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BLOOD RESEARCH

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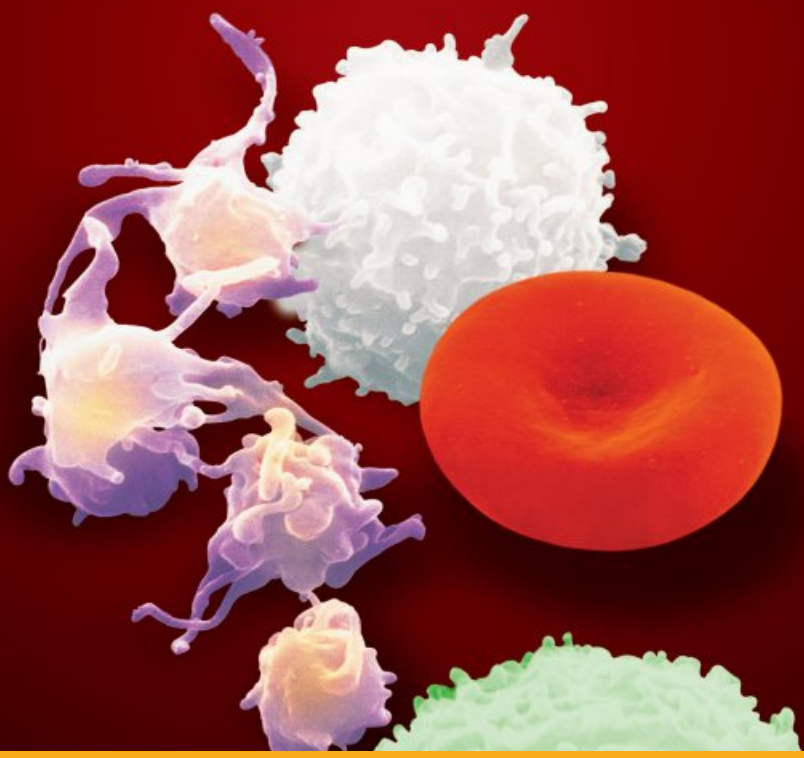
2021 Korean Society of Hematology
International Conference
& 62nd Annual Meeting

Date : April 1(Thu.) - 3(Sat.), 2021
Venue : Virtual



The Korean Society of Hematology

iCKSH 2021

2021 KOREAN SOCIETY OF HEMATOLOGY INTERNATIONAL CONFERENCE & 62nd ANNUAL MEETING

APRIL 1 - 3, 2021 VIRTUAL

ABSTRACT BOOK

BLOOD RESEARCH
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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, 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.

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Open Access Policy

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WELCOME MESSAGE

Dear Colleagues,

On behalf of the Organizing Committee, it is a great honor and privilege to welcome you to the 2021 Korean Society of Hematology (KSH) International Conference & 62nd Annual Meeting, hosted by KSH, from April 1 to 3, 2021.

As our first virtual conference, ICKSH 2021 will provide a unique opportunity to learn about the most recent findings and research from renowned experts and offer an occasion to exchange experiences and information with colleagues for the continued success and progress of our field.

ICKSH 2021 will include not only various scientific programs such as plenary lectures, scientific and education sessions, and several satellite symposiums with specialists on numerous hematology-related topics, but also exciting events for participants like ICKSH Points, SNS Hashtag Event, E-Booth Stamp Tour, and more.

We appreciate your interest in our first virtual conference and hope to see you in person in 2022 in a safe environment.

Kyung-Ha Ryu, MD., Ph.D.
Congress Chair
The Korean Society of Hematology

Je-Hwan Lee, MD., Ph.D.
President
The Korean Society of Hematology

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PROGRAM AT A GLANCE Thursday, April 1

Time	ROOM 1	ROOM 2	ROOM 3
08:00-09:00	Registration		
08:50-09:00	Opening Remark		
09:00-10:30	**SS01** **Acute Lymphoblastic Leukemia**	**SS02** **B-Cell Lymphoma**	**ES01** **Myelodysplastic Syndrome**
	Contemporary Treatment of Pediatric Ph+ ALL (Kirk Schultz, Canada)	Diffuse Large B cell Lymphoma: At the Intersection of Genetics and Epigenetics (Laura Pasqualucci, USA)	Myelodysplastic Syndrome and Overlap Syndrome (Yoon Hwan Chang, Korea)
	Current Treatment Approaches to Newly Diagnosed Adult ALL (Daniel Joseph DeAngelo, USA)	Immunotherapy for Hodgkin Lymphoma (John Kuruvilla, Canada)	MDS with Genetic Predisposition (Meerim Park, Korea)
	Results of High Risk and Novel Subtypes of Pediatric ALL in Japan (Katsuyoshi Koh, Japan)	Optimal Treatment of High-Risk Aggressive B-Cell Lymphoma (Lorenz Trümper, Germany)	Diagnosis and Treatment of Chronic Myelomonocytic Leukemia (Jihyun Kwon, Korea)
10:30-11:15	**PL01** **Cutting Edge of Emerging Therapies**		
	Clonal Hematopoiesis and the Origins of Hematologic Malignancies (Benjamin Ebert, USA)		
11:15-11:30	Break		
11:30-12:10	[Satellite] **SY01** astellas	[Satellite] **SY02** SANOFI GENZYME	[Satellite] **SY03** Celgene | Bristol Myers Squibb Company
	New Treatment Options for FLT3 mutated AML (Alexander Edward Perl, USA)	Latest Treatment for Hemophilia A and B in Japan (Keiji Nogami, Japan)	Optimal Treatment with IMiDs in Newly Diagnosed Multiple Myeloma (Pieter Sonneveld, The Netherlands)

PROGRAM AT A GLANCE Thursday, April 1

Time	ROOM 1	ROOM 2	ROOM 3
12:10-12:55	E-poster Exhibition		
12:55-14:25	**AS01** **Recent Therapeutic Approaches in CML** (12:55-13:55)	**JS01** **KAI-KSH Joint Symposium**	**SS03** **Advances in Technology**
	From Korean Perspective (Young Rok Do, Korea)	Regulating Regulatory T Cells for Enhancement of Cancer Immunotherapy (Sang-Jun Ha, Korea)	Mutational Landscape in Clonal Hematopoiesis of Indeterminate Potential (Elli Papaemmanuil, USA)
	Impact of Socio-demographic Co-variates on Disease Prognosis, TKI Use and Outcomes on Patients with CML (Qian Jiang, China)	IL-17-Producing Cells in Tumor (Yeon Seok Chung, Korea)	Intelligent Image-Activated Cell Sorting: Principles and Application to Hematology (Akihiro Isozaki, Japan)
	From Japanese Perspective (Shinya Kimura, Japan)	Pro-Inflammatory Cytokines in Graft-Versus-Host Disease (GVHD) (Young-Woo Jeon, Korea)	HARMONY: A Big Data for Better Outcomes Project in Hematological Malignancies (Jesús María Hernández Rivas, Spain)
		Harnessing Adaptive Natural Killer Cells for Immunotherapy in Multiple Myeloma (Hyunsoo Cho, Korea)	
14:25-14:40	Break		

PROGRAM AT A GLANCE Thursday, April 1

Time	ROOM 1	ROOM 2	ROOM 3
14:40--16:10	**AS02** **Updates of Hematologic Disease in Asian Population** (14:40-15:40)	**JS02** **KOGO-KSH Joint Symposium** - Genomics for Precision Hematology -	**SS04** **Stem Cell: Biology and Therapeutic Target**
	Management of TDT and NTDT Thalassemia in Indonesia (Tubagus Djumhana Atmakusuma, Indonesia)	Single Cell RNA Sequencing Reveals Transcriptional Programs Associated with Myeloma Progression (Hae-Ock Lee, Korea)	Discovery of New Regulators in Stem Cells and Malignancies (Dongjun Lee, Korea)
	Hemophilia Treatment in Singapore (Tien Sim Leng, Singapore)	Multi-Omics Analysis and Modeling of DNA Methylation in Cancer (Sun Kim, Korea)	AMD1 Is Essentially Required in Leukemic Stem Cells (Hyog Young Kwon, Korea)
	Thalassemia Treatment in Malaysia (Jameela Sathar, Malaysia)	Clinical Application of Next-Generation Sequencing in Acute Myeloid Leukemia (Jae-Sook Ahn, Korea)	BCL-2 as a Stem Cell Target in AML (Daniel A. Pollyea, USA)
		Challenges in the Introduction of Next-Generation Sequencing for Diagnostics of Hematologic Malignancies (Seung-Tae Lee, Korea)	
16:10-16:25	Break		

PROGRAM AT A GLANCE Thursday, April 1

Time	ROOM 1	ROOM 2	ROOM 3
16:25-17:55	**JS03** **EHA-KSH Joint Symposium 1** - Basic - (16:25-18:05)	**SS05** **Multiple Myeloma**	**ES02** **Rare Hematologic Disorders**
	Clonal Evolution under IDH Inhibitor Therapy in AML (Lynn Quek, UK)	Novel Strategies to Overcome Relapsed/Refractory Multiple Myeloma (Suzanne Trudel, Canada)	Molecular Diagnosis of Thalassemia (Jee-Soo Lee, Korea)
	Predicting Drug Sensitivity for Personalized Therapy of AML (Kimmo Porkka, Finland)	MRD Negativity - The Foremost Important Goal of Myeloma Treatment? (Bruno Paiva, Spain)	Current Understanding and Treatment Strategies of Langerhans Cell Histiocytosis (Kyung-Nam Koh, Korea)
	TET Loss-of-Function in Malignant Hematopoiesis (Myunggon Ko, Korea)	Light chain Amyloidosis (Kihyun Kim, Korea)	Pathogenesis and Treatment Overview on Secondary Hemophagocytic Lymphohistiocytosis (Yu Ri Kim, Korea)
	Novel Small Molecule Drug Discovery to Override NRAS-Mutated AML (Taebo Sim, Korea)		

PROGRAM AT A GLANCE Friday, April 2

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
08:00-09:00	Registration			
09:00--10:30	**JS04** **ASH-KSH Joint Symposium** - ALL -	**SS06** **Thrombotic Issues in Hematology**	**ES03** **Lymphoma** - Novel Diagnosis and Management of B-cell Lymphoma -	
	Epigenetic Control in T-ALL (Marjorie Brand, Canada)	Direct Oral Anticoagulants for the Treatment of VTE in Cancer Patients (Marc Carrier, Canada)	B-Cell Lymphoma's New Genomics (Youngil Koh, Korea)	
	CAR T cells for Leukemia: What Is Next? (Renier J Brentjens, USA)	Immune Mediated TTP (iTTP): Differential Diagnosis, Treatment, and Follow Up (Spero Cataland, USA)	Immuno-Oncology for B-Cell Lymphomas (Yoon Seok Choi, Korea)	
	Current Concepts in the Management of Relapsed/Refractory ALL in Korea (Joon-ho Moon, Korea)	Post-Transplant Thrombotic Microangiopathy (Vahid Afshar-Kharghan, USA)	Novel Combination Immunochemotherapy beyond CD20 for B-cell Lymphoma (Jun Ho Yi, Korea)	
	Pediatric Acute Lymphoblastic Leukemia in Korea (Hyoung Jin Kang, Korea)			
10:30-11:15	**PL02** **Clinical Hematology Lecture**			
	Genetic Landscape of Lymphoma and Novel Treatment Approaches (Wyndham Hopkins Wilson, USA)			
11:15-11:30	Break			

PROGRAM AT A GLANCE Friday, April 2

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
11:30-12:10	[Satellite] **SY04** HANDOK	[Satellite] **SY05** Roche	[Satellite] **SY06** AMGEN	[Satellite] **SY07** janssen
	Ravulizumab: Next Generation of C5 Inhibitor for Standard Care of PNH (Jin Seok Kim, Korea)	Treatment of Relapsed/ Refractory DLBCL: Role of Polatuzumab Vedotin (Laurie H. Sehn, Canada)	Treatment Strategies in Relapsed Multiple Myeloma: A Focus on Sequential Treatment for Survival Benefit (Joseph Mikhael, USA)	First-line Treatment of CLL in 2021 (Philip A. Thompson, USA)
12:10-12:40	E-poster Exhibition			
12:40-13:40	**OP01** Acute Leukemia	**OP02** Laboratory Hematology	**OP03** Lymphoma and MM	**OP04** Benign Hematology (Anemia, Thrombocytopenia)
13:40-13:55	Break			
13:55-14:40	Presidential Symposium Evolution in Acute Leukemia Diagnosis and Its Place on Treatment– Lessons from T-ALL to AML (Elizabeth Macintyre, France)			

PROGRAM AT A GLANCE Friday, April 2

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
14:40-16:10	**MS01** **MOU Country Session** - Lymphoid Malignancy - (14:40-15:40)	**SS07** **Benign Hematology**	**ES04** **Myeloproliferative Neoplasm**	
	Outcome of Autologous Transplant in T-Cell Lymphoma: Experience of NIHBT in Vietnam (Nguyen Vu Bao Anh, Vietnam)	Novel Treatment for Immune Thrombocytopenia (ITP) (Cindy Neunert, USA)	The Role of Interferon in MPNs (Seug Yun Yoon, Korea)	
	Subcutaneous Panniculitis-like T-Cell Lymphoma (Udomsak Bunworasate, Thailand)	Recent Understandings of Congenital Neutropenia (Hyoung Soo Choi, Korea)	Allogeneic Hematopoietic Cell Transplantation for Treatment of Myelofibrosis Patients in JAK Inhibitor Era (Sung-Yong Kim, Korea)	
	Update of Extranodal NK/T-cell Lymphoma: Treatment and Biology (Seok Jin Kim, Korea)	Non-Factor Approach including Emicizumab (Keiji Nogami, Japan)	To Modify the Disease Course of MPNs (Sung-Eun Lee, Korea)	
16:10-16:25	Break			

PROGRAM AT A GLANCE Friday, April 2

Time	ROOM 1	ROOM 2	ROOM 3	ROOM 4
16:25-17:55	**JS05** **EHA-KSH Joint Symposium 2** - Clinical-Translational - (16:25-18:05)	**SS08** **Supportive Care**	**SS09** **Bone Marrow Failure Syndrome**	
	Immunotherapy in AML: From alloSCT towards CAR-T Cell Therapy (Charles Craddock, UK)	Improving Palliative Care and Outcomes in Low- and Middle-Income Countries (Scott Howard, USA)	Challenges in the Diagnosis of Bone Marrow Failure Syndromes: The Role of Genetic Panels? (Ghulam J Mufti, UK)	
	The Emerging Role of MRD in AML (Gert Ossenkoppele, The Netherlands)	Renal Supportive Care and Palliative Care in Patients with Hematologic Diseases (Chung Hee Baek, Korea)	Clonal Hematopoesis in Bone Marrow Failure (Austin G Kulasekararaj, UK)	
	Therapeutic Potential of ATO to Overcome Resistance of Bcl-2 Inhibitor in AML (Ji Eun Jang, Korea)	Vaccinations before/after Biologic Agents in Patients with Hematologic Malignancies (Wan Beom Park, Korea)	Current Guidelines for the Treatment of Acquired Aplastic Anemia in Japan: An Immune Marker-Based Approach (Shinji Nakao, Japan)	
	MRD in AML (Byung Sik Cho, Korea)			

PROGRAM AT A GLANCE Saturday, April 3

Time	ROOM 1	ROOM 2	ROOM 3
07:30-08:30	Business Meeting		
08:30-09:00	Working Party Reports		
09:00-10:30	**SS10** **Immunotherapy/ Transplantation**	**SS11** **Pediatric Disease**	**SS12** **T-Cell Lymphoma/HD**
	$CD8^+$ TILs Differentiate into TEMRA via a Bifurcated Trajectory, Deciphering Immunogenicity of Tumor Antigen (Jae-Ho Cho, Korea)	Juvenile Myelomonocytic Leukemia: Learning from Children in a World without Walls (Mignon Loh, USA)	PD1/PDL1 in ENKTL (Won Seog Kim, Korea)
	Immunosenescence in Pediatric Patients with Haploidentical HSCT from Parental Donors (Won-Woo Lee, Korea)	Sirolimus Therapy for Vascular Anomaly (Keon Hee Yoo, Korea)	Novel Therapies for T-cell Lymphoma (Francine Foss, USA)
	CAR-T Cells for AML: Lessons from the Clinic (Saar Gill, USA)	Langerhans Cell Histiocytosis 2021: New Insights and Opportunities (Carl Allen, USA)	Translational Research in Angioimmunoblastic T-Cell Lymphoma: From Genome to Bedside (Sakata-Yanagimoto Mamiko, Japan)
10:30-11:15	**PL03** **Genomics in Hematologic Malignancies**		
	Latest Treatment Developments in Multiple Myeloma (Nikhil Munshi, USA)		
11:15-11:30	Break		

PROGRAM AT A GLANCE Saturday, April 3

Time	ROOM 1	ROOM 2	ROOM 3
11:30-12:10	[Satellite] **SY08** NOVARTIS	[Satellite] **SY09** KYOWA KIRIN	[Satellite] **SY10** Takeda
	Updated ASH ITP Guidelines and Their Implications on Clinical Practice (Waleed Ghanima, Norway)	The Role of Myeloid Growth Factors (MGFs) in Patients with Lymphoma: Benefits, Risks, & Unmet issues (Yong Park, Korea)	Real-World Outcomes and Factors Impacting Treatment Choice in Relapsed/Refractory Multiple Myeloma: Special Focus on Ixazomib-Rd (Ji Hyun Lee, Korea)
12:10-12:55	Award Ceremony & Closing		

VIRTUAL CONFERENCE INFORMATION

VIRTUAL CONFERENCE WEBSITE

http://virtual.icksh.org

REGISTRATION

Please log in using the ID and PW you used to pre-register on the ICKSH 2021 website. If you missed pre-registration, you may also conveniently register on-site.

» On-Site Registration Days
April 1-3, 2021

» On-Site Registration Fees
- Overseas

Category	On-Site Registration Fees
General	USD 50
Resident / Trainee / Nurse / Student	USD 25

- Domestic

Category	On-Site Registration Fees	Note
KSH Member	KRW 50,000	Free for KSH members 65 years or above
Fellow / Nurse / Researcher	KRW 30,000	-
Student / Resident	KRW 20,000	-
Non-Member	KRW 150,000	-

* Please note that simultaneous, duplicate logins with the same ID will not be possible.

SESSION STREAMING

All presentation files will be received in advance and streamed at a designated time (Korea standard time). After the pre-recorded files have been streamed, speakers and chairs will have real-time Q&A.
Participants can watch VOD lectures for free for one month after the conference. VOD lectures are limited to lectures with consent for distribution.

SATELLITE SYMPOSIA

Come and learn the latest information and knowledge!
This is an event in which e-coupons will be awarded to those who complete viewing at least 30 minutes of the satellite symposium hosted by each of our sponsors over the three-day period! Don't miss this great opportunity!

DATE	ROOM 1	ROOM 2	ROOM 3	ROOM 4
APRIL 1, 2021 (11:30 - 12:10)	astellas	SANOFI GENZYME	Celgene | Bristol Myers Squibb Company	
APRIL 2, 2021 (11:30 - 12:10)	HANDOK	Roche	AMGEN	janssen
APRIL 3, 2021 (11:30 - 12:10)	NOVARTIS	KYOWA KIRIN	Takeda	

VIRTUAL CONFERENCE INFORMATION

E-POSTERS

All participants can view the E-Posters in the E-Poster section of the ICKSH2021 virtual conference website. Participants will have an opportunity to win the Lucky Draw after viewing more than 100 of the presented posters.

VIRTUAL EXHIBITION HALL

Meet our sponsors virtually. If you visit more than 12 booths, gold level or higher, gifts will be given.

ICKSH 2021 SECRETARIAT OFFICE

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VIRTUAL CONFERENCE INFORMATION

CME CREDIT INFORMATION (DOMESTIC PARTICIPANTS ONLY)

For online education, annual evaluation will be allowed for a limited time until June 30, 2021. Please mark your attendance record by pressing the enter/exit button for each session.

1) CME Credit Rating: By the Korean Medical Association

Category	April 1st	April 2nd	April 3rd	Remarks
KMA CME Credit	6	6	3	-
KAIM CME Credit		2		During the conference period

2) Confirming Attendance: Only attendance times that include the enter/exit time for each session will be counted.
(It is necessary to mark attendance every day to receive Daily CME credits.)

3) Method: After entering and exiting the session, please click the "Enter" and "Exit" buttons to record your attendance time. The entry/exit records for each session are required for the credit to be recognized.
* Attendance confirmation is not possible when exiting from the browser (PC internet window) [Close].
* When moving between rooms, you must click the "Exit" button, and click the "Enter" button in the new room.

4) Grade recognition criteria for online training attendance confirmation

Credits accrued per hour of attendance per day	
Residence time	Recognition of Credit
From 1 hour or more to less than 2 hours	1 credit
From 2 hours or more to less than 3 hours	2 credit
From 3 hours or more to less than 4 hours	3 credit
From 4 hours or more to less than 5 hours	4 credit
From 5 hours or more to less than 6 hours	5 credit
From 6 hours or more	6 credit

** It is not possible to claim credits after omission, so please be aware of the contents in advance.
** Real-time attendance records can be checked on the Virtual Conference site during the conference period, but the final score cannot be confirmed because breaks and other times are included.

EVENTS

We have exciting events for participants. Participants who complete the mission will win a prize! Feeling Lucky? Go Register Now!

ICKSH POINTS

Earn points and win prizes! Gifts will be given when you reach 300P per day (200P on Saturday) ! You can check your accumulated points on My Page of the virtual conference homepage.

Action	Points
Enter the Platform (Log in)	100P/day
Submit the Congress Survey	50P
Attend an Oral Session	100P
Attend a Session (Except Satellite, Oral)	50P/session
Attend the Closing Ceremony	50P
Ask a question through the Q&A window (When chosen)	10P/each

PRIZES

Daily Gifts

Domestic

APRIL 1st

Tumbler

APRIL 2nd

Headset

APRIL 3rd

Vitamin C

* Those who obtain points on all 3 days can change the prize to a hand cream set or webcam. Contact the secretariat and we will be glad to help you exchange your prize.

Overseas

USD 20 DISCOUNT COUPON OFF ICKSH 2022 REGISTRATION FEES

* Coupons will be issued every day for 3 days as points are accumulated. Coupon use is limited to ICKSH 2022 and is neither refundable nor transferable.

EVENTS

EARLY BIRD PARTICIPANTS

Attend the first session and get an e-Gift card!
- Event Period: April 1st to 3rd, 09:00~10:30 (KST)
- Daily Event: It is required to watch at least 30 minutes of the lecture.

PRIZES

For Korean participants and those living in Korea, KRW 10,000 Starbucks eGift cards will be given for the prize.

For others, USD 10 Amazon eGift cards will be given for the prize.

E-POSTER LUCKY DRAW

View more than 100 of the e-Posters and get the chance to be a winner!
- Event Period: April 1st to 3rd (KST)
  Eligibility to win the Lucky Draw is awarded after viewing more than 100 e-Posters.
  The Lucky Draw will take place at the Closing Ceremony (April 3rd, 12:10~12:55, KST).

PRIZES

For Korean participants and those living in Korea, the following gifts will be given for prizes.

For others, an Amazon eGift card in the amount of the product will be provided.

#ICKSH 2021

Upload your Instagram with the #ICKSH2021 hashtag and get one e-Coupon!
- Event Period: Until April 3rd 23:59(KST)
  To receive the prize, please take a screenshot of your post and send it to the Secretariat by e-mail: icksh@icksh.org

PRIZES

For Korean participants and those living in Korea, KRW 10,000 Starbucks eGift cards will be given for the prize.

For others, USD 10 Amazon eGift cards will be given for the prize.

EVENTS

E-BOOTH STAMP TOUR

If you visit more than 12 booths, gold level or higher, gifts will be given.

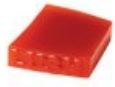
- Event Period: April 1st to 3rd (KST)
  Diamond and Platinum booths are all required. The data from each booth must be downloaded. (New data must be downloaded daily.)

PRIZES

APRIL 1st

Umbrella

APRIL 2nd



Soap

APRIL 3rd

Hand Sanitizer

* For overseas participants, USD 10 Amazon eGift cards will be given for the prize.

ATTEND SATELLITE SYMPOSIA

Attend the Satellite Symposia and get an e-Gift card!

- Event Period: April 1st to 3rd, 11:30~12:10 (KST)
- Daily Event: It is required to watch at least 30 minutes of the lecture.

PRIZES

For Korean participants and those living in Korea, KRW 10,000 Shinsegae Department Store Gift Certificates will be given for the prize.

For others, USD 10 Amazon eGift cards will be given for the prize.

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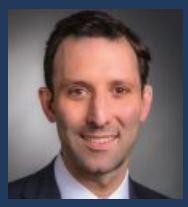
KEY SPEAKERS

APRIL 1 (Thursday)



[PL01] Plenary Lecture 01
10:30 - 11:15 | Room 1

Clonal Hematopoiesis and the Origins of Hematologic Malignancies

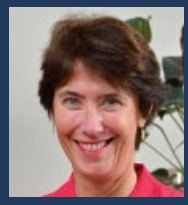
Benjamin Ebert
Dana-Farber Cancer Institute, USA

APRIL 2 (Friday)

[PL02] Plenary Lecture 02
10:30-11:15 | Room 1

Genetic Landscape of Lymphoma and Novel Treatment Approaches

Wyndham Hopkins Wilson
National Cancer Institute, USA

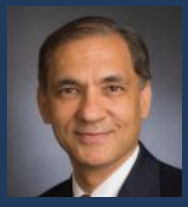


[PS01] Presidential Symposium
13:55-14:40 | Room 1

Evolution in Acute Leukemia Diagnosis and Its Place on Treatment– Lessons from T-ALL to AML

Elizabeth Macintyre
The Hôpital Necker-Enfants Malades, France

APRIL 3 (Saturday)



[PL03] Plenary Lecture 03
10:30-11:15 | Room 1

Latest Treatment Developments in Multiple Myeloma

Nikhil Munshi
Dana-Farber Cancer Institute, USA

DAILY PROGRAM

DAILY PROGRAM Thursday, April 1

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

09:00-10:30 **[SS01] Acute Lymphoblastic Leukemia** Room 1

Chairs Hyoung Soo Choi (Seoul National University College of Medicine, Korea)
Young Rok Do (Keimyung University School of Medicine, Korea)

SS01-1 Contemporary treatment of pediatric Ph+ ALL
Kirk Schultz (Pediatrics University of British Columbia, Canada)

SS01-2 Current treatment approaches to newly diagnosed adult ALL
Daniel Joseph DeAngelo (Dana Farber Cancer Institute, USA)

SS01-3 Results of high risk and novel subtypes of pediatric ALL in Japan
Katsuyoshi Koh (Saitama Children's Medical Center, Japan)

09:00-10:30 **[SS02] B-Cell Lymphoma** Room 2

Chairs Hyeon-Seok Eom (National Cancer Center, Korea)
Ho-Jin Shin (Pusan National University School of Medicine, Korea)

SS02-1 Diffuse large B cell lymphoma: At the intersection of genetics and epigenetics
Laura Pasqualucci (Columbia University, USA)

SS02-2 Immunotherapy for Hodgkin lymphoma
John Kuruvilla (University of Toronto, Canada)

SS02-3 Optimal treatment of high-risk aggressive B-cell lymphoma
Lorenz Trümper (Georg August University of Gottingen, Germany)

09:00-10:30 **[ES01] Myelodysplastic Syndrome** Room 3

Chairs Yoon Hwan Chang (Seoul National University College of Medicine, Korea)
Yoo-Jin Kim (College of Medicine, The Catholic University of Korea, Korea)

ES01-1 Myelodysplastic syndrome and overlap syndrome
Yoon Hwan Chang (Seoul National University College of Medicine, Korea)

ES01-2 MDS with genetic predisposition
Meerim Park (National Cancer Center, Korea)

ES01-3 Diagnosis and treatment of chronic myelomonocytic leukemia
Jihyun Kwon (Chungbuk National University College of Medicine, Korea)

10:30-11:15 **[PL01] Cutting Edge of Emerging Therapies** Room 1

Chair Je-Hwan Lee (University of Ulsan College of Medicine, Korea)

Clonal hematopoiesis and the origins of hematologic malignancies
Benjamin Ebert (Dana-Farber Cancer Institute, USA)

DAILY PROGRAM Thursday, April 1

11:15-11:30 Break

11:30-12:10 **[SY01] Astellas** Room 1

Chair June-Won Cheong (Yonsei University College of Medicine, Korea)

New treatment options for FLT3 mutated AML
Alexander Edward Perl (University of Pennsylvania, USA)

11:30-12:10 **[SY02] Sanofi-Aventis** Room 2

Chair Soon Ki Kim (Inha University Hospital, Korea)

Latest treatment for hemophilia A and B in Japan
Keiji Nogami (Nara Medical University, Japan)

11:30-12:10 **[SY03] BMS-Celgene** Room 3

Chair Kihyun Kim (Sungkyunkwan University School of Medicine, Korea)

Optimal treatment with IMiDs in newly diagnosed multiple myeloma
Pieter Sonneveld (Erasmus MC Cancer Institute, The Netherlands)

12:10-12:55 **E-poster Exhibition**

12:55-13:55 **[AS01] Recent Therapeutic Approaches in CML** Room 1

Chairs Dong-Wook Kim (College of Medicine, The Catholic University of Korea, Korea)
Hawk Kim (Gachon University College of Medicine, Korea)

AS01-1 From Korean perspective
Young Rok Do (Keimyung University School of Medicine, Korea)

AS01-2 Impact of socio-demographic co-variates on disease prognosis, TKI use and outcomes on patients with CML
Qian Jiang (Peking University People's Hospital, China)

AS01-3 From Japanese perspective
Shinya Kimura (Saga University, Japan)

DAILY PROGRAM Thursday, April 1

12:55-14:25 **[JS01] KAI-KSH Joint Symposium** Room 2

Chairs Eui-Cheol Shin (Korea Advanced Institute of Science and Technology (KAIST), Korea)
Duck Cho (Sungkyunkwan University School of Medicine, Korea)

JS01-1 Regulating regulatory T cells for enhancement of cancer immunotherapy
Sang-Jun Ha (Yonsei University, Korea)

JS01-2 IL-17-producing cells in tumor
Yeon Seok Chung (Seoul National University, Korea)

JS01-3 Pro-inflammatory cytokines in Graft-Versus-Host Disease (GVHD)
Young-Woo Jeon (College of Medicine, The Catholic University of Korea, Korea)

JS01-4 Harnessing adaptive natural killer cells for immunotherapy in multiple myeloma
Hyunsoo Cho (Yonsei University College of Medicine, Korea)

12:55-14:25 **[SS03] Advances in Technology** Room 3

Chairs Seongsoo Jang (University of Ulsan College of Medicine, Korea)
Jaewoo Song (Yonsei University College of Medicine, Korea)

SS03-1 Mutational landscape in clonal hematopoiesis of indeterminate potential
Elli Papaemmanuil (Memorial Sloan Kettering Cancer Center, USA)

SS03-2 Intelligent image-activated cell sorting: Principles and application to hematology
Akihiro Isozaki (University of Tokyo, Japan)

SS03-3 HARMONY: A big data for better outcomes project in hematological malignancies
Jesús María Hernández Rivas (University of Salamanca, Spain)

14:25-14:40 Break

14:40-15:40 **[AS02] Updates of Hematologic Disease in Asian Population** Room 1

Chairs Hye Lim Jung (Sungkyunkwan University School of Medicine, Korea)
Nack Gyun Chung (College of Medicine, The Catholic University of Korea, Korea)

AS02-1 Management of TDT and NTDT thalassemia in Indonesia
Tubagus Djumhana Atmakusuma (Cipto Mangunkusumo National Hospital, Indonesia)

AS02-2 Hemophilia treatment in Singapore
Tien Sim Leng (Singapore General Hospital, Singapore)

AS02-3 Thalassemia treatment in Malaysia
Jameela Sathar (Ampang Hospital, Malaysia)

DAILY PROGRAM Thursday, April 1

14:40-16:10 **[JS02] KOGO-KSH Joint Symposium: Genomics for Precision Hematology** Room 2

Chairs Sun Kim (Seoul National University, Korea)
Keon Hee Yoo (Sungkyunkwan University School of Medicine, Korea)

JS02-1 Single cell RNA sequencing reveals transcriptional programs associated with myeloma progression
Hae-Ock Lee (The Catholic University of Korea, Korea)

JS02-2 Multi-omics analysis and modeling of DNA methylation in cancer
Sun Kim (Seoul National University, Korea)

JS02-3 Clinical application of next-generation sequencing in acute myeloid leukemia
Jae-Sook Ahn (Chonnam National University Medical School, Korea)

JS02-4 Challenges in the introduction of next-generation sequencing for diagnostics of hematologic malignancies
Seung-Tae Lee (Yonsei University College of Medicine, Korea)

14:40-16:10 **[SS04] Stem Cell: Biology and Therapeutic Target** Room 3

Chairs Deog-Yeon Jo (Chungnam National University College of Medicine , Korea)
Myung Geun Shin (Chonnam National University Medical School, Korea)

SS04-1 Discovery of new regulators in stem cells and malignancies
Dongjun Lee (Pusan National University School of Medicine, Korea)

SS04-2 AMD1 is essentially required in leukemic stem cells
Hyog Young Kwon (Soonchunhyang University, Korea)

SS04-3 BCL-2 as a stem cell target in AML
Daniel A. Pollyea (University of Colorado School of Medicine, USA)

16:10-16:25 Break

16:25-18:05 **[JS03] EHA-KSH Joint Symposium 1: Basic** Room 1

Chairs John Gribben (Barts Cancer Institute, UK)
Je-Hwan Lee (University of Ulsan College of Medicine, Korea)

JS03-1 Clonal evolution under IDH inhibitor therapy in AML
Lynn Quek (King's College London, UK)

JS03-2 Predicting drug sensitivity for personalized therapy of AML
Kimmo Porkka (Helsinki University Hospital Comprehensive Cancer Center, Finland)

JS03-3 TET loss-of-function in malignant hematopoiesis
Myunggon Ko (Ulsan National Institute of Science and Technology (UNIST), Korea)

JS03-4 Novel small molecule drug discovery to override NRAS-mutated AML
Taebo Sim (Yonsei University College of Medicine, Korea)

DAILY PROGRAM Thursday, April 1

16:25-17:55 **[SS05] Multiple Myeloma** Room 2

Chairs Jin Seok Kim (Yonsei University College of Medicine, Korea)
Myungshin Kim (College of Medicine, The Catholic University of Korea, Korea)

SS05-1 Novel strategies to overcome relapsed/refractory multiple myeloma
Suzanne Trudel (University of Toronto, Canada)

SS05-2 MRD negativity - The foremost important goal of myeloma treatment?
Bruno Paiva (University of Navarra, Spain)

SS05-3 Light chain amyloidosis
Kihyun Kim (Sungkyunkwan University School of Medicine, Korea)

16:25-17:55 **[ES02] Rare Hematologic Disorders** Room 3

Chairs Eun Sun Yoo (Ewha Womans University College of Medicine, Korea)
Young Kyung Lee (Hallym University College of Medicine, Korea)

ES02-1 Molecular diagnosis of thalassemia
Jee-Soo Lee (Seoul National University College of Medicine, Korea)

ES02-2 Current understanding and treatment strategies of Langerhans cell histiocytosis
Kyung-Nam Koh (University of Ulsan College of Medicine, Korea)

ES02-3 Pathogenesis and treatment overview on secondary hemophagocytic lymphohistiocytosis
Yu Ri Kim (Yonsei University College of Medicine, Korea)

DAILY PROGRAM Friday, April 2

09:00-10:30 **[JS04] ASH-KSH Joint Symposium: ALL** Room 1

Chairs Alison Loren (Raymond and Ruth Perelman School of Medicine University of Pennsylvania, USA)
Hyoung Jin Kang (Seoul National University College of Medicine, Korea)

JS04-1 Epigenetic control in T-ALL
Marjorie Brand (Ottawa Hospital Research Institute, Canada)

JS04-2 CAR T cells for leukemia: What is next?
Renier J Brentjens (Memorial Sloan Kettering Cancer Center, USA)

JS04-3 Current concepts in the management of relapsed/refractory ALL in Korea
Joon-ho Moon (Kyungpook National University School of Medicine, Korea)

JS04-4 Pediatric acute lymphoblastic leukemia in Korea
Hyoung Jin Kang (Seoul National University College of Medicine, Korea)

09:00-10:30 **[SS06] Thrombotic Issues in Hematology** Room 2

Chairs Sung-Hyun Kim (Dong-A University College of Medicine, Korea)
Sung Hwa Bae (Daegu Catholic University School of Medicine, Korea)

SS06-1 Direct oral anticoagulants for the treatment of VTE in cancer patients
Marc Carrier (University of Ottawa, Canada)

SS06-2 Immune mediated TTP (iTTP): Differential diagnosis, treatment, and follow up
Spero Cataland (Ohio State University, USA)

SS06-3 Post-transplant thrombotic microangiopathy
Vahid Afshar-Kharghan (The University of Texas MD Anderson Cancer Center, USA)

09:00-10:30 **[ES03] Lymphoma: Novel Diagnosis and Management of B-cell Lymphoma** Room 3

Chairs Yeung-Chul Mun (Ewha Womans University School of Medicine, Korea)
Won Sik Lee (Inje University College of Medicine, Korea)

ES03-1 B-cell lymphoma's new genomics
Youngil Koh (Seoul National University College of Medicine, Korea)

ES03-2 Immuno-oncology for B-cell lymphomas
Yoon Seok Choi (Ajou University School of Medicine, Korea)

ES03-3 Novel combination immunochemotherapy beyond CD20 for B-cell lymphoma
Jun Ho Yi (Chung-Ang University College of Medicine, Korea)

10:30-11:15 **[PL02] Clinical Hematology Lecture** Room 1

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

Genetic landscape of lymphoma and novel treatment approaches
Wyndham Hopkins Wilson (National Cancer Institute, USA)

DAILY PROGRAM Friday, April 2

11:15-11:30 Break

11:30-12:10 **[SY04] Handok** Room 1

Chair Jong Wook Lee (College of Medicine, The Catholic University of Korea, Korea)

Ravulizumab: Next generation of C5 inhibitor for standard care of PNH
Jin Seok Kim (Yonsei University College of Medicine, Korea)

11:30-12:10 **[SY05] Roche** Room 2

Chair Won Seog Kim (Sungkyunkwan University School of Medicine, Korea)

Treatment of relapsed/refractory DLBCL: Role of polatuzumab vedotin
Laurie Sehn (BC Cancer Centre for Lymphoid Cancer, Canada)

11:30-12:10 **[SY06] Amgen** Room 3

Chair Chang-Ki Min (College of Medicine, The Catholic University of Korea, Korea)

Treatment strategies in relapsed multiple myeloma: A focus on sequential treatment for survival benefit
Joseph Mikhael (Translational Genomics Research Institute (TGen), USA)

11:30-12:10 **[SY07] Janssen** Room 4

Chair Deok Hwan Yang (Chonnam National University Medical School, Korea)

First-line treatment of CLL in 2021
Philip A. Thompson (The University of Texas MD Anderson Cancer Center, USA)

12:10-12:40 **E-poster Exhibition**

DAILY PROGRAM Friday, April 2

12:40-13:40 **[OP01] Acute Leukemia** Room 1

Chairs Byung-Soo Kim (Korea University College of Medicine, Korea)
Jae Wook Lee (College of Medicine, The Catholic University of Korea, Korea)

OP01-1 **Physical and psychological impairments as practical frailty markers and/or survival predictors in elderly AML fit for intensive chemotherapy**
Gi June Min (Seoul St. Mary's Hospital, Korea)

OP01-2 **Allogeneic hematopoietic stem cell transplantation can overcome the adverse prognosis of secondary-Type mutation positive acute myeloid leukemia**
Ga-Young Song (Chonnam National University Hwasun Hospital, Korea)

OP01-3 **Epigenetic analysis reveals MiR-128-2-5p and MiR-378c as possible novel biomarkers for detection of relapse B-cell acute lymphoblastic leukemia**
Prateek Bhatia (Postgraduate Institute of Medical Education & Research, India)

OP01-4 **Measurable residual disease assessment, T cell antigen stability and survival among immunophenotypic sub-categories of T-lineage acute lymphoblastic leukemia patients**
Karthik Bommannan (Cancer Institute (W.I.A.), India)

OP01-5 **PTCy-based haploidentical vs matched unrelated donor transplantation using myeloablative targeted busulfan-based conditioning for pediatric acute leukemia**
Kyung Taek Hong (Seoul National University College of Medicine, Korea)

12:40-13:40 **[OP02] Laboratory Hematology** Room 2

Chairs Hyun Kyung Kim (Seoul National University College of Medicine, Korea)
Young-Uk Cho (University of Ulsan College of Medicine, Korea)

OP02-1 **Similar survival and genetic features between clonal cytopenia of undetermined significance and lower-risk myelodysplastic syndrome**
Eun-Ji Choi (University of Ulsan College of Medicine, Korea)

OP02-2 **Clinical performance evaluation of an optical mapping technique for detection of structural variation in hematologic malignancies**
Yeeun Shim (Yonsei University College of Medicine, Korea)

OP02-3 **Single cell analysis and cytoplasmic-Ig FISH on double primary acute myeloid leukemia and plasma cell myeloma**
Dajeong Jeong (Seoul National University Hospital, Korea)

OP02-4 **Immunoglobulin gene rearrangement in Koreans with multiple myeloma: Clonality assessment and repertoire analysis using next-generation sequencing**
Miyoung Kim (Hallym University College of Medicine, Korea)

OP02-5 **Clinical performance of FISH analysis with FACS sorting system for detection of cytogenetic abnormalities in multiple myeloma**
Jihye Ha (Hanyang University College of Medicine, Korea)

DAILY PROGRAM Friday, April 2

12:40-13:40 **[OP03] Lymphoma and MM** Room 3

Chairs Cheolwon Suh (University of Ulsan College of Medicine, Korea)
Ho-Young Yhim (Jeonbuk National University Medical School, Korea)

OP03-1 Genetic profile of primary plasma cell leukemia in Korea: Comparison with plasma cell myeloma
Young Eun Lee (Seoul National University College of Medicine, Korea)

OP03-2 CARTITUDE-1: Phase 1b/2 study of ciltacabtagene autoleucel in relapsed/refractory multiple myeloma
Deepu Madduri (Mount Sinai Medical Center, USA)

OP03-3 Expanded natural killer cells augment anti-myeloma effects of daratumumab, bortezomib, and dexamethasone in a human multiple myeloma xenograft model
Jaya Lakshmi (Chonnam National University, Korea)

OP03-4 Impact of primary prophylaxis with pegfilgrastim for febrile neutropenia receiving rituximab plus fludarabine and cyclophosphamide treatment in patients with chronic lymphocytic leukemia: A multicenter, prospective study
Youngwoo Jeon (College of Medicine, The Catholic University of Korea, Korea)

OP03-5 Mosunetuzumab shows promising efficacy in patients with multiply relapsed follicular lymphoma: Updated clinical experience from a phase I dose-escalation trial
Won Seog Kim (Sungkyunkwan University School of Medicine, Korea)

12:40-13:40 **[OP04] Benign Hematology (Anemia, Thrombocytopenia)** Room 4

Chairs Chul Won Choi (Korea University Guro Hospital, Korea)
Dong-Yeop Shin (Seoul National University College of Medicine, Korea)

OP04-2 Iptacopan effectively controls intra- and extravascular hemolysis and leads to durable hemoglobin increase in patients with treatment-naive PNH
Jun Ho Jang (Sungkyunkwan University School of Medicine, Korea)

OP04-3 Developmental megakaryocytopoiesis: A study on novel role of clinically significant MicroRNA in understanding neonatal thrombocytopenia
Ravi Kumar Gutti (University of Hyderabad, Telangana, India)

OP04-4 Deficiency of immature B-cell tolerance by V(D)J rearrangement causes aberrant accumulation of autoantibodies in immune thrombocytopenia
Zi Sheng (Qilu Hospital, Shandong University, China)

OP04-5 Hematopoietic cell transplantation in patients with non-malignant disease
Sung Han Kang (University of Ulsan College of Medicine, Korea)

13:40-13:55 Break

13:55-14:40 **[PS01] Presidential Symposium** Room 1

Chair Kyung-Ha Ryu (Ewha Womans University School of Medicine, Korea)

Evolution in acute leukemia diagnosis and its place on treatment– Lessons from T-ALL to AML
Elizabeth Macintyre (The Hôpital Necker-Enfants Malades, France)

DAILY PROGRAM Friday, April 2

14:40-15:40 **[MS01] MOU Country Session: Lymphoid Malignancy** Room 1

Chairs Jae-Yong Kwak (Jeonbuk National University Medical School, Korea)
Ki-Seong Eom (College of Medicine, The Catholic University of Korea, Korea)

MS01-1 Outcome of autologous transplant in T-cell lymphoma: Experience of NIHBT in Vietnam
Nguyen Vu Bao Anh (Hanoi Medical University, Vietnam)

MS01-2 Subcutaneous panniculitis-like T-cell lymphoma
Udomsak Bunworasate (King Chulalongkorn Memorial Hospital, Thailand)

MS01-3 Update of extranodal NK/T-cell lymphoma: Treatment and biology
Seok Jin Kim (Sungkyunkwan University School of Medicine, Korea)

14:40-16:10 **[SS07] Benign Hematology** Room 2

Chairs Chuhl Joo Lyu (Yonsei University College of Medicine, Korea)
Soo-Mee Bang (Seoul National University College of Medicine, Korea)

SS07-1 Novel treatment for immune thrombocytopenia (ITP)
Cindy Neunert (Columbia University Medical Center, USA)

SS07-2 Recent understandings of congenital neutropenia
Hyoung Soo Choi (Seoul National University College of Medicine, Korea)

SS07-3 Non-factor approach including emicizumab
Keiji Nogami (Nara Medical University, Japan)

14:40-16:10 **[ES04] Myeloproliferative Neoplasm** Room 3

Chairs Chul Won Jung (Sungkyunkwan University School of Medicine, Korea)
Hyo Jung Kim (Hallym University College of Medicine, Korea)

ES04-1 The role of interferon in MPNs
Seug Yun Yoon (Soonchunhyang University College of Medicine, Korea)

ES04-2 Allogeneic hematopoietic cell transplantation for treatment of myelofibrosis patients in JAK inhibitor era
Sung-Yong Kim (Konkuk University School of Medicine, Korea)

ES04-3 To modify the disease course of MPNs
Sung-Eun Lee (College of Medicine, The Catholic University of Korea, Korea)

16:10-16:25 Break

DAILY PROGRAM Friday, April 2

16:25-18:05 **[JS05] EHA-KSH Joint Symposium 2: Clinical-Translational** Room 1

Chairs Elizabeth Macintyre (The Hôpital Necker-Enfants Malades, France)
Hee-Je Kim (College of Medicine, The Catholic University of Korea, Korea)

JS05-1 Immunotherapy in AML: From alloSCT towards CAR-T cell therapy
Charles Craddock (University of Birmingham, UK)

JS05-2 The emerging role of MRD in AML
Gert Ossenkoppele (Amsterdam University Medical Center, The Netherlands)

JS05-3 Therapeutic potential of ATO to overcome resistance of Bcl-2 inhibitor in AML
Ji Eun Jang (Yonsei University College of Medicine, Korea)

JS05-4 MRD in AML
Byung Sik Cho (College of Medicine, The Catholic University of Korea, Korea)

16:25-17:55 **[SS08] Supportive Care** Room 2

Chairs Seong Kyu Park (Soonchunhyang University Bucheon Hospital, Korea)
Inho Kim (Seoul National University Hospital, Korea)

SS08-1 Improving palliative care and outcomes in low- and middle-income countries
Scott Howard (University of Tennessee Health Science Center, USA)

SS08-2 Renal supportive care and palliative care in patients with hematologic diseases
Chung Hee Baek (University of Ulsan College of Medicine, Korea)

SS08-3 Vaccinations before/after biologic agents in patients with hematologic malignancies
Wan Beom Park (Seoul National University College of Medicine, Korea)

16:25-17:55 **[SS09] Bone Marrow Failure Syndrome** Room 3

Chairs Jin-Yeong Han (Dong-A University College of Medicine, Korea)
Hoon Kook (Chonnam National University Medical School, Korea)

SS09-1 Challenges in the diagnosis of bone marrow failure syndromes: The role of genetic panels?
Ghulam J Mufti (King's College Hospital, UK)

SS09-2 Clonal hematopoesis in bone marrow failure
Austin G Kulasekararaj (King's College Hospital, UK)

SS09-3 Current guidelines for the treatment of acquired aplastic anemia in Japan: An immune marker-based approach
Shinji Nakao (Kanazawa University, Japan)

DAILY PROGRAM Saturday April 3

07:30-08:30 **Business Meeting** Room 1

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

09:00-10:30 **[SS10] Immunotherapy/Transplantation** Room 1

Chairs Jong Ho Won (Soonchunhyang University College of Medicine, Korea)
Ho Joon Im (University of Ulsan College of Medicine, Korea)

SS10-1 $CD8^+$ TILs differentiate into TEMRA via a bifurcated trajectory, deciphering immunogenicity of tumor antigen
Jae-Ho Cho (Chonnam National University Medical School, Korea)

SS10-2 Immunosenescence in pediatric patients with haploidentical HSCT from parental donors
Won-Woo Lee (Seoul National University College of Medicine, Korea)

SS10-3 CAR-T cells for AML: Lessons from the clinic
Saar Gill (University of Pennsylvania, USA)

09:00-10:30 **[SS11] Pediatric Disease** Room 2

Chairs Young-Ho Lee (Hanyang University College of Medicine, Korea)
Jun Eun Park (Korea University Anam Hospital, Korea)

SS11-1 Juvenile myelomonocytic leukemia: Learning from children in a world without walls
Mignon Loh (University of California, Benioff Children's Hospital, USA)

SS11-2 Sirolimus therapy for vascular anomaly
Keon Hee Yoo (Sungkyunkwan University School of Medicine, Korea)

SS11-3 Langerhans cell histiocytosis 2021: New insights and opportunities
Carl Allen (Baylor College of Medicine, USA)

09:00-10:30 **[SS12] T-Cell Lymphoma/HD** Room 3

Chairs Seok-Goo Cho (College of Medicine, The Catholic University of Korea, Korea)
Sukjoong Oh (Sungkyunkwan University School of Medicine, Korea)

SS12-1 PD1/PDL1 in ENKTL
Won Seog Kim (Sungkyunkwan University School of Medicine, Korea)

SS12-2 Novel therapies for T-cell lymphoma
Francine Foss (Yale University School of Medicine, USA)

SS12-3 Translational research in angioimmunoblastic T-cell lymphoma: From genome to bedside
Sakata-Yanagimoto Mamiko (University of Tsukuba, Japan)

DAILY PROGRAM Saturday April 3

10:30-11:15 **[PL03] Genomics in Hematologic Malignancies** Room 1

Chair Jae Hoon Lee (Division of Hematology, Gachon University Gil Medical Center, Korea)

Latest treatment developments in multiple myeloma
Nikhil Munshi (Dana-Farber Cancer Institute, USA)

11:15-11:30 Break

11:30-12:10 **[SY08] Novartis** NOVARTIS Room 1

Chair Jun Ho Jang (Sungkyunkwan University School of Medicine, Korea)

Updated ASH ITP guidelines and their implications on clinical practice
Waleed Ghanima (Østfold Hospital, University of Oslo, Norway)

11:30-12:10 **[SY09] Kyowa Kirin** KYOWA KIRIN Room 2

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

The role of Myeloid Growth Factors (MGFs) in patients with lymphoma: Benefits, risks, & unmet issues
Yong Park (Korea University College of Medicine, Korea)

11:30-12:10 **[SY10] Takeda** Takeda Room 3

Chair Je-Jung Lee (Chonnam National University Medical School, Korea)

Real-world outcomes and factors impacting treatment choice in relapsed/refractory multiple myeloma: Special focus on Ixazomib-Rd
Ji Hyun Lee (Dong-A University College of Medicine, Korea)

12:10-12:55 **Award Ceremony & Closing** Room 1

POSTER LIST

POSTER LIST

BP01 **Outcomes in gilteritinib-treated patients with FLT3-mutated relapsed or refractory acute myeloid leukemia who underwent transplantation**

Yoshinobu Maeda[1*], Naoko Hosono[2], Hisayuki Yokoyama[3], Masahiro Onozawa[4], Shigeru Chiba[5], Yoshinobu Kanda[6], Alexander E Perl[7], Nahla Hasabou[8], Qiaoyang Lu[8], Ramon Tiu[8], Mikiko Kusano[9] and Ja Min Byun[10]

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[2]*Department of Transfusion Medicine, University of Fukui, Fukui, Japan*
[3]*Department of Hematology and Rheumatology, Tohoku University Graduate School of Medicine, Sendai, Japan*
[4]*Department of Hematology, Hokkaido University, Hokkaido, Japan*
[5]*Department of Hematology, University of Tsukuba, Tsukuba, Japan*
[6]*Division of Hematology, Jichi Medical University Saitama Medical Center, Saitama, Japan*
[7]*Division of Hematology/Oncology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA*
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BP02 **Transcriptional landscape profiling of cytogenetically normal acute myeloid leukaemia by high throughput deep sequencing technology**

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BP03 **Differential effects of donor lymphocyte infusion upon treatment response and GVHD according to relapse level and donor sources in patients with myelodysplastic syndrome**

Silvia Park[1], Tong Yoon Kim[1], Jong Hyuk Lee[1], Joon yeop Lee[1], Gi June Min[1], Sung Soo Park[1], Seung-Ah Yahng[2], Young-Woo Jeon[3], Seung-Hwan Shin[4], Jae-Ho Yoon[1], Sung-Eun Lee[1], Byung Sik Cho[1], Ki-Seong Eom[1], Seok Lee1, Hee-Je Kim[1], Chang-Ki Min[1], Seok-Goo Cho[1], Jong Wook Lee[1] and Yoo-Jin Kim[1*]

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BP04 **CXCR2 as a novel target for overcoming resistance to tyrosine kinase inhibitors in chronic myeloid leukemia cells**

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BP05 **SIRT1 regulates SKP2-mediated P27 ubiquitination and degradation in NOTCH induced T-ALL**

Fangce Wang[1], Zheng Li[1] and Aibin Liang[1*]

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BP06 **Development of novel anti-CD19 CAR T cells resistant to immune checkpoint for phase I/II study in patients with relapsed of refractory B cell lymphoma**

Young-Ho Lee[1,2], Hyeong Ji Lee[1,2], Hyung Cheol Kim[2], Yujean Lee[1], Su Kyung Nam[1], Cedric Hupperetz[1], Jennifer SY Ma[3], Xinxin Wang[3], Oded Singer[3], Won Seog Kim[4], Seok Jin Kim[4], Youngil Koh[5], Inkyung Jung[1] and Chan Hyuk Kim[1*]

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BP07 **Comprehensive clinical and molecular features analysis of follicular peripheral T-cell lymphoma and nodal peripheral T-cell lymphoma with T follicular helper phenotype compared to angioimmunoblastic T cell lymphoma and peripheral T-cell lymphoma-NOS**

Sang Eun Yoon[1], Junhun Cho[2], Young Hyeh Ko[2], Yeon Jeong Kim[3], Woong-Yang Park[3], Seok Jin Kim1 and Won Seog Kim[1*]

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BP08 **Immune checkpoint-related gene polymorphisms are associated with sensitivity and treatment response of primary immune thrombocytopenia**

Shuwen Wang
Department of Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, China

BP09 **TINF2 mutations are associated with poor outcome post hematopoietic stem cell transplantation for dyskeratosis congenita**

Yeon Jung Lim[1,2], Yigal Dror[2*], Omri A Arbiv[2], Melanie E Kalbfleisch[2], Mohammed Al Nuaimi[6], MacGregor Steele[3], Geoff Cuvelier[4], Tal Schechter-Finkelstein[5], Bozana Zlateska[2] and Michaela Cada[2]
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BP10 **Two-stage genome-wide association studies of hemoglobin concentration in Taiwan Han Chinese**

Vanessa Joy Timoteo[1*], Kuang-Mao Chiang[2] and Wen-Harn Pan[2]
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PP01-01 **Next generation sequencing (NGS)-based interpretation of FLT3/NPM1 mutations in adult patients with acute myeloid leukemia (AML) in a single institution**

Tong Yoon Kim[1], Hee-Je Kim[1,2*], Jong Hyuk Lee[1], Joon yeop Lee[1], Gi June Min[1], Sung Soo Park[1], Silvia Park[1], Seung-Ah Yahng[3], Young-Woo Jeon[4], Seung-Hwan Shin[5], Jae-Ho Yoon[1], Sung-Eun Lee[1], Byung Sik Cho[1,2], Ki-Seong Eom[1,2], Yoo-Jin Kim[1,2], Seok Lee[1,2], Chang-Ki Min[1,2], Seok-Goo Cho[1,2] and Jong Wook Lee[1,2]

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PP01-02 **Impact of FLT3-ITD gene mutations in acute promyelocytic leukemia in Malaysia**

Siew Lian Chong

Department of Hematology, Hospital Ampang, Selangor, Malaysia

PP01-03 **Overexpression of prohibitn 2 mRNA and protein is associated with poor prognostic indicator in cytogenetically normal acute myeloid leukemia**

Young Eun Lee[1], Ha Jin Lim[2], Ju Heon Park[2], Hye Ran Kim[3], Min Gu Kang[4] and Myung Geun Shin[1,2*]

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PP01-04 **Frequency and characteristics of risk-stratified adult acute myeloid leukemia according to the NCCN guideline version 2.2021 revealing categorization uncertainty and candidate cases for germline testing**

Young-Uk Cho[1*], Hyunji Kim[1], Min-Sun Kim[1], Sang-Hyun Hwang[1], Seongsoo Jang[1], Chan-Jeoung Park[1], Eul-Ju Seo[1], Eun-Ji Choi[2], Je-Hwan Lee[2] and Kyoo-Hyung Lee[2]

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PP01-05 **Clinical efficacy of venetoclax combined chemotherapy for newly diagnosed and relapsed or refractory acute myeloid leukemia (AML): 1-year experience in catholic hematologic hospital**

Silvia Park[1], Tong Yoon Kim[1], Jong Hyuk Lee[1], Joon yeop Lee[1], Gi June Min[1], Sung Soo Park[1], Seung-Ah Yahng[2], Young-Woo Jeon[3], Seung-Hwan Shin[4], Jae-Ho Yoon[1], Sung-Eun Lee[1], Byung Sik Cho[1], Ki-Seong Eom[1], Seok Lee[1], Chang-Ki Min[1], Seok-Goo Cho[1], Jong Wook Lee[1], Yoo-Jin Kim[1] and Hee-Je Kim[1*]

