)	92.3 (64.0 - 99.8)
NGS & Chromosome & FISH	10	2	1	11	90.9 (58.7 - 99.8)	84.6 (54.6 - 98.1)

Abbreviations: CI, confidence interval; MDS, myelodysplastic syndrome; NGS, next-generation Sequencing; FISH, fluorescence in situ hybridization

PP02-8

SF3B1-mutated myeloid neoplasms: pathologic correlation focusing on myelodysplastic syndrome with mutated SF3B1

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Background : SF3B1 mutations are one of the common mutations

in myeloid neoplasms (MNs) and are highly associated with ring sideroblasts (RS), the subtype-defining morphologic indicator of myelodysplastic syndrome (MDS) with RS or MDS/myeloproliferative neoplasm with RS and thrombocytosis (MDS/MPN-RS-T). The new WHO classification recently identified MDS with low blasts and SF3B1 mutation (MDS-SF3B1) as a distinct entity. We investigated the pathologic spectrum and genomic characteristics of SF3B1-mutated MNs, focusing on classifying MDS-SF3B1.

Method : We retrospectively reviewed our bone marrow archive and selected cases with MNs having mutation data from January 2018 to December 2021. Pathologic diagnosis and clinical and laboratory findings were collected by medical chart review. MDS-SF3B1 was classified based on criteria of 5th edition of WHO classification.

Results : SF3B1 mutations were identified in 50 (5.8%) of 864 patients encompassing a full spectrum of MNs, including MDS (n = 29), acute myeloid leukemia (AML, n = 9), MDS/MPN (n = 9), and MPN (n = 3). The most common SF3B1 mutation was located at K700 residue (n = 19, 38.0%) and K666 (n = 19, 38.0%), followed by R625 (n = 7, 14.0%) and other residues (n = 5, 10.0%). The frequency of K700 mutations were significantly higher in MDS (58.3%) compared to non-MDS MNs (13.6%; P < 0.001), whereas the frequency of K666 mutations were significantly lower in MDS (13.9%) compared to non-MDS MNs (68.2%; P < 0.001). Co-mutations occurred in TET2 (20.7%), DNMT3A (15.5%), ASXL1 (13.8%), JAK2 (13.8%), RUNX1 (13.8%), TP53 (10.3%) and NRAS (8.6%). Interestingly, other splicing factor mutations were concurrently identified in 4 patients (8.0%) including mutations in U2AF1 (n = 2), ZRSR2 and LUC7L2 (n = 1 each). Of SF3B1-mutated MDS, MDS-SF3B1 was identified in 21 cases enriched in MDS-RS (n = 17, 81.0%) and lower-risk MDS (n = 15, 71.4%). The K700 mutations were associated with higher RS percentage (median 20.0%) compared to other types (median 9.0%; P = 0.007). In AML, SF3B1 mutations were frequently detected in M0/M2 (66.7%), AML with myelodysplasia-related changes (n = 5, 55.6%) and NCCN-defined poor risk (55.6%). In MDS/MPN and MPN, the majority of SF3B1-mutated cases were MDS/MPN-RS-T (77.8%) and primary myelofibrosis (75.0%), respectively.

Conclusion : We demonstrate that SF3B1 mutations are detected in a full spectrum of MNs with a propensity for MDS-RS, MDS/MPN-RS-T and poor risk AML. The SF3B1 K700 mutations are enriched in MDS with a higher RS count compared with other hot spot alterations. Over half of SF3B1-mutated MDS are classified as MDS-SF3B1, which are associated with lower-risk MDS that may lead to favorable clinical outcome.

Keyword : Myelodysplastic syndrome, SF3B1 mutation, K700, K666, Pathologic correlation

PP03-1

The challenges in managing Philadelphia chromosome negative acute lymphoblastic leukemia in adolescents and young adults (AYA) treated with MASPORE

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Background : Pediatric-inspired treatment protocol has been widely used in treating acute lymphoblastic leukemia (ALL) in adolescents and young adults (AYA). Studies have shown improved overall survival (OS), leukemia-free survival (LFS), and reduced the need of hematopoietic stem cell transplantation (HSCT) in patients receiving pediatric-inspired protocol. However, intensification of chemotherapy has been associated with increased toxicity as compared to pediatric population, and thus, requiring significant dose modification and monitoring for patients. MASPORE, a locally designed pediatric regimen, has been successfully introduced to AYA cohort in Singapore and Malaysia since 2007 with favorable outcomes. Since 2016, our center had started adapting this treatment protocol in AYA. A retrospective analysis of the treatment outcomes and challenges encountered will be reviewed in this study.

Method : Patients from AYA group (defined as less than 45 years old), diagnosed with Philadelphia chromosome-negative ALL from 2016 till June 2022, and treated with MASPORE protocol were included in this retrospective analysis. Demographic data, disease risk profile, adverse events, treatment response, and transplant status were collected and analyzed. OS and LFS were estimated using the Kaplan-Meier method and compared using the log-rank test. The grading for the adverse events was done according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Results : Forty patients with a median age of 19 years (range 12 – 45) were included in this study. Thirty-five of them were less than 30 years old. Majority of these patients were Malay ethnicity (65%) and male (55%). The median white blood cell was 7.85x109/L (range 0.8 – 759.8x109/L) and 75% of these patients were in standard risk. With a median follow-up of 14.5 months, 92.5% of the patients achieved complete remission post induction and only 4 patients (10%) proceeded with allogeneic HSCT. Two patients suffered from induction death (5%), while 6 patients (15%) died of neutropenic sepsis during remission. Eight patients had disease relapsed and succumbed to their disease. Other adverse events included thrombosis (3 patients), transaminitis (27 patients), and peripheral neuropathy (6 patients).

Of these, 4 patients developed grade ≥ 3 transaminitis, while 1 patient developed grade 3 peripheral neuropathy. The OS and LFS at median follow-up were 68.5% and 69.5%, respectively. In univariate analysis, only high-risk disease had been identified to be significantly affecting the OS (p=0.026) and LFS (p=0.028).

Conclusion : Our AYA cohort has experienced significant adverse events, in particular neutropenic sepsis during remission leading to higher mortality. We identified these events commonly occurred during initial induction and protocol III consolidation. Remedies include in-patient chemotherapy and monitoring, has significantly lower the risk of mortality. We foresee improvement in supportive care to be translated into improved OS and LFS in the future.

Keyword : Philadelphia chromosome negative, Acute lymphoblastic leukemia, MASPORE

PP03-6

B-Lymphoblastic leukemia acquiring BCR::ABL1 rearrangement upon relapse: A case report

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Background : BCR::ABL1 rearrangement resulting from t(9;22)(q34;q11.2) is a recurrent genetic abnormality in various hematologic malignancies, including chronic myeloid leukemia, acute lymphoblastic leukemia, and acute myeloid leukemia. It is important in B-lymphoblastic leukemia (BLL) because it not only means poor prognosis but also enables tyrosine kinase inhibitors to be used to improve outcomes. Here we report a case of a Korean patient with BLL who initially did not have BCR::ABL1 rearrangement at diagnosis but was found to harbor the variant at relapse.

Method : A 16-year-old female presented with chest wall pain in October 2022 with no evidence of heart or lung disease. She was diagnosed with BLL in May 2019. She achieved complete remission in July 2019 and received maintenance chemotherapy until December 2021. However, immunoglobulin heavy chain/ kappa light chain (IGH/IGK) gene clonality assay still showed measurable residual disease (approximately 0.04% in her latest follow-up, July 2022). Her complete blood cell count showed white blood cells 8,820/μL, hemoglobin 132 g/L, and platelets 159,000/μL. Peripheral blood smear showed blasts occupying 9% of white blood cells, and bone marrow study confirmed relapse of BLL (blasts occupying 84.6% of all nucleated cells with immunophenotype similar to initial diagnosis). To re-evaluate her disease status and prognosis, several genetic studies were conducted with the marrow sample.

Results : G-banding karyotyping revealed 47,XX,+del(1)(p13),t(9;22)(q34;q11.2)[17]/46,XX[8], which was 46,XX[20] at initial diagnosis. Reverse transcription-polymerase chain reaction and targeted RNA fusion panel confirmed the presence of e1a2 type BCR::ABL1 rearrangement. Next-generation sequencing panel targeting 531 hematologic malignancy-related genes revealed multiple exon deletions in IKZF1 (exon 4-7 deletion) and RB1 (exon 18-27 deletion), which were also not present at diagnosis. IGH/IGK gene clonality assay showed the same combinations as those at diagnosis, suggesting clonal evolution rather than emergence of a new distinct clone.

Conclusion : To our knowledge, this is the first case of BLL acquiring BCR::ABL1 rearrangement upon relapse. Malignancies, including BLL, can undergo clonal evolution, which may lead to more aggressive and treatment-resistant clones. This case indicates that upon relapse of BLL, its status of BCR::ABL1 rearrangement should be re-evaluated in addition to other genetic abnormalities.

Keyword : B-lymphoblastic leukemia, BCR::ABL1, t(9;22)(q34.1;q11.2), Relapse, Clonal evolution

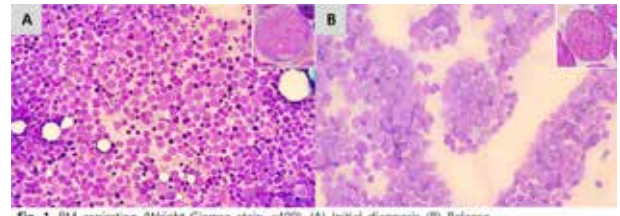

Fig. 1. BM aspiration (Wright-Giemsa stain, ×400). (A) Initial diagnosis (B) Relapse. A representative blast is magnified at the corner (×2000).

PP03-14

Machine learning-based detection of leukocyte counts in microscopic images of acute lymphoblastic leukemia

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Background : Leukemia is one of the causes of death among several types of cancer. According to the French-American-British (FAB) classification, one type of acute leukemia is acute lymphoblastic leukemia (LLA). The existence of LLA is characterized by the aberration of Lymphoblast proliferation in the bone marrow. One of the problems in LLA image segmentation is the separation of cell groups that touch each other. This is required for quantitative analysis which is very important for LLA-type classification. Several methods have been used to separate cell groups including K-Means Clustering, but over or under-segmentation is still common. In this study, the development of Multiple K-Means Clustering machine learning algorithms was used.

Method : In the Multiple K-Means Method, the initial K value is an initial estimate of the number of Leukocytes in contact. The K-Means process is carried out by iterating three to five times with a K value equal to the initial K value minus two to the initial K value plus two, where the initial K value, with a minimum K value of two. In this study, the detection of the number of leukocytes in contact consists of four stages, the first is the image input stage, which is used in this study is the ALLIDB1 database. Then, segmentation is performed using the Otsu Thresholding method. From the segmentation results, the leukocytes are detected and then the leukocytes are separated and counted using the Multiple K-Means method. ALL-IDB1 is a dataset of images of peripheral blood smear samples from individuals without ALL and patients with ALL, which is publicly available with permission. The samples were collected by experts at the Tettamanti Research Center for childhood leukemia and hematologic diseases, Monza, Italy.

Results : The proposed method was able to overcome the weakness of the previous K-Means method, with an average relative error of 0 on 11 images containing 21 groups of touching cells in the ALL-IDB1 database. The proposed method was able to overcome the problem with 100% accuracy.

Conclusion : Based on the high and perfect accuracy obtained, the proposed method is very promising to be reviewed and applied further and is expected to assist the laboratory in the quantitative analysis of LLA so as to reduce the potential for misdiagnosis.

Keyword : ALL, Leukocyte Counts, Machine Learning, Microscopic Images, Detection

PP03-16

Bilateral facial nerve palsy in t-cell acute lymphoblastic leukemia: A case report and review of the literature

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Background : The central nervous system (CNS) is an important site of involvement in patients with acute lymphoblastic leukemia (ALL). Only 5-10% of adult patients have CNS involvement at diagnosis. The facial nerve is commonly affected but bilateral involvement is rare.

Method : We report a rare case of bilateral facial nerve palsy in an adult newly diagnosed with T-cell ALL.

Results : A young adult female, presenting with an acute history of postprandial vomiting and dizziness, was noted to have bilateral cervical lymphadenopathies, severe leukocytosis with numerous atypical cells, and a positive test for COVID 19 infection. Flow cytometry of the peripheral blood revealed a diagnosis of T-cell ALL. When she was about to start induction chemotherapy, she developed an acute-onset unilateral peripheral facial nerve palsy which progressed to bilateral involvement the day after. The rest of neurological examination findings were unremarkable. She eventually underwent induction chemotherapy inclusive of intrathecal treatment. Her neurologic symptoms, however, did not improve. Her white blood cell counts initially improved but went back up to pre-treatment levels at the end of her induction chemotherapy. She is currently undergoing re-induction chemotherapy.

Conclusion : Bilateral facial nerve palsy is a rare presentation of ALL. Our case highlights the poor prognosis of ALL especially when it develops in adults, when it is of the T-cell phenotype, and when it presents with CNS involvement.

Keyword : Bilateral facial nerve palsy, Facial nerve palsy, Acute lymphoblastic leukemia, CNS leukemia

PP03-18

Usefulness of immunoglobulin gene rearrangement analysis using next-generation sequencing in adult and pediatric B-lymphoblastic leukemia

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Background : B-cell acute lymphoblastic leukemia (B-ALL) is known to be caused by uncontrolled expansion of specific B-cell clones, and one of the ways to confirm this clonality is immunoglobulin heavy chain (IGH) and kappa light chain (IGK) gene rearrangement analysis. We aimed to figure out how useful IGH/K rearrangement analysis using next-generation sequencing (NGS) is for detecting clonality in adult and pediatric B-ALL patients, and to profile the IGH/K rearrangement repertoire.

Method : We performed NGS-based IGH/K rearrangement analysis, IGH FR1 assay and IGK assay, using bone marrow (BM) or peripheral blood (PB) samples from 23 adult B-ALL patients and 47 pediatric B-ALL patients between September 2021 and November 2022. In eight of these patients, additional TRB/G rearrangement analysis was performed to confirm cross-lineage.

Results : The median (interquartile range) of total read counts for IGH rearrangement and IGK rearrangement among 70 samples were 40049 (27420-66915) and 39072 (29495-54436), respectively. In adult B-ALL, clonal IGH and IGK rearrangements were observed in 78.3% (18/23) and 60.9% (14/23). 87.0% (20/23) of adult B-ALL patients had clonal IGH and/or IGK rearrangement. In pediatric B-ALL, clonal IGH and IGK rearrangements were observed in 93.6% (44/47) and 55.3% (26/47). 95.7% (45/47) of pediatric B-ALL patients had clonal IGH and/or IGK rearrangement. Although IGH clonality was confirmed in most cases, clonal IGH sequences in three cases showed less than 20% clonal IGH read counts among total IGH rearrangements even when combining all the other clones, suggesting they were not representative of the malignant population. Their total IGH read counts were low at 1427, 2767, and 1938 each. We also could not detect IGK clonality in all these three cases, and the total IGK read counts were 35357, 37563, and 26442. Their blast counts were 96.0% (BM), 46.0% (BM), and 32.0% (PB) each. In additional TRB/G rearrangement analysis, two of them had TRB and/or TRG clonality but were not suitable for measurable residual disease (MRD) monitoring and the other one had no cross-lineage clonality. IGK clonality was detected in three of the eight cases in which IGH clonality was not detected, and we identified index sequence of IGK rearrangement useful for MRD monitoring. In the remaining five cases, clonality was not detected in all of IGH/K, so TRB/G rearrangement analysis was additionally performed and analyzed to confirm the clonal cross-lineage rearrangement. In four of these five cases, clonal cross-lineage TRB and/or TRG rearrangement suitable for MRD monitoring was identified, and in one case, we could not detect any clonality in either IGH/K or TRB/G. One case (1.4%, 1/70), in which any clonality was not detected, was a pediatric patient and the immunophenotyping result was pro B cell type (CD19+/CD10-/CD20-). In total B-ALL patients, the clonality detection rate increased from 88.6% to 98.6% when IGK and TRB/G rearrangement analysis was additionally performed compared to IGH rearrangement analysis alone. In adult B-ALL, IGHV3 (46.4%) was the most frequently identified IGHV gene followed by IGHV4 (25.0%), IGHV1 (10.7%), IGHV6 (10.7%), IGHV2 (3.6%), and IGHV5 (3.6%). In subgroups, IGHV4-34 (21.4%) was the most frequent IGHV gene and IGHV3 genes were relatively diverse, ranging between 3.6% and 10.7%. IGKV2 and IGKV3 (25.0% each) were the most frequent IGKV genes followed by IGKV1 (15.0%), IGKV4 (15.0%), IGKV5 (10.0%), and IGKJ-C-intron-KDE rearrangement (10.0%) in adult B-ALL. In pediatric B-ALL, IGHV3 (52.9%) was the most frequently identified IGHV gene followed by IGHV6 (14.3%), IGHV4 (12.9%), and IGHV2 (5.7%). IGHV1 and IGHV5 were not observed. IGHV6-1 (14.3%) was the most frequent IGHV gene and the other IGHV genes, other than IGHV6, were relatively diverse. IGKV2 (27.1%) was the most frequent IGKV gene followed by IGKV3 (20.8%), IGKV1 (10.4%), IGKV4 (10.4%), IGKV7 (10.4%), IGKV5 (2.1%), and IGKJ-C-intron-KDE rearrangement (18.8%) in pediatric B-ALL. Of the total B-ALL patients, 47.1% (33/70) had two or more clonal IGH rearrangements and 84.8% of them had a percentage of top clonal IGH rearrangement among total IGH rearrangements less than 60%, which seemed reasonable to monitor MRD by summing the percentage of the other coexisting clones. In IGK rearrangement, 30.0% (21/70) had two or more clonal IGK rearrangements and 81.0% of them had less than 60% top clonal IGK rearrangement.

Conclusion : NGS-based IGH/K rearrangement analysis confirmed patient-specific sequence-based clonality in most adult and pediatric B-ALL patients. When the IGH clone is not identified, additional IGK and TRB/G rearrangement analysis increases the clonality detection rate to 98.6% and helps find appropriate index sequences for MRD monitoring. Different clonal IGH/K rearrangement repertoires are observed between adult and pediatric B-ALL patients.

Keyword : B-cell acute lymphoblastic leukemia, Clonality, Immunoglobulin gene rearrangement, Next-generation sequencing, Cross-lineage

PP03-19

Analysis of marrow infiltrating T cell at 3 months after allogeneic hematopoietic stem cell transplantation in patients

with hematologic malignancies

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Background : With the introduction of immune checkpoint inhibitors, the importance of tumor-infiltrating lymphocytes has increased. However, few studies have analyzed the effect of marrow-infiltrating T cells on relapse after allogeneic hematopoietic stem cell transplantation (HSCT) in patients with hematologic malignancies.

Method : We analyzed the marrow-infiltrating T cell at 3 months after allogeneic HSCT in consecutive patients who treated in Chungnam National University Hospital from April 2021 to May 2022. We classified T cells into five subtypes using CD45RA, CD95 and CCR7 by flowcytometry analysis: naïve, stem cell memory (SCM), central memory (CM), effector memory (EM) and effector memory with positive CD45RA (EMRA). And we measured the expression level of the inhibitor receptor (PD-1, LAG-3, CTLA-4, TIM-3 and TIGIT). And we analyzed regulatory T cell (Treg) by defining as CD25highCD-125low and divided them into three categories using CD25 and CD45RA; naïve, active and non-suppressive Treg. We defined early relapse (ER) as relapse within 6 months of allogeneic HSCT.

Results : With this approach, marrow-infiltrating T cells were analyzed in 33 patients with a median age of 58 year (ranged from 25 to 71). AML is the most common disease at 54.5%, followed by MDS (24.2%), ALL (15.2%) and PMF (6.1%). Stem cell source were 36.4% from matched sibling donor, 36.4% from haplo-identical donor and 27.3% from matched unrelated donor. All patients received mobilized peripheral blood stem cell transplantation. Marrow-infiltrating CD3+T cell counts were lower in patients with allogeneic HSCT compared to normal subjects (CD3+T cells: 5.5% in HSCT patient vs. 36.1% in normal subjects, p= 0.0002). However, CD3+CD8+T cells were similar in HSCT patients and normal subject. In patients with early relapse (ER), naïve and SCM was higher, and EM was lower than those in non-ER patients among CD4+T cells (naïve; 1.0% in ER patients vs 12.9% in non-ER patients, p= 0.0004 /SCM; 3.3% in ER patients vs 15.8% in non-ER patients, p= 0.0155 /EM; 61.2% in ER patients vs 39.7% in non-ER patients, p= 0.0284). Of CD4+T cell, the expression of TIM-3 was higher in ER patients than in those without (MFI; 1689.5 in ER patients vs 428.75 in non-ER patients, p= 0.0080). In patients with early relapse (ER), naïve and SCM was higher, and EM was lower than those in non-ER patients among CD8+T cells (naïve; 7.8% in ER patients vs 1.1% in non-ER patients, p= 0.0004 / SCM; 11.7% in ER patients vs 4.3% in non-ER patients, p= 0.0654 / EM; 43.9% in ER patients vs 51.6% in non-ER patients, p= 0.3522). Of CD8+T cell, the expression of TIM-3 was higher in ER patients than in those without (MFI; 748.5 in ER patients vs 301.6 in non-ER patients, p= 0.0037). Treg levels were slightly higher in ER patients, and naïve Treg levels were significantly higher than those in no-ER patient (naïve Treg; 2.3% in ER patients vs 0.3% in non-ER patients, p= 0.0042).

Conclusion : T cell differentiation was delayed in patients with early relapse compared to those without. And TIM-3 expression of effector T cell was higher in patients with early relapse. So, Patients with high risk of relapse after allogeneic HSCT may benefit from the use of TIM-3 inhibitors.

Keyword : Allogeneic hematopoietic stem cell transplantation (HSCT), The inhibitor receptor (IR), T cell, Treg, ER patients, non-ER patients

PP03-20

Poor prognosis of IKZF1 and CDKN2 gene deletions in patients with Philadelphia chromosome-negative acute lymphoblastic leukemia

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Background : Among several genetic cooperative alterations in acute lymphoblastic leukemia (ALL), deletions of the IKZF1 and CDKN2A/B genes were known as poor prognostic abnormalities. Most of the results were from Western pediatric data and the correlation is still controversial. Specifically, IKZF1 was mainly studied in Ph-pos-

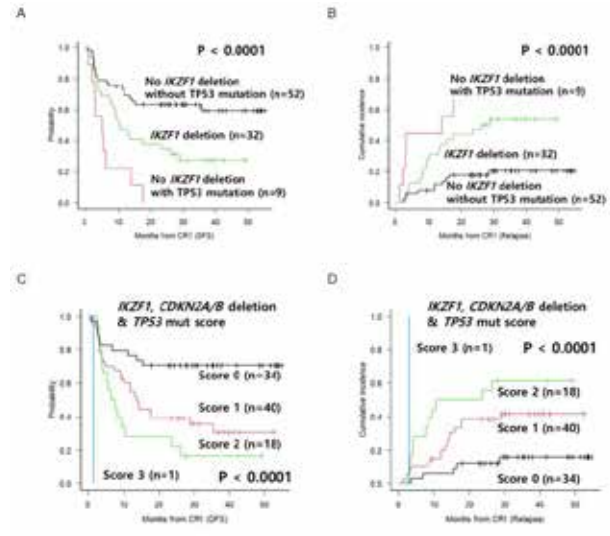
itive ALL because large proportion of this subgroup presents IKZF1 deletions.

Method : We tried to investigate the prognostic relevance of deletions of 8 genes (IKZF1, CDKN2A/B, EBF1, ETV6, PAX5, BTG1, JAK2) detected by multiplex ligation dependent probe amplification (MLPA), and TP53 and RAS mutation were additionally checked by using high throughput sequencing (HTS) analysis in 104 adults with Ph-negative ALL treated with modified hyper-CVAD based chemotherapy followed by allo-HCT based post-remission therapy.

Results : IKZF1 deletion was detected in 35 (33.6%) patients and CDKN2A/B in 41 (39.4%). The other gene deletions were detected in less than 25% each (PAX5 in 23.1%, ETV6 in 16.3%, EBF1 in 15.4%, BTG1 in 12.5% and JAK2 in 6.7%). RAS and TP53 mutation were detected in 22.1% and 12.5% respectively. We found 100% of JAK2, 92.3% of BTG1, and 79.1% of PAX5 deletions were observed with CDKN2A/B-deletion at the same time. Multivariate analysis revealed TP53-mutation (0.0% vs 47.1%), IKZF1-deletion (27.3% vs 50.4%) and CDKN2A/B-deletion (25.3% vs 53.0%) showed significantly poor disease-free survival (DFS) with higher relapse rates. We found most of the TP53 mutation (92.3%) were detected with no-IKZF1-deletion reciprocally, so that 3-year DFS of IKZF1-deletion (n=32), no-IKZF1-deletion without TP53 (n=52), and no-IKZF1-deletion with TP53 (n=9) were 27.3%, 59.2%, and 0.0%, respectively. We finally added CDKN2-deletion status into IKZF1-deletion and TP53 mutation and then calculated DFS based on the number of positive findings. Three-year DFS of score 0 (n=37), 1 (n=40), 2 (n=21), and 3 (n=1) were 64.9%, 30.4%, 14.3%, and 0.0%, respectively. The results were similarly reproduced in patients who underwent allo-HCT in CR1.

Conclusion : Our data showed a significant predictive genetic combination using TP53 mutation with IKZF1 and CDKN2A/B deletions in adults with Ph-negative ALL. Advanced transplantation strategies combined with novel agents must be precisely applied in this group of high-risk patients.

Keyword : Acute lymphoblastic leukemia, IKZF1, CDKN2A, CDKN2B, TP53



PP03-21

Real-world experiences of inotuzumab ozogamicin in adult patients with relapsed/refractory acute lymphoblastic leukemia

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Background : In adult patients with relapsed or refractory (R/R) B-cell precursor acute lymphoblastic leukemia (BCP-ALL), CR rates are low and survival outcomes are very poor. For effective salvage therapy and allogeneic hematopoietic cell transplantation (allo-HCT) in remission, inotuzumab ozogamicin (INO) or blinatumomab (BLIN) have been introduced and revealed their efficacy in clinical trials. We analyzed the treatment outcomes of INO for R/R BCP-ALL patients.

Method : Sixty adult patients with R/R BCP-ALL (Ph-positive 20, negative 40) were treated with INO with median 2 cycles (range: 1-5). We applied weekly INO with a dosage of 0.8mg/BSA for first week followed by 0.5mg/BSA for second and third week. For second cycle, we applied 0.5mg/BSA of weekly INO for 3 weeks in patients

with complete remission (CR) after first cycle. For post-remission treatment, allo-HCT was planned for all patients.

Results : At the time of INO salvage treatment, 6 (10.0%) were primary refractory (3 BLIN-failure), 12 (20.0%) had relapsed during/after consolidation chemotherapy (8 BLIN-failure), and 42 (70.0%) had relapsed after first (n=36) or second (n=6) previous allo-HCT (17 BLIN-failure). At the time of relapse, bone marrow relapse (BMR) alone was observed in 33 (55.0%) and isolated extramedullary relapse (EMR) in 9 (15.0%), and both BMR+EMR in 18 (30.0%). At the end of first INO cycle, overall response was achieved in 36 (60.0%) patients (66.6% for primary refractory, 59.4% for early relapse < 12 months, and 59.1% for later relapse) and 6 of them underwent allo-HCT. We observed 7 (11.6%) early deaths, 17 non-responder and 3 (8.3%) discontinuations due to VOD/SOS and infectious complications. At the end of second INO cycle, cumulative overall response was observed in 35 (58.3%) and 19 (31.6%) underwent allo-HCT. Among the rest 16 responders, 10 died in CR (3 VOD/SOS, 7 sepsis), 3 relapsed, and 3 was delaying next treatment due to thrombocytopenia. Follow-up duration was median 12.1 months (range 5.9-39.0), and 1-year OS was 24.3%, and patients treated with allo-HCT showed 39.0% of 1-year OS.

Conclusion : Our data suggested that INO can be a feasible choice for salvage for adults with R/R BCP-ALL which showed a good CR rate. However, we experienced unexpectedly high regimen-related mortality caused by hepatotoxicity including VOD/SOS and infectious complications or thrombocytopenia due to marrow suppression. Risk-adapted dose adjustment or patient selection for INO are important for better treatment outcomes.

Keyword : Acute lymphoblastic leukemia, Inotuzumab ozogamicin, Allogeneic hematopoietic cell transplantation, Venoocclusive disease, Minimal residual disease

Table. Response to INO treatment and allo-HCT realization

Parameters	Value
At the end of the first cycle (n=60)	
CR, n (%)	36/60 (60.0)
Relapse status	
Primary refractory	4/6 (66.6%)
CRD < 12 mo nths	19/32 (59.4%)
CRD ≥ 12 months	13/22 (59.1%)
Line of salvage	
1st line	10/20 (50.0%)
2nd line	12/19 (63.2%)
3rd line	7/12 (58.3%)
4th line	7/9 (77.8%)
EMR status	
BMR alone	20/33 (60.6%)
BMR+EMR	10/18 (55.6%)
Isolated EMR	6/9 (66.7%)
No response, n (%)	17/60 (28.3%)
Early death, n (%)	7/60 (11.6%)
INO hold after CR (VOD 1, Infection 2)	3/36 (8.3%)
Allo-HCT after 1 cycle of INO	6/36 (16.6%)
At the end of the second cycle (n=32 – CR 27, NR 5)	
Persistent + new CR, n (%)	26 (24+2)/32 (81.2)
Relapse status	
Primary refractory	1/2 (50.0%)
CRD < 12 months	14/17 (82.3%)
CRD ≥ 12 months	11/13 (84.6%)
Line of salvage	
1st line	8/11 (72.7%)
2nd line	9/10 (90.0%)
3rd line	4/5 (80.0%)
4th line	5/6 (83.3%)
EMR status	
BMR alone	11/14 (78.6%)
BMR+EMR	9/11 (81.8%)
Isolated EMR	6/7 (85.7%)
No + loss of response, n (%)	6 (3+3)/32 (18.7%)
Death during CR	10/26 (38.4%)
Relapse after CR	3/26 (11.5%)
Allo-HCT after >=2 cycle of INO	13/26 (50.0%)
MRD negativity in patients with persistent CR, n (%)	9/12 (75.0)
At the end of the first cycle	13/23 (56.5%)
At the end of the second cycle	11/15 (73.3%)
Allo-HCT in Inotuzumab-induced CR, n (%)	19/60 (31.6%)

PP03-22

A fatal pneumatosis intestinalis after ponatinib treatment on a relapsed Philadephia-positive acute lymphoblastic leukemia patient: A case report

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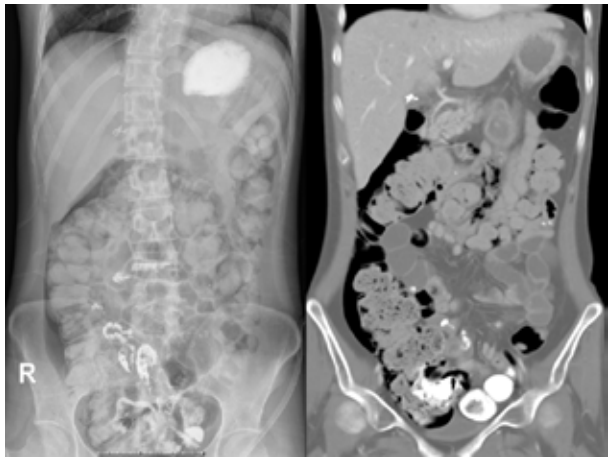
Background : Pneumatosis intestinalis (PI) is a potential life-threatening condition and some tyrosine kinase inhibitors have been associated with PI as a treatment-related complication.

Method : Here we report a fatal case of PI after ponatinib administration to a patient with relapsed Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL).

Results : A 26-year-old female was diagnosed with Ph+ ALL. While being treated with dasatinib due to extramedullary relapse after an allogeneic transplant, she visited the emergency department with headache. Imaging and the cerebrospinal fluid study suggested leptomeningeal involvement of leukemia with infiltrations of the cerebellum and mass effect upon the brainstem. She received radiotherapy on the whole brain and emergent external ventricular drainage (EVD) due to progressive hydrocephalus. Ponatinib 30mg daily was initiated. 16 days after ponatinib administration, the patient reported severe abdominal pain with non-neutropenic fever. Contrast-enhanced computer tomography showed diffuse pneumatosis intestinalis along the ascending and transverse colon and multiple microabscesses in the liver. Blood cultures grew Clostridium ramosum. After ponatinib discontinuation, PI had resolved. Howevere, the patient eventually died due to hepatic failure.

Conclusion : This is the first reported case of pneumatosis intestinalis after ponatinib treatment. Although pneumatosis intestinalis is rare, patients treated with tyrosine kinase inhibitors should be monitored for such complications. Further studies on molecular mechanisms of pneumatosis intestinalis may help identify susceptible patients before TKI treatment.

Keyword : Tyrosine Kinase Inhibitor, Acute lymphoblastic leukemia, Ponatinib, Severe adverse event



PP04-2

A rare case of three way Philadelphia variant (9;11;22)(p11.2;q34;q11.2) & del(12) in chronic myeloid leukemia: A case report

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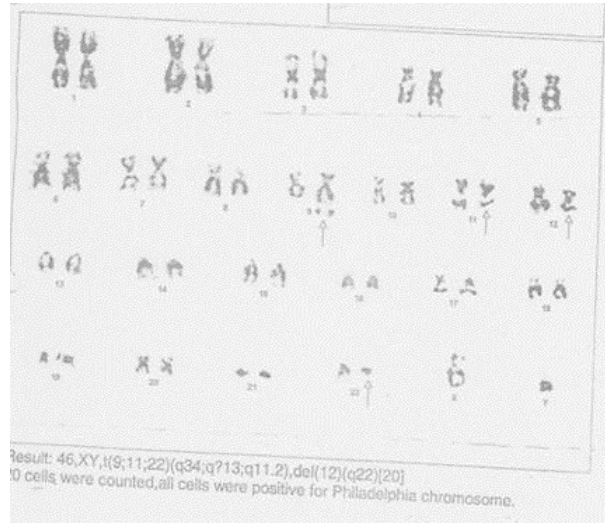
Background : Chronic myeloid leukemia (CML) is a hematologic malignancy associated with increased circulating myeloid cells and platelets in the peripheral blood, with accompanying bone marrow hyperplasia. The Philadelphia chromosome, t(9;22)(q34;q11), is present in 95% of CML patients, resulting in constitutive tyrosine kinase activity; however, ~5% of CML patients possess a Philadelphia variant.

Method : A 56 year old man who presented with leukocytosis, anemia and thrombocytosis that was diagnosed with chronic myeloid leukemia in chronic phase. Cytogenetic analysis by G banding revealed the presence of a three way translocation involving the short and long arms of chromosomes 9, 11 and 22. Fluorescence is situ hybridization utilizing a dual color fusion probe confirmed the presence of the Bcr-Abl fusion gene.

Results : A novel three way Philadelphia translocation variant, t(9;11;22)(p11.2;q34;q11.2) & del(12), was identified in a 56 year old man who presented with leukocytosis, anemia and thrombocytosis that was diagnosed with chronic myeloid leukemia in chronic phase.

Conclusion : In conclusion, we report a rare case of chronic phase CML with a novel complex three way Philadelphia variant t(9;11;22)(p11.2;q34;q11.2) & del(12). Early detection of these additional cytogenetic abnormalities can predict the course of disease on treatment.

Keyword : Chronic myeloid leukaemia, Complex translocation, Cytogenetic



PP04-3

Retrospective study of subsequent line nilotinib in chronic myeloid leukemia patients

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Background : Nilotinib is a 2nd generation TKI which has been approved for use in CML patients in both 1st line and subsequent lines. Second-generation TKIs have higher toxicity compared to Imatinib. Here we have conducted a retrospective study of patients who have received Nilotinib as 2nd or 3rd line TKI.

Method : The treatment details and outcomes of CML patients

who were started on Nilotinib as 2nd or 3rd line during the period of 2012 to 2021 were retrospectively collected from the patient records and analyzed. Event-free survival (EFS) is defined as the duration between the start of nilotinib and till stoppage of nilotinib due to an event. An event is defined as the stoppage of nilotinib due to any reason or death due to any cause. Overall survival (OS) is defined as the duration from the start of nilotinib to death due to any cause. The survival analysis was done by Kaplan Meier analysis and univariate analysis was done comparing variables using the log-rank test.

Results : Median age at diagnosis of 62 patients included in the study was 42years (Range: 12 – 67). Males constituted 49.7% (n=29) and females constituted 53% (n=33). In 62 patients in the study at diagnosis, 59, 2, and 1 were in chronic, accelerated, and blast phases respectively. Imatinib was used as 1st line in 96.7%. In the study population, 49 were non-compliant with the 1st line of treatment. Forty-Nine patients had a failure and 13 had an intolerance to their previous line of TKI. The median age at the start of Nilotinib was 47 years (Range 22-70). The median duration from diagnosis to start of Nilotinib was 45.4 months (Range 2.7-188.5 months). Among Imatinib failure patients (n=49), at the end of one year of Nilotinib, 13 patients achieved MMR, seven achieved CCyR, 21 were in CHR, and three did not achieve CHR. The CCyR achievement at one year was 42.8% in the failure group. In Imatinib intolerance patients (n=13) at the end of one year of Nilotinib, 8 achieved MMR, 3 in CCyR, and one in CHR. The median duration of Nilotinib was 50.6 months (Range: 1.9-117.4). At the time of analysis, 38 were continuing and 24 had stopped Nilotinib. Six, fourteen, and four patients had discontinued Nilotinib due to intolerance, failure, and loss of follow up respectively. The median duration of follow-up was 70.1 months (Range: 2.1-117.4). The median EFS was not reached and the 5-year EFS was 59.7%. The 5-year EFS in compliant and non-compliant patients were 69.2% and 56.3% respectively (p=0.4). The 5-year EFS in failure and intolerant patients were 59.7% and 83.3% respectively (p=0.03). Median OS was not yet reached and the 5-year OS was 91.3%. In compliant and non-compliant patients, 5-year OS was 84.6% and 93.2% respectively (p=0.5). The 5-year OS in failure and intolerant patients were 89% and 100 % respectively (p=0.17).

Conclusion : Nilotinib as a subsequent line after the failure of 1st line TKI has shown a fair rate of achievement of CCyr at 1 year (42.8%) Response of "CCyR or more " in Imatinib intolerance Group was better than Imatinib failure group. The only factor which had significantly influenced the EFS was the reason for the switch to Nilotinib.

Keyword : Nilotinib, Second line Nilotinib, Chronic Myeloid Leukemia, Treatment failure in CML

PP04-4

Targeting CXCR2 overcome intolerance to ponatinib via AKT/mTOR and MYC signaling in chronic myeloid leukemia cells

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Background : Chronic myeloid leukemia (CML) is a hematopoietic disorder by chromosome translocation t(9;22) (q32;q11) presented of a BCR-ABL1 fusion protein it also called The Philadelphia (Ph) chromosome. BCR-ABL1 leads to constitutive activation of the tyrosine kinase activity, which is responsible for continuous proliferation and resistance to apoptosis The most reason why acquired resistance to chemotherapy is point mutations in the BCR-ABL1 gene. Especially the most common detected mutation of TKIs, gatekeeper mutation T315I, can confer resistance to all approved TKIs except ponatinib, a third generation of TKIs. Ponatinib is a multitargeted TKI treatment for patients who have failed with other TKIs or with T315I mutation. Although the initial trial indicated excellent response rates, a significant number of patients discontinued this drug because of resistance or intolerance. Also, other studies showed unable to eradicate quiescent CML stem cells even if treated with TKIs. Therefore, new strategies are required for targeting drug resistance or intolerance in CML.

Method : Generated ponatinib-resistant CML cell lines were confirmed using cytotoxicity assay and immunoblotting. The expression of CXCR2 and their ligands were analyzed by cytokine assay, RT-qPCR, flow cytometry, and ELISA. The effect of CXCR2 antagonist demonstrated cell proliferation assay, colony forming unit assay (CFU), cell cycle analysis, and western blotting.

Results : We established ponatinib-resistant CML cell lines (K562/PR and KU812/PR) and acquired ponatinib-resistant cells were sustained proliferation even if treated with 100 nM of ponatinib. The established ponatinib resistance cells were increased expression of both GRO α/β/γ (CXCL1/2/3) and IL-8, which is hematopoietic ligands. Also, CXCR2 expression was significantly increased in K562/PR and KU812/PR compared to parental cell lines, notably CXCR2 levels were sustained despite the presence of ponatinib. These results implicated the possibility that CXCR2 and cytokines are associated with ponatinib resistance. To confirm whether the targeting of CXCR2 could be therapeu-

tic for ponatinib-resistant CML, we exposed CXCR2 antagonist, SB225002, in a variety of doses. K562/PR and KU812/PR cells showed significantly inhibited cell growth incubated more than 0.5 μM of SB225002. We verified this cell growth was inhibited through p-AKT, p-mTOR, and c-Myc signaling after being treated with SB225002. Also, SB225002 induced apoptotic cell death of ponatinib-resistance cells. These results implicated that targeting CXCR2 signaling affects hamper cell proliferation as well as leads to apoptosis in ponatinib-resistant CML.

Conclusion : This study demonstrated inhibiting CXCR2 could be a novel therapeutic strategy for patients who has ponatinib resistance in CML.

Keyword : CXCR2, IL-8, GRO-α Tyrosine kinase inhibitors, Ponatinib, Drug resistance

PP04-5

A case of chronic myeloid leukemia with novel X-linked four-way Philadelphia chromosome and molecular unresponsiveness with clonal evolution

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Background : Chronic myeloid leukemia (CML) is a type of myeloproliferative neoplasm which characterized by a specific translocation of Philadelphia (Ph) chromosome t(9:22)(q34;q11). The occurrence of X-linked four-way translocation of Ph chromosome is extremely rare. Although recent studies suggested that these complex translocations of Ph chromosome does not affiliated with treatment response, the precise effect of complex translocations remains unknown.

Method : Here, we report a case of 42-year-old male patient who presented dyspepsia and abnormal findings of blood cell count in November, 2019. The blood cell count and blood smear indicated anemia, marked leukocytosis and thrombocytosis (Hemoglobin 64 g/L, Leukocyte 338.7 x 10^9/L, Platelet 1319 x 10^9/L) consisting with 11% of myeloblasts, eosinophilila (3540/uL) and basophilia (4140/uL). The hypercellular Bone marrow (BM) showed marked increases of granulopoiesis and megakaryopoiesis with eosinophilia (13.2%) and basophilia (7.0%). Major BCR-ABL fusion gene with a type of b2a2 was revealed and quantified as 46.81% of BCR-ABL1 International-Scale (IS). BCR-ABL1 fusion was detected in 96% of the 200 nuclei by Fluorescent in-situ hybridization (FISH) analysis. The chromosome study showed four-way translocation 46,Y,t(X;5;9;22)(q26;q15;q34;q11.2) in all analyzed cells.

Results : The patient was diagnosed of CML, in accelerated phase, and received first-line imatinib followed by initial nilotinib treatment, after confirming of no resistant mutation in BCR-ABL1 kinase domain. He reached to early molecular response (9.32% of BCR-ABL1, IS) after two months of the treatment. BCR-ABL1 (IS) was persistently increased up to 24% IS of BCR-ABL1 for five months but no imatinib resistant mutation was found. BCR-ABL1 (IS) levels were persistently increased ranging from 10.99% to 28.97% despite of second-line nilotinib treatment for 23 months. Complete hematologic response was observed but clonal cytogenetic evolution was revealed by follow-up BM study: 46,Y,t(X;5;9;22)(q26;q15;q34;q11.2)[3]/47,XY-,+8[7]/46,XY[10]. Moreover, an unclassified variant (E2992V) of ABL1 domain was identified. BCR-ABL1 (IS) was 3.87% and 2.8% (14/500) of BCR-ABL1 fusion measured by FISH. The treatment changed to third-line dasatinib, though no molecular response was reached by December, 2022.

Conclusion : A novel X-linked four-way translocation t(X;5;9;22)(q26;q15;q34;q11.2) is the first case reported contemporary. This report has value from an extremely rare type of Ph chromosome occurred clonal evolution with a somatic variant possibly related to molecular unresponsiveness to conventional tyrosine kinase inhibitor therapy.

Keyword : X-linked complex translocation, Clonal evolution, Molecular unresponsiveness, Treatment resistance

PP04-6

Investigation of the regulatory landscape of transcription modulators in chronic myeloid leukemia for the new biomarker discovery

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Background : Hematopoietic stem cell disorders with different biochemical and clinical characteristics include chronic myeloid leukemia (CML). The primary cytogenetic and molecular hallmark of CML chronic phase is related to number of dysregulated genes and Philadelphia (Ph) chromosome. However, little is understood about the molecular processes that underlie illness development. Recent research has demonstrated that several transcription factors, including AML1, C/EBPalpha, HOX, and the GATA family, are crucial for hematopoiesis. Additionally, it has been discovered that certain transcription factors' abnormalities, such as mutations or translocations, contribute to the development of the illness. Therefore, dysregulated and abnormal transcription factors may both contribute to the CML blast crisis phenotype. The availability of CHIP-Seq and RNA-seq datasets urge the need for integrative genome analysis to identify the therapeutic targets. Here, we will study a combined approach of ChIP-Seq and RNA-Seq data to unravel the transcriptional and chromatin regulatory landscapes of CML.

Method : We have retrieved both CHIP-Seq (AML1, C/EBPalpha, HOX, and the GATA) and RNA-Seq data (GSE data of CML) and further employed extensive R programming and number of command-line based tools to analyze the data. Then, GREAT (Genomic Regions Enrichment of Annotations Tool) tool was used to associates the TF's binding sites identified during peak calling with TF's putative target genes. Furthermore, RNA-Seq datasets were examined using limma and DESeq of R package. In order to identify the dysregulated genes from the RNA-seq data analysis, we used the False Discovery Rate (FDR). The statistical criterion of log2fold change (2 and -2) and a statistically significant P (probability) value ($P \leq 0.05$) was used to calculate the difference in gene expression between the control and sample. Additionally, we identified target genes exhibiting notable statistical changes in gene expression that may be related to TF regulatory activity using BETA, a program that integrates TF binding and differential expression. Afterwards, we employed molecular docking and dynamics study to reveal the binding site, binding stability and interacting residues in between dysregulated genes and transcription factors.

Results : A number of genes were shown to be dysregulated upon the binding of AML1, C/EBPalpha, HOX, and the GATA transcription factor in both CHIP-Seq and RNA-Seq data. We searched for the hub genes among the dysregulated genes and discovered CD47, Crebl1, MDI1, FZD2, ITGA5, and CEBPA, CEBPE, FOXO3A, ROK13A and XRN2 as the hub genes for upregulated and downregulated genes, respectively. The analysis also identified that CD47, Crebl1, MDI1, FZD2 and ITGA5 gene expression are high in all the transcription factor binding. In contrast, CEBPA, CEBPE, FOXO3A, ROK13A and XRN2 gene expression showed the downregulation in transcription factor binding. The molecular docking study revealed that all the transcription factors posed strong binding affinity. The binding site and interacting residues were investigated and further validated through molecular simulation study. Molecular dynamics confirmed the binding stability between all the transcription factors and identified dysregulated genes. From the selected dysregulated genes, we found that MDI1 and CD47 from upregulated genes of CML and CEBPE and ROK13A from downregulated genes of CML had the strong binding stability and interactions with the transcription factors.

Conclusion : The results of the present study revealed that when patients have CML disease condition, MDI1 and CD47 from upregulated genes and CEBPE and ROK13A from downregulated genes had the significant binding stability and interactions with the transcription factors. These four genes-MDI1, CD47, CEBPE, and ROK13A-could therefore serve as biomarkers for CML disease.

Keyword : CML, CHIP-Seq, RNA-Seq, Hub Genes, Binding site, Molecular dynamics

PP05-1

Outcome of hematopoietic stem cell transplantation for pediatric lymphoma：A retrospective analysis of a single-center

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Background : After acute leukemia and central nervous system tumors, mature lymphomas represent the third most common cancer in pediatric patients. Non-Hodgkin lymphoma (NHL) accounts for approximately 60% in children, with the remainder representing Hodgkin lymphomas (HL). The objective of our study was to evaluate the clinical efficacy of Hematopoietic Stem Cell Transplantation (HSCT) for the treatment of pediatric lymphomas and analyze the prognostic factors.

Method : The clinical data of patients with lymphoma treated with HSCT in Beijing Children's Hospital from August 2006 to November 2020 were analyzed retrospectively.

Results : Among the 54 patients, there were 6 cases of HL and 48 cases of NHL. There were 30 males and 24 females. The age of diagnosis was 92.04 ± 6.13 months, the age of transplantation was 106.30 ± 6.51 months, and the time from diagnosis to transplantation was 6.65 (3.70 ~ 57.57) months. There are tewnty-two cases treated with BEAM conditioning regime, 13 cases with TBI+Flu+-

Cy+ATG conditioning regime, 11 cases with Ara+Bu+Cy+Mu-CCMU conditioning regime, 3 cases with BEA/C conditioning regime, and 4 cases with TBI+Cy±BCNU conditioning regime. Among them, 25 cases accepted Haplo-HSCT, of which 4 from their siblings and 22 from their parents. The median infused mononuclear cell (MNC) count was 8.20×108 [(5.69~11.83)×108]/kg, and the median infused CD34 positive cells was 7.50×106 [(3.20~9.99)×106]/kg. The median platelet engraftment time was 16 days (12 ~ 26 days), and the neutrophil engraftment time was 12 (12 ~ 14) days. Until May 1st 2022, the median follow-up time was 51.40 (0.67-156.07) months. There were 50 cases of free disease progression, 9 cases recurrence, and 7 cases death. The overall 5-year OS and EFS were 88.90% and 84.10%, respectively. After transplantation, the 5-year EFS of HL and NHL were 40.00% ± 21.90% vs. 88.80% ± 4.70% (P = 0.003). The OS of patients without CMV and hemorrhagic cystitis after transplantation were better, the difference were statistically significant, P=0.03 and P=0.002 respectively. The EFS of patients with BEAM conditioning regime before transplantation was better than other conditioning regimes (P=0.05).

Conclusion : HSCT has a good effect on the treatment of childhood lymphoma, with a high survival rate. The survival time of BEAM than other conditioning treatments can be longer for EFS and OS. Better management of related complications after transplantation give better OS about patients.

Keyword : Childhood Lymphoma, Hematopoietic Stem Cell Transplantation, Overall Survival

PP05-2

Loss of ccar2 is associated with a better outcome in burkitt lymphoma cells

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Background : Cell cycle and apoptosis regulator 2 (CCAR2, DBC1 or KIAA1967) is an important regulator of DNA damage responses (DDR) related cell physiology. Its role in tumorigenesis and chemotherapy resistance remains unclear. To date, the studies on CCAR2 as a tumor promoter or suppressor is not yet complete, and the causal relationship between loss of CCAR2 and hematological tumorigenesis has not been fully established.Depending on the genetic background, CCAR2 has been referred as a tumor suppressor or oncogene. Burkitt lymphoma (BL) is a highly aggressive non-Hodgkin's lymphoma with a demonstrated propensity to rapid growth and dissemination.Despite BL is highly responsive to specifically designed short-intensive, rotational multiagent chemotherapy programs, empowered by the anti-CD20 monoclonal antibody rituximab.BL is still associated with poor outcomes accompanied by treatment failure owing to drug resistance.At present, aggressive lymphoma is treated with chemotherapy causing DNA damage. However, DNA damage is an attractive anticancer strategy, as DNA damage can elicit DNA damage response (DDR) to coordinate mechanisms of DNA repair and apoptosis.However,the effect of chemotherapy is often attenuated due to DNA repair, leading to refractory or relapse.It is necessary for us to set up a reasonable gene therapy target for DDR of BL cells. DNA double-stranded breaks (DSBs) is the most serious form of DNA lesions,and non-homologous end-joining (NHEJ) and homologous recombination (HR) are two major and alternative pathways to repair DSBs.Since DNA lesions caused by chemotherapeutic drugs play an important role in the treatment of BL, we intend to establish the association between CCAR2 and DDR related cell physiology in BL cells.

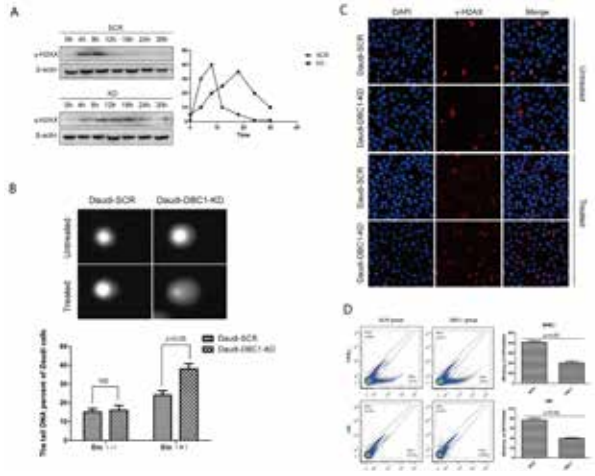
Method : In terms of lymphoma, expression of CCAR2 predict poor prognosis in diffuse large B cell lymphoma. Here, we investigated the role of CCAR2 in Burkitt lymphoma (BL) to explore the association between CCAR2 and DDR relating cell physiology. Moreover, etoposide as a broad-spectrum anticancer drug, is considered as a potent inducer of DSBs . In this study, we analyzed expression of CCAR2 in Daudi cells, and investigated the functional role of CCAR2 under the cytotoxic pressure caused by etoposide to uncover therapeutic vulnerabilities. Thus, we used the RNA interference method to eliminate CCAR2 and investigate its specific role in Daudi cells induced mouse BL model. And we sought to extend these findings by identifying the functional consequence of CCAR2 as well as the association with DBSs repair.

Results : We showed that CCAR2 is highly expressed in BL cells especially in Dauid cells. Our results indicate that loss of CCAR2 reduces cell growth and induces sensitization to etoposide-mediated cytotoxicity. After etoposide treatment, we found that the depletion of CCAR2 may enhance apoptosis of Daudi cells through regulating NF-κB pathway and impair the efficiency of non-homologous end joining (NHEJ) pathway. Besides, downregulation of CCAR2 reduced the tumorigenesis ability of Daudi cells in mouse xenografts model.

Conclusion : Here, we show that CCAR2 protein levels were overexpressed in BL cell lines, indicating CCAR2 may be closely related to the development of BL. Though the function of CCAR2 in tumorigenesis has been controversial, we identified that CCAR2 could promote the progression of BL. Our experimental results show that loss of CCAR2 results in impaired cell growth, increased apoptosis and arrested cell cycle. Further, we found that CCAR2 deficiency results in higher γH2AX expression level accompanied by lower DNA

repair efficiency. Additionally, CCAR2 knock down group exhibit prolonged life span in mouse xenograft model. These results may help shed light on the puzzle of conflicting CCAR2 function in BL and indicate that CCAR2 may be a promising chemotherapy target against BL in humans.

Keyword : CCAR2/DBC1, DNA damage repair, Burkitt lymphoma, Etoposide, non-homologous end-joining (NHEJ)



PP05-3

The iminent role of alk inhibitors in relapsed and refractory ALK positive anaplastic large cell lymphoma

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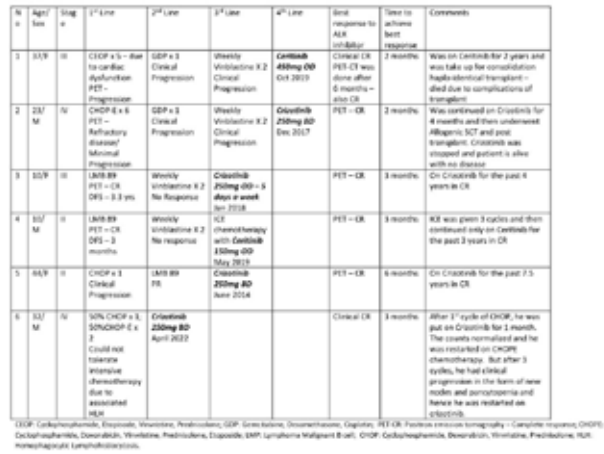
Background : Anaplastic large cell lymphoma (ALCL) is the second most common type of Peripheral T cell Lymphoma (PTCL) and an aggressive mature T cell lymphoma. About 50 -70% of systemic ALCL are Anaplastic Lymphoma Kinase positive (ALK +), the proportion even higher in the pediatric population. The five-year survival after chemotherapy is around 70-80%. But there is a subgroup of ALK+ ALCL patients who are refractory to chemotherapy. Brentuximab Vedotin (BV) is an approved agent for such patients. The activity of ALK inhibitors in ALK-positive Non-Small Cell Lung cancer(NSCLC) is well known and has been approved for use. The efficacy and safety of ALK inhibitors in ALK + ALCL are largely under-reported. Here we have reported our experience in the use of ALK inhibitors in relapsed refractory ALK+ ALCL

Method : Patients who received ALK inhibitors for ALCL were searched in the patient database and those records were retrospectively analysed. Off Label consent was obtained from all patients

Results : Totally six patients received ALK inhibitors for ALK+ ALCL. The median age at diagnosis was 27.5 years. Four patients were adult and two were pediatric. Five out of six patients were chemotherapy refractory to their previous line of treatment. All the six patients who were chemo-refractory achieved CR within 2 to 3 months of starting ALK inhibitors. The overall response rate was 100%. One other patient could not continue the ALK inhibitors due to financial reasons after 2 years and hence the patient was taken up for consolidation allogenic haploidentical stem cell transplantation but unfortunately the patient expired due to transplant regimen-related mortality. The median follow up of the study series was 3.25 years. Five patients were disease free and alive at the time of study analysis (July 2022). The median progression free survival (PFS) was not reached and 3 year PFS was 75%. Out of six patients, 2 patients had pedal edema. Two patients had grade 1/2 diarrhea. There was no dose-limiting toxicity.

Conclusion : ALK inhibitors in ALCL were fairly tolerated and highly efficacious in refractory ALK positive ALCL and given the rarity of refractory ALCL, the drugs should be considered for orphan drugs status for ALCL.

Keyword : Crizotinib in ALCL, Relapsed ALCL, Ceritinib in ALCL, ALK positive anaplastic large cell lymphoma, Anaplastic large cell lymphoma



PP05-4

Reduced dose rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) therapy for diffuse large b-cell lymphoma (DLBCL); A practical approach for the elderly and frail

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Background : Chemoimmunotherapy of rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) is the first-line therapy for diffuse large B-cell lymphoma (DLBCL). The delivery of R-CHOP for elderly and frail patients often requires dose reductions. This is a retrospective analytical study to determine the safety and efficacy of reduced-dose R-CHOP (50% and 70%) in elderly patients aged 70 and above at our center.

Method : We included a 5-year cohort of patients treated from 1st January 2016 to 31st December 2020. Data were obtained through electronic and manual medical records. Event-free survival (EFS) and overall survival (OS) with associated risk factors were estimated using the Kaplan-Meier method and compared using the log-rank test with the software SPSS version 26. The grading for the adverse events was done according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Results : 43 patients were analyzed with a median follow-up of 22 months. The median age was 74 years old (range 70 to 84) with two-thirds being males (n=28). 31 patients received 70% dose while the remainder (n=12) received 50% dose. Most are of non-germinal centre B-cell of origin (n=25, 58.1%). High-risk patients included patients with advanced stage III or IV (n=17, 39.5%) and high international prognostic index (IPI) scores (n=9, 20.9%). The overall response rate (ORR) is 81.4% (n=35) with 67.4% (n=29) achieving a complete remission (CR). The most common grade ≥ 3 adverse event was neutropenia (n=8, 18.7%) with treatment-related mortality (TRM) of 7% (n=3). The EFS and OS at the time of median follow-up were 50.5% and 57.8% respectively. Achieving CR, stage I disease, and a higher albumin level (>30g/L) are associated with significantly better EFS and OS on the univariate analysis. In our cohort, there is no significant difference between the 2 dose-reduced regimens.

Conclusion : The ideal dose adjustment for elderly patients with DLBCL remains to be ascertained with the limited number of patients in our cohort. Nevertheless, both doses of reduced R-CHOP regimens are safe and effective treatment options for elderly and frail patients.

Keyword : Elderly DLBCL, Reduced Dose R-CHOP

PP05-5

Subcutaneous panniculitis-like T-cell lymphoma associated with hemophagocytic lymphohistiocytosis: A systematic review of 63 patients reported in the literature

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Background : To review and summarize the clinical features, treatment strategies, and prognosis of subcutaneous panniculitis-like T-cell lymphoma complicated with hemophagocytic lymphohistiocytosis (SPTCL-HLH).

Method : We searched the Web of Science, Embase, Cochrane Library, and PubMed databases. The keywords were subcutaneous panniculitis-like T-cell lymphoma and hemophagocytic lymphohistiocytosis or hemophagocytic syndrome. The patients were divided into a mutated group and a wild-type group based on the existence of HAVCR2 gene mutation.

Results : A total of 45 reports including 63 patients with SPTCL-HLH were included in the systematic review. Twelve patients detected gene mutations, including 11 with the HAVCR2 gene and 1 with the STXBP2 gene. Compared with the wild-type group, patients in the mutated group were younger (25.16 ±13.68 years vs. 14.55 ±9.06 years, $p < 0.017$), and the autoantibody positive rate was higher (5.8% vs. 45.4%, $p = 0.003$). However, gene mutation was not associated with the response to the initial treatment or the outcome. Four patients were treated with anthracycline-based chemotherapy (CHOP, CHOPE) after controlling HLH, with an overall response rate (ORR) of 100%. Two of them relapsed. The main treatment target of 17 patients was to control HLH, yielding an ORR of 88.2%. Two cases relapsed, and both were treated with corticosteroid monotherapy. The corticosteroids monotherapy experienced higher recurrence rate than the corticosteroids combined with other immunoregulatory agents therapy (66.7% vs. 0.0%, $p = 0.029$). Eighteen patients

received initial anthracycline-based chemotherapy, and 50.0% reached remission. The ORR of initial chemotherapy aiming at controlling HLH was higher than those of anthracycline-based chemotherapy (88.2% vs. 50.0%, p = 0.015). Interestingly, one patient with juvenile idiopathic arthritis developed SPTCL-HLH during tocilizumab therapy, discontinuing tocilizumab led to a remission of the disease spontaneously. Sixteen patients received stem cell transplantation (SCT). All the patients, including 5 with relapsed/refractory SPTCL-HLH, responded well and survived after receiving SCT, but one of them who received a sibling-identical SCT relapsed. Further analysis revealed a homozygous HAVCR2 mutation with the donor. The 2-year OS rate was 91.0% ±4.4%. There was a significant difference in the OS rate among patients of different age groups, and patients aged 40 to 60 had the lowest 2-year OS rate (66.7% ±19.2%).

Conclusion : Patients with HAVCR2 gene mutations are younger and more likely to misdiagnose with autoimmune diseases. Initial treatment of corticosteroids combined with immunoregulatory agents attaches great significance to avoiding too aggressive therapies. Intensive anthracycline-based chemotherapy such as CHOP or CHOP-like regimens can also induce long-term remission for aggressive disease. SCT is still a reliable strategy currently. In addition, a wait and observation strategy is recommended in patients with mild SPTCL-HLH caused by drugs. The occurrence of HLH does not necessarily mean a more rapidly progressive disease and worse prognosis in patients with SPTCL, but older patients with SPTCL-HLH may be associated with the lower survival rate.

Keyword : Subcutaneous panniculitis-like T-cell lymphoma, Hemophagocytic lymphohistiocytosis, Clinical features, Treatment, Prognosis

PP05-6

Indolent extranodal NK/T-cell lymphoma of the gastrointestinal tract mimicking indolent T-cell lymphoproliferative disorder of the gastrointestinal tract

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Background : Primary intestinal T-cell and NK-cell lymphoid proliferations and lymphomas are classified as indolent T-cell lymphoma (TCL) of the gastrointestinal tract (i-TCL-GI), indolent NK-cell lymphoproliferative disorder (i-NK-LPD) of the GIT, enteropathy-associated T-cell lymphoma (EATL), monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), and intestinal TCL, NOS. I-TCL-GI is a clonal T-cell proliferation characterized by the infiltration of the lamina propria by small mature lymphocytes lacking significant epitheliotropism, i.e., no tissue destruction, EBV-negativity, and an indolent clinical course. Extranodal NK/T-cell lymphoma (ENKTL) is an aggressive neoplasm universally associated with EBV, with the majority occurring in the upper aerodigestive tract, and a smaller proportion presenting primarily in non-nasal sites such as the skin and GIT.

Method : A detailed clinicopathological and molecular characterization of a unique case of ENKTL with indolent course, mimicking i-TCL-GI.

Results : The female patient was diagnosed at other hospital in June 2014 as stage IE primary intestinal T-cell lymphoma when she was 28 years old and received 6 courses of CHOP. She presented with cramping abdominal pain, vomiting and diarrhea in October 2021. Colonoscopy in January 2022 showed mild hyperemia in the terminal ileum, while diffuse edematous mucosa, scattered hyperemia, and several shallow ulcers were noted in cecum, ascending colon, transverse colon, descending and proximal sigmoid colon. Multiple biopsies showed similar features of a florid lymphocytic infiltration in the lamina propria, without destruction of the mucosal glands. These atypical cells were T-cells expressing CD2 (weak), CD3, CD8, TIA-1 (partial), granzyme B, and TCR-delta, but not CD4, CD5, CD20, CD56, or TCR-BF1. The proliferation index by Ki67 was high at 90%. In situ hybridization for EBV-encoded mRNA (EBER) was diffusely positive. The sections of the colonic biopsy in 2014 were reviewed and showed essentially the same features as the January 2022 specimens, including florid atypical lymphocytic infiltration without tissue/mucosal destruction and diffuse EBER-positivity. No additional chemotherapy was administered. Follow-up as of October 2022, 8 years after initial biopsy, shows a stable disease. Mutation analysis showed only two mutations. RHOA mutation is highly predominant in the 2014 colonic biopsy, but at a minimal level in all four 2022 biopsies. This suggested that RHOA mutant cells were clonal, the major clonal cell population in the 2014 colonic biopsy, but this clone was presence only at a low level in the 2022 ileum and colonic biopsies. In contrast, TRRAP mutation was at a minimal level in the 2014 colonic biopsy, but increased to a substantiate level in all 2022 ileum and colonic biopsies. The TRRAP mutation may be present in only one of the clonal T-cell populations seen in the 2022 biopsies given its relatively low VAF values. The other predicted clonal cell population did not harbour any mutation in the 250 genes investigated. In brief, this lymphoma showed variable clonal T-cell populations, with dynamic changes during the disease evolution.

Conclusion : This is an ENKTL of γδ T-cell lineage, not i-TCL-GI, based on the EBER-positivity of the infiltrating lymphocytes. However, the clinical course is indolent, mimicking i-TCL-GI. Genetic study shows a low mutation load, probably reflecting the low malignant potential/

behaviour of this neoplasm

Keyword : EBV, Extranodal NK/T-cell lymphoma, Indolent T-cell lymphoma of the gastrointestinal tract, Intestinal T-cell lymphoma, Mutation profile, TRRAP

PP05-7

Transcriptomic profiling of double-hit lymphoma patients identifies aberrant ALOX5 captures vulnerability to ferroptosis

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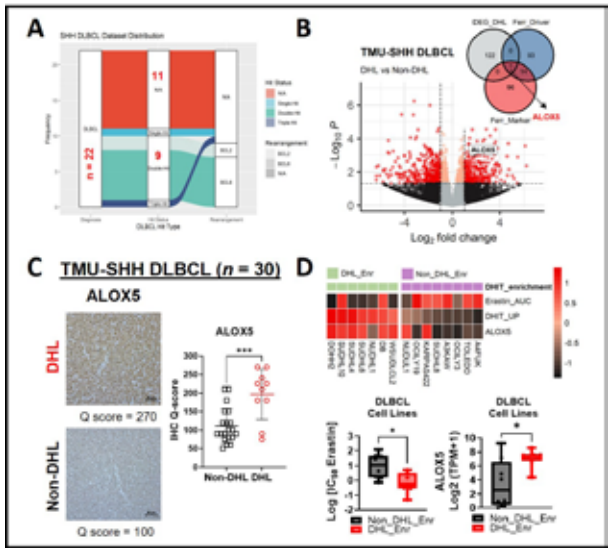
Background : Double-Hit Lymphoma (DHL) is the most aggressive subset of Diffuse Large B-cell lymphoma (DLBCL), which is genetically defined by MYC and BCL2 or BCL6 rearrangements. Despite R-CHOP being the mainstay of treatment, no specific yet effective drug for DHL has been developed, indicating an unmet medical need. The prospect of treating aggressive cancer such as high-grade B-cell lymphoma by exploiting ferroptosis, a novel iron-mediated regulated cell death, has recently gained attention for its potential. A specific marker, which characterizes DHL features while capturing their ferroptosis susceptibility, has not been defined. By using high-throughput transcriptomic profiling, this study identified Arachidonate 5-lipoxygenase (ALOX5) as a potential marker of ferroptosis sensitivity in DHL tumors.

Method : An Illumina NovaSeq sequencer was employed to sequence RNA library from biopsy tumors of 22 DLBCL patients diagnosed in Taipei Medical University-Shuang Ho Hospital (TMU-SHH). Bioinformatics approach was performed, consisting of differential expression genes (DEGs), hierarchical clustering, and functional enrichment analysis. ALOX5 expression was confirmed by using immunohistochemistry (IHC) in TMU-SHH DLBCL cohort (n=30). Transcriptomic profiling and drug perturbation dataset re-analysis of DLBCL cell lines (n=15) treated with ferroptosis inducer, erastin, was conducted to identify cell lines with differential sensitivity to ferroptosis. Knockdown of ALOX5 in DHL cell lines was carried out to determine modulation of ferroptosis pathway.

Results : On the basis of FISH karyotyping, among 22 DLBCL patients, 9 patients were classified as DHL, while others were Single-Hit Lymphoma (n=1), Triple-Hit Lymphoma (n=1), and DLBCL without known rearrangement (n=11). Patients with SHL and DLBCL without known rearrangements were referred to as non-DHL subset (n=12) and compared to the DHL subset (n=9). Analysis of DEGs resulted ALOX5 was significantly overexpressed in DHL subset. Interestingly, hierarchical cluster analysis revealed distinct clusters of patients with highly activated double-hit features and Myc targets were also enriched with ferroptosis-associated genes. As shown by immunostaining, DHL subset patients had aberrant ALOX5 expression, while MYC expression was correlated with ALOX5 aberrations. Double-hit enriched cells were relatively sensitive to erastin-mediated ferroptotic death as shown by significantly lower IC50 of DHL-enriched cells than non-DHL enriched cells. Moreover, ALOX5 was significantly upregulated in DHL-enriched cell lines, speculating contribution of ALOX5 in modulating ferroptosis sensitivity. Eventually, knockdown of ALOX5 suppressed Nrf2 and GPX4, indicating importance of ALOX5 in mediating activation of canonical regulator of ferroptosis in DHL.

Conclusion : Our findings revealed ALOX5 interconnected double-hit features and ferroptosis vulnerability. Implementing ALOX5 as a therapeutic target and/or predictive marker for DHL who benefit from ferroptosis-inducing drugs was expected in future translational studies.

Keyword : Double-Hit Lymphoma, DLBCL, RNA sequencing, ALOX5, MYC, Ferroptosis



PP05-8

Long-term clinical outcomes of follicular lymphoma: A single-center experience of 275 patients in Catholic Hematology Hospital

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Background : Follicular lymphoma (FL) is one common subtype of non-Hodgkin lymphoma (NHL) in Western countries, and its incidence in Asian countries is lower but recently increasing. Since the introduction of rituximab, an anti-CD20 monoclonal antibody, treatment outcomes of FL patients have markedly improved, and for patients with advanced-stage FL or high tumor burden, rituximab-containing immunochemotherapy with maintenance became the standard of care. We hereby present long-term clinical outcomes of FL in the Korean population who received R-CVP (rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, and vincristine 1.4 mg/m^2 on day 1, and prednisone 60 mg/m^2 from day 1 to 5 every three weeks interval), R-CHOP (rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 on day 1, and prednisolone 100 mg/m^2 on days 1 to 5 every three weeks interval), or R-Benda (bendamustine 90 mg/m^2 from day 1 to 2 and rituximab 375 mg/m^2 on day 1) regimens with or without rituximab maintenance (375 mg/m^2 every 2 months).

Method : We reviewed the clinical and laboratory database and enrolled 275 FL patients diagnosed between 2007 and 2020 at Catholic Hematology Hospital. We stratified patients' risk by following both Follicular Lymphoma International Prognostic Index (FLIPI) and FLIPI-2. The primary objective was to evaluate progression-free survival (PFS). We are also interested in adverse events after FL treatment with or without maintenance.

Results : At a median follow-up period of 10 years, overall survival (OS) and PFS were 92.7% (95% confidence interval [CI], 86.8–96.0) and 67.2% (95% CI, 56.3–75.9), respectively. The cumulative incidence of relapse (CIR) was 30.1% (95% CI, 20.8–39.9), and non-relapsed mortality (NRM) was 2.7% (95% CI, 0.8–6.7). The high-risk group showed significantly inferior PFS in both FLIPI and FLIPI-2, but FLIPI presented better discriminate OS and PFS between the good and intermediate-risk groups. Prognostic factors affecting PFS in FL patients were high-risk in FLIPI (hazard ratio [HR], 2.603; 95% CI, 1.458–4.646; p=0.0012), and the interim response was not reached to complete remission (HR, 3.079; 95% CI, 1.751–5.414; p<0.001). There was no difference in CIR between those without and with rituximab maintenance (22.6% vs. 33.4%, p=0.894). However, both FLIPI (CIR: 42.3% vs. 41.5%, p=0.027) and FLIPI-2 (CIR: 63.1% vs. 46.0%, p=0.013) high-risk patients benefited from maintenance therapy, as evidenced by the lowered CIR. Not all patients completed rituximab maintenance due to disease relapse or infectious complications, especially during the coronavirus disease 2019 (COVID-19) pandemic. Forty patients (14.6%) were diagnosed with COVID-19; 15 experienced recurrent COVID-19 with pulmonary fibrosis. Among five NRM patients, three died because of COVID-19-related complications driven by catastrophic respiratory failure. Despite lacking statistical significance, more patients who underwent maintenance showed COVID-19 infection (8.8% vs. 16.4%, p=0.123). Among the patients, 47 (17.1%) and 29 (10.5%) required immunoglobulin replacement due to hypogammaglobulinemia and hospitalization due to major infections after chemotherapy, respectively, with no significant difference in incidence in both maintenance and non-maintenance groups (14.7% vs. 17.9%, p=0.547; and 8.8% vs. 11.1%, p=0.594).

Conclusion : The real-world clinical outcomes of FL treated with different therapeutic modalities were presented in this long-term, retrospective, single-center study with sufficient patients, with

R-Benda considered the first-line treatment of choice. The PFS was mostly related to an elevated CIR, but OS was excellent, and both FLIPI and FLIPI-2 were appropriate prognostic models in Korean FL patients. Rituximab maintenance may be valid for treating FLIPI and FLIPI-2 high-risk patients after achieving CR. During maintenance, monitoring for hypogammaglobulinemia and severe infectious complications, especially COVID-19-related complications, are essential to avoid NRM.

Keyword : Follicular lymphoma, Prognosis, Maintenance, COVID-19, Hypogammaglobulinemia

PP05-9

A case report: primary pulmonary malt lymphoma in Ho Chi Minh City

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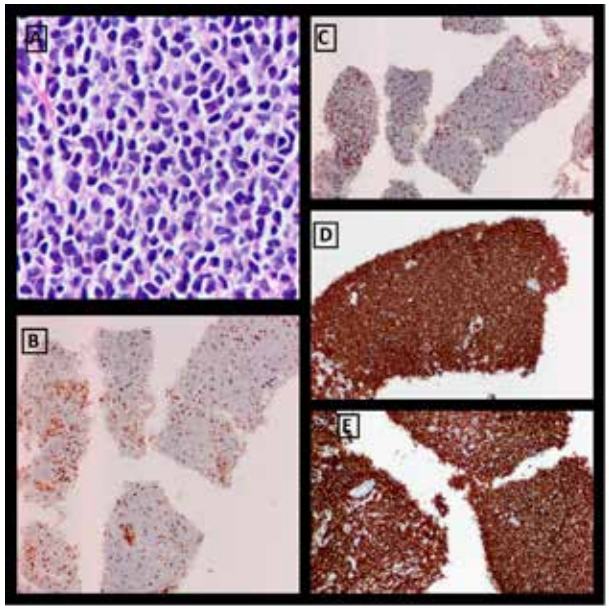
Background : Non-Hodgkin Lymphoma (NHL) is a lymphoid malignancy, representing eighty-five percent of all lymphomas. The most recent 2016 revision of the World Health Organization classification of lymphoid neoplasm estimates that there are at least 86 types of NHL. Bronchial-associated lymphoid tissue (BALT) lymphoma is an indolent marginal zone lymphoma and easily misdiagnosed with other lung diseases due to non-specific symptoms. BALT lymphoma is a rare clinical entity with only a few published reports in the world. We report a case of BALT lymphoma, which is diagnosed and treated for the first time at Blood Transfusion and Hematology Hospital in Ho Chi Minh City.