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PP01-06 **Allelic burden of FLT3-ITD mutation matters in AML patients who received allogene hematopoietic stem cell transplantation**

Cheol Kyung Sin[1], Sang Eun Yoon[1*] and Chul Won Jung[1]

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PP01-07 **Clinical characteristics and prognostic impacts of mutations of RAS pathway-related genes in acute myeloid leukemia patients**

Yusook Jeong[3,4], Hee Sue Park[1,2], Bo Ra Son[1,2] and Jihyun Kwon[3,4*]

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PP01-08 **Treatment patterns and clinical outcomes in unfit AML patients receiving first-line systemic treatment or best supportive care: Korean sub-analysis**

Soo-Mee Bang[1], Ka-Won Kang[2], Ik-Chan Song[3], Alexander Delgado[4], Maria Belen Guijarro Garbayo[5], Cynthia Llamas[6], Yinghui Duan[6] and Je-Hwan Lee[7*]

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PP01-09 **Effect of delayed treatment in acute myeloid leukemia patients: Treatment delay matters in younger patients**
Daehun Kwag[1,2], Hee-Je Kim[1,2*], Byung-Sik Cho[1,2], Gi June Min[1,2], Sung-Soo Park[1,2], Silvia Park[1,2], Seung-Ah Yahng[3], Young-Woo Jeon[4], Seung-Hwan Shin[5], Jae-Ho Yoon[1,2], Sung-Eun Lee[1,2], Ki-Seong Eom[1,2], Yoo-Jin Kim[1,2], Seok Lee[1,2], Chang-Ki Min[1,2], Seok-Goo Cho[1], Dong-Wook Kim[1,2] and Jong Wook Lee[1]
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PP01-10 **A prospective randomized comparison of high-dose cytarabine and high-dose daunorubicin in the induction chemotherapy for acute myeloid leukemia**
Eun-Ji Choi[1], Jun-Hong Park[1], Han-Seung Park[1], Jung-Hee Lee[1], Kyoo-Hyung Lee[1], Young-Shin Lee[1], Young-Ah Kang[1], Mijin Jeon[1], Ji Min Woo[1], Hyeran Kang[1] and Je-Hwan Lee[1*]
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PP01-11 **Quality-adjusted time without symptoms of disease and toxicity analysis of CPX-351 Vs 7+3 in older adults with newly diagnosed high-risk/secondary AML**
Jorge E. Cortes[2], Janet Pong[3*], Robert J. Ryan[1], Stefan Faderl[4] and Tara L. Lin[5]
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PP01-12 **Children acute promyelocytic leukemia in the southern Vietnam: The 10 year experience**
Truc Phan[1*], Nghia Huynh[2,3] and Yi Hyeon Gyu[1,4]
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PP01-13 **Phospholipase C beta 2 protein overexpression is a favorable prognostic indicator in newly diagnosed normal karyotype acute myeloid leukemia**
Mi Suk Park[1], Young Eun Lee[2], Hye Ran Kim[3], Jong Hee Shin[4], Hyun Wook Cho[5], Jun Hyung Lee[4] and Myung Geun Shin[2,4*]
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PP01-14 **Real time PCR based quantitative evaluation of WT1 gene expression from diagnosis to end of induction in acute myeloid leukaemia**
Pranay Tanwar[1*], Dimpy Gupta[1], Ekta Rahul[1], Amar Ranjan[1], Anita Chopra[1] and Sameer Bakhshi[2]
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PP01-15 **Infectious complications of venetoclax-based chemotherapy in acute myeloid leukemia: Baseline for selecting proper antimicrobial prophylaxis**
Raeseok Lee[1], Sung-Yeon Cho[1], Dong-Gun Lee[1*], Sang Woon Bae[1], Silvia Park[2], Byung Sik Cho[2], Yoo-Jin Kim[2] and Hee-Je Kim[2]
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PP01-16 **The application of the updated 2016 WHO classification of AML in pediatric patient cohort: A single center study**
Won Kee Ahn[1], Seungmin Hahn[1], John Hoon Rim[2], Jin Ju Kim[2], Saeam Shin[2], Seung-Tae Lee[2], Jong Rak Choi[2], Jung Woo Han[1] and Chuhl Joo Lyu[1*]
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PP01-17 **Comparison of genetic mutations harbored by myeloid sarcoma and leukemic cells of the bone marrow in a patient treated with decitabine**
Hee Sue Park[1,2], Bo Ra Son[1,2], Seonggyu Byeon[3,4] and Jihyun Kwon[3,4*]
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PP01-18 **Incidence of differentiation syndrome (DS) and other complications in acute promyelocytic leukaemia (APML) – A single centre retrospective observational study**
Niket Mantri[1], Anand Kumar[1*], Poornima P[1], Mahesh Rajashekaraiah[1] and Sunil Udgire[1]
[1]*Hematology and Bone Marrow Transplant, Sparsh Hospital Banglore, India*

PP01-19 **Laboratory profile of acute myeloblastic leukemia promyelocytic type patients in Sardjito Hospital, Indonesia**
Adika Zhulhi Arjana[1], Usi Sukorini[1*], Tri Ratnaningsih[1] and Setyowati Setyowati[1]
[1]*Clinical Pathology and Laboratory Medicine, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Indonesia*

PP01-20 **Infection profile and outcomes of adult acute leukemia patients developing chemotherapy-associated febrile neutropenia**
Camille Ariadne Tanchanco[1*], Monica Pia Reyes-Montecillo[1], Angelina Mirasol[1] and Karl Evans Henson[1]
[1]*Internal Medicine, University of the Philippines - Philippine General Hospital, Philippines*

PP01-21 **Variantion and relationship of homo sapiens acute myeloid leukemia homo sapiens cDNA, mRNA sequence**
Ramlah Ramlah
Biology, Universitas Gadjah Mada, Indonesia

PP01-22 **Src family kinase inhibitor bosutinib and dasatinib enhances differentiation of acute promyelocytic leukemia cell line induced by combination of all-trans-retinoic acid**
Min-Young Lee[1], Hee-Jeong Cheong[2], Seug Yun Yoon[1], Kyoung-Ha Kim[1], Namsu Lee[1] and Jong-Ho Won[1*]
[1]*Department of Internal Medicine, Division of Hematology & Oncology, Soonchunhyang University College of Medicine, Korea*
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PP01-23 **Study of anti-leukemic activity of ethanolic extract of zingiber officinale in a leukemic rat model**
Rahul Kumar
Zoology, J K College, India

PP01-26 **Role of hydro-ethanol extract of citrullus colocynthis seed in benzene-induced toxicity of acute myeloid leukemia mice**
Gireesh Dayma
SLS, Manipal University, India

PP01-27 **Effect of madhuca longifolia on etoposide action in acute myeloid leukemia**
Minakshi Sarswati[1*] and Pooja Gupta[1]
[1]*Internal Medicine, Shakuntla Hospital and research center, India*

PP01-28 **Biological importance and therapeutic benefit of cirsimaritin against human leukemia cells: Medicinal importance through scientific data analysis**
Dinesh Kumar Patel[1*] and Kanika Patel[1]
[1]*Faculty of Health Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Payagraj, India*

PP01-29 **Biological potential of tricetin against acute myeloid leukemia: Therapeutic benefit in the medicine for their anticancer effect through scientific data analysis**
Dinesh Kumar Patel[1*] and Kanika Patel[1]
[1]*Faculty of Health Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Payagraj, India*

PP01-30 **Potency of MicroRNA (miR142, miR302, and miR503): Biomolecular therapy of acute myeloid leukemia cells proliferation by targeting cyclin-D1 pathway: Systematic literature review**
Han Yang
Internal Medicine, University of Sebelas Maret, Indonesia

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PP01-31 **Acute myeloid leukemia with RAM immunophenotype: Distinct or Hazy?**
Chandan Kumar[1], Garima Jain[1], Anita Chopra[1] and Amar Ranjan[1]
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PP01-32 **Impact of COVID-19 on the treatment of acute myeloid leukemia: A systematic review**
Ramlah Ramlah
Biology, Universitas Gadjah Mada, Indonesia

PP01-33 **Repeated and sustained remissions with decitabine therapy in an elderly male with acute myeloid leukemia**
Jeremiah Vallente[1] and Teresita Dumagay[1*]
[1]*Department of Medicine, University of the Philippines – Philippine General Hospital, Philippines*

PP01-34 **A rare case of acute promyelocytic leukemia with BCR-ABL1 rearrangement**
Yonggeun Cho[1], Miyoung Kim[1*], Boram Han[2] and Young Kyung Lee[1]
[1]*Department of Laboratory Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Korea*
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PP01-36 **Nonleukemic myeloid sarcoma involving the ileum, duodenum, lungs, mesentery, posterior cul-de-sac and multiple lymph node groups: A case report**
Jeremiah Vallente[1*], Teresita Dumagay[1] and Rogelio Jr. Velasco[1]
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PP01-37 **Analytical performance of the oncomine myeloid research assay testing for myeloid neoplasms**
A-Jin Lee[1], Sang-Gyung Kim[1] and Chang-Ho Jeon[1]
[1]*Department of Laboratory Medicine, Daegu Catholic University, Korea*

PP02-01 **Screening of dysplastic neutrophils using cell population data by automated hematology analyzer**
Hyunjung Kim[1], Eunhee Han[1], Hae Kyung Lee[1], Yonggoo Kim[1] and Kyungja Han[1*]
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PP02-02 **TET2 mutation and high miR-22 expression as biomarkers to predict clinical outcome in myelodysplastic syndrome patients treated with hypomethylating therapy**
Seong Kyu Park[1*], Young Sok Ji[1], Jina Yun[1], Se Hyung Kim[1], Chan Kyu Kim[1] and Jong Ho Won[1]
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PP02-03 **Molecular profile in adult myelodysplastic/myeloproliferative neoplasms highlighting diagnostic ambiguity in certain cases**
Hyunji Kim[1], Young-Uk Cho[1*], Sang-Hyun Hwang[1], Seongsoo Jang[1], Eul-Ju Seo[1] and Chan-Jeoung Park[1]
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PP03-01 **Germline and somatic mutations in Korean patients with ALL**
Sang-Yong Shin[1], Hyeonah Lee[2], Seung-Tae Lee[3], Jong Rak Choi[3], Chul Won Jung[4], Hong Hoe Koo[5] and Sun-Hee Kim[6*]
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PP03-02 **Spectrum of genetic mutations detected by next-generation sequencing in pediatric acute lymphoblastic leukemia**
Jae Wook Lee[1], Seongkoo Kim[1], Ari Ahn[2], Myungshin Kim[2], Yonggoo Kim[2], Pil-Sang Jang[1], Nack-Gyun Chung[1*] and Bin Cho[1]
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PP03-04 **Minimal residual disease status of patients with B-cell precursor acute lymphoblastic leukemia in South Korea**
Seok Lee[1*], Nack Gyun Chung[3], Myungshin Kim[2] and Jae-Ho Yoon[1]
[1]*Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea*
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PP03-05 **Prognosis of pediatric acute lymphoblastic leukemia treated by SCCLG-ALL 2016 protocol - A single institutional experience**
Huirong Mai[1*], Shilin Liu[1], Ximin Fang[1], Ying Wang[1], Changgang Li[1], Huiying Ye[1], Chunyan Wang[1], Feiqiu Wen[1] and Qi Li[1]
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PP03-06 **Clinicopathological and immunophenotypic profile of T-cell acute lymphoblastic leukaemia**
Priya Pai[1], Sushma Belurkar[1] and Sindhura Lakshmi Koulmane Laxminarayana[1]
[1]Department of Pathology, Kasturba Medical College, Manipal, MAHE, India

PP03-07 **Treatment response to targeted immunotherapy in adult ALL with isolated extramedullary relapse after previous allogeneic HCT**
Seung-Hwan Lee[2], Jae-Ho Yoon[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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PP03-08 **Strategies to prevent and manage complications of acute lymphoblastic leukaemia in young people in Bihar**
Rajeev Sinha
Department of Pharmacology, Agra College, India

PP03-09 **A case controlled study on digital dermatoglyphic patterns among children with acute lymphoblastic leukemia in Guyana**
Ameet Kumar Jha
Pre-clinical sciences, Texila American University, Guyana

PP03-10 **Wearble technology to assess the sleep quality of patients with acute lymphoblastic leukemia after treatment with chemotherapy**
Manvendra Singh
HMFA-MIET, AKTU, AKTU, India

PP03-11 **Methotrexate mitigates leukemia by targeting toll/NF-kB pathway in both in vivo and in vitro model systems**
Dushyant Gautam[1], Indira Paddibhatla[1] and Ravi Gutti[1*]
[1]Department of Biochemistry, University of Hyderabad, India

PP03-12 **Anti-leukemic effects of Ibrutinib on B-cell acute lymphoblastic leukemia cells**
Han-Seung Park[1], Eun-Hye Hur[1], Bon-Kwan Goo[1], Juhyun Moon[1] and Je-Hwan Lee[1*]
[1]Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Korea

PP03-13 **Anti-proliferative and apoptotic effect of zeaxanthin on different malignant cell lines**
Pardeep Kumar[1*] and Vinod Sharma[1]
[1]Applied Sciences, Shri Maha Maya Vaishnav Devi Mandir Research Institute, India

PP03-14 **Anti-leukemia effect of solid lipid nanoparticles of hesperidine against the benzene induced leukemia via regulation of growth factors and inflammatory mediators**
Prakash Bhatt
Biotechnology, Fermentis Biotech, India

PP03-15 **Anti-leukemic effect of ajwain oil against DMBA induced leukemic rat model: Possible mechanism of action**
Niti Singh[1*] and Deepika Singh[1]
[1]Information Technology, Continental Automotive LTD, BAngalore, India

PP03-17 **Association MTHFR gene polymorphisms in promotor-677C/T with risk for adult acute lymphoblastic leukemia in Asia population: An update metaanalysis**
Bastomy Eka Rezkita
Pathology Anatomy, Sebelas Maret University, Indonesia

PP03-18 **Factors related to quality of life of children with acute lymphoblastic leukemia who undergo chemotherapy**
Ramlah Ramlah
Biology, Universitas Gadjah Mada, Indonesia

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PP03-19 **Identification of acute lymphoblastic leukemia (ALL) cells in peripheral blood smear image based on morphology of white blood cells (WBC) with classification technique using support vector machine (SVM)**
Rifaldy Fajar[1*], Nana Indri Kurniastuti[1] and Prihantini Jupri[1]
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PP03-20 **Acute lymphoblastic leukemia with lytic lesions**
Namita Kumari[1], Amar Ranjan[2*], Ekta Rahul[2], Pranay Tanwar[2] and Harshita Dubey[2]
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PP03-21 **A case illustrating therapy-related acute lymphoblastic leukemia eventually progressed to therapy-related myelodysplastic syndrome with clonal branching evolution**
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PP03-22 **Mixed phenotype acute leukemia - A pathologist's nightmare**
Sushma Belurkar
Associate Professor, Pathology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India

PP04-01 **Pulmonary hypertension in newly diagnosed and tyrosine kinase inhibitor-treated chronic myelogneous leukemia patients: A single center retrospective analysis**
Ik-Chan Song[1], Sang-Hoon Yeon[1], Won-Hyoung Seo[1], Myung-Won Lee[1], Hyewon Ryu[1], Hyo-Jin Lee[1], Hwan-Jung Yun[1], Byung-Joo Sun[2], Jin-Ok Jeong[2], Jae-Hyeong Park[2] and Deog-Yeon Jo[1*]
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PP04-02 **Clinically diagnosed chronic myeloid leukemia in hyperleukocytosis complicated by acute respiratory distress syndrome from SARS-CoV-2 (COVID-19)**
Leah Anne Legaspi[1], Camille Ariadne Tanchanco[1] and Loreta Zoleta[1]
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PP04-03 **A case of e1a2 (Minor, P190) BCR-ABL1-positive chronic myeloid leukemia in Korea**
Yu Jeong Choi[1], Ja Yoon Heo[2] and Jongha Yoo[3*]
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PP04-04 **Measuring health related quality of life of chronic myeloid leukemia patients on newer generation TKIs using the Filipino version of the FACT-Leu questionnaire**
Camille Ariadne Tanchanco[1], Karen Kate Tobias[1] and Teresita Dumagay[1]
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PP05-01 **Outcome of non-Hodgkin lymphoma: A single center experience**
Rohit Kapoor[1*], Neha Rastogi[1], Dhwanee Thakkar[1], Goutomi Chatterjee[1] and Satya Prakash Yadav[1]
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PP05-02 **Small extracellular vesicle-derived messenger RNA for liquid biopsy-based biomarker research in non-Hodgkin lymphomas**
Seok Jin Kim[1*], Yeong Hak Bang[2], Joon Ho Shim[2], Kyung Ju Ryu[2], Ji Young Lee[2], Myung Eun Choi[2], Sang Eun Yoon[2] and Won Seog Kim[1]
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PP05-03 **Bone marrow involvement in lymphoma: Flow cytometry verusus bone marrow biopsy; The gold standard?**
Garima Jain[1], Chandan Kumar[1], Pranay Tanwar[1*] and Amar Ranjan[1]
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PP05-04 **Diagnostic accuracy and prognostic relevance of immunoglobulin heavy chain rearrangement and 18F-FDG-PET/CT compared with unilateral bone marrow trephination for detecting bone marrow involvement in patients with diffuse large B-cell lymphoma**
Mihee Kim[1], Seo-Yeon Ahn[1], Jae-Sook Ahn[1], Je-Jung Lee[1], Hyeoung-Joon Kim[1], Jun Hyung Lee[2], Myung-Geun Shin[2], Sang Yun Song[3] and Deok-Hwan Yang[1*]
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PP05-05 **Role of FDG-PET/CT in the management of pediatric burkitt lymphoma**
Ahmed Abdelsalam
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PP05-06 **Clinical outcomes of early-progressed follicular lymphoma in Korea: A multicenter, retrospective analysis**
Jun Ho Yi[1], Seok Jin Kim[3], Dok Hyun Yoon[7], Cheolwon Suh[7], Won-Sik Lee[9], Deok Hwan Yang[6], Jae-Cheol Jo[10], Youngil Koh[5], Jeong-Ok Lee[4], Byeong Su Kim[11], Sung Nam Lim[14], Mi Hwa Heo[13], Byeong Seok Sohn[12], Yoon Seok Choi[15], Hyo Jung Kim[16], Soon Il Lee[8], Sung Yong Oh[2] and Won Seog Kim[3*]
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PP05-07 **Long-term clinical outcomes of gastric MALT lymphoma: A single-center experience of 207 patients in Catholic Hematology Hospital**
Gi June Min[1], Seok-Goo Cho[1*], Byung-Ock Choi[5], Seung-Jun Kim[6], Han Hee Lee[7], Young-Woo Jeon[2], Jong Hyuk Lee[1], Sung-Soo Park[1], Silvia Park[1], Seung-Ah Yahng[4], Seung-Hawn Shin[3], Byung-Su Kim[3], 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], Dong-Wook Kim[1] and Jong Wook Lee[1]
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PP05-08 **Long-term clinical outcome of R-CVP chemoimmunotherapy in treatment-naïve patients with orbital adnexal MALT lymphoma: A single-center experience**
Gi June Min[1], Seok-Goo Cho[1*], Seok-Woo Yang[5], Young-Woo Jeon[2], Jong Hyuk Lee[1], Sung-Soo Park[1], Silvia Park[1], Seung-Ah Yahng[4], Seung-Hawn Shin[3], Byung-Su Kim[3], 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], Dong-Wook Kim[1] and Jong Wook Lee[1]
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PP05-09 **CNS involvement in relapsed mantle cell lymphoma**
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PP05-10 **Efficacy and safety of ibrutinib in mantle cell lymphoma patients: Real world experience in a single center, retrospective analysis**
Jong Hyuk Lee[1], Gi-June Min[1], Young-Woo Jeon[2], 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], Dong-Wook Kim[1], Jong Wook Lee[1], Seok-Goo Cho[1*] and Byung-Su Kim[3]
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PP05-11 **Long-term real-world results of R-CHOP chemoimmunotherapy in 479 previously untreated elderly patients with diffuse large B-cell lymphoma: A single-center experience at Catholic Hematology Hospital**
Gi June Min[1], Seok-Goo Cho[1*], Young-Woo Jeon[2], Jong Hyuk Lee[1], Sung-Soo Park[1], Silvia Park[1], Seung-Ah Yahng[4], Seung-Hawn Shin[3], Byung-Su Kim[3], 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], Dong-Wook Kim[1] and Jong Wook Lee[1]
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PP05-12 **Role of upfront ASCT in patients with bone marrow involvement by immunoglobulin gene rearrangement of diffuse large B-cell lymphoma**
Yu Ri Kim[1], Ho jin Shin[2], Ho-Young Yhim[3], Deok-Hwan Yang[4], Yong Park[5], Ji Hyun Lee[6], Won-sik Lee[7], Young Rok Do[8], Yeung-Chul Mun[9] and Jin Seok kim[1*]
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PP05-13 **Long-term follow-up of limited-stage ocular adnexal lymphoma patients treated with chemoimmunotherapy**
Sung-Yong Kim[1], Won-Sik Lee[2], Sung Yong Oh[3], Deok-Hwan Yang[4], Seong Kyu Park[5], Hyo Jung Kim[6] and Seok-Goo Cho[7*]
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PP05-14 **Use of high dose methotrexate in patients with primary CNS lymphoma without therapeutic drug monitoring of methotrexate levels: Challenges & outcome**
Gaurav Prakash[1*], Charanpreet Singh[1], Pankaj Malhotra[1], Aniruddha Aggrawal[2], Astha Takkar[3] and Arihant Jain[1]
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PP05-15 **Efficacy and safety of high-dose etoposide cytarabine as consolidation in transplant ineligible primary central nervous system lymphoma**
Yu Ri Kim[1], Hyunsoo Cho[1], Soo-Jeong Kim[2], June-Won Cheong[1], Haerim Chung[1], Ji Eun Jang[1], Yoo Hong Min[1] and Jin Seok Kim[1*]
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PP05-16 **Effect of systemic intravenous methotrexate administration on CNS relapse in patients with primary intraocular lymphoma**

Gi June Min[1], Seok-Goo Cho[1*], Young-Hoon Park[5], Young-Woo Jeon[2], Jong Hyuk Lee[1], Sung-Soo Park[1], Silvia Park[1], Seung-Ah Yahng[4], Seung-Hawn Shin[3], Byung-Su Kim[3], 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], Dong-Wook Kim[1] and Jong Wook Lee[1]

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PP05-17 **GIT DLBCL in hospital Malacca, Malaysia**

Siong Leng Hon
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PP05-18 **Subcutaneous mosunetuzumab shows promising safety and encouraging efficacy in relapsed or refractory B-cell lymphoma: Initial results from dose escalation**

Matthew Matasar[3], Chan Yoon Cheah[2], Dok Hyun Yoon[8], Sarit Assouline[1], Nancy Bartlett[4], Matthew Ku[9], Pratyush Giri[10], Anna Johnston[11], Ian Flinn[12], Andre Goy[13], Dimitrios Tzachanis[14], Carol O'Hear[5], Shen Yin[5], Iris To[5], Kati Sarouei[5], Chi-Chung Li[5], Brendan Bender[5], Elicia Penuel[5], Huang Huang[6] and L. Elizabeth Budde[7]

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PP05-19 **Treatment outcomes of involved-field radiotherapy in elderly patients with high-grade or recurrent non-Hodgkin lymphoma**

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PP05-20 **ECHELON-2: 5-year results of a phase 3 study of frontline brentuximab vedotin + CHP vs CHOP in patients with CD30-positive peripheral T-cell lymphoma**

Won Seog Kim[1*], Steven M. Horwitz[2], Owen A. O'Connor[3,4], Barbara Pro[5], Tim Illidge[6], Swami P. Iyer[7], Ranjana Advani[8], Nancy L. Bartlett[9], Jacob Haaber Christensen[10], Franck Morschhauser[11], Eva Domingo-Domenech[12], Giuseppe Rossi[13], Tatyana A. Feldman[14], Tobias Menne[15], David Belada[16], Árpád Illés[17], Kensei Tobinai[18], Kunihiro Tsukasaki[19], Su-Peng Yeh[20], Andrei R. Shustov[21], Andreas Hüttmann[22], Kerry J. Savage[23], Sam Yuen[24], Pier Luigi Zinzani[25], Harry Miao[26], Veronica Bunn[26], Keenan Fenton[27], Michelle A. Fanale[27], Markus Puhlmann[27] and Lorenz Trümper[28]

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PP05-21 **Prognostic effect of C-reactive protein-to-albumin ratio in peripheral T-cell lymphoma**

Jongheon Jung[1], Ja Yoon Heo[2], Eunyoung Lee[1], Hyewon Lee[1], Myung Hee Chang[2] and Hyeon-Seok Eom[1*]

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PP05-22 **Cutaneous T cell lymphoma in Asian patients: A multinational, multicenter, prospective registry study in Asia**

Yong-Pyo Lee[1] and Sang Eun Yoon[1]

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PP05-23 **Long-term clinical outcome of of ProMACE-CytaBOM regimen with sandwiched radiotherapy in newly diagnosed patients with localized extranodal NK/T-cell lymphoma, nasal type**

Gi June Min[2], Sung-Soo Park[2], Silvia Park[2], Jae-Ho Yoon[2], Sung-Eun Lee[2], Byung-Sik Cho[1], Ki-Seong Eom[2], Yoo-Jin Kim[2], Hee-Je Kim[2], Seok Lee[2], Chang-Ki Min[2], Jong-Wook Lee[2], Seok-Goo Cho[1,2,3*] and Youngwoo Jeon[1,3]

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PP05-24 **A novel ICOS gene mutation in a patient with common variable immunodeficiency and T large granular lymphocyte leukemia**

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PP05-25 **Brentuximab vedotin with chemotherapy for previously untreated, stage III/IV classical Hodgkin lymphoma: 5-year update of the ECHELON-1 study**

Won Seog Kim[1*], David J. Straus[2], Monika Długosz-Danecka[3], Joseph M. Connors[4], Árpád Illés[5], Marco Picardi[6], Ewa Lech-Maranda[7], Tatyana Feldman[8], Piotr Smolewski[9], Kerry J. Savage[4], Nancy L. Bartlett[10], Jan Walewski[11], Radhakrishnan Ramchandren[12], Pier Luigi Zinzani[13], Martin Hutchings[14], Javier Munoz[15], Ranjana Advani[16], Stephen M. Ansell[17], Anas Younes[2], Andrea Gallamini[18], Rachael Liu[19], Meredith Little[19], Keenan Fenton[20], Michelle Fanale[20] and John Radford[21]

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PP05-26 **Influence of DNA repair and TLR4 gene variants on response to ABVD regimen in South Indian patients with Hodgkin lymphoma**

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PP05-27 **Multicenter, retrospective analysis of patients with chronic lymphocytic leukemia in Korea**

Jun Ho Yi[1], Gyeong-Won Lee[2], Ji Hyun Lee[3], Kwai Han Yoo[4], Chul Won Jung[5], Dae Sik Kim[6], Jeong-Ok Lee[7], Hyeon Seok Eom[8], Ja Min Byun[9], Youngil Koh[9], Sung Soo Yoon[9], Jin Seok Kim[10], Jee Hyun Kong[11], Ho-Young Yhim[12], Deok-Hwan Yang[13], Dok Hyun Yoon[14], Do Hyoung Lim[15], Won-Sik Lee[16] and Ho-Jin Shin[17*]

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PP05-28 **Possible correlation of torque teno virus/torque teno-like minivirus and human herpes virus-8 in kikuchi-fujimoto disease**

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PP06-01 **Clinical study on risk-stratified treatment in children with HLH**
Ang Wei[1], Tianyou Wang[1] and Rui Zhang[1*]
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PP06-02 **Clinical analysis of chronic active EBV infection with coronary artery dilatation and a matched case-control study**
Ang Wei[1], Honghao Ma[1], Tianyou Wang[1] and Rui Zhang[1*]
[1]*Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, China*

PP06-03 **Outcome of langerhans cell histiocytosis: A single center experience**
Rohit Kapoor[1*], Neha Rastogi[1], Dhawnee Thakkar[1], Goutomi Chatterjee[1] and Satya Prakash Yadav[1]
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PP06-04 **Clinical analysis of pediatric systemic juvenile xanthogranulomas: A retrospective single-center study**
Huixia Gao[1] and Rui Zhang[1*]
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PP07-01 **Generation of potent dendritic cells using interleukin-15 in multiple myeloma**
Tan-Huy Chu[1], Manh-Cuong Vo[1], Jaya Lakshmi[1], Seo-Yeon Ahn[2], Sung-Hoon Jung[2] and Je-Jung Lee[2*]
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PP07-02 **Relationship between number of plasma cells with monoclonal protein levels in myeloma multiple patients**
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PP07-03 **Galectin-3 in multiple myeloma in residents of Gomel region of Belarus**
Zhanna Kozich[1], Victor Martinkov[2], Zhanna Pugacheva[3] and Liudmila Smirnova[4]
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PP07-04 **Translational data supporting the rational combination of iberdomide with proteasome inhibitors**
Michael Amatangelo[1*], Chad Bjorklund[1], Jian Kang[1], Archana Mukhopadhyay[1], María Dolores Jiménez Nuñez[2], Lilly Wong[1], William Pierceall[1], Sagar Lonial[3], Niels W.C.J. van de Donk[4], Rakesh Popat[5], Sundar Jagannath[6], Jeffrey A. Zonder[7], Monique C. Minnema[8], Albert Oriol[9], Jeremy Larsen[10], Ashraf Z. Badros[11], Paula Rodríguez Otero[12], Pieter Sonneveld[13], Tuong Vi Nguyen[1], Kevin Hong[1], April Sorrell[1] and Anjan Thakurta[1]
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PP07-05 **Adaptive natural killer cells facilitate effector functions of daratumumab in multiple myeloma**
Hyunsoo Cho[1], Haerim Chung[1], Yoon Seok Choi[3], Ji Eun Jang[1], Yu Ri Kim[1], June-Won Cheong[1], Yoo Hong Min[1], Eui-Cheol Shin[2] and Jin Seok Kim[1*]
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PP07-06 **Translational data supporting the rational combination of iberdomide with CD38- and SLAMF7-directed monoclonal antibodies**
Michael Amatangelo[1*], Chad Bjorklund[1], Peilin Ma[1], Krista Wollerman[1], William Pierceall[1], Sagar Lonial[2], Niels W.C.J. van de Donk[3], Rakesh Popat[4], Sundar Jagannath[5], Jeffrey A. Zonder[6], Monique C. Minnema[7], Albert Oriol[8], Jeremy Larsen[9], Ashraf Z. Badros[10], Paula Rodríguez Otero[11], Pieter Sonneveld[12], Tuong Vi Nguyen[1], Kevin Hong[1], April Sorrell[1] and Anjan Thakurta[1]
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PP07-07 **Clinical implication of next-generation flow cytometry based minimal residual disease assessment in patients with multiple myeloma**
Hyun-Young Kim[1], Dae Jin Lim[1], Hee-Jin Kim[1], Sun-Hee Kim[1], Sang Eun Yoon[2], Seok Jin Kim[2], Kihyun Kim[2] and Duck Cho[1*]
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PP07-08 **Association between vitamin D receptor (VDR) gene polymorphisms and multiple myeloma susceptibility: A systematic review and meta-analysis**
Indah Sagitaisna Putri
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PP07-09 **Immunomodulatory drugs increase the risk of serious infections in multiple myeloma patients: A meta-analysis**
Zeba Haque
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PP07-10 **Diagnostic impact of non-CRAB myeloma-defining events in multiple myeloma**
Sooyong Park[1] and Yoon Hwan Chang[1*]
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PP07-11 **Determinant factors for early mortality in newly diagnosed multiple myeloma patients**
Javad Alizargar
Research Center for Healthcare Industry Innovation, National Taipei University of Nursing and Health Sciences, Rep of China (Taiwan)

PP07-12 **The clinical characteristics and survival outcomes of multiple myeloma patients aged 80 or over**
Sang Hwan Lee[1], Sung Hwa Bae[2*], Hun Mo Ryoo[2], Jung Lim Lee[1], Hee-Jeong Cho[3], Joon Ho Moon[3], Ji Yoon Jung[4], Min Kyoung Kim[4], Mi Hwa Heo[5] and Young Rok Do[5]
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PP07-13 **Addition of cyclophosphamide to pomalidomide/dexamethasone has a benefit in refractory multiple myeloma?: The comparison with pomalidomide-based chemotherapy in Asian patients**
Hyunkyung Park[1], Ja Min Byun[2], Sock-won Yoon[2], Youngil Koh[2], Dong-Yeop Shin[2], Junshik Hong[2], Inho Kim[2] and Sung-Soo Yoon[2*]
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PP07-16 **Primary plasma cell leukemia with long term survival - A report of two cases**
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PP07-17 **Analysis of overall survival in plasma cell leukemia**
Amar Ranjan, Harshita Dubey, Ekta Rahul and Pranay Tanwar
Lab Oncology, Cancer Institute, All India Institute of Medical Sciences, New Delhi, India

PP07-18 **Multiple myeloma in man 32 years old with metachronous soft tissue sarcoma. A multiple primary malignant tumors with successfull chemotherapy medication**
Loudry Amsal Elfa Gustanar[1*] and Darwin Prenggono[1]
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PP08-01 **Thrombotic and hemorrhagic events in 2016 who-defined Philadelphia-negative myeloproliferative neoplasms**
Deog-Yeon Jo[1*], Myung-Won Lee[1], Sang Hoon Yeon[1], Won-Houng Seo[1], Hyewon Ryu[1], Ik-Chan Song[1], Hyo-Jin Lee[1], Hwan-Jung Yun[1] and Seon Young Kim[2]
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PP08-02 **Effect of CALR mutant type and allele burden on the phenotype of BCR/ABL1-negative myeloid proliferative neoplasms**
Yujin Han[1], Hyun-Young Kim[1], Jun Ho Jang[2], Chul Won Jung[2], Sun-Hee Kim[1] and Hee-Jin Kim[1*]
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PP08-03 **Impact of MPNs on quality of life: Korean landmark survey**
Ja Min Byun[1], Chul Won Choi[7*], Soo-Mee Bang[2], Eun-Ji Choi[3], Ki-Seong Eom[4], Chul Won Jung[5], Hye-seon Kim[6] and Jiwon Park[6]
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PP08-04 **Characteristics of hydroxyurea-resistant or intolerant polycythemia patients in Korea**
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PP08-05 **The risks and benefits of hydroxyurea in children and young adults with essential thrombocythemia and polycythemia vera**
Hyoung Soo Choi[1], Junshik Hong[2], Sang Mee Hwang[3], Ju Hyun Lee[4], Youngeun Ma[1], Sang-A Kim [4], Ji Yun Lee [4], Jeong-Ok Lee [4] and Soo-Mee Bang[4*]
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PP08-06 **Radiologic splenomegaly in patients with essential thrombocythemia and prefibrotic/early primary myelofibrosis**
Myungwon Lee[1], Sang Hoon Yeon[1], Won-Hyoung Seo[1], Hyewon Ryu[1], Ik-Chan Song[1], Hyo-Jin Lee[1], Hwan-Jung Yun[1], Seon Young Kim[2], Kyung Sook Shin[3] and Deog-Yeon Jo[1*]
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PP08-07 **Clinical predictors in diagnosing essential thrombocytosis: A correlational study**
Fatima Louise Gutierrez[1], Joy Ann De Castro[1] and Flordeluna Mesina[1]
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PP08-08 **Soluble ST2 for prediction of bone marrow fibrosis**
Mikyoung Park[1], Mina Hur[2*], Jong Ho Lee[1], Hyung Woo Kim[1], Hanah Kim[2] and Minjeong Nam[2]
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PP08-09 **Coexistence of JAK2 and CALR mutations in a patient with myelofibrosis**
Jung-ah Kim[1], Hae In Bang[1], Woo Yong Shin[1], Jieun Kim and Rojin Park[1]
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PP08-10 **Immune gene signature distinguishes overt primary myelofibrosis from other myeloproliferative neoplasms**
Sung-Eun Lee[1*], Seowon Choi[1], Gi June Min[1], Sung-Soo Park[1], Silvia Park[1], Jae-Ho Yoon[1], Byung-Sik Cho[1], Ki-Seong Eom[1], Yoo-Jin Kim[1], Seok Lee[1], Chang-Ki Min[1], Hee-Je Kim[1], Seok-Goo Cho[1], Dong-Wook Kim[1] and Jong Wook Lee[1]
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PP08-11 **A case of atypical chronic myeloid leukemia with concomitant CSF3R T618I and JAK2 V617F variants**
Eungjun Yoon[1], Hyun-Young Kim[1], Hee-Jin Kim[1], Chul-Won Jung[2] and Sun-Hee Kim[1*]
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PP08-12 **Reslizumab treatment in a Korean adolescent patient with hypereosinophilic syndrome: A case report**
Ye Jee Shim[1*] and Heung Sik Kim[2]
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PP09-01 **Evaluation of the efficacy of CsA combined with recombined human erythropoietin in the treatment of patients with chronic aplastic anemia**
Wanshu Chen[1], Bing Han[1*] and Menglu Zhang[1]
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PP09-02 **The outcome of hematopoietic stem cell transplantation in children with Shwachman-Diamond syndrome**
Yeon Jung Lim[1,2], Yigal Dror[2*], Omri A Arbiv[2], Melanie E Kalbfleisch[2], Yves D Pastore[4], Robert J Klaassen[5], Geoff Cuvelier[6], Conrad Fernandez[7], Meera Rayar[8], MacGregor Steele[3], Mariana Silva[9], Josee Brossard[10], Bruno Michon[11], Sharon Abish[12], Roona Sinha[13], Mark J Belletrutti[14], Vicky R Breakey[15], Lawrence Jardine[16], Lisa Goodyear[17], Lillian Sung[19], Tal Schechter-Finkelstein[18], Bozana Zlateska[2] and Michaela Cada[2]
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PP09-03 **A predictive scoring system for severe aplastic anemia patients treated with antithymocyte globulin and cyclosporine**
Sung-Soo Park[1], Gi June Min[1], Silvia Park[1], Jae-Ho Yoon[1], Seung-Ah Yahng[2], Seung Hwan Shin[3], 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], Seok-Goo Cho[1] and Jong Wook Lee[1*]
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PP09-04 **Long-term outcome of allogeneic hematopoietic stem cell transplantation from HLA-matched sibling donor in young patients with severe acquired aplastic anemia**
Thanh Le Vu Ha
Stem cell transplantation Department, Blood transfusion and hematology hospital, Viet Nam

PP10-01 **Authenticating a common NGS-detected ASXL1 codon 646 mutation using Sanger sequencing**
Miyoung Kim[1,2*], Nan Young Kim[2], Sangkyoon Hong[2], Yonggeun Cho[1], Han-Sung Kim[1], Hee Jung Kang[1] and Young Kyung Lee[1,2]
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PP10-02 **HTLV-1 viral oncoprotein HBZ protects cells from pro-apoptotic stress by upregulating stabilization of HAX-1**
Takayuki Ohshima
Faculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University, Japan

PP10-03 **Complete blood count and cell population data parameters are useful in differentiating myelodysplastic syndromes from other forms of cytopenia**
Sang Mee Hwang[1*] and Youngwon Nam[1]
[1]Laboratory Medicine, Seoul National University Bundang Hospital, Korea

PP10-04 **Comparison of hematology profile between recovery and death group of COVID-19 patient in Jember, East Java, Indonesia: Preliminary study**
Elvia Rahmi Marga Putri[1*], Nanda Eka Sri Sejati[2], Adhista Eka Noveyani[3], Angga Madro Raharjo[4,7], Rini Riyanti[1], Diana Chusna Mufida[5], Eprilia Darma Sari[6] and Putu Ayu Laksmi Lestari[6]
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PP10-05 **Benign variants associated with hematologic malignancy in the catalogue of somatic mutations in cancer**
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PP10-06 **Novel factor VII gene mutations in six families with hereditary coagulation factor VII deficiency**
Xiaoyu Zhang[1] and Jun Peng[1*]
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PP10-07 **Red blood cell deformability and distribution width in patients with hematologic neoplasms**
Yu Kyung Kim[1*], Jae Min Lee[2] and Jang Soo Suh[1]
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PP10-08 **Establishment of reference intervals in Malaysia: A performance evaluation and comparison of haematological parameters between Sysmex XE5000 and XN3000**
Siew Lian Chong
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PP10-09 **Label-free rapid differential diagnosis of lymphocyte and leukemic blast using optical diffraction tomography**
Nuree Park[1], Hyunji Kim[2] and Seongsoo Jang[1,2*]
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PP10-10 **Determination of reference range (Based on CLSI) leukocyte parameters for Indonesian subject**
Adika Zhulhi Arjana[1*], Ninda Devita[2], Sri Irianti[1] and Tri Ratnaningsih[1]
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PP10-11 **Blood smear pitfall of platelet count confirmation examination: A case study**
Adika Zhulhi Arjana[1], Ninda Devita[2] and Usi Sukorini[1*]
[1]Clinical Pathology and Laboratory Medicine, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Indonesia
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PP10-12 **Effectivenes of quality assessment program for blood smear examination**
Nhu Cao Thi Bich[1], Son Nguyen Truong[1], Oanh Le Hoang[1], Tung Tran Thanh[1], Thao Nguyen Van[1], Thao Nguyen Thi[1] and Huy Vu Quang[2]
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PP10-13 **A meta-analysis on the role of the -308 G/A polymorphism of the TNF-α gene with malaria susceptibility**
Raphael Enrique Tiongco[1*], Ivy Cayabyab[1], Benjie Clemente[2], Chastene Christopher Flake[1], Dianne Dizon[1], Joey Kyle Mallari[1] and Maria Ruth Pineda-Cortel[2,3]
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PP11-01 **Hemoglobin polygenic risk score as a tool in elucidating the causal role of elevated iron status on cardiometabolic outcomes in Taiwan Han Chinese**
Vanessa Joy Timoteo[1*], Kuang-Mao Chiang[2] and Wen-Harn Pan[2]
[1]National Yang-Ming University and Institute of Biomedical Sciences-Academia Sinica, Taiwan International Graduate Program in Molecular Medicine, Rep of China (Taiwan)
[2]Academia Sinica, Institute of Biomedical Sciences, Rep of China (Taiwan)

PP11-02 **Association of the V736A polymorphism in the TMPRSS6 gene with the risk of developing iron deficiency anemia: A meta-analysis**
Chastene Christopher Flake[1,2*], Marlex Lee Sanchez[1,3], Maurice Russel Espino[1,2,4], Jemimah Suba[1,5], Jane Nicolas[1,6], Michelle Bautista[1,7], Angelica Gueco[1], Allena Milan[1,8], Raphael Enrique Tiongco[2] and Annalyn Navarro[1,2]
[1]Public Health Program, Graduate School, Angeles University Foundation, Philippines
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[3]Department of Medical Technology, College of Our Lady of Mt. Carmel, Philippines
[4]Department of Pathology, The Medical City Clark Inc, Philippines
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[8]Department of Medical Technology, Central Luzon Doctors' Hospital Educational Institution, Philippines

PP11-03 **Sickle cell anemia: A risk factor for craniofacial abnormalities and dental malocclusion– A systematic review**
Vaibhav Gupta[1*], Amar Ranjan[2] and Poonam Goel[1]
[1]Laboratory Oncology, Research Fellow, AIIMS, India
[2]Laboratory Oncology, Additional Professor, AIIMS, India

PP11-04 **The prevalence of thalassemia in Bangladesh: Evidence from a molecular study**
Md Abdullah Al Maruf[1] and Farhana Sultana Mitu[2]
[1]Department of Health Technology & Informatics, The Hong Kong Polytechnic University, Hong Kong
[2]Department of Biotechnology & Genetic Engineering, Islamic University, Bangladesh

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PP11-05 **A comprehensive study of prevalence and distribution of anaemia among OPD patients visiting Integral Institute of Medical Sciences Research & Hospital, Lucknow**
Smriti Rastogi[1*] and Narsingh Verma[1]
[1]*Physiology, King George's Medical University, India*

PP11-06 **Assessment of knowledge, attitude and practices on iron-deficiency anemia among Filipino teens in Laguna, Philippines**
Cherry Ann Durante[1,2*] and Estrella San Juan[1]
[1]*Nursing, University of Perpetual Help - Dr. Jose G Tamayo Medical University, Philippines*
[2]*Public Health Nutrition, University of the Philippines, Philippines*

PP11-07 **The characteristics of anemia among patients with diabetic foot infection admitted to Dr. Hi. Abdul Moeloek General Hospital, Lampung, Indonesia**
Gusti Ngurah P Pradnya Wisnu[1*], Iswandi Darwis[1] and Sekar Mentari[1]
[1]*Internal Medicine, Dr. Hi. Abdul Moeloek General Hospital, Indonesia*

PP11-08 **Protein, iron, and vitamin C intake with anemia in adolescent girls in Yogyakarta city**
Destriyani Destriyani
Nutrition, Pambusuang Primary Health Center, Indonesia

PP11-09 **Screening of MT-CO3 gene mutations for sickle cell anaemia in tribes from Tamil Nadu, South India**
Balachandar Vellingiri[1*], Nimmisha Eruppakotte[1], Dhivya Venkatesan[1] and Soumya Kizhakkillach[1]
[1]*Human Molecular Cytogenetics and Stem Cell Laboratory, Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore 641046, India*

PP11-10 **Identifications of β-globin gene mutations among the sickle cell anaemia patients from the tribes of Coimbatore, Tamil Nadu**
Krishnaswamy Rangaswamy[1*], Nimmisha Eruppakotte[1], Venkatesh Balasubramanian[1], Arul Narayanasamy[2] and Balachandar Vellingiri[1]
[1]*Human Molecular Cytogenetics and Stem Cell Laboratory, Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore 641046, Tamil Nadu, India*
[2]*Department of Zoology, Bharathiar University, Coimbatore 641046, Tamil Nadu, India*

PP11-12 **Risk factor for anemia in infancy: A literature review**
Nuraliah Nuraliah
Public Health, West Sulawesi Research and Empowerment Center, Indonesia

PP11-13 **Compliance of consuming iron tablets and anemia cases in pregnant women**
Nuraliah Nuraliah
Public Health, West Sulawesi Research and Empowerment Center, Indonesia

PP11-14 **Coping strategy in preventing anemia: Case study of Indonesian pregnant women on WhatsApp groups**
Mahyuddin Mahyuddin[1*] and Kadriah Kadriah[2]
[1]*Sociology, State Islamic Institute of Parepare, Indonesia*
[2]*Public Health, Al Asyariah Mandar University, Indonesia*

PP11-15 **Relationship of economic status with the occurrence of anemia in the third trimester of pregnant women at Caile Health Center, Bulukumba Regency, South Sulawesi**
Sahnaz Vivinda Putri[1*] and Rosmani Bahtiar[2]
[1]*Management, International Universtity Semen Indonesia, Indonesia*
[2]*Community Nutrition, Bulukumba Caile Health Center, Indonesia*

PP11-18 **The influence of health and socio-economic factors on prevalence of anemia among children in six countries based on income**
Putri Ayu[1*] and Ade Kartikasari Sebba[2]
[1]*Economics, Andalas University, Indonesia*
[2]*Health, Universitas Gadjah Mada, Indonesia*

PP11-19 **Effect of lavandula officinalis leaves ethanolic extract on hematological and biochemical parameters in male rats**
Ankit Jain[1*] and DK Singh[1]
[1]*Pharmaceutical Sciences, D. Y. Patil Institute of Pharmaceutical Sciences and Research, India*

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PP11-20 **Study of punica granatum (pomegranate) seed oil extract in phenylhydrazine induced-anemia in albino rats**
Rohit Kumar[1*] and Madhu Vati[1]
[1]*Applied Sciences, HMFA Memorial Institute of Engineering and Technology, India*

PP11-21 **Anemia in pregnancy: Risk factors influencing age and level of education among mothers in Sawangan healthcare center**
Fitri Rachmawati Putri
General Practitioner, Medika Mulya Hospital, Indonesia

PP11-22 **Automatic anemia identification based on machine learning on red blood cell image**
Rifaldy Fajar[1*] and Nana Indri Kurniastuti[1]
[1]*Computational Biology Laboratory, Yogyakarta State University, Indonesia*

PP11-23 **Pregnant women, health crisis and hemogoblin detect in the age of COVID-19 in Indonesia**
Kadriah Kadriah
[1]*Public Health, Alasyariah Mandar University, Indonesia*

PP11-24 **A case of acute intermittent porphyria in a young woman with epilepsy**
Sanka Vijayabandara
Teaching Hospital karapitiya, Galle, Consultant Physician, Sri Lanka

PP12-02 **A delayed presentation of neonatal alloimmune thrombocytopenia (NAIT): A case report**
Jian An Boo
Paediatric, Hospital Sultanah Bahiyah Alor Setar, Malaysia

PP12-03 **Treatment outcomes and profile of patients with immune thrombocytopenia at a tertiary hospital: The TOP-IT study**
Rmin Sheila Miranda
Hematology, Philippine General Hospital, Philippines

PP12-05 **A study on the association of immune thrombocytopenia with viral infection through public health data analysis**
Yu Kyeong Kim[2], So Hyeon Min[2], Jae Hee Lim[2], Young Hwan Lee[1] and Jae Min Lee[1*]
[1]*Pediatrics, College of medicine, Yeungnam University, Korea*
[2]*Medicine, College of Medicine, Yeungnam University, Korea*

PP12-06 **Efficacy of Helicobacter pylori eradication for the treatment of chronic or persistent immune thrombocytopenia patients with moderate thrombocytopenia: multicenter prospective randomized phase 3 study**
Boram Han[1], Hyo Jung Kim[1], Ho-Young Yhim[2], Doyeun Oh[3], Sung Hwa Bae[4], Ho-Jin Shin[5], Won-Sik Lee[6], JiHyun Kwon[7], Hwa Jung Kim[8], Jeong-Ok Lee[9] and Soo-Mee Bang[9*]
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[7]*Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Korea*
[8]*Department of Clinical Epidemiology and Biostatistics, Department of Prevention Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea*
[9]*Department of Internal Medicine, Seoul National University Bundang Hospital, Korea*

PP12-07 **Clinical outcomes after splenectomy for relapsed or refractory immune thrombocytopenia according to first-line intravenous immunoglobulin response**
Daehun Kwag[1,2], Jae-Ho Yoon[1,2*], Gi June Min[1,2], Sung-Soo Park[1,2], Silvia Park[1,2], Sung-Eun Lee[1,2], Byung-Sik Cho[1,2], Ki-Seong Eom[1,2], Yoo-Jin Kim[1,2], Hee-Je Kim[1,2], Seok Lee[1,2], Chang-Ki Min[1,2], Seok-Goo Cho[1], Dong-Wook Kim[1,2] and Jong Wook Lee[1]
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PP12-08 **An escalating treatment strategy for children with severe chronic immune thrombocytopenia: The preliminary report from a single-center**
Lingling Fu[1], Runhui Wu[1*], Jie ma[1], Hao Gu[1] and Jingyao Ma[1]
[1]*Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing Key Laboratory of Pediatric Hematology Oncology; National Key Discipline of Pediatrics (Capital Medical University); Key Laboratory of Major Diseases in Children, Ministry of Education, China, 100045, China*

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PP12-10 **An intronic variant at a splice-site (c.5170+5G>A) of VWF gene causes exon 29 skipping in a patient with von Willebrand disease**
Ye Jee Shim[1] and Jae Min Lee[2*]
[1]*Department of Pediatrics, Keimyung University School of Medicine, Keimyung University Dongsan Hospital, Daegu, Korea*
[2]*Department of Pediatrics, Yeungnam University College of Medicine, Daegu, Korea*

PP12-12 **Performance evaluation of coaguchek pro II in comparison with CoaguChek XS Plus and STA-R Max Analyzer**
Minjeong Nam
Department of Laboratory Medicine, Konkuk University Medical Center, Korea

PP12-13 **Promotion of platelet production by cotransplatation of tonsil-derived mesenchymal stem cells in allogeneic bone marrow transplantation mouse model**
Yu-Hee Kim[1], Hyun-Ji Lee[1] and Kyung-Ha Ryu[2*]
[1]*Department of Microbiology, Ewha Womans University College of Medicine, Korea*
[2]*Department of Pediatrics, Ewha Womans University College of Medicine, Korea*

PP12-14 **Extended platelet parameters on COVID-19**
Usi Sukorini[1*], Tri Ratnaningsih[1], Ika Ridlawati[1], Adika Zhulhi Arjana[1] and Annisa Ginar Indrarsi[1]
[1]*Clinical Pathology and Laboratory Medicine, Dr. Sardjito Hospital/Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Indonesia*

PP13-01 **Low survival rate in patients with veno-occlusive disease whose creatinine levels have already begun to increase when defibrotide is administered**
Seom Gim Kong[1], Je-Hwan Lee[2], Young Tak Lim[3], Ji Hyun Lee[4], Hyeon-Seok Eom[5], Hyewon Lee[5], Do Young Kim[6], Sung-Nam Lim[7], Sung-Soo Yoon[8], Sung-Yong Kim[9] and Ho Sup Lee[10*]
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[8]*Department of Internal Medicine, Seoul National University Hospital, Korea*
[9]*Department of Internal Medicine, Konkuk University Medical Center, Korea*
[10]*Department of Internal Medicine, Kosin University College of Medicine, Korea*

PP13-02 **ABO incompatibility and outcomes of allogeneic hematopoietic stem cell transplantation**
Jun-Hong Park[1], Je-Hwan Lee[1*], Kyoo-Hyung Lee[1], Jung-Hee Lee[1], Han-Seung Park[1], Eun-Ji Choi[1], Young-ah Kang[1], Hyeran Kang[1], Jimin Woo[1], Youngshin Lee[1] and Mijin Jeon[1]
[1]*Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea*

PP13-03 **DEFIFrance registry study: Defibrotide treatment of veno-occlusive disease/sinusoidal obstruction syndrome after hematopoietic cell transplantation**
Mohamad Mohty[1], Ibrahim Yakoub-Agha[2], Myriam Labopin[1], Didier Blaise[3], Delphine Lebon[4], Virginie Gandemer[5], Sébastien Maury[6], Charlotte Jubert[7], Janet Pong[8*], Robert J. Ryan[9], Jean-Hugues Dalle[10] and Régis Peffault de Latour[11]
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[11]*Hematology and Bone Marrow Transplant Department, Hôpital Saint-Louis, Paris, France*

PP13-04 **Haploidentical hematopoietic stem cell transplantation for malignant infantile osteopetrosis and intermediate osteopetrosis : A retrospective analysis of a single-center**
Ang Wei[1], Guanghua Zhu[1*] and Tianyou Wang[1]
[1]*Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, China*

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PP13-05 **Outcome of allogenic hematopoietic stem cell transplantation in chronic granulomatous disease: A single center experience of 31 patients**
Hyun Jin Park[1], Kyung Taek Hong[1], Jung Yoon Choi[1], Hong Yul An[1], Bo Kyung Kim[1], Hee Young Shin[1] and Hyoung Jin Kang[1*]
[1]*Department of Pediatrics, Seoul National University College of Medicine, Korea*

PP13-06 **Benefit of leukemia induction treatment and allogeneic stem cell transplantation for blastic plasmacytoid dendritic cell neoplasm**
Ji Hyun Lee[1], Seok Jin Kim[2*], Won Seog Kim[2], Dok Hyun Yoon[3], Cheolwon Suh[3], Youngil Koh[4], Sung-Soo Yoon[4], Ja Min Byun[4], Hyeon Seok Eom[5], Hyewon Lee[5], Jong Ho Won[6], Ho Sup Lee[7], Deok-Hwan Yang[8], Ho-Young Yhim[9], Ji Yun Lee[10], Jae-Cheol Jo[11] and Yoo Jin Lee[11]
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[10]*Department of Hematology-Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Korea*
[11]*Department of Hematology and Oncology, Ulsan University Hospital, University of Ulsan College of Medicine, Korea*

PP13-07 **Evaluation of the bacterial and fungal infection status in hematopoietic stem cell transplantation patients in HCMC blood transfusion and hematology hospital**
Man Huynh Van
Stem Cell Transplantation, Blood Transfusion and Hematology Hospital, Viet Nam

PP13-08 **Outcome of BK virus induced hemorrhagic cystitis in children undergoing haploidentical stem cell transplant with post transplant cyclophosphamide**
Rohit Kapoor[1*], Dhwanee Thakkar[1], Goutomi Chatterjee[1], Neha Rastogi[1] and Satya Prakash Yadav[1]
[1]*Pediatric Hematology Oncology and Bone Marrow Transplant Unit, Cancer Institute, Medanta The Medicity Hospital, Gurgaon, Haryana, India 122001., Medanta The Medicity Hospital, Gurgaon, Haryana, India*

PP13-09 **Predictive model by machine learning through repetitive internal validation for hepatic SOS/VOD and early death after allogeneic-HCT**
Jae-Ho Yoon[1*], Seung-Joon Lee[3], Eun-Saem Lee[2], Sung-Soo Park[1], Min-Sue Park[2], Jae-Woo Jung[3], Gi June Min[1], Siolvia Park[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], Seok-Goo Cho[1], Jong Wook Lee[1] and Hyung-Ju Hwang[2,3]
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[2]*Department of Mathematics, Pohang University of Science and Technology, Pohang, Korea*
[3]*AMSquare Corporation, Pohang, Gyeongbuk, Korea*

PP13-10 **Metabolic syndrome as a recognized complication after allogeneic haematopoietic stem cell transplantation: A single Asian institute experience**
Ching Soon Teoh[1*] and Ai Sim Goh[1]
[1]*Haematology Unit, Internal Medicine, Hospital Pulau Pinang, Malaysia*

PP13-11 **Efficacy of entecavir versus lamivudine prophylaxis in preventing hepatitis B virus reactivation in patients with allogeneic stem cell transplant**
Dexton Johns
Clinical Research, National Medicity Hospital, India

PP14-01 **Single-cell characterization of hematopoietic stem and progenitor cells in immune thrombocytopenia**
Yan Liu[1,2] and Jun Peng[1,2*]
[1]*Department of Hematology, Qilu Hospital of Shandong University, China*
[2]*Medical department, Shandong University, China*

PP14-02 **SETDB1, histone methyltransferase maintains blood cell homeostasis by modulating the differentiation into cancerous blood cells**
Indira Paddibhatla[1*], Dushyant Gautam[1], Isabel Aymanns[2] and Ravi Gutti[1]
[1]*Department of Biochemistry, University of Hyderabad, India*
[2]*Department of Life Sciences, Westfälische Wilhelms - Universität, Münster, Germany*

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PP14-03 **CH223191, a potent aryl hydrocarbon receptor antagonist promotes the expansion of HPCs and megakaryocyte**
Dongchan Kim[1,2], Dong-Yeop Shin[1,2,3*], Jun Liu[1,2], Na-Rae Jeong[1,2], 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*

PP14-04 **Clonal hematopoiesis in cardio-cerebrovascular diseases**
Jin-Yeong Han[1*], Min-Sun Kwak[1], Ji-Hyun Lee[2], Sung-Hyun Kim[3] and Moo-Hyun Kim[3]
[1]*Laboratory Medicine, Dong-A University College of Medicine, Korea*
[2]*Hematooncology, Dong-A University College of Medicine, Korea*
[3]*Cardiology, Dong-A University College of Medicine, Korea*

PP14-05 **Sivelestat-loaded nanostructured lipid carriers modulate oxidative and inflammatory stress in human dental pulp and mesenchymal stem cells subjected to oxygen-glucose deprivation**
Anas Ahmad
Nano-Therapeutics, Institute of Nano Science and Technology, India

PP15-01 **A combination of immunoadjuvant nanocomplex and dendritic cell vaccine in the presence of immune checkpoint blockade for effective cancer immunotherapy**
Manh-Cuong Vo[1,2], Seo-Yeon Ahn[1], Tan-Huy Chu[2], Saji Uthaman[3], Shammer Pillarisetti[4], Thangaraj Jaya Lakshmi[2], Mihee Kim[1], Ga-Young Song[1], Sung-Hoon Jung[1], Deok-Hwan Yang[1], Jae-Sook Ahn[1], Hyeoung-Joon Kim[1], In-Kyu Park[4] and Je-Jung Lee[1*]
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[3]*Department of Polymer Science and Engineering, Chungnam National University, Korea*
[4]*Department of Biomedical Science, Chonnam National University Medical School, Korea*

PP15-02 **Production and in vivo evaluation of chimeric antigen receptor (CAR)-γδ T cells**
Minsong Kim[1], Hyori Kim[1], Hyun Ju Hwang[1], Eun Seok Choi[2], Ho Joon Im[2], Nayoung Kim[1] and Kyung-Nam Koh[2*]
[1]*Asan Institute for Life Sciences and Department of Convergence Medicine, Asan Medical Center, University of Ulsan College of Medicine, Korea*
[2]*Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Korea*

PP16-01 **ABO blood groups may play a role in the development of dengue hemorrhagic fever: A meta-analysis**
Archie Policarpio[1*], Imoan Shallom Aguas[1], Marc Nicole Mercado[2], Regine Gonzales[3], Czar Kenneth Sarmiento[4], Mark Aaron Buan[5], Jenny David[6], Raphael Enrique Tiongco[1] and Annalyn Navarro[7]
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[5]*Laboratory Department, Rafael Lazatin Memorial Medical Center, Philippines*
[6]*Central Luzon Center for Health and Development, Department of Health, Philippines*
[7]*Graduate School, Angeles University Foundation, Philippines*

PP16-02 **Transfusion of the least-incompatible blood with intravenous immunoglobulin and steroid to a patient with anti-Fy(a)**
Joonsang Yu[1], Jin Seok Kim[1], John Jeongseok Yang[1], Sang-Hyun Hwang[1], Heung-Bum Oh[1] and Dae-Hyun Ko[1*]
[1]*Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea*

PP16-03 **The benefit of lekodepleted PRC transfusion for biliary patient after Kasai procedure**
Adika Zhulhi Arjana[1] and Teguh Triyono[1*]
[1]*Clinical Pathology and Laboratory Medicine, Universitas Gadjah Mada, Indonesia*

PP16-04 **A comparative evaluation of effect of DTT and heat on ABO isoagglutinin titers in 2005 group O donors**
Divya Setya[1], Prashant Pandey[1*], Shweta Ranjan[1] and Supriya Sharma[1]
[1]*Transfusion Medicine, Jaypee Hospital Noida, India*

PP16-06 **Does Rh and Kell phenotyping of donor units complement type and screen method of compatibility testing?**
Prashant Pandey[1*], Divya Setya[1], Shweta Ranjan[1] and Supriya Sharma[1]
[1]*Transfusion Medicine, Jaypee Hospital Noida, India*

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PP16-07 **Convalescent plasma therapy in severe to critical COVID-19 patients in the De La Salle University Medical Center: A case series**
Alyssa Alessandra Hubo[1] and Camille Ariadne Tanchanco[1]
[1]Internal Medicine, De La Salle University Medical Center, Philippines

PP16-08 **Transfusion in coronavirus disease 2019 patients: A preliminary study in tertiary hospital in Daegu**
Hyung Woo Kim[1], Mikyoung Park[1*], Chae Hoon Lee[1], Jong Ho Lee[1], Hee-Jung Chung[2] and Mina Hur[2]
[1]Department of Laboratory Medicine, Yeungnam University College of Medicine, Daegu, Korea
[2]Department of Laboratory Medicine, Konkuk University School of Medicine, Seoul, Korea

PP16-09 **Does ABO grouping have an association with severity and distribution of COVID-19? A cross sectional study**
Elaina Pasangha[1], Arkadeep Dhali[1], Christopher D'Souza[1] and Soumya Umesh[1*]
[1]Internal Medicine, St John's Medical College, India

PP17-01 **Information is power: Hoax news and celebrity health prompt Indonesian audience into finding out more about leukemia**
Khariz Fahrurrozi[1*], Ibnu Agus Aryanto[2] and Agus Jati Sunggoro[3]
[1]Emergency Departement, RSU Islam Klaten, Indonesia
[2]Virology and Cancer Pathobiology Research Center, Universitas Indonesia, Indonesia
[3]Internal Medicine Departement, RSUD Dr. Moewardi, Indonesia

PP17-02 **Clinical characteristic in cancer patients with febrile neutropenia at Sanglah General Hospital, Denpasar – Bali Indonesia**
Joko Anggoro[1*], Ketut Suega[2], Tjok Gde Dharmayuda[2], Wayan Losen Adnyana[2] and Ni Made Renny Anggreni Rena[2]
[1]Hematology and Oncology Division Department of Internal Medicine, University of Mataram, Mataram, Indonesia
[2]Hematology and Oncology Division Department of Internal Medicine, University of Udayana, Denpasar, Indonesia

PP17-03 **COVID-19 infection in hematological patients: Results of a prospective cohort study**
Igor Stoma[1*], Maryia Shapetska[2] and Igor Iskrov[2]
[1]Infectious Diseases, Gomel state medical university, Belarus
[2]Hematology №3, Minsk Scientific and Practical Center of Surgery, Transplantology and Hematology, Belarus

PP18-01 **Vitamins: A cure for oral mucositis induced by cancer chemo/ radiotherapy – A meta-analysis of RCTs**
Poonam Goel[1*], Amar Ranjan[1] and Vaibhav Gupta[1]
[1]Laboratory Oncology, AIIMS, India

PP18-02 **Self-care behavior: Support for improving a quality of life in patients thalassemia in Indonesia**
Mega Dwi Septivani[1*] and Indra Suwardi[2]
[1]Department of Science Management, Universitas Gadjah Mada, Indonesia
[2]Department of Midwifery, Hasanuddin University, Makasar, Indonesia

PP18-03 **Epidemiological burden of anemia and its impact on the quality of life in diabetic kidney disease patients**
Salman Hussain
Department of Pharmaceutical Medicine, Jamia Hamdard, India

PLENARY LECTURE & PRESIDENTIAL SYMPOSIUM

PL01-1

Clonal hematopoiesis and the origins of hematologic malignancies

Benjamin Ebert
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Clonal hematopoiesis of indeterminate potential (CHIP) is a common, age-associated condition in individuals who do not have a hematologic malignancy or altered blood counts. CHIP is defined by the presence of clonal, somatic mutations that are found in hematologic malignancies such as myelodysplastic syndrome, myeloproliferative neoplasms, acute myeloid leukemia. Indeed, the mutations identified in CHIP, including mutations in *DNMT3A*, *TET2*, and *ASXL1*, are lesions that are commonly acquired early in the genetic ontogeny of hematologic malignancies, prior to the development of overt disease. Consistent with the concept that CHIP is a pre-malignant state, CHIP is associated with a striking increased risk of hematologic malignancy. In addition, individuals with CHIP have increased overall mortality and an increased risk of cardiovascular disease. In murine models, Tet2 inactivation in blood cells, transplanted into Ldl receptor knockout mice, leads to accelerated atherosclerosis. Individuals with *JAK2*-mutant CHIP have an elevated risk of venous thrombosis. Individuals with CHIP at the time of autologous stem cell transplant for lymphoma have an elevated risk of developing therapy-related myeloid malignancies. CHIP is therefore a common condition, and clonal mutations in blood cells can contribute to diverse pathologic processes.

PL02

Genetic landscape of lymphoma and novel treatment approaches

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Diffuse large B-cell lymphoma (DLBCL) encompasses a group of aggressive B-cell non-Hodgkin lymphomas with striking genetic heterogeneity and variable clinical presentations. Among these is primary mediastinal B-cell lymphoma (PMBL), which has unique clinical and molecular features resembling Hodgkin lymphoma. Treatment of DLBCL is usually curative, but identifiable subsets at highest risk for treatment failure may benefit from intensified chemotherapy regimens and/or targeted agents added to frontline therapy. Recent comprehensive genomic analyses have identified distinct genetic subtypes of DLBCL with characteristic genetic drivers and signaling pathways that are targetable. Immune therapy with chimeric antigen receptor T cells and checkpoint inhibitors has revolutionized the treatment of relapsed or refractory disease, and antibody drug conjugates have weaponized otherwise intolerable cytotoxic agents. Ongoing clinical trials are further refining the specificity of these approaches in different genetic subtypes and moving them from the setting of recurrent disease to frontline treatment in high-risk patient populations.

PL03

Latest treatment developments in multiple myeloma

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There has been a significant advance in our understanding of the biologic significance and therapeutic impact of MM cell interactions with the BM milieu. Specifically, preclinical models of MM cells in the host BM microenvironment (BMM) have provided the framework for the development of immune- and molecularly-based novel combination therapies, including proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies, which have been rapidly translated from the bench to the bedside and led to multiple new treatments in MM which have transformed the treatment paradigm of multiple myeloma MM and markedly improved patient outcome. Besides Proteasome inhibitors (bortezomib, carfilzomib, ixazomib), immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide), and monoclonal antibodies (daratumumab, isotuximab, elotuzumab), molecules with novel mechanisms of action are now available. This includes histone deacetylase inhibitor panobinostat, nuclear transport inhibitor selinexor, antibody-drug conjugate belantomab mafodotin, and a drug-peptide agent melflufen. These agents have all been translated from our laboratory studies to clinical trials and now available for treatment of multiple myeloma.

Our current focus of research is directed at developing immune-based and targeted therapies. The later demonstrated in effectiveness of venetoclax/proteasome combination therapy in t(11:14) MM. However, the immediate excitement and promise is driven by immunothereutic approaches. Especially the high response rates and survival outcomes in advanced relapsed refractory myeloma patients with the BCMA-targeted CAR T cell therapy leads the way. Our recent results from larger studies show between 75-90% response, with close to half patients achieving deep MRD negative response and manageable toxicity with anti-BCMA CAR T cell therapy has begun to transform our therapeutic algorithm. Multiple efforts are already underway in our Program to improve upon these results, including strategies to understand mechanism of resistance or relapse, enhance memory T cells, utilize alternative targets such as GPRC5d and FcRL5 as well as develop Binary Activated T Cell with Chimeric Antigen Receptor (BAT-CAR) to allow for targeting multiple tumor antigens with already approved therapeutic MoAbs. Simultaneously antibody targeting using bispecfic T cell engagers (BiTes) are achieving high rates of response and favorable side effect profile in RRMM. Novel therapies under investigation will target the ubiquitin proteasome cascade (PIs, ubiquitin receptor and deubiquitylating inhibitors) to overcome PI resistance, induce immunogenic cell death, thereby triggering selective anti-MM immunity, and target DNA repair pathways to impact genomic instability.

We have also led efforts to define Minimal residual disease (MRD) negativity in MM and shown that it can now be achieved with combination therapies both in newly diagnosed and relapsed MM with significant impact on survival. The current state-of-the-art in MM therapy is to use 3- and more frequently 4-drug combination followed by consolidation with therapy such as high-dose melphalan with autologous stem cell transplantation, or in future, therapies such as CAR T cells, to achieve a high level of MRD negativity, including in patients with high-risk disease with prolonged disease-free survival.

PS01

Evolution in acute leukemia diagnosis and its place on treatment– Lessons from T-ALL to AML

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Acute Leukemias (AL) have always been at the forefront of innovative diagnostics, partly since sampling blood and bone marrow is relatively easy but also since hematology in most countries is a mixed clinical and laboratory specialty, thus favoring rapid integration of technological evolution into medical practice.

In the last 3 decades, development of cellular and molecular techniques has allowed division of Acute Leukemias into a large number of subtypes, with an increasing number benefitting from "personalized/targeted" treatment, based on the paradigms of Tyrosine Kinase inhibition in BCR-ABL+ B cell Precursor Acute Lymphoblastic Leukemia (ALL) or Retinoic Acid modulation in Acute Promyelocytic Leukemia (APL). Despite this, the initial, essentially flow cytometric, diagnostic distinction between ALL and AML has changed little and attempts to clarify mixed phenotype AL (MPAL) has so far had little impact on individual patient management, despite the fact that they are generally considered to be of poor prognosis. AL with characteristics of B or T lymphoid and Myeloid lineage differentiation are much more common that mixed B/T AL, in keeping with current understanding of early hematopoiesis and progressive distinction of T/M and B/M MPAL, which are genetically distinct. Whether these cases should be treated as ALL, AML, or on specific interface protocols is unknown and the response may differ in children and adults.

T-ALLs represent a minority of ALLs in both adults (25%) and children (13%). Those with an immature stage of maturation arrest have similarities to AML and have been defined either phenotypically as Early Thymic Precursor (ETP) ALL or immunogenotypically as Immature (IM) T-ALLs lacking T Cell Receptor beta (TRB) complete VDJ rearrangement. Both overlap with, but are not synonymous to, T/M P-MPAL. They are associated with distinct genotypic abnormalities, many of which converge on over-expression of HOXA homeotic transcriptional regulators and/or epigenetic deregulation. Recent data suggest that an immature hematopoietic cell of origin and founding genetic lesions prime pediatric MPAL cells for lineage promiscuity, rather than an accumulation of distinct genomic alterations (Alexander TB et al. Nature 2018 PMID: 30209392). Bioinformatic classification of, predominantly adult, immature T-ALLs and AML, along a continuum of hematopoietic differentiation identified interface AL (IAL) which shared gene expression programs with multi or oligopotent hematopoietic progenitor populations, including the most immature CD34+CD1a-CD7- subset of ETP (Bond J et al. Leukemia. 2020 PMID: 32655144). Surprisingly, within these IALs, transcriptional resemblance to early lymphoid progenitor populations and biphenotypic MPAL was more evident in cases originally diagnosed as AML, rather than T-ALL. Prognostic analyses revealed that expression of IAL transcriptional programs significantly correlated with poor outcome in independent AML patient cohorts. These results suggest that traditional binary approaches to acute leukemia categorization are reductive, and that reproducible identification of T/MPAL and IAL could allow better treatment allocation and evaluation of therapeutic options. Ideally, this distinction will be phenotypic, which implies identification of appropriate markers and modification of current diagnostic criteria. It also requires concerted construction of prospective therapeutic trials for these rare subtypes, both within and between AML and ALL cooperative groups, probably at an international level.

JOINT SYMPOSIUM

JS01-1

Regulating regulatory T cells for enhancement of cancer immunotherapy

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Regulatory T (Treg) cells have an immunosuppressive function in cancer, but the underlying mechanism of immunosuppression in the tumor microenvironment (TME) is unclear. Of interest, tumor-infiltrating (TI) Treg cells display a distinctive phenotype and function compared to peripheral Treg cells. One characteristics of TI Treg cells is very high level expression of PD-1. Indeed, PD-1 expression in TI Treg cells was even higher than in TI CD8 T cells, but its function in Treg cells is yet to be revealed. To investigate the mechanism of PD-1 in Treg cells, we established Treg-specific conditional PD-1 knock-out mouse. When various cancer cells are injected into Treg-specific PD-1 deficient mice, tumor growth was delayed than PD-1 intact mice. Treg cells in Treg-specific PD-1 deficient mice showed more apoptotic phenotype and less suppressive function than in PD-1 intact mice. To compare the phenotype and function of PD-1 deficient and intact Treg cells in the same TME, we used PD-1 heterozygous mice, in which both types of Treg cells co-exist. PD-1 deficient Treg cells show less proliferative and unstable phenotype than PD-1 intact Treg cells in the same TME. Taken together, we suggest that PD-1 signaling maintains stability and function of regulatory T cells in the tumor microenvironment.

JS01-2

IL-17-producing cells in tumor

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Multiple types of immune cells producing IL-17 are found in the tumor microenvironment; however, their roles in tumor progression and CD8+ T cell exhaustion remain controversial. Recent advances revealed that at least two exhaustion states exist among PD-1+ CD8+ TILs based on the expression of TCF-1 and TOX. We found that depletion of CD4+ T cells promoted the exhaustion of CD8+ T cells with a concomitant increase of IL-17-producing CD8+ T cells in tumor. Adoptive transfer of IL-17-producing tumor-specific T cells increased, while depletion of IL-17-producing cells decreased, the frequency of terminally exhausted CD8+ T cells in tumor. Blockade of RORγt or IL-17 pathway not only inhibited terminal exhaustion of CD8+ T cells, but also delayed tumor growth. Moreover, a strong positive correlation between type 17 and terminal exhaustion signature gene sets was found in multiple human cancers. These findings unveil a novel role for IL-17-producing cells as critical pro-tumorigenic cells that promote CD8+ T cell exhaustion in the tumor, and propose type 17 immunity as a promising target for cancer immunotherapy.

JS01-3

Pro-inflammatory cytokines in graft-versus-host disease (GVHD)

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Several studies have demonstrated that genetic variation in cytokine genes can modulate the immune reactions after allogeneic hematopoietic cell transplantation (HCT). High mobility group box 1 protein (HMBG1) is a pleiotropic cytokine that functions as a pro-inflammatory signal, important for the activation of antigen presenting cells (APCs) and propagation of inflammation. HMGB1 is implicated in the pathophysiology of a variety of inflammatory diseases, and we have recently found the variation in the HMGB1 gene to be associated with mortality in patients with systemic inflammatory response syndrome. Various cytokines is biologically distinct in that they are composed of functional heterodimers, which bind to cognate heterodimeric receptor chains expressed on T cells. Of these, HMGB1 have been documented as proinflammatory mediators of GVHD, responsible for T helper 1 (Th1) differentiation and T helper 17 (Th17) stabilization, respectively. The role of IL-27 is less defined, seemingly immune suppressive via IL-10 secretion by Type 1 regulatory (Tr1) cells yet promoting inflammation through impairing CD4+ T regulatory (Treg) development and/or enhancing Th1 differentiation. So, we directed at discussing the current literature relevant to HMGB1 cytokine and cognate receptor engagement, as well as the consequential downstream signaling implications, during GVHD pathogenesis. Additionally, we will provide an overview of translational strategies targeting the HMGB1, their receptors, and subsequent signal transduction to control GVHD.

JS01-4

Harnessing adaptive natural killer cells for immunotherapy in multiple myeloma

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Natural killer (NK) cells are innate lymphoid cells that represent 5~15% of peripheral blood lymphocyte and are endowed with potent cytotoxic function that provide first-line defense against pathogens and cancer cells. NK cells exert their cytotoxic functions by the integration of multiple signals from activating and inhibitory receptors, which are not antigen-specific. This enables NK cells to be active without immunologic priming, leading them to quickly and effectively kill target cells by releasing cytotoxic granules containing perforin and granzyme. In addition, by releasing members of the tumor necrosis factor family of molecules, NK cells upregulate death ligands on their surface, such as FAS ligand and TRAIL, that bind to death receptors on cancer cells, activating the caspase pathway to induce apoptotic cancer-cell death. NK cells also produce IFNγ upon engagement with their cognate receptors and activate the adaptive immune response through pleiotropic effects on their neighboring immune effector cells including T cells, macrophages, and dendritic cells.

Importantly, NK cells are the primary mediator of the antibody-dependent cellular cytotoxicity (ADCC) by which therapeutic antibodies exert antitumor effector functions. Notably, a subset of NK cells have been identified to harbor adaptive immune features including memory-like properties, such as long-term persistence, robust preferential expansion in response to viral infection, and enhanced antibody-dependent effector functions. This distinct subset of NK cells is characterized by a lack of FcεRIγ expression or high expression of NKG2C, which is used as a marker for adaptive NK cells. Unlike conventional NK cells, adaptive NK cells have been shown to robustly induce ADCC in viral infection. In parallel with the recent therapeutic advances for the treatment of multiple myeloma (MM) with monoclonal antibodies such as daratumumab and isatuximab, there are on-going efforts to predict and enhance ADCC by employing adaptive NK cells.

Besides harnessing adaptive immune features of NK cells, NK cells have emerged as an alternative platform for chimeric antigen receptor (CAR) engineering to avoid toxicities induced by CAR T-cell therapy such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS), both of which are obstacles to successful cell-based immunotherapy. Moreover, NK cells have the potential for off-the-shelf cellular immunotherapy that may provide a fast and affordable option for cancer patients by presenting safe and effective option without graft-versus-host disease as demonstrated in recent clinical trials. Recent works are also under active investigation to combine CAR engineered NK cells with checkpoint inhibition to enhance NK-cell effector functions, which implies both biologic challenges and future perspectives imposed by NK cells.

Better understanding of the distinct features and the mechanisms that enable effector functions of NK cells against not only in MM but also in other hematologic malignancies will enable NK cells from a safe treatment option to a major player in cellular immunotherapy in cancer.

JS02-1

Single cell RNA sequencing reveals transcriptional programs associated with myeloma progression

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Single cell RNA sequencing allows characterization of heterogeneous tumor cells along with neighboring stromal and immune cells in the tumor microenvironment. Using the powerful technology, we explored transcriptional changes in the myeloma cells and associated immune microenvironment during myeloma progression, especially dissemination to the ascites or pleural effusion. Comparisons of single cell transcriptomes revealed systematic pathway activation of proliferation, antigen presentation, proteasomes, glycolysis, and oxidative phosphorylation in extramedullary myeloma cells. The myeloma cells expressed multiple combinations of growth factors and receptors, suggesting autonomous and pleiotropic growth potential at the single cell level. Comparisons of the tumor microenvironment revealed the presence of cytotoxic T lymphocytes and NK populations both in the bone marrow and extramedullary ascites. These cytotoxic cells demonstrated a gene expression phenotype indicative of functional defects. For the proliferation and immune adaptation, distinct molecular pathways are employed for different patients, i.e. various set of myeloma growth factors-receptors and tactics for immune evasion. These results suggest that treatment strategies targeting molecular pathways in myeloma require patient stratification according to the molecular pathway activation.

JS02-2

Multi-omics analysis and modeling of DNA methylation in cancer

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DNA methylation is a major gene regulation mechanism in the cell, and analysis of DNA methylation data is naturally related to omics data of other types, in particular, gene transcripts and genomic mutations. We have been analyzing DNA methylation array and sequencing data for more than a decade. In this talk, I will share three of our recent works in analyzing DNA methylation data.

The first work is to investigate on the genome-wide effect of mutations in DNA methylation modifiers to genome-wide methylation landscape and the activation of downstream genes. For this study, we associate differentially methylated regions (DMR) and differentially expressed genes (DEG) between mutated and non-mutated groups in 11 cancer types, and DMR-DEG integrated network analysis. Among DMR-DEG clusters, we identified 54 hypomethylated promoter DMR up-regulated DEGs in LAML and 45 hypermethylated promoter DMR down-regulated DEGs in COAD. The second work is to measure intra-tumor heterogeneity using bulk cell RRBS DNA methylation sequencing data. We present PRISM, a tool for inferring the composition of epigenetically distinct subclones of a tumor solely from methylation patterns obtained by reduced representation bisulfite sequencing (RRBS). A set of statistics collected from each genomic region is modeled with a beta-binomial mixture. Fitting the mixture with expectation-maximization algorithm finally provides inferred composition of subclones. Applying PRISM for two acute myeloid leukemia samples, we demonstrate that PRISM could infer the evolutionary history of malignant samples from an epigenetic point of view. The final work is to use the deep learning technology to model potential energy of DNA methylation pattern (DMP). Abundances of DMPs is modeled as Boltzmann-Gibbs distribution upon the potentials. Having the problem reduced to finding a general function that translates the local biological context (multi-omics) to potential energy levels, we train a deep neural network model that takes genome sequence, abundances of histone marks, and chromatin accessibility levels as input features and produces the potential energy levels of DMPs as output. Dissecting and interpreting the trained model lets us prioritize the genomic or epigenomic elements, such as DNA motifs and histone marks, based on their contribution to shaping the DMP potential landscapes. Furthermore, we develop a web application that allows experimental biologists to freely conduct in silico mutagenesis experiments using our models. We therefore expect that our model will also serve as a powerful hypothesis-generating tool for DNAm studies.

JS02-3

Clinical application of next-generation sequencing in acute myeloid leukemia

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Application of next-generation sequencing (NGS) on acute myeloid leukemia (AML) has expanded our knowledge of genomic alterations. Advances in high-throughput sequencing technology have allowed new insights into risk stratification in AML according to the molecular profile. Diagnostic workup of AML should include screening for mutations for defining the disease categories (NPM1, CEBPA, RUNX1, ASXL1, FLT3-ITD), selecting the targetable agents (KIT, FLT3-ITD, FLT3-TKD, IDH1/2), and predicting the prognoses (TP53, ASXL1, RUNX1). The testing for gene panel allows us to identify such genetic mutations simultaneously, and it also allows simultaneous monitoring of multiple mutations as a target for a measurable residual disease (MRD) monitoring with relatively high sensitivity. NGS-based assays are attractive as an MRD monitoring tool in AML patients because most of AML patients accompanied the targetable mutations with NGS panel. Assessment of measurable residual disease (MRD) after induction therapy using NGS has been shown to predict relapse risk and treatment outcomes in AML. Accordingly, the early intervention of all-SCT could be suggested as a relevant decision to reduce the relapse risk in patients with persistent mutations at remission. However, its application in the clinical setting is still challenging. Here, I briefly introduce the using of NGS to AML for a diagnostic and therapeutic approach.

JS02-4

Challenges in the introduction of next-generation sequencing for diagnostics of hematologic malignancies

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Over the past decade, next-generation sequencing (NGS) has led to an exponential increase in our understanding of the genetic basis of hematologic malignancies. Introduction of NGS methods into clinical diagnostic laboratories has created an opportunity to profile the multiple actionable driver genes in patients with known and/or suspected hematologic malignancies. NGS technologies have been applied to hematological disorders in a variety of contexts: guiding diagnosis, subclassification, prognosis, and minimal residual disease (MRD) testing, often allowing the identification of novel mutations.

Unlike most solid tumors, acute myeloid leukemia (AML) genomes appear to have a limited number of mutations, with an average of 13 mutated genes per case. In addition to the pre-established FLT3 and NPM1 genes, other genes including DNMT3A (20-25%), IDH1/IDH2 (15-30%), TET2 (10%), ASXL1 (5-16%), CEBPA (10-18%), WT1 (10-13%), RUNX1 (5-13%), RAS (20-30%), TP53 (~2%) have been shown to be mutated in AML. Based on functional analysis and known pathways, the genetic abnormalities can be grouped into categories based on biological function: (1) myeloid transcription-factor fusions or mutations, (2) NPM1 mutations, (3) tumor-suppressor gene mutations, (4) epigenome-modifying gene mutations, (5) activated signaling-pathway gene mutations, (6) cohesin-complex gene mutations, and (7) spliceosome-complex gene mutations. From analysis of mutual exclusivity and cooccurrence between these genetic abnormalities, patterns of interplay between pathways were identified that may help delineate further subsets of AML and provide more insight into disease biology.

Somatic mutations in several genes are present in B-cell precursor acute lymphoblastic leukemia (BCP-ALL). These mutations have identified in genes which are involved in RAS signaling (48%), B-cell differentiation and development (18%), JAK/STAT signaling (11%), TP53/RB1 tumor suppressor (6%) and noncanonical pathways and in other/unknown genes (17%). Moreover, copy number changes involving IKZF1, CRLF2, PAX5 and EBF1 have been implicated in BCP-ALL with clinical significance. T-cell acute lymphoblastic leukemia (T-ALL) has been associated with four different classes of mutations: (i) Affecting the cell cycle (CDKN2A/CDKN2B); (ii) Impairing differentiation (HOX genes, MLL, LYL1, TAL1/2 and LMO1/2); (iii) Providing a proliferative and survival advantage (LCK and ABL1); (iv) Providing self-renewal capacity (NOTCH1).

Mutation analysis in multiple myeloma (MM) showed KRAS as the most commonly mutated gene, followed by NRAS, TP53, DIS3, FAM46C, and SP140. Clonal evolution and disease progression was also noted in association with mutations in FAM46C, FAT1, KRAS, NRAS, SPEN, PRDM1, NEB, TP53 and XBP1. In recent years, NGS has also allowed the acquisition of important molecular information in a variety of lymphoid tumors, including Hodgkin's lymphoma, diffuse large B-cell lymphoma, Burkitt's lymphoma, chronic lymphocytic leukemia, follicular lymphoma, mantle-cell lymphoma, hairy-cell leukemia, and splenic marginal zone lymphoma. Key genes include BRAF, MYD88, and NOTCH2 and have provided scientific evidence that might be useful for clinical treatment, as well as for the diagnosis and progression of these diseases.

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JS03-1

Clonal evolution under IDH inhibitor therapy in AML

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Effective and highly targeted therapies have become reality in AML over the past few years. IDH1/2 mutations are present in ~20% of AML patients and as of 2018, two inhibitors targeting mutant IDH enzyme: Ivosidenib (IDH1i) and Enasidenib (ENA, IDH2i) have been FDA-approved for treatment of relapsed-refractory AML. Furthermore, recent clinical trials have demonstrated greater efficacy of IDHi when used in combination with other AML treatments including chemotherapy and hypomethylating agents, thus increasing the likelihood that IDHi has an important role in upfront therapy for AML patients. In this talk I will discuss what we currently understand about the mechanism of action of IDHi in AML, and how clonal heterogeneity in IDH mutant AML can affect response and resistance to IDHi and how this could inform how we combine drugs to improve clinical outcomes.

JS03-2

Predicting drug sensitivity for personalized therapy of AML

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High-dose chemotherapy and allogeneic hematopoietic stem cell transplantation (alloHSCT) can cure up to 60-70% of younger patients with adult acute myeloid leukemia (AML), but many relapse and suffer from life-long toxicities of treatment. Refractory or relapsed AML patients have limited treatment options, and survival has remained poor. Genomic profiling has helped to deconvolute the biological basis and heterogeneity of AML and highlighted novel therapeutic targets and subgroups (e.g. FLT3, IDH1/2, BCL2). However, not all patients respond to these treatments and many experience relapse. In addition, for majority of AML patients, no actionable mutations are available to guide therapy decisions, hence limiting our ability to optimize therapy for individual AML patients.

We and others have utilized ex vivo testing of AML cells to functionally identify individualized treatment options for patients. We have implemented ex vivo drug sensitivity and resistance testing (DSRT) of AML patient cells against 347 emerging and 168 approved cancer drugs. Molecular and functional data were interpreted and integrated for an individual patient to consider novel therapy options for R/R AML patients. To implement the results in real-time for clinical translational, we designed a multidisciplinary functional precision medicine tumor board. Integration of genomics and transcriptomics with functional data identifies predictive biomarkers, subgroups of patients responding to specific drugs, as well as a potential mechanism-of-action of drugs. Such information can then be approved to refine, validate and improve the functional precision medicine tumor board process and the rules that are used to translate data to clinical practice.

JS03-3

TET loss-of-function in malignant hematopoiesis

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The methylation of cytosine followed by subsequent oxidation constitutes a fundamental epigenetic modification in mammalian genomes, and its abnormalities are intimately coupled to the onset and progression of cancer. Proteins of the TET family (TET1, TET2 and TET3) are dioxygenases that utilize a-ketoglutarate, reduced iron and molecular oxygen to catalyze iterative oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and subsequent oxidized products. Besides being transient intermediates in the reversal of cytosine methylation, these oxidized 5-methylcytosine derivatives represent stable epigenetic marks that fundamentally influence chromatin organization and gene expression. Of note, loss of TET function is commonly observed in a wide spectrum of cancers and often leads to marked disruption of DNA methylation and hydroxymethylation profiles in mammalian genome. Particularly, TET loss-of-function is strongly associated with hematologic malignancies of lymphoid and myeloid origin as well as diverse solid cancers and the molecular mechanism underlying oncogenesis driven by loss of TET function has been being unraveled. Here, I will introduce previous key observations on the role of TET proteins in normal and malignant hematopoietic development, with an emphasis on the pivotal functions of TET proteins in controlling genome-wide DNA methylation patterns, cell lineage commitment and genome integrity during hematopoiesis. Understanding the impact of TET dysregulation during oncogenesis may provide novel avenues to develop effective epigenetic therapy applicable to cancers.

JS03-4

Novel small molecule drug discovery to override NRAS-mutated AML

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RAS has long been deemed undruggable mainly due to the lack of traditional druggable pockets even though various attempts have recently been made to directly target mutant KRAS. Oncogenic forms of NRAS are frequently associated with hematologic malignancies and melanoma, especially are common in acute myelogenous leukemia (AML). We have recently reported that a pyrimidopyrimidinone derivative potently and selectively inhibits mtNRAS-dependent cells in pre-clinical models of AML. Mechanistic analysis through chemical biology approaches revealed that its effects are mediated through combined inhibition of ACK1 (Activated CDC42 kinase 1) and GCK (germinal center kinase). The first attempt for overriding AML having NRAS mutations with ACK1-GCK dual kinase inhibitors will be presented.

JS04-1

Epigenetic control in T-ALL

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T-ALLs are aggressive hematological tumors comprised of distinct, clinically relevant subgroups. These subgroups are defined by the mutually exclusive expression of a series of oncogenic transcription factors and by specific gene expression signatures that reflect arrest at specific stages of T cell differentiation. Current chemotherapy treatments do not distinguish between T-ALL subgroups, which results in variable therapeutic responses that are often coupled with high toxicity and relapse.

Here, I will focus on a subtype of T-ALL characterized by expression of the homeobox transcription factor TLX1. While expression of TLX1 is normally restricted to embryonic development, aberrant expression of TLX1 can occur in T cell progenitors as a result of chromosomal translocations that place *TLX1* under control of regulatory elements of the T cell receptor locus, ultimately leading to differentiation arrest and leukemia. The direct role of TLX1 in T cell transformation has been demonstrated through forced expression of *TLX1* in transgenic mice that developed clonal T cell leukemia. Furthermore, the knockdown of TLX1 in T-ALL cells led to massive apoptosis showing that TLX1 is required for leukemia maintenance. However, the epigenetic cofactors that mediate TLX1 activity in T-ALL are currently unknown and we lack a mechanistic understanding of TLX1's role in promoting leukemia development. Using a combination of proteomic and genomic approaches, we identified epigenetic cofactors that interact and co-localize with TLX1 in T-ALL. Furthermore, using knockdown and ectopic expression of TLX1 in leukemic cells and TLX1 transgenic mice, we show that TLX1 is involved in establishing and maintaining an aberrant gene expression program in T-ALL cells, contributing to leukemic cell growth. Furthermore, we provide evidence that pharmacological approaches that target these cofactors could represent promising therapeutic approaches.

Overall, our results provide important new insights to our understanding the mechanism contributing to T-ALL development and maintenance.

JS04-2

CAR T cells for leukemia: What is next?

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T cells may be genetically modified to recognize tumor antigens through the introduction of genes encoding chimeric antigen receptors (CARs) composed of the binding domain of the an antibody specific to the tumor associated antigen fused to a transmembrane domain fused to the cytoplasmic signaling domains of a costimulatory receptor (CD28, 4-1BB and the CD3 zeta chain. Resulting T cells can recognize and kill tumor cells which express the targeted antigen. To date, this CAR T cell approach has seen significant success in the context of B cell tumors including ALL and DLBCL with patient T cells targeted to the CD19 B cell antigen. Further, in the setting of multiple myeloma, clinical success has been seen treating relapsed and refractory disease with T cells modified to express a CAR specific to the BCMA antigen expressed on myeloma tumor cells. While these clinical outcomes are promising, most patients with hematologic malignancies treated with CAR T cells either fail to respond or more commonly ultimately relapse. This may be due to multiple factors including loss of target antigen expression, lack of CAR T cell persistence, or immune suppression within the tumor microenvironment. For this reason, next generation CAR T cells are required to overcome these current limitations. Approaches to enhance CAR T cell efficacy include further genetic modification of the CAR T cells to secrete pro-inflammatory cytokines or co-stimulatory ligands as well as further modification of the CAR itself. These approaches have shown promise in the preclinical setting but will require further evaluation through translation in the clinical setting.

JS04-3

Current concepts in the management of relapsed/refractory ALL in Korea

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Acute lymphoblastic leukemia (ALL) is an aggressive hematological disease arising from lymphoid precursor cells. Modern chemotherapeutic regimens and allogeneic cell transplantation (allo-HCT) improved the remission rates and improved survival rates. However, the outcomes for adult patients remain suboptimal with 5-year survival rates of only 30%-40%. Moreover, the outcomes for relapsed and refractory (R/R) ALL remain poor. With the advent of a bispecific antibody and an antibody conjugate, the outcomes of R/R B-cell precursor ALL (BCP-ALL) have been significantly improved. Salvage therapy with these agents followed by allo-HCT became the standard of care for patients with R/R BCP-ALL. Recent study of the Korean Society of Hematology ALL Working Party showed that among the 49 patients, 22 (44.9%) achieved complete response (CR) or CR with incomplete blood count recovery, and 16 of whom subsequently underwent allogenic stem cell transplantation. The median event-free survival and overall survival of the responders were 7.5 and 8.1 months, respectively. In this session, several cases of R/R BCP-ALL and the data of R/R BCR-ALL treated with these agents will be presented.

JS04-4

Pediatric acute lymphoblastic leukemia in Korea

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The cure rate of acute lymphoblastic leukemia (ALL) in children dramatically improved over past 5 decades from zero to about 80%. The main cause of improvement is owing to the development of chemotherapy by multicenter clinical trial of large study groups with the understanding of leukemia biology. Recently, pediatric ALL protocols were applied to the treatment of adolescent and even adult ALL patients. For about 30 years, clinical factors have been used to risk-stratify therapy for children with ALL, so that the most intensive therapies are reserved for those patients at highest risk of relapse. The risk groups of ALL are divided as standard- , high- and very high-risk group according to the prognostic factors, and treatment results improved by this risk based treatment. The factors used to risk-stratify therapy include age, gender, presenting leukocyte count, immunophenotype, genetic aberrations, and response of treatment. Despite the improvement of outcomes in pediatric ALL, we found some remained problems in Korea in year 2005. First the nationwide outcome of high risk ALL was not so satisfactory. Second, the outcome of very high risk ALL was not so satisfactory. Third, the outcome of relapsed patients was very poor. To improve the nationwide outcome of ALL in children and adolescent, multicenter clinical studies had been conducted for high risk, very high risk and relapsed ALL from 2005 which was supported by a grant from National R&D Program for Cancer Control, Ministry for Health & Welfare and from 2014 second trials were begun for the same risk groups. Now we are planning new trials and will launch those soon. The results of previous and ongoing Korean pediatric ALL clinical trials and future direction will be presented in this talk.

JS05-1

Immunotherapy in AML: From alloSCT towards CAR-T cell therapy

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JS05-2

The emerging role of MRD in AML

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Prognostic factors determined at diagnosis are predictive for outcome while achievement of morphological complete remission(CR) is still an important endpoint during treatment. Residual disease after therapy may reflect the sum of all diagnosis and post-diagnosis resistance mechanisms/factors, its measurement could hypothetically be very instrumental for guiding treatment. The possibility of defining residual disease (measurable residual disease:MRD) far below the level of 5% blast cells has changed the landscape of risk classification.[1,2] Currently the two methods mostly used are flowcytometry based immune MRD(MPFC) and molecular MRD assessed by RT-qPCR. Both have advantages and disadvantages. MPFC can be applied in most cases of AML but is less sensitive then RT-qPCR which can however only be applied in 40% of cases. But new technologies are emerging like next generation sequencing and digital droplet PCR.

Although the concept of MRD negativity as an indicator for the quality of treatment response is the same in AML and other hematological diseases such as chronic myeloid leukemia (CML), multiple myeloma (MM), and acute lymphoblastic leukemia (ALL), application of MRD assessment in AML has lagged behind. Retrospective single center studies already demonstrated that MRD detection by MPFC provides strong prognostic information in AML after both induction and consolidation therapy. A couple of studies have now also been performed prospectively in a multicenter setting showing the independent prognostic value mainly determined after 2 cycles of chemotherapy.[2,3,4,5] An example indicative for the usage of molecular MRD was recently published by Ivey et al who showed that the presence of MRD, assessed by q-PCR of NPM1-mutated transcripts, provided powerful prognostic information independent of other risk factors. Persistence of NPM1-mutated transcripts in blood was present in 15% of the patients after the second chemotherapy cycle and was associated with a greater risk of relapse after 3 years of follow-up than was an absence of such transcripts (82% vs. 30%; hazard ratio, 4.80) and a lower rate of survival (24% vs. 75%; hazard ratio, 4.38 [4.] Recently a meta-analysis of 81 publications reporting on 11 151 patients was performed. The average HR for achieving MRD negativity was 0.36 for OS and 0.37 for DFS. The estimated 5-year DFS was 64% for patients without MRD and 25% for those with MRD, and the estimated OS was 68% for patients without MRD and 34% for those with MRD. The association of MRD negativity with DFS and OS was significant for most subgroups.[4a]

Evidence is accumulating that the presence of MRD assessed by multi-color flow cytometry immediately prior to allogeneic HCT is a strong, independent predictor of post-transplant outcomes in AML.[5] In a recent update, Araki et al showed that in 359 adults, the 3-year relapse rate was 67% in MRD positive patients, compared to 22% in MRD negative patients, resulting in OS of 26% vs 73%, respectively.[6] Depth of response prior to transplant, as measured by level of MRD, has emerged as one of the most important predictors of transplant outcome. Collectively, all these studies showed that low levels of MRD were associated with improved survival and lower risk of relapse superior to other well-defined prognostic factors such as AML type, age, WBC count at diagnosis, and classification of cytogenetic risk. Randomized trials are warranted to determine if MRD-guided pre-emptive therapy is associated with improved outcome. ELN published recommendation for the application of MRD.[9] These will soon be updated.

Most available data are derived form studies with intensive treatment but now also more recent data show that also in non-intensive treated AML patients MRD has prognostic impact.

MRD assessment in AML could be used 1) to provide an objective methodology to establish a deeper remission status, 2) to refine outcome prediction and inform post-remission treatment, 3) to identifyimpending relapse and enable early intervention, 4) to allow more robust post-transplant surveillance, and 5) to use as a surrogate endpoint to accelerate drug testingand approval.

Various major AML trial groups now use MRD status to guide further treatment. The question whether MRD could be used as a surrogate endpoint for survival which would be very helpful for faster dug approval is still unsolved. It is important to recognize that MRD assessment should be part of every clinical trial in order to achieve this important goal.

New technologies evolve rapidly and will be discussed:

- next generation sequencing has been shown of prognostic value in clinical studies, although sensitivity is still low it is expected that this will change rapidly. [10,11]
- assessment of the leukemic stem cell load is also prognostic for outcome. [12]
  Combinations of various methods are additive and increase the sensitivity: examples will be discussed[10].

JS05-2

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JS05-3

Therapeutic potential of ATO to overcome resistance of Bcl-2 inhibitor in AML

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Acute myeloid leukaemia (AML) is a heterogeneous haematological malignancy involving haematopoietic stem cells (HSCs) and progenitor cells [1, 2]. Although a substantial proportion of AML patients achieve complete remission with intensive cytotoxic chemotherapy, most patients succumb to disease relapse [1-3]. AML relapse is considered to originate from leukaemia stem cells (LSCs), which are metabolically quiescent, capable of self-renewal, and responsible for chemotherapy resistance [4, 5]. Therefore, more effective therapeutic strategies targeting LSCs are required to improve the cure rate in AML.

Bcl-2 protein is frequently overexpressed in AML LSCs [6]; this overexpression is associated with chemotherapy resistance, culminating in dismal clinical outcomes [7]. In this regard, development and clinical trials of Bcl-2 inhibitors have been conducted during recent years [8]. Venetoclax (ABT-199) is a BH3 mimetic, which selectively inhibits Bcl-2 and stabilises proapoptotic proteins [9]. It was shown that venetoclax is capable of inducing LSC cytotoxicity while largely sparing normal HSCs [10]. However, the biological and clinical actions of venetoclax employed as a single agent have produced unsatisfactory results in AML [8]. Thus, the combination approach was developed, leading to approval for the use of venetoclax in combination with DNA methyltransferase inhibitors or low-dose cytarabine for elderly patients with newly diagnosed AML and for those patients deemed unfit for conventional cytotoxic chemotherapy [11-15]. However, up to one-third of patients do not respond to these regimens [16, 17]. In addition, the majority of AML patients who achieve a remission after receiving these combination therapies ultimately relapse, with a median duration of response of only about a year [16, 17]. Hence, there is an urgent requirement to elucidate the molecular mechanism underlying venetoclax resistance and develop novel combination strategies to target and overcome this resistance.

According to the mechanism of venetoclax resistance in AML, drugs with different mechanisms are selected in hopes of overcoming the resistance to venetoclax, which can be used in combination with venetoclax. Mcl-1 is a critical antiapoptotic protein that regulates cell survival in AML (18-20). Mcl-1 upregulation coincides with episodes of relapse in chemotherapy-treated AML, emphasising the role of Mcl-1 in the development of drug resistance (21, 22). Furthermore, emerging evidence suggests the upregulation of Mcl-1 protein as one of the mechanisms underlying acquired resistance to venetoclax treatment in AML (20-22). Therefore, selective inhibitors of Mcl-1 are currently being investigated in preclinical and clinical studies on haematological malignancies including AML (20).

A-1210477 is the first high-affinity, selective MCL1 inhibitor. It can synergistically inhibit the proliferation of BCL2/MCL1-dependent AML cell lines and induce apoptosis when combined with venetoclax [23]. VU661013, a novel, potent, selective MCL1 inhibitor, which destabilizes the BIM/MCL1 association, leads to apoptosis in AML and is active in venetoclax-resistant cells and patient-derived xenografts. It can synergize with venetoclax to kill AML cells [24]. S63845 is a selective MCL1 inhibitor that can selectively bind to the BH3-binding groove of MCL1, thereby effectively killing MCL1-dependent tumor cells, including MM, leukemia, and lymphoma cells [25]. A phase Ib clinical trial (NCT03672695) combining venetoclax with the selective MCL1 inhibitor S64315 is currently underway on patients with AML.

However, the clinical development programme for a safe and selective Mcl-1 inhibitor has proven challenging so far. The large size, high lipophilicity, poor pharmacokinetic profile, limited cell membrane permeability, and shallow binding groove on Mcl-1 are the major hurdles impeding the development of Mcl-1 inhibitors (24). Therefore, it is important to identify clinically available agents that interfere with Mcl-1 to augment the therapeutic efficacy of venetoclax in AML. Arsenic trioxide (ATO) is a potent agent against acute promyelocytic leukaemia (APL) (26) and imparts a significant survival benefit in patients with relapsed APL (27). The toxicity profile of the ATO and ATRA combination appeared to be mild, with minimal myelosuppression and manageable adverse effects. We investigated whether the combination of venetoclax and ATO efficiently promotes apoptosis in AML LSC-like cells. Using LSC-like cell lines, as well as CD34+CD38- primary AML cells and bone marrow (BM) cells from healthy donors, we demonstrated that the combination of venetoclax and ATO synergistically and selectively exhibits anti-AML activity in vitro, simultaneously sparing normal HSCs. We demonstrated that venetoclax-induced Mcl-1 upregulation is mitigated by ATO in AML LSC-like cells and revealed that downregulation of increased Mcl-1 levels is associated with the activation of GSK-3β. Our findings support a strategy for the development of an effective and safe non-chemotherapeutic–based AML treatment regimen using a successful combination of venetoclax and ATO.

Based on the mechanism of resistance in AML, the combination of specific drugs with venetoclax was a clinically optional treatment strategy for overcoming resistance to venetoclax. Venetoclax-based combination regimens are important treatment options for the treatment of AML.

JS05-3

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JS05-4

Measurable residual disease in acute myeloid leukemia

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The International Working Group (IWG) response criteria for acute myeloid leukemia (AML), published in 2003, have remained the standard by which the efficacy of new drugs is measured in clinical trials. Over the last decade, concepts related to treatment response have been challenged by several factors; for example, the dissociation between early clinical response and survival outcome in older patients, the recognition that epigenetic and newer differentiating-agent therapies may produce delayed responses and also hematologic improvement/transfusion independence without a morphologic response, and evidence that remissions without measurable residual disease (MRD) may result in outcomes superior to those of morphologic remissions with persistent MRD. The evolving role of MRD status as a potential surrogate for predicting long-term survival has enhanced the clinical need to standardize and incorporate emerging technologies that enable deeper responses beyond those recognized by the IWG, and to pre-emptively identify patients at risk of early relapse. MRD has prognostic importance for patients with AML, which is important in both the pre and post-allogeneic stem cell transplantation (HSCT) setting. Currently, MRD monitoring has been considered part of the standard of care for AML patients, and the European LeukemiaNet (ELN) proposed MRD negative complete remission as a new response criterion in 2017. Quantitative PCR and flow cytometry have been recommended by the ELN as the preferred methods of MRD, but these methods have limitations in cases without a disease-defining genotype and phenotype. Wilms tumor gens 1 (WT1) quantification by quantitative PCR, as an universal marker for MRD assessment, was recommended by ELN only if other MRD markers, including flow cytometric ones, are unavailable. As a new method for MRD assessment, next-generation sequencing (NGS) is a rapidly improving technology whose application to the monitoring of MRD is an active area of research. Clinical trials are currently ongoing to assess the use of NGS in the setting of HSCT for AML. Few studies have so far assessed the optimal methods of MRD monitoring in the posttransplant setting. The potential for therapeutic interventions to erase MRD and alter the natural history represents an important and open research question. This talk will introduce existing methods of MRD in AML with a focus on the utility of WT1 and NSG in patients undergoing HSCT.

ASIAN/MOU COUNTRY SESSION

AS01-1

Recent therapeutic approaches in CML: From Korean perspective

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The treatment of chronic myeloid leukemia (CML) is mainly based on tyrosine kinase inhibitors (TKIs): imatinib (first generation TKI), nilotinib, dasatinib, and bosutinib (second generation TKIs) are approved for front-line treatment; the same TKIs, plus ponatinib (third-generation TKI), are available beyond the first-line treatment in case of resistance or intolerance. The choice among different drugs is an opportunity for treating physicians, but this choice is frequently difficult and always controversial.
In Korea, Imaitinib, Dasatinib, Nilotinib, and Ratotinib is available with insurance reimbursement in front line treatment and ponatinib is available in second or third line treatment with insurance. Radotinib can be prescribed in front line treatment based on the RERISE study result. In clinical trial setting, bosutinib trial in front line treatment was finished and asciminib trial in Rel/Ref setting is ongoing,

The current treatment approach, particularly for first-line treatment, is based on factors additional to survival: age, disease risk, comorbidities, early and late safety, rapidity of response, and patient and physician expectations on TFR(treatment free remission). TFR is an achievable endpoint. Treatment discontinuation, followed by a strict monitoring, is clearly attractive for patients and physicians, minimizing the possibility of TKI-related adverse events, improving the long-term safety, and reducing the economic burden. Prerequisite for TFR in real world situation is long term stable deeper molecular remission (DMR). No direct comparisons of imatinib versus second-generation TKIs with TFR as primary endpoint are available, but, looking at available data, second-generation TKIs seem more promising when TFR is an attractive treatment goal. Nilotinib is the only drug approved for TFR.

Ongoing clinical trials and new trials will be introduced to Korea. CML treatment must be adapted, according to disease and patient characteristics. Comorbidities, tolerability, and long-term safety play a key role, as well as the efficacy. Asciminib appears to be a drug of promise but more information is needed. Living without treatment (treatment-free remission [TFR]) is no more an experimental end point, being more and more largely implemented in clinical practice.

AS01-2

Impact of socio-demographic co-variates on disease prognosis, TKI use and outcomes on patients with CML

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Objective: Define the impact of socio-demographic co-variates on outcomes in patients with newly-diagnosed chronic phase chronic myeloid leukaemia.

Methods: Data of 961 consecutive patients with newly-diagnosed CML were interrogated for these outcomes in multi-variable analyses after adjusting for confounders and interactions.

Results: Age ≥ 60 years was associated with less use of front-line 2nd generation TKI; ELTS in intermediate- or high-risk, more use of front-line 2nd generation TKI rather than imatinib. Rural household registration, co-morbidity and lower educational level were associated with use of a generic rather than branded TKI as initial therapy. Lower education level was associated with CML diagnosis because of CML-related symptom. Rural household registration, lower educational level, ELTS score in intermediate- and high-risk were also associated with a greater likelihood of switching TKI-therapy. Lower education level was associated with a higher likelihood of achieving a MMR and $MR^{4.5}$ and better FFS, PFS and survival after adjusting for TKI-therapy. Males had lower rates of MMR and $MR^{4.5}$ and worse FFS compared with females. Marital state correlated with higher rate of $MR^{4.5}$, better FFS, PFS and survival.

Conclusions: Socio-demographic co-variates have a strong impact on many ways including circumstances of diagnosis, prognosis, use of initial TKI, switching TKIs, response to TKI-therapy and outcomes in patients with chronic phase CML.

AS01-3

Recent therapeutic approaches in CML: From Japanese perspective

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ABL tyrosine kinases (TKIs) have significantly improved the prognosis of chronic myeloid leukemia (CML). The current goal of CML treatment is not prolongation of survival with TKIs but treatment free remission (TFR) to prevent adverse effects of long-term TKI administration and reduce the medical costs (*Cancer Sci*, 2020). Thus, we performed two clinical trials including Dasatinib DIscontinuation (DADI) trial and first-line DADI (1st DADI) trial with Japanese CML patients who had the second generation TKI, dasatinib treatment.

Firstly, the DADI trial which was a prospective, phase II multicentre trial was performed with CML patients who were treated with "*second- and subsequent-line*" dasatinib. After confirming stable deep molecular response (DMR) for at least 1 year, dasatinib treatment was discontinued in 63 CML patients. After discontinuation, loss of DMR was defined as molecular relapse, thereby triggering therapy resumption. The estimated overall TFR rate at 12 months and 36 months were, 48.0% (*Lancet Haematol* 2018) and 44.4% (*Clin Lymphoma Myeloma Leuk* 2018), respectively. The presence of imatinib resistance was as a significant risk factor for molecular relapse. Moreover, high NK cell and low regulatory T cell (Treg) counts before discontinuation correlated significantly with successful therapy discontinuation.

Currently, dasatinib is more popular than imatinib as first line treatment for CML in Japan. Thus, we conducted the 1st DADI, a prospective, phase II multicenter trial to investigate TFR in CML patients with sustained DMR for at least 1 year after discontinuation of "*first-line*" dasatinib. 58 patients were enrolled in this study. Overall probability of TFR at 12 months was 55.9% (*Lancet Haematol*, 2020). Notably, the median time of dasatinib administration was only 40.2 (range, 36–111) months. In 1st DADI trial, we could not find any impact of NK immunity for TFR rate. DADI and 1st DADI indicated that discontinuation of both first or after second- or subsequent-line dasatinib after a sustained DMR of at least 1 year was feasible.

Because of the inconsistencies in the 1st DADI and previous DADI trials with respect to the clinical significance of NK cell, we further examined the NK and T cell-mediated immunity in CML patients. We found that NK cell activation status contributes to achievement of DMR *(Cancer Immunol Res*, 2018), whereas T cell-mediated immunity contributes to TFR in patients with CML-CP (*Mol Cancer Ther*, 2021). To improve TFR rate after stop TKI, it is necessary to inivestigate the immune status in more detail.

AS02-1

Management of TDT and NTDT thalassemia in Indonesia

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Referring to the Weatherall DJ (2012) and the Thalassemia International Federation (TIF, 2013) the management of thalassemia patients in Indonesia can be categorized into the management of patients with thalassemia major (TM), thalassemia intermedia (TI) of transfusion-dependent thalassemia (TDT or TM phenotypes) and TI of non-transfusion dependent thalassemia (NTDT or thalassemia minor phenotypes) as well as thalassemia minor (TMin). TDT includes TM and TI of TDT (mostly HbE/β–thalassemia of severe forms). While NTDT comprises β-TI, HbE/β–thalassemia of minor and moderate forms and α-TI(HbH disease). TDT is defined for those who receive regular blood transfusion every 2 to 5 weeks. While NTDT is defined for those who have occasional/non-regular blood transfusion.

The Indonesian Guideline of Thalassemia Management comprises the main modality of the treatment for TM and TI-TDT which include safe, optimum and regular blood transfusion, adequate and safe iron-chelating agents (for those with serum ferritin > 1000 mg %) as well as the monitoring and treatment of complications. In the meantime for TI-NTDT, besides occasional/non-regular blood transfusion, adequate and safe iron-chelating agents are given to those patients with serum ferritin level lower than the TDT patients.

To provide safe blood donor, Nucleic Acid Testing (NAT) for hepatitis B, hepatitis C, and HIV and VDRL testing for syphilis are performed at regular voluntary non remunerated blood donors and leukocyte depletion of donor blood is recommended to obtain. Monitoring complications of TDT and NTDT includes the chronic anemia monitoring (with the target of Hemoglobin level post-transfusion of > 13 g % for male and > 12 g% for female and pre-transfusion of 10 g% for male and 9 g% for female) as well as iron overload and organ iron toxicities (using MRI T2* for cardiac, liver and pancreas iron toxicities monitoring beside serum ferritin level and transferrin saturation as surrogate markers of iron overload).