Method : We reported the case of a 57-year-old woman with no previous medical history, who was admitted to the hospital with complaints of fever, cough, and back pain. She has been diagnosed with pneumonia and treated with intravenous antibiotics but no improvement. She was re-examined in 7A hospital. Bacteriological examination of sputum was negative. This time, she was diagnosed with interstitial pneumonia with an autoimmune disorder and treated with oral corticosteroids consecutively for six months but there was not any improvement. Physical examination was unremarkable. The results of blood analysis were normal: hemoglobin (Hb) 12,3 g/dL, MCV: 87,6 fl, MCH: 31,3 pg, platelet 218 x 103 /µL, white blood cell 6,27 x 103 /µL. Chest radiographs demonstrated the presence of infiltrates with consolidation in the hilum lung, right and left cardiac margins, monitoring for pneumonia. Computed axial tomography showed bilateral consolidation of the lung, suggesting pneumonia or lung tumor. She had a bronchoscopy and was diagnosed with non-Hodgkin Lymphoma. Positron emission tomography/computed tomography (PET/CT) revealed that the consolidation lesions in the bilateral lung increased metabolic activity suspected by lymphoma. After positron emission tomography (PET) scan-guided percutaneous lung biopsy, histologic examination disclosed mainly small cells, polymorphic nuclei, concentrated chromatin, dark staining, and the presence of pseudostratified epithelium of bronchioles. Immunocytochemically, the neoplastic cells reacted positively for CD 20, BCL2, and CD25 antigens. The Ki-67 positivity was 10-20%. They reacted negatively for CD3, CD10, CD5, Cyclin D1,CD23 and CD103 antigens. Fluorescence in situ hybridization (FISH) analysis revealed t(11;14)(q13;q32) in 80% of cells. The histologic diagnosis was consistent with low-grade marginal zone B-cell lymphoma originating in BALT. The bone marrow biopsy showed that cell density was approximately 30-40% cellular. The ratio of myeloid to erythroid cells was about 2:1. No solid tissue malignant cells infiltrated the marrow. She has normal female karyotype: 46,XX The patient has translocation t(11,14)(q13;q32) which is a specific genetic marker of the mantle cell lymphomas (MCL). However, in this case, based on the clinical and histopathological progress, she was diagnosed with Malt lymphoma. Her diagnosis was consulted with not only the specialist board of the Hospital of Blood Transfusion and Hematology but also a lymphoma specialist doctor from the Ho Chi Minh City Oncology Hospital to agree to diagnose Malt lymphoma.

Results : She was diagnosed with Bronchial-associated lymphoid tissue (BALT) lymphoma, stage IIE low-risk group according to MALT IPI, with CD20 antigen positively. She was treated with the anti-CD 20 antibody rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP regimens). After 6 cycles, she had a partial response. Maintenance rituximab was given once every 2 months for a couple of years. The patient completed maintenance therapy in August 2021. Current clinical status is stable. The patient is followed and re-visited every six months.

Conclusion : Bronchial-associated lymphoid tissue (BALT) lymphoma is a rare disease. Our country is located in the epidemic of tuberculosis, the problem of environmental pollution, the high rate of smoking so BALT is easily misdiagnosed with other lung diseases due to non-specific symptoms. Diagnosis is mainly based on biopsy examination. The patients who cannot be treated by radiotherapy or surgery at the time of diagnosis, chemotherapy with RCHOP regimens is the first-line protocol.

Keyword : Pulmonary Malt Lymphoma, BALT lymphoma, RCHOP



PP05-10

Prognostic significances of molecular assay in primary central nervous system lymphoma

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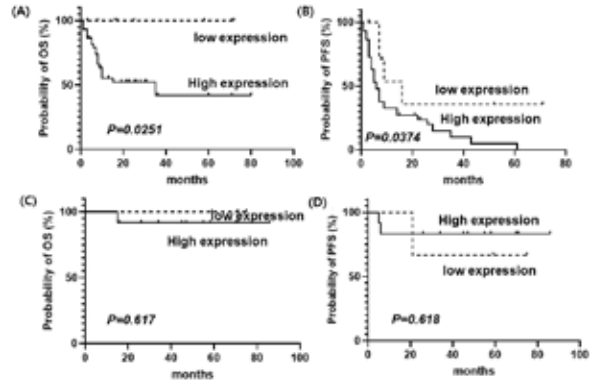
Background : Although the biological characteristics of nodal diffuse large B-cell lymphoma have been elucidated, the biological characteristics of primary central nervous system lymphoma (PCNSL) are yet to be clarified. This study aimed to evaluate the prognostic difference according to the biological characteristics of PCNSL on molecular assays.

Method : Formalin-fixed paraffin-embedded biopsy samples from 67 patients were analyzed. Cell of origin (COO) classification was compared between that on immunohistochemistry and digital gene expression assay using Lymph2Cx assay with additional custom genes related to activated B-cell-like genes and previously identified 20 genes. Survival was also evaluated according to double-hit lymphoma (DHL) or double-expressor lymphoma (DEL).

Results : Lymph2Cx assay results showed activated B-cell subtype was 47 (70.1%) patients and germinal center B-cell subtype was 10 (14.9%) patients. There was no survival difference according to the COO classification between the two methods and between patients classified as having DEL (n=12, 17.9%) and DHL (n=3, 4.5%). Among 52 patients who did not undergo autologous hematopoietic stem cell transplantation (ASCT), high Ikaros expression was correlated with inferior overall survival and progression-free survival (P=0.025 and P=0.037, respectively). Meanwhile, there was no survival difference according to Ikaros expression in patients who underwent upfront ASCT.

Conclusion : In the COO classification by Lymph2Cx assay, most were ABC subtype, COO classification, DEL, and DHL could not discriminate the survival. A high pretreatment RNA expression of Ikaros is related to inferior survival in PCNSL patients who did not receive ASCT but not in patients who received upfront ASCT.

Keyword : Cns lymphoma, Ikaros, Cell of origin, Double hit lymphoma, Double expressor lymphoma



PP05-11

PET-adapted approach in advanced Hodgkin lymphoma: A single centre experience

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Background : The utilization of fluorodeoxyglucose (FDG)-positron emission tomography (PET)-adapted therapy for advanced classical Hodgkin lymphoma (cHL) have been proven benefit with alteration of treatment according to interim response, in reducing toxicity, while maintaining efficacy. A retrospective review was performed in

our centre to assess the clinical outcome of PET-adapted approach, compared to historical cohort without PET-adapted approach.

Method : Patients with the diagnosis of advanced cHL were included in this retrospective analysis. PET-adapted therapy was practised in our centre since 2018. Demographic data, clinical characteristic, treatment regimens, and outcome were collected from the medical record and analysed.

Results : One-hundred and forty-six patients with advanced stage cHL were recruited with the median age of 26 (range 13 – 70) years old. Majority of the patients were male (58.2%), and 77.4% of them were Malay. Nodular sclerosing was the most common histology subtype (67.1%), followed by mixed cellularity (8.9%), and others (24%). Ninety-seven (66.4%) of the patients had International Prognostic Score (IPS) of 3 and below. With the median follow-up of 30.5 (range 1 – 110) months, the overall survival (OS) and progression free survival (PFS) at median follow-up were 90.6% and 68.4%, respectively for the entire cohort. A total of 89 patients were subjected to PET-adapted strategy, of which, 56 patients received escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone), and 32 patients received ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) as their upfront therapy before interim PET assessment. Fifty-two (58.4%) patients achieved interim PET negative and 33 (37.1%) of them had interim PET positive. Following completion of treatment, 61 of them achieved CR, 12 patients had PR, and 13 patients had progressive disease (PD). Two patients died before disease assessment. The 3-year OS and PFS in PET-adapted approach were 91.1% and 73.5%, respectively. Comparing the two treatment arms, 3-year OS for patients receiving upfront escalated BEACOPP and ABVD were 94.3% and 85.0%, respectively (p=0.241). Conversely, the 3-year PFS were 82.6% and 57.9%, respectively (p=0.005). A trend towards better OS and PFS were observed comparing to historical cohort without PET-adapted approach (p=0.776; p=0.137). In patients with interim PET negative, their 3-year OS and PFS were 100% and 95.2%, respectively. Conversely, for patients with interim PET positive, their 3-year OS and PFS were 87.6% and 44.5%, respectively. Among prognostic factors analysed, International Prognostic Score (IPS) of ≥ 4 and extranodal disease had significant impact on OS (p=0.003; p=0.028) and PFS (p=0.002; p=0.005). However, using multivariate cox proportional hazard model, the impact of these factors were not significant for both PFS and OS.

Conclusion : Utilization of PET-adapted therapy has shown a trend towards better outcome in our study with escalated BEACOPP as upfront therapy significantly improved the PFS for our cohort of patients. Longer study duration will be necessary in identifying the long-term complications such as secondary malignancy in this approach.

Keyword : PET-adapted, Classical Hodgkin Lymphoma , Advanced Disease

PP05-13

Subcutaneous epcoritamab + rituximab and lenalidomide (R2) vs R2 for relapsed/refractory follicular lymphoma: EPCORE FL-1

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Background : Background: Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL). There are several approved treatment options available for patients with relapsed or refractory (R/R) FL, including R2. However, advanced FL remains incurable and new treatment options are needed. Epcoritamab is a subcutaneously administered, bispecific antibody that binds CD3 on T lymphocytes and CD20 on B cells, inducing potent and selective T-cell–mediated killing of malignant CD20+ B cells (van der Horst et al, Blood Cancer J 2021). In the phase 1/2 EPCORE NHL-1 trial (NCT03625037), epcoritamab monotherapy showed manageable safety and promising single-agent antitumor activity in heavily pretreated patients with B-cell NHL (Hutchings et al, Lancet 2021). In the ongoing EPCORE NHL-2 trial (NCT04663347) in 62 patients with R/R FL, epcoritamab + R2 had an overall response rate of 95% and a complete metabolic response rate of 73% among 41 efficacy-evaluable patients. Most cytokine release syndrome (CRS) events were low grade (grade 1, 27%; grade 2, 10%; no grade 3–4) and occurred after the first full dose; all CRS events resolved with standard management (Falchi et al, ASH 2022, abstract 609). These encouraging data support further evaluation of epcoritamab + R2 in the treatment of patients with R/R FL.

Method : Study Design and Methods: EPCORE FL-1 (NCT05409066) is a global, randomized, open-label, multicenter phase 3 trial designed to evaluate the efficacy and safety of epcoritamab in combination with R2 vs R2 alone in adults with histologically confirmed grades 1–3a R/R FL after ≥1 prior line of systemic antilymphoma therapy, including an anti-CD20 monoclonal antibody (not in-

cluding prior radiotherapy). Key eligibility criteria include ECOG performance status 0–2, fluorodeoxyglucose PET–avid disease, and ≥1 measurable disease site. Lenalidomide-refractory FL is excluded. Patients will be randomized in a 1:1:1 ratio to receive epcoritamab + R2, 2 alternative full doses of epcoritamab + R2, or R2 alone. Epcoritamab will be administered subcutaneously using a step-up dosing regimen followed by epcoritamab full dose in cycle 1 (28 days/cycle). Full doses of epcoritamab will be administered weekly in cycle 2 and monthly in cycle 3+ for up to 12 cycles. Disease progression is assessed per 2014 Lugano criteria. The primary endpoint is progression-free survival by blinded independent review committee. Secondary efficacy endpoints include response rates per Lugano criteria, overall survival, and minimal residual disease negativity. Additional efficacy endpoints include duration of response, duration of complete response, event-free survival, time to next antilymphoma treatment, and patient-reported outcomes. Safety endpoints include incidence and severity of treatment-emergent adverse events. The study is open for enrollment worldwide. Epcoritamab is jointly developed by Genmab A/S and AbbVie Inc.; AbbVie and Genmab are sponsoring this study.

Results : Not applicable - trial in progress submission.

Conclusion : Not applicable - trial in progress submission.

Keyword : Non-Hodgkins Lymphoma, Follicular Lymphoma, Relapsed Disease, Bispecific antibody, Epcoritamab, Phase 3

PP05-14

Odronextamab in patients with relapsed/refractory (R/R) follicular lymphoma (FL) grade 1–3a: phase 2 Study (ELM-2) prespecified analysis results

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Background : Odronextamab is a hinge-stabilized, human IgG4-based CD20×CD3 bispecific antibody that binds CD20 on B cells and CD3 on T cells, triggering T-cell-mediated cytotoxicity of malignant B cells. In ELM-1 (Ph1, NCT02290951), odronextamab demonstrated encouraging activity in pts with FL Grade 1–3a receiving ≥2 prior lines of therapy (Bannerji R, et al. Lancet Haematol. 2022). The RP2D dose in R/R FL pts was determined as 80 mg weekly. Here, we present for the first time, results from a prespecified analysis of the FL Grade 1–3a cohort from the ELM-2 study (Ph2, NCT03888105), which incorporated an optimized step-up regimen designed to maintain efficacy while minimizing acute toxicity including cytokine release syndrome (CRS).

Method : ELM-2 is a global, multicenter study enrolling pts at 91 sites in 13 countries. Adult pts with FL Grade 1–3a who had relapsed or were refractory to ≥2 prior lines of therapy including an anti-CD20 antibody and alkylator were enrolled. IV odronextamab was administered in 21-day cycles with steroid prophylaxis and weekly step-up dosing during Cycle (C) 1 to mitigate risk of acute toxicity. The initial step-up regimen consisted of 1 mg split over C1 Day (D) 1 and C1D2, and 20 mg split over C1D8 and C1D9, followed by the 80 mg full dose on C1D15 (1/20 regimen). The 1/20 regimen was revised during the study to further mitigate CRS risk. The modified regimen consisted of 0.7 mg split over C1D1 (0.2 mg) and C1D2 (0.5 mg), 4 mg split over C1D8 and C1D9, and 20 mg split over C1D15

and C1D16, followed by the 80 mg full dose on C2D1 (0.7/4/20 regimen). 80 mg weekly continued until the end of C4. After C4, maintenance treatment with 160 mg odronextamab occurred every 2 wks until disease progression or unacceptable toxicity. The primary endpoint was ORR assessed by independent central review (ICR) according to Lugano 2014 criteria. CRS was assessed using 2019 ASTCT criteria.

Results : As of April 20, 2022, 96 pts were evaluable for safety; 85 for efficacy. Median age 59 y (range 22–84), 52% male, 58% FLIPI 3–5, 15.6% had bulky disease, and median prior lines of therapy were 3 (range 2–13). 74% were refractory to their last therapy, 79% refractory to prior anti-CD20 therapy, and 48% had progression of disease within 24 mos. Median duration of study follow-up was 17.3 mos. ORR and CR rate by ICR were 81% and 75% respectively. Responses were durable with both a median duration of response and a median duration of CR of 18.2 mos. Median PFS was 20.2 mos (95% CI 14.8–not estimable [NE]) and median OS was not reached (95% CI 23.0 mos–NE). TEAEs occurred in 95 (99%) pts, considered treatment related in 86 (90%). In the overall safety evaluable population, the most common TEAEs (>30% all grades) were CRS (51%), pyrexia (32%), anemia (31%), and infusion-related reaction (31%). The 0.7/4/20 step-up regimen reduced the incidence of grade 2 and grade 3 CRS. All CRS events resolved. No ICANS was reported with the 0.7/4/20 regimen. Treatment-related Grade 5 AEs were reported for 2 pts; treatment-related AEs led to discontinuation in 6 pts.

Conclusion : Consistent with the ELM-1 Ph1 study, the ELM-2 Ph2 study of odronextamab demonstrated compelling efficacy and a manageable safety profile in pts with FL Grade 1–3a receiving ≥2 prior lines of therapy, with 75% of pts achieving CR. Responses appear to be deep and durable; a clinically important finding in the context of heavily pretreated FL. The 0.7/4/20 step-up regimen compares favorably to other CD20×CD3 bispecifics. Updated safety and efficacy data will be presented.

Keyword : FL, Bispecific antibody, Phase 2, B-NHL, Clinical trial

PP05-15

Patterns of nodal and extranodal involvement in diffuse large B-cell lymphoma

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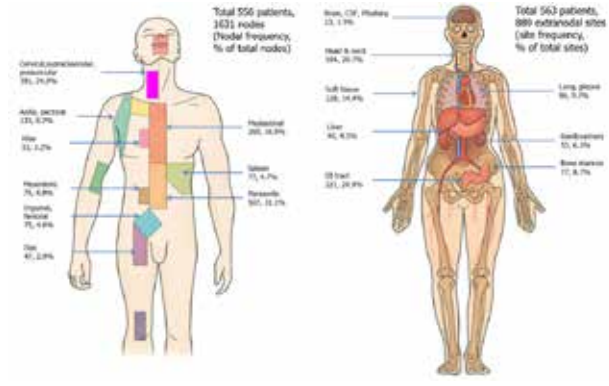
Background : Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of Non-Hodgkin lymphoma but there are few available data on its patterns of nodal and extranodal involvement.

Method : Between 2005 and 2020, pathologically proven 716 DLBCL patients were enrolled in this study. We retrospectively reviewed and described both nodal and extranodal distributions of lymphoma involvement.

Results : 389 males (54.3%) and 327 females (45.7%) were diagnosed with DLBCL at a median age of 56 years (range, 15 - 92). 57 patients (8.0%) had ECOG PS more than 1 and 404 (56.4%) were classified as Ann Arbor stage III or IV. A total of 556 patients had 1631 lymph node involvements: para-aortic (n=507, 31.1%), cervical/supraclavicular/occipital/preauricular (n=391, 24.0%), mediastinal (n=269, 16.5%), axilla/pectoral (n=133, 8.2%), mesenteric (n=79, 4.8%), spleen (n=77, 4.7%), inguinal/femoral (n=75, 4.6%), pulmonary hilar (n=53, 3.2%), and iliac (n=47, 2.9%). No infraclavicular or popliteal involvement was identified. 191 had extranodal involvement of more than 1 (26.7%) and 563 patients had 889 extranodal sites: gastrointestinal (n=221, 24.9%), head and neck (n=184, 20.7%), soft tissue (n=128, 14.4%), bone marrow (n=77, 8.7%), lung and pleura (n=86, 9.7%), genitourinary organs (n=55, 6.2%), liver (n=40, 4.5%), breast (n=13, 1.5%), CNS (n=13, 1.5%) and other abdominal organs (i.e. adrenal, omentum, pancreas, gallbladder, biliary, and peritoneum, n=70, 7.9%).

Conclusion : We found that the most common site of nodal involvement was abdominal followed by cervical and mediastinal LNs, but no infraclavicular or popliteal LNs were observed in our study. We also discovered that the most common extranodal sites were gastrointestinal followed by head & neck, and soft tissue organs. Our findings necessitate further multicenter research to refine our understanding of DLBCL.

Keyword : Diffuse large B-cell lymphoma, Nodal, Extranodal



PP05-16

MYD88 strongly associated with extranodal involvement in diffuse large B-cell lymphoma

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Background : The addition of rituximab has vastly improved the prognosis of diffuse large B-cell lymphoma (DLBCL); however, extranodal involvement remains a poor prognostic factor by revised IPI (R-IPI). In this study, we identify primary extranodal disease sites associated with disease progression in DLBCL and evaluate molecular subtypes in the patients with extranodal DLBCL.

Method : We retrospectively collected and analyzed data from 171 patients with CD20-positive DLBCL treated with R-CHOP therapy. All patients were diagnosed with DLBCL and received primary treatment between January 2016 and April 2022. We evaluated 10 extranodal sites of involvement with respect to prognostic impact. Furthermore, based on the profile of genetic alterations occurring in tumor samples from selected DLBCL patients (40%; 65/162 patients), six genomic clusters (MYD88, BCL2, TET2/SGK1, SOCS1/SGK1, TP53/CAN, and NOTCH2) were identified and analyzed.

Results : The median age was 64 years, ranging from 21 to 89 years. The 5-year progression-free survival (PFS) for 171 patients was 71%. R-IPI scores stratified the three risk groups of this cohort. Based on the R-IPI, 81 patients (47%) were classified as a poor risk group (>3 risk factors). The 5-year PFS for the very good, good, and poor groups was 88%, 73%, and 63%, respectively (p=0.05). In the cohort of 171 adult patients with DLBCL,126 patients (72%) showed extranodal involvement, and 45 patients (28%) had nodal involvement. The most common extranodal sites were the gastrointestinal tract (16%), head and neck (7%) and lung (4%). There was a significant difference in a 5-year PFS between the patients with extranodal DLBCL and nodal DLBCL (5-year PFS; 63% vs. 90%; p=0.03). Also, 50 patients (30%) presented multiple sites of extranodal involvement (two or more sites) at diagnosis, and these patients demonstrated a worse 5-year PFS compared to the patients with nodal involvement (5-year PFS; 50% vs. 90%; p=0.01). Next, we evaluated molecular subtypes in the extranodal DLBCLs. Next Generation Sequencing (NGS) was performed in 75 of 171 patients (44%), and six genomic clusters were identified; MYD88, BCL2, TET2/SGK1, SOCS1/SGK1, TP53/CAN, and NOTCH2, according to the genetic features most enriched in each cluster. 22 patients (30%) were categorized as "not elsewhere classified" (NEC). Only MYD88 strongly associated with extranodal involvement in multivariate analysis (p=0.03). Next, we analyzed molecular subtypes in extranodal DLBCLs (n=45). Molecular subtype analysis revealed that the patients in the TET2/SGK1 (n=3), TP53+(MYD88, NOTCH2 or TET2/SGK1) (n=5), TP53+SOCS1/SGK1 (n=3), and NEC (n=9) clusters resulted in especially poor clinical outcome, with 5-year PFS of 0%, 0%, 50%, 60%, respectively (p=0.00, for each group compared with NEC). TP53 mutation was also associated with an extremely poor prognosis in the NOTCH2, TET2/SGK1, and MYD88 subtypes. In contrast, the patients in the SOCS1/SGK1 (n=2), NOTCH2 (n=2), TP53 (n=7), and MYD88 clusters (n=14) fared better than the patients in NEC, with 5-year PFS of 100%, 100%, 100%, 86% (p=0.00, for each group compared with NEC). Collectively, these data demonstrate that TP53 mutation alone does not confer a poor prognosis in extranodal DLBCL; however, the co-existence of TP53 mutation within other DLBCL genomic clusters dramatically decreases clinical outcomes.

Conclusion : Our study suggests that the specific sites of extranodal involvement are important in predicting prognosis in DLBCL. MYD88 was strongly associated with extranodal involvement, and the presence of TP53 mutation in other DLBCL molecular subtypes led to extremely poor clinical outcomes

Keyword : MYD88, DLBCL, Extranodal involvement

PP05-17

A Novel CD19-directed car t cell therapy (AT101) targeting a pristine membrane-proximal epitope under phase I clinical trial

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Background : All the FDA-approved CD19 CAR T cell therapies are based on FMC63 scFv that binds to the membrane-distal region of

CD19 and showed reduced efficacy in B-cell lymphoma compared to B-ALL. In an effort to develop more potent CD19-directed CAR-T cell therapy, we produced a novel anti-CD19 scFv clone (1218) that binds to an exceedingly membrane-proximal epitope and does not compete with FMC63 in its binding. Using humanized 1218 scFv along with 4-1BB costimulatory and CD3zeta domain in a lentiviral backbone, a novel CD19-directed CAR T cell therapy (AT101) was successfully developed.

Method : Epitope binding of h1218 in comparison to FMC63 The FMC63 antibody was immobilized, then recombinant human CD19-extracellular domain proteins were captured. Additional binding of antibodies was analyzed using biolayer interferometry (BLI). ELISA binding activity of h1218 on chimeric CD19 and mutated CD19 Chimeric human CD19 were generated by using human or cynomolgous three CD19 domains: N-terminal IgG-like domain, bridge domain and C-terminal IgG-like domain of the extracellular region on 293 cells. The h1218 antibody binding was blocked when the membrane-proximal domain was converted to cynomolgous. 13 mutated CD19 were expressed on 293 cells and antibody binding was tested by FACS. In vitro anti-tumor efficacy against different CD19-positive hematological cancer cell lines. The h1218, but not FMC63 CAR19 or Non-transduced (NT) cells, were able to target and kill CD19-positive hematological cancer cell lines at 72 hours. In vivo anti-tumor efficacy in Raji, Nalm6 xenograft models Firefly luciferase (ffLuc)+ Raji or Nalm6-ffLuc cells (5 x 10^5 cells/mouse) were injected in NSG mice on D-7. 1.5 x 10^6 CART cells/mouse were injected intravenously at D0. Tumor burden was monitored using the IVIS100 instrument 5 minutes after i.p. injection of 150 mg/kg of luciferin. Non-transduced T (NT) cells were used as controls. Clinical trial This open-label, multi-center, first-in-human Phase 1 study will assess AT101 in patients with relapsed or refractory B cell Non-Hodgkin's Lymphoma. In the phase 1, patients (n=3 per dose level; up to n=18 in total) are treated with AT101 in 3 dose-escalation cohorts based on a standard 3 + 3 design. We will determine the maximum tolerant dose (MTD) based on the safety and tolerability of AT101 and the recommended dose 2 dose (RP2D) in phase 2 trials. Clinical trial registry number: NCT05338931

Results : We selected an scFv clone (1218) that was not competing with FMC63 for CD19 binding in competition enzyme immunoassay and real-time interaction analysis. Subsequent mutagenesis assay by replacing several residues with monkey residues showed that, as compared to FMC63, the epitope of the 1218 scFv is localized in a membrane-proximal location at three-dimensional modeling. AT101 showed a potent in vitro cytotoxicity against different CD19-positive hematological cancer cell lines. AT101 also showed a potent anti-tumor response in both Raji (CD19+ B-cell lymphoma) and Nalm-6 (B-cell leukemia) xenograft models. Currently, AT101 is under a phase 1 clinical trial for relapsed and refractory B-cell Non-Hodgkin's lymphoma to determine the maximum tolerant dose (MTD) and the recommended phase 2 dose (RP2D). Interim results of a Phase 1 trial will be presented in conference.

Conclusion : In this study, we developed a novel CD19-targeted antibody (1218) and described its antitumor activity in in vitro and xenograft models of B-cell lymphoma and leukemias. The epitope of the 1218 scFv is distinct from the standard FMC63 antibody and that it is localized in a membrane-proximal domain of CD19. h1218-CART19, derived from a humanized version of 1218, recognized leukemic cells expressing CAR19 that are resistant to FMC63-CART19 killing. The anti-tumor efficacy of h1218-CART19 was confirmed in in vivo lymphoma and leukemia xenograft models. These results indicate that h1218-CART19 treatment is a novel potent therapeutic strategy for the treatment of patients with refractory/relapsed B-cell malignancy and relapsed patients with a B-cell expressing FMC63-based CART19. Currently, h1218-CART19 (AT101) is in a phase 1 clinical trial in Korea for relapsed and refractory B-cell Non-Hodgkin's lymphoma patients.

Keyword : CD19, CAR T cells, Lymphoma

PP05-18

Impact of time-variant variable as cycle threshold with COVID19 infection in patients treated with rituximab and bendamustine for mature B cell lymphomas

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Background : Since the outbreak of COVID-19 infection, poor survival outcomes have been consistently published in patients with lymphoma. In particular, several cases of sustained breakthrough or prolonged COVID-19 in patients who received Bendamustine rituximab chemo (BR) have been reported. In a pandemic situation,

COVID-19 infection delaying chemotherapy and adversely affects maintenance therapy. This study aimed to evaluate the impact of COVID-19 cycle threshold (Ct) values on lymphoma patients treated with BR in South Korea.

Method : A total of 80 patients who underwent BR chemotherapy between December 2020 and November 2022 at Yeoido St. Mary's Hospital in South Korea were included in this study. Cycle threshold (Ct) values were calculated before each cycle of the chemotherapy and evaluated when symptoms occurred. We analyzed the Ct with COVID-19 infection by time-variant variable and using joint modeling of time-to-event data with time-dependent predictors.

Results : Among the 80 patients, 56 were diagnosed with follicular lymphoma, 12 mantle cell lymphoma, eight marginal zone lymphoma(MZL), and four lymphoplasmacytic lymphomas. Thirty patients have been infected with COVID-19 after BR chemotherapy. Among them, 16 patients developed pneumonia, and one died. In the total cohort, 24 patients developed pneumonia, and COVID-19 infection correlated with computed tomographic-proven pneumonia (p-value <0.001). The best cut-off in Ct ratio to identify pneumonia was 35, which showed 78.8% sensitivity, 100% specificity, and 89% AUC under the curve. Univariate analysis showed that the subtype of MZL and time-dependent Ct ratio affected developing pneumonia. After applying joint modeling, multivariate analysis showed a higher risk of pneumonia with time variate Ct ratio(HR= 1.28, 95%CI= 1.12-1.46, p-value= 0.0003), but not subtype of MZL(HR= 4.75, 95%CI= 0.76-29.72, p-value= 0.096).

Conclusion : We showed that pneumonia occurred more frequently in those who underwent BR chemotherapy with COVID-19 infection. Furthermore, the Ct ratio could be the indicator to predict prolonged pneumonia and support the decision-making in delaying the chemotherapy or stopping the maintenance therapy who underwent BR.

Keyword : COVID-19, Bendamustine-rituximab, B cell lymphoma, Joint Model

PP05-19

Trial in progress: A phase 2 basket trial of nanatinostat in combination with valganciclovir in patients with EBV-Positive (EBV+) relapsed/refractory lymphomas (NAVAL-1)

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Background : Epstein-Barr virus-positive (EBV+) lymphomas are a heterogeneous group of malignancies that harbor latent EBV within the lymphoma cells, and are associated with variable clinical features, treatments, and prognoses. Outcomes in EBV+ lymphoma patients are typically inferior compared to EBV– lymphomas of the same subtype. For instance. EBV+ DLBCL patients have worse outcomes and share similar poor prognostic indicators, irrespective of age (Lu 2015). While for PTCL, EBV+ patients have been reported to have a shorter OS than EBV– patients (13 vs 72 months respectively, p = 0.04) (Haverkos 2017). As there are no approved targeted treatments specific for EBV+ lymphomas and considering the poor prognosis of relapsed/refractory (R/R) disease, treatment of R/R EBV+ lymphoma is therefore an unmet medical need. The all-oral combination of nanatinostat (Nstat), a potent Class-I HDACi, and valganciclovir (VGCV), a pro-drug of ganciclovir (GCV), is a novel mechanism to kill EBV+ tumor cells through inducing the expression of the lytic BGLF4 protein kinase to activate the nucleoside analog GCV via phosphorylation, resulting in termination of DNA replication and apoptosis. The combination of Nstat plus VGCV was generally well-tolerated and showed promising preliminary activity in a Phase 1b/2 study of patients with R/R EBV+ lymphoma (n=55) (NCT03397706), with an ORR of 40% (17/43) (CR 19%) in efficacy-evaluable patients. Patients with T/NK-NHL (n=15) had an ORR/CR of 60%/27%; in EBV+ DLBCL,NOS (n=6), the ORR/CR was 67%/33% (both CRs were in patients refractory to first-line R-CHOP). In addition, the degree of EBER-ISH positivity (%) was not related to the clinical response, with the majority of patients having a baseline EBER-ISH below 50% (Haverkos 2021).

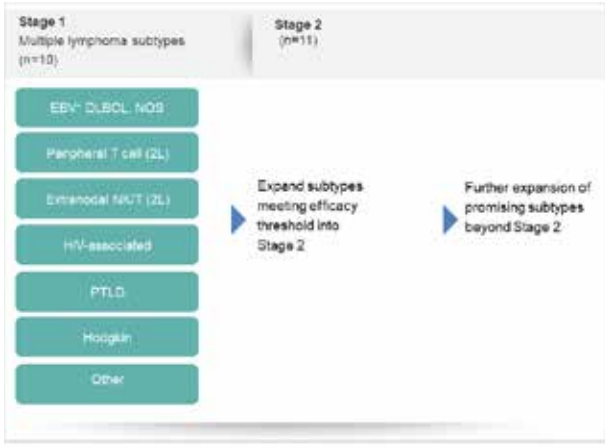
Method : This is an open-label, multicenter, multinational single-arm, Phase 2 basket design study, utilizing Simon's 2-stage design options for discontinuing enrollment into each cohort where treatment appears to be futile (Simon 1989). Six subtypes of EBV+ R/R lymphomas are represented: EBV+ DLBCL, NOS, ENKTL, PTCL (including PTCL-NOS and AITL), Hodgkin, PTLD and HIV-associated lymphoma, with a 7th basket for other EBV+ lymphomas. Eligible patients will have EBV+ R/R lymphoma following 1 or more prior systemic therapies (for PTCL and ENKTCL cohorts) or ≥2 prior sys-

temic therapies for other cohorts, with no available curative therapies, measurable disease per Lugano 2007, and adequate bone marrow, liver, and renal function. Patients will receive Nstat 20 mg orally once daily, days 1-4 per week with VGCV 900 mg orally once daily to evaluate overall response rate, overall survival, progression free survival, time to progression, safety and potential pharmacokinetic parameters. Enrollment began in May 2021. Clinical trial information: NCT05011058.

Results : NA

Conclusion : NA

Keyword : EBV lymphoma, HIV-associated lymphoma, Epstein-Barr Virus (EBV), EBV positive T cell lymphoma, extranodal NK-T Cell Lymphoma (ENKTCL), peripheral T cell lymphoma (PTCL)



PP05-20

The outcome of hematopoietic stem cell transplantation for pediatric patients with lymphoma: A single-center study

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Background : Pediatric patients with lymphoma who do not achieve remission or who experience relapse, are difficult to cure with conventional cytotoxic treatment. Autologous or allogenic hematopoietic stem cell transplantation (HSCT) with a conditioning regimen, has been a salvage treatment for refractory and relapsed lymphoma patients. Although immunotherapy agents have expanded treatment options, HSCT is still used as a treatment to improve survival outcomes.

Method : From January 2013 through December 2022, we registered patients who were diagnosed with Hodgkin disease or non-Hodgkin lymphoma and treated with conditioning treatment and autologous or allogenic HSCT. Outcomes and complications were analyzed retrospectively.

Results : 26 Patients were enrolled. Burkitt lymphoma (26.9%) was the most common, followed by anaplastic large cell lymphoma (23.1%) and peripheral T-cell lymphoma (15.4%). 18 (69.2%) patients underwent allogenic HSCT. All patients underwent salvage chemotherapy (20 patients with cytotoxic agents, 6 patients with immunotherapy and cytotoxic agents) for complete remission, however, 19 (73.1%) patients achieved remission state before HSCT. 3-year event-free survival and overall survival were 79.1% (95% CI 64.3-97.4%) and 80.6% (95% CI 66.7-97.4%), respectively. Remission status before HSCT and refractory cases were prognostic factors for event-free survival and overall survival, respectively. There was no treatment-related mortality.

Conclusion : Autologous or allogenic HSCT for salvage treatment with relapsed, or refractory pediatric patients with lymphoma, is promising favorable EFS and OS. Remission before HSCT is one of the most important prognostic markers.

Keyword : Lymphoma, Pediatric, Hematopoietic stem cell transplantation

PP05-21

A multi-center and non-interventional registry of brentuximab vedotin in patients with relapsed or refractory CD30-positive lymphoma: CISL1803 BRAVO study

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Background : Brentuximab vedotin (BV), a potent antibody-drug conjugate, targets the CD30 antigen. Owing to the remarkable efficacy shown in CD30-positive lymphomas, such as Hodgkin's lymphoma and systemic anaplastic large-cell lymphoma, BV was granted accelerated approval in 2011 by the US Food and Drug Administration. In Korea, BV has been used as a salvage therapy for relapsed or refractory Hodgkin lymphoma, systemic anaplastic large cell lymphoma (ALCL) and cutaneous T-cell lymphomas including mycosis fungoides and cutaneous ALCL. This study analyzed the real-world data of patients receiving BV as a salvage therapy.

Method : This is a multi-center and non-interventional registry study for Brentuximab Vedotin in patients with relapsed or refractory CD30-positive lymphoma (CISL1803 BRAVO study). Researchers from twelve hospitals in Korea participated in the study, and the variables were collected for the analysis of efficacy and safety of BV including age, sex, ECOG performance status. type of disorder, stage, and so on. The outcome was determined by the occurrence of relapse or progression, and overall survival.

Results : A total of 85 patients were enrolled into this study. Patients received up to 16 cycles of BV every three weeks, and the median number of BV was not significantly different between Hodgkin and systemic ALCL. Although the number of patients was relatively small, the duration of treatments was shorter in patients with mycosis fungoides due to its frequent occurrence of disease progression during treatment. The safety profiles were manageable through all subtypes of disorders, and neuropatic pain was the most common in consistent with the results of previous clinical trials.

Conclusion : The treatment outcome of patients with relapsed or refractory CD30-positive lymphoma was improved since BV was introduced, and the safety profile was manageable.

Keyword : Lymphoma, Brentuximab Vedotin, CD30, Outcome

PP05-22

MicroRNA 340-5p-mediated PD-L1 expression in the etoposide-resistant NK/T-cell lymphoma

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Background : Immune checkpoint inhibitors, PD-1/PD-L1 showed promising therapeutic outcomes in various cancers. Extranodal natural killer (NK)/T-cell lymphoma (ENKTL) is an aggressive malignancy, and some of ENKTL patients with relapsed/refractory do not respond to the immune checkpoint inhibitors. The aim of study is to find miRNAs that regulate PD-L1 to overcome resistance to immune checkpoint inhibitors and to investigate the biological mechanism of miRNAs in ENKTL cells.

Method : To identify of miRNAs that regulate PD-L1 expression, small RNA sequencing and miRNA target prediction were performed in etoposide - resistant SNK6 cell line. To determine whether PD-L1 mRNA expression is regulated by the identified miRNAs, we performed RT-qPCR, Western blot, argonaute 2 immunoprecipitation (Ago2 IP), luciferase reporter assay and immunohistochemistry (IHC).

Results : By analyzing miRNA profiles, the 25 up-regulated and 33 down-regulated miRNAs were found in etoposide resistant cell. Among the significantly down regulated mRNAs, miRNA-340-5p was predicted as possible targets of PD-L1. RT-qPCR and western blot analysis revealed that miRNA-340-5p expression was deceased in etoposide- resistant cell line than control cells, whereas PD-L1 expression was dramatically increased in etoposide- resistant cell. Ago2 IP and luciferase assay showed that miRNA-340-5p directly bound to the 3′ UTR of PD-L1 mRNA. Overexpression of miRNA-340-5p decreased PD-L1 expression and inhibition of miRNA-340-5p increased PD-L1 expression. In addition, ENKTL patients with higher PD-L1 expression had lower miR-340-5p expression and had shorter survival time. These data indicated that miRNA-340-5p was inversely correlated with PD-L1 expression in ENKTL patients.

Conclusion : Our results demonstrated that miR-340-5p could target PD-L1 mRNA and modulate PD-L1 expression. These findings suggest that a combination of miR-340-5p regulation and PD1/ PD-L1 blockade can overcome acquired resistance to immune check-

point inhibitors in ENKTL.

Keyword : Extranodal natural killer (NK)/T-cell lymphoma, Immune checkpoint inhibitors, MicroRNA

PP05-23

Role of MiR-155-5p in ibrutinib-resistant diffuse large B cell lymphoma cells

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Background : Diffuse large B cell lymphoma (DLBCL) is the most common aggressive B-cell lymphoma, and ibrutinib, an orally administered BTK inhibitor targeting B-cell has been tried as a treatment for DLBCL. However, ibrutinib-resistance is a problem because patients become resistant to ibrutinib during continuous administration of ibrutinib.

Method : To explore the underlying mechanism for ibrutinib-resistance, we analyzed microRNAs (miRNAs) and mRNAs derived from ibrutinib-resistant DLBCL cell lines because miRNAs might contribute to ibrutinib-resistance via mRNAs regulation. We established ibrutinib-resistant DLBCL cell lines continuously exposed to 1uM, 2uM ibrutinib. Total RNA isolated from ibrutinib-resistant cell lines and analyzed by nanostring.

Results : The ibrutinib-resistant DLBCL-derived microRNA profiles showed 118 up-regulated and 36 down-regulated miRNAs compared to ibrutinib-sensitive DLBCL. Among them, miR-155-5p was an increased in ibrutinib-resistant DLBCL, and intracellular levels was also higher than that of ibrutinib-sensitive DLBCL. The analysis of cellular signaling also showed significant activation of PI3K-AKT, P70S6K, MAPK, NF-κB signaling pathways in ibrutinib-resistant DLBCL cell lines. In addition, miR-155-5p mimic was transfected to OCI-Ly1 to establish miR-155-5p over-expressed cells. The PI3K-AKT, P70S6K, MAPK, NF-κB signaling pathways also increased in miR-155-5p over-expressed cells, and the number of colonies in miR-155-5p over-expressed cells increased compare to control cell in colony formation assay. We found target mRNAs of miR-155-5p, and confirmed that the mRNAs were the actual target of miR-155-5p through Ago2 IP and Luciferase. Thus, the miR-155-5p may be related to ibrutinib resistance.

Conclusion : miR-155-5p might have role in the acquaintance of ibrutinib-resistance in patients with DLBCL.

Keyword : Diffuse Large B-Cell, Ibrutinib, microRNA

PP05-24

Detection of tumor-derived mutations using liquid biopsy of plasma and cerebrospinal fluid in primary central nervous system lymphoma

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Background : Primary central nervous system lymphoma (PCNSL) is a rare disease, accounting for 1-2% of all non-Hodgkin lymphoma and 3% of all brain tumors. Histologically more than 95% of PCNSL is a diffuse large B-cell lymphoma (DLBCL), and PCNSL usually shows a poor prognosis than nodal DLBCL because there is no targeted treatment and frequent recurrences. Because PCNSL occurs in the brain, histological diagnosis and molecular genotyping are difficult because of the need for invasive brain biopsies. Liquid biopsy is drawing attention as an alternative to overcoming the limitations of conventional tissue-based molecular profiling. This study aims to assess the clinical utility of liquid biopsy using blood and cerebrospinal fluid (CSF) for molecular profiling of PCNSL.

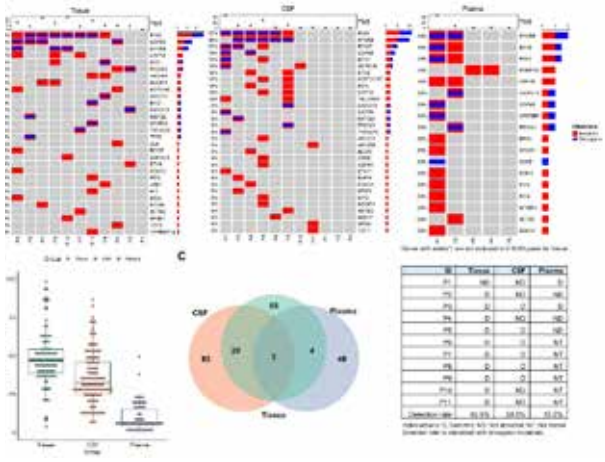
Method : Eleven newly diagnosed PCNSL patients at our institution from June 2022 to September 2022 were enrolled in this study. Tissue biopsy, whole blood, and CSF were collected at PCNSL diagnosis. Genomic DNA extracted from formalin-fixed paraffin-embedded tissue and cell-free DNA extracted from plasma and CSF were used for next-generation sequencing (NGS) analysis. Target enrichment was done with the Illumina TSO-500 panel (Illumina, San Diego, CA, USA) for tissue or custom 112 lymphoma-related gene panel (Dxome, Seongnam, Korea) for plasma and CSF. Paired-end sequencing (2 × 150 bp) was performed using a NextSeq 550Dx Instrument (Illumina).

Results : Potentially oncogenic variants were detected in 10 of 11 tissue samples (90.9%), 6 of 11 CSFs (54.5%), and 2 of 5 plasma sam-

ples (40.0%). Mutations were frequently detected in the following genes in tissue samples: PIM1 (8/11, 72.7%), CD79B (4/11, 36.4%), MYD88 (3/11, 27.3%), LRP1B (3/11, 27.3%), MYC (2/11, 18.2%), PRDM1 (2/11, 18.2%), ARID5B (2/11, 18.2%), NCOR1 (2/11, 18.2%), and NOTCH2 (2/11, 18.2%). PIM1 (6/11, 54.5%), MYD88 (5/11, 45.5%), BTG2 (5/11, 45.5%), CD79B (3/11, 27.3%), BTG1 (2/11, 18.2%), SETD1B (2/11, 18.2%), ETV6 (2/11, 18.2%), HIST1H1E (2/11, 18.2%), IRF4 (2/11, 18.2%), LRP1B (2/11, 18.2%), and TBL1XR1 (2/11, 18.2%) mutations were prevalent in CSF samples. BTG2, HIST1H1E, and TBL1XR1 genes were only included in our custom lymphoma panel. Median variant allele frequencies (VAFs) of somatic variants were 47.4% (range, 3.5-99.6%) for tissue, 32.0% (range, 5.7-86.4%) for CSFs, 6.0% (range, 0.3-49.4%) of plasma samples.

Conclusion : Using liquid biopsy, we identified cancer-associated gene mutations in CSF and plasma from PCNSL patients. Median VAFs of mutations in plasma were lower than those in CSF, suggesting the possibility that the blood-brain barrier might hinder the release of tumor-origin cell-free DNA into blood circulation. Since this study was conducted in a small sample size, further studies are needed for the differences between plasma and CSF samples. Additional research data will be presented at the conference.

Keyword : ctDNA, PCNSL, NGS



PP05-25

Exploratory study on circulating tumor DNA characteristics in various lymphomas

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Background : Circulating tumor DNA (ctDNA) has recently gained increasing attention in multiple cancer types for diagnosis, detection of actionable alterations, assessment of treatment response, and evaluation of minimal residual disease. This study investigated ctDNA features such as ctDNA levels and mutation detection yields for various lymphoma subtypes.

Method : We retrospectively reviewed the results of ctDNA assays from a cohort of 319 unselected consecutive patients diagnosed with Hodgkin or non-Hodgkin lymphomas in our institution from January 2022 to November 2022. Cell-free DNA was extracted from plasma samples obtained at lymphoma diagnosis or progression. Prepared libraries were enriched with a custom capture panel targeting 112 lymphoma-related genes (Dxome, Seongnam, Korea). Pooled libraries were sequenced on a NextSeq 550Dx Instrument (Illumina, San Diego, CA, USA). ctDNA concentration was calculated by multiplying the maximum variant allelic frequency for all detected somatic mutations by the concentration of cell-free DNA (pg/mL of plasma).

Results : Large B-cell lymphomas were the most common subtype of lymphoma (n = 169, 53.0%), followed by follicular lymphoma (n = 50, 15.7%) and marginal zone lymphoma (n = 39, 12.2%). Large B-cell lymphomas were mainly diffuse large B-cell lymphoma (n = 160, 94.7%). More than half of patients with various lymphomas generally had at least one oncogenic mutation (169 out of 319 patients; 57.4%). The mutational profile of large B-cell lymphoma was heterogeneous. Top five mutated genes in large B-cell lymphoma were PIM1 (n = 32, 18.9%), KMT2D (n = 28, 16.6%), TP53 (16.6%), MYD88 (16.0%), and CD79B (13.0%). The median value of maximum variant allele frequency was highest in Burkitt lymphoma (63.8% [interquartile ranges, 57.7-70.0%]), followed by anaplastic large cell lymphoma (36.8%; only one mutation detected) and large B-cell lymphomas (15.0% [5.6-32.4%]). The median number of mutations was greatest in nodal T-follicular helper (TFH) cell lymphoma (n = 5.5 [4.0-6.0]), followed by Burkitt lymphoma (n = 5.0 [4.0-6.0]) and mantle cell lymphoma (n = 4.0 [3.3-5.0]). In large B-cell lymphoma, the median number of mutations was 2.0 [0.0-6.0]. The median level of ctDNA concentration was highest in Burkitt lymphoma (33,290 pg/mL [22,303-44,277 pg/ml]), followed by nodal TFH cell lymphoma (7,896 pg/mL [4,452-10,567 pg/ml]), anaplastic large cell lymphoma lymphomas (2,009 pg/mL [1,005-3,014 pg/mL]) and intestinal T-cell and NK-cell lymphoid proliferations and lymphomas (1,461 pg/mL [0-2,366 pg/mL]). The median level of ctDNA concentration of large B-cell lymphomas and follicular lymphoma were 710 pg/mL [0-4,872

pg/mL] and 70 pg/mL [0-614 pg/mL], respectively. ctDNA concentration was higher in cases with bone marrow involvement than in cases without involvement (median level of 575 pg/mL [3-11,622 pg/ml] vs. 73 pg/mL [0-1,877 pg/ml], p-value = 0.001). Remarkably, the median level of DNA concentration was largely increased in large B-cell lymphoma (62,446 pg/mL [6,174-115,070 pg/mL] vs. 597 pg/mL [0-3,563 pg/mL], p-value < 0.001).

Conclusion : We investigated characteristics of ctDNA in various lymphoma subtypes, and it is expected that ctDNA analysis can be applied in the clinical setting for the detection and management of lymphoma patients due to its sufficient detection rate. Additional research is needed to enable ctDNA concentration for staging and prognostication in lymphoma patients.

Keyword : ctDNA, Lymphoma, Detection rate, ctDNA concentration, NGS

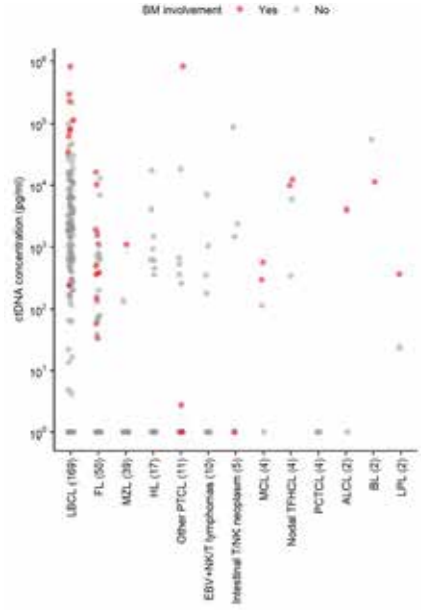

Figure 1. Circulating-tumor DNA concentrations according to lymphoma subtype. The number of patients in each lymphoma subtype is indicated in parentheses. Red dots represent cases with bone marrow involvement.

Abbreviations: ALCL, Anaplastic large cell lymphoma; BL, Burkitt lymphoma; FL, Follicular lymphoma; HL, Hodgkin lymphoma; LBCL, Large B-cell lymphomas; LPL, Lymphoplasmacytic lymphoma; MCL, Mantle cell lymphoma; MZL, Marginal zone lymphoma; PCTCL, Primary cutaneous T-cell lymphomas; PTCL, Peripheral T-cell lymphomas; TFHCL, T-follicular helper cell lymphoma

PP05-26

A comprehensive analysis of relapse pattern in patients with DLBCL after chemoimmunotherapy using national health insurance database of South Korea

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Background : Diffuse large B cell lymphoma (DLBCL) is the most common lymphoma in South Korea and rituximab (R) based chemoimmunotherapy (CIT) has been the standard of treatment since 2004 when rituximab was started to be reimbursed in National Health Insurance. We analyzed the real-world relapse pattern of DLBCL in the era of R-based CIT.

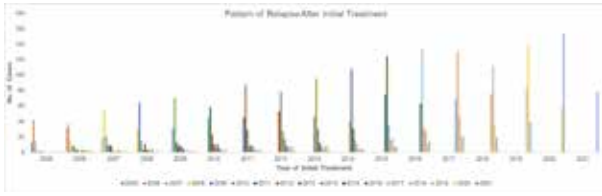
Method : From 2005 to 2021, cases of newly diagnosed DLBCL patients who were completed scheduled Rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone (R-CHOP) as an induction therapy were extracted from National Health Insurance Database of South Korea. Patients with prior history of other malignancies were excluded. Time to next treatment was used as a surrogate marker of relapse free survival and was defined from the first day of R-CHOP to the first day of next salvage treatment for relapsed DLBCL.

Results : From 2005 to 2021, 26,266 patients were diagnosed as de novo DLBCL and the annual trend of DLBCL cases showed gradual increase. Among the newly diagnosed de novo DLBCL, 17,743 (67.6%) patients were completed R-CHOP (comR-CHOP) and the proportion of comR-CHOP group was not changed during every study year. Mean age of comR-CHOP group was 59.8 years. Among the patients who had got R-CHOP, 3,275 patients (18.5%) relapsed after induction therapy. Relapse rate of 10's, 20's, 30's, 40's, 50's, and 60's were 7.6%, 16.9%, 16.0%, 17.7%, 19.3%, and 21.3%, respectively. After age of 70 years, relapse rate stared to decrease 17.9% in 70's and 11.4% in patient group of age over 80 years. Most of the relapses were occurred within 2 years (71.5%) and the proportion of relapsed case decreased after 2 years (Figure 1). Relapse free survival rate (RFSR) at 1 year, 2 year, 5 year, and 10 year were 88.6%, 84.3%, 80.8%, and 78.9%, respectively. Late relapse beyond 5 years was reported in 216 patients (6.6%) and late relapse after 10 years was found in 29 patients (0.88%). A total of 2,176 (66.4%) of patients died after relapse and the median time from relapse to death was 252 days (IQR 125.5- 504.5 days). Overall survival rate at 1 year, 2 year, 5 year, and 10 year were 88.6%, 79.2%, 69.7%, and 59.6%, respectively. Mortality cases from recurrence accounted for the most

of the deaths before the age of 40's, and deaths from other causes were more common after the age of 50's. Patient group with age > 80 years showed relatively low relapse risk (HR 0.7, 95% confidence interval (CI) 0.57-0.85), but higher mortality rate (HR 7.563, 95% CI 2.829 – 10.217) when compared with the patient group with age 40-49 years. Hematopoietic stem cell transplantation (HSCT) was performed in 1,445 relapsed patients (8.1%) and 834 of 1,445 patients (57.7%) survived after HSCT despite recurrence.

Conclusion : Annual incidences of DLBCL increased during study period and the most of the patients were treated with R-CHOP as an induction therapy for newly diagnosed DLBCL. Although treatment outcomes were improved with the R-CHOP, early relapse within 2 years after induction treatment still remained as a huge obstacle for improving DLBCL survival. Still HSCT is meaningful as a salvage treatment option in relapsed disease. Late relapse after 5 years and non-relapse related mortality in the old aged group cannot be ignored future DLBCL management.

Keyword : DLBCL, R-CHOP, Relapse



PP05-27

Whole genome sequencing reveals clinicogenetic characteristics of blastic plamacytoid dendritic cell neoplasms in South Korea: CISL1906 study

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Background : Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic malignancy charaterized by infiltration of clonal plasmacytoid dendritic cells (pDC). The diagnosis of BPDCN is based on the blastic morphology and demonstration of CD4 and CD56 expression, together with markers more restricted to pDC, and negativity for lymphoid, NK and myeloid lineage-markers. The clinical presentation is variable from indolent cutaneous manifestation to systemic involvement, but the coutse of BPDCN is highly aggressive with a median survival of 12-14 months. The true incidence and prevalence of BPDCN, as well as its genetic characteristics, is not precisely known, which is usually seen in most rare type of malignancies. Therefore, this study aimed to reveal the clinico-genetic characteristics of BPDCN in South Korea.

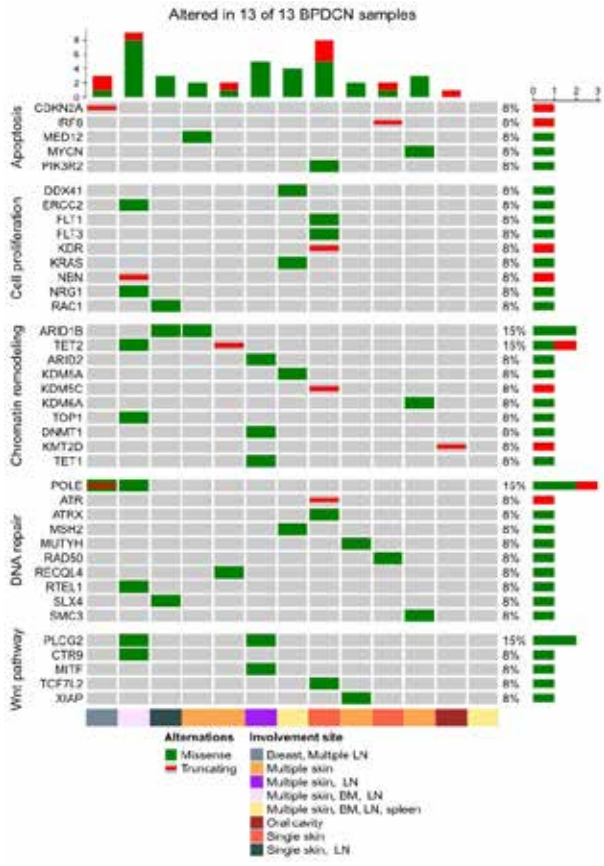
Method : Patients who were diagnosed with blastic plasmacytoid dendritic cell neoplasm, blastic NK-cell lymphoma, agranular CD4+ natural killer cell leukaemia, bastic natural killer leukaemia/lymphoma, agranular CD4+CD56+ haematodermic neoplasm/tumour from April, 2002 to February 2019 was retrospectively seached by chart review in 16 centers of South Korea. Clinical and pathologic data of 39 patients were collected and were reviewed for diagnosis of BPDCN by 2016 WHO classification. Pathologic slides were reviewed in the central lab by the 2 pathologic experts and were finally 35 cases were confirmed for diagnosis of BPDCN. Among these, pathologic slides of 13 patients underwent whole genome sequencing (NovaSeq 6000, Illumina, San Diego, CA, USA).

Results : The median age was 56 years (range, 17 - 88 years) with a male preponderance (71.4%). The most common initial presenting site was skin followed by lymph nodes, bone marrow, spleen, and liver. Whole genome sequencing of 13 BPDCN patients identified 9 patients mutated in 10 epigenetic modifiers (ex, TET2, ARID1B, ARID2, KDM5A, KDM5C, KDM6A, TOP1, DNMT1, KMT2D, and TET1), and 9 patients mutated in 10 DNA repair genes (ex, POLE, ATR, ATRX, MSH2, MUTYH, RAD50, RECQL4, RTEL1, SLX4, and XMC3), respectively. ARID1B, TET2, and POLE were the most frequently affected (15% each). Thiry-one of the included patients proceed to treatment with acute lymphoblastic leukemia (ALL)-like regimen (20 patients), acute myeloid leukemia (AML)-like regimen (6 patients) and lymphoma-like regimen (5 patients). Baseline characteristics of age ≥ 65 years, liver involvement and induction chemotherapy with lymphoma-like

regimens expected worse prognosis in both univariate and multivariate analysis. Among the 31 patients who received induction chemotherapy, 10 cases proceeded to allogenic stem cell transplantation (Allo-SCT) and 3 received autologous SCT. With a median follow-up of 28.90 months (range, 5.9-79.73 months), patients who had been treated with leukemia-like induction regimen compared with lymphoma-like induction regimen (39.30 vs. 6.33 months, P=0.006) and Allo-SCT compared with no allo-SCT (54.13 vs. 12.43 months, P=0.032) showed significanly better outcome in terms of overall survival.

Conclusion : Middle-aged male were the most frequently affected by BPDCN in Korea. Mutations in epigenetic modifiers and DNA repair genes were the most commonly observed by whole genome sequencing. Induction treatment with leukemia-like regimen and proceeding to allogeneic stem cell transplantation can prolong overall survival patients with BPDCN.

Keyword : Blastic plasmacytoid dendritic cell neoplasm, Whole genome sequencing, Epigenetics, Transplantation



PP06-1

Cladribine combined with cytarabine regimen as a salvage therapy for paediatric refractory/relapsed langerhans cell histiocytosis: A single-armed, single-center study

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Background : Langerhans cell histiocytosis (LCH) is a heterogeneous disease caused by the clonal proliferation of immature dendritic cells. Several studies have shown that Cladribine (2-chlorodeoxyadenosine, 2-CDA) combined with Cytarabine (Ara-C) can be used to treat refractory/reactivation (R/R) high-risk LCH in adults. At present, there are few reports about the efficacy and safety of the 2-CDA+Ara-C regimen in pediatric LCH, especially with a large sample size. Here, we report the results of the 2-CDA+Ara-C regimen as the salvage therapy in a group of ninety-four pediatric patients with R/R LCH.

Method : A retrospective analysis was performed in children with R/R LCH, who accepted 2-CDA plus Ara-C treatment at Beijing Children's Hospital, from January 2014 to December 2019.

Results : A total of 94 patients were enrolled in this study, including 64 boys and 30 girls, with a median age of 5.38 (0.45-13.61) years at diagnosis. There were 78, 16, 32 patients with multisystem, single system (multiple bone destruction), and risk-organ involvement respectively. At diagnosis, circulating cell-free BRAFV600E (cfBRAFV600E) was positive in 30 of 61 patients (49.18%). Gene mutations in biopsy tissue was detected positive in 37 of 47 patients (78.72%). The overall response rate was 85.1%. The median follow-up time was 4.60 (1.71-7.08) years. The 3-year event free survival rate was 76.7%±3.4% and the 2-year cumulative rate of progression or reactivation was 20.2%. Multivariate Logistic regression analysis showed that risk organ involvement was independently correlated with reactivation or disease progression after second-line treatment (P=0.027, OR=3.138, 95% CI=1.141-8.633). In 30 patients with pituitary involvement, 90% of the pituitary MRI abnormal signals recovered, 44.4% of the diabetes insipidus symptoms improved after second-line treatment. All the 94 patients had myelosuppression and gastrointestinal reactions during chemotherapy, which were mild to moderate.

Conclusion : 2-CDA plus Ara-C treatment can be used as a salvage therapy with high efficiency and low reactivation rate in paediatric R/R LCH, and had a certain effect on pituitary involvement. The

main side effects were mild to moderate myelosuppression and gastrointestinal reactions. The long-term reactivation rate still needs to be studied.

Keyword : Children, Langerhans cell histiocytosis, Cladribin, Cytarabine, Prognosis

PP06-2

Serum cytokine pattern in children with hemophagocytic lymphohistiocytosis

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Background : This study aimed to compare the serum levels of 34 cytokines of children with hemophagocytic lymphohistiocytosis (HLH) and explored the specific cytokine pattern of HLH subtypes and the relationship between cytokine levels and prognosis.

Method : This retrospective study assessed the clinical data and cytokine levels of newly diagnosed children with HLH in Beijing Children's Hospital, Capital Medical University, from January 2017 to December 2021.

Results : A total of 101 children were enrolled in the study. The levels of IFN-γ and IL-18 increased in more than 90% of patients, and MIP-1α, SDF-1α, IP-10, IL-6, IL-8, IL-10, IL-1 RA, and TNF-α increased at different levels in more than 50% of patients. The levels of IL-10 in EBV-HLH increased significantly, followed by IFN-γ and IL-18, while IL-10 and IFN-γ in CAEBV-HLH had a slight increase. Except for IL-10, the levels of IL-6, Eotaxin, IL-13, IL-18, IFN-γ, and MIP-1β in Rh-HLH increased significantly. F-HLH had significantly high IL-10 levels and a slight increase in IL-13. We showed that various cytokines could assist in differentiating HLH subtypes with ROC curve analysis. When IL-10/IL-6 was 1.37, the sensitivity and specificity of diagnosing EBV-HLH were higher than 80% (AUC=0.837, p<0.001). The effect of cytokine ratio on classifying HLH subtypes (81.8%) was more significant than the single cytokine (18.2%). The 3-year overall survival (OS) rate of children with F-HLH was the lowest during the follow-up. The 3-year OS of patients with EBV-HLH and CAEBV-HLH was significantly higher than that with F-HLH (88.1% ±5.0% vs. 94.1% ±5.7% vs. 57.1% ±14.6%, p=0.017). Cox proportional hazards model revealed that elevated GM-CSF and MCP-1, as well as CNS involvement, were independent risk factors for poor outcomes for patients with HLH.

Conclusion : Various cytokines play important roles in HLH. Different subtypes of HLH have their specific cytokines pattern, and the ratio of cytokines may be more significant in differentiating HLH subtypes than the single one. Elevated GM-CSF and MCP-1 could be useful biomarkers for a poor prognosis for patients with HLH.

Keyword : Hemophagocytic lymphohistiocytosis, Children, Cytokine pattern, Subtype, Prognosis

PP07-3

Immunological features and cytokine regulation in plasma cell neoplasms

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Background : Disorder in the process of maturation and differentiation can lead to malignant transformation. Cytokines are known to be involved in both inflammatory and anti-inflammatory processes. The analysis of immunological features and disorders in the production of cytokines makes it possible to obtain data on the factors associated with the prognosis of the course in the group of plasma cell neoplasms.

Method : The study included 287 patients with PN (MGUS (n=148) and MM (n=139) who were examined from October 2018 to January 2022 at the RRCRM&HE, Gomel. All patients underwent clinical and laboratory studies: a hemogram, a biochemical blood test, a study of blood serum proteins, immunoglobulins and β2-microglobulin, aspiration bone marrow biopsy with immunophenotyping. Expression of surface CD138, CD56, CD200, CD117, CD95 antigens on clonal cell lines was determined by flow cytometry on a FACSCalibur dual laser flow cytometer, Becton Dickinson, USA. The study of cytokines (IL-1β, IL-2, IL-6, IL-8, TNF-α) in blood serum was performed by enzyme immunoassay using ELISA-BEST reagent kits (RF). Statistical processing of the results was carried out using the Statistica 6.1 software package.

Results : The median age in patients with MGUS was 62.0 years (54.0 and 67.0), in patients with MM it was – 64.0 years (58.0 and 70.0). Within patients in MGUS group, female patients predominated (62.8%, p=0.002). In the groups of patients with MGUS

and MM, the monoclonal protein was most often represented by IgG (45.3% with MGUS and 54.7% with MM) and light chains of immunoglobulins κ, λ (20.9% with MGUS and 19.4% with MM).). The combination of two immunoglobulins was detected in 10.1% of cases in patients with MGUS and in 2.2% in MM. The number of CD 138+ cells detected during immunophenotyping significantly affects the overall survival of MM patients. During the observation period, the progression of MGUS to MM was recorded in 8.8% (13) of cases, the progression of MM was determined in 38.1% (53) of cases. MGUS patients with high expression of CD56>20%, CD200>20%, CD117>20% were significantly more likely to progress to MM (p=0.005, p=0.048, p=0.001, respectively). High expression of CD56>20% was found in 64.3% of cases in MGUS patients with progression to MM, and in 73.6% of cases in MM patients with subsequent progression or refractoriness to ongoing chemotherapy. These MM patients were revealed with high expression of CD200>20%. An increase in the number of tumor PCs in BM is associated with the progression of anemic syndrome (p=0.01) and an increase in serum calcium levels (p=0.03). These patients had reduced overall survival rates. When comparing the levels of cytokines in MGUS patients with subsequent progression of the disease to MM, a significant increase of the level of IL-8 pg/ml (p=0.014) and IL-1β pg/ml (p=0.046) was revealed. In MM patients with disease progression and refractoriness to ongoing chemotherapy, the initial diagnosis revealed a significant increase of IL-2 (p=0.001), IL-6 (p=0.006), TNF (p=0.000) levels in blood serum. A significant correlation was revealed in MM patients with progression during the observation period between IL-2 and CD95 r = 0.45; (p=0.001), IL-2 and CD117; r = -0.43; (p=0.002), TNF and CD117; r = -0.39; (p=0.006), TNF and CD95; r=0.49; (p=0.0001). In MGUS patients, a significant correlation was found between IL-6 and CD117; r=-0.66; (p=0.02). TNF and CD117; r=-0.61; (p=0.035).

Conclusion : When studying the immunological and immunochemical profile of patients with MGUS and MM, determining the levels of cytokines, we found an excess of the level of expression of CD56>20%, CD200>20%, CD117>20% with the progression of both MGUS and MM. At the same time, there was a significant increase of the level of IL-1β and IL-8 in patients with MGUS with progression of the disease and the levels of IL-2, IL-6, TNF in patients with progression of MM. Each of the interleukins contributes to the stimulation and proliferation of the tumor at the stages of the malignant process development, from the stage of MGUS to MM. Analysis of changes in these factors has a prognostic value, due to which it is possible to predict the course of the disease.

Keyword : Multiple myeloma, Monoclonal gammopathy of undetermined significance, Cytokines, Prognostic factors

PP07-4

Prognostic value of serum free light chains measurements in newly diagnosed multiple myeloma patients at the Blood Transfusion Hematology Hospital

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Background : Multiple myeloma is a proliferative malignancy of the plasma cells in the bone marrow, and some other organs. The prognosis of multiple myeloma is highly variable due to the biological heterogeneity of multiple myeloma cells, host factors and bone marrow microenvironment. Patient prognostic clustering is important, as it helps to optimize and initiate appropriate treatment to avoid irreversible organ damage as early as possible. Up to now, the serum-free light chain (sFLC) measurement test has been developed and widely used in clinical practice. Presently, there is a debate about the role of the serum free light chains (sFLC) in the prognosis multiple myeloma patients both at diagnosis and after treatment.

Method : We conducted a retrospective study on 74 patients with multiple myeloma who were treated at Ho Chi Minh City Hospital of Hematology and Blood Transfusion from January 2019 to December 2021. Inclusion criteria were: Adult patients > 18 years old; Diagnosis of multiple myeloma according to the criteria of IMWG; Be treated according to the regimen with bortezomib at the hospital; Newly diagnosed and untreated disease. Exclusion criteria were patients who had incomplete medical records (patients who did not have a quantitative sFLC test at the time of diagnosis). Qualitative variables use frequency and percentage tables. Use the chi-square test to test for qualitative variables. Quantitative variables are represented by two parameters: mean and standard deviation if normally distributed or median (interquartile range) if the variable has no normal distribution. Pearson's Chi-squared test was used to evaluate the correlation between sFLCR and patient characteristics, as well as parameters related to multiple myeloma. Kruskal-Wallis test to compare median sFLCR between different treatment response groups. OS, PFS were calculated by Kaplan Meier method and Log-Rank test. The different tests have statistical significance when p-value < 0.05.

Results : Seventy-four patients were included the study with 73 patients had an abnormal sFLC ratio (sFLCR) at admission time.

The sFLCR median is 38 in case of kappa light chain restriction (n= 48) and 55 in lambda light chain restriction patients (n= 26). High sFLCR (sFLCR more than the observed median value for kappa and lambda light chain restriction multiple myeloma) is associated with increased serum M protein concentration (p= 0.007). The data show no stastistically significant difference between sFLCR and creatinine, β2-microglobulin, anemia, presence of lytic bone lesions, percentage of plasma cell infiltration in bone marrow or ISS. sFLC and sFLCR consistently decrease over the course of treatment in terms of response cases and they increase again when the disease relapsed. The normal of sFLC ratio according to IMWG criteria also increase over treatment cycles. In general, three-year Overall survival (OS) and Progression-free survival (PFS) for the whole group were 85.5% and 75% respectively. However, subgroup analysis demonstrates that the patients with high sFLCR had a better outcomes than the cases with low sFLCR with OS and PFS of 96.7% and 87.2% compared with 74.7% and 64% respectively (p<0.05). In addition, fourty-five patients (60.8%) with sFLCR normalization showed superior OS and PFS compared to those who did not (3-yr OS, 94.5% vs. 72.5%; 3-yr PFS, 84% vs. 61%, p< 0.05).

Conclusion : Most patients with multiple myeloma have an elevated sFLCR at admission time. Correlation of high sFLCR with increased serum M protein was noted. Our findings support the observation that the sFLCR at the diagnosis and the normalition of sFLCR over the course of treatment are the strong factors for predicting the outcomes of newly diagnosed myeloma patient. The 3-year OS and PFS of the low sFLCR group and high sFLCR group had statistically significant differences. Similarities between the two sFLCR groups in terms of post-treatment normality with 3-year OS and 3-year PFS were statistically significantly better than OS and PFS of the group whose sFLCR did not return to normal after treatment.

Keyword : SFLC, SFLCR, Multiple myeloma

PP07-5

Open-labeled, multicenter phase II study of prophylactic administration of pegylated granulocyte colony-stimulating factor in relapsed or refractory multiple myeloma who received pomalidomide/dexamethasone-containing regimens (KMM170)

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Background : Pomalidomide is a third generation IMiD that is pharmacologically distinct from lenalidomide and demonstrated efficacy in combination with dexamethasone in patients with double refractory relapsed/refractory MM (RRMM). In the randomized phase 3 trial, pomalidomide in combination with low-dose dexamethasone (Pd) showed significantly better overall response rate (ORR) (31% vs 10%, p < 0.0001) and longer progression-free survival (PFS) (3.8 vs 1.9 months; HR 0.41, p < 0.0001) and overall survival (OS) (11.9 vs 7.8 months; HR 0.53, p = 0.0002) compared to high-dose dexamethasone alone. However, the major toxicity of pomalidomide is severe neutropenia and subsequent infection and in real world, infectious complication is common and grade 3-4 neutropenia and infection were reported to be 97.4% and 63.1% of the patients treated with PCd in a retrospective study.

Method : The present study is a multicenter, prospective phase 2 study, and inclusion criteria is as follows: RRMM patients who are treated with pomalidomide, dexamethasone containing regimen were included. Patients were aged more than 19 and had Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-2. There was no exclusion criterion about absolute neutrophil count (ANC) at the time of enrollment. Patients underwent a 28-day treatment cycle; pomalidomide (4mg on days 1-21, orally) plus dexamethasone (40mg on days 1,8,15, and 22, orally) (Pd) or plus cyclophosphamide (400mg/day on days 1,8,15, orally) (PCd). All patients were given pegfilgrastim subcutaneously with a single administration performed on the first day of each cycle as a primary prophylaxis until forth cycle. The primary endpoints of this study were the incidence of grade 3 or 4 neutropenia (ANC of less than 1 x 109/L) and febrile neutropenia.

Results : Totally, 33 patients with relapsed or refractory MM who received Pd or PCd regimen between March 2018 and September 2021 at 7 institutions in Korea were included in this study. Five patients were treated with Pd and 28 patients were treated with PCd. Median age of the patients at the time of beginning pomalidomide –based treatments was 75 (range 56-85). Median prior line of therapy was 2 (range 2-6). Seventeen patients (51.5%) already had any grade of neutropenia at the time of initiation of pomalidomide treatment, and 20 patients (60.6%) had any grade of thrombocytopenia at the time of pomalidomide treatment. During the 4 cycles of treatment Any grade of neutropenia was occurred in 19 patients (57.6%); 16 patients (57.1%) in PCd, 3 patients (60.0%) in Pd. Grade 3 or more neutropenia was occurred in 17 patients (51.5%); 15 patients (53.6%) in PCd, 2 patients (40.0%) in Pd. Four patients (12.1%) experienced grade 3 or more febrile neutropenia; 3 patients in PCd, 1 patient in Pd. Any grade of infection was occurred in 8 patients (24.2%) and grade 3 or more infection was occurred in 5 patients (15.2%). Dose reduction or treatment interruption of pomalidomide, cyclophosphamide, dexamethasone was occurred in 12/33 patients (36.4%), 12/28 patients (42.9%), 9/33 (27.3%) respectively. Clinical events during the 4 cycles of pomalidomide treatment are described in table 1. Adverse events of pegfilgrastim were all grade 1 or 2 and no medical intervention was needed.

Conclusion : Although it is difficult to draw clear conclusion due to the lack of control group, pegylated G-CSF is well tolerated without severe adverse events and has a prophylactic effect of febrile neutropenia and severe infection in RRMM patients.

Table 1. Clinical events during the 4 cycles of pomalidomide treatment

Event	Total (N=33)	PCd (n=28)	Pd (n=5)
Adverse event			
Overall (Gr1-4) neutropenia, n (%)	19 (57.6)	16 (57.1)	3 (60.0)
Gr3 neutropenia, n (%)	7 (21.2)	6 (21.4)	1 (20.0)
Gr4 neutropenia, n (%)	10 (30.3)	9 (32.1)	1 (20.0)
Duration of Gr3-4 neutropenia (days), median (range)	10 (1-34)	10 (1-34)	7 (4-28)
Overall (Gr1-4) Febrile neutropenia, n (%)	4 (12.1)	3 (10.7)	1 (20.0)
Gr3 Febrile neutropenia, n (%)	1 (3.0)	1 (3.6)	0 (0.0)
Gr4 Febrile neutropenia, n (%)	3 (9.1)	2 (7.1)	1 (20.0)
Overall (Gr1-4) Infection, n (%)	8 (24.2)	8 (28.6)	0 (0.0)
Gr3 infection, n (%)	4 (12.1)	4 (14.3)	0 (0.0)
Gr4 infection, n (%)	1 (3.0)	1 (3.6)	0 (0.0)
Dose adjustment (dose reduction or treatment interruption)			
Pomalidomide, n (%)	12 (36.4)	11 (39.3)	1 (20.0)
Cyclophosphamide, n (%)	12 (36.4)	12 (42.9)	-
Dexamethasone, n (%)	9 (27.3)	8 (28.6)	1 (20.0)
Treatment delay > 2days, n (%)	17 (51.5)	14 (50.0)	3 (60.0)
Total dose of conventional G-CSF (mcg/kg), median (range)	8.5 (2.0-1652.0)	5.0 (3.0-45.0)	12.0 (2.0-1652.0)

PP07-6

Epidemiological characteristics of multiple myeloma and comorbidity-based model predicting for development of multiple myeloma

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Background : Multiple myeloma (MM) is a hematologic malignancy and classified as the spectrum of plasma cell disorder. Early diagnosis and following management are important for prognosis, but screening of MM is not routinely performed mainly because of its low prevalence. In this study, we compared epidemiological differences between patients with MM and the matched general population who had not been diagnosed with MM in population level, and aimed to develop a comorbidity-based risk model which predicts the risk of MM development.