Iron chelating agents which are available in Indonesia include deferoxamine, deferiprone, and deferasirox which are given as monotherapy or in combination therapy (e.g. deferiprone and deferoxamine in patients with severe cardiac iron toxicity)

Those thalassemia patients have special access to the Indonesian National Health Insurance system with regards to blood transfusion and iron chelating agents. However, MRI T2* is only available in a few number of Thalassemia Center. NAT and leucodepleted donor blood are provided not in all blood donor bank/service. In certain areas, these NAT and leucodepleted donor blood are supported by a local government.

Complications of NTDT are similar to TDT complications of iron overload and iron organ toxicities. However, there are several complications occurred in NTDT which not appear in TDT, which include extra-medullary hematopoiesis due to chronic anemia (because NTDT patients do not receive regular blood transfusion which leads to chronic anemia), thrombosis (deep vein thrombosis, pregnancy loss, etc.) and others. A period of 2 to 6 years of age is a critical period for NTDT patient, since if those NTDT patients do not receive optimum blood transfusion during this period stunting may develop. In Indonesia, stunting thalassemia patients can easily be found. Therefore, early detection of thalassemia has been a project in the Current Indonesian Thalassemia Control Program) for early finding and treating appropriately for patients with TM -TDT (2 – 6 years of age) beside TM homozygote (during a period of 6 months to 2 years of age) to avoid those complications. Despite hematopoietic stem cell transplantation (HSCT) available in Indonesia, TM or TI-TDT patients who are eligible and affordable for allogeneic of TM-TDT (between 2 – 6 years of age) are referred to overseas transplantation centers which conduct this transplantation.

Referring to WHO and the Indonesian Ministry of Health, the age of people is grouped into children and adolescence (up to 18 years of age) and adult (18 years of age and more). Transfer of pediatric patients with TM and TI-TDT from pediatric clinics to adult clinics when they are ≥ 18 years of age has become a problem for most patients who have received blood since their beginning of life in the pediatric clinics due to some reasons. Therefore, the pediatric clinics have become a Thalassemia Center where adult hematologists come to the pediatric clinics to treat pediatrics patients with TM and TI TDT who just turn into 18 years of age.

AS02-1

When pediatric patients with TM and TI-TDT are transferred to adult clinics, thalassemia complications are more obviously found in this adulthood period, including complications due to chronic anemia (e.g. stunting, quite enlarged spleen with hypersplenism, bone fractures) and due to organ iron toxicities (mostly cardiac and liver iron toxicities) as well as infections. Therefore, the key performance index (KPI) of reducing complications should be determined when they are transferred to adulthood period and multidisciplinary patients care (which includes more disciplines who are treating TM and TI complications, such as cardiologists, hepatologists, endocrinologists, orthopedists, etc.) is mandatory.

The treatment of TM and TI-TDT are quite costly and have led to a budget impact on the reimbursement of the Indonesian Health Insurance system and belongs to number four of the top ten high expenditure of the health budget. Therefore, the thalassemia prevention program to prevent TM birth has become a priority of the Indonesian Ministry of Health's Disease Prevention Program. One of the strategies of the thalassemia prevention program is a thalassemia minor screening program among the families of TM, TI-TDT and TI-NTDT pregnant women patients. Thalassemia screening program has included into a premarital testing in several areas.

AS02-2

Haemophilia treatment in Singapore

Tien Sim Leng
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The management of haemophilia in Singapore has come a long way and has progressed significantly. While hope of a cure for haemophilia is finally in sight our job in taking care of persons with haemophilia (PWH) is far from finished. This job is carried out by multi-disciplinary personnel including haematologist, paediatrician, specialized nurse, physiotherapist, laboratory staff and medical social worker. Together we provide a holistic and comprehensive care for PWH at the Singapore General Hospital (SGH) and other Haemophilia Treatment Centres.

1. Registry records:
We have progressed from our first person with Haemophilia A recorded manually in a jotter book in SGH coagulation laboratory on 17 June 1963 to a National Haemophilia Register (NHR) from 1 August 1995. SGH was recognized as an International Haemophilia Training Centre (IHTC) by World Federation of Hemophilia since 13 Dec 2000 and we have been training nurses, laboratory scientists and doctors interested in haemophilia care from mainly Asian countries. Data from Singapore NHR showed we had 225 Haemophilia A with about 1/3 mild, 1/3 moderate and 1/3 severe types. We had 46 Haemophilia B with 45% mild, 33% moderate and 22% severe types. 17% of our Haemophilia A had inhibitors and none for Haemophilia B. None of our Singapore PWH ever had HIV infection.

2. Comprehensive treatment:
We progressed from the use of cryoprecipitate to plasma-derived concentrates, recombinant factor products and subcutaneous Emicizumab for a few patients. We switched from episodic treatment to prophylaxis treatment for our moderate and severe Haemophilia A persons to prevent joint damage and bleeds. With prophylaxis we aimed to convert severe Haemophilia A from Factor VIII level of <1% to 1-3% trough level. As more PWH have very active lifestyle we need to target the Factor VIII trough level higher to 3-5%. We are moving towards individualized treatment, tailoring the dose of FVIII to lifestyle activity. Administration of long-acting Factor VIII or Factor IX may allow us to achieve this end. Home treatment with self-administration of clotting factor concentrates is strongly encouraged. Smooth transition from paediatric to adult haemophilia care is being practiced. The most promising targeted therapy is the use of Emicizumab which can be given subcutaneously once a week and potentially every 3-4 weeks. Products limiting the action of natural anticoagulation such as Fitusiran and Concizumab are not available in Singapore yet. We treat bleeds in persons with Haemophilia A with inhibitors using Factor VIIa or FEIBA. Immune tolerization was implemented for a few of them. We widely used radioisotope synovectomy for target joints with 60-90% success rate in reducing frequency of bleeds and improving range of joint movement.

3. Supportive care:
Ancillary care for haemophilia is of paramount importance. We used both 1-stage clotting assay and chromogenic assay in the diagnosis of mild Haemophilia A. Genetic mutation testing for Haemophilia A and B is readily available. Almost all our mild Haemophilia A tested genetically had missense mutation and majority of severe Haemophilia A had intron 22 inversion. Our specialist haemophilia nurses are strong pillars of support to our PWH, to whom they can approach not merely for treatment and counselling but also to pour out their souls. Our physiotherapists play a vital role in increasing the musculoskeletal prowess of our PWH. With increasing medical cost, our medical social workers are indispensable in providing financial counselling and support.

AS02-3

Thalassaemia treatment in Malaysia

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Thalassaemia is a major health problem in Malaysia. As of 2018, there are 7984 patients registered in the Malaysian Thalassaemia Registry. Seventy percent are below 25 years of age. Hb E Beta thalassaemia forms the largest group with 2744 patients (34.4%), followed by Beta thalassaemia major with 2676 patients (33.5%), HbH with 1458 patients (18.3%), Beta Thalassaemia intermedia with 748 patients (9.4%) and other haemoglobinopathies with 358 patients (4.5%).

Of the 7984 patients, 4529 patients (75%) are transfusion dependent. These patients receive regular transfusions between 3 to 4-weekly to keep their pre-transfusion Hb above 9 g/dL to prevent the complications of chronic anaemia. About 70,000 packed red cells are transfused per year for patients with thalassaemia. Although we try to transfuse phenotype-matched blood, less than half of patients receive them due to the high cost of red cell phenotyping.

In the state of Sabah which has the highest number of thalassaemia patients (n=1814), where most of them are transfusion-dependent, getting adequate blood and timely blood transfusion is a big problem. Patients are generally shorter with larger spleens. Rate of splenectomy is also higher here, although generally it is avoided (215 out of 1235 splenectomies).

With chronic transfusions, iron accumulates in the body and causes toxicity to the organs. All 3 forms of iron chelators are available – desferrioxamine, deferiprone and deferasirox. A total of 4928 patients (61.7%) are on iron chelation as monotherapy or combination therapy. Thalassaemia treatment in Malaysia are all borne by the government.

Adherence to therapy is a major issue. Despite having access to free treatment, complications from iron overload are still high. About 20% of patients have serum ferritin levels above 5000 ng/mL. Magnetic Resonance Imaging (MRI) T2* is available in 5 hospitals in Malaysia. From 2007-2018 there were 697 deaths. The majority of the deaths were due to heart failure (42%; n=254) and infections (38%; n=232).

MS01-1

Outcome of autologous transplant in T-cell lymphoma: Experience of NIHBT in Vietnam

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Background: Peripheral T cell lymphomas (PTCLs) are a rare and heterogeneous group of diseases principally characterized by aggressive clinical behavior. Although some subtypes of PTCL, such as ALK-positive anaplastic large cell lymphoma and subcutaneous panniculitis T cell lymphoma, are associated with favorable outcomes, most PTCL has a poor prognosis. Extranodal natural killer (NK)/ T cell lymphoma nasal type (ENKL) is more common in Asia. Most patients with newly diagnosed stage IV, relapsed, or refractory ENKL treated with conventional chemotherapy survive for less than a year. There are some long-term survivors among patients with advanced-stage, relapsed, or refractory T cell lymphoma who undergo stem cell transplantation.

Patient and methods: We performed a prospective study to evaluate the effect of autologous stem cell transplantation in patients with T cell lymphoma. From September 2013 to May 2019, 30 patients were diagnosed with aggressive T cell lymphoma (included ALK-negative anaplastic large cell lymphoma, angioimmunoblastic T cell lymphoma, hepatosplenic T cell lymphoma, PTCL not otherwise specified, ENKL) were prospectively enrolled into this study. Of 30 patients who underwent autologous stem cell transplantation, 15 patients had disease-free at the time of transplant (frontline) and the rest had relapsed/refractory disease.

Results: Median age was 34.2 years old (range 16 – 58), histologic subtype was: PTCL, NOS (36.7%), angioimmunoblastic T cell lymphoma (13.3%), ALK-negative anaplastic large cell lymphoma (10%), hepatosplenic T cell lymphoma (6.7%), extranodal/ nasal type NK/T cell lymphoma (33.3%). Conditioning regimen included: BEAM (20%), Bu/Cy/Etoposide (60%), LEED (20%). Post-transplant: 90% of patients achieved complete remission, 10% had partial remission. Transplant-related mortality at D+100 was 0%. Among relapsed/refractory patients, 9 patients experienced early relapsed. The estimated 3 years progression-free survival was 66.5%, median PFS was 28.5 months (CI 95%: 22.6 – 32.9 months). The estimated 3 years overall survival was 76.1%, median OS was 30.7 months (CI 95%: 25.8 – 34.8 months).

Conclusion: In our experience, autologous stem cell transplantation is safe and effective in patients with T cell lymphoma.

MS01-2

Subcutaneous panniculitis-like T-cell lymphoma

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Subcutaneous panniculitis-like T-cell lymphoma (SPTL) is a rare subtype of peripheral
T-cell lymphoma affecting younger patients. It is more common in females than males. Patients usually present with multifocal subcutaneous nodules commonly at the extremities and trunk. Systemic symptoms are seen in up to 50% of patients. Pathological findings show infiltrates of neoplastic pleomorphic T-cells (CD3+, CD4-, CD8+, CD56-, βF1+ phenotype) and reactive histiocytes. The neoplastic T-cells locate exclusively within the subcutaneous tissue. The disease often runs an indolent course, although some patients may have life-threatening hemophagocytic syndrome. Autoimmune disease may play a role in some patients. Immunosuppressive therapy with cyclosporine yields very good outcomes in SPTL, unlike other lymphomas, which require chemotherapy. The molecular pathogenesis of SPTL is previously poorly understood. Recently, our group suggests that SPTL is an inherited disease which is caused by bi-allelic germline mutations in HAVCR2, encoding T-cell immunoglobulin mucin-3 (TIM-3). TIM-3 is a transmembrane protein expressed on T and innate immune cells. TIM-3 acts as a negative immune checkpoint regulating peripheral tolerance, anti-tumoral immunity, and innate immune responses. Loss of TIM-3 expression promotes uncontrolled immune activation and makes individual susceptible to SPTL. The disease shows an autosomal recessive–inherited pattern. In addition to the germline mutations, recurrent somatic mutations in the genes involved in epigenetic regulation and signal transduction might be associated with clonal expansion of SPTL cells.

Reference
Polprasert C, et al. Frequent germline mutations of HAVCR2 in sporadic subcutaneous panniculitis-like T-cell lymphoma. Blood Adv. 2019 Feb 26;3(4):588-595.

MS01-3

Update of extranodal NK/T-cell lymphoma: Treatment and biology

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Extranodal natural killer (NK)/T-cell lymphoma (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. The guideline of the American Society for Blood and Marrow Transplantation recommends autologous and allogeneic stem cell transplantation (SCT) both as frontline consolidation for disseminated NK/T-cell lymphoma and as salvage consolidation for relapsed–sensitive disease. However, the outcome of autologous SCT is still not satisfactory in patients with stage IV ENKTL, because more than half the patients relapsed even after upfront autologous SCT. Allogeneic SCT could be a valuable treatment option because it can induce long-lived remissions caused by the graft-versus-lymphoma effect. However, it is still difficult to define the exact role of allogeneic SCT, because the outcomes are still unsatisfactory owing to the frequent occurrence of transplantation-related mortality and a high relapse rate. The use of immune checkpoint inhibitors should be done for highly-selected patients as a salvage treatment.

This lecture summarizes the different approaches for the use of nonanthracycline-based chemotherapy with radiotherapy including concurrent, sequential, and sandwich chemoradiotherapy, 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

SCIENTIFIC SESSION

SS01-1

Contemporary treatment of pediatric Ph+ ALL

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Ph+ ALL represents approximately 2.5% of all pediatric ALL cases and was until recently considered to be one of the highest risk subgroups of pediatric ALL. The introduction of tyrosine kinase inhibitor agents in combination with ALL therapy has resulted in a significant improvement in the outcomes of pediatric Ph+ ALL in the last 15 years. These advances have been a result of standardized clinical trials performed by the North American based Children's Oncology Group (COG) and European-based EsPhALL group. These studies helped us to develop a roadmap for the integration of targeted therapies in combination with chemotherapy for other pediatric malignancies as well. A number of controlled trials have been completed and an international COG-EsPhALL study is current accruing the largest cohort of pediatric Ph+ ALL patients worldwide. We have learned a number of things regarding the tolerability of TKIs with backbone chemotherapy, the role of MRD in predicting the outcome of Ph+ ALL therapy, and additional biological risk factors that impact outcome of Ph+ ALL chemotherapy with TKI. Large biology studies have also identified that a large number of Ph- very high risk pre-B ALL have a BCR-ABL-like molecular pattern and are amenable to identical strategies as used for classic Ph+ ALL. The role of hematopoietic stem cell transplantation (HSCT) and other immune based therapies such as bispecific antibodies and CAR T cells continue to be re-evaluated and their role is evolving. In addition, there remain a number of unanswered questions regarding the use of TKIs after completion of chemotherapy and HSCT, and in BCR-ABL-like pre-B ALL.

Objectives:

a. To learn of the results of the past and current COG and EsPhALL therapeutic and biology studies and their impact on the outcomes of pediatric Ph+ ALL.
b. To present the state-of-the-art therapies for pediatric Ph+ ALL and BCR-ABL-like ALL and contrast these results to outcomes in adult Ph+ ALL.
c. To discuss controversies and unanswered questions regarding the role of minimal residual disease, backbone chemotherapies, cell based and monoclonal based immune therapies, and hematopoietic stem cell transplant in the era of TKIs for Ph+ ALL

SS01-2

Current treatment approaches to newly diagnosed adult ALL

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SS01-3

Results of high risk and novel subtypes of pediatric ALL in Japan

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In Japan, pediatric ALL patients have been treated by the four study groups, JACLS, TCCSG, CCLSG, and KYCCSG.

In 2003, Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) was organized and the JPLSG started clinical trials for two distinct and rare subtypes of ALL, including infant ALL and Ph+ALL. In order to promote large-scale clinical trials including randomized control trials and activate biological studies of ALL in Japan, JPLSG started nation-wide study T-cell ALL protocol (T11) in Dec 2011, and B-precursor ALL protocol (B12) in Nov 2012.

For infant ALL, JPLSG conducted MLL03 study as the first nation wide study, in which MLL+ patients received intensification therapy including high-dose cytarabine and proceeded to early SCT to prevent early relapse. The results of MLL03 study was published (K Koh, et al. Leukemia 2013). Although EFS of MLL03 did not improved significantly, OS improved compared to historical controls. After MLL03 study, we conducted MLL10 study to test the efficacy and safety of combined strategy of Interfant and COG studies. I will introduce encouraging results of MLL10 study (D Tomizawa, et al. Blood 2020).

For relapsed ALL, JPLSG conducted R08 study which was the first clinical trial for relapsed ALL in Japan. I will introduce some results R08 study.

Recently, the biology of pediatric ALL has been studied intensively by new methodologies including NGS and many novel subtypes such as ZNF384 fusion, MEF2D fusion, DUX4 fusion, and so on has been identified. The prognostic impact of these novel subtypes has not been studied in east Asia. I will introduce the results of TCCSG study which examined these novel subtypes intensively.

SS02-1

Diffuse large B cell lymphoma: At the intersection of genetics and epigenetics

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Diffuse Large B cell Lymphoma (DLBCL), the most common B lymphoid malignancy, remains a significant clinical challenge in approximately 40% of patients who do not respond to current front-line immuno-chemotherapeutic approaches. This lack of success is related in part to the remarkable heterogeneity of this malignancy, which comprises multiple molecular and genetic subtypes associated with distinct clinical outcome.

Over the past decades, large-scale genomic analyses of DLBCL, spurred by the implementation of powerful genomic technologies, have significantly improved our knowledge of the genomic (and epigenetic) landscape of this disease. These efforts have uncovered a multitude of genomic aberrations that contribute to the initiation and maintenance of the tumor clone, typically by disrupting the ordered regulation of transcription factor networks that are critical for the physiologic germinal center (GC) reaction, the normal counterpart of DLBCL. In addition to lesions that affect these genes directly, a common theme that emerged from these studies is the high recurrence of genetic lesions involving the histone modifiers KMT2D, CREBBP/EP300 and EZH2, which contribute to the epigenetic reprogramming of the lymphoma precursor cell. This wealth of new information is offering unique opportunities for the development of improved diagnostic and prognostic biomarkers that could help guide the clinical management of DLBCL patients. Furthermore, a number of the identified mutated genes are potentially actionable targets that are currently being explored for the development of novel therapeutic strategies. These findings will be discussed in the context of i) recent data obtained from single cell transcriptomic analysis of GC B cells, and ii) a newly identified epigenetic interaction of potential functional impact on the neoplastic transformation process.

SS02-2

Immunotherapy for Hodgkin lymphoma

John Kuruvilla
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Immunotherapy has been established for the treatment of relapsed/refractory (RR) Hodgkin's lymphoma (HL) based on two large registrational pivotal trials using the anti-PD1 antibodies pembrolizumab (Keynote-87) and nivolumab (CHECKMATE-205). Impressive single agent response rates along with encouraging progression-free (PFS) and overall survival (OS) were reported along with favourable toxicity. Subsequently two large randomized trials evaluating these agents were performed in RR-HL; pembrolizumab has been compared to brentuximab vedotin (BV) in the KEYNOTE-204 trial while nivolumab in combination with BV is being compared to BV monotherapy in CHECKMATE-812. The results of the randomized trials are eagerly awaited.

In the curative setting, a number of trials have evaluated incorporating checkpoint inhibitors into primary treatment as well as therapy of RR-HL. Monotherapy in patients not responding to salvage chemotherapy has been evaluated in prospective and retrospective series while novel combinations such as BV and nivolumab prior to autologous transplant has shown favourable activity. Randomized trials are needed in the RR and frontline setting. The North American intergroup is evaluating the combination of nivolumab with AVD (AVD-nivo) versus AVD with BV in advanced stage HL. Immunotherapy approaches in HL have been an important advance in the treatment of this lymphoma.

SS02-3

Optimal treatment of high-risk aggressive B-cell lymphoma

Lorenz Trümper
Georg August University of Gottingen, Germany

SS03-1

Mutational landscape in clonal hematopoiesis of indeterminate potential

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Advances in sequencing technologies have allowed for clinical prospective profiling at diagnosis to characterize the genomic alterations that define each tumor's biology and, by extension, inform treatment decisions, a concept underpinning the vision of precision medicine. However, the genetic diversity and clonal complexity seen in cancer genomes, tied to a dynamic evolutionary process pose significant challenges in controlling and curing cancer. Clinical response is multifactorial and likely determined by the dynamic interplay between selective processes arising from the treatment itself, further mutation acquisition, clonal diversification and adaptive resistance.

In recent years, the detection of pre-leukemic mutations in the blood of healthy individuals, referred to as clonal hematopoiesis (CH) has led to screening and surveillance programs for CH gene mutations. CH shares a common age-related incidence with cancer patients. In the present talk I will present recent data from population genomic studies of CH in cancer patients profiled by MSKCC-IMPACT. We develop methods to map CH gene mutations and allelic imbalances from clinical prospective targeted gene sequencing assays. We integrate clinical, demographic, smoking and treatment histories to study the role of patient specific parameters and environmental exposures shape the clonal trajectories of CH and how these inform risk of tMN development.

SS03-2

Intelligent image-activated cell sorting: Principles and application to hematology

Akihiro Isozaki
University of Tokyo, Japan

In this talk, I introduce an intelligence technology reported as "Intelligent Image-Activated Cell Sorting (iIACS)" [Nitta et al., Cell 175, 266 (2018); Isozaki et al., Nature Protocols 14, 2370 (2019)] that builds on a radically new architecture that realizes real-time image-based intelligent cell sorting at an unprecedented rate. This technology integrates high-throughput cell microscopy, focusing, sorting, and deep learning on a hybrid software-hardware data-management infrastructure, enabling real-time automated operation for data acquisition, data processing, intelligent decision-making, and actuation. Recently, we reported an upgraded version of the iIACS machine that far surpasses the state-of-the-art iIACS machine in system performance for expanding the range of applications and discoveries enabled by the technology [Isozaki et al., Lab on a Chip 20, 2263, (2020)]. Specifically, the upgraded iIACS machine provides a high sensitivity of ~50 molecules of equivalent soluble fluorophores (MESFs) and a high throughput of 2,000 events per second. I introduce the details of its principles in this talk. Furthermore, we are applying this technology to diverse applications, such as microbiology, cancer biology, immunology, hematology, and synthetic biology. I introduce some of these applications conducted in our laboratory.

SS03-3

HARMONY: A big data for better outcomes project in hematological malignancies

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The HARMONY project is a European project from the IMI (Initiative Medicine Innovation) inserted in the H2020 Program, aiming to use 'big data' to deliver information that will help to improve the care of patients with hematological malignancies (HM). Specifically, the project will gather together, integrate and analyse anonymous patient data from a number of high quality sources. This will help the team to define clinical end-points and outcomes for these diseases that are recognised by all key stakeholders. Meanwhile the project's data sharing platform will facilitate and improve decision making for policy makers and clinicians alike to help them to give the right treatment to the right patient at the right time. More broadly, the project will result in a pan-European network of stakeholders with expertise in this disease area.

The project is part of IMI's Big Data for Better Outcomes programme, which aims to facilitate the use of diverse data sources to deliver results that reflect health outcomes of treatments that are meaningful for patients, clinicians, regulators, researchers, healthcare decision-makers, and others IMI's HARMONY project has compromised data on 65 000 patients with blood cancers, meaning it is almost half-way to achieving its goal of collecting data on at least 100 000 patients during the lifetime of the project. The data, which comes from multiple sources such as clinical trials and registries, is gathered in the project's Big Data Platform.

From October, 2020, HARMONY is complemented with a new IMI project named HARMONY PLUS (H+), covering all HM. Moreover, H and H+ will extent the coverage over the European scenario, including high-quality data in registries. All the data are managed in accordance with the European law (RGPD).

HARMONY and H+ researchers are already mining it to answer research questions such as whether one specific treatment improves outcomes in patients with aggressive multiple myeloma, which subgroups of patients with myelodysplastic syndromes benefit from certain treatments or how the gene-gene interactions directly affect the outcome of acute myeloid leukemia patients. Data directly obtained by using this real word data platform will be presented in the Meeting.

Mining this unique Big Data Platform to address pressing research questions will give us better insight in the molecular landscape of blood cancers and the prognostic value of disease related variables, hence increasing our understanding of their pathophysiology. Making use of big data analytics in blood cancer research will lead us faster to identifying novel drug targets. Ultimately, our goal is that, together, we can accelerate drug development, regulatory evaluation, access appraisal, and treatment strategies to improve the care of patients with these blood cancers.

SS04-1

Discovery of new regulators in stem cells and malignancies

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Nutritional status can impact steady-state hematopoiesis, as observed in malnutrition or obesity, as well as be an important determinant in hematopoietic stem cell transplantation. A major molecular sensor of cellular nutritional status is the mTOR. mTOR kinase is in a multiprotein complex along with the scaffolding protein RAPTOR, termed mTORC1, it can sense multiple upstream energy-status inputs and non-nutritional signals. However, the upstream inputs to mTORC1 governing hematopoiesis are not known. To investigate the role of nutrient sensing signaling to mTORC1 in the hematopoietic system, we utilized *Mx1Cre*-mediated homozygous deletion of the *RagA*, which a core recruiter of mTORC1 to the lysosome post amino acid stimulation. *RagA* loss did not impair HSC activity under stress conditions. While *RagA*-deficient HSCs were unresponsive to acute AA changes, they displayed compensatory basal upregulation of mTORC1 activity in response to serum factors, which allowed them to grow under stress conditions. Collectively, manipulation of the nutrient sensing arm of the mTOR pathway is therapeutically attractive in several disease states.

We identified Upstream-of-mTORC2 as a transmembrane molecule altered in leukemic cells that emerged from an animal with modifications in specific bone marrow stromal cells. Hypothesizing that the gene-altered in the malignant cells that emerge from this niche-induced oncogenesis model might reflect how an abnormal microenvironment leads to cancer. We have used engineered mouse models to selectively deplete Upstream-of-mTORC2 from the differential subsets in the bone marrow. Conditional deletion of Upstream-of-mTORC2 effect perturbs normal and leukemic hematopoiesis in vivo. These studies provide mechanistic insight into how a distinctive molecular inhibitor of the mTORC2 signaling pathways can be a possible contributor to the viable therapeutic strategy.

SS04-2

AMD1 is essentially required in leukemic stem cells

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Polyamines are critical elements in mammals, but it remains unknown whether adenosyl methionine decarboxylase (AMD1), a rate-limiting enzyme in polyamine synthesis, is required for myeloid leukemia. Here, we found that leukemic stem cells (LSCs) were highly differentiated, and leukemia progression was severely impaired in the absence of AMD1 in vivo. AMD1 was highly upregulated as chronic myeloid leukemia (CML) progressed from the chronic phase to the blast crisis phase, and was associated with the poor prognosis of CML patients. Mechanistically, AMD1 depletion induced loss of mitochondrial membrane potential and accumulation of reactive oxygen species (ROS), resulting in the differentiation of LSCs via oxidative stress and aberrant activation of unfolded protein response (UPR) pathway, which was partially rescued by the addition of polyamine. These results indicate that AMD1 is an essential element in the progression of myeloid leukemia and could be an attractive target for the treatment of the disease.

SS04-3

BCL-2 as a stem cell target in AML

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For many decades, major advances in the treatment of patients with acute myeloid leukemia (AML) were not seen. In the more recent past, our understanding of the nature of the leukemia stem cell (LSC) has become more sophisticated. LSCs have the potential for proliferation and self-renewal; they are typically not impacted by traditional chemotherapy and are the likely source of relapse when it occurs. If the LSC population were targeted it could result in deep and durable remissions; if eradicated, this could represent a curative strategy. Until recently, relevant and unique weaknesses in LSCs were not appreciated, and few strategies to target LSCs in the clinic were viable.

BCL-2 is overexpressed in the LSC compartment; in vitro, targeting BCL-2 resulted in the selective eradication of LSCs through decreased oxidative phosphorylation (OXPHOS), the preferred source of metabolism that most LSCs are dependent upon[1]. Venetoclax is a highly selective BCL-2 inhibitor; in combination with a hypomethylating agent or low dose cytarabine, in older, newly diagnosed AML patients, it results in deep and durable responses[2]. In vivo, venetoclax with azacitidine in newly diagnosed, older AML patients, targets the LSC population; this occurs through a decrease in amino acid uptake in LSCs, which reduces OXPHOS through decreased amino acid catabolism[3,4].

Not all patients respond to venetoclax-based strategies; resistance in the LSC compartment to the metabolic effects of this regimen may explain this lack of response. Compensatory mechanisms that do not depend on amino acids for OXPHOS may explain venetoclax resistance, and these features may be able to be prospectively identified and targeted with novel therapies.

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SS05-1

Novel strategies to overcome relapsed/refractory multiple myeloma

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Despite tremendous advances in treatment of multiple myeloma (MM), it remains incurable in most patients. Currently, 3 drug classes are widely available for the treatment of MM, proteosome inhibitors (PIs), immunomodulatory drugs (IMiDs) and monoclonal antibodies. The use of these agents, particularly in triplet combinations has significantly improved patient outcomes. The emerging use of daratumamab in first and second line treatment in combinations with PIs or IMiDS has resulted in a paradigm shift in the management of MM, increasing the pool of patients who are triple-class refractory. These patients are characterized by a particular poor prognosis with a median estimated overall survival of approximately 9 months. Thus, one of the most challenging areas in the treatment of MM is to identify treatment options for triple-class refractory MM. The current approach for these patients is limited to recycling of previously used regimens that have generally shown short-lived efficacy. As a result, identification of more effective therapeutic interventions for this patient population has emerged as a key priority in MM research. A variety of new molecules are currently being developed and investigated in clinical studies to address this unmet medical need.

In this presentation, I will summarize available data on new investigational drugs showing anti-myeloma single-agent activity. These are likely to have a role in the future therapeutic armamentarium against MM. Besides their single-agent activity, the synergic potential of these new agents with the currently approved drugs will be pivotal in their integration into consolidated MM backbone therapies. The drugs to be discussed include the XPO-1 inhibitor, selinexor; the bcl-2 inhibitor, venetoclax; iberdomide, a novel cereblon E3 ligase modulator (CELMoD); chimeric antigen receptor T-cell therapy; and next-generation monoclonal antibodies.

SS05-2

MRD negativity - The foremost important goal of myeloma treatment?

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The landscape of multiple myeloma (MM) has changed considerably in the past two decades regarding new treatments, insight into disease biology and innovation in the techniques available to assess measurable residual disease (MRD) as the most accurate method to evaluate treatment efficacy. The sensitivity and standardization achieved by these techniques together with unprecedented rates of complete remission (CR) induced by new regimens, raised enormous interest in MRD as a surrogate biomarker of patients' outcome and endpoint in clinical trials. By contrast, there is reluctance and general lack of consensus on how to use MRD outside clinical trials. I will discuss critical aspects related with the implementation of MRD in clinical practice.

SS05-3

Light chain amyloidosis

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Amyloidosis is a group of complex diseases caused by tissue deposition of misfolded proteins that result in progressive organ damage. More than 20 proteins have been reported to be the cause of local and systemic amyloidosis. Most common types pf systemic amyloidosis are light chain amyloidosis which comprises of 78% followed by TTR amyloidosis and AA amyloidosis. Light chain amyloidosis caused by a clonal population of bone marrow plasma cells. Fragmented monoclonal light chains produced by clonal plasma cells misfold and form amyloid fibrils and deposit in tissues and interfere with organ function. Although AL amyloidosis is clonal plasma cell disorder and some of them have combined diagnosis of myeloma, clinical features of AL amyloidosis are different from multiple myeloma.

Delayed diagnosis is still important issue as it often associated with poor survival outcome. Non-diabetic nephrotic syndrome and non-ischemic cardiomyopathy with "hypertrophy" on echocardiography are most important symptom and sign. Hepatomegaly or increased alkaline phosphatase value with no imaging abnormalities of the liver and peripheral and/or autonomic neuropathy with a monoclonal protein are also need attention for the diagnosis of AL amyloidosis. Stigmatic signs of periocular purpura or macroglossia are not as common and around 10%. Combination of serum free light chain and immunofixation cover 99% of the patients. Histologic confirmation is essential for the diagnosis. Immunohistochemistry and Immunofluorescence are common methods in practice but false negative rates are frequent to 15-20%. Laser microdissection with mass spectrometry is gold standard with limited availability. Misdiagnosis as AL amyloidosis for patients with combined TTR amyloidosis and MGUS were reported.

EKG often shows low voltage in limb leads, echocardiogram increase of septal wall thickness, diastolic dysfunction and longitudinal strain patterns. MRI shows endomyocardial enhancement for patients with cardiac involvement. As TTR amyloidosis shows stronger cardiac uptake with bone scan, it will be helpful for differential diagnosis.

Kidney and heart are most common organ involvement followed by liver, nerve and soft tissue. About 40% of patients have more than 2 organ involvements. Overall survival has been reported 3-4 years. With the improvement of treatment and supportive care the survival outcome has been improved recently from the reports of US, UK, EU and Korea. However early death of advanced stage has not shown any improvement in all the data. Biomarker-based staging was suggested by Mayo group in 2004 and modified by European stage with addition of very advanced 3B stage. Mayo group revised the stage with addition of dFLC to reflect tumor burden. Boston University group proposed another alternative staging system for the hospitals which use BNP and troponin I for biomarker. In addition to the biomarker myeloma features such as CRAB and BM plasma cell percent more than 10% also affect the survival outcome of the patients. Renal staging based on the amount of 24 hour urine protein and eGFR was proposed and validated well for the renal survival. Prognostic value of the cytogenetics of AL amyloidosis is more complex as the outcome is also associated with the treatment regimen. In contrast to myeloma translocation eleven-fourteen is more common and showed poorer survival outcome for patient with AL amyloidosis. This is especially prominent for the patients treated with bortezomib-based regimen. However Melphalan-based treatment overcome the poor survival with t(11;14) and in addition, high dose Melphalan with stem cell transplantation overcome the negative impact of 1q gain.

For the treatment of AL amyloidosis, the mainstay of treatment is removal of plasma cell clone. Initial goal of the treatment are hematologic VGPR and organ response, especially cardiac response. Both of them showed correlation of survival improvement. A major difficulty with organ response as a measure in many studies is that organ response is time dependent, it can be much delayed. As conducted in myeloma research MRD assessment by NGF was also tested in AL amyloidosis. Patients who achieved MRD negative showed higher organ response and lower probability of relapse.

Most of the treatments of amyloidosis owe myeloma treatments. Alkylating agents, proteasome inhibitors and IMIDs become mainstay of the treatment. Monoclonal antibodies, new drugs such as venetoclax and immunotherapy might be future option in the treatment of AL amyloidosis. Risk adaptive approach is very important strategy for current treatment of AL amyloidosis. About 20% of the newly diagnosed patient comprised as low risk group who are eligible to ASCT and another 20% are high risk patient whose outcome is dismal. For the care of high risk patient although we use the same regimen of intermediate risk group, we need intensive monitoring with reduction of the starting dose and escalation and sequential addition of agents in combination. ASCT for AL amyloidosis started in early 90s and reported many phase 2 reports with variable

SS05-3

outcome. Phase 3 trial conducted in France showed inferior outcome in ASCT group. However, with better selection criteria and supportive care long-term follow-up data of ASCT showed much better survival and improvement of TRM. Now ASCT became standard treatment for the row risk patients. Among patients who are eligible for ASCT bortezomib-based induction therapy is considered for patients with BM plasma cell more than 10% or CRAB signs. Consolidation treatments can also be considered for the patients who have response less than VGPR. For stem cell collection G-CSF alone is preferred to the additional high dose cyclophosphamide.

With successful outcome of ANDROMEDA study which compared VCD with and without subcutaneous daratumumab, FDA approved this regimen for the treatment of newly diagnosed AL amyloidosis. This regimen became the first drugs approved specifically to the treatment of AL amyloidosis. Until Dara-VCD become available widely, bortezomib will be main treatment regimen. In addition to lots of good phase 2 results, phase 3 trial which compare BMDex with MDex showed better response and survival. Even with inferior outcome to BMD, MDex is still good treatment for patients who are not eligible for bortezomib and those who have t(11;14).

The timing to start salvage treatment is controversial. Patients who have hematolgic progression are usually recommended to salvage treatment without waiting for the organ progression especially for patients who have cardiac involvement initially; however, there is no firm evidence for this strategy. For patients who have persistent organ dysfunction or organ progression without hematologic progression, it is important to exclude other cause of organ dysfunction and MRD testing is sometimes helpful for decision making. For the treatment of these patients balancing frailty and ability to chemotherapy is important.

Lenalidomide has been reported as salvage treatment with or without combination with Cytoxan or Melphalan. They showed good hematologic response from 40-60%. Hematologic toxicities are main adverse event and renal toxicity is reported. Another IMID pomalidomide has been reported from 5 studies. Hematologic response rate was 47% and Overcame resistance to alkylating agents, lenalidomide, and PIs. The outcome of Daratumumab treatment for relapsed AL amyloidosis was reported for 627 patients in total. Hematologic response was 75% and achieved after a single infusion in most cases. High organ response was also reported and major AE was infection. Another anti-CD 38 monoclonal antibody isatuximab showed similar efficacy in phase 2 trials. The first phase 3 trials with oral proteasome inhibitor ixazomib/Dexamethasome in compared with doctor's choice did not showed improvement of primary endpoint hematologic response. However, ID showed better organ response and time to vital organ progression or death. Another proteasome inhibitor carfilzomib was also tested and showed considerable hematologic response, but high rate of cardiopulmonary toxicities. Bendamustine, alkylating agent with dual mechanism was also tested for AL amyloidosis 35-50% of hematologic response and tolerable toxicity. This drug is also effective for lymphoma and this implies the efficacy for IgM-AL amyloidosis. Venetoclax, effective drug for t(11;14) myeloma, was reported in a retrospective study of 43 patients recently. VGPR or more was 63% for all patients and 78% for t(11;14) patients.

Trials for direct removal of amyloidogenic fibrils are underway. Doxycycline was reported improvement of amyloidosis and phase 3 trial is ongoing. NEOD001, humanized IgG1 designed to directly neutralize soluble toxic aggregates of misfolded LCs showed very good results in phase 2 trial, however phase 3 trial did not show improvement of organ response. Based on the borderline efficacy of Mayo stage 4 patients new phase 3 trial is in preparation. Another monoclonal Ab CAEL-101 showed organ response in phase 2 trials and phase 1 trial of combination with Dara-VCD was reported and phase 3 trial was initiated. Due to frailty and major organ dysfunction the importance of supportive care cannot be overestimated. Salt restriction and diuretics is mainstay of supportive care. Fitted elastic stocking and midodrine for hypotension. Patients with recurrent arrhythmic syncope may benefit from pacemaker implantation Digoxin, calcium channel blocker, ACE inhibitor, beta blocker should be used with great caution due to higher toxicity, Gabapentin or pregabalin is useful for neuropathic pain. Organ transplant can be proposed in patients with irreversible, end-stage organ dysfunction despite CR. In young patients with isolated cardiac involvement and severe heart failure, heart transplant followed by ASCT can be considered.

In conclusion, AL amyloidosis is rare and often delayed in diagnosis with high mortality in advanced disease. However novel treatments with careful supportive care and risk adaptive treatment the outcome have been improving.

SS06-1

Direct oral anticoagulants for the treatment of VTE in cancer patients

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Venous thromboembolism (VTE) is associated with significant mortality and morbidity in patients with cancer. Therefore, tailoring anticoagulation is of utmost importance in order to decrease the risk of recurrent VTE while minimizing the risk of bleeding. Low-molecular-weight heparin (LMWH) monotherapy has been the standard of care for the treatment of acute cancer-associated thrombosis (CAT) for many years. Direct oral anticoagulants (DOACs) have been recently compared to LMWH for the management of acute CAT. DOACs seem to be associated with a lower risk of recurrent VTE (RR: 0.66; 95% CI: 0.39 to 1.13) but higher risk of major bleeding events (RR: 1.32; 95% CI: 0.70 to 2.47) when compared to LMWH for the management of acute CAT. Although DOACs seem to be a convenient, effective, and generally safe alternative to LMWH for the management of acute CAT, several factors must be taken into consideration when determining the anticoagulant of choice for a specific patient. Treatment algorithms for patients with cancer and acute VTE suggest incorporating tumor type, risk of bleeding, drug-drug interactions and patient preference in decision making.

SS06-2

Immune mediated TTP (iTTP): Differential diagnosis, treatment, and follow up

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There have been remarkable advances in our understanding of the underlying pathophysiology of immune mediated TTP (iTTP) in recent years. More importantly many of these new discoveries have led to significant improvement in the diagnosis and treatment of iTTP patients. While ADAMTS13 activity testing is increasingly available to physicians, it may still not be available to all physicians to allow them to confirm the clinical suspicion of iTTP. Predictive models based upon the presenting platelet count and serum creatinine have been developed and are quite useful to predict the likelihood of severely deficient ADAMTS13 activity (<10%) and guiding the initial decision regarding the need to start plasma exchange therapy (PEX). Significant clinical issues including exacerbations of TTP and possibly refractory TTP have also been addressed by the development of the anti-VWF therapy caplacizumab. Future studies will be required to define the optimal application of caplacizumab in iTTP patients. It is also increasingly clear that iTTP patients in remission may be at risk for several long term complications including neurocognitive deficits, mood disorders, and cardiovascular disease that can lead to significant morbidity and even a shorter life expectancy. Longitudinal studies to define the pathophysiology, prevalence, and treatment of these long-term complications are desperately needed to minimize the effects of these complications on the quality of life for iTTP survivors.

SS06-3

Post-transplant thrombotic microangiopathy

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Transplant-associated thrombotic microangiopathy (TA-TMA) is a complication of allogeneic hematopoietic stem transplantation that affects 3-20% of recipients. TA-TMA results in microangiopathic hemolytic anemia, thrombocytopenia, and organ injury, particularly kidney failure. Patients who develop TA-TMA have shorter survival compared to other patients who undergo transplantations. There is a wide range of incidences (anywhere between 0.5-70%) and survival rates reported for TA-TMA. This discrepancy in the literature is due to the difficulty in differentiating TA-TMA from other complications of stem cell transplantation (SCT). Despite various diagnostic criteria for TA-TMA, it remains a challenging disease to diagnose and treat.

The most important risk factors for developing TA-TMA are the presence of severe graft-versus-host disease (GVHD), conditioning regimen containing total body irradiation or high dose busulfan, and viral infections.

The pathology of TA-TMA is defined by the presence of microangiopathy in the kidneys. We investigated the pathogenesis of TA-TMA in mouse models of bone marrow transplant (BMT). We found that severe GVHD in mice is associated with pathologic changes similar to TA-TMA in humans. The clinical course and pathology of TA-TMA resemble those of hemolytic uremic syndrome (HUS). Because of the complement system's role in the pathogenesis of atypical HUS, we investigated in our murine model of BMT the role of complement in the post-transplant kidney injury. We found that lack of C3 reduces the severity of GVHD and the extent of kidney injury in recipient mice. From these observations, we hypothesized that severe GVHD and TA-TMA might have a common denominator. The presence of endothelial injury in severe steroid-refractory GVHD points to the possibility of endothelial injury being the common denominator for GVHD and TA-TMA. The endothelial injury after stem cell transplantation due to a conditioning regimen, complement activation, direct and indirect attack by cytotoxic T cells, and perhaps hereditary or acquired low levels of ADAMTS13 and complement dysregulations can result in severe GVHD and TA-TMA.

Treatment of TA-TMA is based on interventions that reduce endothelial injury. Because of the complement system's role in the pathogenesis of HUS-like microangiopathies, complement inhibition has been used for the treatment of TA-TMA with various degrees of success. The pathogenies and diagnosis of TA-TMA are not established, and the treatment of this disease remains empirical.

SS07-1

Novel treatment for immune thrombocytopenia (ITP)

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Immune thrombocytopenia is an autoimmune condition that results in platelet destruction as well as impaired platelet production. Historically the primary treatment for patients with refractory ITP was splenectomy. This session will provide an overview of the increased knowledge regarding the pathophysiology of ITP and how this has informed drug development. As novel therapies expand for patients with ITP, physicians must be aware of how to balance the efficacy, side effects, and route of administration when selecting an agent for their patients. Following this session participants will have a greater understanding of the novel therapies such as the thrombopoeitin – receptor agonists and sky-inhibitors as well as novel therapies in early development and how to use them in clinical practice.

SS07-2

Recent understandings of congenital neutropenia

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Neutropenia, defined as an absolute neutrophil count (ANC) of less than 1,500/μL, is a common disorder in children and adults, with about 1% of individuals present at any time in a given population. In contrast, congenital neutropenia (CN) is extremely rare regardless of the molecular etiology. The estimated prevalence is less than 1/100,000 and a birth incidence of about 2–5/100,000.

CN is heterogeneous disorder ranging from isolated severe congenital neutropenia (SCN) to complex inherited disorders affecting other organ systems, such as the pancreas, central nervous system, heart, bone and skin. Unfolded protein responses, endoplasmic reticulum stress, elevated apoptosis, deregulated expression of transcription factors, abnormalities in secretory vesicles and mitochondrial metabolism, aberrations in ribosome biogenesis and assembly have been recognized as possible pathogenetic mechanisms.

SCN is a concept that applies to diseases in which severe neutropenia (ANC < 500/μL) arises due to a bone marrow maturation arrest in the myeloid series. Patients with SCN display recurrent bacterial infections, mostly located in the mucous membranes, oral cavity and skin. Cyclic neutropenia (CyN) is characterized by an oscillating ANC that varies between normal and total depletion over a 21-day cycle. CyN is associated with a milder course of disease than SCN since infections only occur during periods of low ANC. More than half of SCN cases and almost all CyN cases are known to be caused by ELANE, an autosomal dominant mutation in the gene encoding neutrophil elastase.

The management of CN has changed since granulocyte colony stimulating factor (G-CSF) became commercially available in 1993. G-CSF reduces the frequency and severity of infections, antibiotic use, risk of sepsis and hospitalization. In addition to the risk of lethal infection, SCN also carries a risk of developing acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). The cumulative incidence of leukemia after 20 years in these patients is more than 20%. Patients requiring higher doses of G-CSF and who have a reduced neutrophil response to G-CSF have an increased risk of malignant transformation. Gene mutations in G-CSF receptor (CSF3R) and the transcription factor RUNX1 are closely related to leukemic transformation. Hematopoietic stem cell transplantation is the only therapeutic option if the patient dose not respond to G-CSF or develops AML/MDS.

The discovery of genes has increased our understanding of CN and myeloid biology diseases. Currently, more than 20 distinct genes, including ELANE, CSF3R, and HAX1, are known to be associated with CN, and their number is growing. The clinical and genetic heterogeneity of CN makes identifying genetic diagnoses increasingly complex, and the next-generation sequencing (NGS) approach based on initial analysis of a panel of gene targets and, secondarily, whole exome sequencing, appear to be the most efficient strategy.

SS07-3

Non-factor approach including emicizumab

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Regular prophylaxis using clotting factor VIII products to prevent hemorrhage in patients with hemophilia A results in significant suppression of the development of chronic arthropathy and contributes to great improvement in their quality of lives. However, some issues of hemostatic treatment for these patients, such as frequent intravenous infusion of factor VIII, the development of factor VIII inhibitor, and so on, have been raised. To overcome these issues, a humanized recombinant anti-factor IXa/factor X bispecific antibody, factor VIIIa cofactor function-mimetic (emicizumab; Hemlibra®) was developed. Several clinical trials have demonstrated that emicizumab has remarkably decreased the bleeding events by simple subcutaneous infusion once a week, once a 2 week, once a 4 week, and this is currently available as a regular infusion for preventing hemorrhage in congenital hemophilia A patients with or without factor VIII inhibitors. A paradigm shift in the hemophilia treatment with non-factor product, emicizumab, is now coming. On the other hand, there are some issues of emicizumab that need to be clinically solved, such as thromboembolism cases at concomitant treatment with bypassing agent, hemostasis monitoring, perioperative hemostatic management, and preventative effect under high-activity lives. On the other hand, other two products, si-RNA anti-antithrombin therapy and anti-tissue factor pathway inhibitor antibody therapy, based on rebalancing coagulation have been currently ongoing in the clinical study. These new approaching therapies for hemophilia could provide the further improvement of quality of lives for these patients.

SS08-1

Improving palliative care and outcomes in low- and middle-income countries

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Scope and guiding principles of palliative care in all countries

Palliative care in low- and middle-income countries (LMIC) resembles that of high-income countries (HIC). It includes key components: establishing explicit goals of care, pain and symptom management, spiritual support, and bereavement care. Palliative care also follows guiding principles: initiation at the time of diagnosis of a life-threatening or life-limiting illness like hematologic cancer, integration with curative therapies, and service delivery across all sites of care (hospital, outpatient facilities, skilled nursing facilities, and home).

Special considerations in low- and middle-income countries

Despite many similarities between palliative care in LMIC and that in HIC, there are some important differences, including the following: 1) greater need for services, 2) less resources to provide those services, 3) greater distances between the patient's home and medical facilities for oncology, and 4) unfavorable policy environments.

1) The need for palliative care for cancer patients is much greater in LMIC due to advanced stage at diagnosis, fewer options for curative care, and additional causes of treatment failure like abandonment of treatment or relapse due to drug shortages or lack of effective access.
2) Resources available for palliative care in HIC usually include multiple members of a multidisciplinary palliative care service with social worker, case manager, nurse, psychologist, spiritual leader, oncology physician, anesthesiology physician, and others. In LMIC this team may consist of only an oncology physician and social worker, both of whom must perform many other duties unrelated to palliative care. Thus, any intervention that requires spending long periods of time with the patient or advocating on behalf of the patient is less feasible in LMIC than HIC.
3) Most palliative care programs strive to keep patients at home as much of the time as possible and to allow them to die at home if that is concordant with the family's wishes. However, when the home is hundreds of kilometers (and 12-48 hours of travel time) away from the oncology facility, coordinating palliative care services, and especially pain and symptom management, becomes increasingly difficult.
4) Policies for prescription of opioid pain medications, reimbursement for healthcare services provided outside of medical facilities, use of therapeutic sedation for refractory pain, and ability to transport a patient's body to another city or state for burial if they die in hospital are taken for granted in most HIC. In LMIC, some countries limit opioid prescriptions to a 3-day supply, which means that a patient who requires opioids and who lives 1.5 days from the oncology facility has no option for pain management at home. In some settings, sedation and pain management practices near the end of life may be unduly scrutinized and physicians using such practices accused of euthanasia or murder. Fear of these outcomes leads to inadequate pain control even for patients with very intense suffering and few days left to live. Laws against transport of bodies may preclude burial near home for patients who die in the hospital and lead some physicians to discharge actively dying patients so that family members can transport them home as they die en route.

Need for palliative care research in low- and middle-income countries

Palliative care delivery in LMIC poses many challenges, but also offers unique opportunities for innovation. During the Covid19 pandemic, delivery of palliative care via telemedicine or video conferencing has become the norm in LMIC and HIC, and many obstructive policies were temporarily suspended, such as the number of days of narcotic that can be provided with a single prescription. Extending and sustaining these innovations requires a robust research program to document the benefits and highlight remaining gaps. Resources available for so support such research include the collaboration platform Resonance Palliative Care Research Network (ResonanceHealth.org/Networks/PCRN) and the Resonance Patient Center (https://resonancehealth.org/RPC/login), which provides free clinical research tools and patient care aids to people in all countries.

Together we can achieve a lot

Together we can improve palliative care during the entire patient journey and work hard to make end-of-life care unnecessary in hematology by curing the patients as they arrive. This is the mission of the Acute Lymphoblastic Leukemia Research and Care Network (ALL-RCaN, https://resonancehealth.org/networks/all-rcan), which brings together people from 17 time zones every Friday (6 am California, 11 pm Korea) to discuss the latest research and clinical practices related to ALL. This group provides a model for global collaboration to improve care and outcomes in a way that is sustainable and relevant everywhere.

SS08-2

Renal supportive care and palliative care in patients with hematologic diseases

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The development of treatment in hematologic diseases have increased survival of affected patients. However, it also increased the risk of kidney diseases. The occurrence of kidney disease such as acute kidney injury (AKI) is known to be associated with higher morbidity and mortality in patients with hematologic diseases compared to patients without kidney complications.

The incidence of AKI with hematologic malignancies is about 30~36%. In addition to the pre-renal azotemia which might be the most frequent cause of AKI, tumor lysis syndrome, urinary tract obstruction, renal parenchymal infiltration and chemotherapeutic agents can cause AKI. Electrolyte imbalance and acid-base disorders are also common in patients with hematologic diseases. Some glomerular diseases occur in associated with lymphoma and leukemia. The advancement of hematopoietic stem cell transplantation (HSCT) has increased patients survival. However, patients who undergo HSCT are at risk of AKI, chronic kidney disease, thrombotic microangiopathy and radiation nephropathy. Identifying patients with risk factors and preventive managements are the most important treatment. After the occurrence of kidney complications, we have to manage and correct the causes of renal problem such as chemotherapeutic agents, infection, and original hematologic diseases with best supportive care. Sometimes, dialysis therapy is necessary temporarily or permanently.

Renal complications in hematologic diseases are varied and associated with poor prognosis. Therefore, efforts to prevent renal events and early interventions are important. Further studies are necessary to find the mechanisms and effective treatment of renal manifestations in hematologic diseases.

SS08-3

Vaccinations before/after biologic agents in patients with hematologic malignancies

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Patients with hematologic malignancies are at increased risk for various infections, some of which are preventable by vaccines. Although patients with hematologic malignancies have lower responses than healthy persons to most vaccines, vaccination may prevent infections in those with hematologic diseases, decrease their severity or hospitalizations, and save lives.

Vaccination in patients with hematological malignancies is complex as the background and characteristics of immunosuppressed states differ between different patient categories. Therapy for hematological malignancies has changed substantially during the last decade with the introduction of monoclonal Ab, drugs with immunomodulatory effects, and targeted drugs. Biological therapy of hematologic malignancies may aggravate immunosuppression and decrease vaccine efficacy in patients with hematologic malignancy. Prior vaccination studies might not accurately represent the current risks and benefits of vaccination.

This presentation will provide overview of vaccination with special focus on biological therapy in patients with hematologic malignancies who did or did not have stem cell transplantations. Patients receiving monoclonal anti-CD20 Ab may not develop adequate antibody response to vaccines. An interval of at least 6 months is recommended between the last anti-CD20 Ab administration and vaccination. In 2017, chimeric antigen receptor (CAR) T-cell therapies were approved by the US FDA for treatment of refractory ALL in children and advanced B-cell lymphomas. The most CAR T-cell therapy is targeted toward CD19, and CD19-directed CAR T-cells destroy not only tumor cells with CD19 but also normal B cells. Although few studies have examined serological response to the inactivated vaccines in patients treated with CAR T-cell therapy, lack reliable responses is expected. Additional research on vaccination before/after biological therapy will be required in patients with hematologic malignancies.

SS09-1

Challenges in the diagnosis of bone marrow failure syndromes: The role of genetic panels?

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SS09-2

Clonal hematopoesis in bone marrow failure

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The concept of clonal hematopoiesis of ageing initially identified somatic variants of low variant allele frequencies (VAF) in more than 2% cells and was predominantly identified in older individuals, with a small risk of subsequent progression to myeloid neoplasms. The mutations were mostly in DNMT3A, ASXL1 and TET2. Further refinement in sequencing techniques increased the sensitivity and were able to identify very low level variants in a larger proportion of healthy individuals over the age of 50 years.

In aplastic anemia (AA) and bone marrow failures (BMF), which in a majority (70%) improves with immuno- suppressive therapies, the disease evolves in a significant minority of patients to MDS and AML, sometimes years after successful treatment and the risk is 10-15% at 10-15 years. The initial studies in AA mainly focussed on the ability of identify somatic mutations, and also ascertain their significance. The data was mainly focussed to ascertain the difference between AA and hypoplastic MDS and use to predict the evolution of such patients to MDS/AML. The opportunity to identify early events in transformation to MDS/AML, was aided by the availability of serial samples during the disease course.

Although earlier data from our group, identified the presence of ASXL1/DNMT3A mutations to increase the risk of transformation to MDS/AML, a subsequent large study did not substantiate this association. The current concept is
- Clonal haematopoiesis is very common (>70%) in AA/BMF, contributed mainly by
  - PIG-A mutations
  - HLA-A mutations and UPD on HLA locus at 6p
  - Immune escape cytogenetic clones e.g 13q deletion and trisomy 8
  - Somatic mutations, predominantly due to PIGA, BCOR/BCORL1, DNMT3A and ASXL1
- Somatic mutations are identified at a low level with a frequency of 18-20% at diagnosis of AA
- Any single acquired somatic mutation in the context of idiopathic AA is not an independent risk factor for transformation to MDS/AML
- Patients carrying a 'favorable'set of genes (BCOR/PIGA) were enriched in those responding to immunosuppressive therapy, whilst patients who evolved to MDS were likely to harbour 'unfavorable' set of mutations in DNMT3A/ASXL/RUNX1
- Serial tracking of somatic clones indicates that this process is complex, with clones growing, shrinking or remaining stable over a period of years with no correlation to blood counts or to relapse or transformation to MDS/AML

The clinical significance and the biological implications of clonal haematopoiesis in AA is still being evaluated, but the until the data is available presence of somatic variants in AA needs to be interpreted with caution. Presence of somatic mutations does not imply transformation to MDS/AML. Acquired AA is an immune-mediated bone marrow failure disorder inextricably linked to clonal haematopoiesis

SS09-3

Current guidelines for the treatment of acquired aplastic anemia in Japan: An immune marker-based approach

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Acquired aplastic anemia (AA) is a rare syndrome characterized by pancytopenia and bone marrow (BM) hypoplasia. The diagnosis of AA has been reliant on the exclusion of other diseases that present laboratory findings similar to those of AA. This indistinct definition of AA often leads physicians to incorrect differential diagnoses of BM failure, particularly when a patient's pancytopenia is not severe. However, currently identified markers that reflect the immune pathophysiology of BM failure have made it possible to diagnose AA proactively as well as early in the course of the disease. These markers include paroxysmal nocturnal (PNH) phenotype cells (PNH-type cells) and HLA-class I allele-lacking leukocytes (HLA-LLs). Physicians are able to diagnose the immune pathophysiology in approximately 75% of newly diagnosed AA patients by detecting these immune markers using flow cytometry and droplet digital polymerase chain reaction (PCR) assays. These markers are particularly useful for discriminating immune-mediated benign BM failure (AA) from preleukemic BM failure (myelodysplastic syndromes [MDSs]) when a patient's BM cells exhibit moderate dysplasia in erythroblasts and granulocytes and help physicians choose the appropriate therapy according to the pathophysiology of BM failure.