Method : A population-based case cohort of 17,879 adult patients who were diagnosed with MM between January 2010 and December 2020 and the control cohort of 142,902 adults from the general population were extracted from the Korean National Health Insurance Service database. Epidemiological characteristics including comorbidities and socioeconomic status (SES) were compared between those cohorts and were used as potential covariates in multivariate logistic regression analysis to develop the score model for prediction of MM risk. Prediction scores were then categorized into four groups considering the distribution and clinical efficiency, and odds ratio of each group was calculated. Also, subcohort analysis was performed to ensure the validity of the developed score system among the individuals with different data collection periods.

Results : Among the all covariates, prevalences of congestive heart failure, autoimmune disease, chronic pulmonary disease, peptic ulcer disease, liver disease, renal disease, diabetes, any malignancies, metastatic solid cancer and medical beneficiary were higher in the case cohort, and that of high SES was lower in the case cohort. Median interval time between diagnosis of comorbidities and MM was around 50 months, but for renal disease and metastatic solid cancer, it was shortened to 30 months. Eleven comorbidities and SES were identified as covariate for the final model based on the multivariate logistic regression, and 8 comorbidities and SES were selected for the score development. Developed score system is as follows: Total prediction score = 2 (Congestive heart failure) + 2 (Autoimmune disease) + 0.15 (Chronic pulmonary disease) + 0.5 (liver disease) + 8.5 (Renal failure) + 1.5 (Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin) + 3 (Metastatic solid tumor) + 6 (Medical beneficiary) - 1.5 (High SES). Total prediction scores were categorized into 4 groups (group without any risk, intermediate-1, intermediate-2, high risk) and risks of MM development in intermediate-1, intermediate-2 and high risk group were 1.31, 2.68 and 5.31 times higher compared to that in the group without any

risk, respectively. Based on analysis on a subcohort which consists of individuals whose comorbidity data was collected for at least 5 years, the odds ratios of risk groups were comparable to those in the original cohort (Odds ratio: 1.29, 2.53 and 4.67 respectively).

Conclusion : Comorbidity- and SES-based score system to predict MM risk was developed at a nationwide population level. The developed score system could benefit the clinician to find potential candidates for screening MM. Further work remained to validate the developed score externally.

Keyword : Multiple myeloma, Big data, Comorbidity, Hematology, Socioeconomic status, Epidermiology

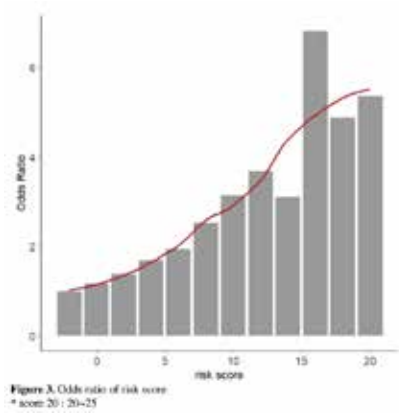

Figure 3. Odds ratio of risk score
* score 20 : 20~25

PP07-7

Development of multiple myeloma treatment using apoptosis multi-protein target tetracyclic triterpene compound

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Background : The tetracyclic triterpene compound is a low-molecular compound extracted from red ginseng and is known to have various physiologically active functions and anticancer activity. Rh2, a PPD-type 20(S)-ginsenoside, has been extensively studied as a major ingredient with antineoplastic properties. The effect of tetracyclic triterpene compound has been actively studied in leukemia but not in multiple myeloma (MM). Thus, the aim of study was to identify tetracyclic triterpene compounds that have toxic effects against MM cells and to elucidate the underlying molecular mechanism.

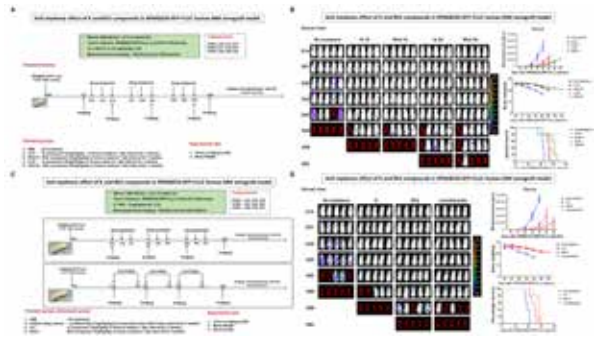
Method : First, we screened the toxic effects of tetracyclic triterpene compounds Rb1, Rb3, Rg1, Rg3, Rh1, Rh2, and CK at a concentration of 50 μM in several MM cell lines (ARH77, U266, and RPMI8226) after 24 hours of exposure. Furthermore, ARH77 cells were incubated with Rh2 and CK at 0, 20 μM, 50 μM, 60 μM, and 70 μM for 24 hours, and the DNA content at each stage of the cell cycle was detected. The potential cytotoxic effect of Rh2 and CK was investigated in normal hematopoietic stem cells (HSCs) isolated from healthy donors using primary peripheral blood stem cells (PBSCs). To establish a human MM xenograft model, RPMI8226-RFP-FLuc cells (5 × 106 per mouse) were intravenously injected into 9-12-week-old male and female NOD/SCID IL-2Rγnull (NSG) mice. To assess the anti-MM effect of CK and Rh2 in the MM xenograft model, NSG mice were divided into the following treatment groups: Experiment set 1: no treatment (PBS control), CK (15 mg/kg/day), Rh2 (15 mg/kg/day), K (30 mg/kg/day), and Rh2 (30 mg/kg/day). Mice were treated with either CK or Rh2 (15 or 30 mg/kg/day) by intraperitoneal injection for 3 days in a week at a 1-day interval. Experiment set 2: no treatment (PBS control), CK (7 mg/kg/day), Rh2 (7 mg/kg/day), and Lenalidomide (1 mg/kg/day). Mice were treated with either CK or Rh2 (7 mg/kg/day) by intravenous injection for 3 days in a week at a 1-day interval. Lenalidomide (1 mg/kg/day) treatment was given by oral administration from day 14 for 5 consecutive days in a week, and it was repeated for 3 weeks at a 2-day interval in each week. Tumor growth was monitored weekly by bioluminescence imaging in the dorsal view; 10 min before imaging, mice were intraperitoneally injected with D-Luciferin (150 mg/kg/mouse).

Results : The tetracyclic triterpene compounds Rh2 and CK inhibited the cell growth, exerted cytotoxicity, and induced G1 phase cell cycle arrest in human MM cells. However, these treatments demonstrated no cytotoxic effect on the self-renewal and the differentiation capacity of normal primary PBSCs. This observation implied that the cytotoxic activity of Rh2 and CK might selectively target MM cells and that these tetracyclic triterpene compounds are safe in other cell types. Finally, we studied the anti-MM effect of CK and Rh2 in a clinically relevant human MM xenograft model. PBS was given in the no treatment control group and all untreated tumor-bearing mice showed rapid tumor growth and severe plasmacytoma, which led to death within 7 weeks. Notably, mice treated with CK and Rh2 showed significant inhibition of tumor growth and a longer survival.

Conclusion : Tetracyclic triterpene compounds CK and Rh2 inhibited the growth of MM cells in an in vitro and in vivo model without any significant cytotoxic effect on the self-renewal and differentiation

capacity of PBSCs. Thus, these ginsenosides could be used in MM treatment and can be combined with drugs without exerting any severe toxic effects.

Keyword : Tetracyclic triterpene compounds, Rh2, Compound K, Multiple myeloma



PP07-10

Naïve B cell as predictor of early and long-term treatment outcome in post-transplant myeloma patients

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Background : The data pertaining to B-cell regeneration profiles in treated MM patients have shown the existence of highly variable features which further lacks the evidence of impact of different B cell subsets (precursor, mature, naïve and memory) on survival outcome. In this study, we explored the potential role of B cell compartments in the bone marrow of day 100 post autologous stem cell transplant (ASCT) MM patients in response evaluation and clinical outcome.

Method : This is a prospective analysis where various B cell immune subsets were identified in the bone marrow of MM patients on day 100 post ASCT. The bone marrow aspirate (BMA) samples were collected in EDTA vial and processed within 6-8 hrs of collection for flowcytometric immunophenotyping as per standard operating procedure followed in our lab. 20 non-MM staging marrow were used as control to determine the immunophenotype of the normal B cell compartment. Hematogones(Stage I & II hematogones) were characterized as CD45dimCD19+CD38++CD81++ events with no expression of light chains. Stage III HGs and mature B cells were defined as events with CD45++CD19+CD38dimCD81mod and polyclonal light chain expression. Naive B cells were defined as CD45+CD19+CD38dimCD27- and memory B cells were CD45+CD19+CD38dimCD27+ cells.

Results : A total of 53 samples were evaluated on day 100 post-ASCT in patients diagnosed with MM. Table 1 shows the distribution of various B cell subsets in bone marrow aspirate on day 100 post-ASCT in all samples. Cases with inferior conventional response on day 100 i.e., < stringent complete response (sCR) demonstrated significantly higher median mature B cell % (< sCR = 0.29%, sCR = 0.17%, p = 0.007) as well as naive B cell% (< sCR = 0.24%, sCR = 0.13%, p = 0.002). Similarly measurable residual disease (MRD) positive status was associated with significantly higher median mature B cell % (MRD+ = 0.30%, MRD- = 0.18%, p = 0.004) and naive B cell % (MRD+ = 0.25%, MRD- = 0.14%, p = 0.003) in comparison to MRD negative status. On evaluating the impact of B cell subsets on long term treatment outcome, higher median naïve B cell% was associated with reduced PFS (HR: 6.92; 95% CI: 1.62 – 29.48; p = 0.004) and OS (HR: 6.82; 95% CI: 1.14 – 40.67; p = 0.03) in post-transplant myeloma patients.

Conclusion : We demonstrated a possible role of naïve B cells as predictive markers in post-transplant myeloma patients with association of increased fraction of naïve B cell% with inferior post-ASCT day 100 response and poor survival outcomes. One potential hypothesis suggests that since naïve B cells exhibits an intricate fate with differentiation to short-lived and long-lived plasma cells upon T-helper cell activation, there may be the possibility of Naïve B cell differentiation to neoplastic plasma as a part of immune mediated phenomenon in transplant patients leading to worsened early as well as long term treatment outcome. However, more clinical studies are required to further explore and validate the potential role of various B cell subsets on treatment outcome in both transplant and non-transplant myeloma patients.

Keyword : Naive B cell, Multiple myeloma, Flowcytometry, Autologous stem cell transplant, Immunophenotyping

Table – 1: B cell subsets distribution in the day-100 bone marrow of post-transplant myeloma patients

	%Total_B_Cells	% Mature_B_ASCT	%NG	%STG I NG	%STG II NG	%STG III	%Naive	%Memory
Minimum	0.028	0.000	0.005	0.000	0.000	0.000	0.000	0.000
25% Percentile	0.517	0.022	0.316	0.090	0.018	0.149	0.013	0.003
Median	1.572	0.058	1.737	0.580	0.064	0.724	0.049	0.008
75% Percentile	4.381	0.291	3.857	2.587	0.145	1.365	0.235	0.021
Maximum	13.33	1.246	13.30	10.05	0.622	3.947	1.231	0.598
Range	13.30	1.246	13.29	10.05	0.622	3.947	1.231	0.598
Mean	2.841	0.237	2.596	1.726	0.112	0.981	0.175	0.041
Std. Deviation	3.008	0.325	2.867	2.110	0.129	1.013	0.264	0.108
Std. Error of Mean	0.413	0.044	0.393	0.289	0.017	0.139	0.036	0.014

PP07-12

The role of minimal residual disease evaluation for patients with multiple myeloma

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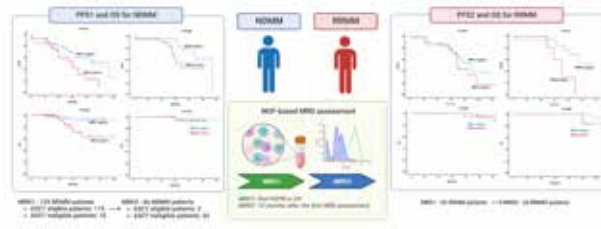
Background : Multiple myeloma (MM) is an incurable hematologic malignancy characterized by monoclonal plasma cells. Survival outcomes have been prolonged due to drastic improvements in various MM immunochemotherapy, and the acquisition of a more profound response through minimal residual disease (MRD) assessment has become a new treatment goal for patients with MM. Herein, we presented the results of the MRD assessment accumulated over 3 years in our institute and discussed the role of MRD for patients with newly diagnosed (NDMM) or relapsed/refractory MM (RRMM).

Method : Since February 2019, we have conducted a prospective study to comprehensively analyze MRD through next-generation flow (NGF) in patients with NDMM and RRMM. The patients who achieved very good response (VGPR) and complete response (CR) were enrolled and underwent bone marrow study for MRD assessment. Regardless of NDMM and RRMM, the first MRD (MRD1) was assessed at the first VGPR or CR, and the second MRD (MRD2) was re-evalauted 12 months after the first MRD assessment. NGF-based MRD assessment was performed through EuroFlow protocol. A minimum of 107 cells per sample were acquired, and the limit of detection was determined as 20 cells among total nucleated cells, resulting in a high sensitivity of 10–5 or higher for all samples. Progression-free survival 1 (PFS1) was calculated from the starting date of front-line chemotherapy to disease progression, death related to any cause, or last follow-up. PFS2 was calculated from the starting date of second-line chemotherapy. Overall survival (OS) was defined from the starting date of front-line chemotherapy to death or last follow-up. Statistical analyses were performed using an IBM PASW version 25.0 software program (IBM SPSS Inc., Armonk, NY).

Results : Of 180 patients, 76.7% were younger than 65 years, and 21.2% (38/179) had high-risk cytogenetics. Of 166 patients who were staged using R-ISS, stage II (60.8%) was more common than stage I (20.9%) and III (18.3%). MRD1 was evaluated in 180 patients (125 NDMM, 55 RRMM), followed by MRD2 in 72 (46 NDMM, 26 RRMM). Among 125 patients with NDMM, 115 (92%) performed MRD1 evaluation after upfront autologous stem cell transplantation (ASCT), and 15 (12%) underwent MRD assessment during chemotherapy due to ASCT being ineligible. The median follow-up duration was 41.0 months (95% CI 35.1–47.0), the median PFS was 33.5 months (95% CI 28.7–38.3), and the median OS was 183.8 months (95% CI 71.6–296.1). The NDMM patients with MRD1-negative (n=85) demonstrated superior median PFS1 to those without MRD1-negative (n=40) (57.1 vs. 29.8 months, P=0.027). Moreover, although not statistically significant, it seemed somewhat better to show median PFS1 in patients with MRD2-negative (n=27) than those without MRD2-negative (n=19) (57.1 vs. 34.3 months, P=0.066). Furthermore, the patients who achieved sustained MRD-negative (n=26) or converted from MRD1-positive to MRD2-negative (n=1) seemed to present better PFS than other groups who did not achieve final MRD2-negative (n=19, P=0.191). OS was also statistically superior in patients with MRD1-negative (P=0.006). Fifty-five patients with RRMM underwent MRD1 and MRD2, while 42 patients were being treated with KRD (carfilzomib, lenalidomide, dexamethasone), 4 with IRD (ixazomib, lenalidomide, dexamethasone), 4 with KD (carfilzomib, dexamethasone), 4 with Rd (lenalidomide, dexamethasone), and 1 with KTD (carfilzomib, thalidomide, dexamethasone). PFS2 between RRMM with MRD1-negative (58%, n=32/55) and MRD1-positive (41.8%, n=23/55) was not statistically different (P=0.353). However, the patients with MRD2-negative (76.9%, n=20/26) presented longer median PFS2 than those with MRD2-positive (23.1%, n=6/26) (NR vs. 35.1 months, P=0.011). Moreover, the RRMM patients with sequential MRD-negative (65%, n=17/26) or converted from MRD1-positive to MRD2-negative (11.5%, n=3/26) seemed to present better PFS2 than other groups (23.1%, n=6/26, P=0.078), although not statistically significant.

Conclusion : We presented the role of MRD for NDMM and RRMM. Although the impact of the sequential acquisition of MRD-negativity after MRD1 could not demonstrate fully in the results, patients with sustained MRD-negativity seemed to have a superior survival advantage over patients who tested positive for MRD1 or MRD2 at least once. From the viewpoint that MM is an incurable hematologic malignancy, the cumulative results of MRD are thought to help decide long-term therapeutic strategies in the future.

Keyword : Multiple myeloma, Minimal residual disease, Newly diagnosed multiple myeloma, Relapsed/refractory multiple myeloma



PP07-14

Machine learning-based sequential analysis to assist selection of front-line treatment: Bortezomib-melphalan-prednisolone vs lenalidomide-dexamethasone in multiple myeloma

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Background : Bortezomib plus melphalan plus prednisone (VMP), and lenalidomide plus dexamethasone (RD) have been administered as the first-line treatment for transplant-ineligible, newly diagnosed multiple myeloma (NDMM). We developed the machine learning models that predict response and survival following the VMP or RD chemotherapy to assist optimal selection between the two treatments.

Method : We used the retrospective data on 514 transplant-ineligible NDMM provided by the Catholic Research Network for Multiple Myeloma in Republic of Korea. The initial data consisted of 45 types of demographic and clinical characteristics, as well as time-course of response and survival outcomes. The machine learning models were developed using the XGBoost method. The minimal set of covariates resulting in the highest predictive performance during 5-fold cross validation were chosen as inputs to each model.

Results : The machine learning models utilized up to seven features to predict with the ROC-AUC ranging from 0.781 to 0.931. Using the response and overall survival (OS) prospects generated by the models, we were able to stratify the patients into the high and low risk subgroups. The hazard ratios between the two subgroups were 0.250 (95% CI: 0.161 – 0.387) and 0.204 (95% CI: 0.077 – 0.538) with respect to OS following the VMP or RD chemotherapy, respectively. 18% and 29% of the patients were classified as the high risk to VMP but low risk to RD, or vice versa.

Conclusion : In conclusion, we used the machine learning models to stratify the transplant ineligible NDMM into the high and low risk subgroups with respect to use of VMP or RD chemotherapy as the first-line treatment. A total of 10 clinical characteristics measured during diagnosis are needed as inputs to the trained models, which we plan to validate in a prospective study.

Keyword : Machine learning, Sequential, Myeloma, Transplant-ineligible, Bortezomib, Lenalidomide

PP07-16

Real-world treatment outcomes of carfilzomib plus dexamethasone in patients with relapsed and/or refractory

multiple myeloma: Impact of trial-fitness and comparison to alternative regimens

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Background : Carfilzomib plus dexamethasone (Kd) was proven to be an acceptable regimen in patients with relapsed and/or refractory MM (RRMM) by the pivotal phase III ENDEAVOR trial. However, the treatment outcomes of Kd, especially of trial-unfit patients, in the real-world setting were not widely explored. The comparison to other alternative regimens also was not previously showed.

Method : To address these issues, we analyzed the outcomes 152 RRMM patients who received Kd at the four referral hospitals of the Catholic University of Korea from April 2018 to March 2022.

Results : Patients' median age at the commencement of Kd was 66 years (range, 40-84). They received two (range, 1-7) lines of prior anti-myeloma therapy. According to the criteria which were defined in the ENDEAVOR trial, 93 (61.2%) and 59 (38.8%) patients were categorized to the trial-fit and the trial-unfit groups, respectively. The overall response (OR) rate of entire cohort was 71.1% (95% CI, 63.2-78.1). The median time-to-next treatment (TTNT) and overall survival (OS) were 8.0 (95% CI, 6.8-10.8) and 22.8 months (95% CI, 13.4-38.0), respectively. No significant difference of the OR rate was observed between the trial-fit and the trial-unfit groups (76.3% vs. 62.7%; P = 0.105). Whereas the median TTNT (5.8 months vs 10.3 months; P < 0.001) and OS (15.0 vs 36.8 months; P = 0.009) of the trial-unfit group were significantly shorter. In multivariate analysis, trial-fitness (unfit vs. fit) remained a significant covariate affecting the TTNT (HR 1.65, 95% CI 1.14-2.40; P < 0.001), but it showed only a trend of shorter median OS (HR 1.51, 95% CI 0.95-2.40; P = 0.081). The treatment-outcomes of 41 patients who received the Kd as the third line of therapy in our cohort and 100 patients who received the pomalidomide (Pom)-based therapy, which were extracted from our database, were compared. The median TTNT of the Kd group was significantly longer compared to the Pom-based group (14.3 months vs 9.0 months, P = 0.042), whereas there was no significant difference in the median OS between the two groups (38.0 months vs 25.2 months; P = 0.134). Furthermore, the treatment outcomes of 30 patients who received the Kd in our cohort were compared to 32 patients who received daratumumab monotherapy (Dara) as fourth line of therapies. The median TTNT and OS of the Kd group were not significantly different compared to the Dara group (14.3 months vs 9.0 months, P = 0.043 and NR vs 45.9 months; P > 0.050).

Conclusion : Our data showed the treatment outcomes of Kd in the real-world setting were relatively inferior compared to the pivotal prospective study. Furthermore, we compared the outcomes of Kd between the trial-fit and -unfit groups, which were significantly different, which provides useful insight in the treatment of patients with RRMM. Our comparison of Kd and other alternative regimens in the identical line of therapy also may offer valuable clinical clues to treating physicians. However, the limitations inherent in a retrospective study needs validation of our results by well-designed prospective observation and/or intervention trials.

Keyword : Carfilzomib, Multiple myeloma, Trial-fitness, Pomalidomide, Daratumumab

PP07-17

Insulin signaling-inducible IFITM1 promotes multiple myeloma progression and bortezomib resistance

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Background : Insulin is more marked in malignant cells that overexpress the insulin receptor (INSR) and effectively stimulate cancer cell growth in vitro. Insulin excess is assumed to be a cancer-promoting factor in patients. Interferon-induced transmembrane protein 1 (IFITM1) is a member of the IFITM family and is overexpressed in numerous human cancers. In this study, we investigated the association of insulin-induced IFITM1 expression in the malignant plasma cells (PCs) with MM progression and drug resistance.

Method : Changes in the expression level of INSR, IFITM1, and apop-

tosis-related factors were measured in the PCs from MM patients by real-time PCR and Western blot analysis. MTT assay and Annexin V/PI staining were used to examine the cell viability and apoptosis, respectively.

Results : Expression of INSR and IFITM1 from isolated BM PCs were significantly increased in symptomatic MM patients (n=61) in comparison to those with MGUS (n=19) or SMM (n=19). High IFITM1 level was also associated with a lower overall survival rate in symptomatic MM patients. To investigate the effect of insulin on IFITM1 expression in MM PCs, IM9 MM cells were transfected with or without si-IFITM1 sequences, and then the cells were treated with insulin. IFITM1 mRNA expression was upregulated by insulin, but this effect was abrogated in cells transfected with si-IFITM1. We also found that insulin treatment induced the proliferation of MM PCs, but the insulin-induced PC growth was alleviated by IFITM1 knockdown. Next, we examined the effect of insulin-induced IFITM1 signal on a proteasome inhibitor, bortezomib (BTZ)-induced apoptosis. BTZ-induced MM cell apoptosis was decreased by insulin treatment, but the apoptosis was enhanced upon the knockdown of IFITM1. Next, we analyzed the cell cycle using flow cytometry. BTZ treatment induced G2/M phase arrest, whereas BTZ + insulin treatment reduced the cell cycle arrest. However, IFITM1 knockdown increased G2/M phase arrest even with concomitant BTZ + insulin treatment. To further identify the molecular mechanisms underlying cell cycle arrest, we examined the effect of IFITM1 on the expression of cell cycle-associated molecules. Expressions of p53 and p21 were significantly increased by BTZ, whereas treatment with BTZ + insulin decreased the expression of both molecules. However, IFITM1 knockdown significantly increased the levels of p53 and p21.

Conclusion : We have identified the insulin signaling inducible IFITM1 as a novel regulator of MM progression. IFITM1 expression is also associated with BTZ resistance and interfering with this pathway could potentially increase the efficacy of BTZ therapy. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (2020R1C1C1008001, 2021R1A2C2093566).

Keyword : Interferon-induced transmembrane protein 1, Insulin, Monoclonal gammopathy of undetermined significance, Smoldering multiple myeloma, Multiple myeloma, Bortezomib

PP07-18

Inflammatory factor-based staging system in multiple myeloma in the new agent era: KMM176 study

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Background : The advent of new agents has contributed to the prolonged survival of multiple myeloma (MM) patients. From the Durie-Salmon staging system, international staging system (ISS) and recently, revised ISS (R-ISS) have been developed to better prognosticate the survival of MM. R-ISS includes chromosomal abnormalities (CA) detected by interphase fluorescent in situ hybridization (iFISH) and lactate dehydrogenase (LDH) in addition to the ISS. However, the R-ISS has still some limitations in the real clinical settings, as it has enrolled patients exclusively on clinical trials which includes more young patients (age < 65 years old), contains non-standardized iFISH results and has short median follow-up duration. The first-line drugs used in the patients could also affect the prognosis. Therefore, a more detailed and standardized but also convenient prognostic system is needed with clinical findings commonly observed in MM patients treated with new agents in the real clinical world.

Method : patients who had received thalidomide and/or bortezomib or lenalidomide-based chemotherapy as a first-line treatment were included for the analysis. A total of 861 patients from 13 centers participating Korean multiple myeloma working party were analyzed. Baseline serum albumin, serum ß2-microglobulin, cytogenetics by iFISH, LDH (lactate dehydrogenase), ALC (absolute

lymphocyte count), CRP (C-reactive protein) and ferritin were measured within 4 weeks before beginning the first line of chemotherapy. Each factors of age ≥ 65 years, serum ß2-microglobulin ≥ 5.5 mg/L, LDH > normal, cytogenetic high risk by FISH (del17p, t(4;14), t(14;16)), ALC < 1500/mm3, CRP ≥ 1.5 mg/dL, and ferritin ≥ 500 ng/mL were defined as abnormal findings, which were given 1 point and the sum of points were used to discriminate inflammatory factor-based staging system (IFBSS). IFBSS were defined as follows: Stage I (point 0), stage II (point 2-3), stage III (point 4-5), and stage IV (point 5-7). Overall survival (OS) was defined by the date of MM diagnosis to the date of death by any cause or follow-up loss.

Results : With a median follow-up duration of 22.70 months (range, 0.20-86.80 months), age ≥ 65 years, serum ß2-microglobulin ≥ 5.5 mg/L, LDH > normal, cytogenetic high risk by FISH (del17p, t(4;14), t(14;16)), ALC < 1500/mm3, CRP ≥ 1.5 mg/dL, and ferritin ≥ 500 ng/mL showed significant higher OS by univariate and multivariate analysis. Albumin < 3.5 mg/dL were excluded into the staging system due the unpredictability to OS in univariate analysis. Study groups of inflammatory factor-based scoring system comprised of 61 patients in stage I, 395 patients in stage II, 189 patients in stage III and 36 patients in stage IV. The median OS were not reached in stage I and II, stage III and IV showed a median OS of 36.57 months (95%CI, 33.96-.39.18) and 17.60 months (95%CI, 9.16-.26.04). The OS according to the IFBSS showed significant differences (P < 0.001), which predicted OS better compared with conventional ISS and R-ISS.

Conclusion : In the new agent era, inflammatory factors incorporated into the staging system can better discriminate prognosis of multiple myeloma patients compared to the ISS or R-ISS. Validation of this finding in a larger cohort is needed to expand usage of this new staging system.

Keyword : Inflammatory Factor-Based Staging System, Multiple myeloma, Bortezomib

PP07-19

Exploration of clinical implication of liquid biopsy targeting circulating tumor DNA in multiple myeloma and its precursor diseases

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Background : It is well known that genetic alterations are one of the crucial causative events in not only development of multiple myeloma (MM) but also resistant to therapy. Genetic profile of MM is generally preformed from bone marrow samples which can be achieved by invasive procedures. To overcome shortcomings caused by bone marrow biopsy, we explored the clinical implications of liquid biopsy targeting circulating tumor DNA (ctDNA) derived from less invasive sampling of peripheral blood in MM.

Method : Custom NGS panels, OncoChase (ConnectaGen, Seoul, Korea) targeting 150 cancer-related genes, were used to generate sequencing libraries. Targeted NGS data of normal circulating free DNA from 10 healthy donors were used as the pooled normal reference. We analyzed the genetic alteration profiles of ctDNA samples at diagnosis from 106 patients with monoclonal gammopathy of undetermined significance (MGUS, n=7), smoldering multiple myeloma (SMM, n=6), or MM (n=93) using targeted deep sequencing.

Results : A total of 173 somatic mutations (149 single nucleotide variants [SNVs] and 24 indels) were identified in the 106 patients. Of the mutated genes, seven were recurrently detected across multiple ctDNA samples (>5%): KRAS (n = 18, 17.0%), TP53 (n = 12, 11.3%), GNAS (n = 12, 11.3%), NRAS (n = 9, 8.5%), BRAF (n = 9, 8.5%), MLH1 (n = 8, 7.6%), and NOTCH1 (n = 8, 7.6%). RAS/MAPK activating mutations (KRAS, NRAS, and BRAF) were significantly enriched in MM genomes (n = 35, 37.6%) but did not detect in MGUS or SMM genomes (P = 0.004, Fisher's exact test). Likewise, recurrent mutations were identified in the entire coding region of TP53 (n = 12, 12.9%;) as a scattered pattern. Regarding the other recurrent gene mutations, they were detected not only in the MM genomes but also in MGUS or SMM genomes, suggesting that the acquisition of GNAS, MLH1 and NOTCH1 mutations during MM progression might be an early event. Considering the somatic mutations, only TP53 mutations were significant associated with poor overall survival

Conclusion : These results suggest that mutations in KRAS, NRAS, BRAF, and TP53 in ctDNA might be an important biomarker for developing MM from MGUS or SMM.

Keyword : Myeloma, TP53, KRAS, NRAS, BRAF

PP07-20

Development of risk model including functional high risk in patients with relapsed/refractory multiple myeloma: Dynamic Risk Model

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Background : Early relapse after treatment or refractory to novel agents has been identified as a high-risk feature resulting in resistance to subsequent therapy and shorter overall survival in patients with multiple myeloma (MM). Symptomatic relapse, not biochemical relapse, has been also associated with poorer survival outcomes. Newly confirmed risk factors after treatments like these are called functional high risk or dynamic high risk. Until now, there was a dearth of attempts to incorporate these functional high risks into the survival prediction model and to reassess risk stratification in the setting of RR. Here, we propose a new risk model to predict survival outcomes in patients with relapsed/refractory MM (RRMM).

Method : We retrospectively reviewed the medical records of RRMM patients who received a second line of therapy at Kyungpook National University Hospital and Chungnam National University Hospital from 2011 to 2021. Overall survival (OS) was defined as from the initiation of the second line of therapy to death from any cause or last follow-up. Early relapse was defined as the biochemical relapse or overt relapse within 18 months after the initiation of frontline therapy. The Cox hazard model was used to distinguish the risk factors relevant to overall survival. To adjust the difference in the magnitude of hazard ratio (HR), we weighted scores differently according to the range of HR. Then, we classified risk groups by the sum of the scores of each risk factor. The newly developed risk model was validated by Kaplan-Meier survival analysis.

Results : One hundred forty-one patients with RRMM were included in the analysis. Their median age at diagnosis was 65.7 years (range, 33 – 80 years) and 76 patients (53.9%) were male. Patients with early relapse were 77 (54.6%). After relapse, 102 patients (72.3%) were treated with carfilzomib-based treatment and 39 patients (27.7%) with ixazomib-based treatment as the second line of therapy. Early relapse was confirmed as a significant risk factor for survival prediction (HR 2.56, p-value 0.002). Other variables at relapse: hemoglobin (Hb), platelet count, LDH, albumin, beta 2 microglobulins, and plasmacytoma, were identified as risk factors relevant to survival outcomes (Table 1). The weighted scores of each factor were described in Table 1. Meanwhile, we excluded platelet count and beta 2 microglobulins from the weighting score because of relatively insignificant HR. The risk model of survival prediction (Dynamic Risk Model) classified RRMM patients into 3 stages: stage I for a total score of 0-2, II for 2.5-4, and III for 4.5-7.5 (Table 2). In the validation of the Dynamic Risk Model, 70 patients were enrolled (Figure 1) and stage I, II, and III were 29 (41.4%) patients, 25 (35.7%), and 16 (22.9%). The new model successfully discriminated survival outcomes according to the stages in patients with RRMM; 24-month OS were 95.7%, 42.3%, and 16.2% in stages I, II, and III, respectively ($p < 0.0001$). 24-month progression-free survival were 57.3%, 35,7%, and 0.0% in stages I, II, and III, respectively ($p < 0.0001$) (Figure 2).

Conclusion : Combining early relapse with easily obtainable variables, the Dynamic Risk Model showed a remarkable prognostic power for estimating survival outcomes in patients with RRMM. Notably, this model is the first adaptation of functional high risk in reassessing risk stratification in RR settings. Further analysis to validate the reliability and reproducibility of the model would be necessary.

Keyword : Relapsed/Refractory multiple myeloma, Functional high risk, Survival prediction, Risk model

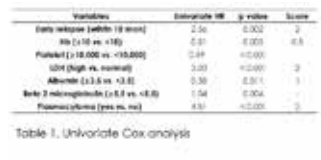

Table 1. Univariate Cox analysis

Figure 1. Consort diagram

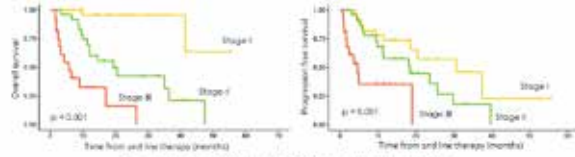

Figure 2. Dynamic Risk Model in relapsed/refractory setting

Dynamic Risk Model	Score	No. of patients (n, %)	24-months OS (%, 95% CI)	24-months PFS (%, 95% CI)
Stage I	0 - 2	29 (41.4)	95.7 (87.7 - 100.0)	57.3 (37.2 - 77.5)
Stage II	2.5 - 4	25 (35.7)	42.3 (24.9 - 72.0)	35.8 (18.3 - 70.1)
Stage III	4.5 - 7.5	16 (22.9)	16.2 (3.8 - 7.9)	0.0 (NA - NA)

Table 2. Survival outcome according to stages in Dynamic Risk Model

PP08-2

Myeloproliferative neoplasms with hypereosinophilia and rearrangement PDGFRB gene in children under 2 years old: First case at Vietnam National Children's Hospital

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Background : Hypereosinophilia (HE) has generally been defined as a peripheral blood eosinophil count greater than 1.5 x109 /L. However severe HE caused by myeloproliferative neoplasms (MPNs) related to rearrangement PDGFRB is very rare in children < 2 years old, accounting for < 1% in totality. Efficacy of imanitib on peaditric remains unclear. First time a case with rearrangement PDGFRB was found at VNCH.

Method : Case study report

Results : A boy from 15 months old to 23 motnhs old complained abdominal pain and fatigue, no fever. He manifested the expansion of an eosinophil clone combined to anemia; enlarge spleen caused initial confused diagnostic. His absolute eosinophilia count level from 11.470/ µL (White blood cell 37x 109/L, eosinophil 31%) to 54.984/ µL (White blood cell 174x 109/L, eosinophil 31,6%). Many test were performed to exclude of secondary HE and to diagnosis primary HE. At last but not least we decided to make FISH technique with genes: PDGFRB, PDGFRA and FGFR1. It showed 95% rearrangement PDGFRB after 8 months from first on admission. Imatinib is the first choice but it only shows a good response in adult. We started Imatinib with dose oral 150 mg/ day in 7 days. After 1 week, the patient status was better when white blood count reduced to normal with eosinophil 2%, spleen was smaller, no anemia, no abdomen pain and fatigue. The boy was remained Imatinib 100 mg/ day until now at home.

Conclusion : Although MPNs with severe HE and PGDFRB rearrangement occurs in adults but it can be found on children under 2 year old. The therapeutic benefit of Imatinib in pediatric was consistent.

Keyword : Hypereosinophil, PGDFRB gene

PP08-3

Incidental abdominal computed tomography findings of patients newly diagnosed with Philadelphia-negative myeloproliferative neoplasm

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Background : Standard guidelines do not recommend abdominal computed tomography (CT) for the initial evaluation of patients with Philadelphia chromosome-negative myeloproliferative neoplasm (Ph– MPN). We retrospectively analyzed abdominal CT scans performed at the time of diagnosis of MPN to determine the clinical utility of abdominal CT for the initial screening of these patients.

Method : We enrolled patients diagnosed with essential thrombocythemia (ET), polycythemia vera (PV), prefibrotic/early primary myelofibrosis (pre-PMF), or overt primary myelofibrosis (PMF) who underwent abdominal CT at the time of diagnosis (between January 2002 and December 2021) at Chungnam National University Hospital, Daejeon, Korea. The medical records of the patients were reviewed. We did not record the presence of splenomegaly, splenic infarction, or prostate abnormalities.

Results : The study included 219 patients with Ph– MPN, including 94 with ET (median age: 62 years; range: 18–90 years), 24 with pre-PMF (median age: 67.5 years; range: 31–88 years), 80 with PV (median age: 64.5 years; range: 18–66 years), and 21 with PMF (median age: 64.5 years; range: 18–90 years). The patients were followed up for a median of 3.4 years (range: 0.1–20.2 years). Of the 219 patients enrolled, 3 (1.4%) had splanchnic thrombosis, of whom 2 did not have any symptoms or signs. Four (1.8%) patients had adrenal adenoma and one (0.5%) had renal angiolipoma. Of the 103 female patients, four (3.9%) and five (4.9%) had benign ovarian tumor and uterine myoma, respectively. Three (1.4%) patients had malignant tumors (two and one with renal cell carcinoma and colon cancer, respectively). All of the aforementioned patients were asymptomatic. Except for splanchnic thrombosis and tumors, the most frequent finding on abdominal CT was abdominal aorta calcification (AAC; n = 149; 68.0%), followed by renal cysts (n = 67; 30.6%), hepatic cysts (n = 38; 17.4%), gallstones (n = 26; 11.9%), fatty liver (n = 12; 5.5%), hepatic hemangioma (n = 10; 4.6%), and duodenal diverticulum (n = 9; 4.1%). The proportion of patients with these findings did not differ among the MPN subtypes. Hepatic calcification occurred more frequently in PMF patients (4 of 21; 19.0%) than in those with other MPN subtypes ($p < 0.001$). Old age (> 60 years) was the only independent risk factor for renal cysts. No independent risk factors were identified for the other incidental findings. In univariate analysis, AAC was a risk factor for thrombotic vascular events and was associated with overall survival (OS); however, the association was not significant in multivariate analysis. The other incidental findings did not affect the occurrence of thrombotic vascular events or OS.

Conclusion : A small proportion of Ph– MPN patients have asymptomatic splanchnic thrombosis and malignant tumors, whereas a large proportion have AAC at the time of diagnosis. Therefore, abdominal CT should be performed during the initial evaluation of newly diagnosed Ph– MPN patients.

Keyword : Myeloproliferative neoplasm, Essential thrombocythemia, Polycythemia vera, Primary myelofibrosis, Splanchnic thrombosis, Malignant tumor

PP08-4

Acquired von Willebrand disease in patients with Philadelphia-negative myeloproliferative neoplasm

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Background : Acquired von Willebrand disease (AVWD) has never been investigated in Korean patients with Philadelphia chromosome-negative myeloproliferative neoplasm.

Method : This prospective study analyzed the prevalence at diagnosis and clinical features of AVWD in patients with essential thrombocythemia (ET), polycythemia vera (PV), prefibrotic/early primary myelofibrosis (pre-PMF), or overt PMF (PMF) diagnosed between January 2019 and December 2021 at Chungam National University Hospital, Daejeon, Korea. AVWD was defined based on being below the lower reference limit (56%) of ristocetin cofactor activity (VWF:RCo).

Results : Sixty-four consecutive patients (36 with ET, 17 with PV, 6 with pre-PMF, and 5 with PMF; 30 males and 34 females) with a median age of 67 years (range: 18–87 years) were enrolled and followed up for a median of 25.1 months (range: 2.6–46.4 months). AVWD was detected in 20 (31.3%) patients at diagnosis and was most frequent in ET patients (41.4%), followed by pre-PMF (33.3%), and PV (17.6%) patients. No AVWD was found in PMF patients. AVWD with VWF:RCo of < 30% was most frequent in PV patients (17.6%), followed by pre-PMF (16.7%) and ET (8.3%) patients. VWF:RCo was negatively correlated with the platelet count (r = –0.937; P = 0.002). Only 1 episode of minor bleeding occurred in an ET patient with AVWD. VWF:RCo was normalized in all 16 patients who were placed on cytoreductive treatment after a median of 8 weeks (range: 2–18 weeks). Younger age (< 50 years) (odds ratio [OR]: 7.08; 95% confidence interval [CI]: 1.27–39.48; P = 0.026) and thrombocytosis (> 600 × 109/L) (OR: 13.70; 95% CI: 1.35–138.17; P = 0.026) were independent risk factors for developing AVWD. The JAK2V617F mutation and its allele burden did not affect the development of AVWD.

Conclusion : AVWD defined based on VWF:RCo was common in ET and pre-PMF patients but less common in PV patients in a Korean population. Clinically significant bleeding was rare among these patients.

Keyword : Myeloproliferative neoplasm, Essential thrombocythemia, Polycythemia Vera, Primary myelofibrosis, Acquired von Willebrand disease

PP08-5

Detection of JAK2 V617F mutation in polycythemia vera diagnosis first time in Mongolia

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Background : Polycythemia vera (PV) is a Philadelphia chromosome negative myeloproliferative disorder (MPD) and characterized by erythrocytosis, presence of the JAK2 V617F mutation. Nearly two decades have passed since JAK2 V617F mutation was described occur in PV. For the first time in Mongolia, we aimed to identify the JAK2 V617F mutation in a PV diagnosis.

Method : A cross-sectional study was 13 outpatient who suspected PV in First Central Hospital of Mongolia and Mongolia-Japan hospital of Mongolian National University of Medical science (MNUMS) between March 8th, 2022 to May 20th, 2022. The study was approved by a Research Ethics Committee of the MNUMS (№2022/3-02). All research participants gave written informed consent. Laboratory tests were performed based on the General Laboratory of Clinical Pathology at the First Central Hospital of Mongolia. We measured red blood cells, Hemoglobin, Hematocrit, Platelets and White blood cells count by using Sysmex XN-2000. Extracted DNA from peripheral blood from all participants by using AccuPrep Genomic DNA Extraction Kit (K-3032) and we detected JAK2 V617F mutation by

using GB ONCO JAK2 (V617F) reagent by ABI Real time PCR 7500 instrument. Statistical analysis was performed using IBM SPSS version 26.

Results : A total of 13 participants aged 43-71 in the study. The ratio of men (n=5; 38.4%) and women (n=8; 61.5%). JAK2 V617F mutation detected in 92.3% (12/13) individuals. Median age of the PV patient population 57.8 (52-68) and women 58.6 (43-71). Among the JAK2 V617F positive participants, Hb 16.4 g/dl ± 1.24 in men, Hb 16.6g/dl ± 2.18 woman, HCT 50.3% ± 5.50 in men, HCT 50.4% ± 7.25 in woman, RBC 5.8 x106 ± 1.20 in men, RBC 5.4x106 ± 1.33 for women, PLT 474.8x103 ± 273.13 in men, PLT 520.5x103 ± 237.34 in women, WBC 9.1x103 ± 4.58 in men, WBC 11.8x103 ± 7.23 in women.

Conclusion : Although this study has several limitations, including the small sample size, other tests should also be considered for diagnosis and we will use it in the diagnosis of MPD in the future.

Keyword : JAK2 V617F mutation, Polycythemia vera

PP08-6

The value of Neutrophil-to-lymphocyte ratio at the diagnosis of myeloproliferative neoplasm

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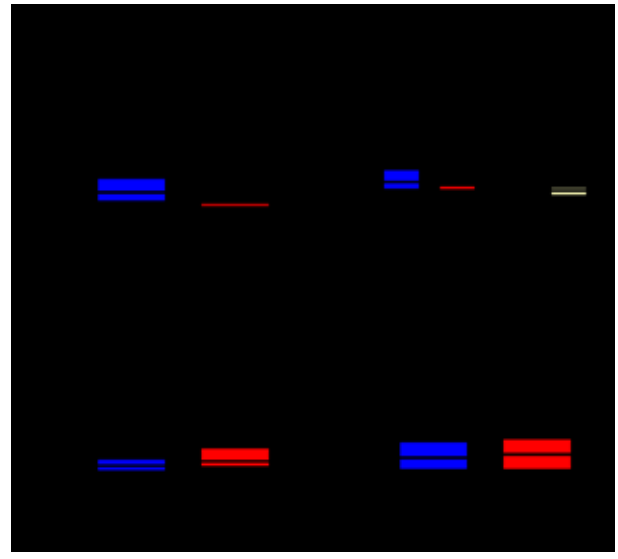
Background : Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), along with polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), are clonal disorders of hematopoietic stem cells. MPNs are cancers in which malignant clones trigger cytokines that sustain inflammatory drive. Neutrophile-to-lymphocyte ratio (NLR), calculated as the ratio of absolute neutrophil count to absolute lymphocyte count, is a fast and simple method in assessing inflammatory status and has been reported to be associated with various diseases. In a previous study, we confirmed that NLR in patients with MPN was higher than that in the normal population. We also suggested that NLR would be more beneficial than EPO in diagnosing PV. In this study, we aimed to investigate clinical significance of NLR at the time of MPN diagnosis.

Method : We retrospectively analyzed electronic medical records of patients who visited Soonchunhyang University Hospital Seoul or Soonchunhyang University Hospital Bucheon. Patients with PV, ET, and MF who met the 2016 WHO criteria were included.

Results : Among 186 MPN patients, the most common diagnosis was ET (40.9%, 76/186), followed by PV (39.2%, 73/186) and MF (19.9%, 37/186). The median NLR was higher in PV group (6 ± 2.92) than in ET group (2.97 ± 1.22) and MF group (4.47 ± 2.29). The median NLR in the JAK2 positive group was significantly higher than that in the JAK2 negative group (5.79 vs. 2.85, respectively, $p < 0.001$). Most patients with PV were proven to be JAK2 positive, and the NLR was high. In patients with PV, there was no change in NLR according to risk. In patients with ET, the NLR was also higher in the JAK2-positive group compared to the other group. In addition, it was established that the NLR was greater in ET patients at high risk compared to those at low risk. (Figure) As the disease advanced in patients with MF, the amount of peripheral blood cells other than neutrophiles and lymphocytes increased, diminishing the clinical significance of NLR.

Conclusion : NLR was shown to be elevated in JAK2-positive MPN patients. This can help in the suspicion and diagnosis of PV/ET in patients.

Keyword : MPN, NLR



PP08-7

Mortality causes in myeloproliferative

neoplasms patients with COVID-19 Infection: A systematic review

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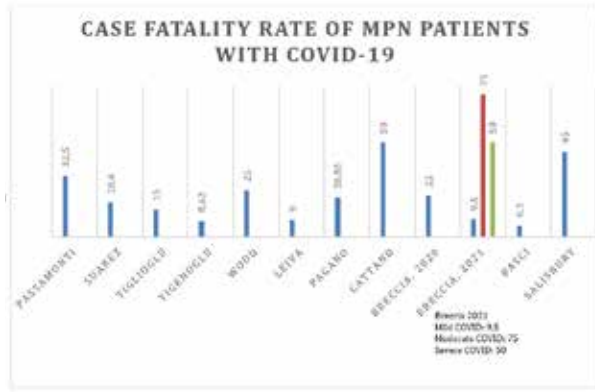
Background : The novel SARS-CoV-2 affecting more than 600 million people, making it a major global epidemic. Several risk factors, including older age, underlying medical conditions such as Myeloproliferative Neoplasm (MPN) have unfavorable consequences. From the recent studies, COVID-19 also predisposes MPN patients to thrombotic and thromboembolic events, increasing the mortality of these patients. We conducted systematic review to measure the case fatality rate and find the mortality causes in MPN patients with COVID-19 infection.

Method : We searched the following database or websites within 5 years period with keywords: "COVID 19" AND "Myeloproliferative neoplasms. We retrieved 16 potentially relevant papers on COVID-19 impact in myeloproliferative neoplasms patients after screening 73 titles and 39 abstracts (after checking duplicates between databases). We examined the full text of these 16 articles. We then excluded 4 articles because they did not meet the study design inclusion criteria.

Results : Mortality in MPN's patients with COVID-19 infection was higher than COVID-19 infection patients in general and MPNs patients without COVID-19 infection. It is caused by some factors such as older age, severe degree of COVID-19 at hospital admission, poorly controlled disease, thrombocytopenia, anemia, severity of MPN, thrombosis event, immunodeficiency condition, usage of mechanical ventilation, and other complication such as Acute Respiratory Distress Syndrome (ARDS), acute renal failure, and sepsis.

Conclusion : MPN patients are categorized into a high risk population with poor COVID-19 outcome and high mortality, therefore further studies about management and adjustment in COVID-19 therapy regiment in MPN's patients are needed.

Keyword : Myeloproliferative Neoplasm (MPN), Covid-19, Mortality



PP08-8

Prognostic value of modified criteria for hydroxyurea resistance or intolerance in patients with high-risk essential thrombocythemia

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Background : Essential thrombocythemia (ET) is a classic Philadelphia-negative myeloproliferative neoplasm associated with increased risk of thrombotic/hemorrhagic complications and transformation to myelofibrosis (MF) or acute myeloid leukemia (AML). However, approximately 20% of ET patients receiving cytoreduction therapy experience intolerance or resistance to HU. Recognizing intolerance or resistance to hydroxyurea (HU), which is associated with increased risk of disease transformation and reduced survival in essential thrombocythemia (ET), is important for making appropriate decisions for second-line therapy. In this study, we aimed to assess the value of the modified ELN (mELN) criteria for resistance and intolerance to HU in the MAJIC-ET trial. We also analyzed the incidence of resistance or intolerance to HU and the survival outcome according to both sets of ELN and mELN criteria.

Method : We retrospectively compared the occurrence of HU resistance or intolerance according to the ELN and mELN criteria for 148 high-risk ET patients receiving HU between 2014 and 2018. The

maximum tolerated dose for defining HU resistance was used in the mELN criteria. Depending on the patient condition, HU usually was administered at a starting dose of 1,000 mg per day and was increased until a minimum effective dose was achieved. If the patient experienced HU intolerance, a reduction of dose was allowed at the discretion of the attending physician.

Results : The median age of patients was 65 years (range, 36-87 years), with a median follow-up of 3.6 years (range, 1.1-6.4 years). The median daily dose of HU was 1,000 mg (range, 500-2,000 mg), and only one patient received more than 2,000 mg/day for at least 8 weeks. HU-related adverse effects occurred in 30.4% of patients and generally were grade 1-2 and developed within 5 months after HU treatment. A total of two thromboembolic events was observed during HU treatment (transient ischemic attack and deep vein thrombosis), which is categorized as resistance as defined by the mELN but not the ELN criteria. Resistance to HU was shown in 5 (3.5%) and 14 (9.8%) patients when using the ELN and the mELN criteria, respectively. HU intolerance was found in 5 (3.4%) and 8 (5.6%) patients when applying the ELN and the mELN criteria, respectively. Mucocutaneous manifestations (hyperpigmentation, aphthous ulcer, mucositis) were the most common HU-related toxicities and developed in 5 (3.4%) patients. Two (1.4%) patients had grade 3 HU-related nausea/vomiting at a dose of 1,500 mg/day, which resolved after HU discontinuation. Transformation to MF and AML occurred in 2 (1.4%) patients and 1 (0.7%) patient, respectively, as defined by the ELN criteria compared to 3 (2.1%) and 2 (1.4%) patients as defined by the mELN criteria. In multivariate analysis of transformation-free survival, HU resistance defined by the mELN criteria but not the ELN criteria was an independent prognostic factor. In addition, HU resistance as defined by both sets of criteria was an independent risk factor for inferior overall survival. Intolerance to HU did not have any prognostic impact on survival.

Conclusion : In conclusion, HU intolerance or resistance, as defined by mELN criteria, is useful for identifying high-risk ET patients who might be eligible for second-line therapy. However, the value of the mELN criteria should be validated in a prospective setting with a large population size.

Keyword : Hydroxyurea, Essential thrombocythemia, Resistance, Intolerance

PP10-1

Neutrophil - lymphocyte ratio and interferon gamma release assay results

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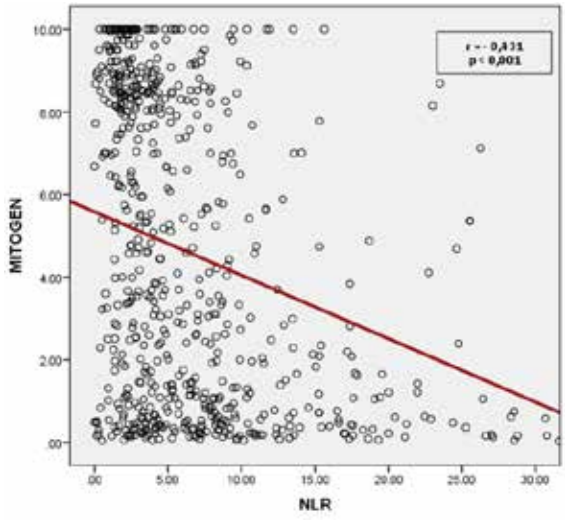
Background : Tuberculosis (TB) has a high number of cases throughout the world, including Indonesia. Most people infected with TB will become latent TB. Gold standard to diagnose latent TB is not established yet but interferon gamma release assay (IGRA) has been widely used. Inadequate interferon gamma secretion to phytohemagglutinin as positive control can cause indeterminate results. Few factors including hematological abnormalities caused by immunosuppression, medication, and comorbidities can cause this. Ratio of neutrophil and lymphocyte (NLR) which is commonly used as marker for inflammation and other disease is also associated with indeterminate result. This study aims to evaluate the relationship between hematological parameters including NLR with IGRA results

Method : This was a descriptive cross-sectional study, using secondary data from patients underwent IGRA test in Sardjito General Hospital Yogyakarta from January 2019 to June 2020. Demographical data, diagnosis, hematology and IGRA results were collected from e-medical record. Positive and negative results were grouped as determinate. Mann-Whitney test to find differences between determinate and indeterminate and Spearman correlation test to find correlation between hematological parameters and result from IGRA tubes were performed. Statistical analysis was done using SPSS 23 with p value <0.05 was considered as significant.

Results : From 668 subjects, 51.6% had negative results. Leukocyte, absolute lymphocyte, absolute neutrophil and NLR was significantly different between groups ($p<0.001$). Correlation between NLR and mitogen tube (positive control) was moderate, negative ($r= -0.431$) and significant ($p<0.001$) as shown in Figure 1.

Conclusion : Neutrophil to lymphocyte ratio is negatively correlated with IGRA results.

Keyword : Tuberculosis, Neutrophil-to-lymphocyte-ratio, IGRA, Indeterminate



PP10-2

The diagnostic value of extended complete blood count parameters for determining infection etiology

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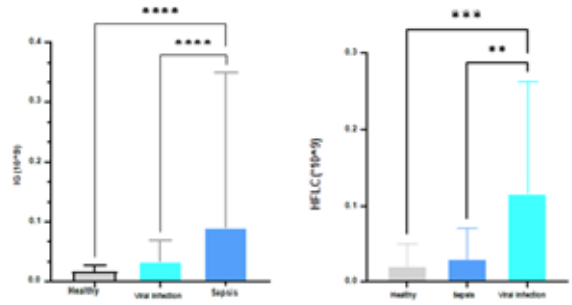
Background : Infectious diseases are the leading cause of death among children in developing nations. In infections, diagnostic markers such as CRP, Procalcitonin, and blood culture are remarkably elevated yet may manifest late. Two extended parameters of a complete blood count, IG (immature granulocyte) and HFLC (High Fluorescent Lymphocyte Count) can facilitate the early and cost-effective diagnosis and distinction of infectious causes. The study aimed to investigate the diagnostic value of IG and HFLC parameters in children with infections.

Method : A retrospective study was conducted on the CBC data with extended parameters of 240 children hospitalized at the National Children's Hospital in Hanoi, Vietnam (120 sepsis children with evidence of positive blood cultures, 120 children with Respiratory Syncytial Virus infection) and a control group of 60 healthy children. The WBC, NEUT, IG, and HFLC indicators of three groups of children were collected and compared. All CBC tests were performed on the Sysmex XN-9100 analyzer.

Results : HFLC and IG values in 3 study groups were respectively: in the healthy children group: HFLC = 0.00 (0.00-0.09) G/l, IG = 0.00 (0.00 - 0.09) G/l; viral infection group: HFLC = 0.12 (0.01 – 1.31) G/l, IG = 0.02 (0.0 - 0.25) G/l; sepsis group: HFLC = 0.03 (0.00 – 1.38) G/l, IG = 0.15 (0.12 – 6.91) G/l. HFLC was significantly increased in the group of viral infection compared to the other 2 groups with a p-value < 0.05. In contrast, IG was significantly increased in the sepsis group compared to the other 2 groups with a p-value < 0.05. Analysis of ROC curves showed that IG, at a cut-off value of 0.035 G/l had a sensitivity of 79.7% and a specificity of 89.5% for sepsis diagnosis.

Conclusion : The HFLC and IG parameters are useful for distinguishing bacterial from viral infections in children. These parameters are cost-effective, useful, and readily available tests.

Keyword : HFLC, IG



PP10-3

A smartphone-based diagnostic platform for detection of abnormal red blood cell in resource–limited settings

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Background : Counting and analyzing Red Blood Cells (RBCs) are vital to clinical diagnosis of certain types of diseases. As the number of patients continues to grow, manual examination by specialists has become too costly and time consuming and, therefore, is not suitable of mass screening patient data in resource limited settings. The aim of this project is to develop a mobile device to classifying abnormal RBC from microscopic blood smear images by using a

deep learning semantic segmentation.

Method : Images of abnormal RBC from various hematological diseases were saved by directly saved from Eclipse Ci-L microscope at 1000x magnification. There were five steps of developing this application i.e. image preparation, image enhancement and RBC segmentation, features extraction, RBC classification and mobile implementation. To determine class of abnormality of the segmented RBCs, basic features such as area, perimeter, diameter, circularity, centroid, moment of inertia are used in classifying. Our multiclass classification uses a hierarchical division of the possible output classes. The algorithm was implemented on the smartphones both android and iOS.

Results : Using a present mobile device, it can filters platelets, particles and overlapped cells out before classifying other segmented cells to fourteen types of abnormalities including normocyte, microcyte, macrocyte, spherocyte, stomatocyte, target cell, teardrop, ovalocyte, elliptocyte, schistocyte, burr cell, keratocyte, acanthocyte, and polychromasia. The classification algorithm was evaluated on real blood smear images and achieved overall precision and recall of 98.97% and 97.15% respectively. Table 1 presents the precision and recall of each class after being classified by the proposed algorithm.

Conclusion : Altogether, this is the first study demonstrates the feasibility of using mobile device for detection of abnormal RBCs in resource limited settings.

Keyword : Smartphone-based diagnosis, Abnormal red blood cell, Image processing

Table 1. Result of red blood cell (RBC) classification

	TP	FP	TN	FN	Precision (%)	Recall (%)
Normal cell	2968	10	2584	54	99.66	98.21
Microcyte	125	0	5472	19	100.00	86.81
Spherocyte	81	17	5518	0	82.65	100.00
Macrocyte	147	11	5455	3	93.04	98.00
Ovalocyte	486	15	5105	10	97.62	9487
Target cell	43	2	5567	4	95.56	91.48
Stomatocyte	198	64	5352	2	75.57	99.00
Teardrop cell	25	13	5576	2	65.79	92.60
Burr cell	111	32	5467	6	77.62	94.87
Schistocyte	179	2	5426	9	98.90	95.21
Uncategorized	272	6	5310	28	97.84	90.67

TP=True positive
FP=false positive
TN=True negative
FN=false negative

PP10-4

Chronic active epstein-barr virus infection of T/NK Cell type systemic form mimicking classic Hodgkin lymphoma

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Background : Chronic active Epstein-Barr virus infection (CAEBV) of T/NK cell type systemic form is an EBV-postive lymphoproliferative disorder. This entity is rare but has high fatality rate due to its life-threatening complications such as haemophagocytic lymphohistiocytosis syndrome, hepatic failure, coronary artery aneurism... Patients usually present with infectious mononucleosis-like illness including fever, hepatosplenomegaly, diarrhoea... However, when Hodgkin/ Reed-Sternberg-like cells are scattered in CAEBV, it is more likely to be misdiagnosed as classic Hodgkin lymphoma. Therefore, it is crucial to combine the clinical datas, site of involvement, biochemical tests and particularly the cytology, histology and immunohistochemistry in order to establish the most appropriate diagnosis and treatment plan for the patients.

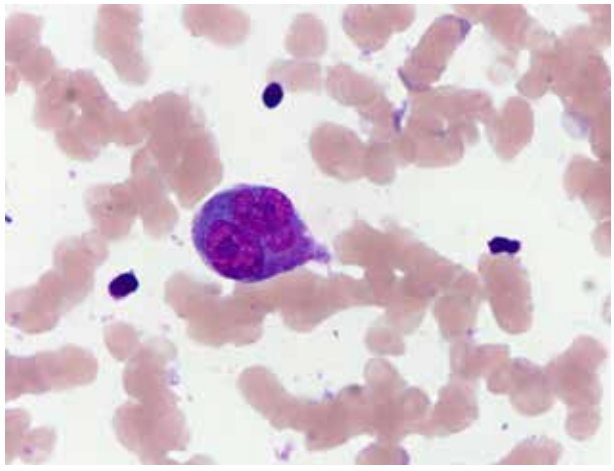
Method : A Case Report

Results : We reported a case of a 14-year-old female patient seeking for medical attention due to her abnormal complete blood count and prolonged fever. She had a history of meningitis 4 years ago and had a sequela of mild visual impairment. She presented with anemia, prolonged fever, hepatosplenomegaly but no lymphadenopathy. Her CBC revealed Hb 8.8 g/dl, MCV 85.2 fl, MCH 27.8 pg, PLT 112 K/ul, WBC 2.9 K/ul and SN 1.6 K/ul. She had high serum Beta2-microglobulin (5.45 mg/L), triglyceride (344.5 mg/dl) and ferritin (1609 ng/ml). Her Other biochemical blood tests are in normal ranges. She had negative EBV-IgM, positive EBV-IgG and high serum EBV viral load (EBV - DNA qPCR: 2635 copies/ml). The abdominal ultrasonography showed hepatosplenomegaly. The whole body CT-scan and soft tissue ultrasonography showed no lymphadenopathy. Flow cytometric immunophenotyping on her bone marrow aspirate detected no abnormalities. She also had a complex karyotype. The bone marrow aspirate and biopsy were performed. The bone marrow aspirate revealed hemophagocytosis and presence of large atypical cells resembling Hodgkin/Reed-sternberg cells. On the core section, we also detected these Hodgkin/Reed-Sternberg-like cells and hemophagocytosis. These cells were positive for CD30 (membranous and Golgi staining), CD2, CD56 and particularly EBER-ISH. They did not express CD45, CD3, CD20, PAX5, CD15, ALK, CD43, CD5, CD7, CD4, CD8 and CD68. With this immunophenotype of these large atypical cells, we could exclude the diagnosis of classic

Hodgkin lymphoma which typically expressed weak PAX5, CD30, CD15 and rarely expressed CD2 and CD56.

Conclusion : Base on the clinical context, site of involvement, pathohistology and immunophenotype of these cells, we made a diagnosis of chronic active EBV-infection of T/NK cell type, systemic form. She was treated with the protocol HLH-94 (Dexamethasone, Etoposide, Cyclosporin A and intrathecal Methotrexate). She now has no fever, her spleen and liver turn back to normal size and her recent CBC: Hb 10.1 g/dl, PLT 246 K/uL, WBC 5.63 K/uL, SN 3.44 K/uL. She still pays a follow-up visit at our hospital every 6 months.

Keyword : Chronic active EBV infection, Classic Hodgkin lymphoma



PP10-5

The clinical application of RNA sequencing and analysis in hematologic malignancies

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Background : RNA sequencing (RNA-seq) provides insight into the diagnosis and treatment of oncological diseases in the era of precision medicine. RNA-seq will be particularly useful in the diagnosis and risk stratification of hematologic malignancies, where the detection of gene fusions is essential. To integrate RNA-seq into clinical practices, stringent analytical and clinical validity standards must be demonstrated. In this study, we validated the performance of RNA-seq (TruSeq Stranded mRNA; Illumina, CA, USA) compared with targeted RNA-seq (Archer FusionPlex Pan-Hema Kit; ArcherDx, CO, USA) and investigated the optimal sequencing depth and split read count to detect various gene fusions in hematologic malignancies.

Method : Forty-three patients with gene fusion and eight patients without gene fusion who underwent targeted RNA-seq using Archer FusionPlex between November 2019 and July 2022 at Severance Hospital were selected for this study. Next-generation sequencing was performed on the NextSeq 550Dx sequencer (Illumina, CA, USA) in 300 bp paired-end format. Data analysis was performed using Archer Analysis version 6.0.3.2 (Invitae, CA, USA) and a customized pipeline for RNA-seq, respectively. The customized pipeline used STAR Grch37 RefSeq for annotation and Arriba for sequence mapping and the detection of gene fusions. To determine the optimal sequencing depth for detecting gene fusions, we performed in-silico analysis to establish the minimum required size of FASTQ file and compared the number of split reads of RNA-seq. In addition, we analyzed the sensitivity of BCR::ABL1 transcripts (e1a2 type) using BCR-ABL1 b2a2 RNA Dilution Set (10^-1 to 10^-5) (Invivoscribe, CS, USA) targeting 20Gb and 50Gb of FASTQ data size.

Results : A total of 42 clinically relevant gene fusions from 43 patients were discovered in the Archer FusionPlex. All of those fusions were also detected in RNA-seq (Table 1). Among those 43 patients, two gene fusions, TPM4::PDGFRB and RAB29::NUCKS1, were discovered solely in the Archer FusionPlex in two patients (acute myeloid leukemia and aggressive NK cell leukemia, respectively); however, they were clinically irrelevant. In three patients, two gene fusions (LILRA2::LILRB5 and DOCK2::GABRB2) that were not detected in the Archer FusionPlex were discovered with well-known gene fusions in RNA-seq, but their clinical significances were not clear. No fusion genes were detected using RNA-seq in eight patients who did not have fusion genes in Archer FusionPlex. Most RNA transcripts had at least five split reads when the size of FASTQ files was greater than 10 Gb, whereas ETV::RUNX, CBFA2T3::GLIS2, and P2RY8::CRLF2 fusions showed less than five split reads. In-silico analysis with FASTQ files of different sizes suggested that a minimum file size of 12Gb was required, although this varied depending on the fusion type. When the size of the FASTQ file was 20Gb, a minor BCR::ABL1 transcript was discovered at a level of 10^-2. However, no substantial improvement was observed when the file size was increased to 50Gb.

Conclusion : We validated RNA-seq in clinical settings to detect gene fusions in hematologic malignancies. The minimum size of FASTQ file required for RNA-seq was 12 Gb when the cut-off value of split reads was set to five for the detection of gene fusions. RNA-seq should be interpreted in the context of clinical and other laboratory findings. In particular, caution should be taken as certain gene fusions tended to have low split read counts.

Keyword : RNA-sequencing, Gene fusion, Clinical validation, Minimum required file size, Split read, Hematologic malignancy

Table 1. Information on gene fusions detected by RNA-seq in hematologic malignancy patients

Gene fusion	N	No. of split read (min, max)	Size of FASTQ file (min, max) (Gb)
KMT2A rearrangement	8	54 (11, 159)	47.5 (33.7, 73.5)
BCR::ABL1	6	89 (31, 292)	13.6 (11.9, 42.0)
ETV6::RUNX1	5	12 (4, 109)	14.5 (12.2, 44.0)
PML::RARA	4	22.5 (8, 35)	13.4 (11.4, 14.8)
RUNX1::RUNX1T1	4	117 (63, 122)	13.5 (13.2, 15.1)
CBFB::MYH11	2	131.5 (53, 210)	24.9 (13.1, 36.7)
CBFA2T3::GLIS2	2	121 (2, 240)	38.2 (38.0, 38.5)
Other	11	7 (1, 301)	44.6 (13.3, 49.9)
Total	42	55.5 (1, 301)	35.2 (11.4, 73.5)

PP10-6

A prospective analysis about the concordance of current tests used for the diagnosis of BM involvement of B-lineage lymphoma with respect to different lymphoma grade: Focused on the fluorescence in situ hybridization lymphoma panel

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Background : We evaluated the concordance of bone marrow (BM) aspirates, biopsy, immunohistochemical (IHC) stain, fluorescence in situ hybridization (FISH) and karyotype analysis used in diagnosis of BM involvement of B-lineage lymphoma, and evaluated the concordance characteristics with respect to lymphoma grade.

Method : 127 B-lineage lymphoma patients [92 high grade (HG), 35 low grade (LG)] diagnosed during recent 54 months and underwent BM study were prospectively enrolled. BM aspiration/biopsy/IHC stain with CD3 and CD20/FISH/karyotype were performed in each case and results were compared.

Results : Discrepancy rates (DR) between BM aspirates/biopsy and IHC stains were 14.2%/6.3%, respectively, and IHC stain detected additional 13.4%/6.5% BM-involved cases in BM aspirates-normal/biopsy-normal cases. DR between integrated BM morphology (IBM, involvement defined as abnormality at least one morphologic evaluation) and karyotype/FISH results was 34.6%/22.0%, respectively, and cases with FISH-abnormal/karyotype-normal are more frequent than those with FISH-normal/karyotype-abnormal. DR among IBM, karyotype and FISH in LG lymphoma (71.4%) was higher than in HG lymphoma (23.9%), and proportion of cases with IBM-involved but karyotype/FISH-normal were higher in LG lymphoma (45.7%) compared to HG lymphoma (8.7%). With FISH analysis, additional 6.5% of HG and 25.7% of LG lymphoma cases could show abnormal results concordant with IBM.

Conclusion : IHC stain would be useful in the sensitive detection of BM involvement. FISH analysis can reduce DR and more sensitively detect BM involved cases compared to karyotyping. LG lymphoma show higher DR, more skewed discrepancy pattern into IBM-involved but karyotype/FISH-normal, and induce higher concordance with IBM-involvement than HG lymphoma when FISH analysis is performed.

Keyword : BM study; Concordance; FISH; Karyotyping; Lymphoma grade

PP10-10

White blood cell counting of Sysmex XN hematology analyzer in severe leukopenic samples: Comparison between whole blood mode and low white blood cell mode

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Background : The Sysmex XN modular system (XN, Sysmex, Kobe, Japan) counts white blood cells (WBCs) using both whole blood (WB) and low WBC (LW) modes in severe leukopenic samples (< 0.5 x 10^9/L). We investigated the analytical performance of WB mode and LW mode in severe leukopenic samples.

Method : In a total of 650 leukopenic samples (0.01 – 0.49 x 10^9/L) by WB mode, correlation, difference, and agreement between WB and LW modes were analyzed. Precision was investigated in four samples by 10 times measurement and compared with the desirable precision criterion (10.8%).

Results : WB and LW modes showed a very high correlation ($r = 1.00$) and acceptable difference (mean difference = 0.01 ± 0.38) with a very good agreement ($\kappa = 0.90$). WB mode met the precision

criterion in all four samples, while LW mode exceeded the criterion in one of the four samples. Two samples (0.3%) showed discrepant WBC counts between WB and LW modes; one sample showed erroneously increased WBC counts in LW mode (0.03 vs. 2.92 × 10^9/L), whereas the other sample showed erroneously decreased WBC counts in WB mode (0.04 vs. 0.41× 10^9/L) verified by manual slide review.

Conclusion : This is the first study to investigate the analytical performance of WB and LW modes in Sysmex XN, and the two modes showed overall reliable analytical performance. Considering the possibility of random errors, samples with discrepant WBC counts between the two modes should be carefully reviewed.

Keyword : Sysmex XN, White blood cells, Severe leukopenia, Comparison, Whole blood mode, Low white blood cell mode

PP10-11

The first Korean case of transcobalamin II deficiency with a pathogenic variant in the TCN2 Gene

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Background : Transcobalamin II (TC II) is a plasma protein that binds to cobalamin (vitamin B12) in the bloodstream after the cobalamin is taken up by the ileal epithelial cell and transported into the portal circulation. TC II deficiency is an inherited disorder caused by variants in the TCN2 gene, in which the patient can present symptoms related to intracellular cobalamin depletion despite the normal serum cobalamin level. TC II deficiency can be manifested in infancy with megaloblastic anemia, pancytopenia, diarrhea, pallor, lethargy, methylmalonic aciduria, homocystinuria and can be accompanied by hemophagocytic lymphohistiocytosis (HLH). We report the first case of Korean patient with TC II deficiency.

Method : A one-month-old boy had persistent fever, anemia, and thrombocytopenia. Initial hemoglobin (Hb) level was 7.8 g/dL, platelet count was 94 x 10^9/L and mean corpuscular volume (MCV) was 95.8 fL. Other laboratory tests showed elevated ferritin and soluble interleukin-2 receptor levels (1,271.5 μg/L and 5,181 IU/mL, respectively). Above all, the cytomegalovirus (CMV) real-time PCR test showed viral load of 190,000 IU/mL in urine and 452 IU/mL in plasma. These results led to the suspicion that the patient's symptoms might be due to HLH by congenital CMV infection. Because his symptoms were relieved without use of antiviral agents, he was given months of follow-up. A few months later, he was admitted again with fever, pallor, and severe pancytopenia. To identify the cause of cytopenia and confirm hemophagocytosis, bone marrow examination was performed. The bone marrow aspiration showed hemophagocytic histiocytes accompanied by megaloblastic changes in erythroid precursors. Given that the CMV infection was persistent, it was reasonable to conclude that the patient's bone marrow findings were due to viral infection. After he was treated with intravascular ganciclovir, CMV viral load was no longer detected. However, despite no further findings of viral infection, the patient's pancytopenia did not improve for several months and recurrent transfusions were needed. Congenital hematologic disease gene panel and mitochondrial DNA testing results were all negative. Therefore, the bone marrow examination was performed once more to rule out progressive bone marrow failure syndrome. However, similar findings, presenting hypercellular marrow (70-100%) with megaloblastic changes in erythroid precursors, were shown. Since the serum homocysteine level and urine methylmalonic acid level were elevated (23.5 μmol/L and 408.1 mmol/mol Cr, respectively) and the serum vitamin B12 level was within normal range (474 pg/mL), congenital metabolic disorder, especially, TC II deficiency was suspected.

Results : DNA sequencing of all coding exons and flanking intronic regions identified the pathogenic variant in TCN2 gene (TCN2, NM_000355.4:c.348_349del, p.Cys116*, homozygote), leading to the diagnosis of TC II deficiency. The patient's clinical manifestations including pancytopenia, diarrhea and lethargy improved dramatically after supplementing high concentration of cobalamin.

Conclusion : This is the first Korean case of TC II deficiency. This report suggests that if the features of megaloblastic anemia are observed in infants, the results of amino and organic acid tests should be investigated, and consequently, TC II deficiency must be considered. Moreover, this report implies that the molecular study targeting TCN2 gene can provide clues to the unexplained cytopenia.

Keyword : Cobalamin (vitamin B12), Transcobalamin II, Transcobalamin II deficiency, TCN2 gene, Megaloblastic anemia, Cytomegalovirus

PP10-12

Clinical performance of a novel next-generation sequencing-based IGH clonality assay in pediatric B-cell acute lymphoblastic leukemia patients

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Background : Identification of minimal residual disease (MRD) is crucial for determining prognosis and establishing treatment strategies in B-cell acute lymphoblastic leukemia (B-ALL). Currently, MRD detection for B-ALL is mainly performed based on the next-generation sequencing (NGS) using immunoglobulin (IG) clonality and next-generation flow (NGF). In this study, we evaluated the clinical performance of a novel NGS-based Celemics IGH assay (Cel-IGH; Celemics, Seoul, Korea) compared to other NGS and NGF assays in patients with pediatric B-ALL.

Method : A total of 31 patients with pediatric B-ALL diagnosed between August 2017 and December 2021 were included, and their bone marrow aspirate samples at diagnosis and follow-up were analyzed. NGS-based MRD assessment was performed using Cel-IGH and LymphoTrack IGH FR1 assay (Lym-IGH; Invivoscribe Technologies, San Diego, CA, USA). NGF-based MRD assessment was performed according to the EuroFlow guideline.