Japanese guidelines for the treatment of AA recommend cyclosporine (CsA) monotherapy for patients with non-severe AA not requiring transfusions when they possess one of these markers or pronounced thrombocytopenia with megakaryocyte hypoplasia, which is a laboratory finding common to marker(+) BM failure patients. An increase (>320 pg/ml) in the plasma thrombopoietin (TPO) level, which reflects systemic megakaryocyte hypoplasia, is another important marker for the immune pathophysiology of BM failure. A relatively low dose of CsA (3.5 mg/kg daily) produces remission in more than 50% of AA patients with immune pathophysiology if CsA is commenced soon after thrombocytopenia is revealed. For patients who fail to respond to CsA monotherapy and become dependent on blood transfusions, a switch to antithymocyte globulin (ATG)+CsA+eltrombopag (EPAG) is recommended. Furthermore, the addition of EPAG or romiplostim (ROMI) to CsA is recommended if patients refractory to CsA monotherapy do not yet require transfusions, as a clinical trial conducted in Japan demonstrated the effectiveness of these TPO-receptor agonists (TPO-RAs) in more than 50% of patients with moderate AA, without inducing clonal disorders.

We recently analyzed factors associated with a good response to EPAG in patients with refractory AA and found that patients possessing PNH-type cells were more likely to respond to EPAG than those without such cells. Similar to our observation, the National Institutes of Health group recently reported a favorable response to EPAG in patients with low-risk MDS possessing PNH-type cells. Our previous studies showed that the presence of PNH-type cells reflects not only the immune pathophysiology but is also a benign feature of BM failure. Healthy hematopoietic stem cells (HSCs) that persist in PNH(+) AA patients may respond to EPAG better than residual HSCs of PNH(-) AA patients that are potentially defective.

For patients with severe AA and those with non-severe AA who require transfusions, ATG+CsA+EPAG therapy is recommended unless a patient is younger than 40 years old and has HLA-identical sibling donors. Although the combined use of EPAG with ATG increased the rate of response, 20%-30% of patients still fail to achieve transfusion independence. The Japanese guideline recommends switching from EPAG to ROMI if the patient does not show any signs of response after three months of the combination therapy. Our recent study showed that 20 μg/kg of ROMI resulted in an increase in at least 1 lineage of cells in more than 70% of AA patients refractory to EPAG and induced transfusion independence in 5 of 15 (33%) patients.

As the recommendations of the guidelines are mainly based on the results of retrospective studies in a limited number of patients, we are currently conducting nationwide prospective studies to validate the recommendations. Nevertheless, we expect that immune marker-based early commencement of therapy including TPO-RAs will greatly improve the prognosis of AA.

SS10-1

CD8+ TILs differentiate into TEMRA via a bifurcated trajectory, deciphering immunogenicity of tumor antigen

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CD8+ tumor infiltrating lymphocytes (TILs) are composed of phenotypically and functionally heterogeneous subpopulations. Of these, effector memory CD45RAexpressing CD8+ T cells (Temra) have been discovered and characterized as a most terminally differentiated subset. However, their exact ontogeny and physiological importance in relation to tumor progression remain poorly understood. Here we analyzed primary tumors and peripheral bloods from 26 non-small cell lung cancer patients and found that TIL Temra largely differs from peripheral blood Temra, with distinct transcriptomes and functional properties. Trajectory analysis revealed that CD8+ TIL undergo divergent sequence of events for differentiation into TIL Temra in a TCR strength dependent manner. Thus, the proportion of TIL Temra well correlated with immunogenic properties of tumor antigens. Together, these data suggest complex interplay between CD8+ T cells and tumors.

SS10-2

Immunosenescence in pediatric patients with haploidentical HSCT from parental donors

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Objectives: Pediatric and adolescent patients in need of allogeneic hematopoietic stem cell transplantation (HSCT) generally receive stem cells from older, unrelated or parental donors when a sibling donor is not available. Despite encouraging clinical outcomes, it has been suggested that immune reconstitution accompanied by increased replicative stress and a large difference between donor and recipient age may worsen immunosenescence in pediatric recipients.

Methods: In this study, paired samples were collected at the same time from donors and recipients of haploidentical hematopoietic stem cell transplantation (HaploSCT). We then conducted flow cytometry-based phenotypic and functional analyses and telomere length (TL) measurements of 21 paired T-cell sets from parental donors and children who received T cell-replete HaploSCT with post-transplant cyclophosphamide (PTCy).

Results: Senescent T cells, $CD28^-$ or $CD57^+$ cells, were significantly expanded in patients. Further, not only $CD4^+CD28^-$ T cells, but also CD4+CD28+ T cells showed reduced cytokine production capacity and impaired polyfunctionality compared with parental donors, whereas their TCR-mediated proliferation capacity was comparable. Of note, the TL in patient T cells was preserved, or even slightly longer, in senescent T cells compared with donor cells. Regression analysis showed that senescent features of $CD4^+$ and $CD8^+$ T cells in patients were influenced by donor age and the frequency of $CD28^-$ cells, respectively.

Conclusion: Our data suggest that in pediatric HaploSCT, premature immunosenescent changes occur in T cells from parental donors and therefore, long-term immune monitoring should be conducted.

Keywords: HaploSCT, immunosenescence, telomere length, immune monitoring, $CD28^-$ T cells

SS10-3

CAR-T cells for AML: Lessons from the clinic

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Acute myeloid leukemia (AML) is a rapidly progressive, poor-prognosis malignancy arising from hematopoietic stem/progenitor cells. While chimeric antigen receptor redirected (CAR) T cells have transformed the treatment of patients with refractory B-cell malignancies, progress towards CART therapy for AML has been slow, partly due to the lack of a leukemia-specific antigen. All currently known cell surface targets on AML blasts are shared with healthy hematopoietic cells or their progeny, and hence targeting myeloid antigens with potent and persistent CART cells is expected to lead to prolonged pancytopenia. We conducted a pilot study of autologous anti-CD123 CART cells in adults with relapsed/refractory AML (NCT03766126). CART-123 cells expanded in vivo leading to complete responses in three of 10 infused subjects (two with incomplete hematologic recovery associated with marrow aplasia). Treatment was associated with cytokine release syndrome in most patients, and disease response was associated with profound myeloablation, necessitating a rescue allogeneic HCT in two subjects. Thus, while CART cells mediate an anti-AML effect in some patients with poor-risk AML, future work studies should evaluate mechanisms to improve their efficacy.

SS11-1

Juvenile myelomonocytic leukemia: Learning from children in a world without walls

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Juvenile myelomonocytic leukemia is a highly aggressive myeloproliferative neoplasm of children in which hematopoietic stem cell transplant (HSCT) is the only known curative therapy. Yet 50% of patients will relapse with some manifesting fulminant disease progression despite receiving HSCT while occasional patients resolve their disease with minimal therapy. JMML is known to be driven by five mutated genes, *NF1*, *NRAS, KRAS, PTPN11*, and *CBL*, that all give rise to aberrant proteins with consequential increases in Ras/MAPK signaling. Recent work focused on dissecting the complete genomic landscape of JMML in which we identified an additional 11 new genes mutated and established that patients harboring two or more somatic events have the worst outcomes. We hypothesize that these secondary events, which are frequently subclonal at diagnosis, contribute to aggressive disease pathogenesis by creating new genetic, epigenetic, and biochemical dependencies. It is necessary to identify the genetic and biochemical dependencies arising from these combinatorial mutations, identify and test relevant therapeutics singly and in combination, and perform in vivo testing to generate essential pre-clinical data. However, human JMML cell lines are non-existent and genetically engineered mice (GEMMs) of some of these combinatorial lesions are in development. We are identifying additional genetic dependencies and therapeutic vulnerabilities through the use of a series of induced pluripotent stem cells (iPSC) that were developed from primary patients. These lines will provide a platform to apply CRISPR screens that we hope will identify the different genetic dependencies of sequentially mutated cells. These iPSC will also provide reagents to test therapeutics with functional readouts that include assessment of GM-CSF hypersensitivity, cell proliferation, and biochemical analyses. Additional data show that many of these patients display extreme hypermethylation at diagnosis while those who do well are relatively hypomethylated, providing an additional layer of complexity to the mechanisms underpinning the most aggressive forms of JMML. This talk will review the current knowledge about the molecular pathogenesis of JMML and approaches to treatment through the lens of assessing genetics and epigenetics to deliver a risk stratified clinical trial for newly diagnosed patients.

SS11-2

Sirolimus therapy for vascular anomaly

Keon Hee Yoo

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Vascular anomalies represent a spectrum of disorders characterized by abnormal growth or development of blood vessels. Patients with vascular anomalies have various clinical problems such as disfigurement, acute/chronic pain, coagulopathy, bleeding/thrombosis, and organ and musculoskeletal dysfunction. The International Society for the Study of Vascular Anomalies (ISSVA) divides vascular anomalies into vascular tumors and vascular malformations, the nature of which is proliferative in the former and relatively static in the latter. Because most vascular anomalies are not able to be completely removed by surgery, multidisciplinary care should be offered to the patients whenever possible. Sclerotherapy is a minimally invasive intervention often performed as a first-line treatment for vascular malformations and frequently requires repetitive treatments. However, this measure is not always very effective and can be accompanied by serious complications such as venous thromboembolism and pulmonary embolism.

Mammalian target of rapamycin (mTOR) activates protein synthesis, resulting in numerous cellular processes including cell proliferation and increased angiogenesis and thus play an important role in the pathogenesis of various vascular anomalies. Recently, sirolimus, an mTOR inhibitor, has emerged as a promising agent for the treatment of vascular anomalies. The purpose of sirolimus therapy is to relieve the symptoms and signs caused by the anomalies. Although a complete response is not achieved in patients with vascular malformations, the Kasabach-Merritt phenomenon, if present, seems to greatly benefit from sirolimus therapy often resulting in complete response.

In 2018, we launched a prospective single center study to determine the efficacy and safety of sirolimus therapy in patients with vascular anomalies. Patients aged between 1 month and 18 years were enrolled and eligibility criteria required the presence of at least one out of 4 following conditions: (1) vascular anomalies accompanied by significant complications (coagulopathy, chronic pain, recurrent cellulitis, ulceration, visceral and/or bone involvement, organ dysfunction, serious disfigurement), (2) vascular tumors not responding to or recurrent after at least one conventional treatment (corticosteroid, interferon alpha, cytotoxic agents, propranolol, surgery, local measures), (3) vascular malformations aggravated despite surgery or local treatments, (4) vascular malformations not amenable to surgery or local treatments.

An interim analysis of this study will be presented.

SS11-3

Langerhans cell histiocytosis 2021: New insights and opportunities

Carl Allen
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Children with Langerhans cell histiocytosis (LCH) develop granulomatous lesions with characteristic clonal CD207+ dendritic cells (DCs) that can arise as single lesions or life-threatening disseminated disease. Despite the wide range of clinical presentations, LCH lesions are histologically indistinguishable based on disease severity. Historically, incomplete understanding of pathogenic mechanisms has challenged development of optimal clinical strategies for patients with LCH. Recently, activating somatic mutations in MAPK pathway genes, most notably the *BRAFV600E* mutation, have been discovered in almost all cases of LCH. Further, the stage of myeloid differentiation in which the mutation arises defines the extent of disease. MAPK activation in LCH precursor cells drives myeloid differentiation, blocks migration, and inhibits apoptosis, resulting in accumulation of resilient pathologic DCs that recruit and activate T cells. These new insights support reclassification of LCH as a myeloid neoplastic disorder. Early phase trials in adults with LCH and the related Erdheim-Chester disease and emerging case studies demonstrate promising responses to MAPK pathway inhibitors, though potential for cure and safety in children remain to be defined. While we now understand the framework for mechanisms of LCH pathogenesis, continued research will uncover opportunities to identify additional targets and inform personalized therapeutic strategies based on cell of origin, somatic mutation, inherited risk factors and residual disease.

SS12-1

PD1/PDL1 in ENKTL

Won Seog Kim
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SS12-2

Novel therapies for T-cell lymphoma

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The Peripheral T-cell lymphomas (PTCL) comprise a heterogeneous group of aggressive lymphomas with overall poor outcomes for many patients who present with advanced disease. The most common subtypes of PTCL in North America include PTCL-not otherwise specified (PTCL-NOS, 34% of cases),angioimmunoblastic T-cell lymphoma (AITL, 14% of cases), and the anaplastic large cell lymphomas(ALK-positive, 9% of cases and ALK-negative ,15% of cases) . In Asia, the most commonly occurring types of PTCL include HTLV-1 associated ATLL (25%) and EBV-related ENKTL (22.4%). For most patients with aggressive PTCL, front line therapy consists of multi-agent chemotherapy regimens such as CHOP, CHOPE, EPOCH, or asparaginase-based regimens for NK/T cell cases, followed by consolidation with autologous stem cell transplantation for patients who achieve a complete response to therapy. Despite these aggressive strategies, up to 75% of patients relapse and median survival at 5 years is 30-40% for PTCLnos and AITL and as low as 0-9% in NK/T cell lymphomas and ATLL. Several novel agents have been approved for use in relapsed PTCL, including three histone deacetylase inhibitors (romidepsin, belinostat, and chidamide), the folate antagonist pralatrexate, brentuximab vedotin for CD30 positive ALCL, and the PNP inhibitor forodesine . While these drugs have single agent activity, complete responses and durable remissions are rare. Other novel strategies are being explored, including pathway-directed agents such as syk/jak inhibitors (certulatib), XIAP inhibitor (ASTX-660), farnesyl transferase inhibitor (tipifarnib). PI3K inhibitors (duvelisib and copanlisib), ALK inhibitor (crizotinib) and hypomethylating agents azacytidine and decitabine. Novel immunotherapy approaches include antibodies to CD47 (don't eat me signaling pathway), bispecific NK engager antibodies such as anti-CD30-CD16a, and checkpoint inhibitors (PD-1, PDL-1). With a goal of developing novel/novel combinations which may be used to improve outcomes in front line, in vitro synergy studies have been conducted and Phase I combination trials are underway. Thus far, the combination of romidepsin with oral 5-azacytidine and romidepsin with pralatrexate have shown significant activity and synergy both in vitro and in vivo. In ongoing studies, checkpoint inhibitors are being added as a third partner with promising results. Precision medicine approaches to identify individual tumor vulnerabilities and select targeted agents based on identified mutational events in PTCL are currently being planned, and cell based approaches such as CAR-T therapies are in clinical trials. The CD5 and CD30 CARs have shown activity thus far, and an allogeneic CRISPR engineered CD70 CAR is in early clinical trials.

SS12-3

Translational research in angioimmunoblastic T-cell lymphoma: From genome to bedside

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During the aging process, the blood system is gradually replaced by apparently normal blood cells harboring somatic mutations: "clonal hematopoiesis (CH)". CH serves as a predisposing state for various blood cancers. Angioimmunoblastic T-cell lymphoma (AITL) is a representative disease originating from CH harboring *TET2* mutations. The subsequent p.Gly17Val (G17V) *RHOA* mutation is thought to drive AITL development from CH. Notably, microenvironmental cells as well as tumor cells are derived from CH. In fact, gene mutation analysis of microenvironemtal B cells clarified that they've also acquired recurrent somatic mutations, i.e. *NOTCH1* mutations. These data suggest that "multistep and multilineage" clonal evolution occurs in AITL development. Now several clinical studies are ongoing based on the molecular understandings of the AITL genome. To establish a new targeted therapy for the G17V RHOA mutant, we firstly performed a high throughput proteomic screening to identify the mutant-specific binding partner and successfully found that the G17V RHOA mutant bound to and activated VAV1, a key molecule in T-cell receptor (TCR) signaling pathway. *VAV1* mutations were also identified in G17V *RHOA* mutation-negative AITL samples, as well as various subtypes of T-cell lymphomas. To further clarify the biology of T-cell lymphomas, we established mouse models harboring G17V RHOA mutations (Ngyuen TB, Sakata-yanagimoto M, et al., Cancer Research 2020) as well as those with *VAV1* mutations (Fukumoto K, Sakata-yanagimoto M, et al., Blood 2020) A translation research is ongoing based on our bench work.

SATELLITE SYMPOSIUM

SY01

New treatment options for FLT3 mutated AML

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Until recently, the presence of a FLT3 mutation indicated a particularly aggressive subtype of acute myeloid leukemia with poor outcome. However, the clinical approach to patients with AML and a FLT3 mutation has changed in the past few years and the overall prognosis has improved. These treatment advances include more widespread use of intensified anthracycline-based chemotherapy and hematopoietic stem cell transplantation. Additionally, randomized studies now show FLT3 inhibitors improve survival when used as part of intensive frontline therapy of FLT3 mutated AML or during salvage therapy of patients with relapsed and refractory AML. Increasingly, FLT3 inhibitors are also being used following transplant, although many questions remain as to their optimal use in this setting. Taken together, the aggressive clinical features of FLT3 mutated AML have not been eliminated by treatment advances, but the overall outlook for patients with FLT3-mutated AML has improved. This lecture will highlight recent data in the field that impact treatment choice for patients with AML and will discuss how the use of FLT3 inhibitors is changing clinical approaches.

SY02

Latest treatment for hemophilia A and B in Japan

Keiji Nogami
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Hemophilia A (HA) and hemophilia B (HA) result from a deficiency or defect of factor VIII and IX procoagulant proteins, respectively, and are the most common of the severe bleeding diseases. The respective supplementation of factor VIII or factor IX concentrates for hemophilia treatment has resulted in preventing the arthropathy and in greatly improving quality of life. In Japan, the numbers of HA patients and HB patients alive are 5,410 and 1,186 in 2019. Approximately 90% of in HA and HB patients with severe type (<1 IU/dL) have received prophylaxis treatments by using regular and extended half-life products of factor VIII and factor IX. About 25 % in HA patients developed inhibitors, and majority of these patients had received the immune tolerance induction therapy. According to the J-ITI Registry, approximately 70% of these patients were successful for the ITI therapy. On the other hand, serious issues of hemostatic treatment using clotting factor concentrates have been the requirement of repeated intravenous infusion of these products, inhibitor development, and hemostatic treatment for patients with inhibitor. To overcome these issues, an anti-FIX/FX bispecific antibody, emicizumab (Hemlibra®), having the characteristics of longer $T_{1/2}$, subcutaneous administration, was developed. Emicizumab prophylaxis treatment has resulted in significant decrease of bleeding in from severely moderate to severe patients with hemophilia A, regardless of inhibitor in Japan as well as the other countries. A paradigm shift in the hemophilia A treatment with emicizumab, is now coming in Japan. Here I will present the latest treatment for hemophilia A and B in Japan in detail.

SY03

Optimal treatment with IMiDs in newly diagnosed multiple myelom

Pieter Sonneveld
Erasmus MC Cancer Institute, The Netherlands

Lenalidomide, as an immune modulating agent (IMiD), has been used many years and improved patients' outcome as a backbone for combination treatments, including new classes such as monoclonal antibodies, proteasome inhibitors, changing treatment landscape in multiple myeloma. This session is focused on general overview of lenalidomide-based first line regimen, lenalidomide-dexamethasone, lenalidomide-bortezomib-dexamethasone(RVD) in both transplant eligible and ineligible newly diagnosed multiple myeloma.

In transplant eligible patients, IFM/DFCI 2009 study compared 8 cycles of RVD vs. 3 cycles of RVD - MEL200/ASCT - 2 cycles of RVD, followed by 12 months of lenalidomide maintenance treatment. RVD group with autologous stem cell transplant (ASCT) group showed significant benefit in PFS, OS compared to RVD alone group. To consider optimal management in first line treatment in transplant eligible patients, pivotal trials has been extended to further investigate outcome of consolidation or maintenance, EMN02/HO95 MM study or STaMINA trial. In transplant ineligible patients, general overview of recent pivotal trials will be addressed. New or ongoing developments will be also discussed to further investigate how we can optimize patients' treatment in NDMM setting.

SY04

Ravulizumab: Next generation of C5 inhibitor for standard care of PNH

Jin Seok Kim
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Paroxysmal nocturnal hemoglobinuria (PNH) is a hematopoietic stem cell disease characterized by the intravascular lysis of red blood cells. Aplastic anemia is the most frequently associated with bone marrow failure syndrome (BMF) in PNH. Eculizumab, the first humanized monoclonal antibody that blocks terminal complement C5 activation, is the first approved medication for PNH. Although the efficacy and safety of eculizumab are well established, the treatment burden associated with the dosing regimen (every-2-week) may affect adherence. In addition, 11-27% of patients may experience breakthrough hemolysis, placing patients at risk for thrombotic events and other potentially life-threatening complications associated with intravascular hemolysis.

Ravulizumab is a second-generation IgG-mediated monoclonal antibody, similar to eculizumab. Ravulizumab has a longer half-life (about 40 days) than eculizumab (about 11 days) and has the advantage of a longer administration interval (every-8-week). In addition, the incidence of breakthrough hemolysis was lower in the patients who received ravulizumab in the phase 3 clinical trial.

In this presentation, ravulizumab is introduced in detail including the mechanism of action and efficacy and safety from clinical trials. In two phase 3 trials (naïve and switching), ravulizumab has been proved non-inferiority to eculizumab in efficacy endpoint.

SY05

Treatment of relapsed/refractory DLBCL: Role of polatuzumab vedotin

Laurie Sehn
BC Cancer Centre for Lymphoid Cancer, Canada

Diffuse large B-cell lymphoma (DLBCL) represents approximately 25% of all newly diagnosed cases of non-Hodgkin lymphoma. Although more than 60% of patients can be cured with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), approximately 15% exhibit primary refractory disease and 20-25% will relapse despite an initial response to therapy. Patients with relapsed/refractory DLBCL continue to present a therapeutic challenge, as outcomes in this setting remain poor. However, the recent availability of novel agents has provided new options for patients, enabling durable disease control and improved survival outcomes.

Polatuzumab vedotin is an antibody drug conjugate targeting CD79b, a component of the B-cell receptor complex that is almost universally present in DLBCL. Early trials demonstrated favourable activity of polatuzumab vedotin with or without rituximab in numerous B-cell lymphoma subtypes, prompting further combination studies. The GO29365 study is a phase 1b/2 trial evaluating the combination of polatuzumab vedotin and bendamustine-rituximab (pola-BR) in patients with transplant-ineligible relapsed/refractory DLBCL, after at least 1 line of prior therapy. Following an initial safety run-in, a randomized phase 2 comparison of pola-BR versus BR alone demonstrated a significant improvement in complete response rate, progression-free and overall survival compared with BR. Overall, the combination was well tolerated, and despite a higher likelihood of cytopenias, an increase in transfusion requirement or infection rate was not observed. Peripheral neuropathy was primarily low grade and reversible. Based on these favourable results, pola-BR has received regulatory approval and offers a novel treatment option for patients with transplant-ineligible DLBCL, providing durable benefit in a significant proportion of patients. More recently, a phase 2 extension cohort including an additional 100 patients treated with pola-BR was reported, confirming the benefit and safety of this combination. Real-world data has also emerged to support its use. Ongoing trials are exploring novel combinations of polatuzumab vedotin for patients with DLBCL, and a phase 3 trial evaluating its use in untreated patients has been completed and results are expected shortly.

SY06

Treatment strategies in relapsed multiple myeloma: A focus on sequential treatment for survival benefit

Joseph Mikhael
Translational Genomics Research Institute (TGen), USA

Survival in multiple myeloma (MM) has dramatically improved over the last decade for many reasons, including the introduction of novel agents, the appropriate use of autologous stem cell transplant, but also due to a strategy of employing a more comprehensive and sequential strategy of agents in the first few lines of therapy.

Nonetheless, nearly all patients will relapse. In relapsed MM several agents from multiple classes can be used and have been validated as doublets or triplets in several phase 3 clinical trials. The majority have demonstrated both an improved progression free survival (PFS) and overall response rate (ORR). However, only a few of them have resulted in long term overall survival (OS) benefit. Although there are limited options for patients in South Korea, several agents may be employed in a strategy to improve both response and survival in relapsed MM. Indeed, combinations with novel proteasome inhibitors, combined with immunomodulatory agents or combined with steroids alone can be considered. The ASPIRE clinical trial was a phase 3 trial of Carfilzomib-Lenalidomide-Dexamethasone vs Lenalidomide-Dexamethasone and demonstrated a superior response rate, PFS and OS. Similarly, Carfilzomib-Dexamethasone showed superiority to Bortezomib-Dexamethasone. Other novel combinations can also be considered with other agents such as Ixazomib, Daratumumab, Pomalidomide, Isatuximab and others.

This lecture will focus on both the strategy of optimizing therapy in relapsed MM, along with the evidence from clinical trials that support better outcomes for patients. A practical guide to using some of these novel agents to minimize toxicity while maximizing efficacy will also be reviewed.

SY07

First-line treatment of CLL in 2021

Philip A. Thompson
The University of Texas MD Anderson Cancer Center, USA

First line treatment of CLL has dramatically evolved over the last 5 to 10 years. For decades, advances in treatment were relatively modest, with the first major advance being the development of FCR chemoimmunotherapy, that was shown in the German CLL study group CLL8 study to improve survival relative to FC chemotherapy. A sub-group of patients, specifically those with mutated immunoglobulin heavy chain variable region (*IGHV*) and lacking high-risk chromosomal and molecular abnormalities, especially del(17p) or *TP53* mutation, but to a lesser extent, del(11q), have prolonged disease-free survival, with a plateau on the PFS curve suggestive of functional cure. However, this regimen has significant toxicities, including myelosuppression, infection and risk of therapy-related myeloid neoplasms, which preclude its use in patients with co-morbid medical conditions, who constitute the majority of patients with CLL. For this reason, the absolute number of patients expected to achieve very prolonged DFS with FCR is small.

Fortunately, major advances have been made in come understanding disease biology, especially the fundamental dependence of CLL cells on B cell receptor signaling and over-expression of BCL2. The development of targeted agents, especially oral small molecules inhibiting BTK, a key enzyme in the B cell receptor signaling pathway and BCL2, an anti-apoptotic protein that is over-expressed in most patients with CLL have improved outcomes for most patients. In particular, targeted agents have markedly improved the outcomes for patients whose age and comorbidities preclude the use of FCR and in those with high risk disease biology, especially patients with *TP53* mutation or deletion, but also in patients with unmutated *IGHV*. An array of ongoing clinical trials are evaluating various combinations of targeted agents, including personalized therapeutic approaches utilizing serial analysis of minimal residual disease. The hope is that shortly, these time-limited, well-tolerated regimens that are capable of achieving deep remission and prolonged treatment-free survival, will be available to the majority of patients for first-line treatment of CLL.

SY08

Updated ASH ITP guidelines and their implications on clinical practice

Waleed Ghanima
Østfold Hospital, University of Oslo, Norway

An updated evidence-based revision of the ASH guidelines for ITP were published in 2019. These guidelines used GRADE methodology and included 21 recommendations covering management of ITP in adults and children with newly diagnosed, persistent, and chronic.

The current American Society of Hematology clinical guidelines recommend managing a newly diagnosed adult patient with a platelet count $<30 \times 10^9$/L with corticosteroids with the addition of intravenous immunoglobulin (IVIG) in patients with active bleeding or those in whom a prompt increase in the platelet count is preferred. The guidelines recommended against using corticosteroids for > 6 weeks to limit potential side effects caused by prolonged use of corticosteroids and because it is unlikely to achieve benefit from longer treatment.

In patients who do not respond adequately to first-line therapy, or become dependent on high doses of corticosteroids, treatment options include thrombopoietin-receptor agonists (TPO-RAs), rituximab, or splenectomy. The choice between these therapies depends on patients preference, availability of medications/regulatory restriction, as well as patients and disease related factors.

The guidelines recommend treatment decisions based on shared decision-making between the physician and patient, recognizing that each individual patient's concerns, values, and preferences regarding treatment differ.

The guideline suggests delaying splenectomy for at least 1 year, because of the potential for spontaneous remission in the first year. TPO-Ra provides greater durability of response than rituximab. Therefore, ASH guidelines suggest TPO-RA rather than rituximab, in general. However, rituximab might be preferable to those who place a high value on avoiding long-term treatment or who cannot afford TPO-RAs.

SY09

The role of Myeloid Growth Factors (MGFs) in patients with lymphoma: Benefits, risks, & unmet issues

Yong Park
Korea University College of Medicine, Korea

Febrile neutropenia (FN) is one of the major toxicity reported in patients with hematological malignancies receiving myelosuppressive chemotherapy. Current guidelines provide recommendations on granulocyte colony-stimulating factors (G-CSF) for prevention of FN. Pegylated G-CSF have longer half-life compared than the conventionl G-CSF and single injection of pegylated G-CSF is enough to manage the patients with cytotoxic chemotherapy. In addition to the convenience of pegylated G-CSF, primary prophylactic use of pegylated G-CSF for the patients with cytotoxic chemotherapy was associated with a reduced risk of duration of Severe Neutropenia (DSN), FN and neutropenia-related or all-cause hospitalization than conventional G-CSF. Peglyated filgrastim is the original drug and many peg-filgrastim biosimilars have been currently approved or in development. In this section, the efficacy and safety of pegylated filgrastim and its biosimilar agents would be reviewed, focusing data in patients with diffuse large b cell lymphoma.

SY10

Real-world outcomes and factors impacting treatment choice in relapsed/refractory multiple myeloma: Special focus on Ixazomib-Rd

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The therapeutic strategy for relapsed and refractory multiple myeloma (RRMM) integrates a holistic approach regarding patient, disease, and drug-related factors. Patient-related factors include age, frailty status, and underlying comorbidities, especially cardiovascular and renal diseases and peripheral neuropathies that affect tolerability to multiple drug combinations or transplantations. Disease-related factors encompass these multiple patient-related factors, particularly the aggressiveness of the disease and cytogenetics. Regarding drug-related factors, the approval of novel proteasome inhibitors (PIs, such as carfilzomib and ixazomib), immunomodulatory agents (IMiDs, such as pomalidomide), monoclonal antibodies (such as daratumumab and elotuzumab), and new classes of drugs increasingly make the choice treatment more complex as data from clinical trials are not able to be applied directly to real-world patients. About 50% of the RRMM patients are not possible to be included in clinical trials due to the strict inclusion and exclusion criteria, which hinders the expectation of the clinical outcomes, factors affecting efficacies and toxicities of the novel drug combinations. In this talk, the real-world data of Korean RRMM patients treated with recently approved next generation PIs and IMiDs including ixazomib in combination with lenalidomide and dexamethasone, which was administered through patient assistance program.

ORAL PRESENTATION

OP01-1

Physical and psychological impairments as practical frailty markers and/or survival predictors in elderly AML fit for intensive chemotherapy

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Background: The comprehensive geriatric assessment (CGA) typically refers to a multidimensional evaluation designed to evaluate an older person's functional ability, physical health, cognition, psychological health, nutritional status, and social support. The purpose of CGA is to develop time-efficient and straightforward tools to evaluate the multiple characteristics of a patient, which may predict the treatment outcomes of elderly acute myeloid leukemia (eAML) patients treated with intensive chemotherapy. We designed a CGA battery with measures that were previously validated, standardized, and widely used. This study is a single-center prospective observational cohort study (#KCT0002172). We investigated the predictive values of each CGA domain to discriminate against the vulnerable eAML patients fit for intensive chemotherapy.

Method: Between November 2016 and December 2019, we enrolled 105 newly diagnosed eAML patients aged ≥60 years with a median age of 64 years (range: 60 – 75). They were considered fit for intensive chemotherapy and showed adequate performances and organ functions. Every enrolled patient answered various questionnaires for an initial CGA. Our functional evaluation was divided into three categories: (1) Social and Nutritional support (OARS and MNA), (2) Cognitive (MMSE-KC and KNU-DESC), and Psychological (SGDS-K, PHQ-9, Montgomery-Asberg Depression Rating Scale, and NCCN distress thermometer), and (3) Physical function (ECOG, KIADL, SPPB, Handgrip strength, and PTA by professional ENT evaluation).

Result: We found that 105 patients received intensive chemotherapy. They showed impairments in each CGA category with a score of 35.2% for OARS, 20.0% for MNA, 59.1% for any physical impairment, and 61.9% for any psychological or cognitive impairment. We also measured that 69.5% of the treated patients achieved first complete remission, 4.8% (5 patients) experienced early death within 60 days, and 59.1% (62 patients) went through transplantation (autologous n=3 and allogeneic n=59). During induction chemotherapy, the median recovery period for the neutrophil and platelet counts was 26 (range: 24-29) and 30 (range: 29-34) days, respectively. The median hospitalization days for induction chemotherapy were 32 days (range: 16-104). The physical impairments were significantly associated with a higher incidence of NCI-CTC-AE based grade III to IV infection (intact vs. any impairment; 51.2% vs. 77.4%, p=0.005) and a trend of more GI complications (intact vs. any impairments; 25.6% vs. 48.4%, p=0.018), resulting in prolonged hospitalization (intact vs. any impairments; 31.4 ± 1.3 days vs. 37.7 ± 1.8 days, p=0.012). The psychological impairments were also significantly associated with a higher incidence of infection rate (intact vs. any impairments; 55.0% vs. 68.6%, p=0.047) and prolonged hospitalization (intact vs. any impairments; 31.6 ± 1.0 days vs. 37.3 ± 1.8 days, p=0.026). An impairment in any of the physical performance domain (intact vs. any impairment OS; 55.0% vs. 42.8%, p=0.046) was also significantly associated with inferior survival outcomes, especially for SBBP (intact vs. any impairment OS; 54.4% vs. 34.1%, p=0.015, and intact vs. any impairment DFS; 48.6% vs. 35.2%, p=0.044) and Gait-speed (intact vs. any impairment OS; 63.4% vs. 35.0%, p<0.001, intact vs. any impairment DFS 55.0% vs. 36.2%, p=0.03, and intact vs. any impairment NRM 27.3% vs. 48.2%, p=0.010). The patients with a lack of nutrition and social support presented inferior NRM (intact vs. any impairment; 36.3% vs. 78.1%, p=0.046).

Conclusions: This study demonstrates that a significant proportion of eAML patients fit for intensive chemotherapy showed social, nutritional, physical, and psychological impairments. The impaired physical and/or psychological functions were practical frailty markers of intolerance to intensive chemotherapy at induction. Our data also demonstrated that any impairment in the objective measures of the patients' physical function assessed at diagnosis was associated with an increased risk of mortality in eAML. CGA, SPPB, and gait speed, which are major physical performance domains in the SPPB battery, were efficient and valuable clinical measures for eAML that could accurately identify frailty and predict survival outcomes. Developing handy and bed-side available CGA measures with validated domains could improve the stratification risk and improve the clinical outcomes of eAML patients.

Keyword: Acute Myeloid Leukemia, Comprehensive Geriatric Assessment, Elderly, Intensive Chemotherapy

OP01-2

Allogeneic hematopoietic stem cell transplantation can overcome the adverse prognosis of secondary-type mutation positive acute myeloid leukemia

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Background : Secondary acute myeloid leukemia (AML), which makes up about 25% of all AML, is known to have worse prognosis than de-novo AML. Lindsley et al. previously reported that 8 genes were mutated with more than 95% of specificity in secondary AML compared with de novo AML, including SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, and STAG2 and named them 'secondary-type mutations' (Blood 2015). In this study, we analyzed the clinical significance of secondary-type mutations in de-novo AML and the outcome of allogeneic hematopoietic stem cell transplantation (HCT) in secondary-type mutation positive AML patients.

Method : Totally, 537 patients who were diagnosed with de-novo AML and received intensive induction therapy from November 1996 to May 2019 were screened for the study. The patients who had cytogenetic abnormalities associated with favorable risk (n=87) and poor risk (n=46) were excluded because the presence of such chromosomal abnormalities might offset the prognostic impact of the genetic mutation, and finally, 404 patients were included in the analysis.

Results : Through the genetic profiling including the targeted deep sequencing of 72 genes, 61 patients (15.1%) had secondary-type mutations (mutation-positive group) and 343 patients did not (mutation-negative group). The complete response (CR) rate was lower in the mutation-positive group (41/61, 67.2% vs. 300/343, 87.5%, p<0.001) than the mutation-negative group. The mutation-positive group showed significantly shorter overall survival (OS) (5-year OS 14.8% vs. 31.5%) (HR 2.011, 95% CI 1.479-2.733, p<0.001) and relapse-free survival (RFS) (5-year RFS 19.5% vs. 31.47%) (HR 1.590, 95% CI 1.088-2.323, p=0.016) than the mutation-negative group. Among the 41 mutation-positive patient, 15 patients who received allogeneic HCT showed better OS (5-year OS 40.0% vs. 11.5%) (HR 0.409, 95% CI 0.178-0.937, p=0.034), and RFS (5-year RFS 40.0% vs. 7.7%) (HR 0.426, 95% CI 0.185-0.981, p=0.045) than the patients who received consolidation chemotherapy only. Cumulative incidence of relapse (CIR) was lower in the patients who received allogeneic HCT than who did not (5-year CIR 33.3% vs. 61.5%) (HR 0.277, 95% CI 0.101-0.757, p=0.012) but cumulative incidence of non-relapse mortality (NRM) was similar (5-year NRM 26.7% vs. 19.2%) (HR1.074, 95% CI 0.303-3.808, p=0.912).

Conclusion : In conclusion, the presence of secondary-type mutation is independently poor prognostic factor for AML, and allogeneic HCT after CR can overcome the adverse prognosis of secondary-type mutation.

Keyword : Allogeneic Hematopoietic Stem Cell Transplantation, Secondary-Type Mutation

OP01-3

Epigenetic analysis reveals MiR-128-2-5p and MiR-378c as possible novel biomarkers for detection of relapse B-cell acute lymphoblastic leukemia

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Background : Epigenetic changes especially DNA methylation and miRNA mediated transcription silencing play a major role in mediating chemo resistance and possibly relapse in pediatric ALL. Recent studies suggest global hypomethylation and upregulation of tumour suppressor transcription controlling miRNAs as likely changes in relapse ALL samples. Hence in current pilot study, we evaluated DNA methylation, miRNA expression as well as secondary copy number variations (CNVs) in a cohort of relapse pediatric B-ALL cases to identify any novel biomarkers for predicting or detecting early relapse in pediatric B-ALL cases.

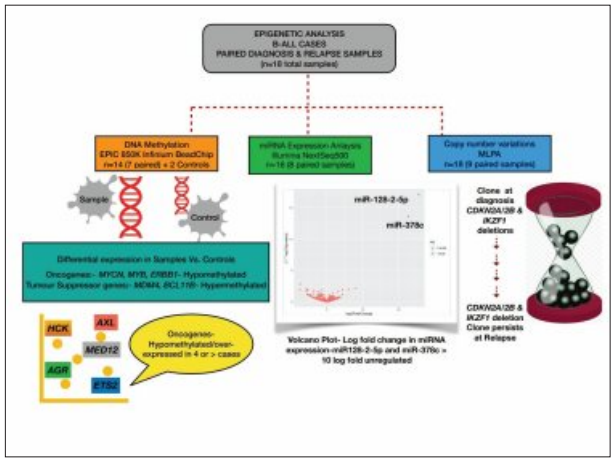
Method : DNA methylation, miRNA expression and CNV analysis were performed in a total of 14, 16 and 18 cases as paired diagnosis-relapse samples. DNA and RNA was extracted from each sample using commercial Qiagen Blood Mini kits on QIAcube platform followed by quality assessment for quality and quantity using both quit and bioanalyzer. DNA methylation was performed after bisulphite conversion using Infinium HumanMethylation 850K chip and data analysed using RnBeads. miRNA were sequenced on illumina NextSeq500 platform for 20M 75bp SE reads and analysed by DESeq including MirBase, Mirdeep2 and Miranda software's. CNVs were assessed by MLPA assay using the ALL P-335 probemix kit and analysed by coffalyzer.net.

Results : On DNA methylation analysis, oncogenes MYCN, MYB, and ERBB1 and tumour suppressor genes MDM4 & BCL11B were found differentially expressed as compared to controls (p-0.03). In addition, protooncogenes-AXL, HCK, MED12, ETS2 and AGR were hypomethylated/overexpressed in 4 or more cases (p-

<0.05). miRNA analysis revealed significant (>10log fold) differential upregulation of miR-128-2-5p and miR-378C (p-4.4e-15 and p-6.4E-12) in relapse samples. CNV analysis revealed frequency of good and intermediate/poor risk CNV profile at diagnosis is nearly equal (40% vs. 60%). However, CDKN2A/2B and IKZF1 gene CNVs if present in initial diagnostic clone usually persisted in relapse clone.

Conclusion : Our pilot study is the first to highlight two pro-oncogenic miRNAs (miR-128-2-5p and miR-378C) as novel candidate biomarkers of relapsed B-ALL. Many recent studies have shown that miR-128-2-5p is significantly overexpressed in pediatric ALL cases at diagnosis than controls and in ALL cases more than in AML cases. In-vitro studies have also shown this miRNA to play a role in vincristine and prednisolone resistance development. This needs to be validated in further functional studies and could be a possible important mechanism of relapse in B-ALL. DNA methylation revealed five proto-oncogenes as significant hypomethylated genes in a subset of cases. However, their role in relapse ALL needs further evaluation in a larger series of cohort along with correlation of miRNA markers with clinical and disease outcome parameters.

Keyword : B-ALL, DNA Methylation, miRNA, CNVs



OP01-4

Measurable residual disease assessment, T cell antigen stability and survival among immunophenotypic sub-categories of T-lineage acute lymphoblastic leukemia patients

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Background : Precursor T-lineage acute lymphoblastic leukemia (T-ALL) patients expressing myeloid/stem cell antigens are classified as either early-T-cell precursor ALL (ETP-ALL) or near-ETP-ALL. Clinical-laboratory features of ETP-ALL patients has been frequently documented, but literature on 'near-ETP-ALL' patients are sparse.

Method : We analyzed the clinical-laboratory profile, flow cytometric (FCM) end-of-induction measurable residual disease (EOI-MRD), overall (OS), relapse-free (RFS) and event-free (EFS) survival of our treatment-naïve T-ALL patients diagnosed between December 2017 to March 2020. For diagnosis, a 6-tube 10-color FCM panel was used. EOI-MRD was assessed in bulk lysed first-pull BMA samples using a single-tube 11-antigen 10-color panel.

Results : Among 81 consecutive T-ALL patients diagnosed, 21% (n=17) and 19% (n=15) were ETP-ALL and near-ETP-ALL, respectively. Among these ETP-ALL and near-ETP-ALL patients, the expression frequency for myeloid/stem cell antigens (ETP-ALL vs near-ETP-ALL) was: CD117 (47% vs 7%, p=0.011), CD34 (82% vs 80%, p=0.865), HLA-DR (53% vs 21%, p=0.073), CD13 (53% vs 20%, p=0.055), CD33 (47% vs 73%, p=0.131) and CD11b (29% vs 21%, p=0.631). Importantly, CD73 expression was restricted only to ETP-ALL & near-ETP-ALL blasts (p=0.007), and CD86 was significantly expressed only among ETP-ALL blasts (p<0.001). There was higher frequency of CD56 expression in our ETP-ALL and near-ETP-ALL patients (p=0.009). But, CD56 expression did not make any difference in the 2-year OS, EFS, and RFS of our near-ETP-ALL and ETP-ALL patients (p>0.05). CD19 expression was observed only among ETP-ALL and near-ETP-ALL blasts and not among conventional-T-ALL (con-T-ALL) blasts (p=0.004). CD79a expression was not predilected towards any of the immunophenotypic subcategories of T-ALL (p=0.172). Aberrant expression of either CD19 or CD79a did not translate into inferior 2-year survival outcomes among any of T-ALL subcategories (p>0.05). EOI-MRD was tested in 59 patients (con-T-ALL=40, ETP-ALL=12, and near-ETP-ALL=7). A median of 2.3 million events (range, 0.18 to 7.3 million) was acquired for analysis, and > 1.5 million events were acquired in 68% of samples. MRD was positive in 39% of samples tested (31.6% of pediatric and 52.4% of adult samples). The frequency of EOI-MRD positivity was higher among ETP-ALL (75% positive, p=0.001) and near-ETP-ALL (71% positive, p=0.009) patients as compared to con-T-ALL patients (22.5% positive). There was upregulation of CD8 (p=0.046) and CD38 (p=0.046) expression in the EOI-blasts of con-T-ALL and ETP-ALL samples, respectively. 2-year OS, RFS and EFS among our T-ALL patients (pediatric vs adult) was 79.5% vs 39.8% with p<0.001, 84.3% vs 60.4% with p=0.026 and 80.3% vs 38% with p<0.001, respectively. By univariate analysis, 2-year EFS & RFS of our pediatric T-ALL patients was independent of immunophenotypic T-ALL subtype and was influenced only by the EOI-MRD status. The 2-year survival among adult T-ALL patients was EOI-MRD independent and was influenced only by the presence of near-ETP-ALL phenotype.

Conclusion : In our experience, both ETP-ALL and near-ETP-ALL are common among adult T-ALL patients. Irrespective of the age at diagnosis, both these entities are associated with a high frequency of EOI-MRD positivity. Among pediatric T-ALL patients, 2-year survival was influenced only by the EOI-MRD status, but not by the immunophenotypic sub-type of the blasts. However, the 2-year survival among adult T-ALL patients was independent of EOI-MRD status; but was influenced only by the presence of near-ETPALL immunophenotype.

Keyword : Measurable Residual Disease, Minimal Residual Disease,

Flow Cytometry, Precursor T Lineage Acute Lymphoblastic Leukemia, ETP-ALL And Near ETP-ALL.

Table 1: Clinical and laboratory characteristics of immunophenotypic T-ALL sub-categories.

Parameters		Overall T-ALL (n=81) Con-T-ALL (n=49)	T-ALL sub categories			P value		
			ETP-ALL (n=17)	Near ETP-ALL (n=15)	ETPALL vs Near-ETPALL	ETPALL Vs Con-T-ALL	Near-ETPALL VS Con-T-ALL	
Median (range) age in years		17 (1-52)	15 (1-50)	17 (13-39)	23 (5-52)	.882	.003	.016
Age Group	Paediatric (%)	47 (58)	34 (72%)	7 (15%)	6 (13%)	1.000	.039	.040
	Adult (%)	34 (42)	15 (44%)	10 (29%)	9 (27%)			
Sex (Male: Female)		3.8:1	4.4:1	3.2:1	2.7:1	1.000	.645	.485
Median (range) Hb in g/L		90 (30-142)	90 (30-142)	92 (30-131)	88 (41-133)	.737	1.000	.751
Median (range) WBC count X10^9/L		64.1 (1-850)	173 (1.1-850)	70(1 – 480)	145 (3-590)	.049	.005	.751
Median (range) Platelet X10^9/L		54 (20-380)	73 (20-366)	125 (30-290)	127 (20-380)	.911	.008	.080
Median (range) BM blast		87 (22 -99)	87 (23-97)	86 (22-98)	89 (50-99)	.473	.795	.663
Median (range) PB blast		78 (2-99)	80 (2-97)	42 (2-98)	83 (2-99)	.193	.174	.411
Hyperleukocytosis		41%	45%	18%	53%	.034	.046	.567
Hepatomegaly		42%	42%	27%	58%	.204	.283	.319
Splenomegaly		56%	56%	47%	67%	.516	.550	.489
Lymphadenopathy		78%	73%	87%	86%	1.000	.290	.342
Mediastinal mass		31%	36%	33%	13%	.388	.842	.095
CNS involvement at diagnosis		3.2%	2 (5)	0%	0%	-	.417	.499
DBBNC		35%	32%	54%	20%	.223	.168	.440
EOI-MRD positive		23 (39%)	9 (22.5%)	9 (75%)	5 (71.4%)	.865	.001	.009
Relapse rate		20%	18%	17%	38%	.292	.947	.204
OS at 24 months		65%	75%	55.4%	40.2%	.180	.551	.019
RFS at 24 months		76.1%	79.8%	78.8%	54.7%	.292	.956	.190
EFS at 24 months		64.5%	70.8%	66.6%	34.6%	.076	.978	.013

BM: Bone marrow; CNS: central nervous system; con-T-ALL: conventional T-ALL; DBBNC: day 8 blast not cleared; EOI-MRD: end of induction-measurable residual disease; NA: not applicable; PB: Peripheral blood; WBC: white blood cell; OS: overall survival; RFS: relapse free survival; EFS: event free survival.

OP01-5

PTCy-based haploidentical vs matched unrelated donor transplantation using myeloablative targeted busulfan-based conditioning for pediatric acute leukemia

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Background : Haploidentical related donor (HRD) has been increasingly used as an alternative donor strategy when a matched donor is not available for hematopoietic stem cell transplantation (HSCT). Among the various methods to prevent graft-versus-host disease (GVHD) in haploidentical HSCT, post-transplant cyclophosphamide (PTCy) is an attractive option because it has shown promising outcomes and is easy to apply. However, few studies have compared HRD and matched unrelated donor (MUD) HSCT for high-risk pediatric acute leukemia.

Method : We retrospectively compared the outcomes in children and adolescents with acute leukemia after HRD HSCT with PTCy (n=36) and MUD HSCT (n=45, [10/10 n=35, 9/10 n=10, respectively]), after targeted busulfan-based myeloablative conditioning using intensive pharmacokinetic monitoring from 2013 January to 2020 April at Seoul National University Children's Hospital. Targeted busulfan (target area under the curve at 75,000μgxh/L), fludarabine were used in both groups for the conditioning regimen, while cyclophosphamide was included in the HRD group and anti-thymocyte globulin in the MUD group.

Results : Diagnosis, age, disease status at HSCT, infused cell count, and infused busulfan area under the curve were similar between the HRD and MUD groups. The median follow-up time was 3.3 and 3.8 years, respectively. The HRD group showed slower neutrophil (median 15 versus 10 days, p<0.001) and platelet (median 26 versus 14 days, p<0.001) engraftment compared to the MUD group. There was no engraftment failure. Subsequently, the outcomes of the HRD and MUD groups were compared. The cumulative incidence of acute GVHD grade II-IV (33.3% versus 48.9%, p=0.118), grade III-IV (2.8% versus 8.9%, p=0.259), extensive chronic GVHD (11.1% versus 18.3%, p=0.395), relapse (24.9% versus 24.5%, p=0.96), and non-relapse mortality (0% versus 2.6%, p=0.399) were not significantly different. The 3-year GVHD-free/event-free, event-free and overall survival rates in the HRD and MUD groups were 64.0±8.5% versus 58.7±7.8% (p=0.381), 75.1±7.8% versus 70.6±7.2% (p=0.723), and 84.4±6.6% versus 83.3±5.8% (p=0.951), respectively. In sub-group analyses of acute lymphoblastic leukemia and acute myeloid leukemia patients, there were no significant differences in outcomes between the MRD and MUD groups.

Conclusion : Our results demonstrated that HRD HSCT with PTCy using targeted busulfan-based myeloablative conditioning regimen shows similar outcomes compared to MUD HSCT. HRD HSCT with PTCy could be considered for pediatric acute leukemia patients who lack an HLA-matched donor.

Keyword : Haploidentical, Post-Transplant Cyclophosphamide, Unrelated Donor, Pediatric Leukemia, Hematopoietic Stem Cell Transplantation

OP02-1

Similar survival and genetic features between clonal cytopenia of undetermined significance and lower-risk myelodysplastic syndrome

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Background : Idiopathic cytopenia of undetermined significance (ICUS) is characterized by a persistent and clinically significant cytopenias which does not meet the diagnostic criteria for myelodysplastic syndrome (MDS). In some patients with ICUS, disease evolution to MDS or acute myeloid leukemia after variable periods of time was observed in several studies. However, the incidence and predictive factors of progression as well as management guidelines for ICUS patients are not well established. We aimed to identify the clinical and genetic characteristics of ICUS in comparison with lower-risk MDS for understanding the pathophysiologic features and providing guidance for treating physicians.

Method : We performed targeted deep sequencing including 61 myeloid neoplasm-related genes with a MiSeqDx sequencer (Illumina) using bone marrow (BM) samples obtained from the patients with ICUS (n=139) and MDS (n=226) between May 2009 and December 2019. The cut-off level of variant allele frequency (VAF) was set to 2.0% of mutant allele reads. Cloncal cytopenia of undetermined significance (CCUS) was defined as ICUS with ≥ 2% VAF of mutations and lower-risk MDS was defined as MDS with revised international prognostic scoring system >3.5.

Results : When we compared the overall survival (OS) of the patients according to the disease subtypes, OS of CCUS (77.0% at 5-year) was significantly better than that of higher-risk MDS (41.0%, P<.001) and worse than non-clonal ICUS (94.1%, P=.050), but it was similar to the OS of lower-risk MDS (67.9%, P=.363). Next, we compared the clinical and mutational features between CCUS (n=78) and lower-risk MDS (n=99). As shown in Table, there was no significant difference of patient characteristics between two groups except for higher hemoglobin level (10.5 vs. 9.0 g/dL, P=.008) in CCUS than lower-risk MDS, and the rate of red blood cell transfusion dependency was not different (P=.738). The median number of mutated genes of CCUS and lower-risk MDS were 1 (range, 0-4) and 1 (range, 0-6) (P=.651), and the median mutation numbers were 1 (range, 0-5) in CCUS and 2 (range, 0-7) in lower-risk MDS, respectively (P=.711). The mutational profiles of 61 genes were also similar between CCUS and lower-risk MDS except for SF3B1 (2.6% in CCUS and 18.2% in lower-risk MDS; P=.001) and STAT3 (5.1% in CCUS and 0% in lower-risk MDS; P=.023). Overall, 11 of 78 CCUS and 24 of 99 MDS died, and the causes of death were not different between two groups (P=.861).

Conclusion : In our study, CCUS and lower-risk MDS showed similar OS which was significantly better than higher-risk MDS and worse than non-clonal ICUS. The clinical and mutational characteristics were also similar except for the degree of anemia and the SF3B1 and STAT3 mutation. Our findings suggest that the patients with CCUS may be regarded and treated as the lower-risk MDS despite a lack of significant dysplasia or MDS-associated definitive chromosomal abnormality.

Keyword : Clonal Cytopenia of Undetermined Significance, Myelodysplastic Syndrome, Idiopathic Cytopenia of Undetermined Significance

	CCUS (n=78)	LR-MDS (n=99)	P-value
Male/female	47 (60.3%) / 31 (39.7%)	66 (66.7%) / 33 (33.3%)	.378
Age, yr, median (range)	65 (19-89)	59 (19-85)	.257
WBC, x10^3/uL, median (range)	3.4 (1.4-10.3)	3.2 (1.4-15.3)	.828
ANC, x10^3/uL, median (range)	1395 (161-9435)	1456 (268-13541)	.430
Hb, g/dL, median (range)	10.5 (5.9-15.8)	9.0 (3.8-15.5)	.008
PLT, x10^3/uL, median (range)	88.5 (2-378)	106 (2-789)	.253*
BM blast, %, average (range)	1.2 (0-4.8)	1.4 (0-7.2)	.080*
RBC transfusion dependency	19 (24.4)	22 (22.2)	.738
Mutated gene no., median (range)	1 (0-4)	1 (0-6)	.651/.817*
Mutation no., median (range)	1 (0-5)	2 (0-7)	.711/410*
IPSS-R chromosome Very good Good Intermediate	 7 (9.0%) 62 (79.5%) 7 (9.0%)	 6 (6.1%) 79 (80.0%) 14 (14.1%)	.481
ABL1 mutation	2 (2.6%)	0	.109
ANKRD26 mutation	1 (1.3%)	1 (1.0%)	.865
ASXL1 mutation	6 (7.7%)	14 (14.1%)	.178
ATM mutation	5 (6.4%)	3 (3.0%)	.283
BCOR mutation	4 (5.1)	6 (6.1%)	.790
BCORL1 mutation	1 (1.3%)	3 (3.0%)	.437
BRAF mutation	0	1 (1.0%)	.373
CALR mutation	0	1 (1.0%)	.373
CBL mutation	1 (1.3%)	1 (1.0%)	.865
CEBPA mutation	0	1 (1.0%)	.373
CSF3R mutation	1 (1.3%)	1 (1.0%)	.865
DDX41 mutation	10 (12.8%)	7 (7.1%)	.197
DNMT1 mutation	1 (1.3%)	0	.259
DNMT3A mutation	16 (20.5%)	10 (10.1%)	.052
EP300 mutation	1 (1.3%)	2 (2.0%)	.706
ENTK1 mutation	3 (3.8%)	2 (2.0%)	.467
ETV6 mutation	3 (3.8%)	2 (2.0%)	.467
EZH2 mutation	0	2 (2.0%)	.207
GATA2 mutation	0	2 (2.0%)	.207
HRAS mutation	1 (1.3%)	0	.259
IDH1 mutation	2 (2.6%)	0	.109
IDH2 mutation	0	4 (4.0%)	.073
IKZF1 mutation	1 (1.3%)	2 (2.0%)	.706
JAK2 mutation	1 (1.3%)	2 (2.0%)	.706
JAK3 mutation	0	1 (1.0%)	.373
KDM6A mutation	0	1 (1.0%)	.373
KIT mutation	1 (1.3%)	1 (1.0%)	.865
KMT2A mutation	2 (2.6%)	1 (1.0%)	.427
KRAS mutation	2 (2.6%)	3 (3.0%)	.853
MALT1 mutation	1 (1.3%)	1 (1.0%)	.865
MPL mutation	0	2 (2.0%)	.207
NF1 mutation	0	3 (3.0%)	.121
NOTCH1 mutation	1 (1.3%)	0	.259
NPM1 mutation	2 (2.6%)	0	.109
NRAS mutation	1 (1.3%)	2 (2.0%)	.706
PHF6 mutation	1 (1.3%)	1 (1.0%)	.865
PTPN11 mutation	1 (1.3%)	2 (2.0%)	.706
RAD21 mutation	0	1 (1.0%)	.373
RUNX1 mutation	2 (2.6%)	5 (5.1%)	.399
SETBP1 mutation	1 (1.3%)	4 (4.0%)	.271
SETD2 mutation	2 (2.6%)	0	.109
SF1 mutation	1 (1.3%)	0	.259
SF3B1 mutation	2 (2.6%)	18 (18.2%)	.001
SMC3 mutation	0	1 (1.0%)	.373
SRSF2 mutation	6 (7.7%)	4 (4.0%)	.296
STAG2 mutation	1 (1.3%)	7 (7.1%)	.066
STAT3 mutation	4 (5.1%)	0	.023
TET2 mutation	18 (23.1%)	14 (14.1%)	.125
TP53 mutation	1 (1.3%)	5 (5.1%)	.169
U2AF1 mutation	5 (6.4%)	11 (11.1%)	.279
WT1 mutation	0	1 (1.0%)	.373
ZRSR2 mutation	2 (2.6%)	1 (1.0%)	.427

OP02-2

Clinical performance evaluation of an optical mapping technique for detection of structural variation in hematologic malignancies

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Background : Structural variation (SV) is a copy number change or genomic rearrangement in a large DNA region. SVs are involved in the development and progression of tumors, thus crucial in tumor diagnosis and treatment. Especially in hematologic malignancies, SV detection plays an essential role as a biomarker in diagnosing, selecting target therapy, and predicting the prognosis. However, conventional methods for detecting SVs have limitations, such as low resolution, long turn-around time, and limited coverage using probes or primers targeting known aberrations. Optical mapping, a single-molecule strategy, constructing ordered, genome-wide, high-resolution maps from high-molecular-weight DNA labeled by fluorescent, is an efficient technique to detect large structural variations and determine breakpoints. Here, we evaluate the performance of optical mapping in detecting SVs by comparing results with conventional methods.