Results : Initial IGH clonality was detected in 83.9% (26/31) and 90.3% (28/31) of diagnostic samples in Cel-IGH and Lym-IGH, respectively. In follow-up samples, median IGH read depths were 349,389 and 415,540 in Cel-IGH and Lym-IGH, respectively, and MRD positive rate was 74.5% (35/47), 61.1% (33/54), and 56.7% (34/60) in Cel-IGH, Lym-IGH, and NGF, respectively. The concordance rate of MRD detection was 78.3% (both positive, 27/46; both negative, 9/46) for Cel-IGH and Lym-IGH, and 70.2% (both positive, 24/47; both negative, 9/47) for Cel-IGH and NGF, respectively. Regarding the MRD value, each test showed a moderate correlation ($r = 0.67$ for Cel-IGH and Lym-IGH, $r = 0.78$ for Cel-IGH and NGF, all $p < 0.001$).

Conclusion : Cel-IGH was a sensitive assay for MRD detection and showed comparable clinical performance to other conventional NGS and NGF assays. Further investigations from a prognostic aspect will help confirm the clinical significance of this assay.

Keyword : Minimal residual disease, B-cell acute lymphoblastic leukemia, IGH clonality, Next-generation sequencing, Next-generation flow

PP10-13

Effect of refrigeration storage time delay and RNA extract kit difference in RNA-seq data quality of blood EDTA samples

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Background : The importance of analysis and clinical application of RNA expression using NGS technology have gradually increased in research and clinical fields. However, there has been only limited reports regarding the influence of the blood EDTA refrigeration time delay and the batch effect by using different RNA extraction kits. In this study, we performed a whole transcriptome analysis to examine the impact of refrigeration storage time and between-kit batch effect on the RNA-seq data quality.

Method : To investigate the influence of refrigeration time, blood RNA extraction and transcriptome sequencing by Illumina hi-seq were performed in four subjects at three different periods: immediately after blood collection (H0), after 24 hours of storage at 4 ℃ (H24), and after 48 hours of storage at 4 ℃ (H48). In addition, blood EDTAs collected from four subjects were examined using QIAamp RNA Blood mini Kit and Roche High Pure RNA Isolation kits to evaluate the batch effect. For statistical analysis, Pearson's correlation test, linear regression, and calculation of the coefficient of variation (CV) were performed using the R software.

Results : Average RNA concentrations measured using NanoDrop were higher in Qiagen samples than Roche samples immediately after blood collection (Qiagen = 210.8 ng/ul, Roche = 68.2 ng/ul), after 24 hours at 4 ℃ (Qiagen = 210.05 ng/ul, Roche = 95.6 ng/ul), and after 48 hours at 4℃ (Qiagen = 213.15 ng/ul, Roche= 89.45 ng/ul). Next, in evaluation of the batch effect by different RNA extraction kits (Qiagen and Roche), three subjects show 0.866, 0.883, and 0.884 respectively in Pearson R value between Qiagen-H0 and Roche-H0. In addition, the slopes by linear regression for the three subjects were 0.4419, 0.4309, and 0.3753. On the other hands, the Pearson R values of Qiagen-H0 among the three subjects were 0.990, 0.993, and 0.994, and those of Roche-H0 were 0.985 and 0.989, showing good correlation when the same RNA extraction kit was used for each subject. In addition, for the three subjects, CV was calculated between samples extracted by Qiagen-H0 and Roche-H0. The number of transcripts with CVs greater than 20% was on average 9161 with 5060 transcripts overlapping among the three subjects. Among samples collected using the Qiagen kit, the

correlation between Qiagen-H0 and Qiagen-H24 was 0.997, and the correlation between Qiagen-H0 and Qiagen-H48 was 0.9945. When CV was calculated between between Qiagen-H0 and Qiagen-H48, 2677 and 4534 transcripts exhibited CV greater than 20%. On the other hand, among the samples collected using the Roche kit, the correlation between between Roche-H0 and Roche-H24 was 0.987, and the correlation between Roche-H0 and Roche-H48 was 0.991. When CV was calculated between Roche-H0 and Roche-H48, 3389 transcripts exhibited CV greater than 20%.

Conclusion : Under storage conditions of 4 ° C, blood RNA samples extracted using the Qiagen extraction kit exhibited excellent performance for up to 48 hours, while samples extracted using Roche showed good performance for up to 24 hours and were acceptable for up to 48 hours. Furthermore, the batch effect between kits observed in our study suggests a need for batch correction.

Keyword : RNA-seq, Transcriptome, Next generation sequencing, Blood test, Blood buffy coat, Illumina sequencing

PP10-14

Comparison study of two analysers for routine coagulation tests

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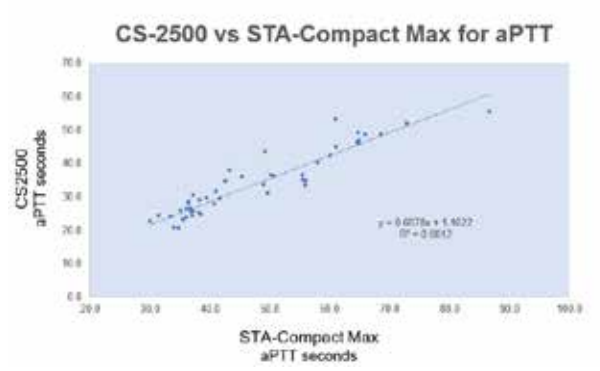
Background : Comparison study between two analysers is part of method verification procedure. Recently we evaluated this scope for our Sysmex Coagulation System-2500 (CS-2500). The CS-2500 is a high performance coagulation system that utilizes clotting principle for the measurements of two routine tests; Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT). The purpose of this study was to compare the PT and aPTT measurements between our CS-2500 and our established analyser; STA-Compact Max Diagnostica Stago coagulometer (STA-Compact Max) that were placed at 25 kilometer apart.

Method : The PT and aPTT were compared between the CS-2500 and STA-Compact Max. Samples were collected from daily diagnostic samples that covered both normal and pathological ranges. Firstly the analysis was performed on the STA-Compact Max. Later the samples were transported to another laboratory and processed on the CS-2500 within 3 hours. The data was tabulated and analysed in Microsoft Excel 2016.

Results : Generally, the CS-2500 shows a good correlation with STA-Compact Max based on r-squared values (PT= 0.9765 and aPTT= 0.8812). Furthermore, a strong positive linear correlation is also supported by r value that is close to 1 (PT (y=0.8531x-1.8195 and r=0.9882 and aPTT (y=0.6878x+1.1022 and r=0.9387). However, the bias for PT and aPTT are 6.0% and 13.8% respectively. The difference in analyser's principle (STA-Compact Max uses mechanical principle in measuring PT and aPTT) and the content of reagents are factors that contribute to the result difference between two analysers. Another factor is the pre-analytical change that may occur in the samples during transportation between two locations of analysers.

Conclusion : In this comparison study, there were small differences between the two analysers when measuring PT and aPTT. Overall, we suggest that these differences may cause the laboratory to use different reference intervals for the CS-2500.

Keyword : Correlation study



PP10-15

HTLV-1 bZIP factor modulates acetylation-dependent functions in cells via suppression of HDAC6

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Background : Human T-cell leukemia virus type-1 (HTLV-1) is known to cause a type of cancer, referred to as adult T-cell leukemia/lymphoma (ATLL), and a demyelinating disease called HTLV-1 associated myelopathy/Tropical spastic paraparesis (HAM/TSP).

HTLV-1-infected T cells have been hypothesized to contribute to the development of these disorders, although the precise mechanisms are not well understood. The HTLV-1 provirus possesses structural and enzymatic proteins typical of all retroviruses (i.e., gag, pol, env) and LTR on both ends. HBZ (HTLV-1 bZIP factor) gene was identified as a gene transcript from the 3'-LTR in a pX region. Notably, HBZ is consistently expressed in all ATLL cells, suggesting that HBZ appears to promote the development of ATLL. In this study, we searched for cellular factors that interacted with HBZ by yeast two-hybrid screening system. This approach identified HDAC6, which belongs to the class IIb HDAC family and is a well-known oncogenic protein.

Method : We conducted a yeast two-hybrid screen using full-length HBZ as bait and newly identified HDAC6. Association of HBZ with HDAC6 was investigated in mammalian cells and binding domains both of HBZ and HDAC6 were detected. Subcellular distribution, when coproduction of HBZ together with HDAC6 in cells were examined confocal microscopic. The degree of protein acetylation was quantified using an anti-acetylated lysine antibody.

Results : Interaction between HBZ and HDAC6 were confirmed in mammalian cells by co-immunoprecipitation (Co-IP) assay. Central domain of HDAC6 bound to the N-terninal domain of HBZ. The molecular interaction of HBZ with HDAC6 might alter the mutual subcellular localization. Thus, we examined the cellular localization of HBZ and HDAC6 in transiently transfected HEK-293T cells. As previously reported, GFP-HBZ localized to the nucleus as granular speckles. However, when GFP-HBZ and mCherry-HDAC6 were co-expressed, GFP-HBZ no longer formed speckles but was distributed in the nuclei together with mCherry-HDAC6, suggesting that a physical interaction with HDAC6 alters the distribution of HBZ. Interestingly, HBZ dramatically suppressed HDAC6-dependent tubulin deacetylation and up-regulated the stability of dynamic microtubule. Our current study is focused on understanding the molecular significance by which the interaction between HBZ and HDAC6 regulates the acetylation-dependent cellular functions.

Conclusion : Our results suggested that HBZ may be affected the function of HDAC6 and help us to understand the pathogenesis of HTLV-1.

Keyword : HTLV-1, HBZ, HDAC6, Adult T-cell leukemia/lymphoma, Deacetylation

PP10-17

Ribosomal component RPS4X as a novel modulator of MDM2 stability: interfering to E3 ubiquitin ligases for MDM2 and prevention of proteasome-mediated degradation

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Background : Mouse double microchromosome 2 (MDM2) was identified as a protein that binds to the tumor suppressor gene p53. It is well known that MDM2 is highly overexpressed in various cancer cells, including acute myeloid leukemia (AML) and adult T-cell leukemia (ATL). MDM2 inhibits the function of p53 and is significantly involved in cell tumorigenesis through promoting cell proliferation and suppressing apoptosis, and its expression correlates with the phenotypes of high-grade, late-stage, and more resistant tumors. However, the molecular mechanisms of MDM2 stabilization in tumor cells is still unclear. Elucidation of the stabilization mechanism of MDM2 is essential to the onset mechanism of these tumors and the development of new anticancer drugs.

Method : We performed a comprehensive search for host factors that interact with MDM2 using an yeast two-hybrid screening system and newly identified RPS4X. Interaction of MDM2 and RPS4X was investigated in mammalian cells, and binding region both of them were determined. To investigate subcellular distribution, coexpression of RPS4X with MDM2 in cells were examined confocal microscopic. We also defined whether RPS4X is involved in the stabilization of MDM2.

Results : We confirmed that RPS4X interact with MDM2 in mammalian cells by co-immunoprecipitation (Co-IP) assay. We also found that RPS4X binds to the central region of MDM2 through its N-terminal region. It has been reported that MDM2 is ubiquitinated and degraded by forming homodimers with itself and heterodimers with its structural analogue MDMX.Overexpression of RPS4X in cells suppressed MDM2 homodimerization and heterodimerization with MDMX, indeed, the ubiquitination level of MDM2 was significantly suppressed and its stabilization was observed. Intriguingly, we also discovered a novel function of RPS4X that interacted with Cullin1 (CUL1). CUL1 functions as an E3 ubiquitin ligase for various proteins including MDM2 that play important roles in cellular fate such as cell cycle regulation, proliferation and tumorigenesis. Overexpression of RPS4X in cells led to an inhibition

the association CUL1 with MDM2. These functions of RPS4X may contribute to the hyper-stabilization of MDM2 within tumor cells. Furthermore, RPS4X markedly suppressed the ubiquitination of not only MDM2 but also other CUL1 target molecules, suggesting that RPS4X may be involved in tumor malignancy and anticancer drug resistance.

Conclusion : Our research suggests that RPS4X may function as a key modulator in MDM2-mediated intracellular mechanisms and seems to play a role in elucidating the pathogenesis of AML, ATL and other intractable cancers. We revealed that RPS4X also interacted with CUL1 and prevented the proteasome-mediated degradation for MDM2 as well as other target proteins of CUL1. Further studies will be needed to define the role of RPS4X in the development of cellular transformation. Clarification of the molecular mechanisms by which RPS4X contributes to tumorigenesis may ultimately facilitate the discovery of a therapeutic agent for many cancers.

Keyword : AML, ATL, MDM2, RP, CUL1, Ubiquitination

PP10-20

Evaluation of monocyte distribution width as an early marker for diagnosis of sepsis

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Background : Since sepsis has a high mortality rate, early diagnosis and treatment can increase the survival rate and improve prognosis. However, it is difficult to diagnose sepsis accurately in actual clinical practice. Determination of Procalcitonin or C-reactive protein (CRP) levels, which are conventionally used for diagnosing sepsis, are time-consuming. Recent studies have shown that monocyte distribution width (MDW), which is observed simultaneously during the complete blood count (CBC)/diff test in Beckman Coulter DxH900, is a potential marker for the early detection of patients with or developing sepsis. This study evaluated MDW for early detection of sepsis in patients visiting the emergency department.

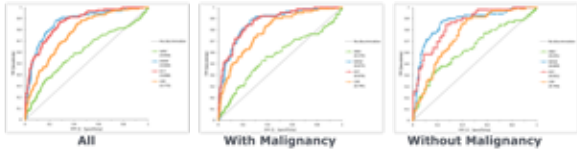
Method : This study enrolled a total of 1,167 patients (>18 and ≤ 80 years of age) who visited the emergency department of a single institution from August 4, 2020 to March 31, 2021, whose initial evaluation included CBC with differential tests and other blood tests (CRP and ProcalcitoninPCT). Samples for CBC and MDW were collected in K3-EDTA tubes and analyzed in a UniCel DxH 900 analyzer (Beckman Coulter, Inc., USA). Sepsis was diagnosed according to the sepsis-3 definition through a medical record review. All patients were grouped into no sepsis, sepsis, and septic shock. The diagnostic performance of MDW and other biomarkers for the detection of sepsis was evaluated through statistical analysis. The subgroup analysis for diagnostic performance was performed in subjects with malignancy or without malignancy. All statistical analyses were carried out using Analyze-it, and $P<0.05$ was considered statistically significant.

Results : Of the 1167 patients enrolled, 156 patients (13.4%) were diagnosed with sepsis (135 (11.6%) sepsis and 21 (1.8%) septic shock). Among sepsis patients, those with positive culture results were 46.8%, and the rest either had negative culture results (43.6%) or did not proceed with culture testing (9.6%). The MDWs of the no sepsis group, sepsis group, and septic shock group were 19.70, 27.20, and 31.10, respectively, CRPs were 1.82 mg/dL, 8.84 mg/dL, and 20.44 mg/dL, and Procalcitonins were 0.19 ng/mL, 1.72 ng/mL, and 18.20 ng/mL (median, $P<0.0001$). All biomarkers showed a higher value in the sepsis group compared to the no sepsis group. Median MDW showed an increasing trend in patients with malignancy and without malignancy. The AUC of MDW, WBC, CRP, and Procalcitonin for the prediction of sepsis were 0.869, 0.604, 0.773, and 0.868, respectively ($P<0.0001$), thus MDW and Procalcitonin showed similar diagnostic performance. At the cutoff of MDW (21.5), the sensitivity was 91.0% and the negative predictive value (NPV) was 98%. The diagnostic performance of MDW showed similar results in cancer patients and cancer-negative patients (AUC 0.873 vs. 0.869).

Conclusion : MDW, which is automatically measured in Beckman Coulter DxH900 hematology analyzer without the requirement of additional reagents during CBC/diff test, has high accuracy in detecting patients with sepsis and could be a reliable tool for early detection of patients with sepsis in the emergency department compared to results of culture or other biomarkers which take longer time to get the result. Furthermore, high NPV may help clinicians rule out sepsis.

Keyword : Sepsis, Emergency department, Monocyte distribution width, DxH900 hematology analyzer

Population	Biomarker	Total	No sepsis	Sepsis	AUC	Cutoff	Sensitivity	Specificity	PPV	NPV
All	MDW	1167	1011	156	0.869	22.3	88.5	74.5	35	98
						21.5	91.0	69.9	32	98
	WBC	1166	1010	156	0.604	10.4	50.6	68.9	20	90
	CRP	1161	1006	155	0.773	3.09	85.8	57.7	24	96
	PCT	563	445	118	0.868	0.40	87.3	71.7	32	97
With malignancy	MDW	752	667	85	0.873	22.3	89.4	73.2	30	98
						21.5	91.8	69.0	27	99
	WBC	751	666	85	0.539	9.4	56.5	61.4	16	92
	CRP	746	662	84	0.795	3.26	89.3	56.6	21	98
	PCT	387	322	65	0.876	0.52	83.1	78.3	33	97
Without malignancy	MDW	415	344	71	0.869	22.3	87.3	77.0	44	97
						21.5	90.1	71.8	40	97
	WBC	415	344	71	0.641	14.0	42.3	84.0	35	88
	CRP	415	344	71	0.764	2.42	85.9	60.5	31	95
	PCT	176	123	53	0.851	0.42	84.9	73.2	40	96



PP10-21

Lower red blood cell distribution width than actual red blood cell anisocytosis from automated hematology analyzer

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Background : Red Blood Cell distribution width (RDW) is an indicator of the size diversity of red blood cells (RBCs), and the results are automatically reported in routine CBC tests using automated hematology analyzers. RDW is expressed as standard deviation (SD, fL) or commonly as a coefficient of variation (CV, %). RDW helps differentiate the causes of microcytic and normocytic anemias (high RDW in iron deficiency anemia vs. normal RDW in heterozygous thalassemia). RDW is increased in hemolytic anemia, hereditary spherocytosis, vitamin B12 or folate deficiency, anemia in myelodysplastic syndrome, and so on. Besides, a higher RDW is considered a new predictive biomarker for worse prognosis in patients with cardiovascular diseases. While evaluating peripheral blood (PB) morphology, we found patients with actual anisocytosis whose RDW was close to normal. We found that the automated hematology analyzers showed different results in these patients. Accordingly, we aim to inform that RDW results may differ between automated hematology instruments.

Method : We identified four patients with significant anisocytosis in peripheral blood smear, but low RDW results from June to July 2022 by using DxH900 (Beckman Coulter). The CBC was then remeasured by XN1500 (Sysmex) hematology analyzer, and we compared the differences in RBC indices, electrical impedance histograms, and peripheral blood smear. RDW-CV is derived from the pulse-height analysis histogram of the impedance channel. The RDW-CV calculation formula for the two CBC devices is as follows. DxH900: RDW-CV=1 standard deviation (SD)/mean corpuscular volume (MCV)×100; XN1500 : RDW-CV=(L2-L1)/(L2+ L1)×100, L1=MCV-1SD, L2=MCV+1SD.

Results : In four patients, there was an average difference of 3.6% (range 2.0-5.5%) in RDW-CV between the two devices but no significant difference in RDW-SD. The RBC histograms of the two devices were similar, but the RDW-CV results were different between two instruments. There was no significant difference in RBC count, hemoglobin, hematocrit, MCV, MCH, and MCHC in cases 1, 3, and 4, but in case 2, MCV, MCH, and MCHC showed differences between the two instruments. In case 2, cold agglutinin was 1:64, and it was confirmed that RBC agglutination increased MCV, MCH, and MCHC through repeated measurement with XN-1500 after warming, while RDW-CV was measured high (23.9% and 21.2%) both before and after warming. Peripheral blood smears showed RBC agglutination in cases 1, 2, and 3. Abnormally shaped RBCs (spherocytes in case 1; elliptocytes, schistocytes in case 3; and tear drop cells, elliptocytes in case 4) were observed in 10-20% of erythrocytes.

Conclusion : RDW-CV may have different calculation methods depending on the automated hematology analyzers, so the results from the analyzers may differ depending on the patient's RBC status. If the RDW results do not reflect actual RBC anisocytosis, analysis with a different type of hematology analyzer together with a peripheral blood smear will be helpful.

Keyword : Red blood cell distribution width, Automated hematology analyzer, RBC histogram, Formula, False result

Table 1. RBC indices of 4 patients with discrepant RDW-CV between automated hematology analyzers

Case No.	Hematology analyzer	RBC parameters (unit) (reference range) RBC (x10⁶/㎕)	Hb (g/dL)	Hct (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW-CV (%)	RDW-SD (fL)	Diagnosis
		F (3.8-5.3) M (4.0-5.4)	(12-16) (14-16.5)	(37-47) (42-50)	(80-96)	(27-33)	(32-36) (33-36)	(11.5-14.5)	(NA)	
1	DxH900	2.0	7.0	20.2	103.7	36.0	34.7	14.3	NA	Autoimmune hemolytic anemia
	XN1500	1.9	7.0	20.6	104.4	35.6	34.1	18.4	49.4	
2	DxH900	1.9	7.8	20.2	108.2	42.0	38.8	15.7	49.4	Hemophagocytic lymphohistiocytosis
	XN1500	1.7	7.7	17.5	101.7	44.8	44.0	23.9	NA	
	XN1500 (warming)	2.1	7.7	20.3	96.7	36.7	37.9	21.2	47.9	
3	DxH900	2.6	8.1	24.6	94.0	30.8	32.8	15.1	48.6	Myelodysplastic syndrome
	XN1500	2.6	8.1	25.2	96.9	31.2	32.1	17.1	48.0	
4	DxH900	2.6	10.7	32.6	127.8	42.0	32.9	17.9	86.6	Treated Polycythemia vera
	XN1500	2.5	10.7	32.6	128.3	42.1	32.8	20.5	85.7	

Abbreviations : RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; CV, coefficient variation; SD, standard deviation; NA, not available

PP10-22

A clinical laboratory-oriented targeted RNA-seq system accurately detected various types of gene fusion reported in Philadelphia chromosome-like B-lymphoblastic leukemia

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Background : Genetic abnormalities that occur in hematologic malignancies can be broadly classified into sequence variants, gene fusion, and abnormal gene expression. Among these genetic abnormalities, gene fusion not only plays an important role in the development of hematologic malignancies, such as acute leukemia, but is also important as an essential marker for the diagnosis, risk assessment, optimal treatment selection, and residual lesion detection. Most clinical laboratories use conventional cytogenetic testing, multiplex reverse transcriptase-polymerase chain reaction (PCR) and fluorescence in situ hybridization, to detect gene fusions. However, the currently used methods have great limitations in detecting various gene fusions occurring in hematologic malignancies. To overcome these shortcomings, RNA sequencing (RNA-seq), a next-generation sequencing technique, is being introduced in clinical laboratories. The authors developed a targeted RNA-seq panel, a bioinformatics pipeline used for targeted RNA-seq to detect sequence variants, gene fusions, and altered gene expression, which can be used more conveniently in clinical laboratories.

Method : The targeted RNA-seq panel (KBB-RNAseq NGS-Leukemia-PHB; KBlueBio Inc., Hwasun, Korea) consisting of 85 genes was developed in consideration of operational efficiency in clinical laboratories and based on information technology with an automated reporting system. This panel was applied to a comparative evaluation with the other commercialized targeted RNA-seq panel (Archer FusionPlex Heme Panel version 2; ArcherDX, Boulder, CA, USA). For comparison with the existing analysis system, the Archer FusionPlex Heme v2 (ArcherDx) based on the cDNA library for specific genes using anchored multiplex PCR was used. To evaluate the performance of these systems, bone marrow specimens were used while diagnosing 93 patients with acute leukemia (15 acute myeloid leukemia (AML), 35 adult B-lymphoblastic leukemia (B-ALL), 30 childhood B-ALL, and 13 T-lymphoblastic leukemia (T-ALL)).

Results : Among all 93 acute leukemia patients, tier 1 or tier 2 gene fusions were observed in 72 (77%) patients. Gene fusions were detected in 83% (25/30) of pediatric B-ALL patients, and in 94% (33/35) of adult B-ALL patients. In patients with AML and T-ALL, the proportions of gene fusions were 53% (8/15) and 46% (6/13), respectively. For the comparative evaluation, 4 cases of B-ALL, 3 cases of AML, and 1 case of T-ALL were used. The results of two analysis systems were consistent in 7 of the 8 evaluated patients, but an IGH::CRLF2 fusion in a B-ALL case was detected only with the panel developed by the authors. It is known that the CRLF2 gene is a causative gene in half of the Philadelphia chromosome (Ph)-like B-ALL cases, which account for 20-25% of all B-ALL cases and are classified as a new type of B-ALL showing a very poor prognosis.

Conclusion : Our targeted RNA-seq system showed a reliable and stable performance in detecting various types of gene fusion occurring in acute leukemia in clinical laboratories. Especially, this system accurately detected gene fusion that causes Ph-like B-ALL and is not detected in the other commercialized targeted RNA-seq system. Therefore, our targeted RNA-seq system was found to be very useful in diagnosing Ph-like B-ALL.

Keyword : Targeted RNA-seq, Clinical Laboratory, Ph-like B-ALL, Acute Leukemia

Table 1. Comparison between the two targeted RNA-seq systems to evaluate the accuracy of gene fusions detection in acute leukemia

Sample no.	Diagnosis	Multiplex RT-PCR	Commercial targeted RNA-seq system	Breakpoint		Our targeted RNA-seq system	Breakpoint	
1	AML	*CBFB-MYH11*	*CBFB-MYH11*	[illegible]	[illegible]	*CBFB-MYH11*	[illegible]	[illegible]
			CBFB-MYH11	[illegible]	[illegible]			
2	AML	*RUNX1-RUNX1T1*	*RUNX1-RUNX1T1*	[illegible]	[illegible]	*RUNX1-RUNX1T1*	[illegible]	[illegible]
			RUNX1-RUNX1T1	[illegible]	[illegible]	*RUNX1-RUNX1T1*	[illegible]	[illegible]
			RUNX1-RUNX1T1	[illegible]	[illegible]	*RUNX1-RUNX1T1*	[illegible]	[illegible]
3	AML	*PML-RARA*	*PML-RARA*	[illegible]	[illegible]	*PML-RARA*	[illegible]	[illegible]
4	B-ALL	*BCR-ABL1*	*BCR-ABL1*	[illegible]	[illegible]	*BCR-ABL1*	[illegible]	[illegible]
						BCR-ABL1	[illegible]	[illegible]
5	B-ALL	*ETV6-RUNX1*	*ETV6-RUNX1*	[illegible]	[illegible]	*ETV6-RUNX1*	[illegible]	[illegible]
			ETV6-RUNX1	[illegible]	[illegible]	*ETV6-RUNX1*	[illegible]	[illegible]
			ETV6-RUNX1	[illegible]	[illegible]			
			ETV6-RUNX1	[illegible]	[illegible]			
6	B-ALL	-	*P2RY8-CRLF2*	[illegible]	[illegible]	*P2RY8-CRLF2*	[illegible]	[illegible]
			EIF4E3-FOXP1	[illegible]	[illegible]			
7	B-ALL	-	-			*IGH-CRLF2*	[illegible]	[illegible]
						IGH-CRLF2	[illegible]	[illegible]
						IGH-CRLF2	[illegible]	[illegible]
8	T-ALL	-	*PICALM-MLLT10*	[illegible]	[illegible]	*PICALM-MLLT10*	[illegible]	[illegible]
			PICALM-MLLT10	[illegible]	[illegible]	*PICALM-MLLT10*	[illegible]	[illegible]
			PICALM-MLLT10	[illegible]	[illegible]	*PICALM-MLLT10*	[illegible]	[illegible]

Abbreviations: RNA-seq, RNA sequencing; RT-PCR, reverse transcriptase-polymerase chain reaction; AML, acute myeloid leukemia; B-ALL, B-lymphoblastic leukemia; T-ALL, T-lymphoblastic leukemia.

PP10-23

Performance evaluation of a digital morphology analyzer for leukocyte differential count

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Background : Leukocyte differential count and morphological analysis are crucial for screening and differential diagnosis of hematological disorders. Conventional gold-standard method for leukocyte differential count is manual morphological evaluation. However, recent development of digital image analyzers enables automation, standardization, and shortening of time and labor of the review process of blood smears. In this study, we evaluated the performance of an automated cell image analyzer (PBIA-12A; UIMD Co., Seoul, Korea) for white blood cell (WBC) differential count.

Method : We included 100 whole blood specimens showing normal WBC differential count and 128 specimens with abnormal values. All samples were smeared two times with an automatic slide preparation system (SP-50 System; Sysmex, Kobe, Japan). A total of 228 slides were scanned with PBIA-12A, and the images of the cells obtained by the automated analyzer were reclassified and confirmed by laboratory experts. A manual differential count of 200 cells was performed by two experts. Accuracy was defined as the concordance rate between pre-classification by PBIA-12A and post-classification results. The correlation between pre-classification result of PBIA-12A and the manual differential count was evaluated using Pearson's correlations coefficient (r).

Results : The overall accuracy of PBIA-12A on normal, abnormal, and total samples was 98.92%, 95.61%, and 97.08%, respectively. Compared with manual differential count, pre-classification results of PBIA-12A showed strong correlations ($r \geq 0.9$) for segmented neutrophils, lymphocytes, monocytes, eosinophils, and blasts. Moderate correlations ($r \geq 0.40$ and < 0.69) were observed for basophils, band neutrophils, and nucleated red blood cells, probably due to low cell counts

Conclusion : The results of this study suggest that the overall accuracy of PBIA-12A for leukocyte differential count was high, and the correlation between the PBIA-12A and manual differential count was acceptable. Incorporation of PBIA-12A as a screening tool for leukocyte analysis may be helpful in clinical laboratories.

Keyword : Automated analyzer, White blood cell differential, Agreement, Correlation, PBIA-12A

PP11-2

Spectrum of haemoglobinopathies; A tertiary care hospital experience

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Background : Haemoglobinopathies includes thalassemia and different structural defects in globin chains. These different types of haemoglobinopathies are prevalent in many countries including Pakistan. The World Health Organization has a effective role in controlling the different types of thalassemia, especially beta thalassemia major and it's carriers, in many developing countries.

Method : The cross sectional retrospective analysis was proceed in hematology deparment of CHK central laboratory, Dr Ruth KM pfau hospital Karachi from 1st jan 2019 – 31 dec 2021. All suspected cases of hemoglobinopathy was included. Complete blood count is done on XN 1000 analyzer and then HPLC is performed on Arkray analyzer

Results : Out of 747 cases, 558 (74.6%) were normal and 189 (25.3%) cases had abnormal haemoglobin pattern. 356 (47.6%) were males and 391 (52.3%) were females. Of all cases of Anaemia 278 (49.8%) were microcytic hypochromic, 22 (3.9%) macrocytic and the rest 258 (46.2%) had normocytic normochromic picture. Of the 189 abnormal cases, Spectrum of haemoglobinopathies prevalent were Beta Thalassemia trait 117(61.9%), followed by Beta thalassaemia major 27(14.2%). Other haemoglobinopathies in descending order of frequency were sickle cell disease 15 (7.9%), Hb D Disease 16 (8.4%), sickle cell trait 01 (0.5%), Sickle/beta thalassaemia in 02 (1.0%) and Hb E in 04(2.1%).

Conclusion : Our study showed higher frequency of Beta Thalassaemia trait. It is suggested that detection of HbA2 should be carried out in all the high-risk groups with anaemia. Further larger studies are needed to screen our population to detect thalassaemia carrier state and Iron deficiency Anaemia.

Keyword : Anaemia, Haemoglobinopathies, Thalassemia

PP11-4

microRNA signature in G6PD gene: Novel insight into miRNA based diagnostic approach

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Background : The single nucleotide polymorphisms (SNP) in glucose-6-phosphate dehydrogenase (G6PD) gene caused enzyme deficiency leading to acute hemolytic anemia and neonatal jaundice. Over 400 SNPs in G6PD have been deposited in G6PD database. Most of the G6PD SNP showing clinical significance caused amino acid substitution. However, the association of G6PD SNP and enzyme activity could not be well established. MicroRNA (miRNA), a 18-23-nt non-coding RNA has been identified as novel regulator of gene expression via post-transcriptional gene regulation. The miRNA function has been previously highlighted in erythropoiesis and hematological disorders. Little is known about the role of miRNA in G6PD deficiency. This study aims to identify miRNA that regulate the G6PD enzymatic activity.

Method : In order to identify potential miRNAs involve G6PD, we initially applied computational approach for selecting candidate miRNA from 500 miRNAs in the human genome. The comparative bioinformatics study showed potential candidate miRNA; miR-451, miR-24, miR-138, and miR-195. We further confirmed the association of G6PD activity with all these 4 selected miRNAs isolated from 108 samples of G6PD deficient individuals and 100 samples of G6PD normal individuals using qRT-PCR.

Results : It was found that the high expression level of miR-24, and miR-138 in G6PD deficient individuals compared with healthy was shown. To evaluate the effect of these two microRNAs, we analyzed the expression of the G6PD enzyme as a measurement of G6PD enzyme activity. The samples were divided by G6PD genetic variation into four groups that consisted of no variants, Mahidol variant, Viangchan variant, and Union variant. All three G6PD variants (Mahidol, Viangchan, Union) group showed the high expression level of both miR-24, and miR-138 and were negatively associated with the degree of G6PD enzyme activity. Luciferase reporter assay confirmed two conserved functional miR-24 and miR-138 binding sites located in the 3'-UTR of G6PD.

Conclusion : This study demonstrates a sensitive and specific biomarker for a miRNAs could serve as biomarkers for the diagnosis of G6PD deficiency.

Keyword : G6PD, miRNAs, Biomarker, Anemia

PP11-5

Sustained complement C1s inhibition with sutimlimab in patients with cold agglutinin disease results in continued efficacy in part B of CADENZA Study

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Background : Cold agglutinin disease (CAD) is characterized by classical complement pathway (CP)-mediated hemolysis. Sutim-

limab (SUT) is a first-in-class humanized monoclonal antibody that prevents CP activation by selectively inhibiting C1s; both the alternative and lectin pathways remain intact. A rapid and sustained improvement in hemoglobin (Hb), hemolytic markers and quality of life (QoL) was seen with SUT therapy in CADENZA Part A.

Aims: To report long-term data from the open-label Part B extension of CADENZA.

Method : In Part A, eligible patients with CAD received SUT or placebo (PBO) through intravenous infusions on Days 0 and 7, then biweekly. All patients completing Part A (26 weeks) were eligible to enter Part B and receive biweekly SUT continuing until 1 year after the last patient completed Part A. Efficacy data up to Week 79 are reported. Safety data was recorded throughout the study.

Results : Overall 39 of 42 (92.8%) patients completed Part A and entered Part B, with 32 (82.1%) completing Part B. SUT treatment rapidly improved Hb levels; mean (SE) Hb at the end of Part A was 11.51 (0.40) g/dL and 9.43 (0.40) g/dL for SUT and PBO groups, respectively. In Part B, improvements in Hb were sustained in the SUT group and the ex-PBO group (patients who received PBO in part A and switched to SUT in part B) saw rapid and comparable increases in Hb upon initiation of SUT; at Week 79 mean (SE) Hb levels were 11.86 (0.54) g/dL and 11.76 (0.58) g/dL in the SUT only and ex-PBO groups, respectively (Panel A). Mean total bilirubin was normalized with SUT treatment in Part A and sustained in Part B; similar decreases were observed for patients in the ex-PBO group when they started receiving SUT in Part B (Panel B). Improvements in mean [SE] FACIT-Fatigue scores (BL: 32.96 [1.79]) observed in Part A were sustained in Part B in the SUT only group (44.31 [2.19] at Week 87); the mean FACIT-Fatigue score increased to comparable levels in the ex-PBO group (41.40 [2.71] at Week 87). Improvements in Hb, bilirubin, and FACIT-Fatigue correlated with normalization of C4 and near-complete inhibition of CP activity, that was maintained through the end of treatment. Reductions in mean absolute reticulocyte count and increases in haptoglobin levels seen with SUT treatment in Part A were maintained in Part B, and upon initiation of SUT in Part B, the ex-PBO group reached comparable levels. In Part B, 9 (23.1%) patients received a ≥1 transfusion. In part B, 36 (92.3%) patients reported ≥1 treatment emergent adverse event (TEAE) and 7 (17.9%) patients reported 11 serious TEAEs (TESAEs) (including 1 TESAE of hypertension event assessed as SUT related). Thromboembolic events were seen in 2 (5.1%) patients (transient ischemic attack; deep vein thrombosis) with underlying risk factors for thromboembolism. One TESAE of urinary tract infection was reported. No meningococcal infections, serious events of hypersensitivity, anaphylaxis or systemic lupus erythematosus were reported. One patient with a history of tobacco use (ex-PBO) died due to TESAE of lung squamous cell carcinoma (SUT stopped before death).

Conclusion : Long-term treatment with SUT, maintained mean Hb levels >11 g/dL, achieved sustained normalization of bilirubin and led to clinically meaningful improvements of FACIT-Fatigue scores, while maintaining a favourable safety profile. Improvements in anemia, inhibition of hemolysis and favourable effects on QoL were rapidly achieved and sustained to a similar extent in those patients administered SUT throughout the study and those who switched to SUT treatment in Part B.

This abstract was previously presented at ASH 2022.

Keyword : Cold aglutinin disease, Sutimlimab, Hemolysis, Hemoglobin, Quality of life

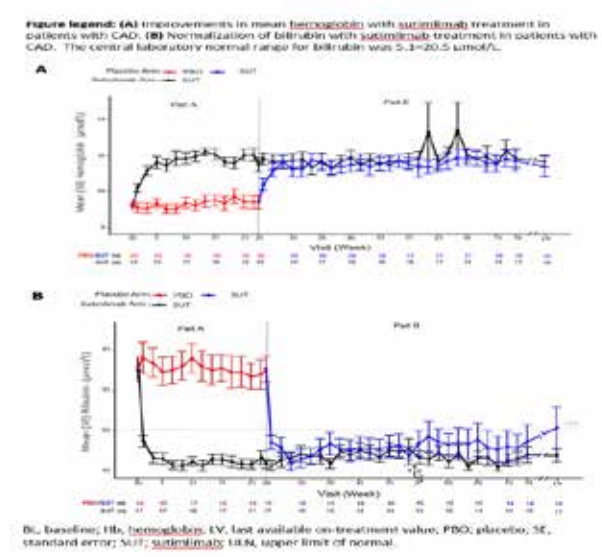

Figure legend: (A) Improvements in mean hemoglobin with sutimlimab treatment in patients with CAD. **(B)** Normalization of bilirubin with sutimlimab treatment in patients with CAD. The central laboratory normal range for bilirubin was 5.1–20.5 µmol/L.

BL, baseline; Hb, hemoglobin; LV, last available on-treatment value; PBO, placebo; SE, standard error; SUT, sutimlimab; ULN, upper limit of normal.

PP11-6

Inhibition of complement C1s with sutimlimab in patients with cold agglutinin disease (CAD): 2-Year follow-up from the CARDINAL Study

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Background : CAD is characterized by classical complement pathway (CP)-mediated hemolysis. Sutimlimab (SUT) is a first-in-class humanized monoclonal antibody that selectively inhibits C1s of the C1 complex, preventing CP activation, while leaving the alternative and lectin pathways intact. One-year interim follow-up from the CARDINAL study (NCT03347396) have previously demonstrated that SUT resulted in sustained improvements in hemolytic markers and quality of life (QoL).

Aims: To report 2-year efficacy and safety from the CARDINAL Part B extension.

Method : CARDINAL was a Phase 3, open-label, single-arm study with a 26-week treatment period (Part A) and a 2-year extension (Part B) after the last patient finishes Part A. SUT was administered through intravenous infusions on Days 0 and 7, followed by biweekly dosing. Efficacy data through Week 131, the last data recording within the 2-year Part B period, are reported here. Safety was recorded until end-of-study visit 9 weeks after their last dose.

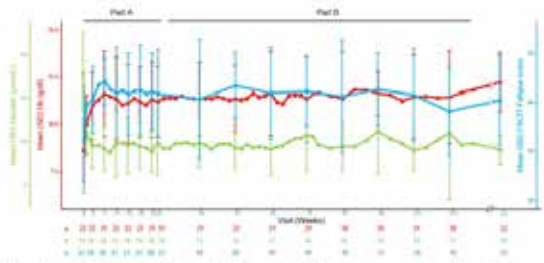
Results : Of the 24 patients enrolled in Part A, 22 completed Part A and entered Part B, with 19 (86.4%) patients completing Part B. SUT treatment improved mean (SD) hemoglobin (Hb) levels within 1 week; mean Hb remained >11 g/dL from Week 5–131 (baseline: 8.64 [SD, 1.67]) (Figure). Mean total bilirubin was normalized from Week 3–131 (Figure). Mean FACIT-Fatigue scores improved within 1 week and remained ≥5 from Week 1–123 (Figure), consistent with a clinically meaningful change. Improvements in Hb, bilirubin, and FACIT-Fatigue correlated with normalization of C4 and near-complete inhibition of CP activity. Normalization of mean absolute reticulocyte count was observed alongside normalized haptoglobin levels and reductions in lactate dehydrogenase (LDH). From Week 26–131, 15 (68.2%) patients remained transfusion-independent. All 22 patients reported ≥1 TEAE (treatment emergent adverse event); 12 (54.5%) reported ≥1 TESAE (serious TEAE). Serious infections were reported in 7 (31.8%) patients, including 1 patient with sepsis due to streptococcus pneumoniae. No meningococcal infections were reported. 3 patients discontinued the study due to AEs (cyanosis and Klebsiella pneumoniae infection (n=1); vitreous hemorrhage (n=1); cyanosis and gastrointestinal symptoms including erosive gastritis (n=1)). No patients developed systemic lupus erythematosus, serious hypersensitivity or anaphylaxis. 2 patients died during the study (klebsiella pneumoniae (n=1); exacerbation of CAD (n=1); in a patient with a femoral neck fracture and complex medical history including myelodysplastic syndrome, approximately 1.5 months after receiving the last dose of sutimlimab).

Conclusion : SUT, a first-in-class selective anti-C1s classical complement pathway inhibitor, maintained mean Hb levels >11g/dL, achieved sustained normalization of mean bilirubin, haptoglobin and reticulocyte count. SUT continued to improve FACIT-Fatigue scores, with no newly identified safety concerns at 2 years of treatment. This study has demonstrated that SUT is an effective and well-tolerated long-term therapy for the management of chronic CAD through continued upstream inhibition of the classical CP.

This abstract was previously presented at EHA 2022.

Keyword : Cold aglutinin disease, Sutimlimab, CARDINAL study, Hemolytic markers, FACIT-Fatigue score

Figure: Improvements in mean hemoglobin, bilirubin and FACIT-Fatigue score after sutimlimab treatment are sustained through Week 131 in patients with CAD. Last available on-treatment values on sutimlimab treatment are also shown.



B, baseline; Hb, hemoglobin; LV, last available on-treatment value; SD, standard deviation

PP11-7

Unusual type of anemia gravis associated with trilogy of hookworm infection, peptic ulcer, and melena: A rare case

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Background : Anemia is a condition of deficiency of hemoglobin (Hb). This disorder is established based on blood hemoglobin levels, women below 12 g/dL, and men below 13 mg/dL. The etiology of anemia is very diverse and is usually detected by examining the size and color of the erythrocytes through routine blood tests and peripheral blood smears. Based on the shape and color, anemia is classified into microcytic hypochromic, normocytic normochromic, and macrocytic hyperchromic. One of the interesting things related to this case is anemia due to worm infection which causes a type of anemia that is difficult to classify into one of the three types, namely the presence of anisocytosis and poikilocytosis. In addition, this worm infection also often causes a massive decrease in Hb which is called anemia gravis (Hb <7 g/dL). Based on CDC 2022, as many as 576-740 million people in the world are infected with hookworm and experience anemia which often occurs in developing and tropical/sub-tropical countries such as Sub-Saharan Africa, South China, the Pacific, and South East Asia. Worm infections, especially hookworms, often cause digestive tract bleeding, decreased appetite, and decreased absorption of nutrients which results in a massive decrease in Hb levels. A peptic ulcer is one of the most common causes of upper gastrointestinal bleeding, the manifestations of which are hematemesis and melena. Ulcers are conditions where the mucous layer of the tissue is eroded which eventually causes injury or rupture of blood vessels which can be confirmed through endoscopy. The most common etiologies of ulcers are the use of NSAIDs, steroids, smoking, alcoholism, and bacterial or parasitic infections such as worms. To determine the presence of helminth infections, routine stool examinations can be done to determine the presence of worm eggs or adult worms and routine blood labs to determine the presence of eosinophilia. One type of Hookworm infection that often causes the digestive tract is Ancylostoma duodenale which has the characteristic of being able to attach to intestinal tissue and enter blood vessels and cause blood vessel damage. The long-term effect of this helminth infection is loss of serum and protein which causes iron deficiency anemia with the characteristic presence of cigarette cells in peripheral blood smears. This proves that helminth infections can manifest not only in the gastrointestinal tract such as diarrhea or vomiting but can also manifest as gastrointestinal bleeding which ends in anemia. So, it would be better if the etiology of anemia must be carried out systematically and thoroughly to find out the possibility of parasitic infections such as helminths or other chronic diseases.

Method : With indirect supervision, a 64-year-old female patient experienced disturbances in the form of weakness, abdominal pain, bloody mucus bowel movements, nausea, and vomiting which she had felt since two months ago. The patient initially came to the ER and was hospitalized for 5 days. The patient's diagnosis was based on anamnesis, physical examination, and initial investigations, which are anemia gravis, suspect ulcer peptic, Diabetic Mellitus (DM), Hypertension, and Acute Kidney Injury. We took follow-up data from the patient's medical record and obtained the patient's consent. The patients were followed-up during hospitalization and post-hospitalization (control of internal medicine). Prior to going to the emergency room, the patient was routinely controlled by the internal medicine polyclinic with a history of DM, HT, and gastric disorders. The results of the physical examination revealed an anemic conjunctiva, epigastric pain, and an irregular heartbeat (pulse: 138x/minute). The results of further examination, from routine blood, obtained Hb levels of 5.3 g/dL, hematocrit 15.7%, erythrocytes 1,680,000/mm3, MCV 93.8 µm3, MCH 31.6 pg, MCHC 33.7 g/ dl, platelets 84,000/mm3, and eosinophils 9.4%. These results indicate the presence of normochromic normocytic anemia gravis, thrombocytopenia, and eosinophilia. In addition, due to a long history of diabetes mellitus, the patient was checked for levels of kidney function (urea, creatinine) and liver function (SGOT, SGPT) with azotemia results (Ur 79 mg/dL, Cr 1.9 mg/dL) and normal liver function. Peripheral blood picture examination revealed anisocytosis (microcytes, normocytes, macrocytes), fragmentation (helmet cells and bizarre cells), poikilocytosis (cigarette cells, pencil cells, ovalocytes, tear drop cells, target cells, stomatocyte cells, bur cells, rouleaux cells, and nucleated erythrocytes), increased leukocytes with a predominance of eosinophils. These results indicate a suspected iron deficiency anemia with an increased erythropoietic response with a dissertation with liver dis-

orders, microangiopathy, and eosinophilia due to parasite (helminth) infection. Routine stool examination; macroscopically found mucus and blood, microscopically found parasites in the form of bacteria, fat, and also larva and eggs of hookworm. Based on the anamnesis, results of physical and supporting examinations, treatment was carried out in the form of three packed red cell (PRC) transfusion, antibiotics, anti-mimetic, anti-pain, vitamins, and single-dose anti-parasitic (pyrantel pamoate). The patient was evaluated for 3 days and found that the clinical condition was improving, the Hb level was increasing (Hb 13.3 g/dL), and the platelet, erythrocyte, and eosinophil levels were normal. After being treated for 5 days, the patient went home and was given education for re-control after 1 week. A routine stool examination will be carried out when the patient is in control.

Results : This case shows the importance of a systematic and comprehensive examination to find out the cause of a disease such as anemia. Early diagnosis and treatment are very important to know the unusual cause of anemia gravis as in this case. The unusual type of anemia in this patient was due to the peripheral blood smears resulting in the form of anisocytosis and poikilocytosis which showed an unusual etiology of the patient's anemia. After further evaluation, based on complaints of bloody mucus bowel stools, and eosinophilia, the patient finally had a routine stool check and found a hookworm infection. The peripheral blood smears result also refers to iron deficiency anemia due to the presence of cigarette/pencil cells. From this result, it can be seen if the anemia experienced by the patient can be sourced from various etiologies based on the examinations that have been carried out. In addition, a history of chronic diseases, which are DM and hypertension, must also be considered as a cause of anemia (anemia of chronic disease) in patients. So that for a definite diagnosis, a comprehensive examination is carried out. However, it turns out that hookworm infections can cause further disorders such as iron deficiency anemia, gastrointestinal bleeding et causa peptic ulcer or damage to the vascular endothelium, and malnutrition. Hookworm infection in the tenue intestine will secrete an anti-coagulant substance that functions to help hookworms penetrate from the tissues into the blood vessels so that it helps to suck blood. This, if it occurs chronically, will cause an accumulation of blood loss per day which results in severe anemia. In this patient, there was a manifestation of gastrointestinal bleeding in the form of melena which could be a source of blood loss other than iron deficiency due to malnutrition. The combination of chronic infection with hookworms, peptic ulcer, and melena is what causes the patient to fall into a state of anemia gravis. Thus, the etiological diagnosis of anemia due to the patient's chronic illness could be ruled out after further examination and evaluation of the pathophysiology of hookworm infection.

Conclusion : In anemic patients, especially unusual types of anemia gravis with a history of chronic disease, it is necessary to carry out an early diagnosis with a comprehensive examination to determine the exact etiology of the patient. The possible causes of anemia based on peripheral blood smears and blood laboratory results where the type of anemia does not match the patient's previous medical history can be a major problem, as was the case in this case where hookworm infection was found which was the main problem for anemia in patients. Chronic/latent Hookworm infection can cause serious problems not only nutritional disorders, but can also cause tissue and blood vessel damage which ends with gastrointestinal bleeding (melena), and ends with anemia gravis. Thus, early diagnosis and appropriate treatment can prevent patients from falling into anemia gravis.

Keyword : Anemia gravis, Hookworm infection, Peptic ulcer, Melena, Anisocytosis, Poikilocytosis

PP11-8

Assessment of knowledge, attitude and practices on iron-deficiency anemia among Filipino teens in Laguna, Philippines

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Background : Iron deficiency anemia (IDA) is common among teens in developing countries. This study aims to describe the current knowledge, attitude and practices of Filipino teenagers with regards to iron deficiency anemia.

Method : In this study, 402 participants, age 13-18 years old, currently studying in Laguna, Philippines were given an online ques-

tionnaire to assess their KAP on IDA from November 2020 – January 2021.

Results : It was found out that four out of ten of the participants have not heard of IDA before the study was conducted. Almost half (47.5%) have low- to very low- levels of knowledge about IDA. The prevalence of IDA among the participants, based on self-reporting, was 14.3%; while family history of IDA was 11.4%. High knowledge (35.32%) was significantly associated with age 17-18, female sex, college educational level, students in private school, higher family income and urban city living. Furthermore, high knowledge was also significantly associated with diagnosis of IDA and family history of IDA. Highly positive attitude (34.58%) and high knowledge were both associated with consumption of iron-rich foods and vitamin C-rich fruits among the participants (chi2=68.44, p-value=<.0001)

Conclusion : Based on the results of the study, information dissemination is necessary to increase awareness about iron deficiency anemia among Filipino teens as preventive measures are practiced by teens, who have high knowledge and highly positive attitude towards IDA. Health teaching should be addressed specifically to students studying in public schools in rural areas.

Keyword : Anemia among Filipino teens, KAP on anemia

PP11-13

Hereditary pyropoikilocytosis: A rare and severe form of congenital haemolytic anaemia

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Background : Hereditary pyropoikilocytosis (HPP) is a rare autosomal recessive disease. First described by Zarkowsky et al in 1975, HPP is due to biallelic (homozygous or compound heterozygous) mutation leading to spectrin self-association defect with concomitant spectrin deficiency. HPP is considered a severe form of hereditary elliptocytosis (HE). Here, we present a case of HPP in a neonate with non-immune haemolytic anaemia.

Method : Case report

Results : **A premature baby was born at 34 weeks of gestation,** admitted and ventilated for persistent pulmonary hypertension due to lung hypoplasia and respiratory distress syndrome. Upon admission, he was diagnosed with non-immune haemolytic anemia with his haemoglobin level 5.7g/dl and reticulocytosis. Initial full blood picture (FBP) revealed normochromic normocytic anemia with anisocytosis. Viral screening included TORCHES (toxoplasma, rubella, cytomegalovirus, hepatitis, syphilis), Ebstein-Barr Virus, and Parvovirus were negative. Inborn error of metabolism screening was carried out with negative finding. In view of persistent low haemoglobin level, he transfused regularly. His post transfusion haemoglobin was more than 10g/dl,but decreased to as low as 3.1g/dl during follow-up. Despite repeated FBP, the reports were inconclusive of definite diagnosis. Further screening for his father and siblings were consistent with HE except his mother. Subsequently, bone marrow aspiration and trephine biopsy (BMAT) was carried out but inadequate for diagnostic interpretation. Whole Exon Sequencing(WES) was performed and revealed SPTB gene mutation. Based on the findings from WES, he was diagnosed with HPP. Currently, he is on regular packed cells transfusion. Fortunately, Human leukocyte antigen (HLA) of his sister is compatible with him and he is awaiting for transplant process.

Conclusion : This case illustrates the diagnostic challenge in a baby with non-immune haemolytic anaemia. Making an accurate diagnosis will guide in managing different causes of non-immune haemolytic anaemia.

Keyword : Hereditary pyropoikilocytosis, Haemolytic anaemia

PP11-14

Classification of anemia level based on fuzzy c-means algorithm

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Background : Determining the classification of anemia levels will make it easier to diagnose a patient's disease further because each classification has many possible types of disease. However, there are still frequent errors in determining the classification of anemia, causing therapeutic errors in patients. Therefore, a system is needed as a tool in determining the classification of anemia. In this study, the

Fuzzy C-Means algorithm is used to determine the level of anemia. The concept of fuzzy logic is very flexible and has tolerance for imprecise data and is based on natural language to determine a result.

Method : This research discusses the application of the Fuzzy C-Means (FCM) algorithm with clustering techniques. Clustering is a method of grouping an object into a number of appropriate groups (clusters). The principle of clustering is to minimize the similarity between members of one cluster and maximize the similarity between members of different clusters. Fuzzy C-Means is (FCM) a clustering technique where each data is determined by its membership degree. The greater the value of the data membership degree in a cluster, the greater the data becomes a member of the cluster. The clustering results are then processed or evaluated using the F-measure value where the precission value and recall value must first be known. Testing is done with different data distributions with the number of datasets, namely 150 datasets, 180 datasets and 210 datasets. The dataset used in this study is anemia disease data on blood test results taken from the Cendana Clinic Laboratory, Bulukumba City in 2021. The amount of data used in this study is 300 total data and six attributes namely Gender, Age, Hemoglobin, Lekocytes, Platelets and Erythrocytes. From these six attributes, the results of the level of anemia disease are obtained.

Results : From the three tests carried out, it shows that the F-measure value of 150 datasets is the highest in cluster 2, namely 0.6102, the F-measure of 180 datasets is the highest in cluster 2, namely 0.5855 and the F-measure of 210 datasets is the highest in cluster 2, namely 0.5599 which is done 10 times. The difference in the f-measure value is because in the initial clustering process there is a random number generation for the formation of the initial matrix and because the distribution of the data used is different in the training data and test data. So in this anemia disease level data clustering, the highest f-measure value is in cluster 2.

Conclusion : The fuzzy C-Means method can be implemented to classify anemia level data using six anemia parameters namely gender, age, hemoglobin, leukocytes, platelets, and erythrocytes, by classifying three categories namely normal, mild and severe. It can also be used to classify data that has various values, integer, double, or a mixture between the two.

Keyword : Anemia, Classification, Fuzzy C-Means, Machine learning

PP11-16

Are the prevalence of stunting height, anemia among women pregnant, undernourishment and GDP percapita influence to prevalence of anemia among children in ASEAN 5

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Background : Anemia is one of the most important diseases to pay attention, especially for Prevalence of anemia among children in the ASEAN-5 a focus of this study. This study analyzes the effect Prevalence of stunting height, anemia among pregnant, undernourishment and GDP Percapita in ASEAN-5 (Indonesia, Malaysia, Philippines, Thailand and Singapore) to Prevalence of anemia among children.

Method : Secondary analysis is done by using panel data for the period 2001-2019 with 2 model (Ordinary Least Square and Random Effect). variable Prevalence of anemia among children as dependent variable. Prevalence of stunting height, anemia among pregnant, undernourishment and GDP Per capita as independent variable. Data from Indonesia, Malaysia, Philippines, Thailand and Singapore that source in world bank data.

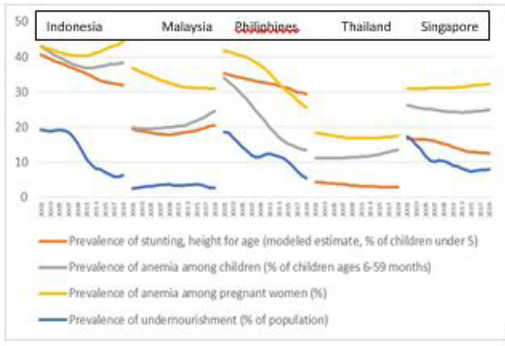
Results : The results of the graph show that on average the level of anemia of children had a decreased in tree countries that are Philippines, Singapore, and Indonesia but Indonesia had an increase in 2011-2019. Thailand and Malaysia had increased since 2000-2019. Indonesia has the highest Prevalence of anemia among children between five countries. Meanwhile, the results of the regression show that the Prevalence of anemia women among pregnant, undernourishment and GDP Per capita has a positive and significant effect on anemia in the children. While the Stunting not significant. When anemia during pregnancy increases by 1%, the probablity of anemia in children will increase. When undernourishment increases by 1%, the probability of anemia in children will increase. When GDP per capita increases by 1 US$, the probability of anemia in children increases

Conclusion : It is expected that the government try to increase the GDP per capita, and needed for special attention regarding for women pregnant to not anemia, children must a good nutrition for ASEAN-5.

Keyword : Anemia in Children, Anemia in pregnant women, Stunting, GDP Percapita, Undernourishment

	(1) ols	(2) Fixed Effects	(3) Random Effects
Prevalence of stunting height	-0.137	0.948***	-0.137
	(0.0712)	(0.186)	(0.0712)
Prevalence of anemia among pregnan	1.476***	0.977***	1.476***
	(0.117)	(0.0542)	(0.117)
Prevalence of undernourishment	0.811***	0.111	0.811***
	(0.121)	(0.0978)	(0.121)
GDPpercapita	0.000968***	0.000883***	0.000968***
	(0.000230)	(0.000101)	(0.000230)
_cons	-34.07***	-36.92***	-34.07***
	(4.046)	(4.320)	(4.046)
N	76	76	76

Standard errors in parentheses
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$



PP11-17

Diagnostic yield of targeted next-generation sequencing for pediatric hereditary hemolytic anemia

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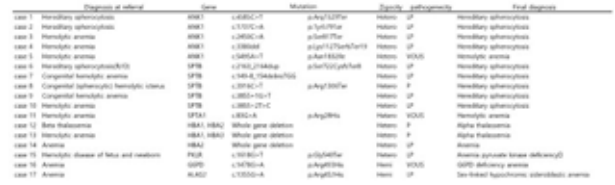
Background : Hereditary hemolytic anemia (HHA) refers to a heterogeneous group of genetic disorders that share one common feature: destruction of circulating red blood cells (RBCs). The destruction of RBCs may be due to membranopathies, enzymopathies, or hemoglobinopathies. Since they are genetic disorders, incorporation of next-generation sequencing (NGS) has facilitated the diagnostic process of HHA.

Method : NGS results of 24 patients with suspected HHA in a tertiary hospital (2017-2022) were retrospectively reviewed to evaluate the efficacy of NGS on the diagnosis of HHA. Targeted NGS was performed with custom probes targeting 497 genes related to hematologic disorders. After genomic DNA was extracted from peripheral blood, prepared libraries were hybridized with capture probes and sequenced using NextSeq 550Dx (Illumina, San Diego, CA, USA).

Results : Among the 24 patients, ANK1 mutation was detected in five patients, four of which were pathogenic variants. SPTB mutation was also detected in five patients, all of which were classified as pathogenic variants. One variant of uncertain significance (VOUS) in SPTA1, and G6PD mutation were each detected in two patients. Whole gene deletions in both HBA1 and HBA2 were detected in two patients while in one patient, only HBA2 deletion was detected. One likely pathogenic variant in PLKR was detected one patient and one likely pathogenic variant in ALAS2 was detected in another.

Conclusion : NGS played a critical role in making a definitive diagnosis in 17 out of 24 patients (70.8%) with suspected HHA. Thus, its incorporation into the diagnostic workflow is crucial.

Keyword : Hereditary hemolytic anemia, Next Generation Sequencing



PP11-20

A delayed manifestation of autoimmune lymphoproliferative syndrome (ALPS)

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Background : Autoimmune lymphoproliferative syndrome (ALPS) is dysregulation of immune systems cells due to an inability to regulate lymphocyte homeostasis through the process of lymphocyte apoptosis. This syndrome typically happened in first year old life.

Method : Case report

Results : A 6 years old girl that was previously healthy presented to hospital with clinical features of jaundice for 2 days. Otherwise, there were no clinical features of infection. However, she had history of taking a Malay traditional medication for the past 1 year. Her abdominal examination revealed hepatomegaly. Other systemic examinations were unremarkable. Her blood investigations had showed hemolytic anemia with high reticulocytes count and direct Coombs test positive with high indirect bilirubin level. Her viral screening such as Hepatitis A, B and C were non-reactive. Her full blood picture showed acute hemolysis likely autoimmune hemolytic anemia. However, her antinuclear antibody was negative and C3 and C4 were within normal range. She was subsequently allowed discharged after a 5 days stay in hospital and under Paediatric clinic follow-up. Multiple investigations were done during follow-up but noted persistent positive direct Coombs test and high reticulocytes count and patient was then referred to Paediatric Hematologist and was started oral prednisolone. However, her hemolysis was unable to control and with steroid toxicity, she was subsequently started on oral cyclosporine. Further investigation noted her Double negative TCRab T cells suggestive of ALPS.

Conclusion : This case illustrates the diagnostic challenge in a patient that although ALPS usually manifested in first year of life but a delayed manifestation still maybe occurred that was happened in this patient. A high index of suspicious is necessary for accurate diagnosis and timely treatment to prevent undesired complications.

Keyword : Autoimmune lymphoproliferative syndrome, Anemia

PP11-24

TMPRSS6 rs855791 polymorphism and iron deficiency anaemia susceptibility among Asian population: A systematic review and meta-analysis

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Background : Iron deficiency anaemia (IDA) is the most common nutritional deficiency worldwide. Transmembrane Protease Serine 6 (TMPRSS6) polymorphisms, specifically rs855791, plays key role in iron homeostasis in the human body. Several studies have described the association between TMPRSS6 rs855791 gene polymorphism and IDA in Asian ethnicity, but the results still inconclusive. Therefore, this study aims to investigate the effect of TMPRSS6 rs855791 gene polymorphisms and IDA susceptibility among Asian population

Method : The literature search was performed using databases such as PubMed and EMBASE until November 2022. Studies included in this meta-analysis were accessed using The Newcastle Ottawa Score (NOS). The association between TMPRSS6 rs855791 gene polymorphism and the risk of IDA were evaluated using pooled odds ratios (ORs) and 95% confidence intervals (CIs).

Results : Seven studies (571 cases/533 controls) were included in this study. In pooled analysis, TMPRSS6 rs855791 gene polymorphism increased the risk of IDA in Asian population (OR= 1.50 [1.07 – 2.09], p= 0.02). Specifically, T>C was associated with the increase risk of IDA (OR= 3.24 [1.75 – 5.99], p= 0.0002). In female subgroup analysis, pooled analysis showed no significant association between TMPRSS6 rs855791 gene polymorphism and IDA. In female, T>C also served as a risk factor of IDA (OR= 2.49 [1.80 – 3.44], p= <0.00001).

Conclusion : Our meta-analysis showed that T allele might serve as a risk factor of IDA in both general and female population in Asian ethnicity. Further studies larger sample are needed.

Keyword : Iron deficiency anemia, Transmembrane protease Serine 6, Gene polymorphism, Asian population

PP12-1

Association of CD16 158F>V gene polymorphisms with risk of idiopathic thrombocytopenic purpura susceptibility : An updated meta-analysis

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Background : Phagocytosis of autoantibody-sensitized coated platelets through Fc gamma receptors on phagocytic cells is an important mechanism of thrombocytopenia in primary immune thrombocytopenia (ITP). Epidemiological studies have evaluated the associations of CD16 158F>V gene polymorphisms with the risk of idiopathic thrombocytopenic purpura (ITP). The aim of this study

is to know the association of CD16 158F>V gene polymorphism with risk of ITP.

Method : This Meta-analysis is accordance with the PRISMA guidelines. Literature search from Pubmed and EMBASE are conducted until October 2022. Literature are limited to English. Included studies in this meta-analysis determine its quality using the Newcastle Ottawa (NOS) scale. The interaction between CD16 158F>V gene polymorphisms with risk of ITP pooled by OR and 95% CI.

Results : 5 studies met the inclusion criteria, with total of sample are 283 case and 324 control. From the results obtained polymorphism CD16 SNP 158F>V was associated with increase risk of ITP (FF vs VV + FV, OR 95% CI = 3.02 [2.13-4.29], p = 0.000; F vs V, OR 95% CI = 1.84 [1.46-2.30], p = 0.000) and decrease risk of ITP (V vs F, OR 95% CI = 0.54 [0.43 – 0.68], p = 0.000) and (FV vs FF+VV, OR 95% CI = 0.46 [0.33-0.63], p = 0.000).

Conclusion : In summary our meta-analysis suggested that F allele and FF genotype of CD16 158F>V Gene Polymorphisms have been association with increasing risk of ITP disease, respectively the V allele and FV genotype have been association with decreasing risk of ITP disease. Further study about interaction between genetic-environment interactions with larger sample is needed.

Keyword : Gene polymorphisms

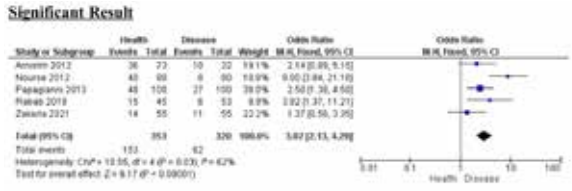

Fig 1. Forest plot of association between CD16 polymorphisms and ITP FF vs VV + FV

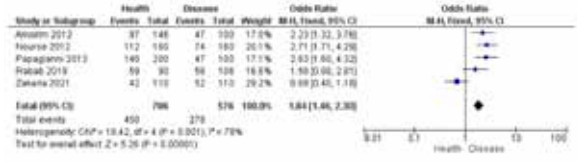

Fig 2. Forest plot of association between CD16 polymorphisms and ITP F vs V

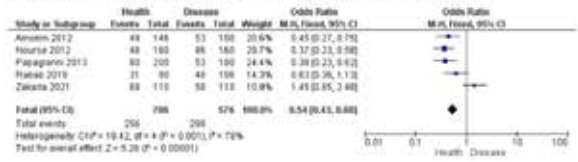

Fig 3. Forest plot of association between CD16 polymorphisms and ITP V vs F

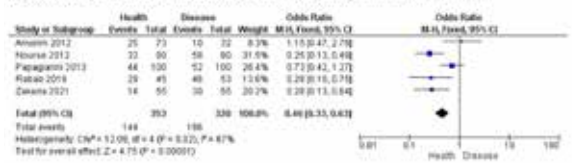

Fig 4. Forest plot of association between CD16 polymorphisms and ITP FV vs VV + FF

PP12-3

Cannabinoid receptor 2 signaling: Role in megakaryocyte development and neuro-immune regulation

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Background : Megakaryocytes (MKs), a rare population of bone marrow cells, are responsible for the production of platelets, which are necessary for normal blood clotting. Thrombocytopenia (low platelet count, <150 × 109/L), may be due to many factors including cancer and autoimmune diseases. This is a common problem among leukemia patients that can lead to hemorrhagic complications. Here, we investigated the role of virodhamine (an endocannabinoid) in megakaryocyte differentiation and subsequent thrombopoiesis.

Method : Human megakaryoblastic leukemia Dami cells were cultured in RPMI1640 medium and were treated with cannabinoid receptor 2 agonist virodhamine and expression of megakaryocyte differentiation specific markers (CD41 and CD61) was assessed by qRT-PCR. Morphological assessment was performed by microscopy. Cell cycle analysis, determination of mitochondrial membrane potential, and Annexin V assay were performed by flow cytometry. Intracellular ROS was determined using DCFDA.

Results : We evaluated role of thrombopoietic potential of virodhamine. Virodhamine treatment increased the number of cells that show platelet-like protrusion and polyploid nucleus that are key features of megakaryocyte differentiation. Virodhamine treatment further induced expression of megakaryocyte specific maturation markers (CD41 and CD61). Cell cycle analysis showed that virodhamine treatment increased the portion of cells in G0/G1 phase, while decreasing the percentage of cells in S phase, suggesting virodhamine induces differentiation of cells. Cell number was also found to be decreased with virodhamine treatment. Platelet production is a result of megakaryocytic apoptosis, which is probably caused by elevated levels of mitochondrial reactive oxygen species (ROS) and enhanced calcium concentration in cell. Virodhamine induced ROS production by changing mitochondrial membrane potential. Intracellular calcium level and early apoptotic cells were found to be increased with virodhamine treatment. Virodhamine treatment showed cleavage of Poly ADP-ribose polymerase (PARP) which is substrate of caspase-3, suggesting induction of apoptosis. We have also observed down-regulation of phospho-PI3K activity and up-regulation of phospho-MAPK activity in virodhamine treated cells.

Conclusion : Megakaryoblastic cells treated with virodhamine underwent differentiation, characterized by loss of its proliferation capability with extended cytoplasmic protrusions, and by expression of surface markers specific for early and late stages of megakaryocyte differentiation. Virodhamine induced megakaryocyte differentiation by altering the mitochondrial function, increase in intracellular calcium and ROS level and apoptosis.

Keyword : Megakaryocyte, Cannabinoid Receptor, Endocannabinoids, Virodhamine, Thrombocytopenia

PP12-4

Evaluation the outcome of primary immume thrombocytopenia purpura (ITP) in children under 2 years old at Vietnam Children's Hospital

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Background : Primary immune thrombocytopenia purpura (ITP) remains the most common benign hematological field in children. The incidence in Vietnam is 4- 6 cases/ 100.000 children. We have now many treatment regimes in other centers of Vietnam for patients from 1 month to 2 years old. VNCH proposed a protocol for ITP from 2013. Aim: Investigate treatment efficacy of corticosteroid in children under 2 years old with ITP at VNCH

Method : Describe prospective study was carried on 73 patients < 2 years old who were diagnosed ITP at Clinical Hematology Department from Aug 2016 to Aug 2017. They were treated by methyl prednisone as protocol with dose slow intravenous 4 mg/ body weight/ 24 hours x 4 days, then taper dose 50% to 25% in few days. Statistical analysis was performed with the SPSS program.

Results : Almost purpura level was III stage with boy/ girl rate: 1.7/1. Children from 1 month to 12 months old had 90.9% of cases. Follow up after 6 months of treatment. Complete response was 80.9% of patients. The rate of a part response was 2.7% and there were 6.4% of patients had incomplete response. The duration of treatment was 5.7 ± 3.4 days. The length stay hospital from 4 to 6 days accounting 50- 54% of total patients.

Conclusion : Overall, almost children with ITP respond completely to treatment with corticosteroid and duration time in the hospital is short.

Keyword : Platelet, ITP

PP12-5

Bone marrow resident memory T cells suppress megakaryocyte apoptosis and promote humoral immunity in immune thrombocytopenia

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Background : Immune thrombocytopenia (ITP) is an autoimmune-mediated thrombocytopenia syndrome characterized by increased platelet destruction or decreased platelet production. Bone marrow (BM) is an important site of immune response in ITP patients. Recent studies have revealed that a large number of resident memory T cells (TRM) exist in the BM. Region-specific TRM in BM may be involved in the development of ITP by secreting inflammatory mediators, affecting the activity and function of BM megakaryocytes and B cells.

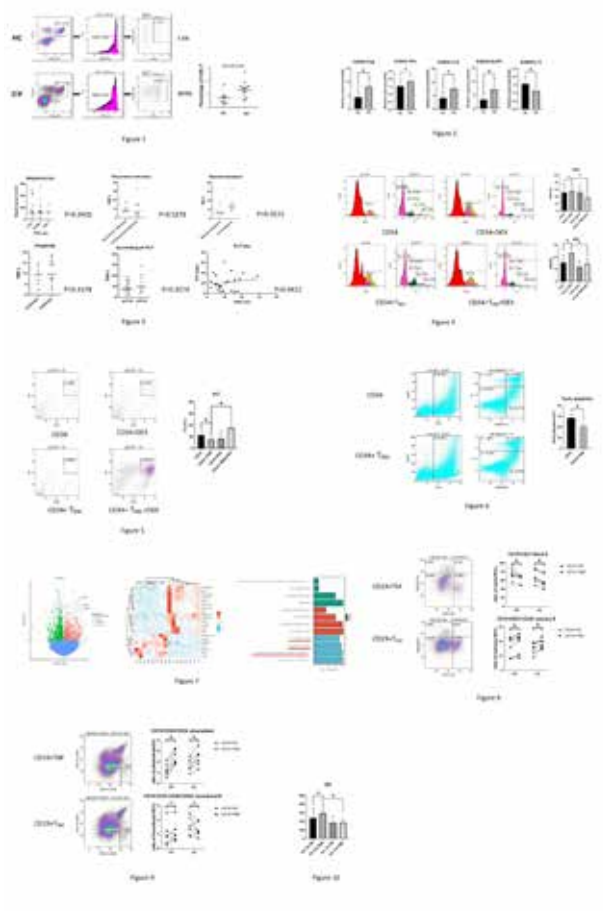
Method : Bone marrow mononuclear cells were collected from patients and healthy donors. The percentage of TRM was analyzed by flow cytometry. We co-cultured TRM with CD34+ stem cells for 14 days and then examined the ploidy of megakaryocytes and platelet production. We also performed RNA-seq of TRM cells from 7 ITP patients and 7 healthy donors. Based on the sequencing results, we co-cultured TRM with cd19+ B cells for 3 days and detected B-cell differentiation.

Results : The proportion of BM TRM (CD3+CD8+CD45RO+CD69+) to CD8+ T cells was significantly increased in the BM of ITP patients compared with controls (Figure 1). RT-PCR revealed that the expression levels of NLRP3, IL-1beta, and TNF-alpha were elevated and IL-10 was decreased in TRM cells of ITP patients compared with controls (Figure 2). Information from the medical records of ITP patients was collected and analyzed together with the proportion of TRM. The levels of TRM in ITP patients were not related to megakaryocyte count, platelet count, anti-platelet antibodies, or relapse refractoriness. But our results revealed a higher proportion of TRM in hormone-sensitive patients than in non-sensitive patients (Figure 3).

After co-culture of CD34+ cells with TRM for 14 days, we found no significant change in the proportion of CD41+ in the culture system; however, the megakaryocyte ploidy assay revealed an increase in the proportion of ≥4N ploidy; the role of TRM in promoting megakaryocyte polyploidy production was suppressed after dexamethasone treatment (Figure 4). The TRM co-culture group produced significantly fewer platelets than the control group; however, TRM with dexamethasone treatment could promote platelet production (Figure 5). Megakaryocyte apoptosis experiments revealed that TRM inhibited early apoptosis of megakaryocytes (Figure 6).

Conclusion : Our study found that BM TRM may be involved in the development of ITP by secreting cytokines that influence the immune environment, promote megakaryocyte ploidy formation, inhibit megakaryocyte apoptosis, and promote humoral immunity. And hormones may play a therapeutic role by correcting TRM function in ITP patients.

Keyword : Bone marrow resident memory T cell, ITP, Megakaryocyte, Humoral immunity



PP12-6

Performance validation of three scoring systems for the prediction of thrombotic microangiopathy due to severe ADAMTS13 deficiency and treatment response to therapeutic plasma exchange: The first study in Korea

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Background : Up to date, three diagnostic scoring systems [Bentley Score (B-S), French TMA Reference Center Score (FTMA-S) and PLASMIC Score (PLASMIC-S)] for the prediction of thrombotic microangiopathies (TMA) have been developed. We retrospectively validated the performance of them for the prediction of TMA by severe (< 10%) ADAMTS13 deficiency and response to therapeutic plasma exchange (TPE) in patients suspected of TMA.

Method : Total 147 patients who were suspected of TMA and ADAMTS13 activity assay were requested from Jan 2014 to Sep 2022 in authors' hospital were enrolled. Three scoring systems were applied and performance in three scoring systems for the prediction of patients with TMA-positive were compared. Comparison of response to TPE and mortality in patients with TMA-positive with respect to risk stratification status was also performed.

Results : For predicting patients with TMA-positive when high risk is assessed, the PLASMIC-S, FTMA-S and B-S showed AUC score of 0.822, 0.623 and 0.513. The PLASMIC-S showed higher sensitivity/NPV/PPV/accuracy (81.82%/91.40%/66.67%/82.31%) than the FTMA-S (72.73%/82.35%/40.51%/59.86%) and the B-S (4.55%/70.63%/50.00%/70.07%). The PLASMIC-S also showed higher specificity than the FTMA-S (82.52% vs. 54.37%). In TMA-positive cases, high risk in the PLASMIC-S could also predict higher platelet recovery rates and smaller number of TPE needed for platelet recovery than low to intermediate risk.