Method : In patients diagnosed with hematologic malignancy, 18 bone marrow samples with SVs from conventional methods were selected and included. 1.5 × 106 cells from bone marrow aspirate were used for the high molecular weight DNA isolation and DNA labeling was processed with the Bionano Prep™ DNA Labeling Kit. Labeled DNA was processed with the Saphyr optical genome mapping instrument (Bionano Genomics, San Diego, California). Data were de novo assembled using Bionano Access™ (v1.5) and Bionano variant annotation pipeline was used. Detected SVs were compared with the G-banding karyotyping, fluorescence in situ hybridization (FISH), and/or next-generation sequencing (NGS) results.

Results : Among 18 samples, 14 samples showed full concordance between the optical mapping and conventional methods. All translocations detected from G-banding karyotyping were detected by optical mapping. One acute myeloid leukemia case progressed from prior chemotherapy; the optical mapping noticed a gain of oncogene amplification known as a drug resistance mechanism. In one case with normal karyotype from conventional methods, the optical mapping detected EP300-ZNF384 fusion, which is reported as the recurrent gene fusion in B-cell precursor acute lymphoblastic leukemia. These were confirmed by FISH and Sanger sequencing, respectively. When translocation with derivative chromosome breakpoints is located near the centromere or telomere region, optical mapping only detected copy number changes but no translocation. Due to the limited sensitivity, the optical mapping did not detect low-level sub-clonal aberrations.

Conclusion : All types of SVs were well detected with optical mapping, and we could define the breakpoints and translocation partners, which was ambiguous by karyotyping. Our study provides optical mapping that shows acceptable performance in detecting structural variation in hematologic malignancies

Keyword : Optical Mapping, Hematologic Malignancies, Structural Variation, Fusion Gene, Immunoglobulin Heavy Chain Gene

OP02-3

Single cell analysis and cytoplasmic-Ig FISH on double primary acute myeloid leukemia and plasma cell myeloma

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Background : Simultaneous occurrence of both primary acute myeloid leukemia (AML) and plasma cell myeloma (PCM) is a rare event and its pathogenesis is still unclear. In the present case, we adopted fluorescence in situ hybridization (FISH), cytoplasmic-immunoglobulin FISH (cytoplasmic-Ig FISH), direct bone marrow (BM) FISH and single cell analysis using spatially resolved laser activated cell sorter (SLACS) and direct library preparation (DLP) to investigate cytogenetic and molecular abnormalities of the plasma cells (PCs) and myeloblasts (MBs) separately.

Method : A total of 5 serial BM specimens of a 69-year-old woman who was diagnosed with both AML and PCM was collected. FISH and/or cytoplasmic-Ig FISH using probes of LSI TCF3, LSI CDKN2A, LSI ETV6/RUNX1, LSI MLL, LSI PML/RARA , LSI CEP8 and LSI 20q was carried out on each specimens. Direct BM FISH was performed to

elucidate whether the cytogenetic abnormalities was present in neutrophils and/or eosinophils. From FISH and/or cytoplasmic-Ig FISH slides, PCs with TCF3 3 copies, PCs with MLL 3 copies, MBs with TCF3 3 copies, neutrophils, eosinophils and normal karyotype cells were isolated by SLACS. DLP protocol was applied for library preparation from low-input genomes which consisted of 30 to 50 cells each. Copy number alteration (CNA) analysis was performed using whole genome sequencing (WGS) data. Meanwhile, G-banding analysis and bulk targeted sequencing using a gene panel consisted of 655 hematologic malignancy and cancer-related genes were performed on the serial BM samples.

Results : FISH and cytoplasmic-Ig FISH results revealed common and/or separate cytogenetic abnormalities of PCs and MBs. The TCF3 3 copies was present in both PCs and MBs, which implies that clones with TCF3 3 copies originated from common progenitor cells. CDKN2A tetrasomy, RUNX1 3 copies, MLL 3 copies and PML 3 copies were identified only in PCs. Alternatively, trisomy 8 and 20q deletion were detected only in MBs. No abnormal signal was found in neutrophils or eosinophils by direct BM FISH. Single cell analysis confirmed the FISH results and gave more detailed CNA information on each cell of interest. Similar numerical abnormalities of trisomy of chromosomes 3, 5, 6, 7, 11, 15, 18, 19, 21, tetrasomy 9 and 1.5 copies of chromosomes 1, 10 and 13 were detected in both PCs with TCF3 copies and PCs with MLL 3 copies. Alternatively, trisomy of chromosome 1p, 3q, 8 and 10 and 1.5 copies of chromosome 6, 7q and 20q were present in MBs with TCF3 3 copies. Meanwhile, 3 copies in chromosome 11, 15 and 21 and 1.5 copies in chromosome 16 was present in neutrophils and 1.5 copies in chromosome 11 and 16q was observed in eosinophils.

Conclusion : In a case of doubly primary AML and PCM, we identified each population-specific CNAs using single cell analysis and cytoplasmic-Ig FISH, which show how they differentiated and acquired mutations. Clonal PCs and MBs shared trisomy 19 and acquired different CNAs as they developed. Neutrophils showed trisomy 11, 15 and 21 which were found in clonal plasma cells, suggesting their common origin

Keyword : Single Cell Analysis, Spatially Resolved Laser Activated Cell Sorter, Cytoplasmic-IG Fish, Copy Number Alteration, Acute Myeloid Leukemia, Plasma Cell Myeloma

OP02-4

Immunoglobulin gene rearrangement in Koreans with multiple myeloma: Clonality assessment and repertoire analysis using next-generation sequencing

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Background : We aimed to understand the repertoire of immunoglobulin (IG) gene usage among Koreans with multiple myeloma (MM), and to explore the applicability of next-generation sequencing (NGS)-based IG gene clonality testing in clinical practice. We evaluated the status of IG heavy chain (IGH) and IG kappa light chain (IGK) gene rearrangement as well as somatic hypermutations (SHMs) in the IGH variable region (IGHV) among Korean patients with MM via NGS using the only commercially available primer sets in Korea for the first time. The IG gene repertoire profile and clonality detection rate in our cohort were compared with those derived in previous Western studies to gain insight into any Korean-specific features of MM.

Method : Fifty-nine bone marrow samples from 57 Korean patients with MM were included. NGS-based clonality testing was performed using the LymphoTrack IGH FR1 assay kit A-MiSeq (Invivoscribe, Inc. San Diego, CA, USA) and LymphoTrack IGK assay kit A-MiSeq (Invivoscribe, Inc.) according to the manufacturer's recommendations. The FASTQ files were analyzed using the LymphoTrack-MiSeq version 2.4.3. software (Invivoscribe, Inc.) according to the manufacturer's guideline.

Results : Clonal IGH and IGK rearrangements were observed in 74.2% and 67.7% of samples from Korean patients with kappa-restricted MM, respectively (90.3% had one or both), and in 60.7% and 95.5% of samples from those with lambda-restricted MM, respectively (85.7% had one or both). In total, 88.1% of samples from Koreans with MM had clonal IGH and/or IGK rearrangement. Clonal rearrangement was not significantly associated with the bone marrow plasma cells as a proportion of all BM lymphoid cells. IGHV3-9 (11.63%) and IGHV4-31 (9.30%) were the most frequently reported IGHV genes and were more common in Koreans with MM than in Western counterparts. IGHD3-10 and IGHD3-3 (13.95% each) were the most frequent IGHD genes; IGHD3-3 was more common in Koreans with MM. No IGK rearrangement was particularly prevalent, but single IGKV-J rearrangements were less common in Koreans with kappa-restricted MM than in Western counterparts. IGKV4-1 was less frequent in Koreans regardless of light chain type. Otherwise, the usages of the IGH V, D, and J genes and of the IGK gene were like those observed in previous Western studies.

Conclusion : Clonal IGH and/or IGK rearrangements were detected in 88.1% of Koreans with MM at baseline, indicating that such tests are applicable to most Korean patients with this disease to determine clonality and to monitor those under treatment. The profile of IGH and IGK gene usage in Koreans with MM was similar to those found in Western MM studies. However, IGHV3-9, IGHV4-31, and IGHD3-3 were overrepresented among Korean patients, whereas IGKV4-1 was underrepresented. No IGK rearrangement was found to be more common in Koreans with kappa-restricted

MM, although the IGKV-J rearrangement type was more frequent in Western counterparts. This implied the existence of certain ethnicity-based differences in the characteristics of patients with MM.

Keyword : Multiple Myeloma, Korea, IGH, IGK, Applicability, Repertoire

Table 1. *IGH* Clonality, *IGH* Somatic Hypermutation, and *IGK* Clonality According to Light Chain Types in 59 Bone Marrow Samples From 57 Korean Patients with Multiple Myeloma.

Light chain type	*IGH* clonality (+)	*IGH* SHM (+) among *IGH* clonality (+) samples	*IGK* clonality (+)	Both *IGH* clonality (+) and *IGK* clonality (+)	*IGH* and / or *IGK* clonality
Kappa	23/31 (74.2%)	21/23 (91.3%)	21/31 (67.7%)	16/31 (51.6%)	28/31 (90.3%)
Lambda	17/28 (60.7%)	13/17 (76.5%)	21/22 (95.5%)	15/22 (68.2%)	24/28 (85.7%)
Total	40/59 (67.8%)	34/40 (85.0%)	42/53 (79.2%)	31/53 (58.5%)	52/59 (88.1%)

SHM, somatic hypermutation; MM, multiple myeloma.

OP02-5

Clinical performance of FISH analysis with FACS sorting system for detection of cytogenetic abnormalities in multiple myeloma

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Background : The detection of cytogenetic abnormalities in multiple myeloma has become more important over past years for risk stratification and new treatment strategies. The challenges in cytogenetic testing are faced due to the dilution effect of bone marrow specimens and poor growth of plasma cells under in vitro culture conditions. In this study, we compared the performances of three different fluorescence in situ hybridization (FISH) techniques for detection of cytogenetic abnormalities in plasma cell disorder; a direct FISH, a fluorescence immunophenotyping and interphase cytogenetics as a tool for the investigation of neoplasms (FICTION) technique, and a plasma cell sorting FISH with fluorescence activated cell sorter (FACS-FISH).

Method : A total number of 477 patients newly diagnosed as multiple myeloma from February 2010 to December 2019 were included in this study. FICTION was performed with the FITC-conjugated anti-kappa and lambda light chain. Plasma cell sorting was conducted on the BD FACSMelody™ (BD Biosciences) with CD45, CD38, and CD138 staining. FISH was conducted for detection of TP53 deletion at 17p53, 13q deletion, amplification at chromosome 1, and recurrent translocations involving IGH [t(4;14) IGH/FGFR3, t(11;14) IGH/CCND1, and t(14;16) IGH/MAF.

Results : In MM, FISH revealed cytogenetic abnormalities in 38.0% by direct FISH, while 56.3% by FICTION, and 95.7% by FACS-FISH. Positive rates of 17p deletion, t(4;14), and t(14;16) were 5.8%, 5.8%, and 0% for direct FISH, 10.7%, 3.1%, and 0% for FICTION, 30.2%, 19.8%, and 1.7% for FACS-FISH, respectively. Abnormal cell percentages were higher when conducted by FACS-FISH than direct FISH or FICTION. The chromosome abnormality detection by direct FISH method and FICTION method were significantly affected by the plasma cell percentage, but positivity by the FACS-FISH method did not significantly correlate with the plasma cell percentage.

Conclusion : We have demonstrated that FACS-FISH allows excellent detection of cytogenetic alterations, even in samples with a low plasma cell percentage, and detection rate of FISH are highly dependent on the enrichment method used. In order to minimize false-negative results of the FISH, target enrichment using FACS is highly recommended in routine clinical practice.

Keyword : Multiple Myeolma, Fluorescence in Situ Hybridization, Plasma Cell Enrichment, Cell Sorting, Fluorescence Activated Cell Sorter

Table 1. Positive rate of FISH by three methods of NDMM patients

	Deletion		Translocation			Amplification	Overall positive rate
	17p13.1	13q14.3	t(11;14)	t(4;14)	t(14;16)	1q21	
Direct FISH	5.8% (8/137)	19.7% (27/137)	5.8% (8/137)	5.8% (8/137)	0.0% (0/137)	17.7% (11/62)	38.0% (52/137)
FICTION	10.7% (24/224)	31.9% (62/116)	8.0% (18/224)	3.1% (7/224)	0.0% (0/224)	23.4% (52/222)	56.3% (126/224)
FACS-FISH	30.2% (35/116)	53.4% (62/116)	19.8% (23/116)	8.6% (10/116)	1.7% (2/116)	46.6% (53/116)	95.7% (111/116)

OP03-1

Genetic profile of primary plasma cell leukemia in Korea: Comparison with plasma cell myeloma

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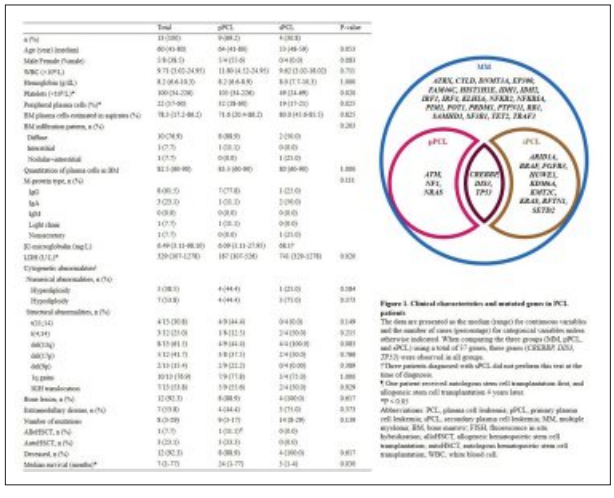
Background : Plasma cell leukemia (PCL) is clinically and genetically distinct from multiple myeloma (MM), despite controversies on the disease definition. The definition of primary PCL (pPCL) is defined by the observation in blood of more than 20% clonal plasma cells by differential count of the leucocytes or by counting more than 2 × 10^9 per liter circulating clonal plasma cells. There are challenges on the disease definition, since patients with lower levels of circulating plasma cells have the same adverse prognosis. Due to its extremely low prevalence, attempts to identify the difference in genetic variation between pPCL, sPCL, and MM have been limited. To find the distinct features of pPCL from advanced myeloma, we compared the genetic property of primary PCL with that of sPCL and multiple myeloma.

Method : We performed multi-gene target sequencing for 647 gene panel in 9 patients with pPCL and four patients with sPCL. G-banding and fluorescent in situ hybridization (FISH) for enumeration of chromosome 1 and detection of 9p21 deletion, 13q14 deletion, 17p13 deletion, 14q32, t(4;14) translocation, and t(14;16) translocation were performed. We also reviewed the Wright-stained BM smears and hematoxylin and eosin (H&E)-stained sections of BM trephine biopsies and assessed the plasma cell burden in the bone marrow.

Results : In pPCL, the median age at diagnosis was 63.3 years (range 41-80). The mean percentage of BM plasma cells was 63.2%, and that of circulating plasma cells was 34.7%. 88.9% of the patients had complex karyotype. 44.4% (4/9) had hypodiploid. The most frequent structural cytogenetic abnormalities were 1q gains detected in 77.8% (7/9), followed by deletions of 13q14 and t(11;14) translocation in 44.4% (4/9). A total of 89 nonsynonymous mutations were observed in 68 genes (median of 9 mutations per patient, range, 3-17), which imply highly heterogeneous and complex mutational features of the disease. The most frequently mutated genes were TP53, TSC2, and TYK2. When comparing with genetic abnormalities of sPCL and MM patients, 54 genes were present only in pPCL group while 34 genes only in sPCL group and 22 genes only in MM. Among the common genes between pPCL and MM, The prevalence of TP53 mutation was significantly higher in pPCL than MM ($P<0.05$). There was no apparent difference when comparing the mutational burden of pPCL and sPCL in the bone marrow. Patients with high-risk cytogenetic abnormalities such as 1q gains and 17p deletion showed adverse survival as in MM.

Conclusion : In conclusion, the mutational profile of pPCL showed a higher level of genetic heterogeneity and high mutational burden. The majority of genetic changes were unique in pPCL, distinct from sPCL and MM, suggesting the role of those variations in clonal plasma cell migration from bone marrow to peripheral blood. Patients with high-risk cytogenetic abnormalities such as 1q gains and 17p deletion showed unfavorable overall survival.

Keyword : Primary Plasma Cell Leukemia, Genomic Profiling, Multiple Myeloma, Secondary Plasma Cell Leukemia



OP03-2

CARTITUDE-1: Phase 1b/2 study of ciltacabtagene autoleucel in relapsed/ refractory multiple myeloma

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Background : Ciltacabtagene autoleucel (cilta-cel) is a chimeric antigen receptor T (CAR-T) cell therapy with 2 B-cell maturation antigen–targeting single-domain antibodies designed to confer avidity. We present updated phase 1b data and initial phase 2 data from the CARTITUDE-1 study (NCT03548207).

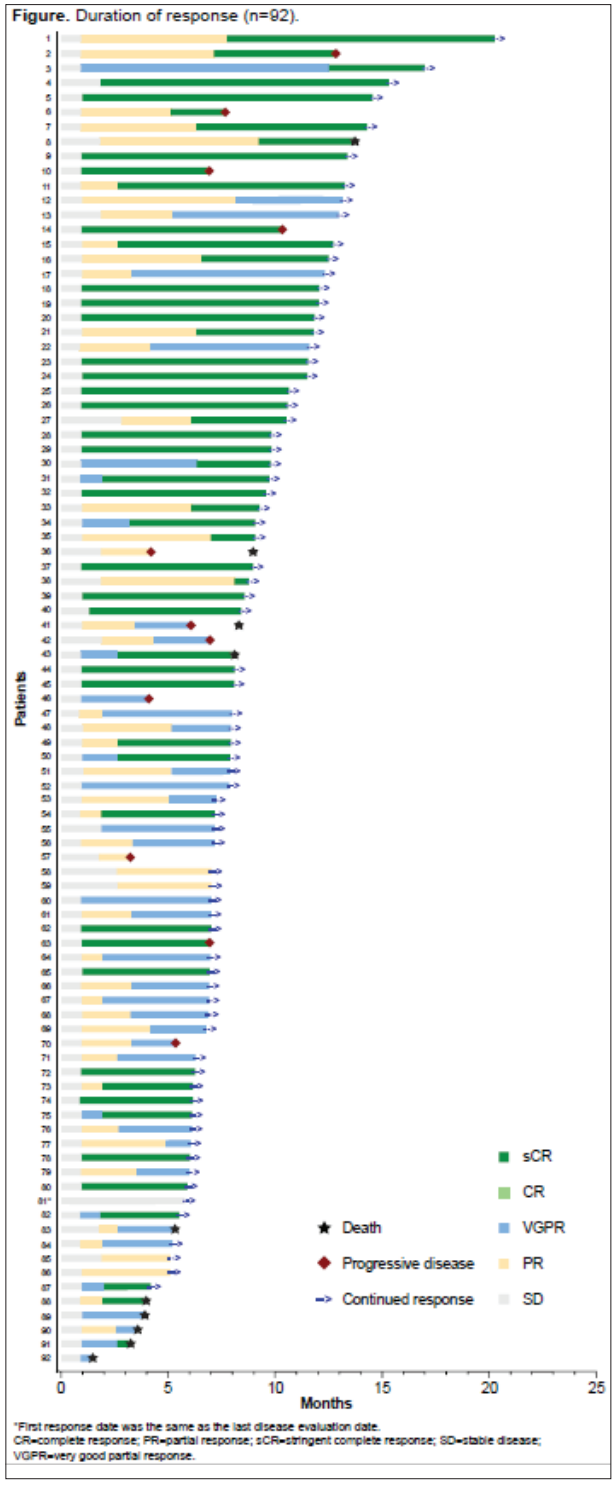
Method : Eligible patients (pts) had multiple myeloma (MM) per International Myeloma Working Group (IMWG) criteria, measurable disease, received ≥3 prior regimens (or double refractory to a proteasome inhibitor and immunomodulatory drug), and received an anti-CD38 antibody. Bridging therapy was permitted after apheresis. After cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 lymphodepletion over 3 days, a single cilta-cel targeted dose of 0.75×10^6 (0.5–1.0×10^6) CAR+ viable T cells/kg was infused. Primary objectives were to characterize the safety and establish the recommended phase 2 dose of cilta-cel (phase 1b) and to evaluate efficacy (phase 2). Response was assessed per IMWG criteria and minimal residual disease (MRD) by next-generation sequencing. Adverse events (AEs) were graded using CTCAE v5.0. Cytokine release syndrome (CRS) was graded by Lee et al (Blood 2014) and neurotoxicity by CTCAE in phase 1b and by American Society for Transplantation and Cellular Therapy (ASTCT) criteria in phase 2. In this combined analysis, Lee et al and CTCAE were mapped to ASTCT criteria for CRS and immune effector cell-associated neurotoxicity syndrome, respectively.

Results : As of 20 May 2020, 97 pts with relapsed/refractory MM received cilta-cel (29 in phase 1b; 68 in phase 2). Median follow-up was 8.8 mo (1.5–20.4). Median prior lines of therapy (LoT) was 6 (3–18); 83.5% were penta-exposed, 87.6% triple-refractory, 41.2% penta-refractory, and 97.9% refractory to last LoT. Overall response rate per independent review committee (primary endpoint) was 94.8% (95% CI 88.4–98.3); 55.7% had stringent complete responses, 32.0% had very good partial responses, and 7.2% had partial responses. All pts had reduction in M-protein. Median time to first response was 1.0 mo (0.9–5.8; 80.4% ≤1.0 mo), and median time to ≥complete response was 1.8 mo (0.9–12.5; 74.1% ≤3.0 mo); responses deepened with time (Figure). Median duration of response was not reached (NR). Of 52 MRD-evaluable pts, 94.2% were MRD-negative at 10^-5. The 6-mo progression-free survival (PFS) and overall survival (OS) rates (95% CI) were 87.4% (78.9–92.7) and 93.8% (86.7–97.2), respectively; median PFS and OS were NR. Ten deaths occurred during the study: 6 related and 2 unrelated AEs (CRS/hemophagocytic lymphohistiocytosis, neurotoxicity, respiratory failure, sepsis, septic shock, pneumonia, lung abscess, and acute myelogenous leukemia [n=1 each]), and 2 from progressive disease. AEs (>70% of pts) were CRS (94.8%; grade [gr] 3/4 4.1%), neutropenia (90.7%; gr 3/4 90.7%), anemia (81.4%; gr 3/4 68.0%), and thrombocytopenia (79.4%; gr 3/4 59.8%). Median time to CRS onset was 7.0 d (1–12) and median duration 4.0 d (1–27, excluding n=1 with 97 d). 20.6% of pts had CAR-T cell–related neurotoxicity (gr 3/4 10.3%). Cilta-cel CAR+ T cells showed peak peripheral expansion at 14 d (9–43). Among pts with 6-mo individual follow-up, 67% had cilta-cel CAR+ T cells below the level of quantification (2 cells/μL) in peripheral blood.

Conclusion : Preliminary phase 1b/2 data from CARTITUDE-1 indicate a single low-dose infusion of cilta-cel leads to early, deep, and durable responses in heavily pretreated pts with MM with safety consistent with LEGEND-2.

Keyword : Ciltacabtagene Autoleucel, CAR-T, Relapsed, Refractory, Multiple Myeloma, B-Cell Maturation Antigen

Figure. Duration of response (n=92).



OP03-3

Expanded natural killer cells augment anti-myeloma effects of daratumumab, bortezomib, and dexamethasone in a human multiple myeloma xenograft model

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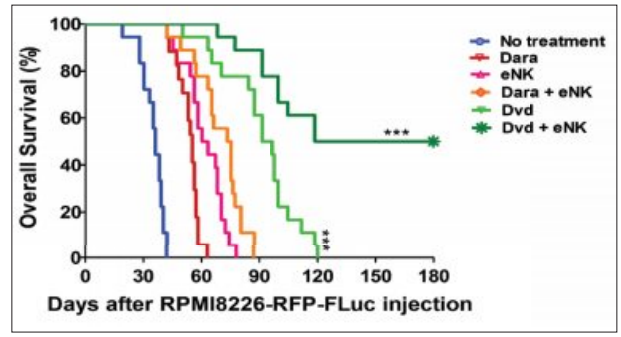
Background : The use of natural killer (NK) cells is a promising and safe immunotherapeutic approach in the field of cancer immunotherapy. However, combination treatments are required to enhance the effector functions and therapeutic efficacy of NK cells. In this study, we investigated the potential of daratumumab (Dara), bortezomib, and dexamethasone (Dvd) to augment the antitumor effects of NK cells in a multiple myeloma (MM) xenograft mouse model.

Method : NK cells were expanded and activated using K562-OX40 ligand and membrane-bound IL-18 and IL-21 in the presence of IL-2 and IL-15 from peripheral blood mononuclear cells of MM patients. A human MM xenograft model was established using human RPMI8226-RFP-FLuc cells in NOD/SCID IL-2Rγnull (NSG) mice. Tumor bearing mice were divided into six treatment groups: no treatment, expanded NK cells (eNK), Dara, Dara + eNK, Dvd, and Dvd + eNK.

Results : Dvd treatment strongly enhanced the cytotoxicity of eNK cells by upregulating NK cell activation ligands, downregulating NK cell inhibitory ligands, and promoting antibody-dependent cellular cytotoxicity. The combination of eNK with Dvd significantly prolonged mouse survival and reduced the tumor burden and serum M-protein level. Furthermore, Dvd pretreatment significantly increased eNK persistence and homing into MM sites.

Conclusion : Our findings suggest that Dvd treatment potentiates the anti-myeloma effects of ex vivo expanded and activated NK cells by modulating immune responses in MM-bearing mice.

Keyword : Natural Killer Cells, Multiple Myeloma, Cancer Immunotherapy



OP03-4

Impact of primary prophylaxis with pegfilgrastim for febrile neutropenia receiving rituximab plus fludarabine and cyclophosphamide treatment in patients with chronic lymphocytic leukemia: A multicenter, prospective study

Youngwoo Jeon[1,3], Gi June Min[2], Sung-Soo Park[2], Silvia Park[2], Jae-Ho Yoon[2], Sung-Eun Lee[1], Byung-Sik Cho[2], Ki-Seong Eom[2], Yoo-Jin Kim[2], Hee-Je Kim[2], Seok Lee[2], Jong-Wook Lee[2] and Seok-Goo Cho[1,2,3*]

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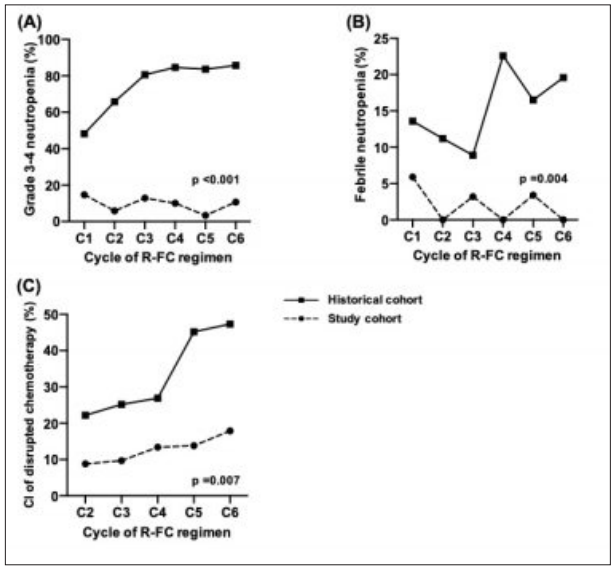
Background : A chemotherapy of rituximab, fludarabine and cyclophosphamide (R-FC) has been accepted as a promising frontline chemotherapy in selected patients with chronic lymphocytic leukemia (CLL) according to current guideline. Despite R-FC is relatively dose-dense regimen, primary prophylactic pegfilgrastim was not fully recommend in clinical field. Therefore, this study was to evaluate the impact of prophylaxis pegfilgrastim for preventing neutropenia during R-FC in CLL patients.

Method : A single-arm, multicenter, prospective phase II study was designed to assess the efficacy of prophylactic pegfilgrastim in enrolled 34 patients, and compared with our historical cohort.

Results : The incidence of grade 3-4 neutropenia was 9.7% (18/186 cycles) and febrile neutropenia was 2.2% (4/186 cycles). Cumulative incidence of disrupted chemotherapy 17.9% at the last cycle of chemotherapy. In indirect comparison with our historical cohort, overall survival, progression-free survival, and relapse rate did not differ between the two groups (hazard ratio [HR] 1.941, p=0.228; HR 1.593, p=0.273; HR 3.240, p=0.315, respectively). However, early morality rate was significantly decreased as 5.9% (HR 0.64, p=0.032) in prophyxis group.

Conclusion : Primary prophylactic pegfilgrastim was well tolerated in patients with CLL receiving R-FC and significantly reduced neutropenia and febrile neutropenia compared to non-prophylaxis group in our historical cohort. Although prophylactic pegfilgrastim did not affect the long-term survival outcomes, early mortality rate was significantly decreased by using pegfilgrastim. It suggested that pegfilgrastim administration is feasible and significant during receiving R-FC regimen in CLL patients.

Keyword : Chronic Lymphocytic Leukemia, Febrile Neutropenia , Chronic Lymphocytic Leukemia, Pegfilgrastim, Prophylaxis



OP03-5

Updated experience from mosunetuzumab in multiply relapsed follicular lymphoma: Promising efficacy from a phase I trial

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Background : While follicular lymphoma (FL) is an indolent disease, it often presents with recurrent relapses and is considered incurable. After each relapse, disease-free intervals reduce, and refractoriness increases. Treatment options for patients (pts) with FL who have received ≥2 prior lines of therapy is limited and their prognosis is poor, especially for those who have progression of disease within 24 months (POD24) of first-line treatment, or are refractory to multiple agents. Mosunetuzumab, a full-length, fully humanized IgG1 CD20/CD3 bispecific antibody, redirects T cells to engage and eliminate malignant B cells. The safety, efficacy and pharmacokinetics of mosunetuzumab in pts with relapsed/refractory (R/R) B-cell lymphoma is currently being investigated in an ongoing open-label, multicenter, Phase I/Ib, dose-escalation and expansion trial (GO29781; NCT02500407). Updated data from the use of mosunetuzumab in R/R FL after ≥2 prior systemic therapies are presented.

Method : Pts received intravenous mosunetuzumab as step-up doses in Cycle 1, Days 1 and 8, and then the target dose on Day 15 and day 1 of each subsequent 21-day cycle (Group B). Treatment continued for 8 cycles in pts with a complete response (CR), and up to 17 cycles in those with a partial response or stable disease.

Results : As of January 21, 2020, mosunetuzumab 0.4/1.0/2.8mg to 1/2/13.5mg (Cycle 1 Day 1/8/15 dose levels) was given to 62 pts

with FL who received ≥2 prior systemic therapies. Pts had a median age of 59 (range 27–85) years, and received a median of 3 (range 2–11) prior therapies. Thirty-three pts (53%) were double refractory (refractory to both a prior anti-CD20 antibody and an alkylating agent), 30 (48%) had POD24, and four (6%) received prior chimeric antigen receptor T-cell (CAR-T) therapy. The overall response rate (ORR) and CR rate were 68% (42/62) and 50% (31/62), respectively. In high-risk pt cohorts, consistent CR rates were observed: 55% (18/33) in pts with double refractory disease, 53% (16/30) in pts who had POD24, 78% (7/9) in pts with PI3Ki refractory FL, and 50% (2/4) in those who received prior CAR-T therapy. At the data cut-off, 26 pts (62% responders; 74% complete responders) remained in remission, after a median time on study of 14.4 months. In responders (n=42), the median duration of response was 20.4 months (95% CI: 11.7 months, upper limit not reached); the median progression-free survival was 11.8 (95% CI: 7.3–21.9) months. Adverse events (AEs) and serious adverse events (SAE) were reported in 60 (97%) and 22 pts (35%), respectively. The most common (>10% of pts) grade (Gr) ≥3 AEs included hypophosphatemia (23%; transient and asymptomatic) and neutropenia (21%; with 2% febrile neutropenia). Fourteen pts (23%) experienced CRS (Lee, et al. Blood 2014); events were mostly Gr1 or 2 (Gr 1, n=11; Gr 2, n=2; and Gr 3, n=1). CRS events occurred largely during Cycle 1 and were reversible. No patient required tocilizumab, intensive care unit admission or use of vasopressors for CRS management.

Conclusion : High CR rate, durable responses and a manageable safety profile were observed with mosunetuzumab monotherapy in heavily pretreated pts with FL, including those who are high-risk. Updated pharmacodynamics and biomarker results will be presented at the congress.

Keyword : Follicular Lymphoma, Mosunetuzumab

OP04-2

Iptacopan effectively controls intra- and extravascular hemolysis and leads to durable hemoglobin increase in patients with treatment-naive PNH

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Background : Paroxysmal nocturnal hemoglobinuria (PNH) is a severe hematological disease caused by an acquired PIGA mutation in hematopoietic stem cells, leading to loss of regulatory proteins affecting the complement alternative pathway, of which factor B is an essential component. The only regulatory approved treatment for hemolytic PNH is based on antibodies targeting complement component 5 (C5), controlling intravascular hemolysis, reducing thromboembolic events, and eventually improving long-term survival. However, 20-50% of patients remain transfusion-dependent due to persistent extravascular hemolysis, and an additional 20-40% exhibit varying degrees of residual anemia. Iptacopan (LNP023) is a new, oral, selective and potent first-in-class factor B inhibitor, designed to block both intra- and extravascular hemolysis. The trial presented here investigates the effect of first-line iptacopan monotherapy on intra- and extravascular hemolysis, the extent of red blood cell (RBC) C3 opsonization, and changes in hemoglobin levels in anti-C5 naive PNH patients with active hemolysis.

Method : CLNP023X2204 (NCT03896152) is a multi-national, randomized Phase 2 efficacy, safety, pharmacokinetics/-dynamics study assessing four iptacopan doses in two separate cohorts with two treatment periods each in treatment-naive adult PNH patients with active hemolysis. The primary objective is to assess the effect of iptacopan on the reduction of PNH-associated hemolysis. Additional objectives include assessing the effect on hemoglobin levels, the dose-response effect, and the effect on markers associated with a risk of thrombosis.

Results : A total of N=13 patients (ages 20-62; n=7 female) were randomized to either Cohort 1 (iptacopan 25-to-100 mg dose increase at Week 4; N=7) or Cohort 2 (50-to-200 mg; N=6). Median (range) lab values at baseline were: Hb 86.5 (68-107) g/L, reticulocytes 209 (30-352) x10E9/L, LDH 1686 (1008-3761) U/L, bilirubin 27.0 (20.0-51.0) umol/L; haptoglobin was below lower limit of detection for all patients. The primary endpoint of lowering LDH by at least 60% was reached for all patients. Mean LDH levels declined by 79.7 and 86.2% in Cohort 1 and by 89.7 and 85.9% in Cohort 2 at weeks 4 and 12, respectively [Figure 1]. Importantly, all patients remained transfusion-free, with the exception of one patient who received a single RBC transfusion on study day 3; Hb levels spontaneously increased by a mean of 23.4 and 37.1 g/L at week 12 in Cohorts 1 and 2, respectively [Figure 1]; and no thromboembolic events were reported. In addition, reticulocyte counts decreased by a mean of 93.0 and 84.9 x10E9/L, and bilirubin decreased by a mean of 21.6 and 23.2 umol/L in Cohorts 1 and 2, respectively. Iptacopan was well tolerated (n=1 discontinued from the trial at Day 1 due to headache); no fatal events and no serious adverse events were reported during the 12-week treatment period.

Conclusion : Iptacopan is a new, well-tolerated oral factor B inhibitor that blocks both intra- and extravascular hemolysis in patients with hemolytic PNH. 12-week study results demonstrate that, in anti-C5 naive patients with active hemolysis, iptacopan therapy ≥50 mg BID results in normalization of various hemolytic markers and resolution of anemia. Maximal effects on various efficacy parameters were obtained at 200 mg BID. These results demonstrate that proximal inhibition of the complement cascade parallel and further improve the hematological benefit seen with anti-C5 therapies, with iptacopan eventually offering an alternative first-line therapy for patients with PNH.

Keyword : Paroxysmal Nocturnal Hemoglobinuria (PNH), Lptacopan (LNP023), Complement Alternative Pathway, Factor B

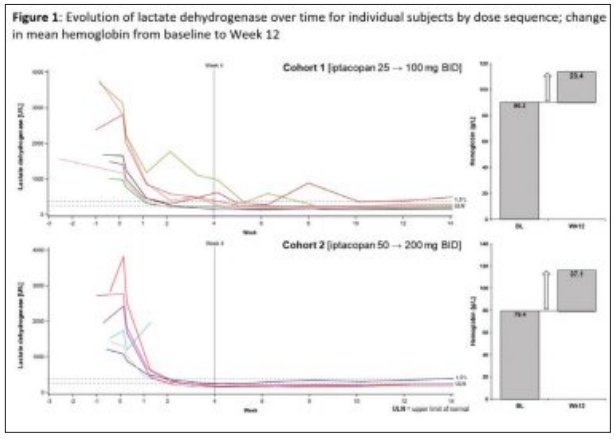

Figure 1: Evolution of lactate dehydrogenase over time for individual subjects by dose sequence; change in mean hemoglobin from baseline to Week 12

OP04-3

Developmental megakaryocytopoiesis: A study on novel role of clinically significant microRNA in understanding neonatal thrombocytopenia

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Background : Neonatal cord blood (CB) cells are promising alternatives to adult bone marrow (PB) in cellular therapies. CB cells have potential to develop into specialized cells, such as erythrocytes or megakaryocytes (MK). MKs are responsible for production of platelets and thrombocytopenia is a condition caused by a low platelet count (<150 x 109/L), which is common among sick infants. We hypothesize that developmental differences between CB and PB-MKs contribute to the vulnerability of neonates to develop severe thrombocytopenia. Non-coding microRNAs (miRNAs) may play a critical role, but their role in regulation of biological differences between adult and neonatal megakaryocytopoiesis is unknown.

Method : Human cord blood (CB) and peripheral blood (PB) derived CD34+ cells were cultured in the presence of thrombopoietin for 14 days. Cultures expressing >90% CD41+ by flow cytometry were collected and 88 miRNAs involved in stem cell development and differentiation were examined. Web-based computational approaches were used for putative target prediction and the protein levels were detected using western blot analysis. miRNA validation studies were performed in cell line models.

Results : Out of 88 miRNAs involved in stem cell development, let-7b was the only miRNA down regulated (~10-fold) in neonates compared to adult megakaryocyte (MK), and the levels of let-7b was differentially expressed in all stages of MK development (progenitors to maturation). LIN28B and IMP-1 emerged as putative targets of let-7b by several bioinformatic databases, such as TargetScan, miRbase, and RNAhybrid. The functional significance of low let-7b levels was studied by nucleofection of CB- and PB-MKs, as well as K562 cells, with pre-let7b, anti-let7b, or Cy-3 (control). Over-expression of let-7b in all cell types induced a 50% decrease in cell number 48 hrs following nucleofection, whereas, suppression of let7b induced a 50% increase in cell number. Up-regulation of let-7b induced a significant decrease in IMP-1 and IGF-II protein levels, as well as a reduction in the proliferation marker phospho-H3 in K562 cells. These factors contribute to the marked hyperproliferative response of neonatal, but not adult MK progenitors.This might explain the susceptibility of neonates to develop myeloproliferative disorder in the presence of trisomy 21 and GATA-1s mutations and help improve therapies for thrombocytopenic neonates and children/adults with thrombocytopenia after cord blood-derived stem cell transplants.

Conclusion : The present study shows functional significance of let-7b in regulation of cell proliferation by targeting Lin28B and IMP-1 in human MKs development. Lower expression of let-7b may contribute to the developmentally different and disease susceptible phenotype of neonatal MKs via regulation of LIN28B/IMP-1/IGF-II axis. Therefore, it could be a potential target in neonatal thrombocytopenia and other platelet disorders.

Keyword : Megakaryocyte, miRNA, let-7b, LIN28B, IMP-1, Thrombocytopenia

OP04-4

Deficiency of immature B-cell tolerance by V(D)J rearrangement causes aberrant accumulation of autoantibodies in immune thrombocytopenia

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Background : Immune thrombocytopenia (ITP) is a common autoimmune disease characterized by over-production of anti-platelet antibodies. Receptor editing is the main part of

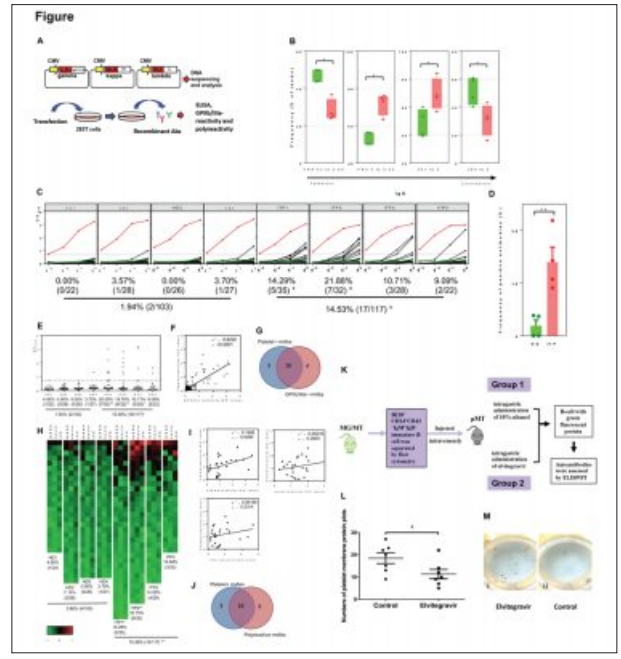
central tolerance of B cells, which could alter the specificity of immature B cell receptors (BCR) by a secondary recombination of immunoglobulin genes. Our previous study revealed an aberrant usage of Vκ and Jκ segments in ITP patients through next-generation sequencing, which may suggest a defective early-B cell tolerance in ITP patients. The aim of this study is to investigate the specific process of deficiency of B-cell tolerance to cause aberrant autoantibody accumulation in ITP patients and a mouse model.

Method : We performed single cell RT-PCR on naïve B cells to clone both Ig heavy chain (IgH) and Ig light chain (IgL) genes from the same cells. The paired IgH and IgL were co-transfected and the recombinant monoclonal antibodies were expressed and purified (Figure A). The reactivity against platelet antigens and cross-reactivity of these antibodies were tested by ELISA. Ig gene sequence features were analyzed by IMGT and IgBLAST. Immature B cells were separated from mG/mT mice (mice with membrane-targeted green fluorescent protein (mG) prior to Cre-mediated excision and membrane-targeted tandem dimer Tomato (mT) after excision) by flow cytometry and transferred to B-cell deficient μMT mice with elvitegravir administration to block recombination activating gene (RAG) function. Eight days later, B cells with mG were isolated from μMT mice and autoantibody-secreting cells were assessed by ELISPOT.

Results : The PCR products confirmed that the ITP-derived Igκ preferentially used the downstream Vκ (71.92% vs. 53.13%, p=0.00155) and upstream Jκ (69.02083% vs. 48.34321%, p=0.0337) segments compared with those derived from healthy controls (Figure B), which further indicated a defective receptor editing of B cells in ITP patients. ELISA assay showed that 14.53% (17/117) of the ITP-derived naïve B cells were platelet-reactive, in contrast to the 1.94% (2/103) in healthy donor-derived naïve B cells (Figure C, D), suggesting a defective B cell tolerance in the early developing stage. ITP patients had significantly higher frequencies of GPIIb/IIIa-reactive or polyreactive naïve B cells than healthy controls. Moreover, platelet-reactive rmAbs and GPIIb/IIIa+/polyreactive rmAbs predominantly overlapped with each other (Figure E-J). To further investigate whether the number of autoantibody-secreting cells was affected by deficiency of receptor editing at the immature B-cell stage, ELISPOT assays were performed. Results showed that after a 20-hour culture, significantly more spots were presented in the group with elvitegravir administration than in controls (Figure K-M).

Conclusion : In conclusion, our results provided both in vitro and in vivo evidence of defective early B-cell tolerance in ITP. And insufficient receptor editing in immature B cells tends to cause abnormal accumulation of autoantibodies in mice model.

Keyword : Immature B-cell Tolerance, V(D)J Rearrangement, Immune Thrombocytopenia



OP04-5

Hematopoietic cell transplantation in patients with non-malignant disease

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Background : Hematopoietic stem cell transplantation (HSCT) has been used as the only curative treatment option for various non-malignant disease. Among the patients in need of allogeneic HSCT, only a limited portion have an HLA compatible donor. The recent improvement of transplant techniques is contributing to the expansion of alternative donors for non-malignant disease. In this report, we evaluated the outcome of allogeneic HSCT in patients with non-malignant disease.

Method : We retrospectively reviewed the medical records of 153 patients with the non-malignant disease who underwent HSCT at Asan Medical Center Children's Hospital between 2009 and 2020. Included diseases were acquired aplastic anemia (AA, n=92), inherited bone marrow failure (IBMF, n=16), hemophagocytic lymphohistiocytosis (HLH, n=20), primary immune deficiency (PID, n=21), and others (n=4). Twenty-five (16.3%) patients received HSCT from matched sibling donor (MSD), 58 (37.9%) from an unrelated donor (URD), and 70 (45.8%) from a haploidentical family donor (HFD) using ex vivo T cell deletion.

Results : Of 153 patients, 148 patients achieved neutrophil engraftment at a median of 10 days (range, 8–13). Five patients from HFD failed to attain primary engraftment (primary graft failure, GF), and an additional 7 patients from HFD experienced graft rejection (GR) within 30 days post-transplant. All 12 patients with primary GF/GR received salvage transplants, and 9 patients achieved engraftment, leading to final engraftment rates of 98%. Three patients (1 each from MSD, URD, and HFD) developed late GF. Cumulative incidence (CI) of acute GVHD (aGVHD) grade II-IV was 39%. CI of aGVHD was significantly higher in URD than those of MSD and HFD (28% for MSD, 54% for URD, 30% for HFD, P=0.005) and greater in HLH and PID than other diseases (32% for SAA, 66% for HLH, 32% for IBMF, 53% for PID and 0% for others, P=0.005). CI of moderate-to-severe chronic GVHD was 12%, which was significantly lower in HFD than other types of the donor (16% for MSD, 22% for URD, 3% for HFD, P=0.025). Sixteen patients died at a median of 7 months (range, 1–39) post-transplant with a 4-year TRM of 12% (2/25 in MSD, 6/58 in URD, 8/70 in HFD, P>0.05). At the time of the report, 137 patients survived. All clear of disease except 4 with autologous recovery. At a median follow-up of 4.4 years (range, 0.2–11.8), the 4-year probability of overall survival (OS) and disease-free survival (DFS) were 88% and 85%, respectively, which was not different according to donor types (OS: MSD 91%, URD 85%, HFD 88%, P>0.05 and DFS: MSD 87%, URD 85%, HFD 83%, P>0.05). The DFS was better in AA and IBMF compared to other diseases (91% for AA, 88% for IBMF, 74% for HLH, 68% for PID, and 50% for others, P=0.017).

Conclusion : In this analysis, HSCT outcomes from alternative donors, including HFD, were comparable with MSD in terms of TRM and DFS in patients with non-malignant disease. HSCT from HFD showed less moderate-to-severe cGVHD but higher GF rates. Although most GF was rescued with the subsequent transplant, further improvement is desired to reduce the GF rates in HFD-HSCT.

Keyword : Non-Malignant Disease, Hematopoietic Stem Cell Transplantation, Haploidentical

POSTERS

BP01

Outcomes in gilteritinib-treated patients with FLT3-mutated relapsed or refractory acute myeloid leukemia who underwent transplantation

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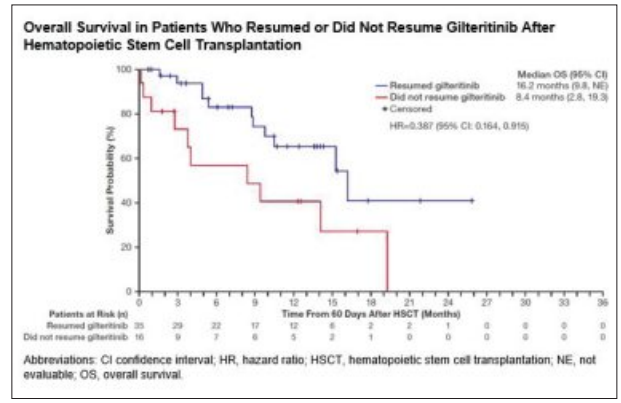
Background : Gilteritinib is a FLT3 inhibitor approved for the treatment of patients with FLT3-mutated relapsed or refractory acute myeloid leukemia based on findings from the phase 3 ADMIRAL trial which demonstrated the superiority of gilteritinib to salvage chemotherapy in this patient population.

Method : Outcomes were evaluated for 51 patients with FLT3-mutated relapsed/refractory acute myeloid leukemia, treated with gilteritinib, who underwent hematopoietic stem cell transplantation during the phase 3 ADMIRAL trial and were without relapse within 60 days after transplantation.

Results : Of these 51 patients, 35 (69%) resumed gilteritinib therapy following hematopoietic stem cell transplantation after a median of 1.9 months. Median duration of gilteritinib exposure before and after transplantation in patients who resumed gilteritinib was 3.0 months and 6.4 months, respectively. With a median follow-up of 12.4 months, patients who resumed gilteritinib had longer median overall survival than patients who did not (16.2 vs 8.4 months; hazard ratio: 0.387; 95% CI: 0.164, 0.915) (Figure). In patients who resumed gilteritinib, pretransplant rates of complete remission and composite complete remission (defined as complete remission with or without hematologic or platelet recovery) were 11% and 71%, respectively; the pretransplant rate of complete remission with full or partial hematologic recovery was 31%. Common adverse events that occurred during the posttransplant period in patients who resumed gilteritinib were increased alanine aminotransferase (46%) and pyrexia (37%); common grade ≥3 adverse events were thrombocytopenia and lung infection (both 14%). Fatal adverse events included cardiac arrest, acute graft-versus-host disease in the intestine, pneumothorax, and pulmonary embolism (all n=1).

Conclusion : Overall, patients with FLT3-mutated relapsed or refractory acute myeloid leukemia who resumed gilteritinib after hematopoietic stem cell transplantation had high response rates prior to transplantation and longer overall survival than patients who did not resume gilteritinib therapy. No new safety signals during the posttransplant period were identified in patients who resumed gilteritinib therapy.

Keyword : Acute Myeloid Leukemia, FLT3 Inhibitor, Hematopoietic Stem Cell Transplantation



BP02

Transcriptional landscape profiling of cytogenetically normal acute myeloid leukaemia by high throughput deep sequencing technology

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Background : Prognostication of cytogenetically normal acute myeloid leukaemia (AML-CN) which comprises about 50% of AML subtypes requires further dissection in order to elucidate the mechanism of leukemogenesis which could pave the way into discovery of biomarkers. Hence, in this study, we unravelled the pivotal pathways and significant genes by performing high throughput deep transcriptome sequencing gene expression profiling of AML-CN.

Method : Transcriptome sequencing was performed on 50 AML-CN samples using Illumina NovaSeq 6000 (150bp paired-end reads, 200 million reads per sample). The quality of sequencing raw data was inspected using FastQC (version 0.11.8). Low quality reads (reads

with Phred score less than Q20), adapter and poly G sequences were removed using Fastp. After performing quality control on raw sequenced data, Salmon (v1.0.0) was used for transcript quantification and followed by DeSeq2 differentially expressed genes (DEGs) analysis. Samples were quadrohotomised based on NPM1 and FLT3-ITD mutational status and compared against healthy control group of 12 samples. Unsupervised cluster analysis was performed to identify distinct clusters based on response to intensive induction therapy. Gene ontology (GO) analysis and pathway analysis were performed to profile function of the candidate genes.

Results : A total of 1341 down regulated and 1282 upregulated genes which met the filtering criteria of baseMean>500, padj <0.01 and fold change of more than two were discovered in comparison of AML-CN versus healthy control groups. Pathway and gene ontology enrichment analysis revealed that the downregulated genes were highly associated with cytokine receptor interaction and chemokine signalling pathway whereas the upregulated genes were highly associated with cell cycle and Rap1 signalling pathways. Upregulated and downregulated genes were also highly associated with pathways in cancer. Following that, unsupervised cluster analyses revealed four groups of AML-CN patients based on molecular signatures (presence and absence of NPM1 and FLT3-ITD mutations). Two unique clusters were identified within AML-CN patients without the presence of NPM1 and FLT3-ITD mutations based on their response to intensive induction chemotherapy: in remission or refractory.

Conclusion : Gene expression profiles for AML-CN versus healthy group and molecular signatures (NPM1 and FLT3-ITD mutations) were identified. Following that, we identified two unique clusters of AML-CN patients without NPM1 and FLT3-ITD mutations that were associated to patient's response to intensive induction therapy were discovered that could potentially provide new insights into the stratification and prognostication of AML-CN in future.

Keyword : Gene Expression, Acute Myeloid Leukaemia, RNA Sequencing

BP03

Differential effects of donor lymphocyte infusion upon treatment response and GVHD according to relapse level and donor sources in patients with myelodysplastic syndrome

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Background : DLI is one of the effective options for post-transplant disease control of myelodysplastic syndrome (MDS). Its success or failure depends on the induction of antitumor immune reactions, durability of clinical responses, and severity of unwanted toxicities mainly from GVHD.

Method : Here, we analyzed 61 MDS patients receiving DLI (median 2 cycles, median 2.1 x 107 CD3+ cells/kg) for treatment outcomes and related factors, especially focusing on the level of relapse: hematological (HemRel), molecular (MolRel) and imminent relapse (ImmRel)].

Results : The response rate was 46.7%, while failure free and overall survival at 2 years were 27.3% and 38.5%, respectively. The response rate (42.1% vs 36.4% vs 72.7%) and overall survival rate at 2 years (43.3% vs 45.5% vs 70.1%) was different for each relapse level with ImmRel group showing the most promising results. Factor analyses showed that DLI response was prognostic for survival, and time to relapse from transplant was prognostic for all DLI outcomes including DLI response, failure free, and overall survival. Additionally, DLI-induced GVHD was predictive of DLI response, but not predictive of survival, suggesting a potential detrimental impact of GVHD on survival. The respective incidence of GVHD and GVHD-related deaths were 37.7% and 10.0%, and CD3+ cell doses triggering GVHD were lowest in cases with haploidentical donor or ImmRel.

Conclusion : This study again showed the therapeutic effects of DLI in MDS and suggested that its efficacy can be maximized through earlier detection of relapse, intervention at lower level relapse and minimizing fatal GVHD through tailored cell dosing schedule based on relapse level and donor source.

Keyword : Myelodysplastic Syndrome, Allogeneic Stem Cell Transplantation, Donor Lymphocyte Infusion, Relapse, Graft-Versus-Host Disease

BP04

CXCR2 as a novel target for overcoming resistance to tyrosine kinase inhibitors in chronic myeloid leukemia cells

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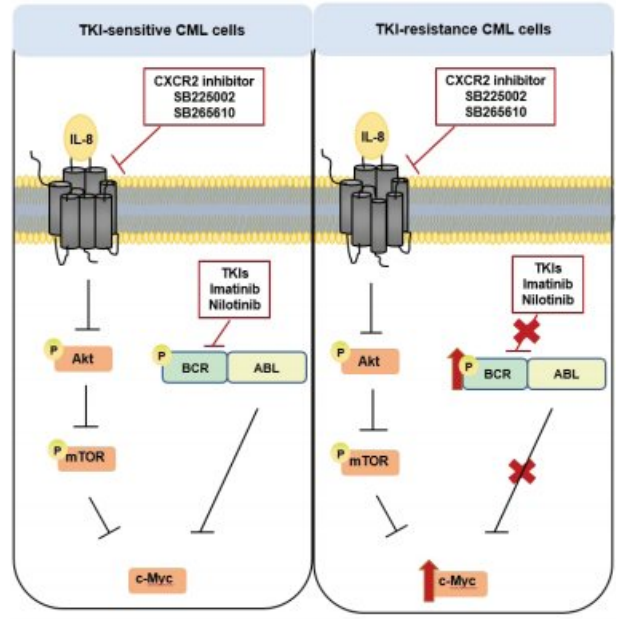
Background : Chronic myeloid leukemia (CML) is a reciprocal translocation disorder driven by a breakpoint cluster region (BCR)-Abelson leukemia virus (ABL) fusion gene that stimulates abnormal tyrosine kinase activity. Tyrosine kinase inhibitors (TKIs) are effective in the treatment of Philadelphia chromosome (Ph)+ CML patients. However, the appearance of TKI-resistant CML cells is a hurdle in CML treatment. Therefore, it is necessary to identify novel treatments that could target a different mechanism than that of tyrosine kinases.

Method : The study was designed to verify whether C-X-C chemokine receptor 2 (CXCR2) could be a novel target for TKI-resistant CML treatment. To establish imatinib- and nilotinib-resistant CML cell lines, K562 and KU812 cell lines were gradually exposed to imatinib or to nilotinib. We examined CXCR2 ligands from CML patient samples and TKI-resistant CML cell lines. Then, we inhibited CXCR2 and examined the effects on cell proliferation and apoptosis using immunoblotting and flow cytometry. The CXCR2 inhibition effect was also confirmed using a mouse xenograft model with TKI-sensitive and -resistant CML cells.