Conclusion : The PLASMIC-S would be most preferred scoring system with the best performance in the detection of patients with TMA-positive and prediction of prognosis before confirmation of ADAMTS13 activity test results.

Keyword : ADAMTS13, Scoring systems, Performance, Prediction, Thrombotic microangiopathy, Therapeutic plasma exchange

PP12-7

Investigation of the immunomodulatory effect of bitter taste receptor on CD4+ T cells in immune thrombocytopenia

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Background : Immune thrombocytopenia (ITP) is an acquired hemorrhagic disease with T cell-mediated immune abnormalities. Bitter taste receptors (TAS2Rs or T2Rs) are cell surface receptors associated to bitterness perception and innate immunity. In this study , we explored their immunomodulatory effect in CD4+ T cells of ITP patients.

Method : We induced CD4+ T cells of ITP patients in vitro and used calcium ion assay to identify T2Rs that may be associated with T cell differentiation, and used flow cytometry to determine their influences on T cell subsets. Then we performed Seahorse metabolic assay to detect the effects of T2R14 inhibitors and agonists on metabolism, and assessed the expression of glycolysis-related genes as well as different subunits of mTOR after different treatments with T2R14.

Results : In this study, we found the expression of T2R14 was significantly increased in CD4+ T cells of ITP patients, T2R14 blocker inhibited the ratio of Th1 and Th17 cells and upregulated the ratio of Th2 cells, while T2R14 agonist caused the exact opposite trend. At the same time, T2R14 can affect metabolism, with its agonist up-regulating glycolysis and oxidative phosphorylation levels in CD4+ T cells and its blocker down-regulating this physiological process. RT-PCR results revealed that T2R14 agonist increased mRNA levels of glycolysis-related genes and the expression of Raptor but inhibited the expression of Rictor, while blockers had the opposite effect.

Conclusion : In conclusion, we elucidate that T2R14 are highly expressed in CD4+ T cells of ITP patients compared to healthy control, regulated the metabolism of CD4+ T cells and adjusted their immunomodulatory effects possibly by acting differently on the two subunits of mTOR, which could be a potential target for the treatment of ITP.

Keyword : Immune thrombocytopenia, Bitter taste receptor, T subsets, Glycolysis, Oxidative phosphorylation

PP12-9

Eltrombopag plays an anti-viral role by elevated function of exhausted T cells

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Background : Thrombocytopenia is a common complication in patients with chronic hepatitis B (HBV-ITP). Eltrombopag (EP), a second-line therapy for Immune thrombocytopenia, is an oral, small molecule, non-peptide TPO receptor agonist that induces the proliferation and differentiation of megakaryocytes. The persistent existence of HBV in patients with chronic hepatitis B is thought to be the abolished function of CD8+ effector T cells, called T cells exhaustion. Recently, CD8+CXCR5+ T cells were considered exhausted T subsets presenting a functional phenotype, but not an exhausting phenotype. Our study aimed to explore the additional effects of eltrombopag in HBV-ITP, besides promoting platelet production.

Method : Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation. The total RNA of PBMCs was extracted for RNA sequence. Differential gene expression before and after EP treatment was performed using DEseq2. Quantitative RT-PCR (qRT-PCR) was used for RNA expression verification. Cell surface markers and cytokine staining were performed using flow cytometry. PBMCs were stained with the following monoclonal antibodies (mAbs) for 15-20 min at room temperature: CD3-FITC, CD4-APC, CD8-APC/Cyanine7, CD69-PE, CXCR5-Brilliant Violet™(BV) 421. Intracellular markers (IFN-γ, TNF-α, and CD107a) were stained after HBV-specific peptide stimulation in the presence of brefeldin A and monensin.

Results : Firstly, we analyzed differential expression genes (DEGs) of PBMC from patients with HBV-ITP before and after treatment with eltrombopag. A total of 988 DEGs (p value≤0.05) were screened, including 782 up-regulated genes and 206 down-regulated genes. Functional enrichment analysis showed that the inflammatory response regulation pathway and MAPK signaling pathway may be involved in this process. The top 10 of these genes were verified by qRT-PCR. We further explore the protein expression level of CD69 on different T-cell subsets using flow cytometry. We found that although the expressions of CD69 both on CD4+ T cells and CD8+ T cells were significantly increased with eltrombopag treatment, the proportion of CD69 expression on the surface of CD8+ T cells was significantly higher than that of CD4+ T cells with or without eltrombopag treatment. To further determine the effect of eltrombopag on the number and function of CD8+CXCR5+/- T cells, we used multicolor flow cytometry to analyze cytokine response as well as cytolytic potential. The results showed that the number of CD8+CX-

CR5+ T cells decreased significantly with eltrombopag treatment, while CD8+CXCR5- T cells did almost no change. Increased expression of CD69 on the surface of both cell subsets indicates that both populations had stronger activation with eltrombopag, but it seems that CD8+CXCR5+ cells had weaker activation than CD8+CXCR5+ cells. Functional detection showed that CD8+CXCR5+ cells showed significantly increased cytotoxic marker CD107a expression, and the expressions of cytokines IFN-γ and TNF-α showed an upward trend, while CD8+ CXCR- subset showed no changes. Moreover, the expressions of CD107a and IFN-γ were positively correlated with those of CD69, while TNF-α was negatively correlated with CD69. Finally, it is indicated that eltrombopag possibly elevated the anti-viral effect of CD8+CXCR5+ T cells, and played an additional promoted anti-viral role when increasing PLT in HBV-ITP patients.

Conclusion : In conclusion, we analyzed the RNA expression profile of patients with chronic hepatitis B combined with thrombocytopenia before and after treatment with eltrombopag and found that the expression of CD69, a marker of early T-cell activation, was increased. Functional enrichment analysis showed that the inflammatory response regulation pathway and MAPK signaling pathway may be involved in this process. Furthermore, further analysis proved that CD8+ effector T cells may be the main cell group activated. Finally, flow cytometry proved that CD8+CXCR5+T cells of exhausted T cells participated in the response of eltrombopag, indicating that eltrombopag may play an antiviral role in improving platelet count and contributing to virus clearance in patients with chronic hepatitis B.

Keyword : HBV-ITP, Eltrombopag, RNA-seq, Exhausted T cells, CD8+CXCR5+ T cells

PP12-10

Predictive value of high ICAM-1 level for poor treatment response in corticosteroid-resistant immune thrombocytopenia patients

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Background : Primary immune thrombocytopenia (ITP) is an acquired autoimmune disease, characterized by reduced peripheral platelet counts and an elevated risk of bleeding. There are still a large number of patients failed or relapsed after the first line and second line treatments. Endothelial cell activation/injury has been found in ITP, but its role in ITP pathogenesis remains unclear. This study attempted to elucidate the correlation between endothelium dysfunction and disease severity and find related markers to predict subsequent ITP-focused treatment response.

Method : The current study was a single center, retrospective cohort study and the study protocol was approved by the Medical Ethical Committee of Qilu Hospital, Shandong University. Participant were randomly enrolled between July 2017 to January 2020, all of whom were free of any ITP-specific therapy for at least one month. All ITP patients, diagnosed according to the guidelines of the American Society of Hematology, were recruited at the Department of Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China. A total of 92 ITP patients, aged between 18 and 80 years of age of both sexes, were enrolled for the study. Weekly platelet number, face-to-face interrogation and physical examination findings were recorded. The criteria for response were defined as follows: (1) complete response (CR): platelet count ≥ 100 × 109/L and absence of bleeding symptoms, (2) response (R): platelet count ≥ 30 × 109/L and at least two-fold growth from the baseline as well as absence of bleeding symptoms, and (3) no response (NR): platelet count < 30 × 109/L or less than two-fold increase from the baseline level or bleeding.

Results : Compared with healthy volunteers, higher plasma levels of soluble intercellular adhesion 29 molecule-1 (ICAM-1), vascular endothelial growth factor (VEGF) and Angiopoietin-2 were found in adult corticosteroid resistant ITP patients. Notably, ICAM-1 levels were negatively correlated with the platelet count, and positively associated with the bleeding score. Recently, we have reported the efficiacy and safety of low-dose decitabine in adult patients with ITP who failed for the first line therapies. Here, we evaluated the correlation of plasma ICAM-1 level with the efficacy of low-dose decitabine therapy for corticosteroid resistant ITP. A total of 29 adult corticosteroid resistant ITP patients, who received consecutive treat-36 ments of low-dose decitabine, were enrolled in this study. Fourteen patients showed response (nine showed complete response and five showed partial response). The levels of ICAM-1 before and after treatment were significantly higher in the non-responsive ITP patients than in the responsive patients. As shown in the multivariable logistic regression model, the odds of developing no-response to low-dose decitabine increased by 36.8% for per 5 ng/ml increase in plasma ICAM-1 level [Odds ratio (OR) 1.368, 95% confidence interval (CI): 1.060 to 42 1.764].

Conclusion : In conclusion, this study first elucidate the relationship between endothelial dysfunction and disease severity and identify the potential predictive value of ICAM-1 level for response to subsequent treatment.

Keyword : ITP, ICAM-1, Retrospective cohort study

PP12-11

Correlation between HDAC3 rs2530223 polymorphism and the susceptibility or severity of ITP

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Background : Primary immune thrombocytopenia (ITP) is an autoimmune hemorrhagic disorder characterized by a low platelet count and increased risk of bleeding. Although glucocorticoids and other drugs are used to treat ITP, approximately 50% of patients fail to respond to therapy or relapse in a short term. Therefore, it is necessary to further explore the risk factors for ITP to identify novel potential therapeutic targets.We previously reported that low-dose chidamide, a histone deacetylase (HDAC) inhibitor, restores immune tolerance in patients with ITP. The histone deacetylase (HDAC) superfamily comprises 11 HDAC isoforms encoded by the mammalian genome. In adult mammals, HDAC3 uniquely regulates environmental challenges, circadian, nutrient, metabolic pathways, and limits autoimmunity, among other homeostatic functions. HDAC3 modulates the functions of immune cells and influences cell homeostasis through systemic immune responses, thereby regulating autoimmunity and inflammation.This study aimed to evaluate the association of a single nucleotide polymorphism (SNP) rs2530223 in the HDAC3 gene with susceptibility to ITP and its clinical features.

Method : According to the ITP international guidelines, patients with ITP and age-matched healthy participants were recruited for this case-control study. To evaluate the association between HDAC3 rs2530223 and more complex clinical data of ITP patients, we further stratified patients according to platelet counts, corticosteroid sensitivity, and ITP refractoriness based on laboratory and clinical information. Genotyping of the HDAC3 rs2530223 polymorphism was performed using MassARRAY platform. SPSS software was used for statistical analyses. Four models (codominant, recessive, dominant, and allelic models) used to analyze the genotyping data.

Results : There were no significant difference was found in age or sex between patients with ITP and healthy controls (p = 0.25 and 0.25, respectively). Individuals with T allele of HDAC3 rs2530223 exhibited a 1.472-fold increased risk of ITP susceptibility (OR 1.472; 95% CI 1.100–1.969; p = 0.009), while ones with the TT genotype under the codominant and recessive models, and the TC/TT genotypes under the dominant model all revealed increased risk of ITP susceptibility (dominant odds ratio(OR) 1.965; 95% CI: 1.046–3.656; p = 0.036; codominant OR 2.264; 95% CI 1.175–4.360; p = 0.015; and recessive OR 1.512; 95% CI 1.028–2.224; p = 0.036, respectively). Regarding platelet counts in ITP patients, we observed that the TC/TT genotypes exhibited a 3.932-fold increased risk for Platelet (PLT) <30×109/L (OR 3.932; 95% CI 1.426–10.842; p = 0.008). However, there was no significant difference in the allelic or genotypic frequencies of HDAC3 rs2530223 between the corticosteroid-sensitive group and the corticosteroid-resistant group (allele, p = 0.968; codominant, p = 0.110; dominant, p = 0.169; and recessive, p = 0.494),as well as between refractory and non refractory groups(allele, p = 0.547; codominant, p = 0.753; dominant, p = 0.606; and recessive, p = 0.871)

Conclusion : The results revealed that HDAC3 rs2530223 polymorphism was obviously related to ITP susceptibility under the genetic and allelic models. The results of the present study revealed that HDAC3 rs2530223 is associated with platelet count in ITP patients, and the T allele of HDAC3 rs2530223 is a risk factor for PLT <30×109/L, suggesting the potential pathogenic role of HDAC3 in ITP. This study indicates that HDAC3 rs2530223 may be an important genetic factor related to ITP susceptibility and platelet count in ITP patients, providing new perspectives on disease progression, new therapeutic targets, and severity prediction.

Keyword : Primary immune thrombocytopenia; HDAC3; single-nucleotide polymorphism; susceptibility; platelet count

Table 2 Association between HDAC3 gene polymorphism and ITP susceptibility

Gene, SNP	Genotype, Allele	Control group		ITP group		Model	χ2 test p value	OR (95% CI)	Adjusted p value
		Count	%	Count	%				
HDAC3 rs2530223	CC	31	14.76	17	8.13	Codominant	**0.035**	1.000 1.965 (0.859–3.224)	0.015
	TC	92	43.81	84	40.19	Dominant	**0.033**	1.000 1.956 (1.046–3.656)	**0.036**
	TT	87	41.43	108	51.68	Recessive	**0.036**	1.000 1.512 (1.028–2.224)	**0.036**
	C	154	36.67	118	28.23	Allele	**0.009**	1.000 1.472 (1.100–1.969)	**0.009**
	T	266	63.33	300	71.77				

CI, confidence interval; ITP, immune thrombocytopenia; OR, odds ratio; SNP, single-nucleotide polymorphism.
Bold indicates statistical significance (P <0.05).

PP12-12

The association between nutritional status and platelet count among pediatric patients with dengue hemorrhagic fever in Pekalongan City, Indonesia

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Background : Dengue Hemorrhagic Fever (DHF) is an acute viral

infectious disease that dramatically spread around the world in recent years. The disease now has more than 100 endemic countries. South-East Asia is one of the regions with the most seriously impacted. Indonesia is in the first rank based on the DHF incidence rate (IR) and case fatality rate (CFR) among countries in South-East Asia. DHF is the main major of morbidity and mortality among children in South-East Asia. Children are the most infected group because of their low immune system. Many factors are related to the immune system such as gender, age, and nutritional status. This study aims to know the association between nutritional status as one of the risk factors of DHF and platelet count among pediatric patients with DHF in Pekalongan City, Central Java Province, Indonesia.

Method : The design of this study was analytical observational with a cross-sectional study using secondary data from medical records in Bendan Regional Public Hospital in Pekalongan City, Central Java Province, Indonesia. Pediatric patients aged 0-18 years participated in this study. The secondary data was collected during the period from January to December 2021. The nutritional status was measured using anthropometric tables of weight for height and Body Mass Index (BMI) for age according to the Indonesian Ministry of Health standard in 2020. The platelet level was measured on the first day of hospitalization. The statistical analysis was conducted using SPSS 23.

Results : A total of 30 pediatric patients participated in this study. The mean age of the patients was 7.7 years old. The gender frequency was found in equal numbers. The disease was found more common in the rainy season. The nutritional status was classified into 2 types which were 76.7% normal and 23.3% abnormal (obese, wasted, and severely wasted). The platelet count was mostly (56.7%) under 100 x 103/mm3. The analysis data using Fisher's test found that there was no significant association between nutritional status and platelet count among pediatric patients with dengue hemorrhagic fever (p = 0.427, OR = 2.292, 95%CI = 0.367 – 14.323).

Conclusion : These findings didn't support the hypothesis that an abnormal nutritional status was related to the lower platelet count. Nutritional status was not associated with platelet count among pediatric patients with dengue hemorrhagic fever at Bendan Regional Public Hospital, Pekalongan, Indonesia.

Keyword : Dengue Hemorrhagic Fever, Nutritional Status, Platelet, Pediatric

PP12-15

Short chain fatty acid butyrate reprogram macrophage function and phenotype in immune thrombocytopenia via immunoepigenitic pathway

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Background : Immune thrombocytopenia (ITP) is an autoimmune bleeding disease in which macrophage contributes to the abnormal autoimmune response of ITP as the antigen presentation cell and phagocyte. Short-chain fatty acids (SCFAs), the most well-characterized gut-microbiota-derived metabolites play an important role in the onset or progression of autoimmune disease (AID). The alteration of circulatory SCFAs content and its influence on autoimmune process in ITP remain unknown.

Method : In this study, we detected the level of SCFAs in the plasma from ITP patients and health controls matched for age and sex and analyzed the correction of platelet counts and plasma SCFAs level. In order to studied the immunomodulatory effect of butyrate to macrophages in vitro, CD14+ monocytes were isolated and induced to macrophages with M-CSF. Then we compared anti-Inflammatory effects, antigen presentation function and platelet phagocytic capacity of macrophages with or without butyrate treatment. Then we studied whether butyrate regulate macrophage function via the inhibition of Histone Deacetylases and its underlying signal pathway.

Results : We found that butyrate level in plasma samples of ITP patients was significantly lower than HCs, and there was no significant difference in acetate, propionate and pentanoate. We found a trend for a positive correlation between platelet counts and plasma butyrate level. Compared to acetate, propionate and pentanoate, we identified that butyrate had the most potent anti-Inflammatory effects to decrease the level of IL-6 and TNF-α secreted by macrophages from ITP and health controls. Further research demonstrated that butyrate suppressed the secretion of IL-6 and TNF-α in a time- and dose-dependent manner. For ITP patients, butyrate significantly reduced costimulatory molecules CD80 and CD86 expression. For health controls, butyrate decreased the expression of CD80 but not CD86. Then we co-cultured the CFSE-labelled CD4+ T cells with butyrate-treated or untreated macrophages and detected proliferation of CD4+ T cells. We demonstrated that butyrate markedly attenuated the ability to promote T-cell proliferation of macrophage from both ITP and HCs. We found that butyrate treatment attenuated platelet phagocytosis compared with un-treated macrophages from both ITP and HCs. HDAC inhibitory activity assay showed that butyrate could enter macrophages to inhibit HDAC activity directly. We analyzed histone acetylation levels by Western blot and found that butyrate increased acetylation of histone 3 lysine 27 (H3k27)

and histone 4 lysine 8 (H4K8). Furthermore, chromatin immunoprecipitation (ChIP) experiments demonstrated that treatment of macrophages with butyrate resulted in an increase of H3K27 and H4K8 acetylation levels at the promoter regions of IL-6 and TNF-a.The aryl hydrocarbon receptor (AHR) is a transcription factor activated by diverse ligand including compounds from the environment, diet and microbiome. We found that butyrate treatment on macrophages resulted in an increase in AhR expression. AhR knockdown reduced the histone acetylation levels of H3K27 and H4K8, indicating AhR may negatively regulate activation of HDAC. Co-IP analysis manifested butyrate treatment led to an increase in AHR/HDAC complex formation, including HDAC1, HDAC2 and HDAC3. Taken together, these data indicated that increase AHR expression induced by butyrate may enhance histone acetylation levels by facilitating interactions between that AHR and HDACs that inhibit HDAC activity. Butyrate supplementation in vivo alleviated thrombocytopenia in passive and active murine models of ITP.

Conclusion : In conclusion, butyrate treatment in vitro restores macrophages dysfunction via HDAC inhibition pathway. Butyrate increases aryl hydrocarbon receptor (AHR) expression, which combine with HDAC to inhibit histone acetylation of macrophages. Furthermore, butyrate supplementation in vivo alleviated thrombocytopenia in passive and active murine models of ITP. Therefore, we propose that butyrate supplementation may provide a potential treatment strategy for ITP.

Keyword : SCFA, Butyrate, HDAC, AhR, ITP

PP12-16

Management of severe hemophilia A: Low-dose prophylaxis vs on-demand treatment

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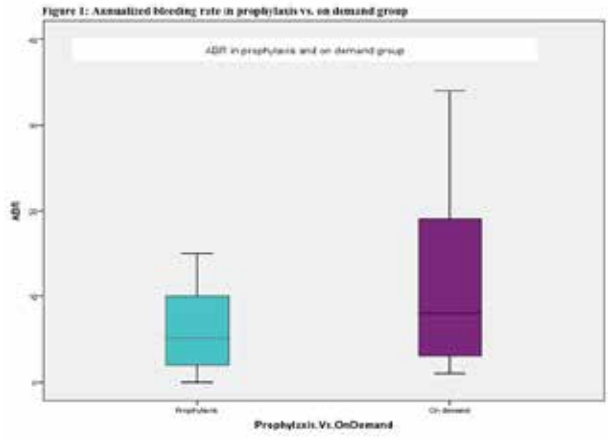
Background : Patients with severe hemophilia have undetectable factor VIII (FVIII) or IX levels, resulting in spontaneous and trauma-related bleeding, especially in the joints. Repeated joint bleeding eventually leads to a crippling arthropathy. Assessment of long-term effects requires decades of follow-up, but the number of patients with hemophilia is limited. Prophylactic clotting factor infusion regimens to prevent bleeding and joint deformity has become the standard of care in severe hemophilia A patients. Although prophylaxis in general is expensive, and the proposed tools to assist with individualization are time consuming and resource intensive, the overall economic savings from improved QoL with almost no bleeding and bleed-related complications, should be more than enough to offset the costs of its implementation in resource adequate nations. The aim of the study is to assess low dose prophylaxis as an alternative approach in our population.

Method : A prospective cohort study that included 68 hemophilia A patients were divided into two groups i.e. Prophylaxis and on-demand compared to annualized bleeding rate (ABR), hospitalization, units of factor VIII infused, or plasma products transfused (FFP and CP) and development of FVIII inhibitors.

Results : Out of the 68 patients recruited in this study, 25 were in the prophylaxis group and 43 in the on-demand group. The on-demand group presented a higher median-range in ABR [8(33) vs 5(15), p-value 0.024] while no of hospitalization (39.7%, p-value 0.001) and inhibitors (9.3%, p-value 0.289) compared to the prophylaxis group. Whereas the prophylaxis approach demonstrated a significant negative correlation of ABR with FVIII prophylaxis (r=-0484, p=value=0.014). Moreover, no hospitalizations or inhibitor development was observed in the prophylaxis group. The estimated annual consumption of FVIII was 328 IU/kg/year in the on-demand group and 1662.6 IU/kg/year in the prophylaxis group. However, a highly significant difference in plasma product utilization was observed between the two groups, i.e., p-value <0.001 and 0.038 for FFP and CP respectively. A significantly higher median-range ABR of 8(33) was observed in the on-demand group compared to 5(15) in the prophylaxis group (p-value 0.024), as depicted in Figure 1.

Conclusion : Low dose factor prophylaxis resulted in improved outcomes in terms of ABR, joint bleeding, hospitalization, and development of inhibitors. This treatment approach may be adopted as an economically feasible alternative to high dose prophylaxis.

Keyword : Prophylaxis, On-demand, Annualized bleeding rate, Hemophilia A, Inhibitor



PP12-17

Characteristics of essential thrombocytosis in children-A single institution retrospective study

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Background : Essential thrombocytosis (ET) is extremely rare in children, with annual incidence of approximately 1 per 10 million. Established treatment guidelines for ET derive from adult patients, and may have limited applicability in children. In this study, we reviewed the characteristics, treatment and outcome of pediatric ET patients diagnosed at our institution.

Method : We undertook retrospective review of 13 pediatric ET patients (female 7) treated at our institution from 2009 – 2022. The 2016 World Health Organization criteria were utilized to diagnose ET. All patients underwent bone marrow study to confirm ET.

Results : Mean age at diagnosis of ET was 11.6 years (range: 5.8 – 18.5), with a mean platelet count at diagnosis of 1,410 x 109/L (range: 820 – 2,693 x 109/L). Three patients were symptomatic at diagnosis. Twelve of 13 patients were evaluated for the JAK2 V617F mutation, and were all negative. Further genetic analysis of mutations in CALR, MPL, and other JAK2 sites revealed 1 patient each with mutations of CALR and other JAK2 (Exon20, c.2600G>A, p.Arg867Gln) respectively. Five patients (38.5%) started therapy at diagnosis, at a mean platelet count of 1,700 x 109/L (range: 1,067 – 2,645 x 109/L). Overall, 9 patients (69.2%) received medication beyond aspirin during the clinical course: either sequentially or in combination-anagrelide and hydroxyurea (N=3), hydroxyurea (N=3), anagrelide (N=2), anagrelide, hydroxyurea and vincristine (N=1). The mean platelet count at diagnosis of patients who received treatment was higher than those who were observed (1,570 x 109/L vs. 923 x 109/L, P=0.100). At a mean duration of follow-up of 6.5 years from diagnosis for the overall cohort (range: 0.2 – 16.9 years), 4 of 9 patients achieved treatment cessation at a mean of 71.8 months from diagnosis (range: 13.1 – 129.0 months). The mean platelet count at treatment cessation was 745 x 109/L (range: 434 – 965 x 109/L). None of the patients experienced major thrombotic or hemorrhagic complications during follow-up; a subsequent bone marrow study in 1 patient who received anagrelide showed myelofibrosis.

Conclusion : In our series of pediatric ET patients, the incidence of key mutations was low (2/13, 15.4%), in contrast to adults. In the context of 9 of 13 patients receiving therapy beyond aspirin, none of the patients experienced major thrombotic or bleeding complications. Further study is necessary to establish appropriate guidelines for the initiation and cessation of cytoreductive treatment in pediatric ET.

Keyword : Essential thrombocytosis, Children

PP12-18

Thrombotic thrombocytopenic purpura treatment at the hematology department of Cho Ray Hospital

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Background : Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, severe thrombocytopenia, and organ ischemia linked to disseminated microvascular platelet rich-thrombi. The disease relies on a severe deficiency in a disintegrin and metalloprotease with thrombospondin type-1 repeats, 13th member (ADAMTS13), the von Willebrand factor cleaving protease which can be either inherited (congenital TTP) or im-

mune-mediated. In immune-mediated TTP treatment includes TPE, corticosteroids. in cases that are resistant to combination therapy with rituximab or cytotoxic drugs. At the Hematology Department of Cho Ray Hospital that received TTP treatment, in order to provide more information about the effectiveness of TTP treatment, we conducted this study to investigate the mortality rate, the rate of resistance to TPE + Corticoids and the effectiveness of Rituximab in the treatment of resistant TTP.

Method : This was a retrospective, descriptive study. Select patients with diagnosis and treatment of TTP according to ISTH criteria.

Results : From 3/2020 to 11/2022, there were 29 patients who met the criteria for diagnosis of TTP according to ISTH. The mean age was 42.37 ± 15.04 (17 - 77), the female/male ratio was 1.41, there was 1 patient 20 weeks pregnant. Patients treated according to ISTH recommendations had the following results: The survival rate was 75.86% (22 patients) and the mortality rate was 24.14% (7 patients). Patients with TTP had a resistance rate to TPE + corticosteroids of 58.62% and were treated with rituximab with a rate of 58.82% (10/17 patients). The success rate in treatment-resistant patients receiving rituximab is 70% (7/10 patients).

Conclusion : In the treatment of TTP, the mortality rate is 24.14% , the rate of resistance to TPE + Corticoids is 58.62% and the effectiveness of treatment with Rituximab in resistant patients is 70%

Keyword : Thrombotic thrombocytopenic purpura, ADAMTS13, Mortality rate, Resistance, Pregnant

PP12-20

Romiplostim in pediatric immune thrombocytopenia: A meta-analytic synthesis

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Background : Immune thrombocytopenia is an autoimmune disorder, that affects both adults and children. It is associated with bleeding complications, occasionally life-threatening. Since thrombopoietin mimetics considered as second-line of therapy for immune thrombocytopenia which includes romiplostim and eltrombopag. It stimulates the production of normally functioning platelets. In 2018, romiplostim was approved for use in pediatric patients ≥1 year of age with immune thrombocytopenia of >6 months' duration and insufficient response to corticosteroids, immunoglobulins, or splenectomy. This study aimed to estimate the effect of romiplostim on increase in platelet counts and health-related quality of life (HRQoL).

Method : A systematic search on PubMed, Embase, and CENTRAL databases was searched to identify English language articles from inception to November 2022. Eligible randomized controlled trials (RCTs) evaluating the effect of romiplostim comparing with control group. The outcome measures included platelet response, incidence of bleeding, and HRQoL. A random effects model was used to calculate the risk ratio (RR) and mean difference (MD) with 95% confidence interval (CI).

Results : A total of seven RCTs with 548 pediatric from 1-17 years of age were included. Follow-up ranged from 12-25 weeks. Results from the meta-analysis favored romiplostim (RR 3.29, 95% CI 1.86 to 5.99, p< 0.001) over placebo, with significant increase in platelet counts. However, it showed no reduction in the incidence of bleeding compared with control group (RR: 0.89, 95% CI: 0.20 to 1.81). The impact of romiplostim on the HRQoL of patients and their parents was measured using e Kids' ITP Tool (KIT). Romiplostim significantly reduces the parental burden and demonstrated improvement in HRQoL (24 ± 17 vs. -6 ± 8; p=0.008) from baseline compared to placebo group.

Conclusion : Romiplostim treatment is effective in pediatric immune thrombocytopenia with a significant increase in the production of platelets. It is also associated with improved HRQoL in pediatric and reduced burden to their parents. Further, well-controlled RCTs with long-term follow-up and real-world studies are required to robust the present findings.

Keyword : Immune thrombocytopenia, Romiplostim, Platelet response, Incidence of bleeding, Health related quality of life

PP12-21

Klinefelter syndrome identified by multi-gene panel testing by massive parallel sequencing as a risk factor for venous thromboembolism

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Background : Sex chromosome aneuploidy has been reported to confer increased risk of venous thromboembolism (VTE). In particular, Klinefelter syndrome (KS) is the most common type of sex chromosome aneuploidy in male (47,XXY) and is clinically characterized by tall stature and infertility. Here we report two patients with KS incidentally identified through the routine laboratory workup for thrombosis risk assessment including by multi-gene panel testing by massive parallel sequencing (MPS).

Method : From June 2019 to December 2022, multi-gene panel tests for thrombosis were performed in 196 patients with VTE along with coagulation screening tests at Samsung Medical Center. Point variants are detected in total 62 genes and sex chromosome dosages are estimated by the ratio of the average value of autosome and X chromosome coverage in the data extracted in the post-processing coverage analysis step using the PICARD v2.19.0 tool.

Results : X chromosome aneuploidy was observed in 2 of 196 patients (1%). The first case was a 23-year-old man with pulmonary thromboembolism, superior mesenteric artery thrombosis, and left renal infarction confirmed on CT. He had a history of suspected mental retardation and attention deficit hyperactivity disorder. His stature was 179 cm. Chromosome and FISH analysis confirmed the karyotype 47,XXY, and genetic counseling was delivered accordingly on an outpatient basis. The second case was a 59-year-old man who had undergone pulmonary endarterectomy and balloon pulmonary angioplasty for deep vein thrombosis on both legs. His stature was 172 cm and he is a married man with 2 children. The results of chromosome and FISH analysis are pending. In both patients, no other diagnostic findings were observed on coagulation tests including antiphospholipid Ab or on multi-gene panel testing.

Conclusion : Conventional tests for sex chromosome aneuploidy is not included in the laboratory workup for VTE risk; however, the current multi-gene panel testing by MPS can screen its presence and reveal positive signals. To our knowledge, this is the first report of KS identified by MPS for VTE risk. Since KS not only increases risk of VTE and compromises reproduction but also is a multisystem disorder, confirmation by chromosome/FISH studies and genetic counseling are critical for further comprehensive care of the patients.

Keyword : Klinefelter syndrome, Sex chromosome aneuploidy, Venous thromboembolism

PP13-1

Analysis of BK virus infection in children after hematopoietic cell transplantation: A retrospective single-center study

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Background : BK virus (BKV) is one of the most common causes of hemorrhagic cystitis (HC) in children undergoing hematopoietic stem cell transplantation (HSCT). Viruses can be found in the urine and serum of immunocompromised patients.

Method : Retrospectively analyzed children who underwent HSCT at Beijing Children's Hospital, Capital Medical University from June 2020 to June 2022. Data related to the clinical manifestations, engraftment, and prognosis were extracted from medical records. Patients were divided into the case group and the control group, according to the BKV infection or not after HSCT.

Results : A total of 149 patients were enrolled in this study, and 61 (40.9%) patients developed BKV infection after HSCT. Among the 61 patients, BKV load was detected in all patients in urine samples and 22 patients in blood samples. The median value of BKV DNA copies in urine and plasma were 9.50x107 (5.37x102 – 6.84x109) copies/mL and 9.50x107 (5.37x102 – 6.84x109) copies/mL, respectively. The median time from the beginning of the conditioning regimen to BKV infection was 23 (0-273) d, and the first positive time of urinary BKV was earlier than that of blood (30.5 (7.0-165.0)d vs.13.5 (0.0-123.0)d, P=0.003). Among the patients with BKV infection, 36 (59.0%) patients met the diagnosis of hemorrhagic cystitis (HC), and the incidence was higher than that in the control group ($P < 0.001$). Similarly, 15(24.6%) patients developed renal function damage in the case group and the proportion was higher than that in the control group. The median follow-up was 5.67 (0.03-24.90) months, and there was no significant difference in 1-year overall survival rate between the case group and the control group (84.2% ±5.7% vs. 95.3% ±2.3%, P=0.688), but the incidence of TA-TMA/VOD and diffuse alveolar hemorrhage in the case group was higher than that in the control group (P=0.002 and 0.038, respectively). Multivariate analysis showed that age > 5 years old (OR=9.039, 95%CI: 3.561-24.333, P< 0.001) and use of MMF (OR=2.708, 95%CI: 1.041-7.044, P< 0.05) were independent risk factors for BKV infection after HSCT.

Conclusion : Among children after HSCT, the incidence of BKV infection was high and BKV infection was associated with an increased incidence of TA-TMA/VOD and diffuse alveolar hemorrhage. Patients older than 5 years of age at the time of HSCT and treated

with MMF were more likely to develop BKV infection.

Keyword : Children, Hematopoietic stem cell transplantation, BK virus, Hemorrhagic cystitis, Prognosis

Table 1 General information of BKV patients

Items	Case group (N=61)	Control group (N=88)	Statistic	P value
Basic information				
Male	40	59	<0.001	0.991
Age(year)	10.20 (3.66-15.49)	5.17(0.57-14.29)	-6.084	<0.001
Age(>5year)	55	44	24.295	<0.001
Primary disease				
Neoplastic disease	36	38	3.008	0.083
Non-Neoplastic disease	25	50		
Malignant disease	50	51	8.445	0.004
Non-Malignant disease	11	37		
AL	22	24	1.064	0.302
EBV-associated-disease	19	17	2.144	0.143
HLA				
Matched	11	17		
Haploid	48	64	3.622	0.425
Auto	2	7		
Source of stem cell				
Parents	40	59		
Sibling	12	10	1.771	0.425
Unrelated	7	12		
BM+PB	52	69	0.701	0.402
PB	7	12	0.019	0.889
Conditioning regimen				
With Bu	50	73	<0.001	1.000
With Cy	58	79	0.748	0.387
With ATG	54	72	0.781	0.377
With CsA	59	82	0.382	0.567
With MMF	53	62	4.629	0.031
Time of neutrophil engraftment (d)	11.0 (9.0-28.0)	11.5 (9.0-20.0)	1.355	0.175
HSCT related complications				
aGVHD	33	50	0.026	0.872
aGVHD (I-II)	28	37	0.813	0.367
aGVHD (skin)	23	42	1.626	0.202
EBV	8	10	0.004	0.947
CMV	23	40	0.597	0.440
Herpes virus	9	9	0.334	0.563
Fungi	8	3	3.645	0.056

Note: AL, acute leukemia; HLA, human leukocyte antigen; BM, bone marrow; PB, peripheral blood; Bu, busu cyclophosphamide; ATG, anti-thymocyte globulin; CsA , cyclosporine A; MMF, mycophenolate mofetil; GVH versus-host disease.

Table 2 Multivariate analysis of risk factors for BKV

Risk factor	B	S.E.	Wals	Sig.	EXP(B)	EXP(B) 95% C Lower limit	Up
Age (>5year)	2.231	0.490	20.708	<0.001	9.039	3.561	2
Using MMF	0.956	0.468	4.173	0.041	2.708	1.041	

PP13-2

High dose etoposide based chemo-mobilization for autologous stem cell transplantation – Revisited

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Background : Patients with relapsed lymphoma who have undergone multiple lines of chemotherapy will need consolidation with Autologous stem cell transplantation (ASCT). Chemo-mobilization was used routinely before granulocyte–colony stimulating factor (G-CSF) was available. Most centers have now switched to G-CSF-based stem cell mobilization ± Plerixafor. Despite the usage of plerixafor, about 6%-23% of patients may fail mobilization. Such patients either undergo allogeneic stem cell transplantation which carries increased mortality or they do not undergo any consolidation which carries an increased risk of relapse. So we started using high-dose etoposide with GCSF and plerixafor as mobilization (chemo-mobilization) in patients who failed conventional GCSF with plerixafor (G-CSF mobilization). Here we present a short series of seven patients who underwent chemo-mobilization after the failure of G-CSF mobilization.

Method : The treatment details, mobilization details, collection details, and transplant details of those who underwent chemo-mobilization from Jan 2021 – June 2022 were collected from patient records and analyzed. The patients were given high dose etoposide 1.6g/m2 on D1 followed by G-CSF 300mcg daily till the morning of collection. Peripheral blood CD34 was done daily in the morning from the day when total WBC counts raise above 1000 cell/cc and once the peripheral blood CD 34 count reaches 5 cells/cc, Plerixafor was given on that day night and the collection was done the next day morning.

Results : There were 7 patients who underwent chemo-mobilization in the above period. Males were five. The median age was 35 years (Range: 19-49). Four patients were primary progressive Hodgkin Lymphoma, two were relapsed Non-Hodgkin Lymphoma, and one was HIV-positive plasmablastic lymphoma. The median number of lines of chemotherapy received by these patients before ASCT was 2 (1-4). Six out of 7 patients failed G-CSF mobilization. One patient was taken up for direct chemo-mobilization as we anticipated failure with G-CSF mobilization due to four lines of prior chemotherapy. Out of the 7 patients, six patients had a successful mobilization with chemo-mobilization. The success rate was 85.7%. The only patient who failed chemo-mobilization was the HIV-positive plasmablastic lymphoma who has got only one line of therapy. Only one patient had febrile neutropenia during the chemo-mobilization. The median stem cell dose (n=6) collected during chemo-mobilization was 6.35x106 cells/kg (2.89-10.4). All 6 patients had engraftment before D15 of ASCT.

Conclusion : This series is presented to increase awareness of the usage of chemo-mobilization in patients who fail conventional G-CSF mobilization before offering the allogeneic stem cell transplantation which carries increased morbidity and mortality.

Keyword : Apheresis failure, Stem cell mobilization failure, Plerixafor failure, High dose chemomobilization, Mobilization using chemotherapy

PP13-3

Autologous stem cell transplantation in relapsed Hodgkin lymphoma – A single centre experience from India

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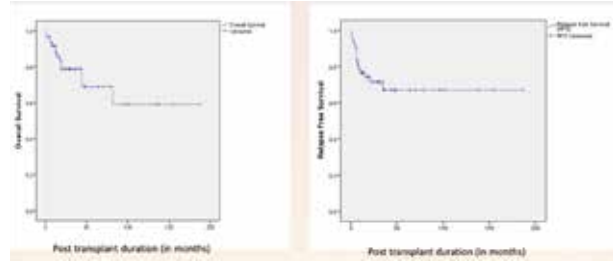
Background : Hodgkin Lymphoma is a type of lymphoid neoplasm named after Thomas Hodgkin first described in 1832. It is the first cancer that was successfully treated with radiation and is considered as a curable malignancy. The standard of care is now chemotherapy with or without RT in upfront setting and Relapsed Hodgkin's is treated with salvage chemotherapy to bring into remission followed by Autologous Stem cell Transplant (ASCT). This data is on Relapsed Hodgkin's lymphoma patients who underwent Autologous transplant at a single center from India

Method : This study is collection of Retrospective data on ASCT in patients with Relapsed Hodgkin's lymphoma during period from treatment details and outcomes of patients who underwent ASCT for Relapsed HL during the period of January 1997 to December 2021. The survival analysis was done by Kaplan Meier analysis and the comparison was done by Log Rank test.

Results : In this study which included 62 patients, the median age of the patients at diagnosis was 22.5 years (Range: 4-47 years) and Median age at Transplant was 24.5 years (Range: 4-50 years). Study compromised 63% Males (n=39) and 64.5% (n=40%) had Advanced disease at presentation. Most. Common regimen used upfront was ABVD/AVD (82%, n=51). In relapse setting 33.3%, 36.6% & 30% had Stage 2,3 and 4 respectively(n=60). Bone marrow involvement at the time of relapse was seen in 13.5% (n=59). Last salvage chemotherapy regimen used was GVD in 38 patients, DHAP in 13 patients and ICE/others in 11 patients. 63% had Complete remission of disease prior to transplant. 74% (n=46) patients underwent transplant after 1st line salvage regimen (CR2).LACE, BEAM/BEAC, CBV was used as conditioning regimen in 33.8% (n=21), 45% (n=28) and 19.3% (n=12) respectively. Out of 62 patients, dose of stem cell collected was available for 55 patients and median was 5.3x106 cells/kg (Range: 1.5x106 – 14.8x106 cells/kg). Febrile neutropenia (FN) was seen in 93.5%. It took a median duration of 11 days and 14 days for neutrophil and platelet recovery. Treatment related mortality was 4.8% (n=3). The median duration of follow up was 30 months. Three out of 62 patients underwent chemo-mobilization for stem cell collection followed by ASCT. The median relapse free survival (RFS) and overall survival (OS) was not reached in the study. The 3- year RFS and OS were 67.1% and 78% respectively. OS and RFS in Primary Progressive Hodgkin's lymphoma were significantly less compared to other patients(3 year OS: 56.6% vs 84.7% and 3 year RFS 25.2% vs 77%). The factors influencing OS and RFS were remission post 1st or 2nd salvage regimen, Type of salvage regimen used. Advanced stage of disease at diagnosis had poor outcome in terms of OS.

Conclusion : ASCT in Hodgkin's lymphoma can improve overall survival in Relapse setting. About 2/3rds of the patient are alive and without disease after ASCT in relapsed disease. ASCT considered after 2nd line has better RFS and OS. Complete response before ASCT has better RFS. Patients with Primary Progressive Hodgkin's lymphoma would require novel strategic treatments

Keyword : Relapsed Hodgkin's lymphoma, Autologous stem cell transplantation, Overall survival, Relapse free survival, Primary Progressive Hodgkin's lymphoma



PP13-4

Clinical impact of recipient-derived isoagglutinin levels in ABO-incompatible hematopoietic stem cell transplantation

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Background : The ABO blood group is expressed throughout the body system, such as in red blood cells (RBC), platelet (PLT), organ endothelium, and even in plasma, not in pluripotent or hematopoietic progenitor cells. ABO incompatibility is not considered the main barrier. Although not as critical as human leukocyte antigens mismatching, the clinical outcomes in ABOi HSCT are generally considered worse than those in ABO-compatible (ABOc) HSCT: adverse effects on survival, graft-versus-host disease (GVHD), relapse, and engraftment of neutrophil and PLT. We hypothesized that recipient-derived isoagglutinin (RDI) levels could play a critical role in clinical outcomes.

Method : We analyzed 103 recipients (ABOc, 53; ABOi with low RDI, 36; ABOi with high RDI. This study compared clinical outcomes such as survival, GVHD, infection, relapse, transfusion, and engraftment among ABO-compatible (ABOc), ABO-incompatible (ABOi) with low RDI, and ABOi with high RDI groups. ABOi with high RDI group was defined as recipients with more than 4 to 7 RDI levels, converted by log2 scales.

Results : ABOi with high RDI group showed a decreased 1-year survival and increased acute GVHD grade IV and RBC transfusion ($p = 0.017$, 0.027, and 0.032, respectively). ABOi with high RDI group was an independent risk factor for increased death, RBC transfusion, and poor platelet engraftment (odds ratio [OR] = 3.20, $p = 0.01$; OR = 8.28, $p = 0.02$; OR = 0.18, $p = 0.03$, respectively). ABOi with high RDI group showed significantly delayed PLT engraftment.

Conclusion : This study is the first to suggest high RDI levels as a marker explaining the unfavorable outcomes in ABOi HSCT. In terms of survival, acute GVHD, RBC transfusion, and PLT engraftment, ABOi with high RDI group indicated unfavorable outcomes, and ABOc group and ABOi with low RDI group showed comparable outcomes. In conclusion. the clinical outcomes can be predicted by measuring the RDI levels before HSCT, and intense prophylactic treatment and precision medicine for the recipient can be adopted.

Keyword : Hematopoietic stem cell transplantation, Recipient-derived isoagglutinin, Survival, Graft-versus-host disease, RBC transfusion, Platelet engraftment

PP13-5

Efficacy and safety of cytokine-induced killer cells infusion after autologous hematopoietic stem cell transplantation: an interim result of investigator's initiated clinical study

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Background : For high-risk non-Hodgkin's lymphoma (NHL), especially diffuse large B-cell lymphoma (DLBCL), high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (auto-HSCT) provides additional benefits to patients who achieved complete remission (CR) in salvage or frontline settings. However, auto-HSCT has limitations due to the relapse of minimal residual disease despite an intensive conditioning regimen and an increased risk of viral reactivation or other atypical infections because of delayed immune reconstitution. Therefore, we conducted an investigator-initiated clinical study to provide autologous cytokine-induced killer (CIK) cell infusion early after auto-HSCT for high-risk NHL patients with CR to kill chemo-surviving lymphoma stem cells and support immune reconstitution, which may protect against opportunistic infections in the early transplantation period.

Method : In this study, we aimed to enroll 32 lymphoma patients receiving auto-HSCT as frontline or salvage treatment. For auto-HSCT, peripheral blood stem cell (PBSC) mobilization was performed based on chemo-mobilization. The target CD34 stem cell dose was above 5.0 × 10^6/kg. Autologous CIK cells were collected during apheresis, which was generated from the patients' PBSCs, and infusion for 2 weeks after auto-HSCT was planned. All patients had CR before auto-HSCT. After CIK cell infusion, we performed efficacy and safety evaluation as well as further immunological analysis on a regular basis. The primary endpoint of this study was the 2-year progression-free survival from CIK cell infusion. The secondary endpoint was the safety profile based on the analysis of the different immune cell subsets and biomarkers associated with immune reconstitution.

Results : We currently enrolled 14 high-risk NHL patients, consisting of 10 patients with DLBCL, 2 patients with primary mediastinal large B-cell lymphoma (PMBCL), 1 patient with monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), and 1 patient with plasmablastic lymphoma (PBL). Among them, 11 patients were treated with frontline auto-HSCT, and 3 patients were treated with salvage auto-HSCT after the 1st relapse of the disease (2 cases of DLBCL and 1 case of MEITL). The amount of CIK cells generated during apheresis ranged from 2.65 × 10^7/kg to 3.78 × 10^9/kg, and all patients received infusion for a median of 14 days (range, 11–20) following auto-HSCT without specific adverse events. During a median follow-up of 221 days (range, 29–610), the rate of progres-

sion-free survival was 91.7% (95% confidence interval, 53.9–98.8) as an interim result. A patient diagnosed as having PBL showed a relapse of the disease 148 days after CIK cell infusion. CMV reactivation was observed in 3 patients with peak levels of 23,229 IU/mL, 28,173 IU/mL, and 10,312 IU/mL in 31, 18, and 22 days, respectively, after CIK cell infusion. These patients received intravenous or oral ganciclovir, and the CMV DNAemia subsided within a median of 17 days (range, 5–30). No uncontrolled CMV DNAemia or CMV disease was found, which may be associated with T-cell recovery at 4 weeks of auto-HSCT. Furthermore, there were no other infectious complications during the follow-up period.

Conclusion : CIK cells are CD3 T-cells that express the NK cell markers CD56 and NKG2D; thus, they can interact with the TCR and MHC complex and are also involved in the non-MHC-restricted killing of abnormal cells. CIK cells target residual lymphoma cells by upregulated NKG2D ligands, which can help achieve long-term CR. Moreover, intensive conditioning during auto-HSCT causes severe damage to the bone marrow, leading to vulnerability to opportunistic infections until reconstitution of the immune system. As the administration of CIK cells can exert toxic effects against infectious pathogens through central or effector memory T-cells, infection prevention can be expected and promote immune reconstitution. Therefore, autologous CIK cell infusion as a personalized post-remission therapy for high-risk NHL patients after auto-HSCT may be promising for preventing relapse and opportunistic infections without significant adverse events. Further monitoring will be needed to confirm the role of CIK cells in the early transplantation period.

Keyword : Autologous hematopoietic stem cell transplantation, Post-remission treatment, Cytokine-induced killer cells, Immune reconstitution

PP13-6

Comparable outcomes of allogeneic peripheral blood versus bone marrow hematopoietic stem cell transplantation from a sibling donor for pediatric patients

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Background : Traditionally, bone marrow (BM) have been a common stem cell source in pediatric hematopoietic stem cell transplantation (HSCT), however the use of peripheral blood stem cell (PBSC) has recently increased. With the advances of graft-versus-host disease (GVHD) prophylaxis, it is controversial whether bone marrow is still a better stem cell source than peripheral blood in sibling donor HSCT. Here, we compared the results of BM and PBSC transplantation in pediatric patients with malignant or non-malignant disease receiving a sibling HSCT by using a total of 7.5mg/kg of ATG.

Method : From 2005 to 2020, we retrospectively reviewed children who received HSCT from a sibling donor at Seoul National University Children's Hospital. Of the 86 patients, 40 were transplanted with BM, 46 with PBSC. Fifty six patients had malignant diseases and 30 patients had non-malignant diseases. All conditioning regimens comprised anti-thymocyte globulin (ATG) (2.5mg/kg/day, once daily from days -4 to -2). Busulfan-based myeloablative conditioning regimens was administered in the patients with malignant diseases and about half of patients with non-malignant diseases. The other half of the patients with non-malignant diseases were given cyclophosphamide-based reduced intensity conditioning regimens. All BM donors received G-CSF 10 μg/kg/day for 2 days prior to harvest for achieving early engraftment according to the studies of our center.

Results : In all 86 patients, the median age at the time of HSCT was 11.4 years (range 0.7-24.6) and the patients were 47 male and 39 female. The median follow-up period was 57.9 (range, 0.9 to 228.6) months, and the corresponding values for those with BM and PBSC were 77 (range, 2.4 to 228.6) months and 48.7 (range, 0.9 to 213.2) months, respectively. Engraftment failure occurred in 1 patient with BM and no patient with PBSC. The cumulative incidence of acute graft-versus-host disease (GVHD) with grade II-IV was higher in PBSC (BM 2.5%, PBSC 26.1%, p=0.002), but there was no significant difference in those of acute GVHD with grade III-IV (BM 0%, PBSC 6.5%, p=0.3703) and extensive chronic GVHD (BM 2.5%, PBSC 11.6%, p=0.1004). There were no significant differences in the treatment-related mortality (TRM) (BM 14.2%, PBSC 6.8%, p=0.453), the 5-year event free survival (EFS) (BM 71.5%, PBSC 76.2%, p=0.874) and overall survival (OS) rates (BM 80.8%, PBSC 80.3%, p=0.867) between BM and PBSC in univariate analysis. In the multivariate analysis, which included all factors with a P <.50 in the univariate analysis, there was no significant prognostic factor for EFS or OS. There was no significant difference in relapse incidence between BM and PBSC among patients with malignant diseases (BM 14.2%, PBSC 6.8%, p=0.453). Furthermore, there were no significant differences in the TRM, the 5-year EFS and OS rates between malignant and non-malignant disease and also between busulfan-based myeloablative regimen and reduced intensity chemotherapy using cyclophosphamide.

Conclusion : In this study, we showed that there were no significant differences in EFS, OS TRM, and GVHD except for acute GVHD grade II-IV between BMT and PBSCT from sibling donors by using a total of 7.5mg/kg of ATG. Therefore, peripheral blood, which is less invasive for donors and less labor-intensive for doctors, also could be considered as an acceptable stem cell source of sibling donor HSCT in children.

Keyword : Sibling hematopoietic stem cell transplantation

PP13-7

Better fitness of body surface area-based dosing of mycophenolate mofetil in pediatric patients undergoing HSCT: A prospective model-informed drug development approach

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Background : Mycophenolate mofetil (MMF) is one of the important drugs for graft-versus-host disease (GVHD) prophylaxis after allogeneic hematopoietic stem cell transplantation (HSCT). Particularly, MMF is widely used after haploidentical HSCT using post-transplant cyclophosphamide in the recent decade. However, the use of MMF in this setting is off-label in Korea and the population pharmacokinetics of MMF in pediatric patients have not been solely assessed. Moreover, the approved dosing of MMF for GVHD prophylaxis (15mg/kg twice a day) is different from that after renal transplantation (600mg/m2 twice a day). This study aimed to develop a population pharmacokinetic model for oral MMF in pediatric patients undergoing allogeneic HSCT and to evaluate the influence of clinical covariates on the pharmacokinetic parameters

Method : A total of 20 pediatric patients who underwent allogeneic HSCT at Seoul National University Children's Hospital and received oral MMF 15-20 mg/kg twice daily for GVHD prophylaxis (n=16) or treatment (n=4) were prospectively included in this study. A total of 80 samples were collected before, 1-hour, 2-hour, and 4-hour after MMF administration, and mycophenolic acid (MPA), and 7-O-glucuronide conjugate concentrations were measured. Clinical data were collected prospectively. A population pharmacokinetic analysis was conducted using a nonlinear mixed-effects modeling method. Demographic and clinical data were assessed as covariates using the stepwise covariate method. The final model was evaluated and validated for its robustness using a goodness-of-fit plot and a bootstrap method.

Results : The median age, body weight, and body surface area (BSA) of patients were 9.6 years (range, 1.4-15.6), 28.9 kg (range, 9.9-51.0), and 1.13 m2 (range 0.49-1.65), respectively. 14 patients had malignancy and the others not. The majority of patients received a busulfan-based myeloablative conditioning regimen (n=17), 2 patients total body irradiation-based regimen, and the remaining patient fludarabine plus melphalan. Concomitant tacrolimus was administered in 16 patients. Among them, the purpose of MMF was for GVHD prophylaxis in 16 patients and for GVHD treatment in 4 patients. The population parameter estimates for Cmax, the area under the curve0-6 (AUC0-6), the volume of distribution (Vd/F), and apparent clearance (CL/F) were 8.5 mg/L, 22.4 mg·h/L, 57.2 L, and 23.4 L/h, respectively. Among 16 patients who used MMF for GVHD prophylaxis, there was a significant difference in MPA AUC0-6 between acute GVHD and non-acute GVHD groups with values of 28.20 mg·h/L and 13.26 mg·h/L ($p<0.05$). Using stepwise covariate modeling, BSA was finally included in the final model. We found that BSA had a significant impact on the Vd/F of MPA. The population parameter estimates for absorption rate constant (Ka), Vd/F, and CL/F were 5.06 h-1, 82.1 L, and 18.3 L/h, respectively. Furthermore, the Vd/F of MMF in this pediatric population was found to significantly associate with BSA.

Conclusion : BSA was derived as a statistically significant covariate affecting the pharmacokinetic parameters of pediatric patients undergoing allogeneic HSCT in the MMF pharmacometric model developed from a total of 20 clinical trial patients. Furthermore, a lower AUC of MPA showed a significant correlation with a higher incidence of acute GVHD. Taken together, BSA-based dosing could be considered when MMF is administered for GVHD prophylaxis in pediatric patients.

Keyword : Mycophenolate mofetil, Pediatric, Hematopoietic stem cell transplantation, Body surface area-based dosing, Model-informed drug development approach

PP13-10

Role of short tandem repeat (STR) in leukemia patients received allogeneic hematopoietic stem cell transplantation

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Background : Short tandem repeat (STR) is a useful tool for predicting disease recurrence and graft rejection in leukemia patients treated with allogeneic hematopoietic stem cell transplantation. Although a few malignant cells called minimal residual disease (MRD) could be very effective markers for anticipating relapse, they can be detected only by highly sensitive methods, and are not ready yet to be used in many hospitals. The aim of the present study is to evaluate the applicability of STR in the era of MRD.

Method : We retrospectively analyzed data from 149 patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) who underwent allogeneic hematopoietic cell transplantation (allo-HCT) from February 2007 to November 2020. Patients between 14 and 79 years were included in the present study. STR-PCR was conducted with simple PCR coupled with capillary electrophoresis.

Results : A total of 145 patients who underwent allo-HCT at Kyungpook National University Hospital were included in this study, and median age was 43.0 (range, 30-55) years. Patients diagnosed with AML were 89, and ALL were 56. Allo-HCT were conducted in CR1 (n = 105), CR2 (n=32) and refractory (n=8). After transplantation, 47 patients (32%) were relapsed. Mixed chimerism was detected in 19 patients (13%) according to STR-PCR using peripheral blood (PB). Among the 19 patients with mixed chimerism, 8 patients (5.5%) showed average >5% recipient DNA in PB, and five of them (62.5%) experienced disease relapse, while other 11 patients (57.9%) presented detectable but average of <5% recipient DNA in PB, and three of them (27%) showed relapse. Seven out of 8 relapsed patients with mixed chimerism did not stop the immunosuppressive agents due to graft-versus-host-disease (GVHD). Three patients with average of >5% recipient DNA in PB who stopped immunosuppression therapy did not relapse. In addition, five of 6 patients with average <5% recipient DNA in PB who discontinued immunosuppression therapy also did not show disease relapse. The only one patient who stopped the immunosuppression therapy showed the chloroma without overt bone marrow relapse.

Conclusion : STR can be used for predicting relapse as a surrogate marker. Discontinuation of immunosuppressive agent can be an effective method for preventing relapse in patients with acute leukemia received allo-HCT presenting mixed chimerism by STR.

Keyword : Hematopoietic stem cell transplantation, Acute leukemia, Short tandem repeat, Chimerism, Relapse, Immunosuppression therapy

PP13-11

A case report of central nervous system autoimmune demyelinating disease following allogenic hematopoietic stem cell transplantation

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Background : Neurological problems involving the central nervous system (CNS) can be fatal for patients who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT). There are several causes, including neurotoxic medications, infection, immune-related illnesses, and graft-versus-host disease (GVHD), although the exact association is unknown.

Method : Here, we report a 76-year-old man with acute myeloid leukemia who developed immune-mediated demyelinating illness after allo-HSCT from haploidentical family donor. He struggled with recurring acute and chronic GVHD following allo-HSCT, but has been stable without immunosuppressive drugs for the past 13 months. At 34 months post-transplantation, he presented to the emergency room with acute left lower limb paralysis. Other organs showed no definitive symptoms of GVHD.

Results : The magnetic resonance imaging revealed an open ring enhancing lesion suggestive of a demyelinating lesion, and the cerebrospinal fluid investigation revealed an increased IgG, protein level. Antibodies against myelin oligodendrocyte glycoprotein were found in the serum. Other potential sources of demyelinating CNS problems, including multiple sclerosis, neuromyelitis optica,

and acute disseminated encephalomyelitis, were less likely due to a presence of MOG antibody, and most likely diagnosed as MOG antibody associated disease, the cause of autoimmunity is difficult to explain. We thought he had an autoimmune demyelinating disease, so we gave him a methylprednisolone pulse and intravenous immunoglobulin. The patient's clinical symptoms and MRI results eventually improved, and he was able to walk independently.

Conclusion : Allo-HSCT is associated with a risk of CNS complications, which was often linked to either acute or chronic GVHD. On the other hand, the absence of GVHD symptoms and signs in the current patient suggests that the autoimmune CNS issues observed following allo-HSCT were not directly caused by GVHD. This indicate that careful further research based on clinical, radiological, immunological, and pathological evidences is necessary to completely understand the pathobiophysiology of CNS problems following allo-HSCT.

Keyword : Autoimmune demyelinating disease of CNS, Allogenic hematopoietic stem cell transplantation

PP13-12

How the caregiver status could increase the quality of life among elderly after allogeneic-HSCT (allo-HSCT) with dementia status?

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Background : The potential curative treatment is Allogeneic hematopoietic cell transplantation (Allo-HCT) although the long-term survival is quite poor. Indonesia is entering an aging society and the prevalence of Elderly with independence barriers reaches 3.7% (MoH, 2018). The elderly with post-Allo-HSCT is very dependent on the presence of a caregiver to maintain their QoL. However, the availability of certified informal caregivers is not available in Indonesia.

Method : Using longitudinal and large-scale data (Indonesia Family Life Survey (IFLS) wave 5 of 2014), this study aims to explore how the availability of caregivers in maintaining the quality of life of Elderly post-Allo-HSCT with Dementia commodity.

Results : Indonesian seniors reach 10.8% of the total population and 48% have chronic diseases. 7.36% of patients with blood cancer recorded in Indonesia are Elderly. 34.7% of elderly with post-Allo-HSCT were identified as having dementia symptoms with moderate to severe (using mini-cognitive test scoring). The elderly needing long-term care due to these health conditions reached 9.7% and 88% of them did not have a caregiver. Less than 1% of seniors are cared for by paid caregivers and are concentrated in urban areas. Most of the elderly are cared for by their families (aging in the community). 36% of post-Allo-HSCT elderly with dementia are holders of social protection programs. Using the Geriatric Depression Scale (GDS) it was found that the percentage of post-Allo-HSCT elderly with dementia who had a caregiver with mental health problems was lower than respondents who did not have a caregiver.

Conclusion : As a country that will become the second-largest Silver Economy in the world after China, Indonesia is an aging market pushed to meet the availability of certified informal caregivers. Indonesia needs to expand health insurance, and standardize policies for certified caregivers, and senior living.

Keyword : Dementia, Elderly with HSCT, Caregiver, Quality of Life, Mental health, Silver economy

PP14-1

Bitter receptor agonist denatonium benzoate promotes hematopoietic reconstitution after hematopoietic stem cell transplantation in mice

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Background : Hematopoietic stem cells (HSCs) reside in the apical part of the hematopoietic layer and have the capacity for self-renewal and multidirectional differentiation, producing all the cells required by the blood and immune system. Hematopoietic stem cell transplantation is a very important treatment to reconstruct the normal hematopoietic system and can treat a variety of hematologic malignancies and non-malignant hematologic refractory diseases. The effective homing of hematopoietic stem cells determines the successful recovery of hematopoietic function after transplantation. Stem cell homing to specific niches within the bone marrow is a rapid and coordinated process. The homing of

stem cells to specific niches in the bone marrow is a rapid and coordinated process that is tightly regulated by a variety of adhesion molecules, chemotaxis, glycoproteins, integrins, and other factors. Various adhesion molecules, chemotactic factors, glycoproteins, and integrins are involved in the nesting of hematopoietic stem cells after transplantation. Bitter taste receptors (T2Rs) were originally found in taste bud cells and are responsible for bitter taste perception. Bitter taste receptors (T2Rs) belong to the G protein-coupled receptor family. Bitter taste receptors are not only expressed in taste bud cells, but also present in organs outside the taste system. Several studies have revealed that bitter taste receptors are widely expressed in different cells and tissues and perform different functions. In 2020 study found that acute myeloid leukemia cells express T2R isoforms and are involved in regulating the cycle regulation and apoptotic functions of leukemic cells, however, the role of bitter receptors in post-transplantation hematopoietic reconstitution has not been investigated. Denatonium benzoate (DB) is one of the most bitter substances known and has been increasingly studied as an agonist of bitter taste receptors and has been widely shown to activate the bitter taste receptors. It has been widely demonstrated that it can activate bitter receptors in many different cell types, but its role in hematopoiesis has not been reported. In the present study, we will use DB as a bitter taste receptor agonist to study the role of bitter taste receptors in hematopoiesis for the first time.

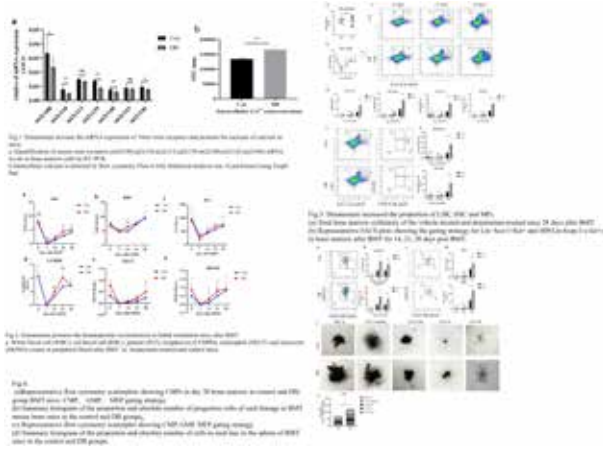
Method : 1.Mice C57BL/6J mice were used for the experiment, which were purchased from Model Organism (Nanjing, China). All mice were 8 weeks old male mice and weigh between 22 and 25 grams. Mice were kept in an environment free of specific pathogens and maintained on a 12 hour light/dark cycle for 12 hours, at a temperature of 21 ± 1℃, a humidity of 40-60%. 1.2.Radiation and Bone Marrow Transplantation Recipient mice were given a lethal irradiation dose of 9Gy in two doses with an interval of 4 hours at a dose rate of 82±1cGy/min. After irradiation for four hours, 2×10^6 total bone marrow cells derived from donor (C57BL/6J mice) were injected into irradiated mice via tail vein. Transplanted mice were given autoclave water supplemented with neomycin (1mg/ml) and polymyxin B (2000U/ml) for two weeks. 1.3.Drug Treatments and Sucrose Supplementation Denatonium was administerd to the mice by gavage at a dose of 10mg/kg once a day beginning from the second day of BMT and through the experiment. The control group was given vehicle by gavage. 1.4.Peripheral blood analyses Peripheral blood (PB) samples (5 μL) were collected from the saphenous vein and mixed with anticoagulant ACD solution (38 mM citric acid, 75 mM sodium citrate, 100 mM dextrose).We analyzed peripheral blood samples with a hematology analyzer (KX-21N; Sysmex). 2.Flow cytometry Peripheral blood was collected by posterior orbital vein of mice anaesthetized with isoflurane and was collected in polypropylene tubes containing EDTA. Bone marrow cells were flushed from femurs and tibias using a 1ml syringe with PBS via a 21-gauge needle. Spleen cells were grinding by a plug of 1 ml syringe onto a 60-um cell strainer (BD Biosciences). 3.Quantitative real-time PCR Total RNA from bone marrow cells form BMT mice was isolated by RNA FAST PURIFING KIT (Yi Shan biological;China). RNA was converted into cDNA using the PrimeScript RT reagent kit (Perfect Real Time; Takara) according to the manufacturer's instructions. Then, real-time PCR was performed using a SYBR green PCR Kit (Takara, DRR820S, Dalian, China). andAll data were normalized to β-actin. mRNA levels of Mus-Tas2r108 (F: GTATTTGTGTTTGCTGCCTCG; R: TCTGCGACTGTTGACCCAAG), Mus-Tas2r143(F:TCCCAGTTAGTTCCCAGGCT; R: AAGTTCCCGGTGGCTGAAAT),Mus-Tas2r146(F:TCACTTTGCTGTGGTACCTGT; R:TGGTGGCCAGCCATATACTA)were quantitated by real-time PCR on LightCycler® 480 System (Roche Applied Science, Mannheim, Germany).Relative changes in gene expression were analysed using delta Ct (2-ΔΔCt) method. 4.CFU-assay Clonogenic progenitors were determined in methylcellulose colony assay medium (MethoCult GF M3434, Stem Cell Technologies). In brief, 1 × 104 total BM cells from WT and KO mice were plated in 35-mm tissue culture dishes containing colony assay medium. After 7 days of incubation at 37 °C in 5% CO2, CFUerythroid colonies (E), granulocyte colonies (G), macrophage colonies (M), granulocyte-macrophage colonies (GM), and GEMM colonies were counted with an inverted microscope. 1 × 104 cells from primary CFU were replated for serial colony formation, 7 days later, colonies were counted with an inverted microscope to evaluate the proliferation and differention.5x 103BM cells were plated in the presence of Methocult M3434. Colonies were scored two weeks later. All assays were conducted in triplicate.

Results : 1.1Denatonium increase the expression of bitter taste receptor in mice Previous study has confirmed that denatonium benzoate can activate eight bitter taste receptors (T2R4, T2R8, T2R10, T2R13, T2R39, T2R43, T2R46 and T2R47) in human[7-9]. Using quantitative reverse transcription PCR, we verified the stimulation of denatonium benzoate. The mRNA expression of bitter taste receptor of recipient mice was quantified. The mRNA of mt2r108(homologous gene-human T2R4,8), mt2r146(homologous gene-human T2R43), mt2r148(homologous gene-human T2R46) is higher in denatonium treated mice bone marrow cells than control group. 2.Denatonium promote hematopoiesis after BMT To evaluate the role of DB in hematopoiesis after bone marrow transplantation. Lethally irradiated mice were administered bone marrow transplantation and divided into two groups: water or denatonium by gavage. After the irradiation, there is a dramatic reduction of white blood cells (WBC) in both groups, especially on days 7 after bone marrow transplantation the count dropped nearly to zero (0.10±10.13 vs 0.17±0.16, p=0.37) , but red blood cells (RBC) and platelet (PLT) were less affected. The recovery of total WBC in denatonium group was increased more rapidly in mice in contrast with the vehicle group (14 days:

0.1±0.13 vs 0.17±0.16, p=0.05, 21 days: 2.88±0.65 vs 4.38±1.26, p=0.02, 28 days: 4.0±0.87 vs 5.18±0.19, p=0.05). The increase in WBC can be explained to large extent by lymphocyte. The count of lymphocyte was approximate two fold in mice treated by denatonium on 21 and 28 days post BMT (14 days: 0.1±0.13 vs 0.17±0.16, p=0.05, 21 days: 2.70±0.56 vs 4.17±1.18, p=0.02, 28 days: 2.28±0.57 vs 4.6±0.79, p=0.02). The count of neutrophils and monocyte were also higher than control team, however, the difference did not reach the statistical significance. 3.Denatonium benzoate increased the proportion of BM hemopoietic stem cell post BMT As shown in figure 2a, there is no significant difference of bone marrow cellularity in recipient mice between the water-treated and denatonium-treated mice. We assessed the effect of denatonium on the hematopoietic stem cell. Notably, both of the frequency of Lin-Scal-1+c-kit+(LSK) and Lin-Scal-1-c-kit+(MP) dramatically increased in the denatonium group 14,21,28 days after BMT. The absolute number of Lin-Scal-1+c-kit+(LSK) and Lin-Scal-1-c-kit+(MP) were also increased significantly. The data is showed by the column figure, the difference is significant via two-tail T-test. Then we compared the HSCs of bone marrow cells in recipient mice, we found that, compare with the control group, there was three fold of increase of the frequency of long term HSC(LT-HSC:Lin-Scal-1+c-kit+CD150+CD48-), two fold increase of the frequency of short term HSC(ST-HSC:Lin-Scal-1+c-kit+ CD150-CD48-),one fold of hematopoietic progenitor cells (HPC, Lin-, Sca1+, c-Kit+, CD150-, CD48+) in these mice. The absolute number of LT-HSC,ST-HSC and HPC were all significantly increased.

Conclusion : 1. Denatonium benzoate as a bitter receptor agonist can promote ST-HSCs and pluripotent group cells The proportion is increased. 2. Denatonium benzoate can promote HSCs into the proliferation cycle and promote cell growth in various lineages Breed. 3. Denatonium benzoate promotes hematopoietic reconstruction in bone marrow transplanted mice.

Keyword : Hemopoietic stem cell, Bone marrow transplantation, Denatonium benzoate



PP14-2

Novel mechanism of thrombopoiesis by the human megakaryoblastic leukemia cell lines

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Background : Human megakaryoblastic leukemia cell lines (MEG-01) have been broadly used to study megakaryopoiesis and the molecular mechanisms of thrombopoiesis. Previous studies have shown that MEG-01 was used to generate platelet. Extracellular vesicles (EVs) are protein- and RNA-containing vesicles released from activated cell. We hypothesized that EVs might also generate during platelet formation from megakaryocytes. However, little is known about the role of megakaryocyte-derived extracellular vesicles (MEPs) and platelet-derived extracellular vesicles (PEVs) during thrombopoiesis. This study aims to study the characterization of MEPs and PEVs in thrombopoiesis using MEG-01 as a model.

Method : To generate platelets, MEPs and PEVs from MEG-01 cell lines, MEG-01 cells were grown in the presence of RPMI with 2 mM Valproic acid and maintained for up to 21 days. Cells were analyzed for the expression of surface markers using anti-CD41a, anti-CD61, anti-CD34 and analyzed by the FACSCalibur flow cytometer. In addition, cells were harvested for visualization under a confocal microscope and analyzed by ImageJ software. Representative platelets-like particles and EVs were analyzed directly from the culture and analyzed by flow cytometry. The number of MEPs, PEVs and platelets in the culture medium were analyzed base on the particles size less than 1 µm-bead and the positivity with annexinV together with CD41, CD61 and CD34 using flow cytometry. The function of EVs were tested using platelet aggregation by flow cytometry.

Results : Flow cytometric analyses of cell surface markers revealed that EVs cells had a high level of GP IIb/IIIa expression as well as apparent expressions of CD61, and CD34 antigens, but no expression of GP Ib nor glycophorin A. Moreover, the fraction of MEPs and PEVs was four time higher than number of platelets. Confocal microscopy demonstrated MEG-01 with abundant pseudopod formation like-proplatelet, extensive membrane blebbing, and distinctive platelet-sized particles. In order to analyses the performance of EVs induced platelet aggregation, flow cytometry showed that the

platelet aggregation was significantly increased in the presenting of enriched EVs.

Conclusion : In conclusion, our data reveal that MEPs and PEVs was higher generated during thrombopoiesis than the ordinary platelet. These EVs also have a role in promoting platelet aggregation. This novel data may provide a useful for a better understanding the study of human thrombopoiesis.

Keyword : Thrombopoiesis, Extracellular vesicles, Platelet aggregation, MEG-01

PP14-4

Telomere shortening in survivors of childhood hematologic malignancies

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Background : Telomeres are involved in maintenance of genomic stability and DNA repair. Telomeres of hematopoietic cells shorten with age, and accelerated telomere shortening is seen with replicative stress, such as during administration of chemotherapy for the treatment of cancer. We aimed to analyze leukocyte telomere length (LTL) among survivors of childhood hematologic malignancies, and to evaluate the associations of LTL with disease characteristics, treatment, and chronic health conditions.

Method : This is a single center, retrospective study with cohort aged between 15-39 years with longitudinal follow-up of ≥3-year survivors of childhood hematologic malignancies. Blood samples were collected from consenting participants at a minimum 3 years off therapy. LTL was measured by telomere flow-FISH cytometry using whole blood samples.

Results : Telomere flow-FISH was performed for 35 survivors of childhood hematologic malignancies. Median age at diagnosis and at DNA sampling were 13.8 years (range, 6-18) and 22.6 years (range, 15-34), respectively. Survivors had leukemia (57.1 %), lymphoma (31.4 %), and myelodysplastic syndrome (11.4 %). LTL in survivors was shorter overall compared to age standard reference values with statistical significance (10.1 ± 0.87 vs. 11.6 ± 0.08, p<0.01). There was no difference in LTL according to disease subtypes. Among 35 survivors, 20 (57.1%) had LTL ≥50th percentile, while 15 (42.9%) had LTL <50th percentile with 9 (25.7%) showing LTL <10th percentile. In survivors having LTL <10th percentile, the average LTL corresponded to age of 51.7 ± 14.9 year, suggesting an approximately 30 year acceleration in telomere attrition. Compared to survivors who diagnosed after their age of 10 years, survivors who diagnosed before their age of 10 years was more associated with having LTL <10th percentile (5/29 vs. 4/6, p=0.03). LTL decreased significantly in survivors who experienced relapse (7.5 ± 1.0 vs. 12.2 ± 5.3, p<0.01) and who had hematopoietic stem cell transplantation (8.8 ± 3.5 vs. 13.1 ±5.4, p<0.01). There was no significant difference in LTL between patients with chronic health condition and patients without (10.84 ± 4.76 vs. 12.35 ± 5.77, p=0.31).

Conclusion : LTL is significantly shorter among survivors of childhood hematologic malignancies than age standard references. For survivor who experienced hematologic malignancies before their age of 10 years, telomere shortening might accelerate further. Relapse and having HSCT was significantly associated with senescence of hematopoietic tissues, as shown by LTL attrition.

Keyword : Telomere, Survivor, Childhood, Hematologic malignancy

PP14-5

Clonal hematopoiesis: Somatic mutations in blood cells from patients with acute ischemic stroke

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Background : Clonal hematopoiesis is the proportionate clonal expansion of blood stem cells and their progeny driven by leukemia-associated somatic mutations. It is also associated with an increased risk of hematologic cancers and ischemic cardiovascular disease. Although the biology of clonal hematopoiesis remains not fully understood, In this study, we investigated the mutation profiles using the next generation sequencing (NGS) in patients admitted

to Busan Regional Cardio-cerebrovascular Center, Busan in Korea.

Method : We enrolled acute cerebral ischemia patients for the study. The site of arterial occlusion was analyzed with magnetic resonance angiography. NGS analysis was done by targeted sequencing using DNA isolated from peripheral blood and Illumina MiSeqDx and reagent kit (Illumina, Inc., San Diego, CA, USA). The panel employed was from HEMEaccuTest covering about 51 prevalent genes (NGeneBio Co., Seoul, Korea). Somatic variants were evaluated in terms of correlation with clinical and laboratory findings.

Results : For 34 acute cerebral ischemia patients, middle cerebral artery (MCA) infarction was most common (17 cases) and pontine (5 cases) and thalamic (4 cases) infarction followed. The age varied between 38 and 94 years. Tier 1 mutation was found in five cases (17.6%) and each of two DNMT3A and TP53 mutations and one ASXL1 mutation was also observed. Another two cases (5.9%) showed TET2 and STAT3 mutations (both tier 2), respectively. The age of those seven patients varied between 61 and 94 years. Two patients with DNMT3A mutations showed anemia. In 10 cases of control group, there were no tier 1 or tier 2 mutations identified.

Conclusion : Clonal hematopoiesis can be detected in at least 10-20% of individuals over the age of 70 years using NGS from peripheral blood DNA. Here we could show higher incidence of commonly mutated clonal hematopoiesis gene in ischemic stroke patients. Further studies clarifying the relationship between clonal hematopoiesis and stroke diseases are needed.

Keyword : Clonal hematopoiesis, Acute ischemic stroke, Next generation sequencing

PP16-1

Analysis of blood product and laboratory resource wastage due to non-severe allergic transfusion reaction

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Background : Blood transfusions are often needlessly aborted following a non-severe allergic reaction despite responding well to medication resulting into partial transfusion of the implicated blood product. This results in the wastage of un-transfused blood component and resources, spent on unnecessary laboratory testing for work-up of these reactions.

Method : We aimed to review the amount of blood product and laboratory resource wastage associated with non-severe allergic transfusion reaction (ATR) in an academic tertiary care hospital.

Results : During a period of three-year (2019-2021), a total of 174,632 blood products were released and transfused. There were 336 adverse transfusion reactions with an estimated rate of 1.9 per 1000 blood products administered. Out of 336, 145 (43%) were ATR, of which 141 (97%) were non-severe and 4 (3%) were severe. The most common associated symptom was found to be urticaria in 31 (22%). All (100%) non-severe ATR responded and completely resolved with medication. Seventy nine percent of the transfusions associated with non-severe ATRs were aborted, resulting in partial transfusion. The estimated loss of blood product volume was found to be 11,185 ml (11L) [mean 113 ±62.5 ml] at a cost of USD $2,352.25. Additionally, the cost of transfusion workup was estimated to be $6,114.87 resulting in a total expenditure of $8,467.12. Table I shows patients' characteristics having non-severe ATR.

Conclusion : Non-severe ATR was found to be associated with a significant proportion of laboratory resource wastage and that of blood product in our institution. Revision of institutional guidelines for management and lab workup of transfusion reactions would be helpful in alleviating this unnecessary loss in a resource constraint transfusion-setting.

Keyword : Transfusion, Allergic reaction, Blood wastage, Laboratory resources

Table I: Patients' characteristics having non-severe allergic transfusion reaction

***Mean age** (years)*	32.6 ±21.6
***Male/Female** (n)*	62/81
***Blood group**, n (%)*	
A	38 (27)
B	45(33)
O	44 (31)
AB	14 (10)
***Indications**, n (%)*	Total n=134
Anemia	49 (37)
Cancer related	44 (33)
Bleeding	19 (14)
Thrombocytopenia	7 (5)
Trauma	6 (4)
Hemoglobinopathy	6(4)
Coagulopathy	3 (2)
***Implicated blood product**, n (%)*	
RBC	106 (75)
Irradiated PRBC	14 (10)
Platelets	9 (6)
Plasma	7 (5)
Irradiated platelets	4 (3)
Cryoprecipitate	1 (1)
***Treatment**, n (%)*	Total n=126
Antihistamines	38 (30)
Antihistamines + corticosteroids	34 (27)
Acetaminophen + corticosteroids	33 (26)
corticosteroids	11 (9)
Acetaminophen + corticosteroids + antihistamines	7 (6)
Acetaminophen	3 (2)
Amount of blood product wasted in ml (Mean ±SD)	
Packed Red cells	9135 (119 ±62)
Platelet	205 (34 ±8)
Plasma	525 (87.5 ±41)
Irradiated Packed Red cells	1320 (132 ±60.8)

PP16-2

Platelet transfusion in pediatric intensive care unit patients

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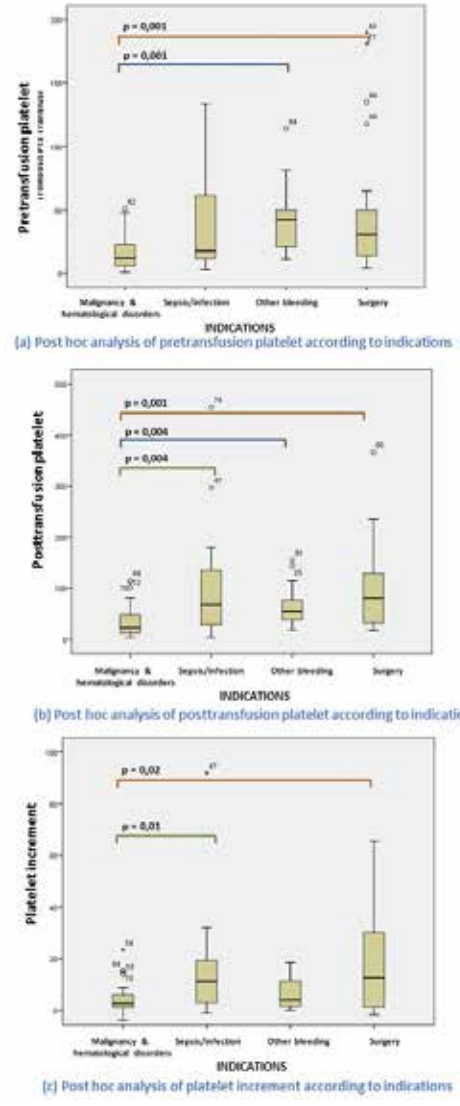
Background : Thrombocytopenia is commonly found in pediatric patients who were admitted to pediatric intensive care unit (PICU). Thrombocytopenia is often associated with bleeding manifestation and increased risk of mortality. Platelet transfusion can be given as a prophylactic or therapeutic in patients with bleeding manifestations. However, guideline for platelet transfusions in critically ill patients are not established yet.This study aimed to understand pattern of platelet transfusion among PICU patients, including indications, platelet count before and after transfusions, and platelet increment.

Method : This was a cross sectional descriptive study. Patients who were admitted to PICU and received platelet transfusions during July 2020 to July 2021 in Sardjito General Hospital Yogyakarta were obtained through electronic medical record. Sex, age, diagnosis, and clinical conditions were recorded. Categorical and numerical data was presented as percentage and median (min-max), accordingly. Analysis was performed using Kruskall-Wallis test, using SPSS 23.

Results : Patients were grouped according to their indication for transfusion, such as malignancy (hematological and non-hematological), infection and sepsis, other bleeding, and for surgery. Forty -wo patients were included as subjects. Most frequent blood type was O and all patients had positive rhesus. Distribution of patients according to indications were not much different, patients with infection and sepsis were 30,9%, followed by surgery and hematological malignancy (28,5% and 26,1%, respectively). The lowest platelet count before and after transfusions and platelet delta was found in group of hematological malignancy and was significantly lower than other groups ($p<0,05$). This group also shows significant differences in post-hoc analysis compared to other groups.

Conclusion : Pediatric patients who received transfusions mostly because of any severe infection and sepsis or bleeding manifestations. Patients with malignancy and hematological disorder had lower platelet count and delta compared to patients with other causes.

Keyword : Transfusions, Platelet, Platelet concentrate, PICU



PP16-3

The effect of premedication in transfusion reaction : Systematic review and meta-analysis

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Background : Blood transfusion can save lives, patients get the benefit but also the risk of transfusion-related. Acetaminophen and diphenhydramine are commonly used as premedication transfusion to prevent transfusion reactions. The efficacy of premedication for the prevention of transfusion reactions remains controversial. The aim of this study is to investigate the effect of premedication in transfusion reaction.

Method : This study is a systematic review and meta-analysis with PRISMA guideline. The research data for eligible publications were from PubMed and Embase databases until October 2022. Randomized control trial enrolling patients requiring an allogenic blood transfusion that compared acetaminophen and diphenhydramine premedication as case group to placebo or no treatment for prevention of febrile nonhemolytic transfusion reaction and urticaria as control group were eligible. There were no restrictions on age, sex, underlying diagnosis, or clinical setting. Observational studies were excluded due to concerns around biases in patient selection and outcome assessment. Pharmacologic therapies may be administered in any route of administration, dose, duration, and frequency.

Results : Three studies (242 cases/252 controls) were included. Case group significantly improve febrile nonhemolytic transfusion reaction (RR 95%CI= 0.55[0.30-0.98] p= 0.04). Two studies (227 cases/235 controls) were included. Case group does not significantly improve urticarial reaction (RR 95%CI= 0.88[0.55-1.40] p= 0.59).

Conclusion : Premedication transfusion (acetaminophen and diphenhydramine) decrease the risk of febrile nonhemolytic transfusion reaction. However, premedication transfusion does not significantly improve urticarial reaction.

Keyword : Febrile nonhemolytic, Premedication, Transfusion, Urticaria

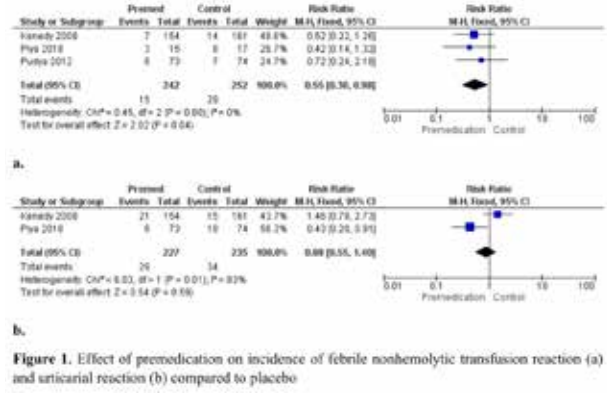

Figure 1. Effect of premedication on incidence of febrile nonhemolytic transfusion reaction (a) and urticarial reaction (b) compared to placebo

PP16-4

Variables affecting immunogenicity of blood group antigens: reflections on the formula calculating immunogenicity

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Background : The immunogenicity of a blood group antigen is a measure of its likelihood of inducing alloantibodies. All the previous studies about immunogenicity have been based on a formula using antigen frequencies in the population and the relative frequencies of unexpected antibodies to the corresponding antigens. This study examined other variables that may affect the results of calculation using the widely used formula.

Method : We examined the effect of multiple transfusions, as there is more chance for a patient to receive multiple repeated transfusions rather than only once; the effect of antigen density, which may vary depending on homozygote/heterozygote; and the effect of unreliability of the observed frequency of rare antibodies and antigens.

Results : For multiple transfusions, the expected antibody frequency showed increment as the number of transfusion episodes increased, but the effects were dependent on the antigen frequency. For antigen density, the antigenicity was calculated to be falsely low for the low-prevalence antigen and this tendency intensified as the effect of antigen density increased. Expected frequencies of antibodies were significantly affected by the uncertainties of small number estimation.

Conclusion : In this study, the effects of various factors that can affect the estimation of immunogenicity with formula using antigen frequencies and the relative frequencies of unexpected antibodies were investigated. A well-designed prospective study with large cohort number is needed to correctly estimate the immunogenicity of blood group antigens.

Keyword : Blood group, Antigen, Immunogenicity

PP16-5

Assessment of platelet consumption in malignant blood disorders; Can we develop a rationale way to save platelet?

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Background : The consumption of platelets has significantly increased as compared to other blood products. In addition to high consumption, irrational use of platelet is also evident. We are a referral institute for treating blood disorders in the country with huge representation of patients from rural regions. There is scarcity of voluntary donation and exchange donors are reluctant to donate also at times of utmost need. On the other hand, inappropriate consumption of platelet transfusion adds financial burden on patients. The study was conducted to evaluate usage of platelets in terms of issuance, wastage and transfusions.

Method : A 6 month platelet audit was carried out at NIBD PECHS campus from June to November 2021. Platelet issuance and wastage rate was retrieved from internal software 'zaviya'. Two hundred and fifty platelet transfusions were evaluated to assess the restrictive and liberal transfusion. Platelets transfusion in case of sepsis and count <20x109/L, sepsis with bleeding and<50x109/L, patients on active chemotherapy without bleeding but count <10 x 109/L and in patients presenting with bleeding was considered genuine.

Results : During the study period, 960 platelets were issued, out of which 10 (1%) were apheresis platelet. There was no wastage seen in consumption. Out of 250 transfusions, 3(1.2%) were apheresis platelet that were genuinely transfused. Out of 247, 60(24%) platelets were non genuinely transfused as per the criteria described in methods. However, in non genuine group, all patients received more than 1 unit platelet and the increment of platelet count post transfusion was found statistically non significant (P= 0.121).

Conclusion : Regular assessment of blood and blood products is necessary in order to enhance the supply of products when it is obligatory needed in order to decrease the economic burden on patients and also limit the liberal and non genuine transfusions.

Keyword : Platelet consumption , Malignant blood disorders

PP16-6

Quality of life in transfusion-dependent thalassemia patients in Bihar

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Background : Thalassemia is the most common genetic disorder in the state of Bihar . Despite recent advances in the management of thalassemia, people living in developing countries do not receive satisfactory treatment. For such chronic conditions, not only is patients' survival important but their quality of life (QOL) is also important, which is primarily driven by psychological and social constraints. This study explores various factors that affect QOL in transfusion-dependent thalassemia patients.

Method : This case control study included children with thalassemia major who received regular transfusions for the last five years. Controls were matched for age, gender and socio-economic status and included only healthy children. Different types of QOL were assessed using the World Health Organization (WHO) Quality of Life Assessment tool.

Results : Our study included 100 cases and 100 control, with an average age of 12.5+/- 3.6 yrs in cases and 14.3 +/- 5.4 in the control group. The total mean aggregate score of all patient questions was 65.09 +/-14.78; in the control group, the score was 77.46+/- 13.9. In nearly all factors, differences between cases and controls were most significant in males. There were no significant differences for the variables of physical pain, appearance and relations with others in both groups

Conclusion : Although there was no significant difference in the QOL score in thalassemia children, a more significant difference was observed in male patents than in females. The implications of this finding must be explored in further case-control studies.

Keyword : Thalassemia, QOL score

PP16-11

Successful plasmapheresis for patients with catastrophic antiphospholipid syndrome

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Background : Plasmapheresis or Therapeutic plasma exchange (TPE) is a safe and effective method for treating various diseases including infection and autoimmune. The procedure aims to exchange the plasma of patients with albumin or another plasma. However, this procedure was limited to stable patients since the exchange could worsen the condition of critical patients. This case shows the utility of plasmapheresis in patients with Catastrophic Antiphospholipid Syndrome with good outcomes.

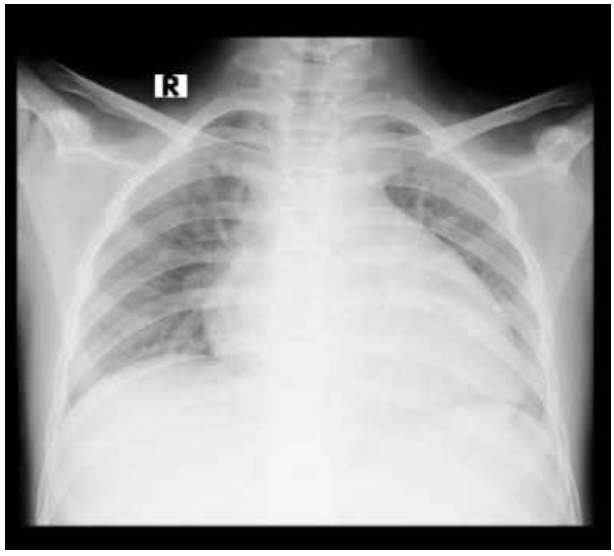
Method : A 13-year-old girl was brought to the hospital with complaints of sudden pain in the thigh to the lower left leg. The patient also complained of fever and tingling. There was no history of trauma in the patient. Doppler ultrasound results suggest an acute limb injury. The patient then performed an angiography examination and found a total occlusion of the common iliac artery. The patient is then prepared for a thorough evaluation before undergoing surgery. The results of the echocardiography examination showed moderate to severe mitral regurgitation and suspected vegetation. The results of the culture examination revealed the presence of Staphylococcus epidermidis vegetation supporting infective endocarditis. Before surgery, the patient had a myocardial infarction and Percutaneous Coronary Intervention (PCI) was performed and found a thrombus in the left anterior descending (LAD) artery. The laboratory examination results showed an increase in the Erythrocyte Sedimentation Rate (ESR) 3x from normal. The results of the ANA IF examination revealed a positive result with a mitotic centrosome pattern. Follow-up evaluation with the examination of IgM Beta2 Glycoprotein and IgG Beta2 Glycoprotein within normal limits. Lupus anticoagulant test showed 1.38 mild positive while anticardiolipin antibodies were within normal range. This patient was then treated with Catastrophic Antiphospholipid Syndrome and performed plasmapheresis using albumin. 24 hours after plasmapheresis there was a clinical improvement and a decrease in ESR to normal limits. The patient can then be discharged and home-treated with warfarin 3 mg/24 hours.

Results : Catastrophic Antiphospholipid Syndrome is a rare condition but has a high fatality. The sudden and unpredictable onset results in a high burden. Recommended treatment includes heparin, steroids, plasmapheresis, and intravenous immunoglobulins. Intravenous therapy Immunoglobulins are the main treatment. Howev-

er, in this case, due to limited resources, plasmapheresis is preferred. Plasmapheresis aims to eliminate circulating antibodies so that it is expected to reduce organ damage.

Conclusion : This case shows a patient with Catastrophic Antiphospholipid Syndrome who improved after plasmapheresis. However, the risk of this procedure should be considered if performed on another patient.

Keyword : Plasmapharesis, Catastrophic antiphospholipid syndrome



PP16-13

Advanced Red Cell Immunohematology for Direct Antiglobulin Test (DAT) In Healthy Blood Donors During COVID-19 Pandemic

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Background : Direct antiglobulin test (DAT) is an assay that is used for detection of any immunoglobulins or components of complement system which are bound to red blood cells (RBCs) in vivo. An increase in the prevalence of positive DAT was reported in patients suffering from COVID-19. This DAT positivity impacted pre-transfusion compatibility testing in transfusion services. These findings were observed in donor samples from healthy whole blood donors too. The present study was conducted with an aim to determine the prevalence and profile of DAT positivity in donors during the COVID-19 pandemic.

Method : This was a prospective observational study conducted in the department of Transfusion Medicine at a tertiary level healthcare facility in India from January 2021 to April 2022. A careful history of COVID-19 disease and vaccine was taken from all the blood donors. All consecutive donors were tested for DAT during the study period. Two EDTA pilot tubes were collected from the blood bag. One was sent for red cell serology testing and the other was preserved for hematology examination in case DAT was found to be positive. If DAT tested positive, reflex testing was performed. All results were recorded for statistical analysis.

Results : During the study period, a total of 1847 donors participated in the study. Out of the 1847 donors, 125 (6.8%) tested DAT positive. Twenty-nine (23.2%) donors tested positive for IgG only, 92 (73.6%) donors tested positive for IgG as well as C3d, and 4 (3.2%) donors tested positive for C3d only. A little more than half the eluates (55.2%) containing IgG tested positive with a panel of RBCs prepared from DAT-negative COVID-19 patients and tested negative with a panel of commercially available reagent red cells from healthy donors. Out of 125, a total of 39 donors showed findings of agglutinates on peripheral smear examination. None of the peripheral smears showed any spherocytes, polychromatophils or nucleated red cells.

Conclusion : Present study suggests that a history of COVID-19 infection is related to DAT positivity in healthy whole blood donors. However, severity of the disease does not impact DAT.

Keyword : Pandemic, DAT, Donors, Monospecific DAT, Polyspecific DAT, Covid-19

PP17-1

Predicting hematologic cancer using artificial intelligence

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Background : Artificial Intelligence (AI) solves many problems in data science. AI is the prediction of an outcome based upon existing data such as electronic health record. Text classification is

an AI technology that uses natural language processing (NLP) to transform the free text in documents and databases into normalized, structured data suitable for analysis or to drive AI algorithms. The machine learns patterns from the existing dataset then applies them to an unknown dataset for predicting the outcome. Classification is used for prediction. AI can play an essential role in predicting presence or absence of hematologic cancer. This can provide important insights to doctors who can then adapt their diagnosis and treatment. This paper investigates classification method, which is used for predicting hematologic cancer from clinical note by multilabel classifiers.

Method : We collected clinical notes from the hospital electronic health record data of 2016. We used keras python tool for analyzing the data. Our method is multilabel text classification using convolutional neural network (CNN) to predict hematologic cancer from clinical notes. Experiments with this tool were performed using a hematology dataset. The concentration of this paper is to achieve state of art accuracy of classification algorithms, and to show its utility to predict disease.

Results : The results of this study show that ensemble technique, such as CNN, is effective in improving the prediction accuracy of classifiers, and exhibit satisfactory performance in identifying risk of Hematologic cancer. Our study model achieves better precision 61 %, recall 89 % and F-measure 72 % for the hematologic cancer classification. This study also shows the higher-ranking prediction through probability.

Conclusion : Our study achieves the state of art accuracy through prediction model. Thus, physician can find some alerts to identify most probable disease with different ranking of disease. In future we may include more important variables that can help to identify more convenient prediction.

Keyword : Convolutional neural network, Text classification, Hematologic cancer, Artificial intelligence

PP17-5

Chemotherapy induced thrombocytopenia and its association with coagulopathy; A single centre experience

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Background : Chemotherapy induced thrombocytopenia is perilous and may complicate disease treatment resulting in extended hospitalization, bleeding, platelet transfusion and increase economic burden on the patients. Typically patients with hematological malignancies are at high risk of thrombosis and hemorrhage which may lead to poor outcome and overall survival. As coagulopathy in hematological malignancies is a predictor of thrombotic and bleeding complications, by adding the intellectual observation of platelet count, we may segregate patients and identify the susceptibility to either thrombosis or bleeding apparently. Our center is a referral institute for management of blood disorders with huge representation of patients with hematological malignancies. The study was done to observe the association of chemotherapy induced thrombocytopenia with coagulopathy in patients with hematological malignancies.

Method : This was a retrospective cohort study done at NIBD PECHS campus from 2020-2021. All the patients diagnosed with hematological malignancies receiving chemotherapy during the study period were included. Patients who had thrombocytopenia before chemotherapy were excluded. PT, APTT and platelet count, post chemotherapy was assessed. Chi square test and Fisher exact test was applied to observe the association. P-value <0.05 was considered to be statistically significant.

Results : A total of 34 chemotherapy cycles for hematological malignancies were analyzed. Median and range of age of patients was 36(9-75years) with predominant representation of male patients. Median platelet count post chemo was 39x109/L (4-398). The overall incidence of chemotherapy induced thrombocytopenia was 18%. Overall PT and APTT were deranged in 21(61.8%) and 24(70.6%) cases respectively. The association between chemotherapy induced thrombocytopenia and PT and APTT was observed however it was found out that deranged PT and APTT results were not associated with thrombocytopenia and found to be statistically non-significant (P-value >0.05).

Conclusion : In conclusion, the association of chemotherapy induced thrombocytopenia with coagulopathy was not found statistically significant. However, the findings might suggest the identification of high risk cohort at risk of bleeding and/or thrombosis. Longitudinal studies with larger sample size are needed in this regard.

Keyword : Chemotherapy, Thrombocytopenia, Coagulopathy

PP17-6

Secondary hematological malignancies in sarcoma patients: A single-center retrospective study

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Background : Several studies have been reported on therapy-related myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) that occurred in patients who were treated by conventional chemoradiotherapy for cancer. However, secondary hematological malignancies after sarcoma treatment have not been studied. Therefore, we aimed to investigate the characteristics of secondary hematological malignancies after treatment in patients with sarcoma.

Method : This single-center, retrospective study included the patients who were diagnosed with secondary hematological malignancies after sarcoma treatment at the Korea Cancer Center Hospital from January 2000 to November 2022. Clinical data were retrospectively collected from the medical records.

Results : Among a total of 3485 patients with sarcoma, 14 patients (0.4%) were diagnosed with secondary hematological malignancies (Table1). The median age at diagnosis of secondary hematological malignancies was 48 years (range 15–77), and 71% (n = 10) of patients were males. The majority of the patients (n = 10, 71.4%) had localized disease, and the most common primary site at the initial diagnosis of sarcoma was thigh (n=6, 42.8%) followed by femur (n=5, 35.7%). The histology of sarcoma consisted of seven osteosarcoma (50%), four malignant fibrous histiocytoma or undifferentiated pleomorphic sarcoma (28.5%), and Ewing sarcoma, chondromyosarcoma, and synovial sarcoma (7.1%) in each 1 case. All patients underwent surgical treatment and twelve patients (85.7%) received chemotherapy, none of the patients received radiation therapy. As for secondary hematological malignancies, AML was the most common (n=6, 42.8%), followed by MDS (n= 3, 21.4%), acute lymphocytic leukemia (n=2, 14.2%), follicular lymphoma, chronic myeloid leukemia, and multiple myeloma (n=1, 7.1%, respectively). The median interval of diagnosis of secondary hematological malignancies were 28.5 months (range 11.2-110.6) after diagnosis of sarcoma, and half of the patients (n=7, 50%) had no residual sarcoma lesion. Nine patients (64.2%) were treated for secondary hematologic malignancies. Median OS after diagnosis of secondary hematologic malignancies was 13.1 months. (range 0.4-149.6).

Conclusion : In our study, the incidence of secondary hematological malignancies in sarcoma patients were consistent with prior studies on other malignancies. Due to the small number of cases, it was not possible to identify a related factor for secondary hematological malignancies in sarcoma patients. Further nationwide studies are needed because of an identified associated factor for secondary hematological malignancies in sarcoma patients.

Keyword : Secondary hematological malignancies, Sarcoma, Therapy-related MDS, Therapy-related AML

PP17-10

Study of agricultural vulnerability to organic compound fungides and herbicides and myeloproliferative neoplasms incidence in rural population in India

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Background : Agriculture pesticides exposures could be implicated in the excess of myeloproliferative neoplasms experiential in Indian farmers, but facts relating to specific agriculture pesticides remain partial. Organic compound derivative pesticides, including fungicides and herbicides have shown facts of carcinogenicity in investigational studies in animals. In the Indian Miticides cohort, we assessed the unions between prospective exposures to organic

fungicides and herbicides and the incidence of myeloproliferative neoplasms, generally and by histological subgroup.

Method : Miticides registered 17,542 participants in Dewas district , Madhya Pradesh, India, implicated in agriculture. Incident myeloproliferative neoplasms were recognized by linkage with cancer registries from enrollment (2018-2020) until April 2020. specific exposures were assessed by combining information on time duration periods of insect killer use on crops and the Indian crop-revelation medium synergists, for each of the 18 organic and thiocarbamate herbicides and the 24 carbamate and Mothballs fungicides registered in Indian since 1966. Conjugated were approximate using comparative hazard models with age period as the underlying timescale, smoking, adjusting for gender and educational level.

Results : For the period of an average proceedings of 2.4 years, 48 confrontation cases of myeloproliferative neoplasms occurred, include 26 chronic neutrophilic leukaemia and 23 eosinophilic leukaemia. Analyses showed improved risks of myeloproliferative neoplasms with overall exposure to organic fungicides (Hazard Ratio, HR = 2.88; 96% CI: 2.27-3.79) and, to a slighter extent, to organic herbicides (HR = 2.44; 965% CI: 0.97-3.22). optimistic relations were observed with specific organic, including some fungicides (Copper, maneb, jojoba, metiram) and herbicides (diallate propham and chlorpropham, ,) already suspected of being carcinogens in animal and plants.

Conclusion : Although some relatives need to be substantiate in additional studies and should be interpreted carefully, these findings provide supplementary carcinogenicity facts for several carbamate herbicides and fungicides.

Keyword : Herbicides, Agriculture pesticides, Myeloproliferative Neoplasms, Chronic neutrophilic leukaemia

PP17-15

Treatment, outcomes and prognostic factors of patients with prolymphocytic leukemia

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Background : Prolymphocytic leukemia (PLL) is very rare disease that occurs primarily in older patients and is characterized by a predominant proliferation of lymphocytes referred to as prolymphocytes. The disorder is distinct from chronic lymphocytic leukemia (CLL) and prolymphocytoid transformation of CLL. Despite advances in understanding of the biology and pathogenesis, the prognosis for this group remains poor with early relapse and short overall survival (OS). Choice of treatment is mainly guided by the presence of high-risk genetic features, side effect profile, clinician experience and patient choice. In spite of this situations, the incidence of PLL is very low, so there are few studies on this so far. Therefore, this study discusses the characteristics of PLL patients and the outcomes of treatment, prognostic factors.

Method : Given such, in this study, we retrospectively evaluated prolymphocytic leukemia patients who were treated or followed up in our institution, between May 2009 and Dec. 2020. By analyzing 33 patients with B-PLL and T-PLL, we assessed overall survival(OS) and contributing factors for prognosis.

Results : Of the 33 patients, 21 were B-PLL and 12 were T-PLL. The median age was 65 years (range, 35-84 years), and male was the majority (60.6%). The characteristics of patients at the time of diagnosis were analyzed, and splenomegaly was present in 18/21 (85.7%) in B-PLL and 7/12 (58.3%) in T-PLL. Lymph node involvement was found in 13 (61.9%) and 6 (50.0%), respectively. The chromosome types were 18 normal karyotype (58.1%), 3 complex karyotype (39.7%), and 10 others (32.2%), and others belonged to t (8;14), +3, +12, +18, etc (Table 1). Of the 21 patients with B-PLLs, 8 patients were treated with alemtuzumab, 10 with fludarabine+cyclophosphamide (FC), and 1 were alemtuzumab+ fludarabine+cyclophosphamide (A-FC) as a first-line treatment. 2 patients were closed followed without treatment. Patients who relapsed or did not respond to the first-line treatment were given alemtuzumab, rituximab+bendamustine (BR), FC, etc. as a second line treatment. First-line treatment for patients with T-PLL (N= 12) included alemtuzumab (N=5), FC (N=2) and A-FC (N=1), fludarabine monotherapy (N=1), cyclophosphamide+ adriamycin+vincristine+prednisolone (CHOP; N=1), and 1 patient was closely followed. FC and allogeneic stem cell transplantation were implemented as a third line or higher for patients with relapsed/refractory disease. For all patients, median follow-up duration was 89.9 months, and probabilities of OS at 3 years were 71.4% in B-PLL, and 55.6% in T-PLL, respectively. For patients who were treated with alemtuzumab as first-line treatment, median progression-free survival was 8.7 months in B-PLL and 4.9 months in T-PLL, respectively. In univariate analysis for OS, the patients were divided into two groups based on the mean value at the time of diagnosis and the highest or lowest value; white blood count (WBC) (≥43.17 vs < 43.17, 109/L, p=0.018), peak WBC (≥90.59 vs < 90.59, 109/L, p=0.01), absolute lymphocyte count (≥38.32 vs < 38.32, 109/L, p=0.018), lowest hemoglobin (Hb) (≥8.0 vs < 8.0, g/dl, p=0.011), peak LDH (≥3,095 vs < 3,095, U/L, p<0.00) were statistically significant factors. In multivariate analysis, peak WBC (p=0.008, HR 6.829

[95%CI; 1.640-28.440]), lowest Hb (p=0.012, HR 0.134 [95%CI; 0.280-0.646]), and peak LDH (p=0.008, HR 6.829 [95%CI; 1.640-28.440]) were statistically significant for OS.

Conclusion : Since there was no standard treatment for patients with PLL, various treatments have shown various outcomes, and patients who have no indications for treatment initiation showed a relatively good survival only with close follow-up. Therefore, it is necessary to recognize criteria for the treatment initiation accurately, and consider the prognostic factors. PLL continues to pose a therapeutic challenge and newer treatment modalities should be developed to achieve a better treatment outcome. Rarity of this disease limits the conduct of large-scale clinical trials, and multicenter collaborative effort is required to conduct prospective studies.

Keyword : Prolymphocytic leukemia

Table 1. Patients characteristics

	All	B-PLL	T-PLL	*p*-value
Total Number	33	21	12	
Age at Dx.				
Median	65	67	58	0.026
Range	35-84	52-84	35-79	
Sex				
Male	20 (60.6%)	15 (71.4%)	5 (41.7%)	0.092
Female	13 (39.4%)	6 (28.6%)	7 (58.3%)	
Treatment N.				
Median	1	1	1	1.000
Range	0-4	0-4	0-2	
Splenomegaly				
+	25 (75.8%)	18 (85.7%)	7 (58.3%)	0.106
-	8 (24.2%)	3 (14.3%)	5 (41.7%)	
Hepatomegaly				
+	5 (15.2%)	3 (14.3%)	2 (16.7%)	1.000
-	28 (84.8%)	18 (85.7%)	10 (83.3%)	
LN involve				
+	19 (57.6%)	13 (61.9%)	6 (50.0%)	0.506
-	14 (42.4%)	8 (38.1%)	6 (50.0%)	
Chromosome	31	20	11	
Normal	18 (58.1%)	9 (45.0%)	9 (81.9%)	0.015
Complex	3 (9.7%)	1 (5.0%)	2 (18.1%)	
Others	10 (32.2%)	10 (50.0%)	0	
Lab at Diagnosis				
WBC (10^9/L), mean±SD	26.87 ± 46.26	25.52 ± 32.03	31.98 ± 64.75	0.793
ANC (10^9/L), mean±SD	3.69 ± 2.52	3.76 ± 2.86	3.33 ± 1.69	0.369
ALC (10^9/L), mean±SD	22.03 ± 44.33	21.58 ± 30.49	26.99 ± 62.15	0.822
Hb (g/dl), mean±SD	10.60 ± 2.42	10.50 ± 2.30	12.00 ± 2.68	0.524
PLT (10^9/L), mean±SD	177.00 ± 84.79	174.00 ± 73.58	192.50 ± 105.13	0.765
LDH (U/L), mean±SD	465 ± 490	465 ± 504	457 ± 484	0.970

PP17-16

Combination of red cell distribution width and serum human epididymis secretory protein 4 levels as a predictor of malignant ovarian tumors

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Background : The Risk of Ovarian Malignancy algorithm (ROMA), which comprises cancer antigen 125 (CA125) and human epididymis secretory protein 4 (HE4), is a U.S. Food and Drug Administration-cleared ovarian cancer prediction algorithm. The Copenhagen Index (CPH-I), which consists of age, along with CA125 and HE4, performs better than the ROMA. However, further improvements are required in this regard. Recently, the addition of new biomarkers to CA125 and HE4 to improve their performance in predicting malignant ovarian tumor (MOT) or epithelial ovarian cancer (EOC) has been attempted; however, it did not significantly improve the results. This study aimed to determine the optimal combination of biomarkers that can predict MOT or EOC, and compare the combination with ROMA or CPH-I.

Method : Data from 221 patients with MOTs and 820 patients with benign ovarian masses (BOMs) who underwent definitive tissue diagnosis of adnexal masses between January 2017 and June 2021 were analyzed. MOTs included borderline ovarian tumors (n=67), EOC (n=122), and non-epithelial ovarian cancer (n=32). The correlation between variables was determined using the Pearson's correlation coefficient. Differences in the median values of the two groups for each variable were determined using the Mann–Whitney U test. Logistic regression was used to establish the predictor models. The area under the curve (AUC) for the variables was determined using receiver operating characteristic curves.

Results : The median age of the patients was 43 years. There were significant differences in the median values of age, body mass index, white blood cell count, hemoglobin concentration, red cell distribution width (RDW), platelet count, mean platelet volume, platelet distribution width, plateletcrit, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, lymphocyte/monocyte ratio, serum albumin level, prognostic nutritional index, CA125, HE4, ROMA, and CPH-I between the MOT and BOM groups and EOC and BOM groups. Multivariate logistic regression analysis revealed that RDW and HE4 level were significant predictors of both MOT and EOC. While the AUCs of HE4 for predicting MOT and EOC were 0.724 and 0.885, respectively, the AUCs of the full model consisting of RDW and HE4

for predicting MOT and EOC were 0.820 and 0.952, respectively. The full model had a higher AUC than ROMA or CPH-I in predicting MOT or EOC, but the difference was not statistically significant.

Conclusion : RDW and HE4 levels were significant predictors of MOT and EOC in multivariate analysis. The AUC of the combination of RDW and HE4 was comparable to that of ROMA or CPH-I for predicting MOT or EOC. The use of RDW in the model has the advantage of obtaining results while examining complete blood counts and avoiding additional costs. Further prospective studies are required to validate these results of present study.

Keyword : HE4 Protein, Humans, Red cell distribution width, Adnexal disease

PP17-19

Empowering communities for anemia prevention: Lesson learnt from Indonesian government program

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Background : One of the priority agendas for the government's current development, as stated in the Nawacita, is to create a healthy Indonesia. The policy directions for health development include focusing on improving the nutritional status of the Indonesian people. The government's focus on improving the nutritional status of the community is to reduce the prevalence of anemia in pregnant women. The Indonesian government has made various efforts to tackle anemia in pregnant women, starting from encouraging adherence of pregnant women to consuming iron tablets, to increasing nutrition education for health cadres in health centers and policy makers in districts/cities.

Method : This study used a qualitative approach. Data collection methods in this research are observation, visual analysis, literature study, and interviews (individual or group)

Results : The efforts made by the Indonesian government to prevent anemia are by providing health education to increase knowledge. By empowering women's organization, participation level of community members in the intervention group was significantly increase, shown by family's willingness to provide and consume iron-sufficient foods in their daily diets. As an outcome, hemoglobin level of reproductive-aged women at the intervention group was slightly raised from its initial level, whilst in the control group relatively stagnant.

Conclusion : It is necessary to seek alternative ways of dealing with the problem of anemia that are acceptable to the community. An anemia prevention program must involve the community from identifying problems, recognizing local resource potential, implementing programs, monitoring, evaluating activity results.

Keyword : Anemia, Empowering, Women's organization

PP17-24

Risks of surgical treatment when appendicitis is diagnosed in hematologic patients

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Background : Patients with hematological diseases commonly have complete blood count (CBC) abnormalities that increase the risk of surgery. This study aimed to identify the risk of surgical treatment for acute appendicitis in patients with underlying hematologic disease.

Method : The patients diagnosed with appendicitis with underlying hematologic disease from 2000 to 2021 at Seoul St. Mary's Hospital were retrospectively reviewed. The hematologic disease was classified as low, intermediate, high risk, and others (idiopathic thrombocytopenic purpura).

Results : In 89 patients, 75 underwent surgery, and 14 had antibiotics with or without drainage. The surgery group showed a better tendency of initial CBC findings than the non-surgery group, and only absolute neutrophil count (ANC) showed statistical significance. The in-hospital mortality rates were higher in the non-surgery group (2.7% vs. 14.3%, respectively, p=0.115) without statistical significance. There were no significant related values, including clinical characteristics and disease-related risk with postoperative complications. Only postoperative hospital stay prolongation was affected by decreased ANC and platelet, intermediate or high disease-related risk, ileocecectomy, or right hemicolectomy with statis-

tical significance in multivariate analyses.

Conclusion : Surgery would help reduce the in-hospital mortality from appendicitis in patients with hematologic disease, although they have a very high risk for surgery. In addition, the CBC findings would not be related to postoperative complications. Active surgical treatment would be required for patients with appendicitis with underlying hematologic disease.

Keyword : Appendicitis, Appendectomy, Surgery

PP18-3

Assessment of the quality of life by the SF-36 questionnaire in patients with chronic myeloid leukemia in chronic phase after treatment with imatinib mesylate achieved complete cytogenetic response

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Background : Chronic myeloid leukemia is a chronic myeloproliferative disorder caused by abnormalities in hematopoietic stem cells. The disease is characterized by the presence of the Philadelphia chromosome, which produces BCR-ABL1 fusion gene. This fusion gene encodes a protein that carries Tyrosine kinase activity, which has important role in cell proliferation. There are many methods to treat chronic myeloid leukemia, however, the effectiveness of treatment has improved significantly since the appearance of drugs that target molecular biology, especially the first generation Tyrosine kinase inhibitor - Imatinib Mesylate. From the 10 year summary results of the big research on chronic myeloid leukemia such as IRIS and at Blood Transfusion Hematology Hospital in Ho Chi Minh City, Imatinib helped achieve a high and prolonged treatment response and improved overall survival. The drug is currently recommended as the standard treatment for patients with newly diagnosed chronic myeloid leukemia. Recent data suggest that the overall survival in patients achieving a complete cytogenetic response is not statistically significant compared with the general population, however, quality of life is different distinctly. Therefore, in parallel with the assessment of treatment effectiveness, the assessment of health-related quality of life is a very important issue that needs more attention and care. Recent studies on new drugs, therapeutic methods, surgery…all mention quality of life as an integral part of treatment outcomes. Especially, in patients with chronic myeloid leukemia, which is a chronic disease requiring long-term drug use. In the chronic stage, when a good response to treatment is achieved, not only the patients but also the doctors want to have a completely normal life.

Method : Objectives: Assessment of the quality of life by the SF-36 questionnaire in patients with chronic myeloid leukemia in chronic phase after treatment with Imatinib Mesylate achieved complete cytogenetic response. Subjects: Patients were diagnosed with chronic myeloid leukemia in chronic phase with BCR-ABL1 fusion gene and/or Philadelphia chromosome-positive were being treated with Imatinib mesylate achieved complete cytogenetic response in Blood Transfusion Hematology Hospital, Ho Chi Minh City. Method: Cross-sectional study. Sampling criteria: satisfy every following criteria: - 16 years old and up. - Newly diagnosed disease with chronic myeloid leukemia in chronic phase with BCR-ABL1 fusion gene and/or Philadelphia chromosome-positive in Blood Transfusion Hematology Hospital, Ho Chi Minh City. The data was entered into the computer and analyzed using the statistical software SPSS 18.0. - Be treated with Imatinib. - A complete cytogenetic response has been achieved. - Able to read and write Vietnamese fluently. - Agree to participate in the study.

Results : The total number of patients in the study was 261. The median age of the research population at the present time: 47 years old (16 years old – 80 years old). The male to female ratio is about 1,23:1. Approximately 40% of patients have comorbidities. The hematological parameters were all within normal values. The cases with low indices, are due to the hematological toxicity of Imatinib. Most of the patients in the study had a period of Imatinib use lasting many years. More than 50% of patients in the study achieved a deep molecular response to Imatinib treatment. Over 80% of patients experience toxicity with Imatinib. The number of patients with non-hematological toxicity is high, accounting for more than 2/3. Among hematological toxicities, anemia accounts for the highest proportion. Among the non-hematological toxicities, muscle spasms, musculoskeletal pain, nausea and fatigue are the toicities with high proportion. Most are at level 1 or 2. The mean physical health score: 74.4 ± 20.8. The mean mental health score: 75.5 ± 20.1. Factors affecting the physical and mental health: The higher the age, the lower the physical health score ($p = 0.02$); the higher the severity of anemia, the lower the physical health score ($p = 0.017$); patients with eyelid and facial edema and nausea had low mental health score ($p = 0.004 – p = 0.002$); patients with comorbidities had low physical and mental health score (p =

0.003 – p = 0.023); patients with musculoskeletal pain had low physical and mental health score (p = 0.008 – p = 0.014).

Conclusion : Patients were diagnosed with chronic myeloid leukemia in chronic phase after treatment with Imatinib Mesylate achieved complete cytogenetic response and had the quality of life at an medium-good level in the physical and good level in the mental aspect. Factors affecting the patient's quality of life include age, comorbidities and drug toxicities such as anemia, musculoskeletal pain, eyelid and facial edema and nausea.

Keyword : Chronic myeloid leukemia, Quality of life, Imatinib mesylate, Complete cytogenetic response, SF-36 questionnaire

Factors	The physical health	The mental health
Age	0,02	-
Comorbidities		
No comorbidities	0,003	0,023
1 comorbidity		
≥ 2 comorbidities		
Anemia	0,017	-
Musculoskeletal pain		
No	0,008	0,014
Yes		
Eyelid and facial edema		
No	-	0,004
Yes		
Nause		
No	-	0,002
Yes		

Factors related to physical and mental scores.

PP18-6

Study of reality and perspectives factors for blood donating motivation among urban population of Delhi, India

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Background : n India, there is a widespread shortfall between blood requirements and blood supplies and as a result, many patients die or suffer unnecessarily because they do not have access to blood and blood products and blood donation is voluntary, anonymous and non-remunerated. Furthermore, man-made natural disasters, road traffic accidents, and armed conflicts further increase the demand for blood transfusion in India. The aim of the study is to analyze donor motivation and sociology at SMVD centre in the urban population of Delhi, India.

Method : A cross-sectional sample survey of active blood donors in Delhi, India was conducted. Between 14 July 2021 and 15 August 2021, a total of 1354 urban population blood donors filled a questionnaire including the measures of demographic information, empathetic concern, altruism, social responsibility and blood donation motivation during donation.

Results : Among the donors, 78.8% were men and have a mean age of 31.2 years and the majority of them have an age between 18 and 27 years. The middle social class was majority (67.8%) as well as the liberal profession (75.1%). Primary and secondary education were dominant (89.3%). Among the blood donors, 51.6% were new donors and 37.6% had a history of a single donation, 51.3% were voluntary and 45.7% replacement donors. The reasons motivating the voluntary donation were solidarity (74.9%), religion (32.2%), health benefit (5.6%) and insurance for the family (7.2%). The replacement donors refuse the voluntary donation for not obvious reasons (58%), lack of availability (17.3%), difficulties of accessibility of the sites of collection (8.6%), phobia of the blood and the stings (5.02%) or by refusal of blood donation (1.89%). The information and the raising awareness of the replacement donors could change in a near future their attitudes to become voluntary and regular donors. The results with regression analyses showed that only social influence of friends and family had an significant effect independent of age, income, and education on blood donation motivation.

Conclusion : The implication of donor associations in the organization of the collections and the promotion of the blood donation would be of considerable contribution. It was observed that the altruism and empathy was the most important and significant factor followed by the influence of friends and family and strengthening of self-esteem.

Keyword : Blood donation, Perspectives factors f

PP18-8

Quality of life matters in hematopoietic stem-cell transplantation (HSCT)

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Background : Quality of life has been a focus of research in recent decades, especially in the field of oncology. Developments in the treatment of blood cancer and advances in technology have increased the chances of patients living longer. This is reflected in a growing interest in quality of life, which is starting to become as important as survival, and in researchers' interest in understanding how patients' lives are affected. by illness. Indonesia has long been associated with BMT services. In 1987, the first allogeneic and autologous BMT in Indonesia was performed by his Telogorejo Hospital and Dr. Kaliadi in Semarang, Central Java. Although hematopoietic stem cell transplantation (HSCT) has begun to develop in Indonesia and has been successfully used in the treatment of various malignant and non-malignant, usually life-threatening diseases, HSCT is associated with significant risks of physical and psychosocial morbidity. Transplant-related morbidity is evident throughout HSCT, starting with pre-transplant conditioning and continuing through the post-transplant recovery phase. Recognition of this spectrum of physical and psychosocial end effects has come with the realization that for many HSCT survivors, improvement or control of the underlying disease may be unrelated to recovery.

Method : Articles starting from 2002-2022 are collected from an electronic database. Then as many as 10 (ten) selected articles were reviewed to answer the objectives of this study.

Results : During the healing process, the affected person undergoes a few vital tiers wherein complications, except placing their lifestyles at risk, can negatively have an effect on their QoL, as signs and symptoms which have a disabling ability may also appear. In addition to the bodily complications, the affected person may also go through with emotional and social adjustments for the duration of remedy. They may also experience worry and anguish, and pass over the own circle of relatives and friends, given that social isolation is essential withinside the early tiers of remedy. Research has installed most cancers survivors, together with HSCT-survivors, frequently document their disorder revel in has advanced interpersonal relationships, greater appreciationfor lifestyles, reordered lifestyles priorities, extended empathy and selfesteem, or deepened spirituality. Theoretically, the emergence of effective sequelae is probably understood in phrases ofpost-demanding boom due to the fact lifestyles-threatening diseaseand remedy may be considered as a demanding stressor. Althoughtrauma publicity can cause bad sequelae (eg, distress,social estrangement), version to trauma can bring about newmodes of notion and conduct that constitute improvementsfrom pretrauma status.

Conclusion : The QoL of sufferers worsens because the severity of the signs increases. Knowing the precise modifications withinside the QoL of the affected person at every degree of the remedy allows the specialists worried on this context, specifically the nurse, to set up an individualized and powerful care plan, helping the affected person in going through their scientific condition, in addition to aiming at a higher survival.Indonesia's Ministry of Health has advanced numerous fitness investment initiatives, which includes the National Health Insurance Program, the Healthcare and Social Security Agency, and the Indonesian Health Card. Therefore, coping with signs of despair and QOL deterioration all through HCT hospitalization can be essential to enhancing QOL.

Keyword : Quality of life, Hematopoietic stem cell transplantation (HSCT), Indonesia

PP18-9

Spirituality as an alternative to reduce depression in leukemia patients

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Background : Leukemia is a blood cell malignancy originating from the bone marrow, characterized by uncontrolled proliferation of white blood cells (leukocytes), so that their function becomes abnormal. Patients with leukemia must undergo chemotherapy in a relatively long time. This results in many side effects, both physical and psychological. Various studies to reduce the impact of chemotherapy have been carried out, but all were carried out separately for each aspect. Handling to reduce the impact of chemotherapy in children with leukemia needs to be done comprehensively covering physical, psychological, social and spiritual aspects. This study aims to analyze the effect of spirituality as an alternative to reduce depression in leukemia patients.

Method : Literature search through Google Scholar, EBSCO, Springer Link, Elsevier, Sage databases using keywords: spiritual, leukemia. The journals taken have a range from 2018 to 2022, which are then filtered according to the inclusion criteria set by the author.

Results : One of the studies in Indonesia involved a total sample of 31 people who were taken by consecutive sampling. Each respondent was given the intervention 4 times in a duration of 1 month. Quality of life was measured using the Pediatric Quality of Life (PedsQL) 3.0 cancer module and the results showed that there was a difference in the average score of children's quality of life (p value 0.001) between before and after treatment. The resulting conclusion is that play, eating, spiritual and acupressure interventions have a positive effect on the quality of children with leukemia so that they can be used as part of nursing actions. Research in different locations, with a qualitative phenomenological study involving a sample of children and adolescents in Spain. Data were collected through in-depth interviews with seven children aged between 9 and 18 years and analyzed using ATLAS.Ti 7.1. software to identify themes in participant narratives. The results of the study reveal three themes in the participants' stories about their experiences of being hospitalized: 1) Feeling afraid when being treated in a hospital is normal; 2) Needle procedures are associated with pain, disease, and death; and 3) Difficulty expressing the suffering experienced in the hospital.

Conclusion : The implementation of the spiritual care program is non-invasive, cheap, safe, and practical in managing the patient's depressive status. Education can increase patient understanding of radiotherapy and its side effects to improve the quality of life of leukemia patients.

Keyword : Leukimia, Sprituality, Quality of life

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*The image does not represent efficacy

효능·효과[1]

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[Reference] 1. 브루킨사캡슐80밀리그램(자누브루티닙) 제품설명서 (개정년월일 2022년 10월 30일) 2. Clinical Hematology International (2022) 4:21-29

BTK, Bruton's Tyrosine Kinase; BTKi, Bruton's Tyrosine Kinase inhibitor; R/R, Relapsed/Refractory

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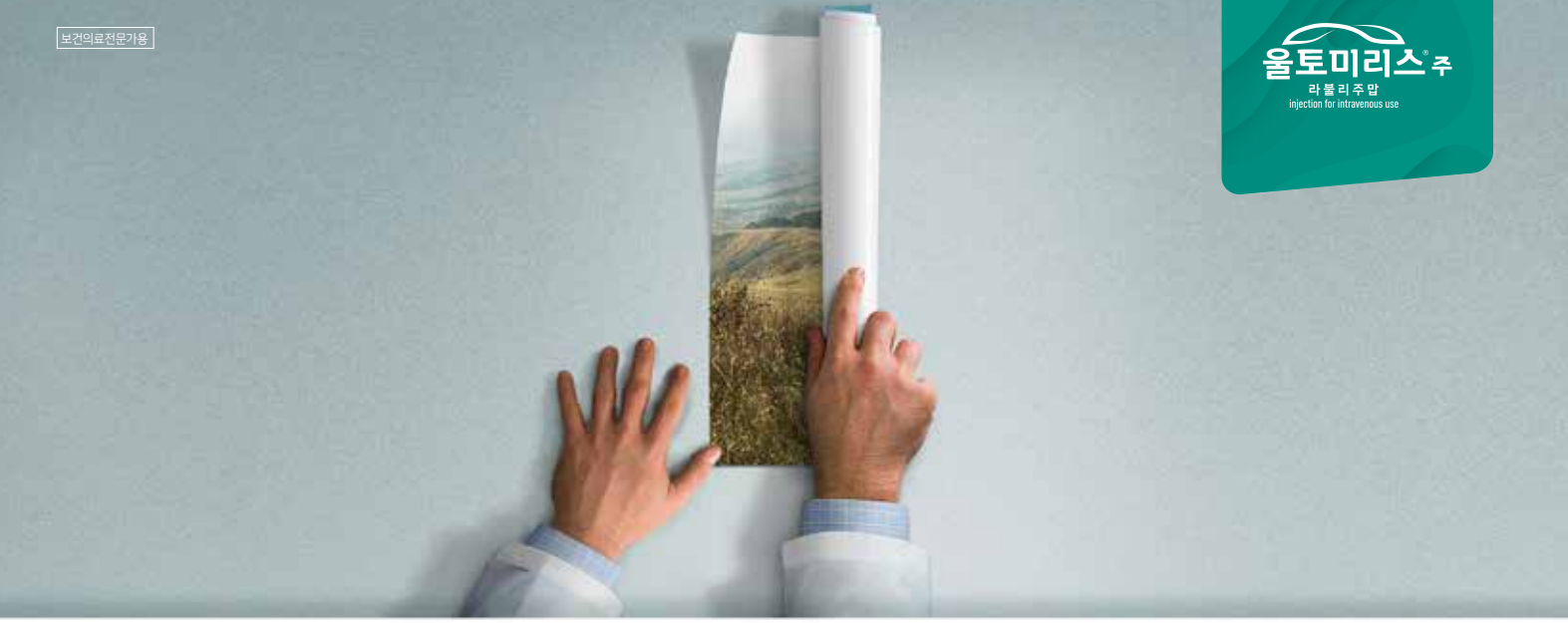

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울토미리스주(라불리주맙), 울토미리스주100mg/mL(라불리주맙) 전문의약품

[성분·함량] 울토미리스주(라불리주맙) 1바이알(30mL)중 유효성분 : 라불리주맙(발규) 300mg 울토미리스주100mg/mL(라불리주맙) 1바이알(3ml)중 유효성분 : 라불리주맙(발규) 300mg, 1바이알(11ml)중 유효성분 : 라불리주맙(발규) 1100mg [효능·**효과**] 1. 성인의 발작성 야간 혈색소뇨증 (PNH : paroxysmal nocturnal hemoglobinuria)의 치료 2. 성인 및 소아에서 보체 매개성 혈전성 미세혈관병증(TMA)을 억제하기 위한 비정형 용혈성 요독 증후군(aHUS : atypical Hemolytic Uremic Syndrome)의 치료 (사용제한: 시가(Shiga) 독신 생성 대장균에 의한 용혈성 요독 증후군(STEC-HUS) 환자에는 허가되지 않았다.) **[용법·용량]** 성인(18세 이상) 발작성 야간 혈색소뇨증 또는 비정형 용혈성 요독 증후군 환자의 경우, 이 약은 환자의 체중에 따라 표1의 용량 및 투여간격으로 정맥 내 점적 투여한다. 초기 용량 투여 2주 후부터 8주 마다 한 번씩 유지 용량으로 투여한다.
표 1. 성인 환자에서 체중에 따른 이 약의 용량 및 투여간격

체중 범위(kg)	초기 용량(mg)	유지 용량(mg)*	투여 간격
40이상 60미만	2400	3000	8주마다
60이상 100미만	2700	3300	8주마다
100이상	3000	3600	8주마다

* 유지 용량은 초기 용량 투여 2주 후에 투여한다.
체중 40 kg 이상의 소아 비정형 용혈성 요독 증후군 환자에게는 체중에 따라 표1의 성인 용량 및 투여간격으로 정맥 내 점적 투여한다. 체중 40kg 미만의 소아 비정형 용혈성 요독 증후군 환자에게는 체중에 따라 표2의 용량 및 투여간격으로 정맥 내 점적 투여한다. 초기 용량 투여 2주 후부터 4주 또는 8주마다 한 번씩 유지용량으로 투여한다.
표 2. 체중 40kg 미만의 소아 비정형 용혈성 요독 증후군 환자에서 체중에 따른 이 약의 용량 및 투여간격

체중 범위(kg)	초기 용량(mg)	유지 용량(mg)*	투여 간격
5이상 10미만	600	300	4주마다
10이상 20미만	600	600	4주마다
20이상 30미만	900	2100	8주마다
30이상 40미만	1200	2700	8주마다

* 유지 용량은 초기 용량 투여 2주 후에 투여한다.

투여일정은 예정된 투여일의 ±7일까지(이 약의 첫 번째 유지 용량 제외) 때때로 변경될 수 있지만, 그 다음 투여는 원래 일정에 따라 투여해야 한다. 에쿨리주맙 제제에서 이 약으로 바꾸는 경우, 에쿨리주맙 제제 마지막 투여 2주 후에 이 약을 환자의 체중에 따라 표1 및 표2에서 정한 초기용량을 투여하고, 초기용량 이후 2주 후부터 8주마다 한 번씩 유지용량으로 투여한다. 혈장반출 또는 혈장 교환, 또는 신선 동결 혈장 주입(PE/PI)는 이 약의 혈청 수치를 감소시킬 수 있다. 임상시험에서 PE/PI 사용 후 이 약의 보충 용량 투여에 대한 경험은 없다. **[사용상의 주의사항]** 1. 경고 1) 중대한 수막구균 감염 작용 기전에 의해, 이 약의 사용은 수막구균 감염/패혈증 (Neisseria meningitidis)에 대한 환자의 감수성을 증가시킨다. 수막구균성 질환은 어느 혈청군에 의해서도 발생할 수 있다. 감염의 위험성을 낮추기 위하여, 이 약의 투여가 지연됨으로 인한 위험성이 수막구균 감염 발생의 위험성보다 큰 경우를 제외하고는 모든 환자들은 반드시 이 약의 투여를 시작하기 최소한 2주 전에 수막구균 예방접종을 해야만 한다. 수막구균 예방접종을 한 후 2주가 지나기 전에 이 약의 투여를 시작하는 환자는 예방접종 후 2주까지 적절한 예방적 항생요법 치료를 받아야 한다. 흔한 병원성 수막구균 혈청군을 예방하기 위하여 가능하다면 혈청군 A, C, Y, W135 및 B에 대한 백신이 권장된다. 환자들은 백신 사용을 위한 최신의 예방접종 지침에 따라 백신을 접종 혹은 재접종 받아야 한다. 만약 환자가 에쿨리주맙 제제를 투여하다가 이 약으로 바꾸는 경우, 의사는 최신의 예방접종 지침에 따라 수막구균 예방접종이 되었는지 확인해야 한다. 예방접종이 수막구균 감염을 막는데 충분하지 않을 수 있다. 적절한 항생제 사용에 대한 공식적인 지침 제공을 고려해야 한다. 이 약을 투여받은 환자에서 중대한 수막구균 감염/패혈증 사례가 보고된 바 있고, 다른 말단 보체 억제제로 치료받은 환자에서 중대하거나 치명적인 수막구균 감염/패혈증 사례가 보고되었다. 모든 환자에 대하여 수막구균 감염 및 패혈증의 초기 증상이 나타나는지 반드시 모니터링 해야 하며, 감염이 의심되는 경우에는 즉시 평가하고, 적절한 항생제로 치료한다. 환자는 이러한 증상이나 징후에 대해 통보받아, 즉각적인 의학적 조치를 받을 수 있어야 한다. 의료진은 환자에게 환자용 정보 안내서 및 환자용 안전성 카드를 제공해야 한다. 2) 예방접종 예방접종으로 보체가 다욱 활성화 될 수 있다. 결과적으로, 보체-매개 질환이 있는 환자의 경우, 용혈과 같은 기저질환의 증상과 징후가 증가할 수 있다. 그러므로, 환자는 권장 예방접종 후 질병 증상을 더욱 면밀히 관찰해야 한다. 2. 다음 환자에는 투여하지 말 것 1) 이 약의 주성분 또는 첨가제에 과민반응이 있는 환자 2) 치료되지 않은 수막구균 (Neisseria meningitidis) 감염 환자 3) 수막구균(Neisseria meningitidis) 백신을 현재 접종하지 않은 환자 또는 백신 접종 이후 2주 이내 이 약 투여를 시작한 환자로서 적절한 예방적 항생요법 치료를 받지 않은 환자다, 이 약 투여 지연에 따른 위험이 수막구균 감염 발생 위험보다 중대한 경우는 제외)(1. 경고 1) 중대한 수막구균 감염 항 참조)) 개정년월일: 2022년 12월 28일 **※ 보다 자세한 사항은 제품설명서 전문을 참고하시기 바랍니다.** aULTUTM20230202

KR-13021 I Exp. 2025-02 (Prep. 2023-02)

PNH, Paroxysmal Nocturnal Hemoglobinuria

1. Jong Wook Lee et al, The role of the alternative pathway in paroxysmal nocturnal hemoglobinuria and emerging treatments, Expert Review of Clinical Pharmacology 2022, Vol. 15, No.7, 851-861

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[효능·효과] A형 혈우병(선천성 VIII 인자 결핍) 환자에서의 - 출혈 억제 및 예방 - 수술전후 관리 (외과적 수술 시 출혈 억제 및 예방) - 출혈의 빈도 감소 또는 예방을 위한 일상적인 예방요법 이 약은 본 빌레브란트 인자를 함유하고 있지 않으므로 본 빌레브란트 (von Willebrands disease) 환자의 치료에는 사용하지 않는다. **[용법용량]** 이 약은 재구성한 후 정맥주사용으로만 사용한다. 이 약은 A형 혈우병에 대한 치료경험이 있는 의사의 감독 하에 투여하여야 한다. 이 약 한 바이알은 라벨에 표시된 국제단위 역가에 해당하는 재조합 VIII인자 (recombinant FVIII)를 함유한다. 이 약 1 IU는 정상사람 혈장 1 mL당 VIII인자의 활성과 동등하다. 이 약의 투여 용량 및 기간은 VIII인자 결핍정도, 출혈 부위 및 범위, 환자의 임상적 상태에 따라 결정된다. **투여량 계산** 이 약 1 IU는 체중 kg 당 VIII인자의 혈중활성도를 2 % [IU/dL]까지 증가시킬 것으로 예상한다. 이 약을 연장된 순환 반감기를 갖는 것으로 나타났다. IU/dL(또는 정상 %)로서 표현되는 VIII인자 활성에 대해 예상되는 생체 내 피크의 증가 및 필요한 용량은 다음의 식을 사용하여 계산한다. IU/dL (또는 정상 %) = [총 용량(IU)/체중(kg)] x 2 (IU/kg 당 IU/dL) 또는 용량(IU) = 체중(kg) x 필요한 VIII인자 증가치 (IU/dL 또는 정상 %) x 0.5 (IU/dL당 IU/kg) 환자의 약동학적 반응(반감기, 회복률(in vivo) 등) 및 임상적 반응은 다양할 수 있다. 이 약의 용량 및 투여빈도는 개별 환자의 임상적 반응에 따라 조정한다. 12세 미만의 소아에서 용량 조절이 필요할 수 있다. 12세 이상의 환자의 경우 용량 조절은 대체로 필요하지 않다. **출혈의 억제·예방 및 수술전후 관리** 이 약의 용량 및 투여빈도는 환자의 임상적 상태에 따라 결정한다. 최대 활성 시간이 연장될 것으로 예상하지 않는다. 표1에 나타난 출혈이 발생하는 경우, VIII인자 활성이 주어진 시간 동안 제시된 혈장 내 활성 수준 (정상의 % 또는 IU/dL) 이하로 떨어져서는 안 된다. 출혈이 발생한 경우와 수술 용량 결정에 표1을 참조한다. (제품설명서 용법용량 표1 참조) **일상적 예방요법** 권장용량은 3 ~ 5일 간격으로 1회 50 IU/kg이다. 용량은 25 ~ 65 IU/kg의 범위 내에서 환자의 임상반응에 기초하여 결정한다. 12세 미만의 소아에 대해서 투여 횟수를 증가시키거나 80 IU/kg까지 증량하는 것이 필요할 수 있다. **[사용상의 주의사항] 금기** 이 약 및 이 약의 성분에 아나필락시스를 포함한 중증 과민반응이 있는 환자 **신중투여** 1) 아나필락시스 및 과민반응: 이 약에서 과민반응이 보고되었다. 과민성 증상으로 병원을 방문하거나 즉각적인 응급처치가 요구될 경우, 이 약의 중단을 고려한다. 2) 중화항체(저해제): 이 약을 사용하는 환자는 적절한 임상적 관찰 및 실험실적 검사를 통해 VIII인자 저해제의 형성을 모니터링 해야 한다. 이전에 치료 경험이 없는 환자를 포함한 A형 혈우병 치료 시 이 약에서 중화항체(저해제)의 형성이 보고되었다. 만약 혈장 내 VIII인자의 값이 예상대로 증가하지 않거나, 이 약의 투여 후 출혈이 멈추지 않으면 저해제(중화항체)의 존재여부를 검사해야 한다('3) 실험실적 검사' 참고) 3) 실험실적 검사: 적절한 VIII인자 농도를 확인하기 위해 1단계 응고시간분석법(one-stage clotting assay)을 통한 혈장 내 VIII인자의 활성농도를 확인하고 유지시킨다. 혈장에서 예상된 VIII 인자 활성이 나타나지 않거나 권고된 양으로 이 약의 투여 시에도 출혈이 조절되지 않을 경우 VIII인자 저해제의 형성을 모니터링 한다. VIII 인자 저해제를 확인하기 위해 베데스다 분석(Bethesda assay)을 수행한다. **약물이상반응** 임상시험에서 일반적으로 보고된 약물이상반응(발현율 ≥0.5%)은 관절통, 권태, 근육통, 두통, 발진이었다. 이 약을 투여 받은 환자에서 중대한 이상반응은 보고되지 않았다. 국외 시판 후 경험에서 FVIII 저해제 형성, 과민반응이 보고되었다.

※ 기타 자세한 내용은 홈페이지(www.sanofi.co.kr)나 제품설명서를 참고하시기 바랍니다. 최종 문안 개정연월일: 2020.07.03

알프로릭스®주 [혈액응고인자IX-Fc융합단백(rFIXFc),에프트레노나코그-알파(유전자재조합)]

[효능·효과] B형 혈우병 (선천성 IX 인자 결핍증) 환자에서의 - 출혈의 억제 및 예방 - 수술전후 관리 (외과적 수술 시 출혈억제 및 예방) - 출혈의 빈도 감소 및 예방을 위한 일상적 예방요법(routine prophylaxis) **[용법용량]** 이 약은 B형 혈우병에 대한 치료경험이 있는 의사의 감독 하에 투여하여야 한다. 이 약의 투여 용량 및 기간은 IX인자 결핍정도, 출혈 부위 및 범위, 환자의 임상적 상태에 따라 결정된다. 환자의 약동학적반응 (반감기, 회복률(in vivo) 등) 및 임상적 반응이 다양할 수 있다. 이 약의 용량 및 투여빈도는 개별 환자의 임상적 반응에 따라 조정한다. 이 약에 대한 임상검사에서 IX인자의 활성도는 활성화 부분트롬보플라스틴 시간 (activated partial thromboplastintime, aPTT) 시약 또는 사용한 표준품에 따라 다르게 나타날 수 있다. **투여량 계산** 이 약 1 IU는 체중 kg 당 IX인자 혈중활성도를 1% [IU/dL]만큼 증가시킨다. IU/dL (또는 정상대비 %)로 표시하는 IX인자의 필요 용량 또는 예상 in vitro 최고농도 증가량은 다음의 식을 사용하여 계산한다. 필요한 IX인자 증가치 IU/dL(또는 정상 %) = [총 용량(IU) /체중(kg)] × 회복률(R)(IU/kg 당 IU/dL) 투여량 계산 용량(IU) = 체중(kg) × 필요한 IX인자 증가치(IU/dL 또는 %) × 회복률(R)의 역수 (IU/dL 당 IU/kg) 12세 이상의 환자 용량(IU) = 체중(kg) × 필요한 IX인자 증가치(IU/dL 또는 %) × 0.985 (IU/kg per IU/dL)[1] 12세 미만의 환자 용량(IU) = 체중(kg) × 필요한 IX인자 증가치(IU/dL 또는 %) × 1.424 (IU/kg per IU/dL)[1] 12세 이상의 환자에 대해 회복증가(incremental recovery) 값, 1.0154 IU/dL per IU/kg을 기초로 계산됨[2] 12세 미만의 환자에 대해 회복증가(incremental recovery) 값, 0.7022 IU/dL per IU/kg 을 기초로 계산됨 12세 미만의 소아에서 용량 조절이 필요할 수 있다. 12세 이상의 환자의 경우 용량 조절은 대체로 필요 하지 않다. **출혈의 억제·예방 및 수술전후 관리** 표1의 출혈의 경우, FIX 활성도는 혈장 활성치 (% 또는 IU/dL) 이하로 떨어지면 안 된다. 출혈 억제 및 예방 및 수술 전후 관리를 위한 투여량은 표1을 따른다. (제품설명서 용법용량 표1 참조) **일상적 예방요법** 권장초회 투여량은 주 1회 50IU/kg 또는 10-14일 간격으로 1회 100 IU/kg 이다. 개별 임상반응에 기초하여 약물 투여요법을 조절한다. **[사용상의 주의사항] 금기** 이 약 및 이 약의 성분에 아나필락시스를 포함한 중증의 과민반응 병력이 있는 환자 **신중투여** 1) 과민반응: 이 약에서 과민반응이 보고되었다. 아나필락시스를 포함한 기타 알레르기성 과민반응이 IX인자 제품에서 보고되었으며 이 약에서도 나타날 수 있다. 저해제의 생성은 이 약을 포함한 IX인자 제품에서 알레르기성 반응과 관련이 있으므로, 알레르기 반응을 경험한 환자들에서는 저해제의 존재여부를 평가한다. 아나필락시스로 진행할 수 있는 알레르기 반응의 초기 증상은 혈관부종, 흉부압박, 저혈압, 발진, 구역, 구토, 갑각이상, 불안, 천명, 호흡곤란으로 나타난다. 과민성 증상이 일어나면 이 약 사용을 중단하고 적절한 처치를 시작한다. 2) 중화항체(저해제): 적절한 임상적 관찰 및 실험실적 검사를 통해 모든 환자들에게서 저해제의 형성을 정기적으로 모니터링 한다. (4)항 참고). 저해제에 의한 알레르기 반응을 경험한 환자들을 평가하고, 특히 이 약의 노출 초기단계에서 급성 과민반응의 징후 및 증상을 면밀하게 관찰해야 한다. IX인자 저해제를 지닌 환자의 차후 치료(challenge)에서 아나필락시스의 위험이 증가할 수 있다. 3) 혈전색전증 합병증: IX인자 제제의 사용은 혈전색전증 합병증의 발생과 관련 있으며, 특히 중심 정맥 카테터를 통해 지속적으로 투여 받은 환자에서 발생한다. 이 약은 bolus 정맥주사로 수 분에 걸쳐 투여해야 한다. 이 약의 지속적 정맥주입 투여의 안전성은 연구되지 않았다. 4) 실험실적 검사 : 적절한 IX인자 농도를 확인하기 위해 1단계응고시간분석법(one-stage clotting assay)을 통한 혈장 IX인자 활성농도를 측정한다. IX인자 활성농도 결과는 사용된 aPTT시약의 형태에 따라 영향을 받을 수 있다. 카올린 기반(kaolin-based)의 aPTT 시약을 사용한 1단계응고시간분석법 사용시 활성농도가 낮게 나올 수 있다. 혈장에서 예상된 IX인자 활성이 나타나지 않거나 권고된 양의 이 약 투여 시에도 출혈이 조절되지 않을 경우 IX인자 저해제의 발생을 모니터링 한다. IX인자 저해제 존재를 확인하기 위해 베데스다 분석(Bethesda assay)을 수행한다. **약물이상반응** 임상시험에서 일반적으로 보고된 약물이상반응(발현율≥1%)은 두통, 구강감각이상 및 폐쇄요로병증이었다. 약물이상반응으로 인한 임상시험의 중도탈락 임상시험 대상자는 없었다. 저해제는 검출되지 않았고 아나필락시스도 보고되지 않았다. 국외 시판 후 경험에서 FIX 저해제 형성, 과민반응이 보고되었다. 최종 문안 개정연월일: 2020.07.07

MAT-KR-2300091-1.0-02/2023

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제품명: 엑스포비오정20밀리그램 **원료약품 및 그 분량:** 1정(167.2밀리그램) 중 유효성분: 셀리넥서 20.0 밀리그램 성상 파란색의 원형 필름코팅정 **효능·효과: 1.** 이전에 네 가지의 치료 요법에서 적어도 두 가지 프로테아좀 억제제, 적어도 두 가지 면역조절 이미드 치료제 그리고 적어도 한 가지의 anti-CD38 항체 치료를 받은 경우로, 재발 또는 불응성 다발골수종이 있는 성인환자에 대한 덱사메타손과의 병용요법 **2.** 두 가지 이상의 전신치료 후 재발 또는 불응성 미만성 거대 B-세포 림프종 성인 환자의 치료 **용법·용량: 1)** 이전에 네 가지의 치료 요법에서 적어도 두 가지 프로테아좀 억제제, 적어도 두 가지 면역조절 이미드 치료제 그리고 적어도 한 가지의 anti-CD38 항체 치료를 받은 경우로, 재발 또는 불응성 다발골수종이 있는 성인환자에 대한 덱사메타손과의 병용요법: 이 약을 매주 첫째 날 및 셋째 날, 80 mg씩 주2회 복용한다. 경구용 덱사메타손은 매주 첫째 날 및 셋째 날, 20mg씩 주2회 이 약과 병용하여 복용한다. **2)** 두 가지 이상의 전신치료 후 재발 또는 불응성 미만성 거대 B-세포 림프종 성인 환자의 치료: 이 약을 매주 첫째 날 및 셋째 날, 60mg씩 주2회 복용한다. **다음 환자에는 투여하지 말 것:** 이 약의 주성분 및 첨가제 성분에 과민증이 있는 환자 **이상반응: 1)** 다발골수종 환자: 다발골수종 환자의 가장 흔한 이상 반응(증상 ≥20%)은 혈소판감소증, 피로, 오심, 빈혈, 식욕저하, 체중 감소, 설사, 구토, 저나트륨혈증, 호중구 감소증, 백혈구 감소증, 변비, 호흡 곤란, 상부 호흡기 감염이다. **2)** 미만성 거대 B 세포 림프종 환자: 미만성 거대 B 세포 림프종 환자의 진단 검사 이상을 제외한 가장 일반적인 이상 반응(증상 ≥20%)은 피로, 오심, 설사, 식욕 저하, 체중 감소, 변비, 구토, 발열이다. 등급 3-4의 진단 검사 이상은(≥15%) 혈소판감소증, 림프구 감소증, 호중구 감소증, 빈혈, 저나트륨혈증이다. **일반적 주의:** 혈소판 감소증, 호중구 감소증, 위장관 독성, 저나트륨혈증, 심각한 감염, 신경 독성, 백내장 **임부, 수유부에 대한 투여:** 이 약은 비임상시험 결과 및 작용 기전에 근거할 때 임신한 여성에게 투여될 경우 태아 독성의 가능성이 있다. 이 약을 임부에게 투여하여 약물 관련 위험성을 평가한 자료는 없다. 이 약 또는 그 대사체가 모유로 이행되는지 여부를 평가한 자료는 없다. 이 약의 투여기간 및 최종 투약 후 1주일 동안은 모유 수유를 중단해야 한다. **보관 및 취급상의 주의사항: 1)** 어린이의 손이 닿지 않는 곳에 보관하도록 주의한다. **2)** 30℃ 이하에서 보관한다. **수입판매원: 안텐진제약 주식회사** 서울특별시 강남구 테헤란로 152 강남파이낸스센터 41층 디이그제큐티브센터 **개정년월일:** 2022년 7월 5일 ***제품을 처방하시기전 상세 제품설명서를 참고하여 주시기 바랍니다.**

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KR-XPO-CM-2022-027

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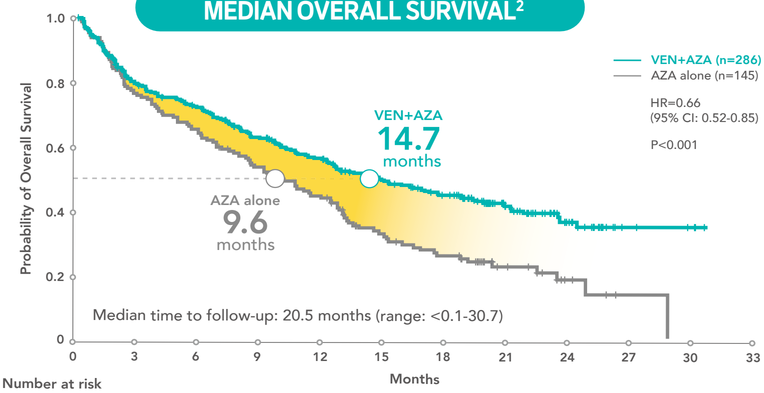
Indication[1]

In **combination with azacitidine or decitabine** for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

Viale–A trial[2] : A phase III, multicenter, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of azacitidine plus venetoclax, as compared with azacitidine plus placebo (the control regimen) in older patients with AML.