Results : Interleukin 8 (IL-8), a CXCR2 ligand, was significantly increased in the bone marrow serum of initially diagnosed CML patients. CML cell lines expressed CXCR2, regardless of their sensitivity to TKIs. IL-8 stimulated CXCR2, mTOR, and c-Myc mRNA expression in CML cell lines. CXCR2 antagonists suppressed the proliferation of CML cells via cell cycle arrest in the G2/M phase. In addition, CXCR2 inhibition attenuated mTOR, c-Myc, and BCR-ABL expression, leading to CML cell apoptosis, irrespective of TKI responsiveness. Moreover, SB225002, a CXCR2 antagonist, caused higher cell death in CML cells than TKIs. Using a mouse xenograft model, we confirmed that SB225002 suppresses CML cells, with a prominent effect on TKI-resistant CML cells.

Conclusion : Taken together, our findings demonstrate that IL-8 is a prognostic factor to the progress of CML. Inhibiting the CXCR2-mTOR-c-Myc cascade is a promising therapeutic strategy to overcome TKI-sensitive and -insensitive CML. Thus, CXCR2 blockade is a novel therapeutic strategy to treat CML, and SB225002, a commercially available CXCR2 antagonist, might be a drug candidate to treat TKI-resistant CML.

Keyword : CXCR2, IL-8, mTOR, c-Myc, Tyrosine Kinase Inhibitors, Drug Resistance



BP05

SIRT1 regulates SKP2-mediated P27 ubiquitination and degradation in NOTCH induced T-ALL

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Background : Despite marked advances in the clinical therapies, clinical outcome for most acute T-cell lymphoblastic leukemia(T-ALL) patients remains poor ,due to the high risk of relapse ,even after complete remission. Activating Notch mutation was commonly found in T-ALL leading to hyperactivation of various notch targets, such as hes1, myc and skp2. Recent studies suggest that The NAD-dependent deacetylase sirtuin 1(SIRT1) has a dual role in hematologic malignancies which acts as a tumor suppressor in MDS or tumor promoter in AML and CML. However, little is known about the SIRT1's functions in T-ALL. Thus, we sought to determine the role of SIRT1 in T-ALL leukemogenesis.

Method : We blocked NOTCH signaling using γ-secretase inhibitor in MOLT4 cell line and overexpressed a constitutively active form of NOTCH1 in mouse hematopoietic stem/progenitor cells to investigate the relationship between NOTCH1 and SIRT1.Then we knocked down SIRT1 in MOLT4 cell line and analyzed the impact of SIRT1 deficiency in MOLT4 cells.The sirt1 conditional knock-out transgenic mouse line was used for in vivo experiments. And the relationship between SIRT1 ,SKP2 and their targets p27kip1 was defined by western blot, immunofluorescence and co-immunoprecipitation.

Results : Notch pathway inhibition using γ-secretase inhibitor

reduced SIRT1 expression and expression of a constitutively active form of Notch1 in BM progenitors resulted in T cell leukemia and SIRT1 overexpression. It is observed that the NOTCH1 direct target c-MYC plays a role in increased SIRT1 expression in T-ALL. Inhibition of c-MYC expression in MOLT4 cells using shRNA reduced SIRT1 protein expression and led to accelerated reduction in SIRT1 levels following CHX treatment. Silencing of SIRT1 expression suppressed the proliferation and growth in the colony formation assay in vitro and prolonged the lifespan of T-ALL model mice in vivo ,correlated with a reduction in cell cycle activity and increased levels of p27kip1. Previous studies demonstrated that Notch activation drives transcriptional activation of SKP2 and SKP2 is the major ubiquitin ligase that controls abundance of cell cycle regulatory proteins p27kip1. We found SIRT1 promoted p27kip1 ploy-ubiquitination while the SIRT1 deacetylase mutant(SIRT1-H363Y)did not have this effect. SIRT1 or SIRT1-H363Y directly interacts with p27kip1. Expression of SIRT1 increased the interaction between SKP2 and p27kip1 but expression of the SIRT1 deacetylase mutant did not.

Conclusion : Our finding suggests that SIRT1 is a promising target for T-ALL and offers a mechanistic link between the upregulation of SIRT1 and the downregulation of p27kip1.

Keyword : SIRT1, p27kip1, SKP2, Ubiquitination, T-ALL

BP06

Development of novel anti-CD19 CAR T cells resistant to immune checkpoint for phase I/II study in patients with relapsed of refractory B cell lymphoma

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Background : Although CD19-targeting chimeric antigen receptor (CAR) T cells have become an important therapeutic option for patients with relapsed and refractory B cell malignancies, recent clinical data indicate that a significant portion of patients still do not benefit from the therapy owing to various resistance mechanisms, including high expression of multiple inhibitory immune checkpoint receptors.

Method : We designed a lentiviral two-in-one CAR T approach in which two checkpoint receptors are downregulated simultaneously by a dual shRNA cassette integrated into a CAR vector, evaluated the functionality of CD19 specific CAR T cells in the context of four different checkpoint combinations—PD-1/TIM-3, PD-1/LAG-3, PD-1/CTLA-4, and PD-1/TIGIT.

Results : We found that PD-1/TIGIT downregulation uniquely exerted synergistic antitumor effects of CAR T cells in mouse xenograft models compared with PD 1 single downregulation. Significantly, downregulation of PD-1 enhances short-term effector function, whereas downregulation of TIGIT is primarily responsible for maintaining a less-differentiated/exhausted state, providing a potential mechanism for the observed synergy. Moreover, The PD-1/TIGIT–downregulated CAR T cells generated from diffuse large B-cell lymphoma patient-derived T cells using a clinically applicable manufacturing process also showed robust antitumor activity and significantly improved persistence in vivo compared with conventional CD19-targeting CAR T cells.

Conclusion : Overall, our results demonstrate that the cell-intrinsic PD-1/TIGIT dual downregulation strategy may prove effective in overcoming immune checkpoint-mediated resistance in CAR T therapy.

Keyword : Cancer Immunotherapy, T Cell Engineering, Chimeric Antigen Receptor, Immune Checkpoint Receptor.

BP07

Comprehensive clinical and molecular features analysis of follicular peripheral T-cell lymphoma and nodal peripheral T-cell lymphoma with T follicular helper phenotype compared to angioimmunoblastic T cell lymphoma and peripheral T-cell lymphoma-NOS

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Background : Follicular helper T-cells (Tfh cells) categorize a subset of CD4+T-cells that plays two roles, such as memory cells in the T-cell zone of lymphoid organs or effector T cells in areas of inflammation site depend on CCR7 homing chemokine expression. The 2016 World Health Organization (WHO) classification introduced nodal lymphomas of T follicular helper (TFH) cell origin through the expression of at least 2 or 3 TFH markers, including CD279/PD1, CD10, BCL6, CXCL13, ICOS, SAP, and CCR. It has been categorized into three different subtypes under the same umbrella,

such as angioimmunoblastic T-cell lymphoma (AITL), follicular peripheral T-cell lymphoma (F-PTCL), and nodal peripheral T-cell lymphoma with T follicular helper phenotype (nodal PTCL with TFH phenotype). However, we did not know the accurate incidence rate and clinical characteristics of F-PTCL and nodal PTCL with TFH yet. Thus, we analyzed the clinical and histologic, and molecular characteristics of the Tfh cell origin lymphomas like AITL, F-PTCL, and nodal PTCL with TFH defined under the WHO 2016 guidelines.

Method : We reviewed the clinical and pathologic data of patients with neoplasms of mature T-cell and NK-cells in Samsung Medical Center between February 2012 to June 2020. We collected patients' clinical and pathological data by screening only patients with AITL, F-PTCL, nodal PTCL with TFH, or PTCL-NOS. Three different subtypes under the same umbrella with T-follicular helper (Tfh) phenotype were sorted through the presence of follicular dendritic cell (FDC) meshwork and follicular growth pattern by CD21 and Tfh markers (CD4, PD-1, CXCL13, BCL6, and CD10) staining. Besides, we performed four kinds of immunohistochemistry (IHC) stains, such as T-bet, CXCR3, GATA3, and CCR4, to classify PTCL-GATA3 (T-helper 2 like origin) and PTCL-TBX21(T-helper 1 like origin). Additionally, target gene analysis was performed on a few patients with sufficient blood and tissue samples. All data were analyzed using the Statistical Package for Social Sciences software, version 24.0 (IBM Corp, Armonk, NY, USA).

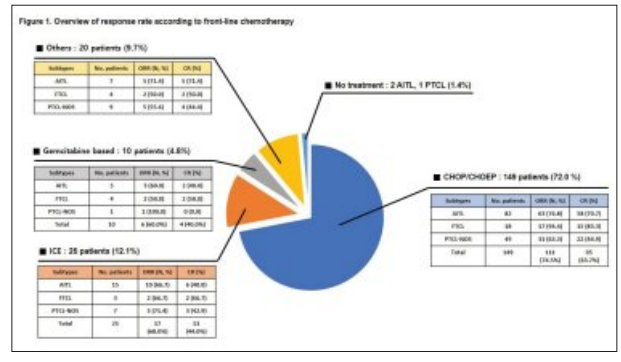
Results : Among 207 patients screened, the number of patients diagnosed with AITL was most common (N=111, 53.6%). Sixty-seven patients (32.4%) were diagnosed with PTCL-NOS, and the minority of patients were confirmed F-PTCL (N=19, 9.2%) and nodal PTCL with TFH phenotype (N=10, 4.8%). We re-defined and analyzed F-PTCL and nodal PTCL with TFH phenotype into Follicular T-cell lymphoma (FTCL). All subtypes showed a higher incidence rate in males than females. The number of patients in stage III/IV (N=176/207, 85.0%) at diagnosis was more common than stage I/II (N=31/207, 15%). In particular, AITL (N=101/111, 91.0%) was found to have a higher frequency of stage III/IV than FTCL (N=22/29, 75.0%) and PTCL-NOS (N=53/67, 79.1%; P-value =0.03). The percentage of patients evaluated with high-intermediate or high IPI groups (IPI ≥ 2) was 67.6% of AITL (N=75/111), 37.9% of FTCL (N=11/29), and 50.7% of PTCL-NOS (N=34/67; P-value =0.01), two times higher than the low or low-intermediate IPI groups (IPI < 2, Table 1). Among 149 patients who received anthracycline combined chemotherapies, patients diagnosed with AITL achieved ORR of 76.8% (N=63/82) and CR of 70.7% (N=58/82), and those diagnosed with PTCL-NOS obtained ORR of 63.6% (N=31/49) and CR of 44.9% (N=22/49). Notably, patients diagnosed with FTCL obtained a slightly higher ORR of 94.4% (N=17/18) and CR of 83.3% (N=15/18) than those diagnosed with AITL and PTCL-NOS (Figure 1). Moreover, we found that the patients diagnosed with AITL and FTCL showed the similarity of PFS (17.7 months, 95% CI 10.5-24.9; 23.8 months, 95% CI 6.3-41.3; 9.1 months, 95%CI 5.4-12.8, P-value =0.04) and OS (60.0 months, 95%CI 55.8-64.2; 60.0 months, 95%CI 12.4-107.6; 2.6 months, 95% CI 18.5-28.7, P-value =0.02), and superior compared to PTCL-NOS (Figure 2). Comparing the staining results, AITL and FTCL seemed to show more commonly TBX21 subtypes than GATA3 subtypes (Figure 3). Mutation related to the RAS family (RHOA) and epigenetic regulators (IDH2, DNMT3A, and TET2) were showed mainly in AITL and FTCL. However, it was presented that mutations belonging to the TCR pathway, transcription factors, and tumor suppressor were expressed equally in AITL, FTCL, and PTCL-NOS (Figure 4).

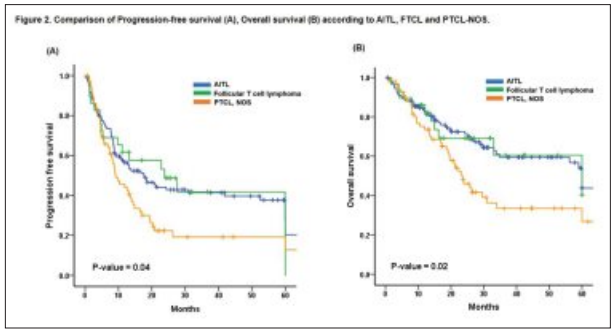
Conclusion : Given that to the rarity of the F-PTCL, and nodal PTCL with TFH, we were unable to separate the two diseases and analyze them as different diseases. Although we integrated and analyzed the two diseases by FTCL, we were able to observe the relative proportion, clinical features, and molecular characteristics of FTCL. Consequently, it seems that FTCL showed a unique disease entity utterly different from PTCL-NOS and AITL. However, some of the characteristics, such as the cell of origin and genetic variation, were shared with AITL. Even though FTCL is completely classified into a separate specific entity, the PTCL-NOS remains a basket term inclusive of all unknown entities within the 2016 WHO classification. Thus, further studies are continually needed to identify the specific disease characteristics of PTCL-NOS. Also, we emphasize the approach of classifying FTCL as a separate disease category from PTCL-NOS in further study settings.

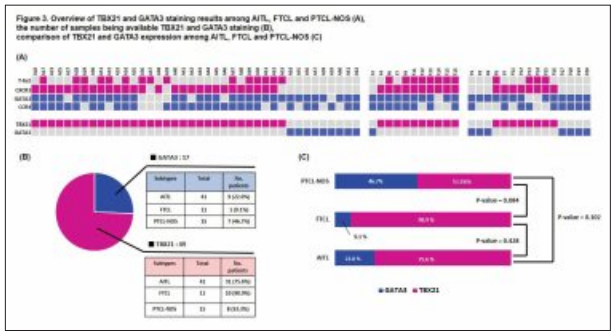
Keyword : Peripheral T-Cell Lymphoma-NOS, Angioimmunoblastic T-cell Lymphoma, Follicular Peripheral T-Cell Lymphoma, Nodal Peripheral T-Cell Lymphoma with T Follicular Helper Phenotype

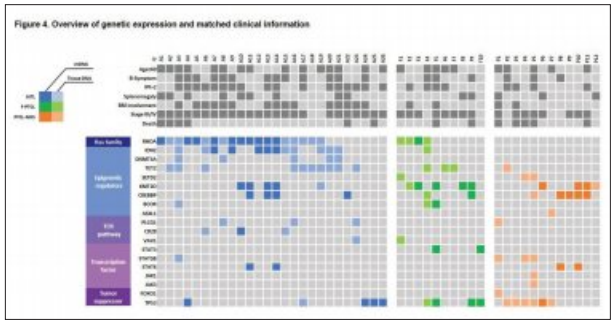
Table 1. Comparison of clinical characteristics according to each subtype.

Patients characteristics	Total	AITL	FTCL	PTCL-NOS	p-value
N (%)	207	111 (53.6)	29 (14.0)	67 (32.4)	
Age ≥ 60 years	99 (47.8)	66 (61.1)	15 (51.7)	27 (40.3)	0.05
Gender					
Male	132 (63.8)	64 (57.7)	16 (55.2)	52 (77.6)	0.01
Female	75 (36.2)	47 (42.3)	13 (44.8)	15 (22.4)	
ECOG					
0-1	182 (87.9)	95 (85.6)	24 (82.2)	63 (94.0)	0.15
>2	25 (12.1)	16 (14.4)	5 (17.2)	4 (6.0)	
Stage					
I/II	31 (15.0)	10 (9.0)	7 (24.1)	14 (20.9)	0.03
III/IV	176 (85.0)	101 (91.0)	22 (75.9)	53 (79.1)	
IPI					
<2	87 (42.0)	36 (32.4)	18 (62.1)	33 (49.3)	0.01
≥2	120 (58.0)	75 (67.6)	11 (37.9)	34 (50.7)	
B-symptom, presence	80 (38.6)	56 (50.5)	8 (27.6)	16 (23.9)	0.00
Hb < 10g/dL)	43 (20.8)	31 (28.4)	2 (6.9)	10 (14.9)	0.01
Hemolytic anemia	9 (4.3)	9 (8.1)	0	0	0.00
Platelet <100k	36 (17.4)	20 (18.3)	0	16 (23.9)	0.01
Elevated LDH.	119 (57.5)	71 (65.1)	10 (34.5)	38 (56.7)	0.01
Elevated B2M	107 (51.7)	65 (58.6)	7 (24.1)	35 (52.2)	0.00
IgG ≥ 1600mg/dL	44 (21.3)	33 (29.7)	2 (6.9)	9 (13.4)	0.00
IgA ≥ 400mg/dL	23 (11.1)	16 (14.4)	2 (6.9)	5 (7.5)	0.00
IgM ≥ 230mg/dL	30 (14.5)	29 (26.1)	1 (3.4)	0 (0.0)	0.00
Serum EBV, positive	62 (30.0)	45 (40.5)	9 (31.0)	8 (11.9)	0.00
Splenomegaly	83 (40.1)	53 (47.7)	6 (20.7)	24 (35.8)	0.02
BM involvement	73 (35.3)	46 (41.4)	9 (31.0)	18 (27.7)	0.17









BP08

Immune checkpoint-related gene polymorphisms are associated with sensitivity and treatment response of primary immune thrombocytopenia

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Background : Immune checkpoints, including co-stimulation and co-inhibition signal pathways, are among the central mechanisms that regulate T-cell mediated immune responses. Cancer immunotherapy by immune checkpoint blockade has been effective in the treatment of certain tumors. However, the association between immune checkpoints and autoimmune diseases remains elusive and requires urgent investigation. Primary immune thrombocytopenia (ITP), characterized by reduced platelet count and a consequent increased risk of bleeding, is an autoimmune disorder with a hyper-activated T cell response. Therefore, investigating the relationship between immune checkpoint gene polymorphisms and susceptibility or treatment response of ITP may reveal the mechanism of pathogenesis and development of ITP.

Method : Here, we investigated the contribution of immune checkpoint-related single-nucleotide polymorphisms (SNPs), including CD28, ICOS, PD1, TNFSF4, DNAM1, TIM3, CTLA4, and LAG3 to the susceptibility and therapeutic effects of ITP. In this case-control study, 307 ITP patients and 295 age-matched healthy participants were recruited. We used the MassARRAY system for genotyping immune checkpoint-related SNPs. We performed flow cytometry and rt-PCR to test the CD28 expression at the mRNA and protein levels.

Results : Our results revealed that rs1980422 in CD28 was associated with a 1.788-fold increased risk of ITP after false discovery rate correction (codominant, CT vs. TT, OR =1.788, 95% CI =1.178–2.713, p=0.006). In addition, CD28 expression at both the mRNA and protein levels was significantly higher in patients with CT genotype (p=0.028 and p=0.001, respectively). Furthermore, the T allele of PD1 rs36084323 was a risk factor for ITP severity (OR =1.649, 95% CI =1.186–2.291, p=0.003) and the T allele of DNAM1 rs763361 for corticosteroid-resistance (OR =1.939, 95% CI =1.278–2.942, p=0.002). In contrast, the T allele of LAG3 rs870849 was a protective factor for ITP severity (OR =0.506, 95% CI =0.312–0.818, p=0.005, and the T allele of ICOS rs6726035 was protective against corticosteroid-resistance (OR =0.538, 95% CI =0.366–0.791, p=0.002). The TT/CT genotypes of PD1 rs36084323 also showed an 8.889-fold increase in the risk of developing refractory ITP. This study indicates that immune checkpoint-related SNPs, especially CD28 rs1980422, may be genetic factors associated with the development and treatment of ITP patients.

Conclusion : In summary, we have found that immune checkpoint-related SNPs, especially CD28 rs1980422, may be genetic factors associated with the development and treatment of ITP. Our results provide new clues for the identification of therapeutic targets and prognosis prediction in ITP.

Keyword : Single-Nucleotide Polymorphism, Immune Checkpoint, Primary Immune Thrombocytopenia, T Cell, CD28

Tables

Table 1 Selected SNPs associated with ITP risk.

Gene	SNP	Model	Genotype /allele	Control Count	Control %	ITP Count	ITP %	OR (95% CI)	Adjusted *p* value
TIM3	rs10515746	Codominant	CC	291	98.6	293	95.4	1.000	
			AA	0	0.0	0	0.0	_	
			CA	4	1.4	14	4.6	3.572 (1.153-11.064)	**0.027**
		Dominant	CC	291	98.6	293	95.4	1.000	
			CA/AA	4	1.4	14	4.6	3.628 (1.175-11.200)	**0.025**
		Allele	C	586	99.3	600	97.7	1.000	
			A	4	0.7	14	2.3	3.509 (1.140-10.798)	**0.029**
CD28	rs1980422	Codominant	TT	246	83.4	233	75.9	1.000	
			CC	4	1.4	0	0.0	_	0.999
			CT	45	15.2	74	24.1	1.798 (1.181-2.711)	**0.006**
		Dominant	TT	246	83.4	233	75.9	1.000	
			CC/CT	49	16.6	74	24.1	1.646 (1.095-2.472)	**0.016**
ICOS	rs6726035	Recessive	TT	62	21.0	89	29.0	1.000	
			CC/CT	233	79.0	218	71.0	1.510 (1.037-2.198)	**0.032**
		Allele	C	320	54.2	292	47.6	1.000	
			T	270	45.8	322	52.4	1.303 (1.037-1.637)	**0.023**

CI, confidence interval; ITP, immune thrombocytopenia; OR, odds ratio; SNP, single-nucleotide polymorphism. Adjusted p value calculated with univariate logistic regression. **Bold** highlights $p < 0.05$.

Table 2 Selected SNPs associated with ITP risk by multivariate logistic regression analysis.

Gene	SNP	Model	Genotype/ allele	Controls		ITP patients		OR (95% CI)	Adjusted *p* value
				Count	%	Count	%		
TIM3	rs10515746	Codominant	CC	291	98.6	293	95.4	1.000	
			AA	0	0.0	0	0.0	_	
			CA	4	1.4	14	4.6	3.509 (1.128-10.914)	**0.030**
		Dominant	CC	291	98.6	293	95.4	1.000	
			CA/AA	4	1.4	14	4.6	3.617 (1.170-11.185)	**0.026**
		Allele	C	586	99.3	600	97.7	1.000	
			A	4	0.7	14	2.3	3.218 (1.043-9.924)	**0.042**
CD28	rs1980422	Codominant	TT	246	83.4	233	75.9	1.000	
			CC	4	1.4	0	0.0	_	0.999
			CT	45	15.2	74	24.1	1.788 (1.178-2.713)	**0.006**
		Dominant	TT	246	83.4	233	75.9	1.000	
			CC/CT	49	16.6	74	24.1	1.645 (1.093-2.475)	**0.017**
ICOS	rs6726035	Allele	C	320	54.2	292	47.6	1.000	
			T	270	45.8	322	52.4	1.276 (1.015-1.605)	**0.037**

CI, confidence interval; ITP, immune thrombocytopenia; OR, odds ratio; SNP, single-nucleotide polymorphism. Adjusted p value calculated with multivariate logistic regression. **Bold** highlights $p < 0.05$.

Table 3 Selected SNPs associated with ITP severity.

Gene, SNP	Model	Genotype/ allele	Non-severe		Severe		OR (95% CI) [a]	Adjusted *p* value [a]	OR (95% CI) [*]	Adjusted *p* value [*]
			Count	%	Count	%				
PD1, rs36084323	Codominant	CC	48	28.2	24	17.5	1.000			
		TT	28	16.5	36	26.3	2.558 (1.274-5.138)	**0.008**		
		CT	94	55.3	77	56.2	1.640 (0.922-2.919)	0.093		
	Dominant	CC	48	28.2	24	17.5	1.000			
		TT/CT	122	71.8	113	82.5	1.851 (1.064-3.221)	**0.029**		
	Recessive	TT	28	16.5	36	26.3	1.000			
		CC/CT	142	83.5	101	73.7	1.797 (1.029-3.138)	**0.039**		
	Allele	C	190	55.9	125	45.6	1.000		1.000	
		T	150	44.1	149	54.4	1.507 (1.093-2.076)	**0.012**	1.649 (1.186-2.291)	**0.003**
LAG3, rs870849	Allele	C	280	82.4	243	88.7	1.000		1.000	
		T	60	17.6	31	11.3	0.579 (0.362-0.925)	**0.022**	0.506 (0.312-0.818)	**0.005**

CI, confidence interval; ITP, immune thrombocytopenia; OR, odds ratio; SNP, single-nucleotide polymorphism. Calculated with [a]univariate or [*]multivariate logistic regression under allele model. **Bold** highlights $p < 0.05$.

Table 4 Association between selected SNPs and corticosteroid-sensitivity of ITP patients.

Gene, SNP	Model	Genotype/ allele	Corticosteroid-sensitive		Corticosteroid-resistant		OR (95% CI) [a]	Adjusted *p* value [a]	OR (95% CI) [*]	Adjusted *p* value [*]
			Count	%	Count	%				
DNAM1, rs763361	Codominant	CC	56	52.3	54	39.4	1.000			
		TT	5	4.7	18	13.1	3.719 (1.276-10.838)	**0.016**		
		TC	46	43.0	65	47.5	1.413 (0.825-2.421)	0.208		
	Recessive	TT	5	4.7	18	13.1	1.000			
		CC/TC	102	95.3	119	86.9	3.151 (1.116-8.892)	**0.030**		
	Allele	C	158	73.8	173	63.1	1.000		1.000	
		T	56	26.2	101	36.9	1.623 (1.092-2.412)	**0.017**	1.939 (1.278-2.942)	**0.002**
ICOS, rs6726035	Allele	C	89	41.6	143	52.2	1.000		1.000	
		T	125	58.4	131	47.8	0.634 (0.439-0.914)	**0.015**	0.538 (0.366-0.791)	**0.002**

CI, confidence interval; ITP, immune thrombocytopenia; OR, odds ratio; SNP, single-nucleotide polymorphism. Calculated with [a]univariate or [*]multivariate logistic regression under allele model. **Bold** highlights $p < 0.05$.

Table 5 Selected SNPs associated with ITP refractoriness.

Gene, SNP	Model	Genotype	Non-refractory ITP		Refractory ITP		OR (95% CI)	Adjusted *p* value
			Count	%	Count	%		
PD1, rs36084323	Codominant	CC	71	25.4	1	3.7	1.000	
		TT	58	20.7	6	22.2	7.314 (0.854-62.612)	0.069
		CT	151	53.9	20	74.1	9.500 (1.249-72.289)	**0.030**
	Dominant	CC	71	25.4	1	3.7	1.000	
		TT/CT	209	74.6	26	96.3	8.889 (1.183-66.771)	**0.034**

CI, confidence interval; ITP, immune thrombocytopenia; OR, odds ratio; SNP, single-nucleotide polymorphism.
Adjusted p value calculated with univariate logistic regression. **Bold** highlights $p < 0.05$.

BP09

TINF2 mutations are associated with poor outcome post hematopoietic stem cell transplantation for dyskeratosis congenita

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Background : Dyskeratosis congenita (DC) is a telomere biology disorder with a high risk of bone marrow failure, cancer, pulmonary and liver disease. Mutation in multiple telomere related genes including DKC1, TINF2, RTEL1, TERC, TERT, WRAP53, CTC1, NOP10, NHP2 and TPP1 have been reported. Patients with TINF2 mutations typically have severe bone marrow failure (SBMF) at a young age, non-hematological manifestations and very short telomeres. Currently, allogeneic hematopoietic stem cell transplantation (HSCT) is the only available curative treatment for bone marrow failure and leukemia in DC patients. Relatively few case series of patients with DC undergoing HSCT have been reported, which generally suggested a poor outcome. The present study aimed to characterize the outcome of HSCT in a Canadian cohort of patients with DC and determine potential relationships between outcome and genotype.

Method : The Canadian Inherited Marrow Failure Registry (CIMFR) is a multicenter registry that includes tertiary centers that care for IBMFS patients across all Canadian provinces. Patients with DC who had been enrolled in CIMFR and underwent HSCT between January 2001 and December 2019 were included. Data were extracted from the CIMFR database.

Results : Among 35 patients with DC enrolled in the CIMFR, 11 underwent HSCT. Seven patients were male. Median age at presentation, diagnosis and HSCT was 2.1 years (range: 0 to 9.13), 5.5 years (range: 1.94 to 35.25), and 7.0 years (range; 0.5-37), respectively. The diagnosis of 3 patients was made after HSCT. The median follow up time from HSCT was 5.89 years (range; 0.2-14.0 years). Among transplanted patients, five had TINF2 mutations, two had RTEL1 mutations, and one patient had DKC1 mutation. Eight patients underwent HSCT for severe bone marrow failure, and three patients for single or multilineage cytopenia. All patients had normal bone marrow karyotype before HSCT. All patients had a full matched donor; two were related and nine were unrelated. Ten patients received reduced-intensity conditioning, and one received myeloablative conditioning. Two patients experienced engraftment failure and underwent a second HSCT. Five years and ten years overall survival after HSCT was 90.9% (95% CI 73.9-100%) and 80% (95% CI 27.2- 97.5%), respectively; however, complications and deaths started appearing thereafter, mainly in patients with TINF2 mutation. All of the five patients with TINF2 mutation died,

and the other patients were alive. The causes of death were:1) pulmonary fibrosis (N=2), 2) gastrointestinal bleeding (N=2), and 3) EBV infection (N=1). Two patients were diagnosed with pulmonary fibrosis after 8 and 11 years from HSCT and died 13.7 and 14 years post-transplant. Two patients were noticed gastrointestinal bleeding after 3.9 years and 4.8 years from HSCT and died 6.6 and 5.7 years post-transplant. Of the patients with GI bleeding, both had hepatic fibrosis and one had pulmonary fibrosis.

Conclusion : Patients with TINF2 mutations have resolution of the bone marrow failure and relatively good quality of life in the first few years post HSCT. However, longer outcome is dismal because of DC complications, especially pulmonary fibrosis and gastrointestinal bleeding. Effective therapies to prevent these complications are critically needed. Additional reports about HSCT outcome of patients with DC are necessary to characterize HSCT in patients with other genetic groups and to replicate the above results in TINF2 patients.

Keyword : Dyskeratosis Congenita, Hematopoietic Stem Cell Transplantation, Outcome, Genotype, TINF2

BP10

Two-stage genome-wide association studies of hemoglobin concentration in Taiwan Han Chinese

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Background : Among the most common diseases in humans are those linked to iron metabolism and homeostasis, ranging from anemia (i.e., iron deficiency) to hemochromatosis (i.e., iron overload). However, there has been scarcity of data on the susceptibility genes and variants of iron homeostasis in humans, especially among the East Asians. Hemoglobin (Hb), being a stable and handy iron status indicator, essentially reflects the amount of functional iron in the body. This paper presents the first genome-wide association study (GWAS) of Hb concentration among the Han Chinese of Taiwan.

Method : We conducted sex-stratified two-stage GWAS involving 68,064 adult Han Chinese of the Taiwan Biobank (TWB). Quality control steps for genetic data were carried out following these criteria: (a) high degree of missingness at SNP-level and individual-level, (b) sex disconcordance, (c) low minor allele frequencies in autosomal SNPs, and (d) deviations from Hardy-Weinberg equilibrium. Genetic principal components were calculated and adjusted for as covariates in order to correct for population stratification. Correction for multiple tests was applied in multivariate linear regression analyses, wherein SNPs were tested in association with Hb as a quantitative outcome measure.

Results : We identified 92 SNPs that were significantly associated with Hb in males while there were 96 Hb-associated SNPs in female Taiwan Han Chinese. TMPRSS6 rs5756504 (padjusted=4.30x-16) in chr 22 and AXIN1 rs11866815 (padjusted=9.18x-29) in chr 16 emerged as the top SNPs, respectively. AXIN1 and few genes along chr 16 are considered novel in the TWB Han Chinese group. Furthermore, we replicated the association of SNPs in the PRKCE (chr 2), ABO (chr 9), and TMPRSS6 (chr 22) genes with Hb concentration.

Conclusion : Our findings contribute to the growing evidence of the ethnic-specific allelic heterogeneity of iron status and systemic iron homeostasis. This will paved way in further understanding the physiology of iron in humans and in identifying high-risk subgroups among Taiwan Han Chinese.

Keyword : Genome-Wide Association Study, Hemoglobin, Iron Status, Iron Nutrition, Taiwan Han Chinese, Taiwan Biobank

PP01-01

Next generation sequencing (NGS)-based interpretation of FLT3/NPM1 mutations in adult patients with acute myeloid leukemia (AML) in a single institution

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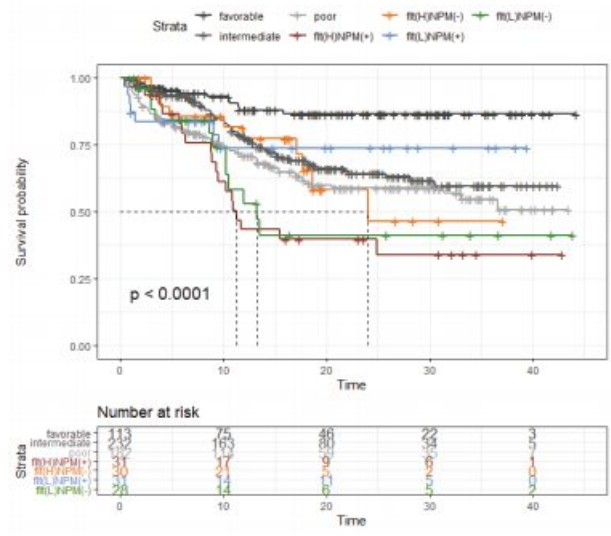
Background : Although NGS technique has been well introduced and applied in many ways as an important prognostic tool, there has been limited data on a comprehensive genomic overview for Korean patients only. Our project aimed to provide insights into genetic profile of adult AML and to validate the prognostic impact of 2017 ELN risk stratification with particular attention to AML with mutated FLT3-ITDhigh, low/NPM1wt, mut, by gathering large-scale, a single center data.

Methods : A total of 683 patients whose NGS testing was performed at initial diagnosis between Jul 2017 and Dec 2020 were enrolled and the mutation profiles were analyzed with cytogenetic results as well as clinical data for their relevance to clinical outcomes. Excluding 36 patients who were not treated, the data from 647 patients receiving treatment in our hospital were used for validation of ELN risk group.

Results : We analyzed using our own NGS panel for AML including 67 genes in 594 (86%) detected patients. The most common somatic mutation was NPM1 (22.3%) followed by FLT3-ITD (18.4%), DNMT3A (16.2%), NRAS (13.2%), TET2 (11.4%), IDH2 (10.7%), RUNX1 (10.6%), CEBPA (double mutation 7.6%), ASXL1 (7.6%), FLT3-TKD (7.4%), KIT (7.2%), PTPN11 (7.0%), WT1 (6.1%), IDH1 (5.4%), and KRAS (5.3%) in order. Distribution and frequencies of genetic mutations were different according to age groups. With the cut-off age of 60 years old (≥ 60 vs < 60), in elderly population, higher proportion of TET2, PTPN11, IDH2, TP53, ASXL1, DNMT3A mutations were found with 64.1%, 54.2%, 52.1%, 51.4%, 50%, 48.2%, respectively. In contrast, younger patients showed higher proportion of WT1, KIT, KRAS, CEBPA (double mutation), NRAS mutations with 83.3%, 75.5%, 72.2%, 71.2%, 71.1% respectively. After a median follow-up of 16 months (range, 0.3 to 44 months), the median was not reached for the all-3 risk groups. The Kaplan-Meier survival curve could discriminate 3 risk groups (p<0.001), but the difference between intermediate and adverse risk groups was not statistically significant (p=0.300). For identifying significance of NPM1 mutation status in FLT3-ITD mutated patients, data of FLT3-ITDhigh, low/NPM1wt, mut AML patients of different combinations were analyzed separately, which were later combined and compared to the rest of cohort population. As a consistent result, only in the FLT3-ITDlow group, NPM1mut was associated with better prognosis. Whereas both FLT3-ITDlow, /NPM1wt and FLT3-ITDhigh/NPM1wt AML, designated as intermediate-risk group by ELN 2017, showed comparable prognosis to FLT3-ITDhigh/NPM1mut, and notably worse survival even than that of other ELN adverse risk groups.

Conclusions : The distribution of the gene mutations in adult patients with AML in our institution reveals similar trends showed in other studies. There were some specific mutations that found characteristically different frequencies by age-specific groups. We found a difference according to FLT3-ITD related risk stratification as not shown in other studies. This study showed that FLT3-ITD mutation high burden with NPM1 mutation showed no superior prognosis than the poor-risk group in our population. We suggest that the patients having FLT3-ITD mutation high burden, regardless of NPM1 mutation, might be managed as the same poor-risk group needing more integrated approaches with sequential targeted therapies followed by allogeneic hematopoietic stem cell transplantation, including with such a maintenance strategy based on very cautious ways of MRD monitoring.

Keyword : FLT-ITD Mutation



PP01-02

Impact of FLT3-ITD gene mutations in

acute promyelocytic leukemia in Malaysia

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Background : APML is a unique subtype characterized by coagulopathy and accumulation of morphologically aberrant promyelocytes carrying one of the rearrangement involving the RARAα gene, which encodes the retinoic acid receptor alpha located at 17q21. Among these, the rearrangement of RARAα with the promyelocytic leukaemia gene in the translocation t(15;17)(q22;q12) occurs in approximately 95% of APML patients. The frequency of APML varies by ethnic group, and APML accounts for 10–25% of all AML cases. FMS-like tyrosine kinase 3 (FLT3) that results in internal tandem duplication (ITD) is common in AML, which results in high risk of relapse and poor prognosis, However, the clinical impact of FLT3-ITD in APML remained controversial. Literature on APML survival were often derived from strict trial studies from developed country. To our knowledge, there were no publications on Malaysia's APML study with FLT3-ITD mutation. This study aimed to study the epidemiology and real-world treatment outcome and impact of flt3 gene mutation of adults with APML in a real world setting in Malaysia.

Method : Data was retrospectively collected and analysed for all adolescents and adult patients (more than 12 year-old) with APML who undergone treatment from 2009 until 2018 in Ampang Hospital, a national haematology referral centre in Malaysia. Overall survival (OS) was analysed using Kaplan-Meier survival function, calculated from the time of treatment initiation till death and divided into 2 groups of patients who is FLT3-ITD positive and FLT3-ITD negative. At the same time, the the overall survival (OS) of patients with different white blood cells (WBC) count (≥10x10^9/L or <10x10^9/L) and FLT3-ITD mutation (positive or negative) were compared.

Results : A total of 163 adult patients with acute promyelocytic leukaemia (APML) were identified with median age of diagnosis of 30 years old (range from 13 to 80 years old), female predominance (57%), and majority Malay ethnicity (49%). As a preliminary observation for 60 patients, with 20 mortality cases (33.3%), the overall survival (OS) of patients with different white blood cells (WBC) count (≥10x10^9/L or <10x10^9/L) and FLT3-ITD mutation (positive or negative) were compared. Patients with WBC ≥10 x 10^9/L were having significantly inferior OS than patients with WBC count <10x10^9/L (p=0.0047). A 26% difference in OS was observed. Patients with FLT3-ITD positive were having inferior OS than patients with FLT3-ITD negative, however the difference in OS (22%) was not statistically significant (p=0.0512). Total 9 of them with FLT3-ITD+, there are 4 patients (44%) with FLT3-ITD+ presented with high WBC > 10 x 10^9/L, median 85.6 x 10^9/L. Among FLT3-ITD+, 5 of them die of intracranial bleed during induction period (2 of them presented with high WBC on presentation). 67% (6) of them passed away at the follow up period of 24months with 1 die of relapse and 5 die of intracranial bleed.

Conclusion : Our cohort of patients with FLT3-ITD mutation had significant poorer outcome. The strong association of mutation with specific clinical features and the poor outcome demonstrated in analysis, allow a subset of aggressive subtype of APML at diagnosis to be identified, which probably deserved an intensification of treatment in order to prevent relapse. Furthermore, the use of an FLT3 inhibitor in APML has yet to be established, it will be interesting to explore the efficacy of arsenic trioxide in APML patients harbouring FLT3-ITD.

Keyword : APML, Acute Promyelocytic Leukaemia, FLT3-ITD

PP01-03

Overexpression of prohibitn 2 mRNA and protein is associated with poor prognostic indicator in cytogenetically normal acute myeloid leukemia

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Background : Cytogenetically normal acute myeloid leukemia (CN-AML) accounts for 40% to 50% of all AML. Despite advancements in molecular pathophysiology of CN-AML, its clinical outcome remains unsatisfactory and unpredictable. The objective of this study was to investigate protein and gene expression levels of prohibitin2 (PHB2) and their clinical implications in CN-AML.

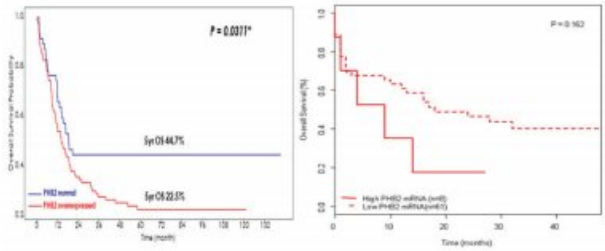
Method : PHB2 protein expression was performed using immunohistochemical staining (IHCS) on paraffin-embedded bone marrow sections in 133 CN-AML patients. IHCS results were semiquantitatively measured with a scoring system. PHB2 mRNA was quantified using laboratory-developed quantitative reverse transcriptase PCR system in 69 CN-AML patients. Clinical outcome was analyzed in comparison with other prognostic markers such as age, NPM1 mutation, and FLT3-ITD.

Results : Using cut-off positivity score of IHCS at 6.0 in PHB2, CN-AML patients with overexpressed PHB2 protein showed inferior overall survival (OS) (22.5% vs. 44.7%; p=0.031). In PHB2 mRNA expression study, patients with mRNA-overexpressing group showed as inferior OS (17.5% vs. 40.0%; p=0.16) and high hazard ratio (1.93 [95% CI: 0.739–5.042]; p=0.18).

Conclusion : Overexpression of PHB2 mRNA and protein was associated with inferior OS in CN-AML patients. The expression

status of PHB2 gene could serve as an independent prognostic indicator in CN-AML.

Keyword : AML, Prohibitin, Clinical Implication



PP01-04

Frequency and characteristics of risk-stratified adult acute myeloid leukemia according to the NCCN guideline version 2.2021 revealing categorization uncertainty and candidate cases for germline testing

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Background : The National Comprehensive Cancer Network (NCCN) guidelines for acute myeloid leukemia (AML) provides recommendations for the diagnosis and treatment of adult AML based on clinical trials leading to therapeutic improvements or new information on prognostication. The most updated recommendations specifically emphasized germline testing for patients with a variant allele frequency (VAF) of 40% to 60% of genes associated with a predisposition syndrome. We analyzed the frequency and characteristics of risk-categorized adults with AML, and presented cases of potential germline predisposition according to the NCCN guideline.

Method : We retrospectively searched adult patients with AML from the bone marrow archive of Asan Medical Center from 2018 to 2020. We classified patients into one of the 3 risk categories (favorable, intermediate and poor) according to the NCCN guideline Version 2.2021. Mutation profiling was performed by targeted next-generation sequencing for 61 genes, in which 6 genes associated with a predisposition syndrome were included (RUNX1, ANKRD26, CEBPA, DDX41, ETV6 and GATA2). FLT3-internal tandem duplication (ITD) allelic ratio was assessed by in-house DNA fragment analysis.

Results : A total of 267 adult patients with AML were reviewed: favorable risk in 94 (35.2%), intermediate risk in 55 (20.6%), poor risk in 117 (43.8%) and unavailable in 1 (0.4%). The five most common criteria were "-5 or del(5q); -7; -17/abn(17p)", "complex karyotype, monosomal karyotype", "mutated NPM1 without FLT3-ITD or with FLT3-ITDlow", "mutated TP53", and "mutated ASXL1". We identified 5 cases of cross-risk categorization (favorable + poor) including mutated NPM1 with complex karyotype or -17 or -7, and mutated CEBPA 17p abnormality or monosomal karyotype for one case each. We also identified 2 cases of cross-risk categorization (intermediate + poor) including mutated NPM1 with complex karyotype and t(9;11) with del(5q). Candidate for germline testing was 39 (14.6%), and had mutations in RUNX1 (N=13), CEBPA (N=13), DDX41 (N=6), ETV6 (N=4), GATA2 (N=5), RUNX1 and GATA2 (N=1), and CEBPA and GATA2 (N=1).

Conclusion : This study demonstrated that approximately 44% of AML adults were categorized into a NCCN poor risk. A small number of patients with mutated NPM1 or CEBPA has an ambiguity of risk categorization. Cases of potential predisposition syndrome was found to be approximately 15% and these cases should be under consideration for germline testing, genetic counseling or donor selection.

Keyword : Acute Myeloid Leukemia, NCCN Guideline, Risk Category, Uncertainty, Predisposition, Germline Testing

PP01-05

Clinical efficacy of venetoclax combined chemotherapy for newly diagnosed and relapsed or refractory acute myeloid leukemia (AML): 1-year experience in catholic hematologic hospital

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Background : Venetoclax, a selective B-cell leukemia/lymphoma-2 inhibitor, has emerged as a new therapeutic option for elderly AML and for relapsed or refractory AML (R/R AML) patients. Here, we report our institutional experience with this novel agent, mainly focusing on efficacy results.

Method : Patients with AML were allowed to have venetoclax (VEN) combined chemotherapy if the patients ≥ 65 years old were not eligible for intensive chemotherapy, or the adult patients at any age had R/R AML. A total of 103 consecutive patients who received VEN with decitabine (n=97), with azacitidine (n=4) or with low dose cytarabine (n=2) in our hospital between Feb 2020 and Nov 2020 were retrospectively reviewed, in which 29 newly diagnosed (28.2%) and 74 R/R AML patients (71.8%) were included.

Results : At cut-off date of 19 January, 81 patients (78.6%) had discontinued VEN combined treatment while 22 patients were still on treatment (21.4%), and allogeneic stem cell transplantation (allo-SCT) was the most common reason for treatment discontinuation (n=39, 48.1%). The median age was 60 years (range, 22-83), and de novo AML comprised majority (n=81, 78.6%). The overall response rate including CR (n=35), CRi (n=6), and MLFS (n=9) among the assessable patients (n=95) was 52.6%; and was 68% for newly diagnosed AML and 47.1% for R/R AML patients. Most responders had their first response before the initiation of cycle 2 (42 out of 50, 84%), and none of clinical factors including age, sex, AML type (de novo vs others), treatment setting (new vs R/R), ELN risk group, karyotype and somatic mutations, was able to predict response to VEN combined chemotherapy. During a median follow-up of 6.2 months (95% CI, 5.5-6.9), the median overall survival (OS) for all patients was not reached with showing 42.9% mortality at the time of analysis, which was 14.6% for newly diagnosed and 49.4% for R/R AML cases (p=0.095). Significant difference in OS was observed between de novo and secondary AML patients (median not reached vs 4.6 months, p=0.002), and between responder and non-responder groups (median 9.8 vs 7.7 months, p=0.002); whereas, we could not observe any OS difference according to other clinical characteristics.

Conclusion : Venetoclax combined treatment resulted in significant response in newly diagnosed elderly AML patients. Moreover, it appeared highly effective in obtaining high response rate in R/R AML patients, which potentially provide an effective bridge to allo-SCT. Hopefully, the use of venetoclax could become more affordable under the cost coverage of the Korean national health insurance system.

Keyword : Acute Myeloid Leukemia, Venetoclax, Response, Survival

PP01-06

Allelic burden of FLT3-ITD mutation matters in AML patients who received allogene hematopoietic stem cell transplantation

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Background : We investigated to evaluate the clinical implication of the internal tandem duplication of the fms-like tyrosine kinase-3 gene (FLT3-ITD) allelic burden on the outcome of allogene hematopoietic stem cell transplantation (HSCT) in acute myeloid leukemia (AML) patients.

Method : FLT3-ITD allelic burden was measured by PCR/GeneScan analysis and direct sequencing (exon 14, 15) at the time of diagnosis in AML 74 patients with FLT3-ITD mutation who received the HSCT at Samsung Medical Center, Seoul, Korea, and clinical outcome was analysed by review of medical records, retrospectively.

Results : Twenty six patients were intermediate risk, twenty four patients were poor risk, and twenty four patients were unknown by NCCN molecular risk classification. The median FLT3-ITD allelic burden was 0.64 (0.02-29.53). Twenty-six patients (35.1%) had concurrent NPM1 mutation. Most of the patients received IA induction chemotherapy (n=69, 93.2%), and fifty seven patients (77%) achieved complete remission. Median Leukemic Free Survival and median Overall Survival was 2.47 years and 2.9 years, respectively. In the univariate analysis, no statistically significant difference was observed for LFS and OS according to the FLT3 allelic burden in the range of 0.2 to 0.7, however OS was significantly poor in the patients who had allelic burden > 0.9 (p=0.012).

Conclusion : High allelic burden of FLT3-ITD imposes worse outcome even after alloHSCT that necessitated the incorporation of FLT3 inhibitors before or after HSCT.

Keyword : Acute Myeloid Leukemia, FLT3-ITD Allelic Burden, Allogene Stem Cell Transplantation

Table 1.Baseline characteristics (n=88)	
	Value
Sex	
Female	40 (45.45%)
Male	48 (54.55%
Age	
<60	47 (53.41%)
≥60	41 (46.59%)
Stage	
II	7 (7.95%)
III	44 (50%)
IV	37 (42.05%)
BMI	
<20	24 (27.27%)
20-25	50 (56.82%)
>25	14 (15.91%)
OP history	
operation	59 (67.05%)
operation x	29 (32.95%)
HER2	
positive	17 (19.32%)
negative	71 (80.68%)
Chemotherapy number	
two	45 (51.14%)
three	27 (30.68%)
≥four	16 (18.18%)
1st regimen	
XELOX	64 (72.73%)
TS-1	6 (6.82%)
Others	18 (20.45%)
2nd regimen	
Ramu/paclitaxel	58 (65.9%)
Clinical trial	6 (6.82%)
Others	24 (27.23%)

PP01-07

Clinical characteristics and prognostic impacts of mutations of RAS pathway-related genes in acute myeloid leukemia patients

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Background : In acute myeloid leukemia (AML), patterns of gene mutations are intrinsically related to the clinical characteristics and disease course. The RAS pathway is known to play an important role in the development of several types of tumors, including myeloid neoplasms. Mutations of genes involved in the RAS pathway are commonly found in AML, but the underlying mechanism of development and progression of AML remains to be elucidated, and the prognostic significance of these genes is still uncertain. Therefore, this study aimed to determine the clinical characteristics and prognostic impact of mutations of RAS pathway-related genes in acute myeloid leukemia patients.

Method : We performed next-generation sequencing (NGS) on aspirated bone marrow (BM) samples from 107 patients diagnosed with AML in Chungbuk National University Hospital between January 2015 and December 2020. The NGS data of the BM aspirates were analyzed to examine the mutational status of 49 genes. Among them, NRAS, KRAS, FLT3, KIT, CBL, and PTPN11 were classified as RAS pathway-related genes. We analyzed the relationship of the mutational status with the data collected on the clinical characteristics, treatment response, and survival of these patients.

Results : The median age of the enrolled patients was 70.2 years. Eight had an antecedent hematologic disease. Combination chemotherapy anthracycline and cytarabine was used for the treatment of 46 patients and 49 were treated with decitabine. The most common gene mutation found in the AML patients was DNMT3A followed by RUNX1, FLT3, and TP53. Mutations in genes related to the RAS pathway were found in 40 patients (37.4%), of which 17 (15.8%) had FLT3 mutations and 15 (14.0%) had NRAS mutations. Patients with RAS pathway-related gene mutation had a higher percentage of blast cells in BM and peripheral blood, a higher mean number of mutations, and a lower treatment response rate compared to those without these mutations. Mutations in the RAS pathway-related genes and TP53 mutation were mutually exclusive. Patients with the TP53 mutation were mostly older and samples from them exhibited features such as lower percentage of blast cells in peripheral blood and BM, lower white blood cell count, and a lower mean number of mutated genes compared to patients without TP53 mutations. The BM cells of patients with RAS pathway-related gene mutations rarely harbored dysplastic changes. However, in the BM of patients with the TP53 mutation, dysplastic cells were found very frequently even if they did not have secondary AML. The patients with RAS pathway-related gene and TP53 mutations had shorter median survival than those without those mutations, although this result was not statistically significant.

Conclusion : AML patients harboring RAS pathway-related gene mutations show adverse clinical features, including high leukemic cell burden and low response rates to treatment. Although our study did not show significant differences in survival rates due to the limitation of the small sample size of patients enrolled in the study, a more aggressive treatment approach along these lines could be considered for these patients. AML with RAS pathway-related gene mutations has contradictory clinical characteristics compared to AML with TP53 mutations. Based on our observations, we hypothesize that the RAS pathway-related gene mutations and the TP53 mutation contribute to leukemogenesis and disease progression via different mechanisms.

Keyword : Acute Myeloid Leukemia, Next-Generation Sequencing, Ras Pathway, Genetic Mutation

PP01-08

Treatment patterns and clinical outcomes in unfit AML patients receiving first-line systemic treatment or best supportive care: Korean sub-analysis

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Background : Acute myeloid leukemia (AML) is the most frequent type of leukemia in adults, and most commonly affects older adults, with a median age at diagnosis of 68–70 years in Korea. The current standard of care includes intensive chemotherapy (ICT); however, most of the elderly patients with AML are ineligible for ICT owing to their advanced age, poor performance status and comorbidities. Treatment options for these patients remain limited and include low-intensity chemotherapy, targeted therapy or best supportive care (BSC). With increasing incidence of AML in ageing population

and the emergence of new agents, there is a growing need to understand current treatment pathways and their associated clinical outcomes in patients who are unfit for ICT. The global CURRENT study is a real-world, non-interventional retrospective chart review to evaluate the overall survival (OS) and other clinical outcomes, clinicopathologic characteristics, and treatment patterns of patients with AML deemed unfit for ICT. Here, we present the results from the subgroup of Korean patients included in the study.

Method : The study included adults with primary or secondary AML who were ineligible for ICT and who initiated low-intensity chemotherapy, targeted therapy, or BSC between January 1, 2015, and December 31, 2018 in the first line (1L) setting from across four centres in Korea. The primary endpoint was OS from diagnosis of AML. Secondary endpoints included progression-free survival (PFS), complete remission (CR) + CRi (CR with incomplete hematologic recovery), and response rates. The data analyses are primarily descriptive, with the Kaplan-Meier method used to estimate time-to-event outcome measures.

Results : Among the 194 patients included in the Korean sub-analysis, 84.02% (n=163) received 1L systemic therapy, and 15.98 % (n=31) received BSC. Of those who received 1L systemic therapy, 5 (3.1%) received azacitidine (AZA), 140 (85.9%) received decitabine (DEC), 5 (3.1%) received low dose cytarabine (LDAC) and 13 (8.0%) received other systemic therapy (OST). For 1L systemic therapy and BSC groups, median age at diagnosis was 74 and 78 years, respectively; patients receiving systemic therapy were more likely to have de novo AML and an ECOG PS <2. The cytogenetic risk stratification of patients who received systemic therapy showed about 59% with favorable or intermediate risk and 30% with poor risk; the corresponding proportion of patients in the BSC group were 35% and 16%, respectively. Median OS was 7.83 mos in patients who received systemic therapy, including 7.53, 8.07, 6.30, and 7.63 mos for patients who received AZA, DEC, LDAC, and OST, respectively, and 4.50 mos for patients who received BSC. Median PFS was 7.53, 6.17, 6.30, 6.97, and 4.47 mos in patients who received AZA, DEC, LDAC, OST, and BSC, respectively. CR+CRi was achieved by 22.7% of patients who received 1L systemic therapy, with a median duration of response of 9.16 mos.

Conclusion : The clinical outcomes in patients with AML who are unfit to receive ICT and are treated with currently available treatment options remain poor. Further investigation of novel therapies and combination regimens is needed to improve outcomes in this patient population.

Keyword : Acute Myeloid Leukemia, Elderly, Treatment Patterns, Best Supportive Care, Non-Intensive Chemotherapy, Overall Survival

Table 1. Outcomes of first-line systemic treatment

	First-line systemic therapy					BSC
	AZA	DEC	LDCA	Other	All	
n (%)	N=5	N=140	N=5	N=13	N=163	N=31
Best overall response						
CR	1 (20.00)	21 (15.00)	1 (20.00)	4 (30.77)	27 (16.56)	0
CRi	0	7 (5.00)	0	3 (23.08)	10 (6.13)	0
PR	0	5 (3.57)	0	0	5 (3.07)	0
SD	2 (40.00)	51 (36.43)	0	4 (30.77)	57 (34.97)	2 (6.45)
PD	0	13 (9.29)	0	1 (7.69)	14 (8.59)	1 (3.23)
Unknown	2 (40.00)	43 (30.71)	4 (80.00)	1 (7.69)	50 (30.67)	28 (90.32)
Median time from start of treatment to best response, days (Range)	78.00 (78.00-78.00)	103.00 (4.00-336.00)	63.00 (63.00-63.00)	90.00 (51.00-203.00)	97.00 (4.00-336.00)	-
Median duration of CR + CRic, days (Range)	-	296.00 (47.00-919.00)	-	252.50 (69.00-763.00)	275.00 (47.00-919.00)	-
Median Overall Survival, mos (95% CI)	7.53 (2.80-8.43)	8.07 (6.27-10.03)	6.30 (2.37-9.80)	7.63 (1.77-23.43)	7.83 (6.30-9.27)	4.50 (2.93-11.83)
Median Progression Free Survival, mos (95% CI)	7.53 (2.80-8.43)	6.17 (5.43-7.23)	6.30 (2.37-9.80)	6.97 (1.77-16.23)	6.27 (5.77-7.23)	4.47 (2.93-11.83)

AZA, Azacitidine; BSC, best supportive care; CR, complete response; CRi, CR with incomplete hematologic recovery; Dec, Decitabine; LDAC, low-dose cytarabine; PD, disease progression; PR, partial response; SD, stable disease

AUTHOR DISCLOSURE

Soo-Mee Bang, Ka-Won Kang, Ik-Chan Song, Alexander Delgado, Maria Belen Guijarro Garbayo, Cynthia Llamas, Yinghui Duan: Nothing to declare.
Je-Hwan Lee ; playing advisory roles for AbbVie, Astellas, Celgene, Janssen, and Novartis.
Alexander Delgado, Maria Belen Guijarro Garbayo, Cynthia Llamas, Yinghui Duan ; being employed by Abbvie.

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PP01-09

Effect of delayed treatment in acute myeloid leukemia patients: Treatment delay matters in younger patients

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Background : Recently, there has been a debate about how long treatment delay would be possible for establishing a personalized treatment in acute myeloid leukemia (AML). A few previous studies from the Western region evaluated the impact of treatment delay on survival and treatment outcomes. They revealed no significant impact of delayed treatment in elderly AML in common, whereas conflicting results for young AML. All these previous studies were

limited by the relatively selective or small number of patients and the lack of clarity about the timing of diagnosis. Besides, the data on this issue are inevitably biased due to their retrospective nature and considerably affected by various demographic and social environments. Given these facts, we investigated the effects of treatment delay from a large data set from Asian patients.