MEDIAN OVERALL SURVIVAL[2]



Number at risk

	0	3	6	9	12	15	18	21	24	27	30
VEN+AZA	286	219	198	168	143	117	101	54	23	5	3
AZA alone	145	109	92	74	59	38	30	14	5	1	

Overall survival (OS)

VEN+AZA **14.7mo** Vs. AZA+pla **9.6mo**

VEN+AZA significantly increased mOS by 5.1mo vs AZA: OS benefit across subgroups

34.0%

Risk Reduction of mortality

HR=0.66 (95% CI: 0.52–0.85)
P<0.001

Doubled remission (CR+CRi)[2]

VEN+AZA **66%** (95% CI, 60.6 – 71.9) vs. AZA alone **28%** (95% CI, 21.1 – 36.3)

Median time to first remission (CR or CRi)[2]

VEN+AZA **1.3 mo** (range: 0.6 – 9.9) vs. AZA alone **2.8 mo** (range: 0.8 – 13.2)

Longer remission, Median duration (CR+CRi)[2]

VEN+AZA **17.5 mo** (95% CI, 13.6 – not reached) vs. AZA alone **13.4 mo** (95% CI, 5.8 – 15.5)

- The appropriate dose-modification is required for the management of adverse events.[1]

AML, acute myeloid leukemia; CI, confidence interval; CR, complete response; CRi, complete response with incomplete hematologic recovery; HR, hazard ratio; mo, month; pla, placebo; VEN+AZA, venetoclax with azacitidine.
[Reference] 1. 벤클렉스타®정 제품설명서. 개정년월일 2021년 1월 8일 2. DiNardo CD, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020;383:617-629.

벤클렉스타®정 제품요약정보 [효능효과] 만성 림프구성 백혈병: 이전에 치료받은 적이 없는 만성 림프구성 백혈병 성인환자에서 오비누투주맙과의 병용 요법. 이전에 적어도 하나의 치료를 받은 만성 림프구성 백혈병 성인 환자에서 리툭시맙과의 병용 요법. 화학면역요법 및 B 세포 수용체 경로 저해제에 재발 또는 불응인 만성 림프구성 백혈병 성인 환자에서 단독 요법. 급성 골수성 백혈병: 만 75세 이상, 또는 집중 유도화학요법에 적합하지 않은 동반질환이 있는 새로 진단된 급성 골수성 백혈병 성인 환자에서 아자시티딘 또는 데시타빈과의 병용요법. **[용법용량]** 이 약은 1일 1회 동일한 시간에 식사 및 물과 함께 복용하도록 한다. 이 약은 통째로 삼켜야 하며, 삼키기 전에 씹거나, 으깨거나, 조각 내서는 안 된다. 종양용해증후군(tumor lysis syndrome, TLS)의 위험을 낮추기 위해 이 약 첫 용량 투여 시작 전 TLS 위험 정도에 대한 환자별 요인을 평가하고 예방적으로 수분 섭취 및 항고요산혈증제제를 투여한다. 만성 림프구성 백혈병. 용량 증량 일정 (Dose Ramp-Up Schedule): 이 약은 1일 1회 20mg씩 7일간 투여로 시작하여 표1에 제시된 이 약의 용량에 따라 1일 용량 400mg이 될 때까지 5주 동안 매주 용량 증량 일정에 따라 투여해야 한다. 이 5주간의 용량 증량 일정은 종양 부담(tumor burden)을 서서히 줄이고(debulk) TLS의 위험을 낮추기 위해 설계되었다. 표1. 만성 림프구성 백혈병 환자에서의 용량 증량 기간 동안의 용량 일정(Dosing schedule for ramp-up phase) (지면 관계상 표의 내용을 기술함.) 1/2/3/4/5주: 이 약의 1일 용량 20/50/100/200/400mg. 오비누투주맙과의 병용: 이 약은 총 12주기 동안 투여한다. 6주기는 오비누투주맙과 함께 투여한 후, 나머지 6주기는 이 약을 단독 투여한다. 오비누투주맙은 1주기 1일차에 100mg을 투여한 후 1일차(연속) 또는 2일차에 900mg을 투여한다. 추가 정보는 오비누투주맙 허가사항을 참조한다. 1주기 8일차와 15일차 및 뒤따르는 다섯 주기의 각 1일차에 1000mg씩 투여한다 (각 28일로 구성된 총 6주기). 이 약은 1주기 22일차부터 2주기 28일차까지 증량 일정에 따라 투여한다 (표1 참조). 증량 일정 종료 후, 오비누투주맙 투여 3주기 1일차부터 12주기까지 이 약 400mg을 1일 1회 투여한다. 리툭시맙과의 병용: 이 약의 용량 증량 일정(표1)에 따라 7일간 이 약 400mg 투여를 완료한 후, 리툭시맙의 투여를 시작한다. 리툭시맙은 총 6주기(1주기 28일) 동안 각 주기 1일째 투여하며 첫 번째 주기 1일째 375mg/m² 투여하고 두 번째~여섯 번째 주기 동안 각 주기 1일째 500mg/m² 투여한다. 리툭시맙의 첫 번째 치료주기 1일째부터 24개월간 이 약 400mg을 1일 1회 지속적으로 투여하여야 한다. 단독 요법: 이 약의 권장 유지 용량은 5주간의 용량 증량 일정(표1)을 완료한 후 1일 1회 400mg이다. 이 약은 질병이 진행되거나 수용할 수 없는 독성이 관찰될 때까지 1일 1회 경구 투여해야 한다. 급성 골수성 백혈병. 용량 일정 (증량 일정 포함)은 표2에 나와 있다. 표2. 급성 골수성 백혈병 환자에서의 용량 증량 기간에 대한 용량 일정 (지면 관계상 표의 내용을 기술함.) 1/2/3/4일 및 그 이후: 이 약의 1일 용량 100/200/400/400mg 아자시티딘 또는 데시타빈과 병용하여 투여하는 경우 이 약은 아자시티딘 또는 데시타빈과 함께 1주기 1일차에 개시한다. 아자시티딘은 각 28일 주기의 1-7일차에 75mg/m²을 정맥 또는 피하로 투여해야 한다. 데시타빈은 각 28일 주기의 1-5일차에 20mg/m²을 정맥 투여해야 한다. 이 약의 투여는 혈액학적 독성 및 혈구수 회복 관리를 위해 필요 시 일시 중단될 수 있다(독성에 따른 용량 조절 참조). 추가 정보는 아자시티딘 또는 데시타빈의 허가사항을 참조한다. 이 약은 아자시티딘 또는 데시타빈과 함께 병용하는 경우, 질병의 진행이나 수용할 수 없는 독성이 관찰될 때까지 투여를 지속해야 한다. 약물 복용을 놓친 경우: 환자의 복용 누락 시점이 원래 복용 시간을 기준으로 8시간 이내라면, 해당 용량을 가능한 빨리 복용하고, 평상 시의 1일 용량 일정을 다시 시작한다. 환자의 복용 누락 시점이 8시간을 경과한 경우, 누락된 용량을 복용해서는 안 되며 평상 시의 1일 용량 일정을 다음날부터 다시 시작해야 한다. 환자가 복용 후 구토를 한 경우, 같은 날 추가 용량을 복용해서는 안 된다. 다음 처방된 용량은 평소와 같은 시간에 복용해야 한다. 종양용해증후군(TLS)의 위험 평가 및 예방: 이 약을 투여받는 환자에게 종양용해증후군(tumor lysis syndrome, TLS)이 발생할 수 있다. 관리에 대한 자세한 사항은 아래 해당 내용을 참조한다. TLS의 위험을 낮추기 위해 이 약 첫 용량 투여 시작 전 TLS 위험 정도에 대한 환자별 요인을 평가하고, 예방적으로 수분 섭취 및 항-고요산혈증 제제를 투여한다. 만성 림프구성 백혈병: 이 약은 종양의 급속한 감소를 일으킬 수 있으며, 따라서 초기 5주 용량 증량 기간에 TLS가 발생할 위험이 있다. 즉각적인 조치가 필요한 TLS에 해당하는 혈액화학적 변화는 이 약의 첫 복용 후 및 각 용량 증량 때마다 빠르면 6~8시간 이내에 발생할 수 있다. TLS는 투여 중단 후 이 약 재시작 시에도 발생할 수 있다. 투여 중단 후 이 약에 대한 용량조절은 표4와 표5를 참조한다. TLS의 위험은 동반 질환들, 특히 신기능 감소(크레아티닌 청소율 [CrCl]<80 mL/min)와 종양 부담(tumor burden)을 포함하는 다양한 요인을 기반으로 연계하여 존재한다. 비장 비대는 전체 TLS 위험의 한 원인이 될 수 있다. 모든 환자에서 방사선 평가(CT 촬영 등)를 포함한 종양 부담 평가를 실시하며, 혈액화학검사(칼륨, 요산, 인, 칼슘 및 크레아티닌)를 실시하고, 이 약의 치료를 시작하기 전에 기존의 비정상치를 정상화한다. 이러한 위험도는 이 약의 치료로 종양의 부담이 줄어들면서 감소할 수 있다. 종양부담에 따른 TLS 예방 및 모니터링은 표3을 따른다. 예방 및 모니터링 일정을 최종 결정하기 전에 모든 환자의 동반질환을 고려한다.

표3. 만성 림프구성 백혈병 환자의 종양 부담에 따른 TLS 예방 및 모니터링

종양 부담		예방		혈액화학 모니터링[c,d]
		수분[a]	항-고요산혈증 제제[b]	평가 빈도
낮음	모든 림프절 5cm 미만 및 ALC 25 x10⁹/L 미만	경구 섭취 (1.5-2L)	알로푸리놀[b]	외래환자: 20mg 및 50mg 첫 투여: 투여 전, 6-8시간, 24시간. 용량 증량 단계: 투여 전.
중간	어느 림프절이든 5cm 이상 10cm 미만 또는 ALC 25x10⁹/L 이상	경구 섭취 (1.5-2L) 및 추가적인 정맥 주입 고려	알로푸리놀[b]	외래환자: 20mg 및 50mg 첫 투여: 투여 전, 6-8시간, 24시간. 용량 증량 단계: 투여 전. 20mg 및 50mg 첫 투여: CLcr <80ml/min인 환자는 입원을 고려한다; 입원 시, 하단의 모니터링을 참조한다.
높음	어느 림프절이든 10cm 이상 또는 ALC 25 x10⁹/L 이상 및 림프절 5cm 이상	경구 섭취 (1.5-2L) 및 정맥 주입 (가능한 한 150-200mL/시간)	알로푸리놀[b]; 요산 기저치가 상승한 경우 라스부리카제 고려	입원환자: 20mg 및 50mg 첫 투여: 투여 전, 4, 8, 12, 24시간. 외래환자: 용량 증량 단계: 투여 전, 6-8시간, 24시간.

ALC=절대 림프구수(absolute lymphocyte count); CLcr=크레아티닌 제거율(creatinine clearance). [a]경구 수분 섭취가 불가한 모든 환자에 대해서는 정맥으로 수분을 투입한다. [b]이 약을 시작하기 2-3일 전에 알로푸리놀 또는 잔틴 산화효소 저해제를 시작한다. [c]혈액화학수치(칼륨, 요산, 인, 칼슘, 크레아티닌)을 평가한다; 실시간으로 검토한다. [d]TLS 위험이 있는 환자는, 각 용량 증량 시 6-8시간 및 24시간째에 혈액화학수치를 모니터링한다.

급성 골수성 백혈병: 이 약의 일일 용량 증량 기간은 아자시티딘 또는 데시타빈 병용 시 3일이다 (표2 참조). 아래 방법으로 증상을 예방한다: •모든 환자는 이 약 개시 전에 백혈구수가 25X10⁹/L 미만이어야 하며 치료를 시작하기 전에 세포수 감소가 필요할 수 있다. •모든 환자는 이 약의 첫 용량 개시 이전 및 용량 증량 기간 중, 충분한 수분을 공급받고 항-고요 산혈증 제제를 받아야 한다. •모든 환자에 대해 혈액화학검사(칼륨, 요산, 인, 칼슘 및 크레아티닌)를 실시하고, 이 약 개시전에 기존의 비정상 수치를 교정한다. •투여 전과, 증량 기간 중 각 새로운 용량을 투여한 6-8시간 후 및 최종 용량에 도달한 24시간 후에, TLS에 대한 혈액화학수치를 모니터링한다. •TLS 위험요인 (예. 순환 모세포, 높은 골수 내 백혈병 침범, 치료 이전 높은 젖산 탈수소 효소(lactate dehydrogenase, LDH) 수치 또는 신기능 저하)이 있는 환자는 실험실 수치 모니터링 증가 및 이 약 시작 용량 감량을 포함한 추가적인 조치가 고려되어야 한다. 독성에 따른 용량 조절: 만성 림프구성백혈병. 독성으로 인한 복용 중단 및/또는 용량 감소가 필요할 수 있다. 이 약과 관련된 독성에 따라 권고되는 용량 조절에 대하여, 표4와 표5를 참조한다. 첫 5주 동안의 용량 증량 기간 중 1주 이상 복용 중단했거나, 용량 증량 기간 완료 후 2주 이상 복용 중단한 환자의 경우, TLS 위험을 재평가하여 감소된 용량으로 투여를 다시 시작해야 할 필요가 있는지 평가해야 한다(용량 증량 일정의 모든 또는 일부 단계).표4. 만성 림프구성 백혈병에서 독성[a]으로 인한 이 약의 용량 조절(지면 관계상 표의 내용을 기술함.) 종양 용해 증후군-혈액화학 수치 변화 또는 TLS를 암시하는 증상. 매번: 다음날의 이 약 투여를 중단한다. 마지막 투여 이후 24-48시간 이내에 해결이 될 경우에는, 동일한 용량으로 이 약의 치료를 다시 시작한다. 해결에 48시간 이상이 필요한 혈액화학 수치 변화가 발생한 경우, 감소된 용량으로 치료를 시작한다 (표5 참조). 임상적 TLS[b]가 발생한 경우, 해결 후 감소된 용량으로 치료를 시작한다(표5 참조). 비혈액학적 독성-3 또는 4등급의 비혈액학적 독성. 1번째 발생: 이 약을 일시 중단한다. 독성이 1등급 또는 베이스라인 수치로 해결되면, 동일한 용량으로 이 약의 치료를 재개할 수 있다. 용량 조절은 필요하지 않다./2번째 또는 추가 발생: 이 약을 일시 중단한다. 독성을 해결한 후 이 약의 치료를 재개할 때, 표5에 제시된 용량 감소 가이드라인을 따른다. 의사의 재량에 따라 용량이 더 많이 감소될 수 있다. 혈액학적 독성-감염이나 발열이 있는 3등급의 중성구 감소증, 또는 4등급의 혈액학적 독성(림프구 감소증 제외). 1번째 발생: 이 약을 일시 중단한다. 중성구 감소증과 연관된 감염 위험을 낮추기 위해 임상적으로 필요한 경우 과립구집락자극인자(G-CSF)를 이 약과 병용 투여할 수 있다. 독성이 1등급 또는 베이스라인 수치로 해결되면, 동일한 용량으로 이 약의 치료를 재개할 수 있다./2번째 또는 추가 발생: 이 약을 일시 중단한다. 임상적으로 지시된대로 G-CSF 사용을 고려한다. 독성을 해결한 후 이 약의 치료를 재개할 때, 표 5에 제시된 용량 감소 가이드라인을 따른다. 의사의 재량에 따라 용량이 더 많이 감소될 수 있다. (2주 이상 100mg 미만으로의 감량이 필요한 환자의 경우 이 약의 중단을 고려한다. a 이상반응은 NCI CTCAE version 4.0을 사용하여 분류됨. b 임상적 TLS는 급성 신부전, 심부정맥, 또는 급사 및/또는 발작과 같은 임상적 예후가 있는 실험실 검사 수치상 TLS로 정의됨 [이상반응 항 참조].) 표5. 이 약으로 만성 림프구성 백혈병 치료 도중 독성으로 인한 용량 감소 (지면 관계상 표의 내용을 기술함.) 중단 시 용량, mg: 400/300/200/100/50/20, 재시작 용량, mga: 300/200/100/50/20/10. (a 용량을 증가시키기 전에 감소된 용량으로 1주일간 지속한다.) 급성 골수성 백혈병. 다른 독성으로 인한 용량 조절: 1주기 종료 시 관해를 평가한다. 그 후 및 치료하는 동안 필요에 따라 골수 평가를 권고하고, 혈구 감소증의 해결을 위해 혈구 수를 자주 모니터링한다. 필요한 경우 이상반응 관리 또는 혈구수 회복을 위해 이 약을 일시 중단하거나[경고 및 이상반응 항 참조], 이 약을 영구 중단한다. 열 또는 감염을 동반하거나 동반하지 않은 4등급 중성구 감소증(절대 중성구 수[ANC]<500/microliter); 또는 4등급 혈소판 감소증(혈소판 수 <25,000/microliter)에 대한 용량 조절은 표6을 참조한다[경고 항 참조]. 표6. 이 약으로 급성 골수성 백혈병 치료 도중 독성[a]으로 인한 용량 조절 (지면 관계상 표의 내용을 기술함.) 열 또는 감염을 동반하거나 동반하지 않은 4등급 중성구 감소증, 또는 4등급 혈소판 감소증의 혈액학적 독성[a] 관해[b] 도달 전 발생-임상적 지시대로, 혈액 제제 수혈, 예방약학 투여 및 항-감염약 치료. 대부분의 경우, 관해 도달 전에는 이 약과 아자시티딘, 데시타빈 주기를 혈구 감소증으로 인해 일시 중단해서는 안 된다. 관해[b] 도달 후 (7일 이상 지속)-이 약과 아자시티딘, 데시타빈의 다음 투여 주기를 연기하고 혈구 수를 모니터링 한다. 중성구 감소증에 대하여 임상적으로 지시된 경우, 과립구-집락자극인자(G-CSF)를 투여할 수 있다. 처음 발생: 독성이 1 또는 2등급 수준으로 해결되면, 이 약은 동일한 용량으로 아자시티딘, 데시타빈과의 병용 투여를 재개한다./차후 발생: 독성이 1 또는 2등급 수준으로 해결되면, 이 약은 동일한 용량으로 아자시티딘, 데시타빈과의 병용 투여를 재개하고, 각 후속 주기 동안 이 약의 투여기간을 7일씩 단축한다(즉, 28일 대신 21일). (a 이상반응의 등급은 NCI CTCAE version 4.0을 사용하여 분류되었다. b 골수에서 모세포 5% 미만의 혈구 감소증 확인.) 3등급 또는 4등급 비혈액학적 독성은 보조치료로 해결되지 않을 경우 이 약을 일시 중단하고 독성이 1등급 또는 베이스라인 수치로 해결되면 동일한 용량으로 이 약 투여를 재개한다. CYP3A 저해제 또는 P-gp 저해제와 병용 시 용량 조절: 이 약을 강력한 또는 중등도의 CYP3A 저해제, 또는 P-gp 저해제와 병용 시 이 약의 노출(즉, C_{max} 및 AUC)이 증가하므로 치료 시작 시와 용량 증량 기간 동안 TLS 위험이 증가할 수 있다. 만성 림프구성 백혈병 환자들은, 치료 시작 시와 용량 증량 기간 동안에는 이 약과 강력한 CYP3A 저해제를 병용투여해서는 안 된다. 모든 환자들은, CYP3A 저해제 또는 P-gp 저해제를 반드시 사용해야 할 경우, 약물 상호작용을 관리하기 위하여 표7을 따른다. 독성의 징후가 있는지 환자를 면밀하게 모니터링 한다. CYP3A 저해제 또는 P-gp 저해제 중단 후 2-3일 후부터 CYP3A 저해제 또는 P-gp 저해제와 병용투여 시작 이전의 용량으로 이 약의 투여를 재개한다.표7. 이 약의 CYP3A 저해제 및 P-gp 저해제와의 잠재적인 상호작용 관리 (지면 관계상 표의 내용을 기술함.) 강력한 CYP3A 저해제 시작 및 용량 증량 기간-만성 림프구성 백혈병: 금기, 급성 골수성 백혈병: 1일차 10mg/2일차 20mg/3일차 50mg/4일차 100mg 이하. 일일 용량 (용량 증량 기간 이후)[a]–이 약의 용량을 100mg 이하로 줄임. 중등도의 CYP3A 저해제, P-gp 저해제 이 약의 용량을 적어도 50% 줄임. (a 만성 림프구성 백혈병 환자들은, 이 약과 강력한 또는 중등도의 CYP3A 저해제, 또는 P-gp 저해제와의 병용을 피한다. 대체제를 고려하거나 표7에 기술된대로 이 약의 용량을 감량한다.) **[주요 사용상의 주의사항] 1. 경고** 1) 종양용해증후군(tumor lysis syndrome, TLS) 2) 중성구 감소증 3) 중대한 감염 4) 예방접종 5) 이 약을 보르테조밉과 덱사메타손 병용 요법에 추가 시 다발성골수종 환자 사망률 증가 **2. 다음 환자에는 투여하지 말 것** 1) 이 약의 성분에 과민증이 있는 환자 2) 만성 림프구성 백혈병 환자에서, 이 약은 치료 초기와 용량 증량 기간 동안에는 강력한 CYP3A 저해제와 병용 투여해서는 안 된다. [용법·용량 및 상호작용 항 참조]. **[제조원]** AbbVie Deutschland GmbH & Co. KG, Knollstrasse 67061 Ludwigshafen, 독일(압출물 제조) AbbVie Ireland NL B.V., Manorhamilton Road, Sligo, 아일랜드 (필름코팅정 제조) AbbVie Inc, 1 N Waukegan Rd., North Chicago, IL 60064, 미국 (필름코팅정 1,2차 포장) Zuellig Pharma Specialty Solutions Group Pte. Ltd., 15 Changi North Way #01-02, #02-02, #02-10 Singapore 498770, 싱가포르 (필름코팅정 2차 포장) **[수입·판매원]** 한국애브비㈜, 서울특별시 강남구 영동대로 421 삼탄빌딩 6층, 전화: (02)-3429-9300 www.abbvie.co.kr **[개정년월일]** 2021년1월 8일. *의약품 부작용 신고 및 피해구제 신청: 한국의약품안전관리원 (1644-6223, www.drugsafe.or.kr) *자세한 제품정보는 제품설명서를 참조해 주십시오.

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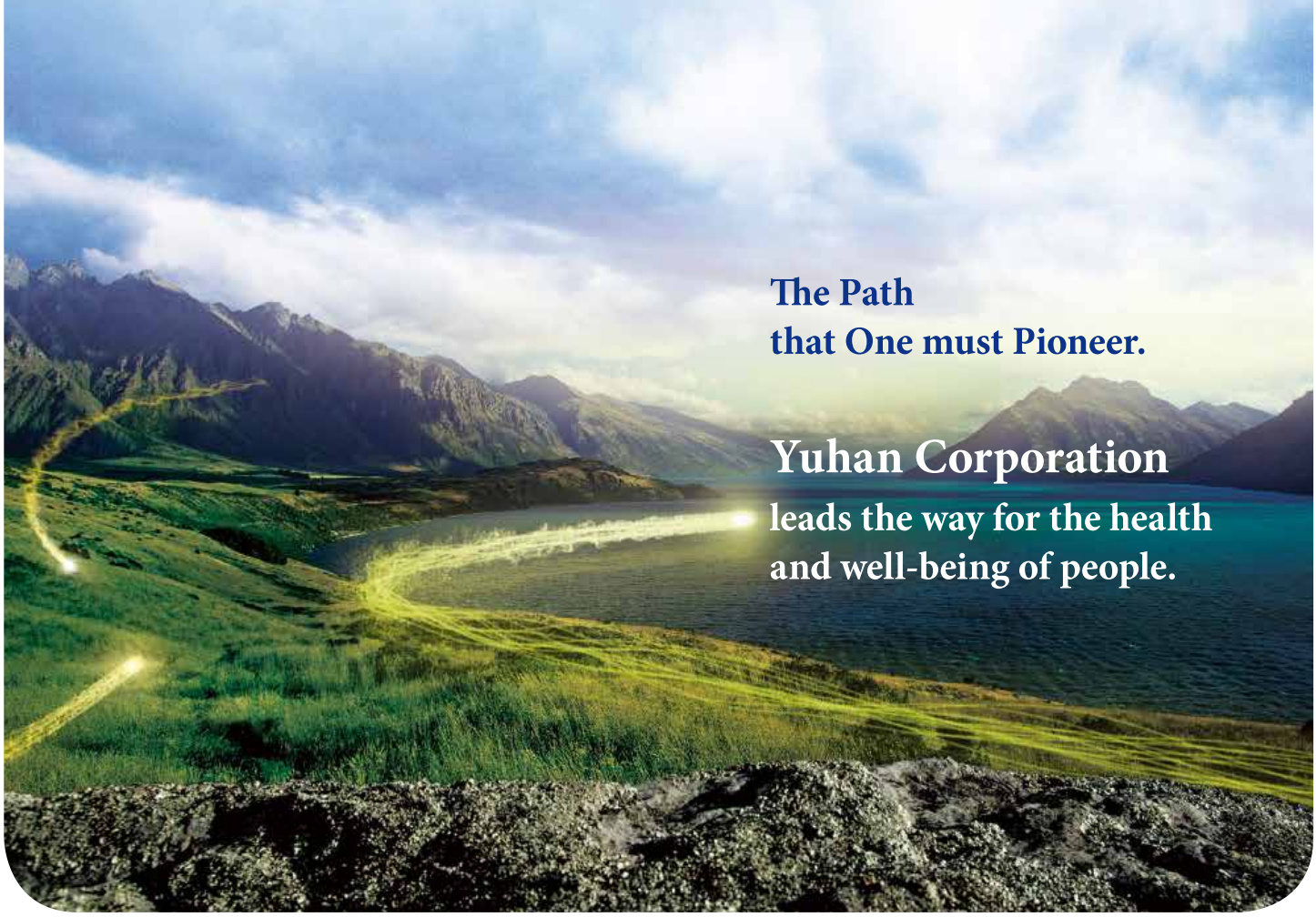

The Way of Yuhan

Yuhan Corporation, a group loved by the people and grown together with the people
For the last 90 years, the corporate culture of honesty and integrity,
and the strong beliefs in social responsibility are what made Yuhan what it is today.

Looking back on the path that we moved on and thinking of the path ahead,
Yuhan will make the leap as a global pharmaceutical company through innovative new drug development,
and by enabling healthiness and happiness for all the people in the world.

In the next 100 years, Yuhan Corporation will follow the noble spirit of our founder, Dr. New Ilhan,
and write the history of challenge and development moving forward.

Our challenge has already begun.

YUHAN

[제품명] 트룩시마®주 500mg/50mL, Truxima® (리툭시맙) (단클론항체, 유전자재조합) **[원료약품 및 그 분량]** 1 바이알 (50 mL) 중 Rituximab 500 mg **[성상]** 무색 또는 미황색이고 투명에서 탁한 용액이 무색 투명한 바이알에 든 주사제 **[효능·효과]** 1) 림프종 : 재발성 또는 화학요법 내성인 여포형 림프종(B세포 비호지킨 림프종 IWF분류중 B, C, D군) / 이전에 치료받은 적이 없는 여포형 림프종에서 화학요법과 병용투여 / 여포형 림프종에서 유도요법 실시 후 유지요법 / CD20 양성의 미만형 대형 B세포 비호지킨 림프종(DLCL)[CHOP화학요법(cyclophosphamide, doxorubicin, vincristine, prednisolone 으로 구성, 8주기 투여)과 병용하여 투여해야 한다.] 2) 만성 림프구성 백혈병 3) 류마티스 관절염 4) 베게너육아종증 및 현미경적 다발혈관염 **[용법·용량]** (주입방법) 별도의 전용관을 써서 정맥 점적 주입하며 매회 30~60분전 해열제 및 항히스타민제 투여하여야 하고 비호지킨 림프종 및 만성림프구성 백혈병 환자의 치료계획 중 글루코코르티코이드가 포함되어 있지 않은 경우 전처치를 고려해 보아야 한다. 1차 주입 시 초기 주입 속도는 50 mg/h이 권장되며 30분마다 50 mg/h씩 속도를 높여 최고 400 mg/h까지 증가할 수 있다. 이후 이 약의 주입 속도는 100 mg/h에서 시작하여 30분마다 100 mg/h씩 증가시켜 최고 400 mg/h까지 높일 수 있다. (림프종) 치료기간 중 용량 감량은 바람직하지 않으며 이 약을 표준 화학요법과 병용투여하는 경우 화학요법제의 감량지침을 적용하도록 한다. ① 여포형 비호지킨 림프종 1) 병용요법: 이전에 치료받은 적이 없거나 재발성/불응성인 환자에게 유도요법으로 화학요법과 병용할 경우 권장용량은 375 mg/m²이며 8주기까지 투여한다. 이 약은 글루코코르티코이드 정맥 투여 후(해당되는 경우만), 매 화학요법 투여 주기 제1일에 투여한다. 2)유지요법: 이전에 치료받은 적이 없고 유도요법에 반응하는 환자는 2개월에 한번씩 375 mg/m²(유도요법 최종 투여로부터 2개월 후 유지요법 시작)을 재발성/불응성이고 유도요법에 반응하는 환자는 3개월에 한번씩 375 mg/m²(유도요법 최종 투여로부터 3개월 후 유지요법 시작)을 질환 진행 시까지 또는 최대 2년간 유지요법으로 투여한다. 3)단독요법: 재발성/불응성 환자에서 유도요법으로 투여할 경우 권장용량은 375 mg/m²이며 매주 1회씩 4주에 걸쳐 투여한다. 1차 치료 시 반응했던 환자가 재발한 경우 재투여하였으며 이때 반응률은 처음과 유사하였다. 권장용량은 375 mg/m²이며 매주 1회씩 4주에 걸쳐 투여한다. ② 미만형 대형 B세포 비호지킨 림프종: CHOP 화학요법과 병용투여한다. 권장용량은 375 mg/m²이며 매 화학요법 투여 주기의 제1일에 투여한다. 화학요법 구성약물들은 이 약 주입 후에 투여해야 한다. ※ 만성 림프구성 백혈병, 류마티스 관절염, 베게너육아종증 및 현미경적 다발혈관염의 용법·용량 및 제품에 대한 보다 자세한 정보는 제품설명서를 참조하시거나 아래의 연락처로 문의하여 주시길 바랍니다.

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In CMV prophylaxis

A PATH OF PROTECTION FROM THE START

Start PREVYMIS™ as early as day zero for prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).[1-4†]

Indication

- PREVYMIS™ is an antiviral drug indicated for prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).[1,2]

†[NCCN guideline] Consider letermovir as primary prophylaxis for CMV+ allogeneic HCT recipients.
CMV, cytomegalovirus; **HSCT,** hematopoietic stem cell transplantation; **R+**, recipient positive.

PREVYMIS™ (letermovir)
240 mg, 480 mg tablets
Injection 20 mg/mL

Reference 1. PREVYMIS™_Tab. Prescribing Information. MSD Korea.(Revision date 23 November 2021) **2.** PREVYMIS™_IV. Prescribing Information. MSD Korea. (Revision date 23 November 2021) **3.** Ljungman P, et al. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect Dis.* 2019 Aug;19(8):e260-e272. **4.** 2021, 07/02/21 2021 National Comprehensive Cancer Network(NCCN) ; Prevention and Treatment of Cancer-Related Infections.

CRESEMBA®
(ISAVUCONAZOLE)

Broad spectrum with activity across *Aspergillus* species and *Mucorales*[1,2]

CRESEMBA®

As effective as the standard of care[1] in IA and better tolerated[4,5]

PROVEN EFFICACY

CRESEMBA was non-inferior to voriconazole in patients suspected of having invasive mould desease.[3*]

SAFETY PROFILE

CRESEMBA was effective as voriconazole and better tolerated, and no dose adjustment is necessary in patients with renal impairment.[2-4,7]

IV & PO OPTIONS

CRESEMBA has high oral bioavailability (98%) – Switching between intravenous and oral administration is appropriate when clinically indicated.[2,3]

IA, invasive aspergillosis; **IM,** invasive mucormycosis; **IV,** intravenous; **PO,** per os (oral administration)

* Voriconazole
† In SECURE trial, All-cause mortality from first dose of study drug to day 42 for the ITT population was 19% with isavuconazole (49 patients) and 20% with voriconazole (52 patients), with an adjusted treatment diff erence of –1.0% [95% CI: –7.8 to 5.7] and the modified ITT (mITT) population (–5.7%, 95% CI: –16.9 to 5.5).[3]
‡ In SECURE trial, significantly fewer patients reported events considered drug-related by the investigator for isavuconazole than for voriconazole [109 (22%) vs 155 (32%); P<0.001]. Additionally, fewer isavuconazole-treated patients experienced drug-related treatment-emergent adverse events within the following system organ classes: hepatobiliary disorders, laboratory investigations, eye disorders, and psychiatric disorders. Permanent drug discontinuation due to treatment-emergent adverse events were less common with isavuconazole [27 (14%) vs 59 (27%)]. Permanent drug discontinuation due to drug-related adverse events was lower for isavuconazole than for voriconazole [11 (6%) vs 35 (16%)].[3]

[Study design] SECURE: This was a phase 3, double-blind, global multicentre, comparative-group study. Patients with suspected invasive mould disease were randomised in a 1:1 ratio using an interactive voice–web response system, stratified by geographical region, allogeneic haematopoietic stem cell transplantation, and active malignant disease at baseline, to receive isavuconazonium sulfate 372 mg (prodrug, equivalent to 200 mg isavuconazole; intravenously three times a day on days 1 and 2, then either intravenously or orally once daily) or voriconazole (6 mg/kg intravenously twice daily on day 1, 4 mg/kg intravenously twice daily on day 2, then intravenously 4 mg/kg twice daily or orally 200 mg twice daily from day 3 onwards). The investigators tested non-inferiority of the primary efficacy endpoint of all-cause mortality from first dose of study drug to day 42 in patients who received at least one dose of the study drug (intention-to-treat [ITT] population) using a 12% non-inferiority margin. Safety was assessed in patients who received the first dose of study drug. 527 adult patients were randomly assigned (258 received study medication per group) between March 7, 2007, and March 28, 2013.[3]

[Safety information][2] There are no data from the use of CRESEMBA in pregnant women. And the safety and efficacy of CRESEMBA in children aged below 18 years has not yet been established. Isavuconazole has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks. For long-term treatment beyond 6 months, the benefit-risk balance should be carefully considered. Vomiting; Diarrhoea; Nausea; Abdominal pain; Elevated liver chemistry tests are commonly reported as adverse drug reactions. Caution should be used in prescribing isavuconazole to patients with hypersensitivity to other azole antifungal agents.

References 1. Jenks JD, et al. Spotlight on isavuconazole in the treatment of invasive aspergillosis and mucormycosis: design, development, and place in therapy. Drug Des Devel Ther. 2018;12:1033–1044. **2.** CRESEMBA IV Prescribing information (Final revision date: 2023.1.30) **3.** CRESEMBA Capsule Prescribing information (Final revision date: 2023.1.30) **4.** Tissot F, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica. 2017;102(3):433–444. **5.** Maertens JA, et al. Isavuconazole **VITA**minate for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016;387(10020):760–769.

CRESEMBA Injection 200 mg/Capsules 100 mg (isavuconazonium sulfate) [Indications] 1. For the treatment of invasive aspergillosis in adults ≥ 18 years of age 2. For the treatment of invasive mucormycosis in adults ≥ 18 years of age for whom amphotericin B is inappropriate
[DOSAGE AND ADMINISTRATION] 1 Loading Dose ① Injection : one vial after reconstitution and dilution (equivalent to 200 mg of isavuconazole) every 8 hours for the first 48 hours ② administrations in total ② Capsules : two capsules (equivalent to 200 mg of isavuconazole) every 8 hours for the first 48 hours (6 administrations in total) 2 Maintenance Dose ① Injection : one vial after reconstitution and dilution (equivalent to 200 mg of isavuconazole) once daily, starting 12 to 24 hours after the last loading dose ② Capsules : two capsules (equivalent to 200 mg of isavuconazole) once daily, starting 12 to 24 hours after the last loading dose. For long-term treatment beyond 6 months, the benefit-risk balance should be carefully considered.
[PRECAUTIONS FOR USE] 1. Contraindications 1) In patients with hypersensitivity to the active substance or to any of the excipients. 2) Co-administration with strong CYP3A4 inhibitors such as ketoconazole or high dose ritonavir (>200 mg every 12 hours) 3) Co-administration with strong CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long-acting barbiturates (e.g., phenobarbital), phenytoin and St. John's wort or with moderate CYP3A4/5 inducers such as efavirenz, nafcillin and etravirine. 4) In patients with familial short QT syndrome. 2. The most common treatment-related adverse drug reactions : elevated liver chemistry tests, nausea, vomiting, dyspnoea, abdominal pain, diarrhoea, injection site reaction, headache, hypokalaemia, and rash.

* For more details of the product, please refer to the latest Product Package Insert available on Pfizer corporate website (www.pfizer.co.kr) # Final revision date : IV. 31, January 2023 PO. 31, January 2023

5,6th floor 100, Toegye-ro, Jung-gu, Seoul, Korea (04631) Tel : 02-317-2114 Toll free : 080-022-1400 www.pfizer.co.kr Medical Information Service www.pfizermedinfo.co.kr Tel : 080-210-2114 Email : MIS.Korea@pfizer.com

Pfizer Korea

PP-MO-KOR-0856-2.1(Jul)2023

Make Your Shot Strong[1,2]

BESPONSA® achieved 73.8% CR/CRi rate, ($P^{\P}$<0.0001 vs SC*)[1,†]
And, 73% of responders with BESPONSA® achieved CR/CRi within 1 cycle and 97% of responders achieved CR/CRi within 2 cycles.[2,‡,3]

BESPONSA®
inotuzumab ozogamicin

* Standard chemotherapy: FLAG or Ara-C+MXN (≤ 4 cycles) or HIDAC (≤ 1 cycles) ¶ one-sided P values

† [Data cut-off date: 2017.4.4] ‡ [Data cut-off date: 2014.10.2]
CR, complete remission; **CRi,** complete remission with incomplete haematological recovery of peripheral blood counts; SC, standard chemotherapy, FLAG, fllutarabine/ara-C/granulocyte colony-stimulating factor; HIDAC, high-dose ara-C; MXN, mitoxantrone

Reference 1, Kantarjian HM, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: Final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. Cancer. 2019 Jul 15;125(14):2474–2487 **2,** Kantarjian HM, et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. New Engl J Med. 2016;375:740–53. **3,** 베스폰사® 주 제품설명서 (2023.1.31)

[INO-VATE ALL Study design][1] CD22+, Ph+/- 재발 또는 불응성 B세포 ALL 성인 환자 326명(베스폰사 164명, 표준화학요법 162명)을 대상으로 표준화학요법과 베스폰사® 유효성과 안전성을 비교하기 위한 3상 임상시험으로 일차 평가변수는 complete response 및 overall survival이었음

[Safety information] 베스폰사® 투여받은 환자에서 가장 흔한(20% 이상) 이상사례는 혈소판감소증, 호중구감소증, 감염, 빈혈, 백혈구감소증, 피로, 출혈, 발열, 구역, 두통, 발열성 호중구감소증, 트랜스아미나제 증가, 복통, 감마-글루타밀전달효소 증가 및 고빌리루빈혈증이 있었고, 가장 흔한 (≥ 5% 이상) 중증(≥ 3등급) 이상 사례는 감염, 발열성 호중구감소증, 출혈, 복통, 발열, VOD 및 피로였음 베스폰사®를 투여 중이거나 투여 후 또는 투여 완료 후 HSCT를 받은 환자 23/164명(14%)에서 VOD가 보고되었음

[Product information] BESPONSA (inotuzumab ozogamicin) **[Composition]** Inotuzumab ozogamicin **[Indication]** Treatment of adults with relapsed or refractory B-cell acute lymphoblastic leukemia. Adult R/R B-cell ALL patients with Philadelphia chromosome positive should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI). **[Posology and method of administration]** 1) Pre-medication as required prior to dosing 2) For the first cycle, the recommended total dose of BESPONSA for all patients is 1.8 mg/m2 per cycle, given as 3 divided doses on Days 1 (0.5 mg/m2), 8 (0.5 mg/m2), and 15 (0.5 mg/m2). Cycle 1 is 3 weeks in duration but may be extended to 4 weeks if the patient achieves a CR or CRL and/or to allow recovery from toxicity. 3) For subsequent cycles, the recommended total dose of BESPONSA is 1.5 mg/m2 per cycle given as 3 divided doses on Days 1 (0.5 mg/m2), 8 (0.5 mg/m2), and 15 (0.5 mg/m2) for patients who do not achieve a CR/CRL or 1.8 mg/m2 per cycle given as 3 divided doses on Days 1 (0.8 mg/m2), 8 (0.5 mg/m2), and 15 (0.5 mg/m2) for patients who do not achieve a CR/CRL. Subsequent cycles are 4 weeks in duration, if patients who have not achieved CR/CRI within 3 cycles, treatment should be discontinued. 4) For patients proceeding to haematopoietic stem cell transplant (HSCT), the recommended duration of treatment is 2 cycles. A third cycle may be considered for those patients who do not achieve a complete remission (CR) or complete remission with incomplete haematological recovery (CRI) and minimal residual disease (MRD) negativity after 2 cycles. 5) For patients not proceeding to HSCT, a maximum of 6 cycles may be administered. [Special warnings and precautions for use] 1. Warnings 1) Hepatotoxicity(including VOD/SOS): Hepatotoxicity, including severe, life-threatening, and sometimes fatal hepatic VOD/SOS, was reported in patients.Elevation of liver tests may require dosing interruption, dose reduction, or permanent discontinuation of BESPONSA. Treatment should be permanently discontinued if VOD/SOS occurs. If severe VOD/SOS occurs, the patient should be treated according to standard medical practice. This risk was more marked in patients who underwent subsequent HSCT: there was a higher frequency of early deaths post-HSCT at day 100. 2. Contraindications 1) Hypersensitivity to the active substance or to any of the excipients of BESPONSA 2) Patients who have experienced prior confirmed severe or ongoing veno-occlusive liver disease/sinusoidal obstruction syndrome (VOD/SOS) 3)Patients with aerosol ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis) **[Amendment date]** 2022 Jan 31 ¶ For further information, please see updated product information or visit www.pfizer.co.kr

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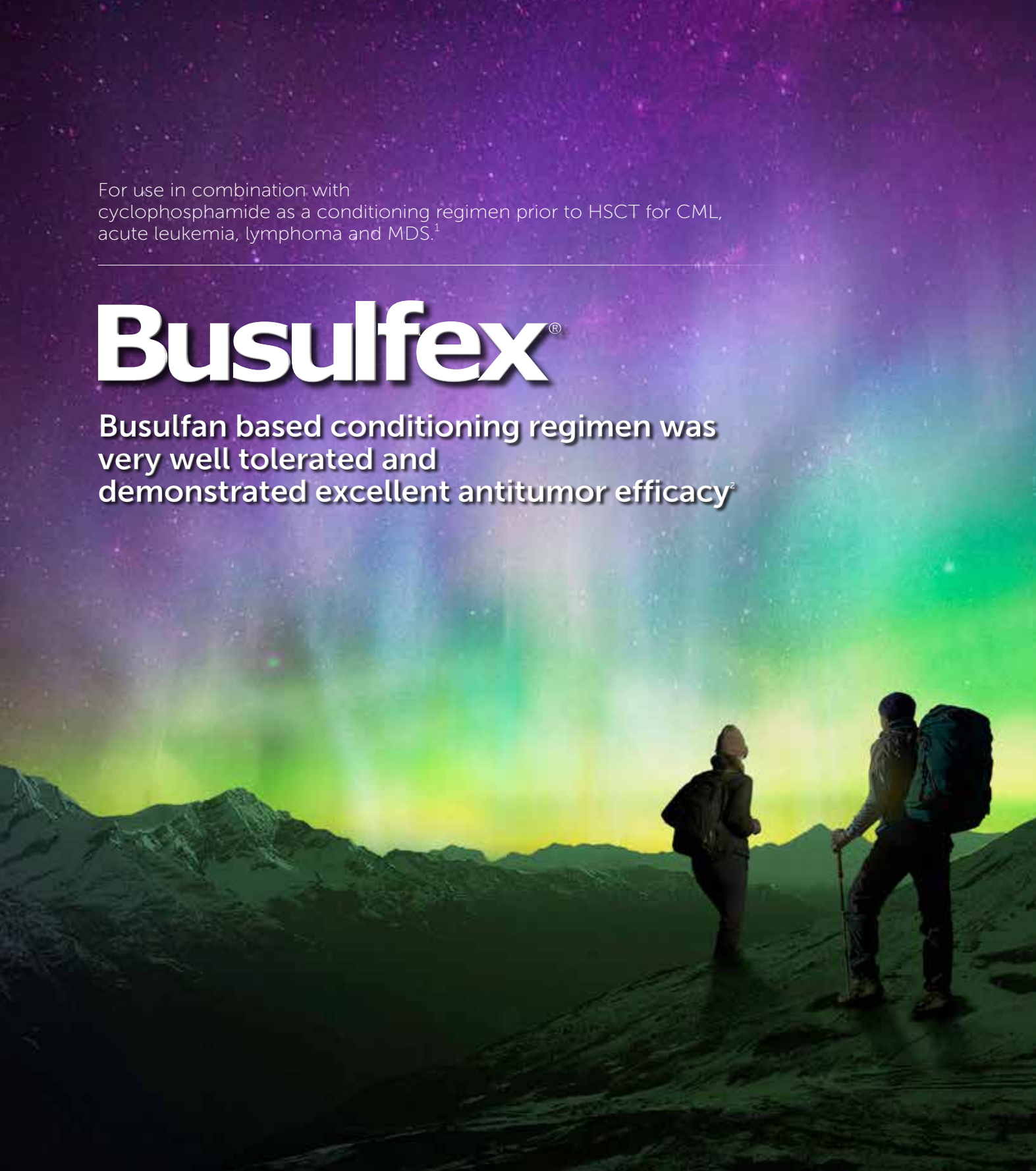
PP-AVS-KOR-0812-1.1(Jul)2023

For use in combination with
cyclophosphamide as a conditioning regimen prior to HSCT for CML,
acute leukemia, lymphoma and MDS.[1]

Busulfex®

Busulfan based conditioning regimen was very well tolerated and demonstrated excellent antitumor efficacy[2]



HSCT, hematopoietic stem cell transplantation; **CML,** Chronic Myelogenous Leukemia; **MDS,** myelodysplastic syndrome.

References : 1. 부설펙스 제품설명서. **2.** Andersson BS, et al. *Biol Blood Marrow Transplant*. 2002;8(3):145-54.

제품명 : 부설펙스®주(바이알)(부설판)(성분명 : Busulfan) **성상 :** 이 약은 바이알에 충전된 무색의 액상주사제이다. **성분·함량 :** 이 약 1바이알(10ml)중 (주성분) 부설판(USP) : 60.0mg (첨가제) 폴리에틸렌글리콜400 6.7mL, 디메틸아세트아미드 3.3mL **효능·효과 :** 다음 질환에 대하여 시클로포스파미드 와 병용하여 조혈모세포 이식시 전처치요법으로 사용한다 : 급성 백혈병, 만성 골수성 백혈병, 림프종, 골수 이형성증후군 **용법·용량 :** 1) 성인 0.8 mg/kg으로서 이상 체중 또는 그 보다 낮은 실제 체중을 적용하여 4일간 매 6시간마다 16회를 중심 정맥 카테터를 통하여 2시간 동안 투여한다. 시클로포스파미드는 이 약 16회째 요법이 완료된 6시간 후, 골수이식 개시 3일전에 60 mg/kg용량으로 한시간 동안 이들간 주입한다. 과체중 혹은 심각한 비만 환자의 경우, 교정 이상 체중(AIBW)에 근거하여 용량을 산정하여야 한다. 이상 체중(IBW)은 다음과 같이 계산된다 (단위 : 신장 cm, 몸무게 kg) IBW(남성) = 50 + 0.91 ×(신장 − 152) IBW(여성) = 45 + 0.91 ×(신장 − 152) 교정 이상 체중(AIBW)은 다음과 같이 계산된다. AIBW = IBW + 0.25 ×(실제체중 − IBW) 이 약은 교정 이상 체중 (AIBW)을 근거로 한 용량을 투여하였을 때 가장 좋은 클리어런스를 예상할 수 있다. 마른환자, 정상 및 비만 환자들의 경우 실제 체중, 이상체중(IBW) 또는 다른 인자들을 근거로 하여 투여했을 경우, 클리어런스에 유의성 있는 차이를 나타낼 수 있다. 이 약은 뇌-혈관 장벽을 통과하여 발작을 일으키는 것으로 알려져 있기 때문에 모든 환자는 페니토인으로 이를 예방하여야 한다. 페니토인은 부설판의 혈중농도- 시간곡선하면적(AUC)을 15% 감소시킨다. 다른 항경련제를 사용하면 부설판의 혈장 AUC가 높아지므로 간정맥 폐쇄성질환(HVOD) 또는 발작의 위험성이 높아진다. 다른 항경련제를 사용할 경우에는 혈장 부설판 노출을 모니터해야 한다. 5-HT3제열의 구토억제제를 이 약 초회 사용 이전에 투여하여야 하며, 이 약의 계획된 투여 기간동안 계속 투여하여야 한다. 최적의 치료를 위하여 가능한한 약동학적 모니터링을 실시하는 것이 좋다. 2) 소아(n=24)에 대한 약물동태학적 결과에 근거한 권장용량은 환자의 실제 체중(ABW)을 적용하여 12 kg 이하일 경우 1.1 mg/kg, 12 kg 초과일 경우 0.8 mg/kg를 4일간 매 6시간마다 16회를 중심 정맥 카테터를 통하여 2시간 동안 투여한다. 이 약의 초회 투여 후, 투여용량의 조절 및 치료 약물농도 모니터링(TDM)의 실시가 권장된다. 시클로포스파미드는 이 약 16회째 요법이 완료된 후, 골수이식 개시 5일전부터 50 mg/kg용량으로 1일 1회, 4일간 주입한다. ※ 치료 약물농도 모니터링에 근거한 소아 환자의 투여용량의 조절 초회 투약 후 목표 AUC(1,125 μM·min)에 도달하기 위한 소아 환자의 교정 투여용량은 다음과 같이 계산된다. 교정투여용량(mg) = 실제 투여용량(mg) × 목표 AUC (μM·min) / 실제 AUC (μM·min) 3) 정맥 내 투약을 위한 준비 이 약은 60mg의 부설판을 6mg/ml의 농도로서 함유하고 있는 10ml 무균 용액이며, 일회용 유리 바이알로 공급된다. 이 약은 사용 전 0.9% 생리식염수 주사액 또는 5% 포도당 주사액에 희석되어야 한다. 희석액의 양이 이 약 부피의 10배가 되어야 하며, 최종농도가 약 0.5mg/ml 으로 유지되어야 한다. **제품코드 :** 648900341 **포장단위 :** 10ml x 1, 바바이알 저장방법 : 2-8℃보관, 일회용기 **사용기한 :** 제조일로부터 30개월 * 기타 상세한 사항은 최신제품설명서를 참조하시기 바랍니다.

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FLT3, Fms-Like Tyrosine kinase 3

References 1. Perl AE, et al. Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML. N Engl J Med. 2019 Oct 31;381(18):1728-1740. **2.** HIRA Notice 2022-38 Released on Feb 25th 2022, Effective on Mar 1st 2022. **3.** XOSPATA® Prescribing Information

Precaution in use

1. Warnings 1) Differentiation Syndrome 3% of 319 patients treated with this drug experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with this drug included fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as 1 day and up to 82 days after this drug initiation and has been observed with or without concomitant leukocytosis. If differentiation syndrome is suspected, initiate corticosteroids and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt this drug until signs and symptoms are no longer severe (see Posology and method of administration and '4. Adverse reactions' section). **2) Posterior Reversible Encephalopathy Syndrome (PRES)** There have been reports of PRES with symptoms including seizure and altered mental status in patients (1%) treated with this drug. Symptoms have resolved after discontinuation of treatment. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue this drug in patients who develop PRES (see Posology and method of administration and '4. Adverse reactions' section). **3) Prolonged QT interval** Among the patients with this drug, 1% were found to have a QTcF greater than 500 msec and 7% had an increase from baseline QTcF greater than 60 msec. This drug has been associated with prolonged cardiac ventricular repolarisation (QT Interval) (see '4. Adverse reactions' section). Perform electrocardiogram (ECG) prior to initiation and during treatment with this drug, on day 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt this drug or reduce the dose of this drug for treatment reinitiation in patients who have a QTcF >500 msec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during this drug administration (see Posology and method of administration and '4. Adverse reactions' section).
2. Contraindications Hypersensitivity to the active substance or to any of the excipients of the product. Anaphylactic reactions have been reported. **3. Precautions** There have been reports of pancreatitis in patients (4%) treated with this drug. Evaluate and monitor patients who develop signs and symptoms suggestive of pancreatitis. Until symptoms resolve, interrupt and reduce the dose of this drug for treatment reinitation in patients who develop pancreatitis. **4. Adverse reactions** The safety of this drug was evaluated in 319 patients with relapsed or refractory AML who received at least one dose of 120 mg of this drug. The clinical trials included one multinational active-controlled, phase 3 trial (2215-CL-0301) and two supporting dose-escalation phase 1/2 trials (120mg dose arms of 2215-CL-0101 and 2215-CL-0102). At the time of final analysis, the median duration of exposure to this drug was 111 days (range 4 to 1320 days). The most frequent adverse drug reactions (ADRs) with this drug were, alanine aminotransferase (ALT) increased (82.1%), aspartate aminotransferase (AST) increased (80.6%), blood alkaline phosphatase increased (68.7%), Blood creatine phosphokinase increased(53.9%), diarrhoea (35.1%), fatigue (30.4%), nausea (29.8%), constipation (28.2%), cough (28.2%), peripheral oedema (24.1%), dyspnea (24.1%), dizziness (20.4%), hypotension (17.2%), pain in extremity (14.7%), asthenia (13.8%), arthralgia (12.5%) and myalgia (12.5%). The most frequent serious adverse reactions (≥ 2 %) reported in patients were acute kidney injury, diarrhea, ALT increased, dyspnea,, AST increased, hypotension and differentiation syndrome. Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

[Table 2] Adverse reactions observed during clinical studies

Adverse drug reaction	this drug 120 mg daily (N=319)		
	All Grades %	Grades ≥3 %	Frequency category
Cardiac disorders			
Pericardial effusion	4.1	0.9	Common
Pericarditis	1.6	0	Common
Cardiac failure	1.3	1.3	Common
Electrocardiogram QT prolonged	8.8	2.5	Common
Gastrointestinal disorders			
Diarrhea	35.1	4.1	Very common
Nausea	29.8	1.9	Very common
Constipation	28.2	0.6	Very common
General disorders and administration site conditions			
Fatigue	30.4	3.1	Very common
Peripheral edema	24.1	0.3	Very common
Asthenia	13.8	2.5	Very common
Malaise	4.4	0	common
Immune system disorders			
Anaphylactic reaction	1.3	1.3	common
Investigations			
Alanine aminotransferase increased*	82.1	12.9	Very common
Aspartate aminotransferase increased*	80.6	10.3	Very common
Blood alkaline phosphatase increased*	68.7	1.6	Very common
Blood creatine phosphokinase increased*	53.9	6.3	Very common
Musculoskeletal and connective tissue disorders			
Pain in extremity	14.7	0.6	Very common
Arthralgia	12.5	1.3	Very common
Myalgia	12.5	0.3	Very common
Musculoskeletal pain	4.1	0.3	common
Nervous system disorders			
Dizziness	20.4	0.3	Very common
Posterior reversible encephalopathy syndrome	0.6	0.6	Uncommon
Renal and urinary disorders			
Acute kidney injury	6.6	2.2	common
Respiratory, thoracic and mediastinal disorders			
Cough	28.2	0.3	Very common
Dyspnea	24.1	4.4	Very common
Differentiation syndrome	3.4	2.2	common
Vascular disorders			
Hypotension	17.2	7.2	Very common

Preferred term in MedDRA (v. 19.1). * Frequency is based on central laboratory values.

Description of selected adverse reactions 1) Differentiation syndrome Of 319 patients treated with this drug in the clinical studies, 11 (3%) experienced differentiation syndrome. Of the 11 patients who experienced differentiation syndrome, 9 (82%) recovered after treatment or after dose interruption of this drug. For recommendations in case of suspected differentiation syndrome (see Posology and method of administration and '1. Warning' section). **2) Posterior Reversible Encephalopathy Syndrome (PRES)** Of the 319 patients treated with this drug in the clinical studies, 0.6% experienced PRES. PRES is a rare, reversible, neurological disorder, which can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension. Symptoms have resolved after discontinuation of treatment (see Posology and method of administration and '1. Warning' section). **3) QT prolongation** Of the 317 patients treated with this drug at 120 mg with a post-baseline QTC value in clinical studies, 4 patients (1%) experienced a QTcF >500 msec. Additionally, across all doses, 12 patients (2.3%) with relapsed/refractory AML had a maximum post-baseline QTcF interval >500 msec (see Posology and method of administration and '1. Warning' and '(1) Pharmacodynamic properties section of 14. Information for experts' section)

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*애드세트리스®주는 a. 이전에 치료받은 적이 없는 3기 또는 4기 호지킨 림프종 환자에서 화학요법제와 병용요법, b. 이전에 치료받은 적이 없는 CD30 양성 말초T세포림프종 환자에서 화학요법제와 병용요법, c. 자가조혈모세포이식 이후 재발 또는 진행의 위험이 높은 호지킨 림프종 환자의 치료, d. 자가조혈모세포이식을 실패 혹은 비대상 환자에서의 최소 두 가지 이상의 이전 복합 화학요법에 실패한 호지킨림프종 환자의 치료, e. 최소 한가지 이상의 이전 복합 화학요법에 실패한 전신역형성대세포림프종 환자의 치료, f. 이전에 한 가지 이상의 전신요법을 받은 CD30양성 피부T세포림프종 환자의 치료에 적응증을 가지고 있습니다.

References 1. 애드세트리스®주 국내허가사항. Available at: https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetail?itemSeq=201307373. Accessed on Dec 16, 2022. **2.** 닌라로 캡슐 국내허가사항. Available at: https://nedrug.mfds.go.kr. Accessed on Dec 16, 2022.

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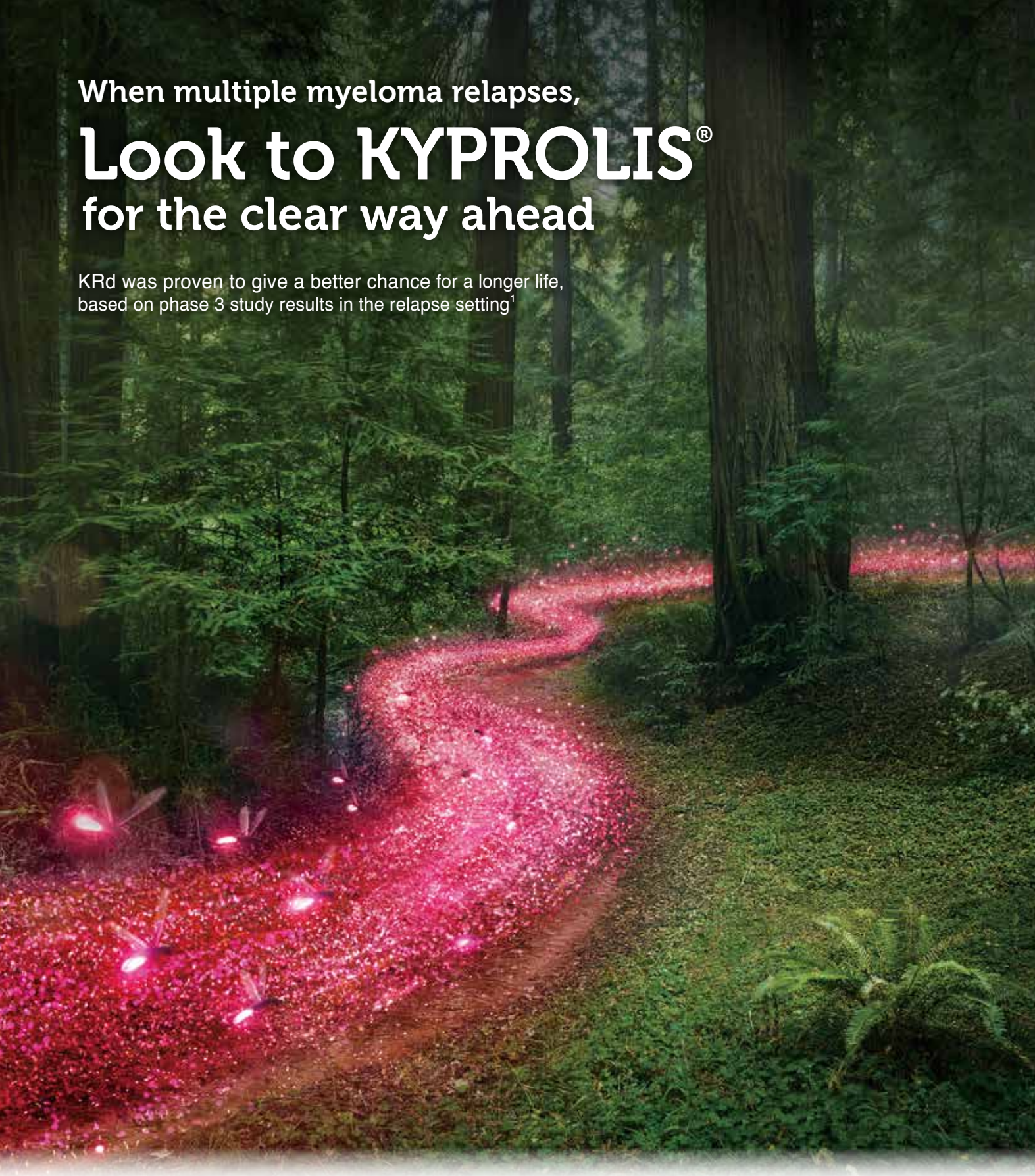

KRd, Kyprolis® (carfilzomib)+lenalidomide+dexamethasone.

Reference 1. Siegel DS, et al. *J Clin Oncol*. 2018;36(8):728-734.

키프롤리스®주 제품요약정보 **제품명:** 키프롤리스주60밀리그램, 30밀리그램(카르필조밉), **효능효과** 이전에 한 가지 이상의 치료를 받은 다발성골수종 환자의 치료에 레날리도마이드 및 덱사메타손 또는 덱사메타손과의 병용요법 **용법용량:** 3주 동안 매주 2일 연속으로 투여 후 12일간 휴약하여 총 28일을 1 치료주기로 한다. 첫 번째 주기의 1일, 2일에 20mg/m²의 시작용량으로 투여한다. [레날리도마이드 및 덱사메타손과의 병용요법] 10분 동안 정맥내 주입으로 투여. 시작 용량 투여 후, 첫 번째 주기의 8일에 목표 용량 27mg/m²로 증량한다. 13주기부터는 8일과 9일에 투여하지 않으며 18 주기 이후에는 투여를 중단한다. 레날리도마이드는 1-21일에 25mg을 경구 투여하고, 덱사메타손은 28일 주기의 1일, 8일, 15일, 22일에 40mg을 경구 또는 정맥투여한다. [덱사메타손과의 병용요법] 30분동안 정맥내 주입으로 투여. 시작용량 투여 후, 첫 번째 주기의 8일에 목표용량 56mg/m²로 증량한다. 매 28일 주기의 1, 2, 8, 9, 15, 16, 22, 23일에 덱사메타손 20mg을 경구 또는 정맥투여 한다. **다음 환자에게는 투여하지 말 것:** 이 약의 주성분 또는 다른 성분에 과민반응이 있는 환자. **이상반응:** [레날리도마이드 및 덱사메타손과의 병용요법] 임상시험에서 10% 이상 보고된 이상반응은 빈혈, 호중구감소증, 혈소판감소증, 설사, 변비, 구역, 피로, 발열, 말초부종, 무력증, 상기도감염, 비인두염, 기관지염, 바이러스성 상기도감염, 폐렴, 저칼륨혈증, 고혈당증, 근육경련, 등 통증, 기타 미분류 말초신경병증, 불면증, 기침, 호흡곤란, 발진, 색전증 및 혈전증, 고혈압이었고, 10% 이상 보고된 3-4등급 임상검사치 이상은 림프구, 절대호중구수, 인, 혈소판, 총 백혈구수, 헤모글로빈, 감소 및 당 증가이었다. [덱사메타손과의 병용요법] 임상시험에서 10% 이상 보고된 이상반응은 빈혈, 혈소판감소증, 설사, 구역, 변비, 구토, 피로, 발열, 말초부종, 무력증, 상기도감염, 기관지염, 근육경련, 요통, 두통, 말초신경병증, 불면증, 호흡곤란, 기침, 고혈압이었고, 10% 이상 보고된 3-4등급 임상검사치 이상은 림프구수, 혈소판, 인, 크레아티닌 청소율 감소 및 요산, 칼륨증가이었다. 시판 후 용혈요독증후군 (HUS), 위장관 천공, 심낭염이 자발보고 되었다. **일반적 주의:** 심장독성, 급성신부전, 종양용해증후군, 폐독성, 폐동맥고혈압, 호흡곤란, 고혈압, 정맥혈전증, 주입반응, 출혈, 혈소판감소증, 간독성 및 간부전, 혈전성 미세혈관병증, 가역성 후두부 뇌병증 증후군(PRES), 배태자독성이 발생할 수 있으므로 모니터링, 용량감량, 투여중지, 중단 등의 필요한 의학적 조치를 취하여야 한다. **임부 및 수유부:** 작용기전과 동물시험 결과로 볼 때, 태아독성을 야기할수 있으므로 적절한 피임 조치를 해야 한다. 임신 중 사용하거나 환자가 투약 중에 임신하게 되면, 환자에게 태아에 위험이 있음을 알려야 한다. **보관 및 취급상의 주의사항:** 차광 냉장 (2-8℃) 보관. **정맥 투여를 위한 재구성 및 조제방법:** 과량투여를 막기위해 투여량 계산에 주의해야 하며, 재구성하기 전 조제방법을 숙지하여야 한다. **수입판매원:** 암젠코리아유한회사 (서울특별시 중구 을지로5길 19 페럼타워 20층). **제품을 처방하시기 전 상세 제품설명서를 참고하여주시기 바랍니다.**

KR-04033-KYP-2020-Feb

AMGEN®
암젠코리아유한회사
대한민국 서울특별시 중구 을지로5길 19 페럼타워 20층 | 수신자 부담: 00798 611 3554

Kyprolis® (carfilzomib) Powder for solution for infusion

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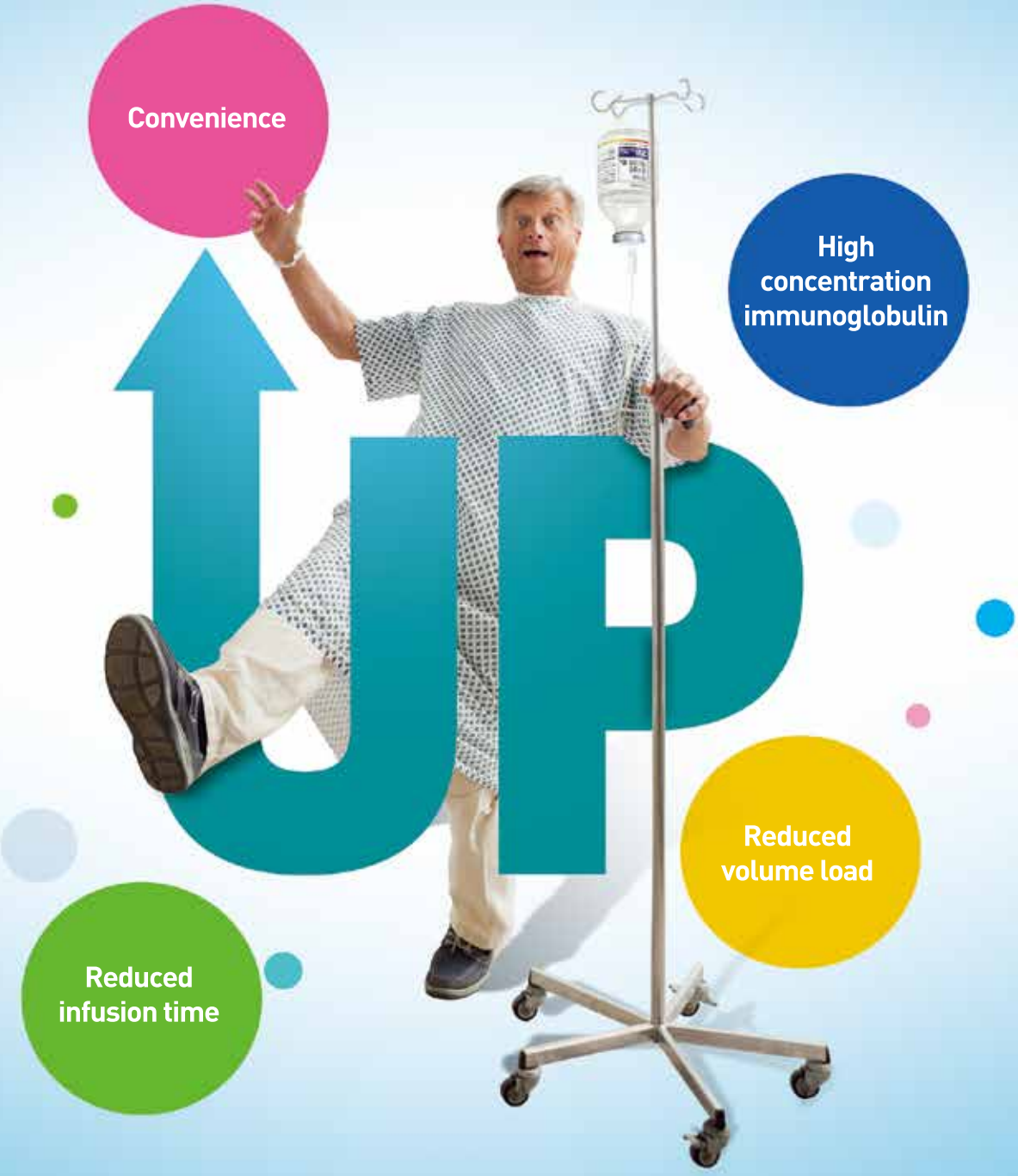

High Concentration

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The First STAMP inhibitor[1], SCEMBLIX®

SCEMBLIX® demonstrated superior response rate and favorable tolerability by Specifically Targeting the ABL1 Myristoyl Pocket (STAMP) in BCR-ABL1[1,3]

For Adult with Ph+ CML-CP after 2 or more TKIs

- **SUPERIOR EFFICACY** (vs. bosutinib)
  - Nearly doubled MMR rate (25.5% vs. 13.2%) and higher CCyR[a] (39.8% vs. 16.1%) at Week 24[1]
  - Maintained higher MMR rate (37.6% vs. 15.8%) and CCyR[a] (39.8% vs. 16.1%) at Week 96[4]
- **FAVORABLE TOLERABILITY** (vs. bosutinib)
  - Tolerability profile consisted based on a longer median duration of exposure (23.7 months vs. 7.0 months) at Week 96[b,4]
  - Nearly 4 times lower discontinuation rate due to AEs (7.7% vs. 26.3%)[4]

The median follow-up was 14.9 months (Data cutoff of May 25, 2020)[3].
The median follow-up was 2.3 years (Data cutoff of October 6, 2021)[1].

[a] In patients without CCyR at baseline (SCEMBLIX®, n=103; bosutinib, n=62).

[b] The median duration of exposure (range) by the data cutoff was 23.7 (range, 0.0–46.2) months for SCEMBLIX® and 7.0 (0.2–43.3) months for bosutinib.

Study design[1]: In this randomized, open-label, active-controlled, multicenter, phase 3 trial study, eligible patients (n=233) who were ≥ 18 years of age, with CML-CP previously treated with ≥ 2 TKIs were randomized in a 2:1 ratio to receive either SCEMBLIX® 40mg twice daily (n=157) or bosutinib 500mg once daily (n=76). The primary end point was the rate of MMR at week 24. Median follow-up was 14.9 months.

Study design[4]: Adults with CML-CP after ≥2 prior TKIs, with intolerance or lack of efficacy were randomized 2:1 to SCEMBLIX® 40 mg twice daily (n=157) or bosutinib 500 mg once daily (n=76), stratified by baseline MCyR status. After a median follow-up of 2.3 years (16.5 months additional follow-up since the primary analysis), updated efficacy and safety results were reported (cutoff: October 6, 2021). The key secondary objective was to compare MMR rate at week 96 on SCEMBLIX® versus bosutinib.

CML, chronic myeloid leukemia; **TKI,** tyrosine kinase inhibitor; **STAMP,** Specifically Targeting the ABL1 Myristoyl Pocket; **Ph+ CML-CP,** Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase; **MMR,** major molecular response; **CCyR,** complete cytogenetic response; **CML-CP,** chronic myeloid leukemia in chronic phase; **MCyR,** major cytogenetic response

References 1. Réa D, et al. Blood. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. 2021 Nov 25;138(21):2031-2041. **2.** [셈블릭스정] 식품의약품안전처 의약품통합정보시스템(nedrug.mfds.go.kr) **3.** Manley PW, et al. Leuk Res. 2020 Nov;98:106458. **4.** Hochhaus A, et al. Asciminib vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibitors: longer-term follow-up of ASCEMBL. Leukemia. 2023 Jan 30. Online Published. <doi: 10.1038/s41375-023-01829-9.>

PRODUCT INFORMATION

처방하시기 전 QR 코드 또는
식품의약품안전처
의약품통합정보시스템
(https://nedrug.mfds.go.kr)을 통해
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(애시미닙염산염)

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(애시미닙염산염)

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daunorubicin / cytarabine

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Delivery of daunorubicin and cytarabine to increase efficacy versus conventional chemotherapy **,2

SUPPORTING

High-risk* AML patients with a proven survival benefit over conventional chemotherapy **,3

LAYING THE FOUNDATION
TOWARDS LONG-TERM SURVIVAL IN HIGH-RISK AML*,2,3

TOGETHER LONGER

The **first** dual-drug advanced liposomal formulation[1]

Superior overall survival vs. conventional chemotherapy** in patients with high-risk AML*,2,3

*High-risk AML defined as newly diagnosed t-AML or AML-MRC. **Conventional chemotherapy:7+3/5+2.

References 1. Tolcher AW, Mayer LD. *Future Oncol.* 2018;14(13):1317–1332. **2.** Lancet JE, et al. *J Clin Oncol.* 2018;36(26):2684–2692.
3. Lancet JE, et al. *Lancet Haematol*. 2021;8(7):e481–e491.

Selected Prescribing Information

전문의약품(희귀)

[제품명] 빅시오스리포좀주 **[원료약품 및 분량]** 1바이알 중 시타라빈 100mg, 다우노루비신 44mg **[효능효과]** 1) 성인에서의 새로 진단받은 치료 관련 급성 골수성 백혈병(t-AML)의 치료 2) 성인에서의 새로 진단받은 골수이형성증 관련 변화를 동반하는 급성 골수성 백혈병(AML-MRC)의 치료 **[용법·용량]** 이 약은 정맥으로만 투여한다. 근육주사, 척수강내주사, 피하주사를 금한다. 이 약은 주입펌프를 이용하여 중심 정맥용 카테터(central venous catheter) 또는 말초삽입형 중심정맥 카테터(peripherally inserted central catheter)를 통해 90분간 정맥주입 한다. 혈관외유출로 인한 조직 괴사가 일어나지 않도록 각별히 주의한다. 이 약 치료는 화학요법 의약품 사용 경험이 있는 의사의 감독 하에 개시하고 모니터링해야 한다. 환자는 메스꺼움과 구토에 대해 전 처치를 받을 수 있다. 이 약을 개시하기 전에 항고요산혈증 약물(예. 알로푸리놀)를 고려해야 한다. 이 약은 다우노루비신 주사제 및 시타라빈 주사제와 다른 용법을 가지므로 다른 다우노루비신 및/또는 시타라빈 함유 제제를 대체할 수 없다. 이 약은 세포독성이 있는 의약품이므로 해당되는 특수 취급 및 폐기절차를 따라야 한다. 이 제품은 1회용이다. 미사용 의약품은 적절한 세포독성물질 취급 절차에 따라 폐기하여야 한다. (투여 전 제품의 조제방법과 투여 방법은 제품정보 원문 참고) **<관해유도요법 투여일정에 관한 권고 [제품정보 원문 용법·용량 [표1: 투여일정] 참고]>** 이 약 다우노루비신 44 mg/m² 및 시타라빈 100 mg/m²을 90분간 정맥투여 시 권장하는 투여일정: • 1차 유도요법 제 1, 3, 5일에 투여 • 필요 시, 2차 유도요법 제 1, 3일에 투여 유도요법 실시 전, 환자의 심기능 평가 및 간기능·신기능에 대한 검사가 수행되어야 한다. 1차 유도요법으로 관해에 도달하지 않은 경우, 질병이 진행되지 않거나 허용할 수 없는 독성이 나타나지 않는 환자에게는 1차 유도요법 종료 후 2-5주 시점에 2차 유도요법을 실시할 수 있다. 1차 유도요법 후 골수를 평가하여 2차 유도요법 실시 필요성을 결정한다. 환자가 이익을 얻는 한, 또는 질병이 진행될 때까지, 최대 2차까지의 유도요법 치료를 지속하여야 한다. **<공고요법 투여일정에 관한 권고 [제품정보 원문 용법·용량 [표1: 투여일정] 참고]>** 표1의 투여일정에서 최초 공고요법은 최종 유도요법 개시 후 5-8주 시점에 투여하여야 한다. 이 약 다우노루비신 29 mg/m²/일 및 시타라빈 65 mg/m²을 90분간 정맥투여 시 권장하는 투여일정: • 필요 시, 1차 및 2차 공고요법 각각 제 1, 3일에 투여 공고요법 실시 전, 환자의 심기능에 대한 평가 및 전혈구검사, 간기능·신기능에 대한 검사가 수행되어야 한다. 공고요법은 절대호중구수(absolute neutrophil count, ANC)> 500/μL 및 혈소판수> 50,000/μL로 회복되어 관해를 달성하고 허용할 수 없는 독성이 나타나지 않은 환자에서 권장된다. 2차 공고요법은 질병이 진행되지 않고 허용할 수 없는 독성이 나타나지 않은 환자에게 1차 공고요법 개시 후 5-8주 시점에 투여할 수 있다. 환자가 이익을 얻는 한, 또는 질병이 진행될 때까지, 최대 2차까지 공고요법 치료를 지속하여야 한다. **<치료 중 용량 조절에 관한 권고>** 환자에게 혈액학적 반응과 독성이 나타나는지 모니터링 해야 한다. 필요하다면, 투여를 연기하거나 영구 중단해야 한다(제품정보 원문 용법 · 용량 [치료 중 용량 조절에 관한 권고] 참고). **<특수환자군>** 신장애 환자, 간장애 환자, 고령자의 용량 조절에 관하여 제품정보 원문 용법 · 용량 [특수환자군] 참고 **[사용상의주의사항] 1. 경고** • 다른 다우노루비신 및/또는 시타라빈 함유 제제: 이 약은 다른 다우노루비신 및/또는 시타라빈 함유 제제와 약동학적 특성이 상당히 다르고 권장되는 투여용량과 투여일정 또한 동일하지 않으므로 대체 또는 교환할 수 없다. 투여 오류를 피하기 위해, 투여 전 의약품의 이름과 용량을 확인하여야 한다. • 중증의 골수억제: 치료용량의 이 약을 투여한 환자에서 중증의 골수억제(치명적인 감염과 출혈 포함)가 보고된 바 있다. 이 약 투여 환자에서 중증의 혈소판감소증이 동반된 중대한 또는 치명적인 출혈(치명적인 중추신경계 출혈 포함)이 발생하였다. 이 약으로 치료 시 베이스라인 혈구 수를 평가해야 하며, 환자에게 골수억제로 인한 임상적 합병증이 나타나는지 주의 깊게 모니터링 해야 한다. 이 약의 혈장반감기가 길기 때문에 ANC 및 혈소판 회복 시간이 길어질 수 있으며 추가적인 모니터링이 필요할 수 있다. 중성구감소증이 심각한 시기에는 ANC가 500/μL 이상으로 회복될 때까지 예방적 항생제(항균제, 항바이러스제, 항진균제 포함)를 투여할 수 있다. 골수억제 합병증이 나타날 경우, 항생제, 집락자극인자, 수혈 등의 적절한 보조요법을 실시해야 한다. 혈구 수는 회복될 때까지 정기적으로 모니터링 해야 한다. • 심독성: 안트라사이클린계 치료 시 심독성의 위험은 널리 알려져 있다. 이전에 안트라사이클린계 약물로 치료를 받은 적이 있거나(이전에 독소루비신이나 다우노루비신 염산염의 권장 최대 누적 투여량을 이미 투여받은 환자 포함), 심장질환을 이미 가지고 있거나(심기능 장애 포함), 이전에 종격에 방사선요법을 받은 적이 있거나, 심독성 약물을 병용하는 경우, 다우노루비신에 의한 심독성 위험이 증가할 수 있다. 비-리포좀 제제의 다우노루비신의 누적 투여량이 550 mg/m²을 넘으면 치료에 의해 유발되는 울혈성 심부전의 발생이 증가한다. 종격에 방사선요법을 받은 환자에서는 이 상한선이 더 낮아지는 것으로 보인다(400 mg/m²). 이 약 누적 투여량과 심독성 위험 간의 관련성은 아직 밝혀지지 않았다. 이 약 치료에 따른 다우노루비신 누적 노출량이 아래 표에 제시되어 있다(제품정보 원문 사용상의 주의사항 [표2: 이 약 치료 주기별 다우노루비신 누적 노출량] 참고). 심독성이 증가할 수 있는 위험 인자가 있는 환자에서는 심전도검사(ECG)와 함께 다중게이트 방사성핵종 혈관조영술(multi-gated radionuclide angiography, MUGA) 또는 심초음파 검사(echocardiography, ECHO)를 이용하여 베이스라인 심장 평가를 할 것을 권장한다. 심기능을 면밀히 모니터링해야 한다. 심기능 장애가 있는 환자는 이 약 치료 개시나 지속의 이익이 위험을 상회하지 않는 한 이 약 치료를 중단하여야 한다. • 임신/가임기 여성: 이 약을 투여 받는 동안에는 임신을 피하도록 환자에게 권고해야 한다. 남성 환자와 가임기 여성은 이 약 치료기간 동안, 그리고 최종 투여 후 6개월까지 효과적인 피임법을 사용하여야 한다. **2. 다음 환자에는 투여하지 말 것** 이 약의 활성성분이나 부형제에 중대한 과민성 이력이 있는 환자 **3. 이상반응**(안전성 프로파일 요약 부분 발췌) 가장 흔히 나타난 약물이상반응은 발진을 포함한 과민성(66.9%), 발열성 중성구감소증(63.5%), 부종(52.3%), 설사/장염(49.9%), 점막염증(49.9%), 피로(46.4%), 근골격 통증(44.5%), 복통(36.3%), 식욕감소(33.9%), 기침(33.9%), 두통(32.3%), 오한(31.2%), 부정맥(30.4%), 발열(29.6%), 수면장애(25.1%), 저혈압(23.7%)이었다. 가장 흔히 나타난 중대한 약물이상반응은 감염(58.7%), 심독성(18.7%), 출혈(13.1%)이었다. **[수입·판매자]** ㈜한독, 서울시 강남구 테헤란로 132 **[최종개정일]** 2022-11-30
***보다 자세한 정보는 제품 설명서를 참조하시기 바랍니다.**

빅시오스리포좀주 제품설명서
※ 상세 제품 정보는 QR 코드 또는 식품의약품안전처 의약품통합정보시스템(https://nedrug.mfds.go.kr)을 통해 확인하여 주시기 바랍니다.

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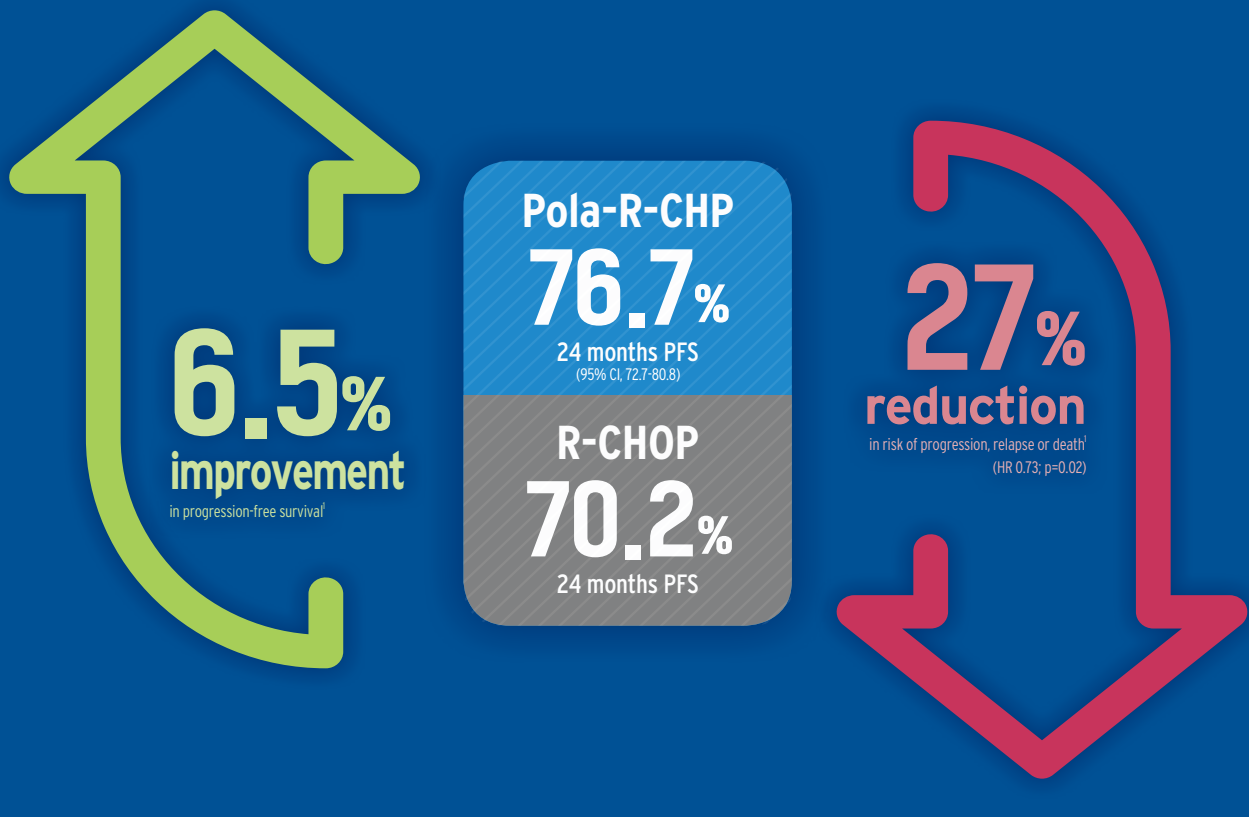
POLIVY®
polatuzumab vedotin

Roche

for the first-line treatment of adult patients with diffuse large B-cell lymphoma (DLBCL).

POLARIX trial demonstrated that treatment with Pola-R-CHP shows clinically meaningful improvement.[1]

Median follow-up of 28.2 months



POLIVY® INDICATIONS[2]

- Polivy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone/prednisolone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).
- POLIVY in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for haematopoietic stem cell transplant and who have failed at least one prior therapy.

PFS, Progression-free survival CI, Confidence interval

[Study design1] International, randomised, double-blind, placebocontrolled, phase III trial. The study compared R-CHOP to R-CHP + Pola from 2017 Nov.14 to 2019 Jun. 27. The trial enrolled 879 patients of previously untreated DLBCL in 23 countries. 440 participants were randomly assigned to receive Pola-RCHP and 439 patients were randomly assigned to receive R-CHOP. Primary endpoint is PFS and secondary endpoints are OS and safety.

Reference 1. Tilly H, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. New Engl J Med 2022;386:351-63. **2.** 폴라이비 제품설명서 Version: Polivy-2022-11-28-1.0

폴라이비®주 (폴라투주맙베도틴) **[원료약품 및 그 분량]** 이 약 1바이알(448.5 mg) 중 유효성분: 폴라투주맙 베도틴 (별규) 140mg, 첨가제(안정화제): 백당 288mg, 기타 첨가제: 수산화나트륨, 숙신산, 폴리소르베이트20. **[성상]** 백색 내지 화백색의 동결건조물이 충전된 무색 바이알의 주사제로서 조제된 용액은 무색 내지 미갈색이고 투명하거나 약간의 유백색을 띤 액상 **[효능·효과]** • 이전에 치료받은 적이 없는 미만성 거대 B세포 림프종(DLBCL) 성인 환자에서 리툭시맙, 시클로포스파미드, 독소루비신 및 프레드니손/프레드니솔론(R-CHP)과 병용투여 • 조혈모세포이식이 적합하지 않고 한 가지 이상의 이전 치료에 실패한 재발성 또는 불응성 미만성 거대 B세포 림프종(DLBCL) 성인 환자에서 벤다무스틴 및 리툭시맙과의 병용요법 **[용법·용량] 미만성 거대 B세포 림프종** • 이전에 치료받은 적이 없는 환자: 이 약은 1.8mg/kg의 용량을 6주기 동안 리툭시맙, 시클로포스파미드, 독소루비신 및 프레드니손/프레드니솔론(R-CHP)과 병용하여 21일 간격으로 정맥 내 투여한다. 이 약과 리툭시맙, 시클로포스파미드 및 독소루비신은 제 1일에 프레드니손/프레드니솔론 투여 후 순서와 무관하게 투여할 수 있다. 프레드니손/프레드니솔론은 각 주기의 제1-5일에 투여한다. 7주기 및 8주기는 리툭시맙 단독요법으로 구성된다. • 재발성 또는 불응성 환자: 이 약은 1.8 mg/kg의 용량을 6주기 동안 벤다무스틴 및 리툭시맙과 병용하여 21일 간격으로 정맥 내 투여한다. 이 약과 벤다무스틴 및 리툭시맙은 각 주기의 제1일에 순서와 무관하게 투여할 수 있다. 이 약을 리툭시맙과 함께 투여 할 때 벤다무스틴의 권장 용량은 제1일 및 제2일에 90 mg/㎡/day이다. • 이전에 치료받은 적이 없거나 재발성 또는 불응성 환자: 전투여가 이루어지지 않았다면 이 약 투여 전에 항히스타민제 및 해열제를 전투여한다. 이 약의 최초 용량은 90분 동안 정맥 내 투여해야 한다. 최초 용량 투여 도중 및 최초 용량 투여 완료 후 적어도 90분 이상 동안 주입 관련 반응에 대해 환자 모니터링을 해야 한다. 이전 주입 시 내약성이 양호하였다면 이후 이 약은 30분동안 투여할 수 있으며 투여 도중과 투여 완료 후 30분 이상 환자 모니터링을 해야 한다. 계획된 이 약의 투여가 누락된 경우 가능한 한 빨리 투여해야 하며 투여 간격이 21일이 되도록 투여 일정을 조정해야 한다. **용량 조정** 환자에게 주입 관련 반응이 발생하는 경우 이 약의 주입 속도를 늦추거나 주입을 중단한다. 환자가 생명을 위협하는 반응을 경험한다면 이 약의 투여를 즉시 영구적으로 중단한다. 이 약의 용량은 이전에 치료받은 적이 없는 DLBCL 환자와 재발성 또는 불응성 DLBCL 환자에서 다르게 조정한다(제품설명서 전문 표 1 및 표 2 참조). 말초신경병증 관리를 위한 용량 조정은 제품설명서 전문 표 1을 참조한다. 골수억제 관리를 위한 용량 조정은 제품설명서 전문 표 2를 참조한다. 주입 관련 반응에 대한 용량 조정은 제품설명서 전문 표 3을 참조한다. **[사용상의 주의사항] 1. 경고** 1) 골수억제: 중대한 그리고 중증 호중구감소증 또는 발열성 호중구감소증이 이 약을 투여 받은 환자에서 투여 제1주기 초기부터 보고된 바 있다 (제품설명서 전문 3.이상반응 항 참조). 예방적 G-CSF 투여를 고려해야 한다. 이 약 투여 시 3-4등급 혈소판감소증 또는 빈혈이 발생할 수 있다(제품설명서 전문 3.이상반응 항 참조). 이 약의 투여 전에 전혈구수를 모니터링해야 한다. 3-4등급 호중구감소증 또는 혈소판감소증 환자에게는 보다 빈번한 실험실 수치 모니터링 및 이 약의 투여 연기 또는 중단을 고려해야 한다. 2) 말초신경병증: 말초신경병증이 이 약을 투여받은 환자에서 투여 제1주기부터 보고된 바 있으며 순차적 투여에서 그 위험이 증가하였다 (제품설명서 전문 3.이상반응 항 참조). 기존에 말초신경병증이 있는 환자는 상태 악화를 경험할 수 있다. 이 약 투여에서 보고된 말초신경병증은 주로 감각 말초신경병증이지만 운동 및 감각 운동 말초신경병증도 보고된 바 있다. 감각저하, 지각과민, 지각이상, 감각장애, 신경병성 통증, 작열감, 약화 또는 보행 장애 등의 말초신경병증 증상에 대해 환자 모니터링을 해야 한다. 말초신경병증이 새로 발생하거나 악화된 환자는 이 약 투여를 연기하거나 용량을 감소하거나 투여를 중단할 수 있다. 3) 감염: 폐렴(pneumocystis jirovecii 및 기타 진균성 폐렴 등), 바이러스재활성, 패혈증, 헤르페스 감염 및 거대세포바이러스 감염 등 기회감염을 포함한 중대하거나 생명에 위협적이거나 치명적인 감염이 이 약 투여 환자에서 보고된 바 있다(제품설명서 전문 3.이상반응 항 참조). 이 약 치료 중 바이러스성 감염의 징후에 대해 환자를 면밀하게 모니터링하여야 한다. 항감염 예방요법을 고려해야 한다. 중대한 감염이 발생한 환자는 이 약 및 모든 병용 화학요법을 중단해야 한다. 4) 진행성 다초점 백질뇌병증(PML): 이 약 투여 시 PML이 보고된 바 있다(제품설명서 전문 3.약물이상반응 항 참조). PML을 암시하는 신경적 인지적 또는 행동적 변화 발생이나 악화에 대해 환자를 면밀하게 모니터링하여야 한다. PML이 의심된다면 이 약 및 모든 병용 화학요법을 보류해야 하며 진단이 확인되면 영구 중단해야 한다. 5) 종양 용해 증후군: 종양 부담이 높고 종양이 빠르게 증식되는 환자는 종양 용해 증후군 발생 위험이 높을 수 있다. 이 약 투여 전에 가이드라인에 따른 적절한 조치를 취해야 한다. 이 약 투여 중 종양 용해 증후군에 대해 환자를 면밀하게 모니터링하여야 한다. 6) 배태아 독성: 작용 기전 및 비임상 시험 결과에 기초하여 이 약은 임부에게 투여 시 태아에게 유해할 수 있다(제품설명서 전문 6.임부, 수유부, 가임여성에 대한 투여). 임부에게 태아에 대한 위험을 설명하여야 한다. 가임 여성은 이 약 투여 도중 및 마지막 투여 후 9개월 이상 동안 효과적인 피임법을 사용하여야 한다. 가임 여성을 파트너로 둔 남성 환자는 이 약 투여 도중 및 마지막 투여 후 6개월 이상 동안 효과적인 피임법을 사용하여야 한다. 7) 간독성: 아미노전이효소 또는 빌리루빈 상승을 포함한 간세포 손상과 일치하는 간독성의 중대한 증례가 이 약 투여 환자에서 발생한 바 있다. 기존에 간 질환을 가지고 있거나, 기저 간효소 수치가 높거나 약물 병용 시 간 손상 위험이 증가할 수 있다. 간효소 및 빌리루빈 수치를 모니터링해야 한다. **2. 다음 환자에는 투여하지 말 것** 이 약의 주성분 또는 첨가제에 알려진 과민증이 있는 환자 **3. 임부, 수유부, 가임여성에 대한 투여** 1) 임부: 모체에 대한 잠재적 유익성이 태아에 대한 잠재적 위험을 초과하지 않는다면 임신 중 이 약의 투여는 권장되지 않는다. 동물 시험과 이 약물의 작용 기전에 기초할 때 이 약은 태아에게 유해한 영향을 미칠 수 있다. 동물 시험에서 모노메틸 오리스타틴 E(MMAE)는 유전독성 및 배태아 독성을 야기하였다.(전문가용 사용상의 주의사항 중 4. 독성시험 정보 참조) 진통 및 분만 중 이 약의 안전한 사용에 대해서는 확립되어 있지 않다. 2) 수유부: 이 약이 사람 모유로 배출되는지 여부는 알려져 있지 않다. 이 약이 모유 생성 또는 모유 내 존재에 미치는 영향을 평가한 연구는 수행된 바 없다. 많은 약물이 모유로 배출되고 이 약으로 인해 수유아에게 중대한 이상반응이 발생할 수 있는 위험성이 있기 때문에 여성은 이 약 투여 중과 마지막 투여 후 적어도 3개월 동안 수유를 중단해야 한다.

*보다 자세한 제품 문의 또는 제품 관련 부작용 보고는 (주)한국로슈(02-3451-3600)로 연락주시기 바랍니다. 가장 최신 제품정보는 ㈜한국로슈 홈페이지(www.roche.co.kr)에서 확인하실 수 있습니다.

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인레빅™캡슐 (페드라티닙염산염수화물)

전문의약품

[원료약품 및 그 분량] 1캡슐 (298.75 mg) 중, - 유효성분: 페드라티닙염산염수화물(미분화) (별규) 117.3 mg (페드라티닙으로서 100 mg) - 기타 첨가제: 규화미결정셀룰로오스, 스테아릴푸마르산나트륨, 캡슐 **[성상]** 흰색의 과립이 들어있는 상하부 적갈색의 경질 캡슐 **[효능 · 효과]** 이전에 룩소리티닙으로 치료를 받은 성인환자의 다음 질병과 관련된 비장비대 또는 증상의 치료 - 일차성 골수섬유증 - 진성적혈구증가증 후 골수섬유증 - 본태성혈소판증가증 후 골수섬유증 이 약의 유효성을 치료적확증시험에서 입증한 자료는 없다. **[용법 · 용량]** 이 약의 권장 용량은 1일 1회 페드라티닙으로서 400mg이다. 항암제 사용에 숙달된 의사의 감독 하에 이 약의 치료를 시작하고 모니터링 해야한다. 룩소리티닙 치료를 받고 있는 환자는 이 약의 치료를 시작하기 이전에 룩소리티닙의 허가사항에 따라 용량을 서서히 줄여 투여를 중단해야한다. 이 약의 치료를 시작하기 이전과 치료기간 중 주기적으로 베이스라인 티아민(비타민 B1) 검사, 전혈구수, 간 패널, 아밀라아제/리파아제, 혈중 요소 질소 (BUN, blood urea nitrogen) 및 크레아티닌 수치를 확인해야한다. 티아민 결핍증이 있는 환자는 티아민 수치가 정상으로 회복될 때까지 이 약의 치료를 시작해서는 안된다. 또한 베이스라인 혈소판 수치 50 x 10^9/L 미만, 절대호중구수 1.0 x 10^9/L 미만인 환자들은 이 약의 치료를 시작하는 것을 권장하지 않는다. 캡슐을 열거나, 부수거나 씹어서 복용해서는 안된다. 가급적 물과 함께 캡슐을 그대로 삼키도록 한다. 음식물 섭취와 관계없이 복용할 수 있으나, 이 약을 고지방식이와 함께 투여할 경우 오심과 구토의 발생을 감소시킬 수 있으므로 식후 복용할 것을 권장한다. 치료 첫 8주 동안 예방적으로 항구토제의 사용을 권장하며, 항구토제 치료를 계속할 수 있다. 복용을 놓친 경우에는 다음 날 계획된 정상 용량을 복용해야 한다. 놓친 용량을 보충하기 위해 추가적으로 용량을 복용해서는 안된다. 이 약의 치료는 환자에게 임상적 유익성이 있는 한 계속할 수 있다. 혈액학적 또는 비혈액학적 독성에 대해서 용량조절을 고려해야한다 (표1). 1일 1회 200mg의 용량에 내약성을 보이지 않는 경우에는 이 약의 치료를 중지한다. 용량 조절: 혈액학적 독성, 비혈액학적 독성 및 베르니케 뇌병증 관리를 위한 용량 조절이 아래 표1에 나와있다. 1) 티아민 수치에 따른 용량 관리: 이 약의 치료를 시작하기 전에 티아민 수치가 낮을 경우 보충해야한다. 치료 중에는 티아민 수치를 정기적으로 평가해야한다 (첫3개월 간은 매 달, 이후 매 3개월 마다). 2) 강력한 CYP3A4 저해제와의 병용투여 시 용량 조절: 강력한 CYP3A4저해제의 사용이 불가피한 경우, 이 약의 용량을 200mg으로 조절해야한다. 안전을 위해 환자의 상태를 최소한 1주일 간격으로 주의깊게 모니터링 해야한다. 강력한 CYP3A4저해제와의 병용 투여를 중단한 경우에는 이 약의 용량을 첫 2주 동안은 1일 1회 300mg으로 증량하고, 이후에 내약성을 보이면 1일 1회 400mg으로 증량한다. 이 약과 관련한 안전성 및 유효성 모니터링 결과에 따라 추가적인 용량 조절이 필요하다. 3) 용량 재증량; 용량 감량을 야기한 이 약의 약물이상반응이 효과적인 관리를 통해 제어되고 28일 이내에 독성이 해소된 경우에는 용량을 1개월에 1단계씩 최초 용량 수준까지 증량할 수 있다. 4등급의 비혈액학적 독성, 3등급 이상의 ALT(alanine aminotransferase), AST(aspartate aminotransferase) 또는 총 빌리루빈 수치의 상승, 4등급 혈액학적 독성의 재발로 인한 용량 감량의 경우에는 용량의 재증량을 권장하지 않는다.

표 1. 치료로 인한 혈액학적, 비혈액학적 독성 및 베르니케 뇌병증 관리를 위한 용량 감량

혈액학적 독성	용량 감량
활동성 출혈을 동반한 3등급의 혈소판 감소증 (혈소판 수치 < 50 x 10^9/L (< 50 x 10^3/mm^3)) 또는 4등급의 혈소판 감소증 (혈소판 수치 < 25 x 10^9/L (< 25 x 10^3/mm^3))	2등급 이하 (혈소판 수치 < 75 x 10^9/L (< 75 x 10^3/mm^3)) 또는 베이스라인 수치로 회복될 때까지 투여를 중지한다. 마지막 투여 용량보다 100 mg/일 낮은 용량으로 투여를 재개한다.
4등급 호중구 감소증 (절대 호중구수 < 0.5 x 10^9/L (< 500/μL))	2등급 이하 (절대 호중구수 < 1.5 x 10^9/L (< 1500/μL)) 또는 베이스라인 수치로 회복될 때까지 투여를 중지한다. 마지막 투여 용량보다 100 mg/일 낮은 용량으로 투여를 재개한다.
수혈이 적용되는 3등급 이상의 빈혈 (헤모글로빈 수치 < 8.0 g/dL)	2등급 이하 (헤모글로빈 < 10.0 g/dL) 또는 베이스라인 수치로 회복될 때까지 투여를 중지한다. 마지막 투여 용량보다 100 mg/일 낮은 용량으로 투여를 재개한다.
4등급 혈액학적 독성의 재발	의사의 판단에 따라 투여를 중단한다.
비혈액학적 독성	**용량 감량**
지지 요법에 48시간 이내에 반응 하지 않는 3등급 이상의 오심, 구토 또는 설사	1등급 이하 또는 베이스라인 수준으로 회복될 때까지 투여를 중지한다. 마지막 투여 용량보다 100mg/일 낮은 용량으로 투여를 재개한다.
3등급 이상의 ALT, AST 수치 상승 (정상 상한치의 5배초과-20배이하) 또는 빌리루빈 수치 상승 (정상 상한치의 3배초과-10배이하)	1등급 이하 (AST/ALT: 정상 상한치1배 초과-3배 미만, 빌리루빈 정상 상한치의 1배 초과-1.5배 미만) 또는 베이스라인 수치로 회복될 때까지 투여를 중지한다. 마지막 투여 용량보다 100 mg/일 낮은 용량으로 투여를 재개한다. 용량 감량 이후에는 ALT, AST 및 빌리루빈(총빌리루빈 및 직접 빌리루빈) 수치를 최소 3개월간 매 2주마다 모니터링한다. 3등급 이상이 재발할 경우 투여를 중단한다.
3등급 이상의 아밀라아제, 리파아제 수치 상승 (정상 상한치의 2배초과-5배이하)	1등급 이하 (정상 상한치 1배초과-1.5배 미만) 또는 베이스라인 수치로 회복될 때까지 투여를 중지한다. 마지막 투여 용량보다 100 mg/일 낮은 용량으로 투여를 재개한다. 용량 감량 이후에는 아밀라아제 및 리파아제 수치를 최소 3개월간 매 2주마다 모니터링한다. 3등급 이상이 재발할 경우 투여를 중단한다
기타 3등급 이상의 비혈액학적 독성	1등급 이하 또는 베이스라인 수준으로 회복될 때까지 투여를 중지한다. 마지막 투여 용량보다 100mg/일 낮은 용량으로 투여를 재개한다.
티아민 수치 및 베르니케 뇌병증의 관리	**용량 감량**
티아민 수치가 정상 수치 74-222 nmol/L 미만이나, 30 nmol/L (1 μg/dL) 이상이고 베르니케 뇌병증의 징후나 증상이 없는 경우	이 약의 투여를 중지한다. 티아민 수치가 정상으로 회복될 때까지 경구 티아민을 100 mg/일의 용량으로 투여한다. 티아민 수치가 정상범위* 내에 있을 경우 이 약의 치료재개를 고려한다.
티아민 수치가 30 nmol/L 미만이고 베르니케 뇌병증의 징후나 증상이 없는 경우	이 약의 투여를 중지한다. 티아민 수치가 정상으로 회복될 때까지 비경구 티아민을 치료용량으로 투여한다. 티아민 수치가 정상범위* 내에 있을 경우 이 약의 치료재개를 고려한다.
티아민 수치와 관계없이 베르니케 뇌병증의 징후나 증상이 있는 경우	이 약의 투여를 중단하고 즉시 비경구 티아민을 치료용량으로 투여한다.

* 티아민 수치의 정상 범위는 실험실에서 사용하는 검사방법에 따라 다를 수 있다.

4) 신장애 환자에 대한 투여: 중증의 신장애 (Cockcroft Gault 크레아티닌 청소율 15-29 mL/min) 환자의 경우, 1일 200mg으로 감량한다. 경증 또는 중등증 신장애 환자 (Cockcroft Gault 크레아티닌 청소율 30-89mL/min)에 대한 시작 용량의 조절은 필요하지 않다. 잠재적인 노출 증가의 가능성 때문에, 기존에 중등증의 신장애를 가진 환자들은 최소 주 1회의 안전성 모니터링을 실시해야 하며, 이상반응에 근거하여 용량 조절을 실시한다. 5) 간장애 환자에 대한 투여: 간장애 환자에서 이 약의 약동학 평가는 이루어지지 않았다. 중증의 간장애 환자 (Child-Pugh C등급, 또는 AST 상승을 동반한 총빌리루빈 수치가 정상 상한치의 3배 초과)에게 이 약을 투여하는 것은 피해야한다. 경증 또는 중등증 간장애 환자에 대한 용량 조절은 필요하지 않다. **[사용상의 주의사항]** 1. 경고 1) 베르니케 뇌병증을 포함한 뇌병증: 이 약을 투여한 환자에서 베르니케 뇌병증을 포함한 중대하고 치명적인 뇌병증 사례가 보고되었다. 베르니케 뇌병증은 티아민 (비타민 B1) 결핍으로 인한 신경학적 응급상황이다. 베르니케 뇌병증의 징후와 증상에는 운동실조, 정신상태 변화, 눈근육 마비 (예: 안진, 복시)가 포함될 수 있다. 정신 상태 변화, 혼동 또는 기억 장애가 발생한 경우 베르니케 뇌병증을 포함한 잠재적인 뇌병증의 가능성을 의심해야 하며 신경학적 검사, 티아민 수치 검사 및 영상검사를 포함한 신속하고 전체적인 평가를 실시해야한다. 이 약의 치료를 시작하기 전과 치료를 시작한 후 주기적으로 환자의 티아민 수치와 영양학적 상태를 평가해야한다 (예, 치료 첫 3개월 동안은 매월, 이후 매 3개월마다). 티아민 결핍증이 있는 환자에서는 이 약의 치료를 시작해서는 안된다. 치료 전과 치료 중에 티아민 수치가 낮은 경우 티아민 보충을 실시해야한다. 뇌병증이 의심되는 경우, 이 약의 치료를 즉시 중지하고 모든 가능한 원인을 평가하는 동시에 비경구 티아민 치료를 시작해야한다. 증상이 해소되거나 개선되고, 티아민 수치가 정상화되기까지 환자들을 모니터링 해야한다. 2. 다음 환자에는 이 약을 투여하지 말 것 1) 이 약의 유효성분 또는 첨가제에 과민반응이 있는 환자 3. 다음 환자에는 신중히 투여할 것 1) 빈혈, 혈소판감소증 및 호중구 감소증: 이 약은 빈혈, 혈소판 감소증 및 호중구 감소증을 유발할 수 있다. 베이스라인과 치료 기간 중에 주기적으로 전혈구검사(complete blood count)를 실시한다. 혈소판 수치 50 x 10^9/L (50 x 10^3/mm^3) 미만 및 절대 호중구수 1.0 x 10^9/L (1,000/μL) 미만인 환자에 대한 연구는 없다. · 빈혈: 빈혈은 일반적으로 치료 첫 3개월 이내에 발생한다. 치료 시작 시 헤모글로빈 수치가 10.0 g/dL 미만인 환자는 치료 중에 3 등급 이상의 빈혈이 발생할 가능성이 더 높으므로 주의 깊게 모니터링해야한다 (예: 헤모글로빈 수치가 개선될 때까지 첫 달 동안 매주 1회). 빈혈이 발생하는 환자는 수혈이 필요할 수 있으며, 특히 적혈구 수혈 의존성이 있는 환자에서 빈혈이 발생할 경우 용량 감소를 고려해야한다. · 혈소판감소증: 혈소판감소증은 일반적으로 치료 첫 3개월 이내에 발생한다. 치료 시작 시 혈소판 수치가 낮은 환자 (<100 x 10^9/L (100 X 10^3/mm^3))는 치료 중에 3 등급 이상의 혈소판 감소증이 발생할 가능성이 더 높으므로 주의 깊게 모니터링해야한다 (예: 혈소판 수치가 개선될 때까지 첫 달 동안 매주 1 회). 혈소판 감소증은 일반적으로 가역적이며 필요한 경우 투여 중지, 용량 감소 및/또는 혈소판 수혈과 같은 지지 치료에 의해 통상적으로 관리할 수 있다. 환자들은 혈소판 감소증과 관련된 출혈 위험 증가에 대해 알고 있어야 한다. · 호중구 감소증: 호중구 감소증은 일반적으로 가역적이며, 일시적인 투여 중지를 통해 관리할 수 있다. 2) 위장관 약물이상사례: 이 약으로 치료받은 환자에서 가장 흔하게 보고된 약물이상반응은 오심, 구토 및 설사이다. 대부분의 약물이상반응은 1등급 또는 2등급이었고 전형적으로 치료 첫 2주 내에 발생하였다. 적절한 예방적 항구토 치료 (5-HT-3 수용제 길항제)를 고려해야한다. 설사 증상이 첫번째로 발현하면 지사제로 신속하게 치료해야한다. 48시간 내에 지지 요법에 반응하지 않는 3등급 이상의 오심, 구토, 설사의 경우에는 1등급 이하 또는 베이스라인으로 회복될 때까지 투여를 중지해야한다. 투여 재개 시에는 마지막 투여 용량보다 100 mg/일 낮은 용량을 투여한다. 티아민 수치를 모니터링하고 필요할 경우 티아민 보충을 실시한다. 3) 간독성: 이 약으로 치료받은 환자에서 ALT와 AST수치의 상승 및 1건의 간부전 사례가 보고되었다. 베이스라인, 치료 첫 3개월 간 적어도 매월, 그 이후에는 주기적으로 환자들의 간기능을 모니터링해야 한다. 독성이 관찰되면, 해소될 때까지 적어도 2주마다 모니터링한다. ALT와 AST수치의 상승은 일반적으로 용량 조절에 따라 가역적이었거나, 영구적으로 치료를 중단하였다. 4) 아밀라아제, 리파아제 수치 상승: 아밀라아제 및/또는 리파아제 수치의 상승 및 1건의 췌장염 사례가 보고되었다. 베이스라인, 치료 첫3개월 간 적어도 매월, 그 이후에는 주기적으로 환자들의 아밀라아제 및 리파아제 수치를 모니터링해야 한다. 독성이 관찰되면, 해소될 때까지 적어도 2주마다 모니터링한다. 3등급 이상의 아밀라아제 및/또는 리파아제 수치 상승 시 용량조절을 권장한다. 5) 크레아티닌 수치 상승: 크레아티닌 수치 상승이 보고되었다. 베이스라인, 치료 첫 3개월 간 적어도 매월, 그 이후에는 주기적으로 환자들의 크레아티닌 수치를 모니터링해야 한다. 중증의 신장애 환자 (Cockcroft Gault 크레아티닌 청소율 15-29 mL/min)의 경우, 용량 조절을 권장한다. 4. 약물이상반응: 이전에 룩소리티닙 치료를 받은 환자(97명, JAKARTA2연구)를 포함하여, 일차성 골수섬유증, 진성적혈구 증가증 후 골수섬유증, 본태성혈소판증가증 후 골수섬유증 환자를 대상으로 한 이 약의 임상시험들(203명)에서 노출 기간의 중앙값은 35.6주 (범위 0.7 - 114.6주) 였으며 투여 주기 (1주기 28일)의 중앙값은 9주기였다. 203명의 환자 중 63%가 6개월 이상 투여를 받았으며 38%가 12개월 이상 노출되었다. 임상시험에서 이 약 400mg 용량으로 치료받은 203명의 환자들 중에서 가장 흔한 비혈액학적 약물이상반응은 설사 (67.5%), 오심 (61.6%), 및 구토 (44.8%) 였다. 가장 흔한 혈액학적 약물이상반응은 실험실적 검사치에 근거한 빈혈 (99.0%) 및 혈소판감소증 (68.5%)이었다 (표2). 이 약 400mg 용량으로 치료받은 환자들 중에서 가장 흔한 중대한 약물이상반응은 빈혈 (2.5%, 보고된 약물이상사례에 근거함) 및 설사(1.5%)였다. 이 약과의 인과관계와 상관없이 약물이상사례로 인해 영구적으로 투여를 중단한 비율은 이 약 400mg 용량을 투여받은 환자에서 24% 였다. · 약물이상반응 목록: 임상시험의 전체 치료 기간 동안 보고된 MedDRA (Medical dictionary of regulatory activities) 기관계에 따라 정리한 약물이상반응을 표2에 제시하였다. 같은 기관계 내에서는 빈도가 높은 순에서 낮은 순으로 나열하였다. 빈도는 매우 흔하게 (≥ 1/10), 흔하게 (≥ 1/100 에서 < 1/10), 흔하지 않게 (≥ 1/1,000 에서 < 1/100), 드물게 (≥ 1/10,000 에서 < 1/1,000), 매우 드물게 (< 1/10,000) 및 알려지지 않음 (활용 가능한 자료로부터 추정할 수 없음)으로 분류한다.

표 2. 기관계 및 우선순위 용어에 따른 모든 약물이상반응

기관계	약물이상반응	모든 등급의 빈도
감염	요로 감염	매우 흔함
혈액 및 림프계 이상	빈혈[a]	매우 흔함
	혈소판감소증[a]	매우 흔함
	호중구감소증[a]	매우 흔함
	출혈[b]	매우 흔함
대사 및 영양 이상	리파아제 증가[a]	매우 흔함
	아밀라아제 증가[a]	매우 흔함
신경계 이상	두통	매우 흔함
	베르니케 뇌병증	흔함
	어지러움	흔함
혈관 이상	고혈압	흔함
위장관 이상	설사	매우 흔함
	구토	매우 흔함
	오심	매우 흔함
	변비	매우 흔함
	소화불량	흔함
간담도 이상	ALT 증가[a]	매우 흔함
	AST 증가[a]	매우 흔함
근골격계 및 결합조직 이상	뼈 통증	흔함
	근육경련	매우 흔함
	말초 통증	흔함
신장 및 비뇨기 이상	혈중 크레아티닌 상승[a]	매우 흔함
	배뇨곤란	흔함
전신 및 투여부위 이상	피로/무력증	매우 흔함
임상 검사	체중 증가	흔함

[a] 빈도는 실험실적 검사 수치에 기반함.

[b] 혈소판 감소증과 관련한 모든 종류의 출혈을 포함함. 출혈은 MedDRA SMQ (Standardized MedDRA Query) 출혈 용어를 사용함 (넓은 범위).

· 주요 약물이상반응 1) 베르니케뇌병증을 포함한 뇌병증: 베르니케뇌병증으로 확인된 1건의 사례를 포함하여 중대한 뇌병증 사례가 이 약의 임상시험에 참여한 환자의 1.3% (8/608명)에서 보고되었다. 7명의 환자는 신경학적 증상이 발현되었을 때 1일 500mg의 용량을 투여받고 있었으며, 티아민 결핍을 유발할 수 있는 영양실조, 위장관계 약물이상사례 및 다른 위험인자들을 가지고 있었다. 1명의 환자는 1일 400mg의 용량을 투여받았으며 간성 뇌병증으로 확인되었다. 1건의 치명적인 사례(0.16%, 1/608명)를 제외하고 대부분의 이상사례는 기억 소실, 인지 장애 및 어지러움과 같은 신경학적 잔여 증상과 함께 회복되었다. 1건의 치명적인 사례는 골수섬유증이 아닌 다른 효능효과를 위한 임상시험에서 1일 500mg을 투여받은 환자로 두경부암, 뇌전이, 섭식 장애 및 체중감소를 가지고 있었다. 2) 위장관계 독성: 오심, 구토, 설사는 이 약으로 치료받은 환자에서 가장 흔한 약물이상반응이다. 1일 400mg을 투여받은 골수섬유증 환자에서 설사 68%, 오심 62% 및 구토45%의 빈도로 발생하였다. 3등급의 설사, 오심 및 구토는 각각 5%, 0.5% 및 2%에서 발생하였다. 모든 등급의 오심, 구토 및 설사 발현까지 기간의 중앙값은 2일이었고, 75%가 치료 시작 3주 이내에 발생하였다. 위장관계 이상반응으로 인한 투여 중지 및 용량 감량은 11% 및 9%에서 보고되었다. 1일 400mg 용량을 투여받은 환자에서 위장관계 독성으로 인한 영구적인 투여 중단은 4%에서 발생하였다. 3) 빈혈: 1일 400mg 용량으로 치료받은 일차성 또는 이차성 골수섬유증 환자의 52%에서 3등급의 빈혈이 발생하였다. 3등급 빈혈이 처음으로 발현하기까지 기간의 중앙값은 약 60일 이었으며, 75%가 치료 시작 후 4개월 이내 발생하였다. 1일 400mg을 투여한 환자의 58%가 적혈구 수혈을 받았고, 빈혈로 인해 영구적으로 투여를 중단한 환자는 1.5% 였다. 4) 혈소판감소증: 1일 400mg 용량으로 치료받은 일차성 또는 이차성 골수섬유증 환자에서 3등급 혈소판 감소증은 14%, 4등급 혈소판 감소증은 9%에서 발생하였다. 3등급 또는 4등급의 호중구 감소증이 처음으로 발현까지 기간의 중앙값은 약70일이었으며, 75%가 치료 시작 후 7개월 이내 발생하였다. 1일 400mg을 투여한 환자의 9%가 혈소판 수혈을 받았다. 임상적 처치가 필요한 혈소판 감소증과 관련한 출혈은 11%의 환자에서 발생하였으며, 혈소판 감소증으로 인해 영구적으로 투여를 중단한 환자는 3% 였다. 5) 호중구감소증: 4등급의 호중구감소증이 3.5%의 환자에서 발생하였고, 호중구 감소증으로 인해 투여를 중지한 비율은 0.5% 였다. 6) 간독성: 모든 등급의 ALT 수치 상승은 52%에서 AST 수치 상승은 59%에서 발생하였다. 1일 400mg 용량을 투여받은 환자에서 3등급은 3%, 4등급은 2% 빈도로 발생하였다. 모든 등급의 ALT 및 AST 수치 상승까지 기간의 중앙값은 약 1개월이었으며, 75%가 치료 시작 후 3개월 이내 발생하였다. 7) 아밀라아제/리파아제 수치 상승: 이 약으로 치료받은 골수섬유증 환자에서 모든 등급의 아밀라아제 및/또는 리파아제 수치 상승은 각각 24% 및 40%에서 발생하였다. 대부분의 약물이상사례는 1또는 2등급이었으며, 3등급은 2.5%, 4등급은 12%에서 발생하였다. 모든 등급의 아밀라아제 또는 리파아제 상승이 처음 발생하기까지 기간의 중앙값은 16일이었으며, 75%가 치료 시작 후 3개월 이내 발생하였다. 1일 400mg을 투여받은 환자에서 아밀라아제 및/또는 리파아제 수치 상승으로 인해 영구적으로 투여를 중단한 비율은 1.0% 였다. 8) 크레아티닌 수치 상승: 1일 400mg을 투여받은 골수섬유증 환자에서 모든 등급의 크레아티닌 수치 상승은 74%에서 발생하였다. 일반적으로 무증상의 1등급 또는 2등급 사례였으며, 3등급은 3%의 환자에서 발생하였다. 모든 등급의 크레아티닌 수치 상승이 처음 발생하기까지 기간의 중앙값은 27일이었으며, 75%가 치료 시작 후 3개월 이내 발생하였다. 크레아티닌 수치 상승으로 인해 투여 중지 또는 감량을 실시한 비율은 각각 1.0% 및 0.5% 였다. 1일 400mg을 투여받은 환자에서 크레아티닌 수치 상승으로 인해 영구적으로 투여를 중단한 비율은 1.5% 였다. 5. 일반적 주의사항 1) 운전 및 기계 조작 능력에 대한 영향: 이 약은 운전 및 기계조작 능력에 경미한 영향을 준다. 투여 후 어지러움을 경험한 환자는 운전 및 기계 조작을 삼가야 한다. 6. 약물상호작용 1) 강력한 CYP3A4 저해제: 강력한 CYP3A4 저해제와의 병용투여는 이 약의 노출을 증가시킨다. 이 약 300mg 단회 투여 시, 케토코나졸과의 병용투여 (강력한 CYP 3A4저해제: 200mg 1일 2회)는 이 약의 혈장 농도-시간 곡선 하 면적 (AUC_{inf})을 약 3배 증가시켰다. 노출의 증가는 약물이상반응의 위험을 증가시킬 수 있다. 강력한 CYP3A4 저해제 대신 CYP3A4의 활성을 강하게 억제하지 않는 약물의 사용을 고려해야한다. 만약 강력한 CYP3A4 저해제(예: 케토코나졸, 리토나비르)를 다른 약제로 대체할 수 없다면, 병용 투여 시 이 약의 용량을 감량해야한다. 안전을 위해 환자의 상태를 주의깊게 모니터링해야한다. 2) 중등도 CYP3A4 저해제: 생리학적 약동학 시뮬레이션에 근거하여 중등도 CYP3A4 저해제인 에리트로마이신 (500mg 1일 3회) 또는 딜티아젬(120mg 1일 2회)과 병용투여 시에 정상 상태에서 이 약의 곡선 하 면적을 각각 1.2배 및 1.1배 증가시키는 것으로 예측되었다. 중등도 CYP3A4저해제와의 장기간 병용투여에 따른 약물이상반응 발생의 가능성을 배제할 수 없다. 중등도의 CYP3A4와 장기간 병용투여 시에는 면밀한 모니터링이 필요할 수 있으며, 필요할 경우에 약물이상반응에 근거하여 용량 조절을 실시한다. 3) CYP3A4와 CYP2C19의 동시 억제: CYP3A4와 CYP2C19을 동시에 억제하는 저해제나, CYP3A4저해제와 CYP2C19저해제를 함께 투여했을 경우에 대한 연구는 실시되지 않았다. 생리학적 약동학 시뮬레이션에서는 CYP3A4저해제 및 CYP2C19저해제와의 병용투여는 이 약의 곡선 하 면적 (AUC_{inf})을 약 4배 증가시켰으며, CYP효소들의 자가 저해와 자가 유도와 같은 복잡한 작용으로 인해 이 약을 반복 투여할 경우 상황이 변할 수 있다. 이 약의 노출을 증가시킬 수 있으므로 병용투여를 피해야한다. CYP3A4와 CYP2C19을 동시에 억제하는 저해제(예: 플루코나졸, 플루복사민)나, CYP3A4저해제와 CYP2C19저해제를 함께 투여할 경우, 이 약의 노출을 증가시킬 수 있으므로 병용투여를 피해야한다. 4) 강력한 또는 중등도의 CYP3A4유도제: 이 약 500mg 단회 투여 시, 강력한 CYP3A4유도제인 리팜핀(600mg 1일 1회) 또는 중등도의 CYP3A4유도제인 에파비렌즈 (600mg 1일 1회) 와의 병용투여는 이 약의 곡선 하 면적 (AUC^{inf})을 각각 약 80% 및 50%씩 감소시켰다. 강력한 또는 중등도의 CYP3A4유도제 (예: 페니토인, 리팜핀, 에파비렌즈)는 이 약의 노출을 감소시킬 수 있으므로 병용투여를 피해야한다. 5) 프로톤펌프 억제제: 이 약 500mg 단회 투여 시, 프로톤펌프 억제제인 판토프라졸 (1일 40mg)과의 병용투여는 이 약의 곡선 하 면적 (AUC^{inf})을 유의하지 않게 증가시켰다 (1.15배). 따라서 위 pH의 증가는 이 약의 노출에 임상적으로 유의한 영향을 주지 않을 것으로 예상되며, 위의 pH을 증가시키는 약제들과의 병용투여 시 용량조절은 필요하지 않다. 6) 효소에 대한 영향: CYP3A4의 기질, CYP2C19의 기질 또는 CYP2D6의 기질: 이 약과 CYP3A4의 기질인 미다졸람 (2mg), CYP2C19의 기질인 오메프라졸(20mg) 및 CYP2D6의 기질인 메토프롤롤(100mg)과 병용투여했을 때 각각의 곡선 하 면적 (AUC_{inf})은 3.8배, 2.8배, 1.8배씩 증가하였고, 각각의 최대 농도(C_{max})는 1.8배, 1.1배 및 1.6배씩 증가하였다. 따라서 CYP3A4의 기질 (예: 미다졸람, 심바스타틴), CYP2C19의 기질(예: 오메프라졸, S-메페니토인) 또는 CYP2D6의 기질(예: 메토프롤롤, 덱스트로메토르판)과 이 약을 병용투여할 경우 안전성 및 유효성을 면밀하게 모니터링하고 필요에 따라 병용투여하는 약물들의 용량 조절을 실시해야한다. 7) 수송체에 대한 영향: in vitro 연구에서 이 약은 P-당단백질 (P-glycoprotein), 유방암 저항 단백질 (BCRP, Breast Cancer Resistance Protein), 다약제 및 독소 배출 수송체 1 (MATE1, multidrug and toxin extrusion 1), 다약제 및 독소 배출 수송체 2-K (MATE2-K), 유기 음이온 수송 단백질1B1(OATP1B1, organic anion transporting polypeptide1B1), 유기 음이온 수송 단백질1B3(OATP1B3) 및 유기 양이온 수송체 2 (OCT2, organic cation transporter2)를 억제했다. 이 약의 수송체 기질에 대한 in vivo에서의 영향은 연구되지 않았다. 좁은 치료역을 가진 이들 수송체의 민감한 기질에 대해서 주의를 기울여야한다. 8) 조혈 성장인자: 이 약과 조혈성장인자와의 병용투여는 연구되지 않았다. 이 약에 의한 JAK 억제가 조혈 성장인자의 유효성을 감소시키는 지와 조혈성장인자가 이 약의 유효성에 영향을 주는지는 알려져 있지 않다. 7. 임부 및 수유부에 대한 투여 1) 가임 여성 및 피임: 가임 여성은 이 약으로 치료받는 동안 임신을 피해야하며, 치료를 받은 동안과 마지막 투약 이후 적어도 1개월 동안은 효과적인 피임법을 사용해야한다. 2) 임부에 대한 투여: 임신한 여성에게 이 약을 사용한 데이터는 없다. 동물을 대상으로 한 연구에서 사람의 권장용량보다 낮은 용량에서 생식 독성을 보였다. 작용기전에 근거하여 이 약은 태아 손상을 유발할 수 있다. 이 약은 임상적으로 관련이 있는 노출 수준에서 임신한 랫트와 토끼에서 배태자 사망과 최기형성을 유발한 JAK 저해제군에 속한다. 임신한 여성에게 이 약을 사용해서는 안된다. 만약 임신 중에 투여하였거나, 투여 중에 환자가 임신했을 경우 환자에게 발생할 수 있는 잠재적인 위험에 대해 조언해야한다. 3) 수유부에 대한 투여: 이 약과 이 약의 대사체가 모유로 분비되는 지에 대해서는 알려져있지 않다. 모유 수유를 하는 아이에 대한 위해성을 배제할 수 없다. 이 약으로 치료받는 동안과 마지막 투약 이후 적어도 1개월까지는 수유를 해서는 안된다. 4) 수태능: 사람의 수태능에 대한 영향과 관련한 데이터는 없다. 이 약의 임상적 노출 수준에서 동물의 수태능에 대한 영향과 관련한 데이터는 없다. 8. 소아에 대한 투여: 18세 이하에 대한 이 약의 안전성과 유효성은 확립되지 않았다. 9. 고령자에 대한 투여: 고령자 (65세 초과)에 대한 추가적인 용량 조절은 필요하지 않다. 10. 과량 투여 시의 처치: 이 약의 과량투여에 대한 경험은 제한적이다. 골수섬유증 환자를 대상으로 한 임상시험에서 용량을 1일 600mg까지 증량하였고, 실수로 인해 800mg까지 투여한 1건의 사례가 있었다. 400mg을 초과하는 용량에서 위장관계 독성, 피로, 어지러움, 빈혈 및 혈소판 감소증이 더 흔하게 발생하였다. 임상시험의 통합분석 데이터에서 베르니케 뇌병증을 포함한 뇌병증은 1일 500mg 용량과 관련이 있었다. 과량 투여 시, 추가적으로 이 약을 투여해서는 안되며, 환자를 임상적으로 모니터링하고 지지 요법을 실시해야한다. 11. 보관 및 취급상의 주의사항 1) 어린이의 손이 닿지 않는 곳에 보관한다. 2) 의약품을 원래 용기에서 꺼내어 다른 용기에 보관하는 것은 의약품 오용에 의한 사고 발생이나 의약품 품질 저하의 원인이 될 수 있으므로 원래의 용기에 넣고 꼭 닫아 보관한다. 12. 전문가를 위한 정보 12.1 약력학적 특성 1) 작용기전: 이 약은 인산화효소 저해제로 야생형 및 돌연변이로 인해 활성화된 JAK2 (Janus Associated Kinase 2) 및 FLT3 (FMS-like tyrosine kinase 3)를 억제한다. JAK2 선택적 저해제로 동일 효소군에 속한 JAK1, JAK3 및 TYK2보다 JAK2에 대해 높은 억제활성을 가진다. 이 약은 JAK2에 의해 매개되는 세포 신호전달 인자 및 전사 활성인자 (STAT3/5) 단백질의 인산화를 감소시켜 in vitro와 in vivo에서 악성 종양세포의 증식을 억제한다. 2) 약력학적 효과: 이 약은 골수섬유증환자의 혈액에서 사이토카인에 의해 유도되는 세포 신호전달인자 및 전사 활성 인자 (STAT3)의 인산화를 억제한다. 300, 400 및 500mg의 단회 투여 시에 투여 후 대략 2시간 이후에 STAT3 인산화를 최대로 억제하였고, 24시간 이후에 베이스라인 수준으로 돌아왔다. 1일 300, 400 및 500mg의 용량으로 투여했을 때 제1주기의 제15일에 유사한 수준의 약동학적 정상 상태에 도달하였다. 12.2 임상적 안전성 및 유효성: 이전에 룩소리티닙으로 치료를 받은 골수섬유증 환자를 대상으로 한 임상시험: 룩소리티닙으로 치료를 받은 증상이 있는 중간위험-1, 중간위험-2 및 고위험의 일차성 골수섬유증, 진성적혈구 증가증 후 골수섬유증, 본태성혈소판증가증 후 골수섬유증과 관련된 비장비대 가 있고 혈소판 수가 50 x 10^9/L (50 x 10^3/mm^3) 이상인 환자를 대상으로 다기관, 라벨 공개, 단일 군 임상시험을 실시하였다. 이전에 여러 치료를 받은 총 97명의 환자 (2가지 이상의 치료를 받은 비율 79%, 4가지 이상의 치료를 받은 비율 13%)가 등록되었고, 이 약을 1일 400mg 용량으로 시작하여 최대 1일 600mg까지 증량을 허용하였다. 55%의 환자가 남성이었고, 65-74세가 46%, 75세 이상이 17% 였으며, 연령의 중앙값은 67세였다 (범위 38-83세). 증상을 가진 중간위험-1 환자가 16%, 중간위험-2 환자가 49%, 고위험환자가 35% 였다. 베이스라인에서 헤모글로빈 수치의 중앙값은 9.8 g/dL (범위 6.8 - 15.3 g/dL)였고, 혈소판 수치의 중앙값은 147.0 x 10^9/L (147 x 10^3/mm^3) (범위 48.0 - 929.0 x 10^9/L (48 - 929 x 10^3/mm)) 였다. 혈소판 수치 100 x 10^9/L (100 x 10^3/mm^3) 미만인 환자가 34%였고, 100 x 10^9/L (100 x 10^3/mm^3) 이상인 환자는 66%였다. 베이스라인에서 감지할 수 있는 비장 길이의 중앙값은 18 cm (범위 5-36 cm)였고 자기공명영상 및 컴퓨터 단층 촬영에 의해 베이스라인에서 측정된 비장의 용적은 2893.5 mL (범위 737-7815 mL). 이전에 룩소리티닙에 노출된 기간의 중앙값은 10.7개월 (범위 0.1 - 62.4개월)이었다. 71%의 환자가 임상시험에 등록되기 이전에 1일 30mg 또는 40mg의 용량으로 룩소리티닙을 투여받았다. 1차 유효성 평가변수는 6주기 종료 시에 자기공명영상 및 컴퓨터 단층 촬영으로 측정한 베이스라인 대비 35% 이상의 비장용적 감소를 달성한 환자의 비율이었다. 1일 400mg의 용량을 투여한 환자에서 1차 평가변수를 달성한 비율은 22.7% (22/97명, 95%CI: 14.8%, 32.3%)이었다. 12.3 약동학적 특성 1) 흡수: 이 약을 1일 300-500mg 용량으로 투여했을 때 (권장 용량의 0.75-1.25배), C_{max}의 기하평균과 투여간격 동안의 혈장 중 농도-시간 곡선 하 면적 (AUC_{tau})은 용량에 비례하여 증가하였다. 평균 정상상태 수치는 투여 후 15일 내에 달성하였다. 평균 축적률은 일차성 골수섬유증, 진성적혈구 증가증 후 골수섬유증, 본태성혈소판증가증 후 골수섬유증 환자에서 3-4배로 유사하였다. 골수섬유증 환자에게 1일 400mg 용량을 투여했을 때, $C_{max,ss}$의 기하평균은 1804 ng/mL (변동계수49%)이었고, $AUC_{tau,ss}$는 26870 ng.hr/mL (변동계수43%)로 나타났다. 1일 400mg 용량을 투여 후, 이 약은 빠르게 흡수되어 정상상태 에서의 C_{max}에 3시간 후 도달하였다 (범위 2-4시간). 인체 대상 질량-균형시험에서 이 약의 경구 흡수율은 대략 63-77%로 평가되었다. 이 약 500mg을 단회 투여하였을 때, 저지방/저칼로리 (총 162칼로리, 지방 6%, 탄수화물78%, 단백질 16%) 식이 또는 고지방/고칼로리 (총815칼로리, 지방 52%, 탄수화물 33%, 단백질 15%) 식이는 AUC_{inf}를 최대 24%, C_{max}를 최대 14%까지 증가시켰다. 식이에 의한 임상적으로 유의미한 약동학적 효과가 관찰되지 않았으므로 이 약은 식사와 관계없이 투여할 수 있다. 고지방 식이와 함께 복용할 경우 오심과 구토의 발생을 감소시킬 수 있으므로 음식과 함께 복용할 것을 권장한다. 2) 분포: 이 약을 1일 400mg 용량으로 투여받은 골수섬유증 환자의 정상상태에서 평균 겉보기 분포용적은 1770L로 광범위한 조직 분포를 암시한다. 인간 혈장 단백질과의 결합율은 95%이며 대부분 알파1산 당단백질(α1-acid glycoprotein)과 결합한다. 3) 생체변환: 이 약은 in vitro에서 다양한 CYP 효소에 의해 대사되는데, 주로 CYP3A4가 관여하며 CYP2C19 및 플라빈 함유 모노옥시게나제 (Flavin-containing monooxygenase, FMO)도 관여한다. 방사능으로 표지한 이 약을 경구 투여한 후 전신 순환혈에 주로 분포한다(혈장 방사능의 약 80%). 혈장에서 모성분과 관련한 총 노출의 10% 이상을 차지하는 대사체는 없었다. 4) 제거: 방사능으로 표지된 약의 단회 투여 후, 일차적으로 대사를 통해 제거되며, 방사능의 약 77%가 대변으로 배설되고, 약 5% 만이 소변으로 배설된다. 대사되지 않은 모성분은 주로 배설물에 포함되어 있으며, 평균적으로 투여용량의 23%가 대변에, 3% 가 소변에 존재한다. 이 약은 골수섬유증환자에서 유효반감기 41시간, 최종반감기 114시간, 겉보기 청소율 13 L/hr (변동계수51%)을 보이며, 2상 배치라는 약동학적 특징을 가지고 있다. 5) 특정 집단에 대한 투여: · 연령, 체중, 성별 및 인종: 452명의 환자로부터 축적된 데이터의 인구 약동학적 분석에서 연령 (65-74세 170명, 75-84세 54명, 85세 이상 4명), 체중 (40-135kg), 성별 (남성 249명, 여성 203명) 및 인종 (백인 399명, 흑인 7명, 아시아인 44명 및 기타 2명)은 이 약의 약동학에 유의미한 임상적 영향을 미치지 않았다. · 신장애 환자: 이 약을 300mg의 용량으로 단회 투여했을 때, 중등증의 신장애 환자(Cockcroft Gault 크레아티닌 청소율 30-89mL/min)에서 AUC_{inf}가 정상 신기능을 가진 환자 (Cockcroft Gault 크레아티닌 청소율 90mL/min이상)에 대비 1.5배 증가하였고 중증의 신장애 (Cockcroft Gault 크레아티닌 청소율 15-29 mL/min) 환자에서는 1.9배 증가하였다. 452명의 환자로부터 축적된 데이터의 인구 약동학적 분석에서 경증의 신장애(Cockcroft Gault 크레아티닌 청소율 60 mL/min이상, 90 mL/min미만)는 이 약의 약동학에 유의미한 임상적 효과를 보이지 않았다. · 간장애 환자: 정상 간 기능을 가진 환자과 경증의 간 장애 (Chilid-Pugh 등급A)를 가진 환자에서 이 약 300mg용량 단회 투여의 안전성과 약동학을 평가하였다. 정상 간 기능을 가진 환자와 비교하였을 때, 경증의 간 장애는 이 약의 약동학에 유의미한 임상적 효과를 보이지 않았다. 452명의 환자로부터 축적된 데이터의 인구 약동학적 분석에서 경증의 간장애 (115명, 총 빌리루빈 ≤ ULN 및 AST > ULN, 또는 총빌리루빈이 ULN의 1-1.5배 및 모든 AST 증가) 또는 중등증의 간장애 (17명, 총빌리루빈이 ULN의 1.5-3배 초과 및 모든 AST 증가)는 이 약의 약동학에 유의미한 임상적 효과를 보이지 않았다. 중증의 간장애 환자 (Child Pugh 등급 C)에서 이 약의 약동학은 평가되지 않았다. 12.4 비임상 안전성 데이터: 안전성 약리시험, 반복투여독성시험, 유전독성시험, 생식발생독성시험 및 발암성 시험을 실시하였다. 이 약은 유전독성을 나타내지 않았으며 형질전환 마우스 모델(Tg.rasH2 transgenic mouse model)을 대상으로 한 6개월 간의 시험에서 발암성을 나타내지 않았다. 임상적 투여와 관련된 용량에서 이 약은 위장관 및 뇌의 티아민 수송체를 억제하지 않는 것이 비임상시험에서 입증되었다. 마우스, 랫트 및 비글견을 대상으로 한 9개월 간의 반복투여 독성 시험에서 골수 형성 부전, 담관 비대, 괴사 및 증식, 림프 위축/고갈, 신세뇨관 퇴화/괴사, 위장관염, 골격근 및 심근의 퇴화/괴사, 폐의 조직구성 침윤, 폐렴 및/또는 농양을 포함한 면역억제의 증가와 같은 주요 독성이 관찰되었다. 반복투여 독성시험에서 달성한 최대 혈장 노출은 사망을 포함한 유의한 독성과 관련이 있었으며, 최대 권장용량인 400mg을 투여한 환자에서의 내성 혈장 노출보다 낮았는데, 이는 인간이 이 약의 독성에 비임상 시험에 사용한 종들보다 덜 민감하다는 것을 의미한다. 독성학 연구에 사용된 종에서 임상적으로 관련이 있는 노출이 이루어지지 않았으므로 이러한 시험들은 임상 관련 안전성 데이터를 생성하는 데 있어 제한적이다. 1) 수태능 및 초기 배아 발달: 이 약은 수컷 또는 암컷 랫트의 발정주기 매개 변수, 교배능, 수태능, 임신률 또는 생식 매개 변수에 영향을 미치지 않았다. 노출 (AUC)은 1 일 400mg의 권장용량 기준 임상 노출의 약 0.10 - 0.13 배였다. 반복 투여 독성 연구에서, 인간 임상적 노출과 거의 동일한 노출 수준에서 이 약은 수컷 개에서 무정자증, 정자감소증 및 정관 변형을 일으켰다. 2) 배태자 발달: 기관 형성 기간 (임신 6-17 일) 동안 임신한 랫트에게 투여했을 때, 이 약은 착상 후 손실, 태아 체중 감소, 골격 변이를 포함한 배태자의 독성과 관련이 있었다. 이러한 영향은 인간의 권장 복용량인 1일 400mg에서 임상 노출의 약 0.1 배에서 발생하였다. 토끼에서 이 약은 평가된 최고 용량 수준에서 발생 독성을 일으키지 않았다(인간 1일 권장 용량 기준 임상 노출의 약 0.08 배). **[사용기한]** 제조일로부터 24개월 **[저장방법]** 기밀용기, 실온보관(1-30℃) **[포장단위]** 120캡슐/병 **[수입자]** (유)한국비엠에스제약 서울특별시 강남구 테헤란로 504 12층(대치동, 해성1빌딩) Tel. 02-3404-1300 **[제조의뢰자]** Bristol-Myers Squibb Pharma EEIG, 아일랜드 Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867 **[제조자]** Celgene International Sarl, 스위스 Route de Perreux 1, 2017 Boudry **[개정연월일]** 2022.04.27 ※ 의사 또는 약사의 지시에 따라 사용하십시오. ※ 본 의약품은 엄격한 품질관리를 필한 제품입니다. 만약 구입시 유효기한 또는 사용기한이 경과되었거나 변질, 변패 또는 오염되었거나 손상된 의약품은 구입한 병원/약국을 통하여 교환해 드립니다. ※ 부작용 발생 시 한국의약품안전관리원(https://karp.drugsafe.or.kr, 1644-6223)에 의약품 부작용 피해구제 신청을 하실 수 있습니다. ※ 이 첨부문서의 개정년월일 이후 변경된 내용은 식품의약품안전처 의약품통합정보시스템 의약품 안전나라(https://nedrug.mfds.go.kr)에서 확인하실 수 있습니다. ※ 의약품 용어 설명 및 기타 자세한 문의는 02)3404-1300으로 연락하십시오.

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Reference 1. NCCN Clinical Practice Guidelines in Oncology, Multiple Myeloma. Version 3.2023

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[효능 · 효과] 1) 새롭게 진단된 조혈모세포이식이 적합하지 않은 다발골수종 환자에 대한 보르테조밉, 멜팔란 및 프레드니솔론과 병용요법 2) 새롭게 진단된 조혈모세포이식이 적합한 다발골수종 환자에 대한 보르테조밉, 탈리도마이드 및 덱사메타손과의 병용요법 3) 새롭게 진단된 조혈모세포이식이 적합하지 않은 다발골수종 환자 또는 이전에 한 가지 이상의 치료를 받은 다발골수종 환자에서 레날리도마이드 및 덱사메타손과의 병용요법 4) 이전에 한 가지 이상의 치료를 받은 다발골수종 환자에서 보르테조밉 및 덱사메타손과의 병용요법 5) 프로테아좀억제제와 면역조절제를 포함하여 적어도 세 가지 치료를 받은 경우로서, 재발 또는 불응성 다발골수종의 치료 [용법 · 용량] 이 약은 주입관련반응이 나타났을 시 응급 장비에 즉각적인 접근과 적절한 의료 지원을 할 수 있는, 자격을 갖춘 전문의료인에 의해 투여되어야 한다. [모니터링] 환자는 이 약을 주입하기 전/후에 주입관련반응에 대해 면밀히 모니터링 되어야 한다. [투여방법] 주입 전/후 약물을 투여해야하며, 만일 주입관련반응이 나타나는 경우 적절한 의료처치를 행해야 한다. 1. 전 처치: 주입관련반응의 위험을 줄이기 위하여 다음의 약을 매번 주입하기 약 1~3시간 전에 모든 환자에게 투여한다. 1) 코르티코스테로이드 (장시간 또는 중간시간 작용형) 단독요법 시: 첫 번째 및 두 번째 투여 전, 메틸프레드니솔론 100 mg 또는 이와 동등한 용량을 정맥 투여한다. 세 번째 투여부터 용량을 감량할 수 있다. (경구 또는 정맥주사 메틸프레드니솔론 60 mg) 병용요법 시: 덱사메타손 20mg(또는 이와 동등한)을 이 약을 투여하기 전 매번 투여한다. 덱사메타손이 기저요법으로의 코르티코스테로이드인 경우, 이 약의 투여일에는 덱사메타손 치료 용량이 전 처치 약물을 대신한다. 이 약 첫 번째 투여 시에는 투여 전 덱사메타손을 정맥 주사하고, 이후부터는 이 약 투여 전 경구 투여를 고려할 수 있다. 환자가 전 처치 약물로 덱사메타손을 투여받은 경우, 추가적인 기저요법으로의 코르티코스테로이드(예, 프레드니솔론)는 이 약 투여일에 투여해서는 안 된다. 2) 해열제 (경구 아세트아미노펜 650 – 1,000 mg) 3) 항히스타민제 (경구 또는 정맥투여 디펜히드라민 25 – 50 mg 또는 이와 동등한 약물) 2. 이 약의 투여 만 18세 이상의 성인에 대한 이 약의 권장용량은 16 mg/kg이며 스케줄에 따라 정맥 주입한다. 1) 새로 진단된 다발골수종: 조혈모세포이식이 적합하지 않은 환자에 대한 보르테조밉, 멜팔란, 프레드니솔론과 병용 요법 시 투여일정 (6주 사이클) 1주에서 6주까지 1주 간격 투여 (총 6회), 7주에서 54주까지 3주 간격 투여 (총 16회), 55주부터 질병 진행 전까지 4주 간격 투여. 병용약물의 투여: 보르테조밉은 제1주기(6주) 피하주사로 체표면적 당 1.3mg/m2 용량으로 1, 2, 4, 5주차에 주 2회 투여(8회 투여), 제2~9주기: 1, 2, 4, 5 주차에 주 1회 투여한다.(각 주기당 4회 투여). 멜팔란은 9mg/m2 용량으로, 프레드니솔론은 60mg/m2 용량으로 9주기(1 치료주기 당 각 6주) 동안 각각 1~4일차에 경구 투여한다(제1~9주기). 조혈모세포이식이 적합한 환자에 대한 보르테조밉, 탈리도마이드, 덱사메타손과 병용요법 시 투여일정 (4주 사이클) [유도요법] 1주에서 8주까지 1주 간격 투여 (총 8회), 9주에서 16주까지 2주 간격 투여 (총 4회) [공고요법] 1주에서 8주까지 2주 간격 투여 (총 4회) 병용약물의 투여: 보르테조밉은 체표면적 당 1.3mg/m2 용량으로 2주 동안 주 2회(1, 4, 8, 11일) 투여하는 28일(4주)을 한 주기로 하여 유도요법(제1~4주기)과, 제 4주기 이후 조혈모세포이식에 이어 두 주기의 공고요법(제5~6주기)을 반복한다. 탈리도마이드는 보르테조밉을 투여하는 6주기 동안 100mg 1일 1회 경구 투여한다. 덱사메타손은 경구 또는 정맥투여로서 제1~2주기의 1,2,8,9,15,16,22,23 일에 40mg을 투여하고, 제3~4주기의 1,2 일에는 40mg, 그 이후 투약일(8, 9, 15, 16일)에는 20mg을 투여한다. 제5~6주기에는 1, 2, 8, 9, 15, 16일에 덱사메타손 20mg을 투여한다. 조혈모세포이식이 적합하지 않은 환자에 대한 레날리도마이드/덱사메타손과의 병용요법 (4주 사이클): 재발/불응성 레날리도마이드/덱사메타손 병용요법과 동일 2) 재발/불응성 다발골수종: 단독요법 및 레날리도마이드/덱사메타손과의 병용요법 (4주 사이클) 1주에서 8주까지 1주 간격 투여 (총 8회), 9주에서 24주까지 2주 간격 투여 (총 8회), 25주부터 질병 진행 전까지 4주 간격 투여. 병용약물의 투여 레날리도마이드는 28일(4주)을 1 치료주기로 하여 반복 투여하며, 1일~21일까지 25mg 1일 1회 경구 투여하고, 덱사메타손은 40mg/주(75세 초과 혹은 BMI 18.5 미만의 경우 20mg/주로 감량)로 경구투여 또는 정맥투여한다. 보르테조밉/덱사메타손과의 병용요법 (3주 사이클) 1주에서 9주까지 1주 간격 투여 (총 9회), 10주에서 24주까지 3주 간격 투여 (총 5회), 25주부터 질병 진행 전까지 4주 간격 투여. 보르테조밉은 체표면적 당 1.3mg/m2 용량으로 2주 동안 주 2회(1, 4, 8, 11일) 투여하는 21일(3주)을 한 주기로 하여 총 8번의 주기를 반복한다. 덱사메타손은 보르테조밉을 투여하는 8주기 동안 1, 2, 4, 5, 8, 9, 11, 12일에 20mg씩 경구 투여하거나(보르테조밉 1 치료주기(3주) 중 2주 간 80mg/주), 75세 초과, BMI 18.5 미만, 당뇨가 잘 조절되지 않거나 이전에 스테로이드 요법에 내약성이 낮았던 경우 20mg/주로 감량하여 투여한다. 3. 주입 후 약물 지연된 주입관련반응의 위험을 줄이기 위하여 주입 후 약물을 다음과 같이 투여한다. 단독요법 시 매번 이 약을 투여한 이후 2일 동안(주입후 다음 날 부터 시작) 경구 코르티코스테로이드(메틸프레드니솔론 20 mg 또는 이와 동등한 용량의 중간 시간 또는 장시간 작용형 코르티코스테로이드)를 투여한다. 병용요법 시 이 약 투여 다음 날 저용량 경구 메틸프레드니솔론(20mg 이하의 용량) 또는 이와 동등한 약물 투여를 고려한다. 그러나 기저 요법(background regimen)으로 코르티코스테로이드(예, 덱사메타손, 프레드니솔론)를 이 약 투여 다음 날 투여할 경우, 추가적인 주입 후 약물은 필요하지 않을 수 있다. [사용상의 주의사항] 1. 다음 환자에는 투여하지 말 것: 이 약 또는 이 약의 구성성분에 중증의 과민반응 이력이 있는 환자 2. 다음 환자에는 신중히 투여할 것. 1) 이전에 이 약에 대한 주입관련반응 이력이 있는 환자 2) 기저요법으로 인해 유도된 호중구감소증이 있는 환자 3) 기저요법으로 인해 유도된 혈소판감소증이 있는 환자 [수입판매원] ㈜한국얀센 ※ 다잘렉스®에 대한 자세한 정보는 한국얀센 홈페이지(www.janssen.com/korea)의 제품 허가사항 전문을 참고하여 주시기 바랍니다.

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