Method : We retrospectively reviewed the data of non-acute promyelocytic leukemia AML patients aged 18 years or older who visited a single center in Korea and received anthracycline-based intensive chemotherapy from 2002 to 2016 (N=1282). The time from diagnosis to treatment (TDT) was counted in days from the diagnosis date to the treatment start date. The diagnosis date was defined as the date when AML was first confirmed through microscopic findings by BM examination and the treatment start date was the date on which anthracycline was administered. The effects of TDT to complete remission or complete remission with incomplete hematologic recovery (CR/CRi) after the first induction, early death, and overall survival (OS) were analyzed. The TDT was analyzed as a continuous variable while also grouped into four ordinal groups of 1~5, 6~10, 11~15, and 16 or more. When the TDT was treated as a continuous variable, the restricted cubic splining method was considered. To reflect the effects of variables other than the TDT, multivariate analyses were also performed.

Results : The total numbers of patients in young AML and elderly AML were 1104 and 178. There were significant differences in etiology, MRC risk, antifungal prophylaxis, and treatment patterns between young and elderly AML. There was a substantial difference in WBC count by TDT considering log scale indicating that highly proliferative AML patients had shorter treatment delay. When the TDT was divided into 4 groups, longer TDT groups showed both a higher early death rate (P=0.0463) and worse overall survival (OS, P=0.0150) in patients less than 60 years old. The longer TDT was still associated with early death (P=0.0127) and worse OS (P=0.0015) when TDT was treated as a continuous variable. Especially, the difference in OS before and after 10 days of TDT was remarkable. In multivariate analysis, TDT was also identified as significant on early death (P=0.0325) and worse OS (P=0.0133) in younger patients, and the risk of death increased dramatically around the TDT 10. No impact of TDT was observed in elderly patients aged over 60 years old, neither in univariate or multivariate nor in any subgroup analyses.

Conclusion : The effects of TDT on survival and early deaths in young AML were identified, which were still significant in multivariate analyses considering the effects of other variables, whereas no effects in elderly AML. The current data suggest that prognostic information for patients or AML-specific features for comorbidities and actionable mutations need to be acquired within 10 days after diagnosis in young AML if possible. Further studies with diverse regional groups and patients with molecular profiling are warranted to confirm our findings.

Keyword : Acute Myeloid Leukemia, Treatment Delay, Young AML, Early Death, Survival

PP01-10

A prospective randomized comparison of high-dose cytarabine and high-dose daunorubicin in the induction chemotherapy for acute myeloid leukemia

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Background : Over the past four decades, induction chemotherapy for acute myeloid leukemia (AML) has been standardized as so-called 7+3 regimen comprising 7 days of cytarabine and 3 days of anthracycline including daunorubicin and idarubicin. To improve the treatment outcomes of AML patients, several prospective trials had been conducted with regards to the dosing schedule of induction chemotherapies. The Eastern Cooperative Oncology Group E1900 trial showed improved complete remission (CR) rate and survival with high-dose daunorubicin (90 mg/m2/d for 3 days) than standard-dose daunorubicin (45 mg/m2/d for 3 days)1. During the similar period, our group also conducted a randomized study comparing high-dose and standard-dose daunorubicin (90 vs. 45 mg/m2/d for 3 days) and confirmed superior CR rate and survival of high-dose daunorubicin.2 A randomized trial of Australian group comparing standard dose cytarabine (100 mg/m2/d for 7 days) and high-dose cytarabine (3 g/m2 q12hr for 4 days) showed improved duration of response, disease-free survival and overall survival (OS) after CR of high-dose cytarabine.3 Later, another randomized trial also revealed that high-dose cytarabine (3 g/m2 q 12hr for 4 days) was associated with higher CR rate and longer survival than standard-dose cytarabine (100 mg/m2/d for 10 days), and the benefit was significant for some subgroups of patients.4 Based on these results, the guideline from national comprehensive cancer network suggests 7+3 regimen and high-dose cytarabine-based regimen as standard induction chemotherapies in category 1 (for patients ≤45 years in high-dose cytarabine). To optimize the induction treatment of AML, we designed a randomized study comparing high-dose cytarabine and high-dose daunorubicin for newly diagnosed AML patients.

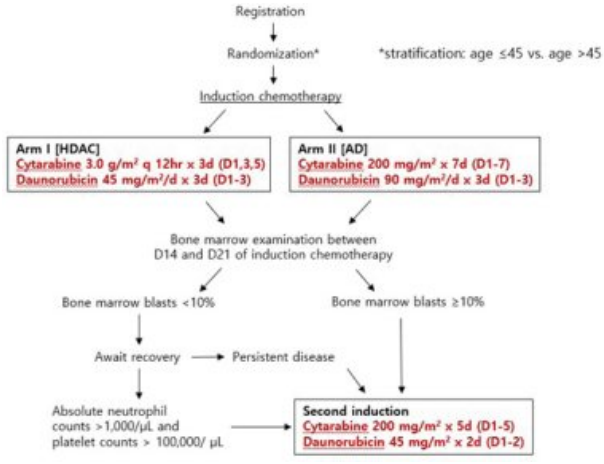
Method : The patients with previously untreated AML who are ≤60 years old and eligible for intensive induction chemotherapy excluding acute promyelocytic leukemia or AML with BCR-ABL gene rearrangement have been recruited in the study. Patients are randomized to one of the two induction treatment arms; high-dose cytarabine plus daunorubicin ([HDAC], cytarabine 3.0 g/m2 q12hr on days 1, 3, 5 plus daunorubicin 45 mg/m2/day on day 1-3) or cytarabine plus high-dose daunorubicin arm ([AD], cytarabine 200 mg/m2/day on day 1-7 plus daunorubicin 90 mg/m2/day on day 1-3). At random assignment, patients are stratified according to their age (Figure). Patients who achieve CR receive consolidation chemotherapy or can proceed with hematopoietic cell transplantation (HCT) based on their genetic risk. The study was designed as a sin-

gle-center, non-blind, two-arm randomized prospective controlled trial and plans to expand into a multicenter study. The primary endpoint is event-free survival (EFS, time from registration to induction failure, relapse, or death), and the secondary endpoints include CR rate, cumulative incidence of relapse, regimen-related toxicities, and OS.

Results : From March 2018, 103 patients were enrolled in the study; 48 in HDAC and 46 in AD arm. The median age was 49 (range, 16-60) and 61 patients were male (59.2%). Of 103 patients, nine secondary AML were included, and 8 patients showed complex chromosomal abnormalities. FMS-like tyrosine kinase 3-internal tandem duplication mutations were detected in 18 of 98 (18.4%) evaluable patients. Overall, 75 and 2 patients achieved CR and CR with incomplete hematologic recovery, and 47 and 2 patients proceeded with allogeneic and autologous HCT, respectively. Eighteen patients died, and 2 died within 30 days from randomization.

Conclusion : We are currently conducting a randomized controlled trial for newly diagnosed AML patients comparing two induction chemotherapeutic regimens; high-dose cytarabine and high-dose daunorubicin. We expect to get insights from this study into optimal induction chemotherapy for AML patients and to reveal the relationship between genetic risk based on the mutational study and the benefits of each induction regimen.

Keyword : Acute Myeloid Leukemia, Induction Chemotherapy, High-Dose Cytarabine, High-Dose Daunorubicin



PP01-11

Quality-adjusted time without symptoms of disease and toxicity analysis of CPX-351 Vs 7+3 in older adults with newly diagnosed high-risk/secondary AML

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Background : CPX-351 (Europe: Vyxeos® Liposomal; United States: Vyxeos®), a dual-drug liposomal encapsulation of daunorubicin/cytarabine in a synergistic 1:5 molar ratio, has been approved by the EMA and US FDA for the treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes. The primary analysis of the pivotal phase 3 study (NCT01696084) that formed the basis for these approvals evaluated patients aged 60 to 75 years with newly diagnosed high-risk/secondary AML and found that, with a median follow-up of 20.7 months, CPX-351 significantly improved median overall survival (OS) vs conventional 7+3, with a comparable safety profile. Final 5-year follow-up results demonstrated that the OS benefit was maintained. To evaluate both quality and quantity of life, we conducted a Quality-adjusted Time Without Symptoms of Disease and Toxicity (Q-TWiST) analysis of the phase 3 5-year data to compare survival between patients receiving CPX-351 vs 7+3.

Method : OS for each patient was partitioned into 3 health states: TOX (time before response plus any time with a grade 3/4 toxicity), TWiST (valuable time without relapse or grade 3/4 toxicity), and REL (time after relapse). Q-TWiST gain was assessed as the mean time spent in each state weighted by its respective quality of life, represented by health utility (U; scale of 0.0 [death] to 1.0 ["perfect" health]), calculated as (UTWiST×TWiST)+(UTOX×TOX)+(UREL×REL). The base case scenario used the intent-to-treat population, any grade 3/4 toxicities, TOX and REL utility weights of 0.5, and a TWiST utility weight of 1.0. Sensitivity analyses were performed for various populations, types of toxicities, and TOX and REL utility weights. Reporting relative Q-TWiST gains, calculated as Q-TWiST gain ÷ mean OS of control arm × 100, permits the comparison of clinical benefit across populations or studies. A relative Q-TWiST gain of ≥15% is considered a clinically important difference (CID) in oncology.

Results : In total, 309 patients were randomised to CPX-351 (n=153) or 7+3 (n=156). In the base case scenario, the means difference (95% CI) for CPX-351 vs 7+3 was 183 days (60, 306) for the TWiST state, 7 days (–63, 78) for the TOX state, and 22 days (5, 38) for the REL state. The resulting means difference (95% CI) for Q-TWiST gain was 197 days (76, 319) for CPX-351 vs 7+3, and the relative Q-TWiST gain was 53.6%. Among patients who achieved complete remission (CR) or CR with incomplete neutrophil or platelet recovery (CR or CRi; CPX-351: n=73; 7+3: n=52), the means difference (95% CI) for Q-TWiST gain was 248 days (–1, 496) for CPX-351 vs 7+3, and the relative Q-TWiST gain was 39.8%. Both relative Q-TWiST gains were considerably above the standard CID of 15% for oncology. Across the various sensitivity analyses, the relative Q-TWiST gains for CPX-351 vs 7+3 varied from 48.0% to 57.6%, all remaining well above the standard CID threshold (Table).

Conclusion : Results of this post hoc analysis suggest the survival benefit with CPX-351 for patients with high-risk/secondary AML is

mostly from valuable time (TWiST), thus supporting the clinical benefit for patients. The relative Q-TWiST gains were well above what is considered CID (15%) in the cancer literature and were maintained across various sensitivity analyses, supporting the robustness of the benefit. In the absence of direct measures of quality of life, these results can be used together with the antileukaemia effect when considering treatment options for this patient population.

Keyword : Acute Myeloid Leukaemia, Chemotherapy, Relapse, Survival, Toxicity, Quality of Life

Table. Q-TWiST results.

Population	AEs	TOX utility weight	REL utility weight	Mean Q-TWiST gain (95% CI), days[a]	Relative Q-TWiST gain[b]
Base case analysis					
ITT population[c,d]	All grade 3/4 AEs	0.5*TOX	0.5*REL	197 (76, 319)	53.6%
CR+CRi analysis					
Achieved CR+CRi[e]	All grade 3/4 AEs	0.5*TOX	0.5*REL	248 (−1, 496)	39.8%
Sensitivity analyses					
ITT population[d]	All grade 3/4 AEs	0*TOX	0*REL	183 (60, 306)	49.7%
			0.5*REL	194 (71, 316)	52.6%
			1*REL	204 (81, 327)	55.6%
		0.5*TOX	0*REL	186 (65, 308)	50.7%
			0.5*REL	197 (76, 319)	53.6%
			1*REL	208 (87, 329)	56.6%
		1*TOX	0*REL	190 (59, 321)	51.7%
			0.5*REL	201 (71, 331)	54.6%
			1*REL	212 (82, 342)	57.6%
Safety population[f]	All grade 3/4 AEs	0*TOX	0*REL	177 (52, 302)	48.0%
			0.5*REL	188 (63, 312)	50.9%
			1*REL	198 (73, 323)	53.8%
		0.5*TOX	0*REL	183 (60, 307)	49.8%
			0.5*REL	194 (71, 317)	52.7%
			1*REL	205 (81, 328)	55.5%
		1*TOX	0*REL	190 (57, 323)	51.5%
			0.5*REL	200 (68, 333)	54.4%
			1*REL	211 (79, 343)	57.3%
ITT population[d]	Treatment-related grade 3/4 AEs	0*TOX	0*REL	186 (62, 310)	50.5%
			0.5*REL	197 (73, 320)	53.4%
			1*REL	207 (83, 331)	56.4%
		0.5*TOX	0*REL	188 (65, 310)	51.1%
			0.5*REL	199 (77, 321)	54.0%
			1*REL	210 (88, 332)	57.0%
		1*TOX	0*REL	190 (59, 321)	51.7%
			0.5*REL	201 (71, 331)	54.6%
			1*REL	212 (82, 342)	57.6%
Safety population[f]	Treatment-related grade 3/4 AEs	0*TOX	0*REL	180 (54, 306)	48.8%
			0.5*REL	191 (65, 316)	51.7%
			1*REL	201 (75, 327)	54.6%
		0.5*TOX	0*REL	185 (60, 309)	50.2%
			0.5*REL	196 (72, 319)	53.1%
			1*REL	206 (82, 330)	55.9%
		1*TOX	0*REL	190 (57, 323)	51.5%
			0.5*REL	200 (68, 333)	54.4%
			1*REL	211 (79, 343)	57.3%

Q-TWiST, Quality-adjusted Time Without Symptoms of Disease and Toxicity; TOX, time with any grade 3/4 toxicity before relapse; TWiST, time without relapse or grade 3/4 toxicity; REL, time after relapse; CR, complete remission; CRi, CR with incomplete neutrophil or platelet recovery; AE, adverse event; ITT, intent-to-treat.

[a]Q-TWiST gain was assessed as the mean time spent in each state weighted by its respective quality of life, represented by health utility (U; scale of 0.0 [indicates death] to 1.0 [indicates "perfect" health]) and was calculated as follows:

$Q\text{-}TWiST=(U_{TWiST}\times TWiST)+(U_{TOX}\times TOX)+(U_{REL}\times REL)$. ***All analyses used a TWiST utility weight of 1.0.***

[b]Relative Q-TWiST gain was calculated as follows: Q-TWiST gain ÷ mean OS of control arm × 100.

[c]The base case scenario used the intent-to-treat population, any grade 3/4 toxicities, TOX and REL utility weights of 0.5, and a TWiST utility weight of 1.0. Sensitivity analyses were performed for all treated patients and the intent-to-treat population, any and treatment-related grade 3/4 toxicities, and TOX and REL utility weights of 0, 0.5, and 1.0. A variation of the base case scenario was also performed for the subset of patients who achieved CR+CRi.

[d]The ITT population included all patients who were randomised to induction treatment (CPX-351: n=153; 7+3: n=156).

[e]Patients achieving remission (CPX-351: n=73; 7+3: n=52).

[f]The safety population contained all patients who received ≥1 dose of study treatment (CPX-351: n=153; 7+3: n=151).

PP01-12

Children acute promyelocytic leukemia in the southern Vietnam: The 10 year experience

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Background : Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML), historically characterized by harboring specific genetic abnormality on PML/RARα related to outstanding outcomes with all-trans retinoic acid (ATRA) and arsenic trioxide, and a tendency to life-threatening coagulopathy and early deaths. Due to rare incidence in children, many of the knowledge and treatment to this population are still referred from that of from that of adults. However recent publications show many different characteristics between pediatric and adult APL. In this retrospective study, we aimed to provide comprehensive information in term of diagnostic approach and management of pediatric APL in our center.

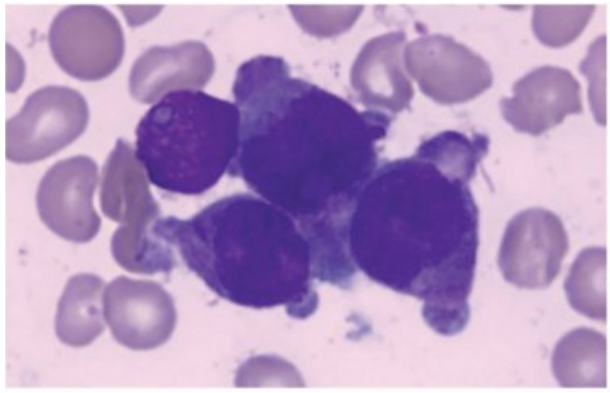
Method : We retrospectively reviewed the medical records of children (age < 16 years) diagnosed with APL in our pediatric hematology department between May 2010 and May 2020.

Results : Thirty one patients were included in the study and mean follow-up period was 42.7 months. The median age was 7 years (range from 3 to 15), male prominence with ratio of 1.82. Hemorrhage and hepatomegaly were the most common signs at admission. Anemia and thrombocytopenia were observed in all patients with various severity. Leukocytosis (>10 x10^9/L) was found among 38.7% of the patients at presentation, corresponding to high-risk group according to Sanz classification, median WBC counts was 4.91 x 10^9/L which seems higher than that of adults. Only 16% of total patients were in low-risk group. Abnormalities in coagulation tests were found in 64.5% of the patients, and it was mainly mild prolongation of prothrombin time that was irrelevant to clinical manifestations. D-Dimer was elevated in all patients. Breakpoint of bcr3 accounted for 22.6%. There was strong correlation between bcr3 and leukocytosis (p=0.029). All patients were treated with induction with ATRA+Anthracycline during induction, two cycles of consolidation with anthracycline + cytarabine and maintenance with ATRA + MTX + Purinethol for 2 years. Early death (16.1%) was the only cause of mortality during follow-up period. All patients who completed the induction regimen achieved hCR. After consolidation, 95.6% of the patients achieved mCR, and 94.7% after maintenance. Only 6.5% of the patients relapsed. 5 year-OS and DFS were 83.9% and 70.1% respectively. Severe complications (intracerebral hemorrhage and infarction, retinoic acid syndrome) were only encountered in induction phase. Infections and elevated liver enzymes were found fre-

quently in all treatment phase. The pseudotumor cerebri syndrome was found in 12.9% of the patients without significant sequela.

Conclusion : Pediatric APL is a distinct entity with many different clinical and biological characteristics from that of adults, with a tendency to have worse prognosis. However, the efficacy of ATRA-Anthracycline regimen is still very promising, thereby it's reasonable for those who cannot approach to new agents, although the long-term effects of therapy remain unclear and early death is a challenge.

Keyword : Acute Promyelocytic Leukemia, Children, ATRA, Anthracycline



PP01-13

Phospholipase C beta 2 protein overexpression is a favorable prognostic indicator in newly diagnosed normal karyotype acute myeloid leukemia

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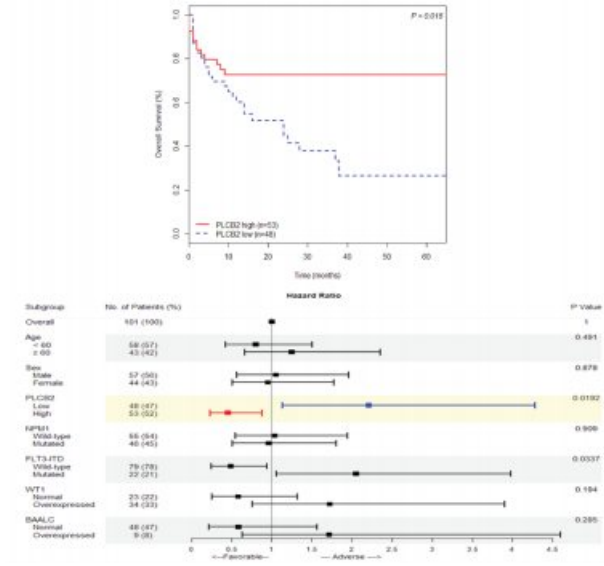
Background : Phospholipase C beta 2 (PLC-β2) regulates various essential functions in cell signaling, differentiation, growth, and mobility. We investigated the clinical implications of PLC-β2 protein expression in newly diagnosed normal karyotype acute myeloid leukemia (NK-AML).

Method : The PLC-β2 expression status in bone marrow tissues obtained from 101 patients with NK-AML was determined using semiquantitative immunohistochemistry (IHC). IHC results were compared with those for known prognostic markers.

Results : Using a cutoff score for positivity of 7.0, the PLC-β2 overexpression group showed superior overall survival (OS) (72.6% vs. 26.5%; P=0.016) and low hazard ratio (HR) (0.453; P=0.019) compared with the PLC-β2 low-expression group. The PLC-β2 overexpression group showed no significant gain in event-free survival (50.6% vs. 43.0%, P=0.465) and HR (0.735; P=0.464). Among the known prognostic markers, only FLT3-ITD positivity was associated with a significantly low OS and high HR.

Conclusion : PLC-β2 overexpression was associated with favorable OS in NK-AML patients. Our results suggest that PLC-β2 expression assessment using IHC allows prognosis prediction in NK-AML.

Keyword : Phospholipase C Beta 2 Protein, Normal Karyotype Acute Myeloid Leukemia, Prognosis



PP01-14

Real time PCR based quantitative evaluation of WT1 gene expression from diagnosis to end of induction in acute myeloid leukaemia

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Background : Various published studies have stated that overexpression of the gene Wilms tumor 1 (WT1) has a poor prognostic marker in acute myeloid leukemia (AML). However, there has been a

paucity of expression studies of WT1 gene expression in the Indian scenario. The study tried to understand the pattern of WT1 gene expression among therapy-naive cases of AML. Hence the objective of the study was to evaluate Real-time PCR based quantitative evaluation of WT1 gene expression at the time of diagnosis and at the end of induction

Method : A total of 51 cases of AML having blast count more than equal to 20% in peripheral blood or bone marrow and 5 normal healthy controls were enrolled for this study. Bone marrow aspirates samples were taken at diagnosis (labeled as Day-0) and then post-induction (labeled as Day-28). Hematological workup for counts and flowcytometry based phenotypes was done on both occasions. RNA was extracted out from all the samples. WT1 expression of each sample was done using quantitative real-time PCR, and was normalized against endogenous control gene HBG2, GAPDH, and β2microgolbulin.

Results : The expression of WT1 gene was high at the time of diagnosis and was reduced to significant levels at the end of induction in 43/51(84%) cases where the blast count also reduced to≤5%. However, among cases 8/51(16) where there was no morphological remission its expression increased when compared with normal internal control.

Conclusion : WT1 gene expression along with blast count can act as a good biomarker for assessment of response to therapy. The expression significantly correlated with the blast count at diagnosis and at the end of induction remission.WT1 gene expression may be a potential marker for measurable disease assessment.

Keyword : AML, WT1 Gene, Real Time, MRD

PP01-15

Infectious complications of venetoclax-based chemotherapy in acute myeloid leukemia: Baseline for selecting proper antimicrobial prophylaxis

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Background : Venetoclax (VEN) in combination with a hypomethylating agent or low-dose cytarabine has emerged as a promising therapeutic option for patients with acute myeloid leukemia (AML). However, infectious complications such as bloodstream infections (BSIs) and invasive fungal disease (IFDs) associated with this combination has not been thoroughly evaluated. The objective of this study was to investigate the incidence and the impact of infectious complications.

Method : From February 1st to December 10th, 2020, adult patients treated with VEN-based chemotherapy for newly diagnosed and relapsed/refractory AML were included in this retrospective cohort study. We performed descriptive analysis and multivariate analysis using the logistic regression model to identify independent factors of BSIs and IFDs respectively.

Results : There were a total of 28 newly diagnosed and 75 relapsed/refractory AML patients including post allogenic transplant relapse. The median age was 60 years (interquartile range (IQR); 45.5 to 68.5) and the median treatment cycle was 2 (IQR; 1 to 3). During the study period, the prophylaxis protocol of this institute was fluconazole 400mg/D without antibacterial agents. Among 103 patients, 99.0% (102/103) of patients were administered antifungal agents; 84.3% (86/102) of the intended antifungal prophylaxis, and 15.7% (16/102) of the empirical or targeted anti-mold antifungal agent under prior IFDs or prolonged neutropenic fever. Twelve cases (11.7%) of IFI occurred during the median 2nd cycle (IQR, 1 to 2). Invasive pulmonary aspergillosis was developed in 12 patients, of which 91.7% (11/12) patients were under intended fluconazole prophylaxis. The incidence of IFDs was significantly higher in the patients using steroids within 1 month of chemotherapy (Odds ratio (OR); 21.04, 95% Confidence interval [CI]; 2.57-174.57, p<0.01), in secondary or therapy-related than de novo AML (OR; 4.56, CI; 1.07-18.60, p=0.04) and showed increasing trends in relapsed/refractory than previously untreated AML (OR; 4.14, CI; 0.58-29.41, p=0.15) in multivariate analysis. There were 33 patients (32.0%) with BSI which included 30.3% (10/33) of breakthrough BSI that occurred while using an empirical or targeted antibacterial agent. Gastrointestinal origin due to mucosal injury was the most predominant site of BSI (26/33, 78.8%) followed by catheter-related infection (4/33, 12.1%) and primary BSI (3/33, 9.1%). Overall mortality was 34.9% (36/103) and infection (IFDs or BSIs)-related mortality was 8.7% (9/103). IFDs-related mortality (5/12, 41.7%) was higher than that of BSIs (4/33, 12.1%).

Conclusion : The incidence of IFDs and BSIs were 11.7% and 32.0%, respectively. Patients with using steroid, secondary or therapy-related AML, and relapsed/refractory AML status are identified as a high-risk group of IFI and they may need a mold-active antifungal agent rather than fluconazole. BSI would be tolerated and manageable with appropriate empirical therapy. Future larger studies are needed to clarify the risk group and the impact of IFI and BSI.

Keyword : Venetoclax, Acute Myeloid Leukemia, Invasive Fungal Infections, Bacteremia, Prophylaxis

PP01-16

The application of the updated 2016 WHO classification of AML in pediatric patient cohort: A single center study

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Background : The prevalence of acute myeloid leukemia (AML) is estimated to be 5.3-6.7% in the Korean pediatric population with cancer. As the updated 2016 WHO classification on AML diagnosis has incorporated genomic information, newly introduced mutations in several genes have gained definitive diagnostic entities from previous provisional ones. Herein, we prospectively applied the 2016 WHO classification to estimate the prevalence of AML with mutated NPM1 and AML with double CEBPA mutations in Korean pediatric patients.

Method : All pediatric AML patients who were newly diagnosed between the year 2017 and 2020 in Yonsei Cancer Center were enrolled in this study. Mutational spectrums on AML associated genes (n=497) were extensively profiled using next-generation sequencing panel on bone marrow samples. The clinical significance of somatic variants identified in the patients was interpreted by the AMP/ACMG/CAP guideline through discussion between pediatricians, hematopathologists, and geneticists. Patients' survival according to genetic mutation was analyzed.

Results : A total of 16 pediatric AML patients were newly diagnosed in the study period with a mean age of 8.4 years-old (range: 19 months-old ~ 15 years-old). 25% (n=4) of all patients harbored bi-allelic mutations in CEBPA. Among four patients with CEBPA mutations, karyotyping results in 3 patients were abnormal, suggesting a differential prognostic role in pediatric patients compared to adult patients. Mutation types were various including frameshift (n=3), inframe insertion (n=3), nonsense (n=1), and inframe deletion (n=1) mutations. In contrast, only one patient (6.25%) was revealed to possess NPM1 mutation. Two patients with CEBPA mutation were survived after hematopoietic stem cell transplantation, and the others and a patient with NPM1 mutation are undergoing chemotherapy. Most other patients (n=10) presented variants with strong/potential(tier1/2) clinical significance(tier 1/2) in various genes, including FLT3, GATA1, KIT, KRAS, NF1, PHF6, and PTPN11. 2 patients with KRAS mutation died related to treatment and hyperleukocytosis related complication.

Conclusion : The application of the updated 2016 WHO classification of AML in pediatric patient cohort provided additional diagnostic yield for approximately 30 %. More accurate risk stratification based on the upgraded WHO guideline with genomic profiling will benefit pediatric patients in terms of evidence-based personalized medicine.

Keyword : Acute Myeloid Leukemia, Classification, NPM1, CEBPA

PP01-17

Comparison of genetic mutations harbored by myeloid sarcoma and leukemic cells of the bone marrow in a patient treated with decitabine

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Background : Myeloid sarcoma (MS) is an uncommon hematological malignancy. Risk stratification of acute myeloid leukemia (AML) through a combination of chromosomal analysis and evaluation of the mutational profile through next-generation sequencing (NGS) is important. Although many studies have been conducted on the molecular profile of AML, little is known about the myeloblasts in MS. Here, we report a case of recurrence in bone marrow (BM) in an isolated MS patient after treatment with decitabine.

Method : Decitabine was administered intravenously in accordance with the standard regimen of 20 mg/m2 at 4-week intervals to our patient (a 65-year-old woman) who was diagnosed with MS located in front of the vertebra; the tumor was positive for CD34, CD117, and myeloperoxidase. Target sequencing using Illumina MiSeqDx was performed on formalin fixed paraffin-embedded MS tissues (obtained at the time of initial diagnosis) and cellular components in BM aspirate samples (obtained at relapse). The following 43 genes were analyzed and compared between samples: ASXL1, ATRX, BCOR, BCORL1, BRAF, CALR, CBL, CSF3R, DNMT3A, ETV6, EZH2, FLT3, GATA1, GATA2, HRAS, IDH1, IDH2, JAK2, JAK3, KDM6A, KIT, KRAS, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PHF6, PTPN11, RAD21, RUNX1, SETBP1, SF3B1, SMC1A, SMC3, SRSF2, STAG2, STAT3, TET2, TP53, TP53, WT1, and ZRSR2.

Results : No pathological findings were observed in the peripheral blood and BM samples. The patient obtained a partial response with decitabine treatment, but the disease was found to have progressed after ~9 months. The recurrent lesions disappeared completely in response to an intensive cytotoxic chemotherapy regiment. Approximately 7 months later, MS tumors reappeared in the paravertebral space and pleural wall, and an increase in blast percentage was observed in the BM, so the patient was initiated on intensive chemotherapy (currently underway) and is maintaining a complete response. A comparison of the NGS results in the MS tissue (April 2019) and BM samples (November 2020) revealed the presence of ASXL1 c.2088_2089ins and the TET2 c.5650A>G in both samples. The missense mutation, KRAS c.38G>A was only found in the MS tissue samples, but the allele frequency was very low. KIT c.1328G>A was also identified only in the MS tissue, although its clinical significance remained unknown. Additionally, TET2 c.4044+1G>A (splice mutant) and DNMT3A c.1903C>T (missense mutation), which were not identified in MS tissue, were reported in BM samples obtained at relapse.

Conclusion : We have confirmed that decitabine can effectively treat isolated MS, although the duration of the response was not long. There might be a possibility that the ASXL1 c.2088_2089ins mutation found in both MS and BM samples may be the first driver mutation that induces leukemogenesis in this case. In addition, the results of NGS indicate that alteration of the RAS pathway may contribute to the extramedullary expansion of the myeloblasts. The TET2 and DNMT3A mutations found in BM specimens obtained at relapse following failure of decitabine treatment—which were not present in the MS samples before decitabine treatment—suggest that these mutations may be responsible for the development of resistance against decitabine.

Keyword : Myeloid Sarcoma, Acute Myeloid Leukemia, Decitabine, Next-Generation Sequencing, Mutation

Table 1. Results of target sequencing in myeloid sarcoma and myeloid leukemia at relapsing.

Gene	Myeloid sarcoma (initial diagnosis)			Leukemic cells in bone marrow		
	DNA change	Type	VAF (%)	DNA change	Type	VAF* (%)
KRAS	c.38G>A	Missense	1.1	No mutation		
KIT	c.1328G>A	Missense	30.51	No mutation		
ASXL1	c.2088_2089ins	Frameshift	21.3	c.2088_2089ins	Frameshift	20
TET2	c.5650A>G	Missense	31.44	c.5650A>G	Missense	22
				c.4044+1G>A	splicing	20
DNMT3A	No mutation			c.1903C>T	Missense	7

*VAF, variant allele frequency

PP01-18

Incidence of differentiation syndrome (DS) and other complications in acute promyelocytic leukaemia (APML) – A single centre retrospective observational study

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Background : DS formerly known as retinoic acid syndrome, is the main life threatening complication of therapy with differentiating agents (all-trans retinoic acid [ATRA] or arsenic trioxide [ATO]) in patients with acute promyelocytic leukemia (APML) . Hyperleukocytosis frequently but not always accompanies DS and often precedes the clinical manifestations of DS. DS leads to a systemic inflammatory response syndrome–like syndrome. The most common problem seen with DS is acute respiratory distress caused by diffuse interstitial pulmonary infiltrates, which appear as a pleural effusion and pulmonary infiltration on chest imaging. Other features that may indicate DS include fevers, weight gain, pericardial effusions, acute renal insufficiency, hyperbilirubinemia, or peripheral edema. This clinical picture may be be due to cellular migration, endothelial activation, release of interleukins, and vascular factor responsible for tissue damage. Severe DS can be fatal. Various APML studies state percentage of DS as stated, Zhu 2013 (24.8%), Iland 2012 (13.7%) Abaza 2017(11.2%), Dai 2009 (3.3%) Platzbecker2016 (14.3%) , Lococo 2013 (12.4%). Hence the aim of our study was to estimate the incidence, characteristics, severity of DS and other complications in patients receiving induction therapy for APML at our centre.

Method : This is a single centre retrospective study conducted in patients diagnosed with APML (confirmed by Flowcytometry and FISH for PML-RARA fusion) who got admitted at our centre for induction chemotherapy over a period from July 2019 to December 2020. Risk stratification was done as per Sanz criteria. Intermediate and low risk group were treated as per Lococo protocol using ATRA and ATO while high risk group were treated with APML 4 protocol using idarubicin, ATO and ATRA. For prophylaxis of DS prednisolone 0.5mg/kg was started from day 1 of induction till end of induction. Patients were initiated on dexamethasone 10 mg every 12 hours on developing differentiation syndrome until the disappearance of signs and symptoms for a minimum of 3 days. The outcome parameters included incidence, severity of differentiation syndrome, duration of steroid use, complications due to medications (ATRA, ATO, Idarubicin and steroid) like Idiopathic Intracranial hypertension (IIH), intracranial bleed, myelosuppression, infections, hyperglycemia, treatment interruptions, critical care stay during induction therapy and any other complications.

Results : 13 patients were diagnosed as APML, out of which 2 patients were non-compliant to treatment, 2 patient died before initiating treatment. The incidence of differentiation syndrome was 66% among APML induction patients (n=6/9). The median duration from onset of induction therapy to differentiation syndrome was 6 days (1-17). Incidence of differentiation syndrome in low and intermediate risk patients was 62.5% (n=5/8) while of differentiation syndrome in high risk group was 100% (n=1/1). Prophylaxis for DS was used in 2 patients, out of which one patient developed differentiation syndrome, Both the patients developed IIH which was attributed to prednisolone and ATRA, leading to treatment interruptions and prolonged hospitalization. Hence prophylactic prednisolone was not used in other APML patients. Therapeutic dexamethasone was used in 55 % patient (n=5/9) with a median duration of 5 days (3-20) while tapering dose of prednisolone post dexamethasone was used in 44% (n=4/9) with a median duration of 11.5 days (9-18). Median duration of steroid use was 14 days (3-25). Overall steroids were used in 77% (n=7/9). 23% of the patients with APML (n=3/13) required cytoreductive agents like hydroxyurea to control the leucocytosis in addition to the induction therapy. The incidence of DS was higher in high risk group (100% n=1/1). In low/intermediate risk the incidence was also significantly more 62.5%, n=5/8. Complications related to treatment were ATRA and steroid induced IIH in 22% (n=2/9), QTc prolongation in 11% (n=1/9), ATO induced myelosuppression in 44%(n=4/9), febrile neutropenia in 44% (n=4/9), catheter associated blood stream infection (CLABSI) in 11% (n=1/9), lower respiratory infections in 33% (n=3/9), otitis externa in 11% (n=1/9). Steroid related hyperglycemia in 55% (n=5/9). 44% (n=4/9) had treatment interruptions in induction therapy. Patients requiring ICU stay (for various reasons like hypoxia requiring non invasive ventilator support, septic shock secondary to febrile neutropenia, etc) were 44% (n=4/9).. Bone marrow morphological

remission was achieved in 100% (n=9/9) patient at end of induction.

Conclusion : The incidence of DS is remarkably higher in population who received treatment at our centre 66% compared with reported literature. Prophylactic prednisolone use did not prevent DS and was associated with complications like IIH, prolonged hospital stay and treatment interruption. It has to be confirmed by further randomized studies. Complications other than DS were seen in 77% (n=7/9) and 44% patients required ICU stay.

Keyword : APML, Differentiation Syndrome, ATRA, ATO

PP01-19

Laboratory profile of acute myeloblastic leukemia promyelocytic type patients in Sardjito Hospital, Indonesia

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Background : Acute myeloblastic leukemia promyelocytic type is hematology malignancy with dual characteristics. Patients with acute myeloblastic leukemia promyelocytic type mostly manifest with bleeding. This condition resembles with disseminated intravascular coagulation. Bone marrow examination needed to diagnose this condition. Unfortunately because of resource limitations in Indonesia, only tertiary hospitals could do this examination. This study aims to know the laboratory characteristics of patients diagnosed with acute myeloblastic leukemia promyelocytic type through bone marrow examination.

Method : This study used a retrospective design. All data were obtained from the medical record and laboratory data. This study includes all patients in 2018 who underwent bone marrow puncture examination. Exclusion criteria were incomplete data

Results : One thousand one hundred six patients were included in this study with 180 patients (16.3%) were diagnosed with acute myeloblastic leukemia. Only 23 patients (12.78%) were diagnosed with acute myeloblastic leukemia promyelocytic type. Eighteen patients (78.26%) were undergoing a coagulation problem with bleeding manifestation. Hemostasis profile showed prolonged prothrombin time in 15 patients (65.22%), 19 patients (82.61%) have prolonged activated partial thromboplastin time, 18 patients (78.26%) have a low level of fibrinogen, and 17 patients (73.91%) have low thrombocyte counts.

Conclusion : The majority of acute myeloblastic leukemia promyelocytic type patients showed coagulation abnormality with bleeding manifestation. The majority of treatment management should focus on bleeding prevention

Keyword : Acute Myeloblastic Leukemia, Promyelocytic, Leukemia, Malignancy

PP01-20

Infection profile and outcomes of adult acute leukemia patients developing chemotherapy-associated febrile neutropenia

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Background : Chemotherapy induced myelosuppression is one of the major dose-limiting toxicities of systemic chemotherapy. It results to dose reductions and treatment delays hence compromising treatment-efficacy and long-term clinical outcomes. Moreover, the burden of these complications to patients as well to their caregivers could be economically troublesome and would require substantial resource allocation. This study determined the infection profile and outcomes of adult acute leukemia patients developing chemotherapy-associated febrile neutropenia and identified the antimicrobial sensitivity patterns of the bacterial blood isolates.

Method : This was a single-center retrospective study which reviewed medical records of 100 adult acute leukemia patients who developed chemotherapy-associated febrile neutropenia. Descriptive statistics was used to summarize demographic and clinical characteristics. Independent Sample T-test, Mann-Whitney U-test and Fisher's Exact/Chi-square test determined difference of mean, rank and frequency between AML and ALL. STATA 13.1 was used for data analysis.

Results : There were 106 microbiological isolates. Most commonly isolated were Escherichia coli (ESBL-48.39%), Klebsiella pneumoniae (ESBL-61.90%) and coagulase-negative Staphylococcus (CoNS). Organisms were isolated from blood (57.55%), sputum (15.09%), urine (12.26%), and stool (7.55%). More ALL patients had Klebsiella pneumoniae isolates (p-value: <0.001). Presence of Carbapenemase-producing Klebsiella was statistically significant in the mortality group (p-value: 0.018). Susceptibility patterns show: (1) E. coli susceptible to Carbapenems, Cefepime and Aminoglycosides (2) K. pneumoniae to Carbapenems and Aminoglycosides (3) CoNS to Vancomycin.

Conclusion : This study emphasized the need to identify the most commonly isolated pathogens to aid physicians decide on the appropriate empiric antibiotic/s to use during chemotherapy-associated febrile neutropenia to avoid serious morbidity and mortality. Proper coordination between clinician and microbiological laboratory for prompt pathogen identification and monitoring of microbial susceptibility patterns is vital to provide the best treatment option for this patient population.

Keyword : Febrile Neutropenia, Acute Leukemia, Chemotherapy

PP01-21

Variantion and relationship of homo sapiens acute myeloid leukemia homo sapiens cDNA, mRNA sequence

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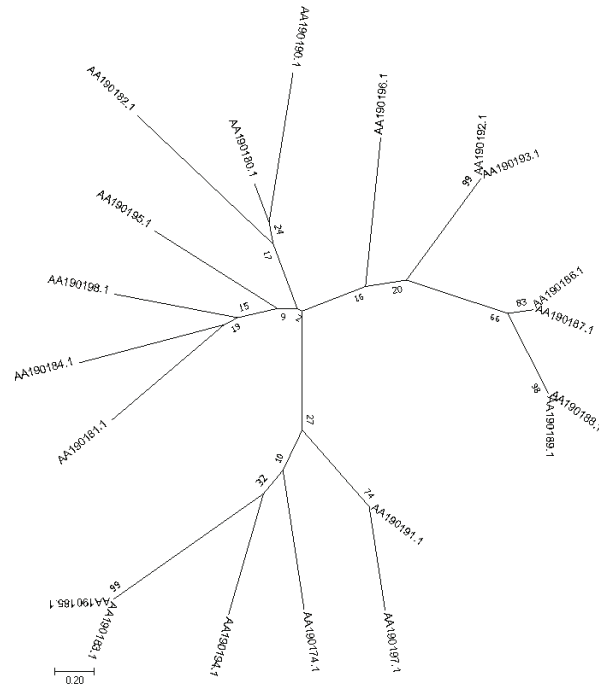
Background : Acute Myeloid Leukemia (AML) is the most common acute leukemia affecting adults. Older people are more likely to develop AML than younger adults or children. However, AML is the most common type of leukemia diagnosed during infancy. About 15 to 20 percent of cases of acute childhood leukemia and 80 percent of cases of acute adult leukemia are AML. AML results from acquired changes in the DNA (genetic material) of a developing marrow cell. Once the marrow cell becomes a leukemic cell, it multiplies into 11 billion or more cells. These cells, called "leukemic blasts," do not function normally. However, they grow and survive better than normal cells. DNA arrays capable of simultaneously measuring expression of thousands of genes in clinical specimens from affected and normal individuals have the potential to provide information about superior characteristics gene from organism. Genes can be used as markers for cell recruitment, and activation of immunoregulatory molecules. This study aims to evaluate the variantion and relationship of homo sapiens acute myeloid leukemia homo sapiens cDNA, mRNA sequence.

Method : Data obtained from 20 accession of acute myeloid leukemia Homo sapiens cDNA, mRNA sequence on secondary data form on https://www.ncbi.nlm.nih.gov/ and 17 selected articles journal evaluated by searching in PubMed, EMBASE, and the Cochrane Library database that have been carried out in the last 10 years (2011-2020). The phylogeny analysis of variations and relationships of DNA sequences Constructed with Neighbor Joining by Bootstrap 1000x using MEGA 7.0 software.

Results : Based on the analysis of variations and relationships, it is known that on the dendogram, 20 specimens are divided into 2 main clusters, namely cluster A consisting of 14 specimens and cluster B consisting of 6 specimens. This grouping is based on the existence of a similar genetic makeup equation with a high bootstrap value indicating the degree of kinship between specimens and the strength of the philogenous trees. Specimens that are in the same sub-cluster show a degree of close kinship. On the other hand, specimens from different sub-clusters display distant kinship. Clustering was achieved on the basis of differences in expression levels across individual specimens.

Conclusion : It can be concluded that the variation and relationship of homo sapiens acute myeloid leukemia homo sapiens cDNA, mRNA sequence have highly variation. Information about this kinship can be used as an informative source in the assembly of superior genes in living cells of human.

Keyword : Variantion, Relationship, Homo Sapiens, Acute Myeloid Leukemia, cDNA, mRNA



PP01-22

Src family kinase inhibitor bosutinib and dasatinib enhances differentiation of acute promyelocytic leukemia cell line induced by combination of all-trans-retinoic acid

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Background : The acute promyelocytic leukemia (APL) has been treated with all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) for decades. Emerging evidence has implicated Src family kinase (SFK) as regulator of proliferation and survival of myeloid lineage cells. Our group studies showed that inhibition of SFK resulted enhancement of retinoic acid (RA)-induced myeloid differentiation. Recently, we founded the efficacy of the SFK inhibitor bosutinib and dasatinib on RA-induced differentiation. In this study, we investigated that SFK inhibitor enhances RA-induced differentiation with ATRA, comparing with ATRA and ATO.

Method : In order to induce differentiation in different settings, NB4 cells were treated with ATRA in the absence or presence of SFK inhibitors. NB4 APL cells were treated for 72 hours with following

settings; (1) untreated control; (2) ATRA 10 uM alone; (3) ATO 0.5 uM alone; (4) PP2 10 uM alone; (5) bosutinib 0.5 uM alone; (6) dasatinib 0.5 uM alone; (7) ATRA plus ATO; (8) ATRA plus PP2; (9) ATRA plus bosutinib; (10) ATRA plus dasatinib. The dose of each experimental agent was decided according to previous in vitro and in vivo data. Flow cytometry was performed for analysis of CD11b expression in cells. These results were confirmed in morphologic analysis by Wright stain and NBT staining.

Results : To determine the effect of SFK inhibitor (PP2, bosutinib, or dasatinib) to enhance differentiation of NB4 cells induced by combined ATRA, we examined CD11b expression by flow cytometry. Treatment of NB4 cells with 10 uM of ATRA alone, 0.5 uM of ATO alone, 10 uM of PP2 alone, 0.5 uM of bosutinib alone, or 0.5 of dasatinib alone for 72 hours resulted in only 15%, 4.6%, 6.6%, 11.8%, or 7.9% of CD11b-positive cells, respectively. Co-treatment with ATRA plus ATO resulted in enhancement of CD11b-positive cells (19.5%, respectively). However, SFK inhibitor combined with ATRA resulted in significant enhancement of CD11b-positive cells. Co-treatment with PP2 plus ATRA, bosutinib plus ATRA, or dasatinib plus ATRA resulted in 56.8%, 29.5%, or 54.2% of CD11b-positive cells, respectively. The synergistic effect of SFK inhibitor combined with ATRA was more significant than that of ATRA combined with ATO.

Conclusion : Bosutinib and dasatinib are US Food and Drug Administration (FDA)-approved compound that was developed as an inhibitor of ABL and SFK. Some investigators demonstrated that these SFK inhibitors promotes ATRA-induced differentiation of AML cells and suggested this combination may beneficial in the treatment of APL and non-APL AML. Our data showed that bosutinib and dasatinib enhanced RA-induced myeloid differentiation when combine with ATRA. The synergistic effect of SFK inhibitors and ATRA on NB4 cell differentiation was more effective than combined ATRA and ATO. These findings suggest the combination of FDA approved SFK inhibitors, such as bosutinib and dasatinib, may be beneficial for the treatment of APL with a combination of ATRA.

Keyword : Src Kinase, Cell Differentiation, Acute Promyelocytic Leukemia, All-Trans-Retinoic Acid , Arsenic Trioxide

PP01-23

Study of anti-leukemic activity of ethanolic extract of zingiber officinale in a leukemic rat model

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Background : Leukemia is a malignant blood disease caused by the overproduction of a large number of immature blood cells that enter the peripheral blood. Because of the side effects associating the chemotherapy of leukemia, the identification of medicinal herbs, therefore, remains to be an attractive goal to treat leukemia.

Red ginger (Zingiber officinale) has been prescribed as an analgesic for antidiabetic and anti-inflammatory in Indian traditional medicine. Aim of study was to evaluated anti-leukemic activity of ethanolic extract from dried red ginger (red ginger extract [RGE]) in a leukemic rat model

Method : In this study, leukemia was experimentally induced in male Wistar rats by 7, 12-dimethyl benza[a]anthracene (DMBA) and rats were treated with RGE.

Results : Application of RGE extract successfully recovered weight loss and restored the normal total WBC, lymphocyte and neutrophil counts in a leukemia rat model compared to either the DMSO treated rats or the leukemic rats before applying the RGE. Moreover, RGE decreased the percentage of blasts by two thirds in leukemic rats. By quantitative real-time PCR, sphingosine-1-phosphate receptor-1 mRNA expression in lymphocytes was downregulated in leukemic rats, and this downregulation was significantly alleviated by treating the leukemic rats with RGE.

Conclusion : This study investigates anti-carcinogenic effect of RGE and highlights the possibility of its use in leukemia treatment to avoid the negative side effects of the usual therapy.

Keyword : Anti-leukemic Activity, Red Ginger Extract, Anti-carcinogenic, Ethanolic Extract

PP01-26

Role of hydro-ethanol extract of citrullus colocynthis seed in benzene-induced toxicity of acute myeloid leukemia mice

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Background : Citrullus colocynthis is one of the folk medicinal plants found in India, Bangladesh, and Sri Lanka. C. colocynthis contains large amounts of phenolics and flavonoids that have antioxidant activity in its seed extract.

Objective: In this study, our research aims to analyze the chemopreventive effect of Cucurbitacin, especially a natural phenol catechin present in the seed hydro-ethanol extract of C. colocynthis on acute myeloid leukemia (AML) mice.

Method : The total seed extract was partitioned and analyzed on thin-layer chromatography (TLC) plate. The yellow-brown material of spot 2 was analyzed and identified as catechin and tested for their chemopreventive potential on AML mice model. Hematological parameters (Hb %, red blood cell, and white blood cell count), expression of cell cycle regulatory proteins, and DNA fragmentation analysis were performed.

Results : After treatment of benzene-exposed mice with the major flavonoid compound, namely catechin, the above parameters

increase significantly (P < 0.01). There was an upregulation of p53 and p21, caspase 11 myeloperoxidase, bcl2, and CYP2EI in catechin-treated group. DNA was less fragmented in flavonoid-treated group compared to that of control (P ≤ 0.01). The present study indicates that the secondary metabolites of C. colocynthis seed extract, comprising flavonoid catechin as major constituents, have modulatory effect in cell cycle deregulation and hematological abnormalities induced by benzene in mice.

Conclusion : Present data suggest that catechin from C. colocynthis extract effectively attenuates benzene-induced secondary AML in bone marrow, which is likely associated with the anticell cycle deregulation properties of this flavan-3-ol.

Keyword : Benzene-Exposed Mice, Citrullus Colocynthis, Acute Myeloid Leukemia Mice

PP01-27

Effect of madhuca longifolia on etoposide action in acute myeloid leukemia

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Background : Madhuca longifolia leaves has been used as a traditional medicine for a long history in developing countries and showed significant free radical-scavenging activities, antioxidant activities and anti-leukemia effects in experimental rats. The effect of Madhuca longifolia , a promising anticancer agent, on the action of certain cytostatic drugs, including etoposide, is not well understood. Aim of present study was to investigate the effect of Madhuca longifolia leaves extract (MLLE) on etoposide action in leukemic and normal bone marrow cells in vivo conditions.

Method : The experimental model used was Wistar albino rats with a transplantable acute promyelocytic leukemia. Leukemia was induced by intravenous injection of WAML (Wistar albino Myeloid Leukemia) cells. MLLE was administered by oral gavage (100 mg/kg) for 27 consecutive days and etoposide was used intraperitoneally (50 mg/kg) for the last three days of the experiment. Control leukemic and healthy rats received the solvent for the tested compounds only.

Results : MLLE significantly reduced the number of leukemic promyelocytes in the bone marrow of WAML rats in comparison to the leukemic control. Treatment with MLLE plus etoposide led to a decrease in the number of promyelocytes to the normal values occurring in healthy individuals. In contrast, the percentage of the normal precursors of granulocytes ($p < 0.001$) and erythrocytes ($p < 0.001$) increased significantly in comparison to the group treated with only etoposide.

Conclusion : The results of the study indicate that MLLE may protect healthy myeloid cells against the cytotoxic effect of etoposide and potentiate the antileukemic action of this anticancer drug.

Keyword : Etoposide, Madhuca Longifolia Leaves, Acute Myeloid Leukemia

PP01-28

Biological importance and therapeutic benefit of cirsimaritin against human leukemia cells: Medicinal importance through scientific data analysis

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Background : Flavonoids are widely found in plants in nature and these secondary metabolites of plants have antioxidant activity, anticancer, anti-inflammatory, hepatoprotective potential and antibacterial activity. Cirsimaritin is the flavonoidal class organic chemical compounds having methoxy groups attached to the C7 position of the main flavonoid backbone. Cirsimaritin have been well known for their presence in the numerous medicinal plants and was initially isolated from Cirsium martimum.

Method : Cirsimaritin have anti Hpylori activity, anti-oxidant, anti-bacterial, anti-spasmodic and cyclooxygenase- 1 inhibitory potential in the medicine. Biological potential and therapeutic benefit of cirsimaritin in the medicine have been investigated through scientific data analysis of various research works of the scientific fields in the present investigation. Numerous scientific databases have been searched to collect all the needed scientific information of cirsimaritin and analyzed in the present investigation. Detailed pharmacological activities and therapeutic benefit of cirsimaritin in the medicine and other allied health sectors have been investigated through scientific data analysis. Biological potential of cirsimaritin against human leukemia cells have been investigated through scientific data analysis of various research works.

Results : Scientific data analysis of various research works revealed the biological potential and therapeutic benefit of cirsimaritin in the medicine for the treatment of numerous health disorders and associated secondary complications. Biological effect of cirsimaritin against human leukemia cells revealed their therapeutic benefit in the medicine due to their effectiveness on inhibition of cell proliferation and induction of apoptosis.

Conclusion : Scientific data analysis revealed the biological importance and therapeutic benefit of cirsimaritin against human leukemia cells.

Keyword : Biological Importance, Cirsimaritin, Human Leukemia, Therapeutic Benefit

PP01-29

Biological potential of tricetin against acute myeloid leukemia: Therapeutic benefit in the medicine for their anti-

cancer effect through scientific data analysis

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Background : Herbs are natural products derived from various natural sources such as plants, animals, minerals and other biological sources and presence of phytoconstituents varies depend on the sources of the raw material. Tricin is an important phytoconstituents found to be present in the Lathyrus pratensis, Metasequoia glyptostroboides and Eucalyptus globules. Tricetin has been well known in the medicine for their effectiveness against various forms of cancerous disorders.

Method : In order to know the biological potential of tricetin in the medicine, here in the present investigation numerous scientific research data have been collected and analyzed. Detailed pharmacological activities of tricetin have been investigated through scientific data analysis of various research works of the scientific fields. Biological potential of tricetin for their anticancer effects on acute myeloid leukemia cells have been investigated through scientific data analysis of various research works.

Results : Scientific data analysis of various research works revealed the biological potential and therapeutic benefit of tricetin in the medicine and other allied health sectors. Detailed pharmacological study of tricetin through literature data analysis revealed their biological potential against various form of tumors including breast, liver, lung, bone and brain. Biological effects of tricetin in the medicine for their effectiveness against acute myeloid leukemia (AML) cells have been investigated in the scientific field and revealed that tricetin inhibited cell viability in various types of AML cell lines. Further data analysis also signified that tricetin significantly activated caspase-8, -9 and 3 activation in HL-60 AML cells.

Conclusion : Scientific data analysis of various research works revealed the biological potential and therapeutic potential of tricetin against acute myeloid leukemia.

Keyword : Tricetin, Acute Myeloid Leukemia, Anticancer, Medicine, Cancerous Disorders

PP01-30

Potency of MicroRNA (miR142, miR302, and miR503): Biomolecular therapy of acute myeloid leukemia cells proliferation by targeting cyclin-D1 pathway: Systematic literature review

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Background : Disorders of the cell cycle regulatory machinery play a key role in the pathogenesis of cancer. Over expression of cyclin D1 protein has been reported in several solid tumors and certain lymphoid malignancies, but little is known about the involvement of cyclin D1 in acute leukemia. Certain types of MicroRNAs (miRNAs), named miR-142, miR-302 and miR-503, are down-regulated in Acute Myeloid Leukemia (AML) and have potential role to inhibit AML cells migration and proliferation and promotes cancer cells apoptosis. We aimed to explore the potency of these miRNAs as a treatment that blocked cell-cycle.

Method : This literature review was conducted using a protocol PRISMA (Preferred Reporting Items for Systematic Review and Meta-analyses) guidelines for reporting systematic reviews and capturing data last 10 years. Studies were identified from electronic search of the PUBMED. 60 publications were considered to be relevant for this review.

Results : Present miRNAs had been proved that they have same binding site on their sequence, C-terminal cyclin-D1 gene (CCND1). These miRNAs could down-regulate the CCND1 activity, which regulate cancer proliferation. Two of them, miR-142 and miR-503, blocked on specific phase that resulted in G0/G1-S phase arrest, while miR-302 could arrest G0/G1-S and G2-M phases. In addition, miRNAs led to apoptosis of AML cell via various pathways. Currently, the treatment options for AML are limited. Palbociclib, rapamycin, paclitaxel and metformin are some of treatment that give promising anti-growth for patient. Unfortunately, those treatments have side effect for long-term used such as increase gastrointestinal toxicity and sporadic lung disease. Compared to those treatments, miRNAs have potential activity against tumor progression in AML especially in early stage. They enhanced rapidly to the subset of anti-growth.

Conclusion : miR-142, miR-302 and miR503 could induce anti-growth, reduce the risk of metastasis and trigger apoptosis. These miRNAs could be potential therapy against AML in following clinical application.

Keyword : Acute Myeloid Leukemia, MicroRNA, Biomolecular Therapy

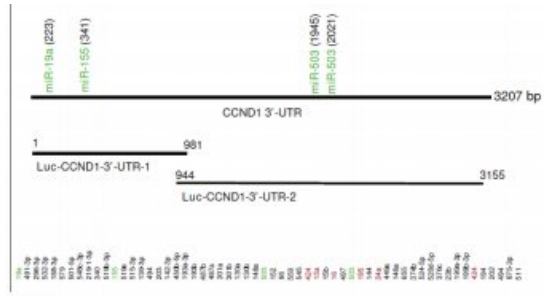

Figure 1
The CCND1 3'-UTR with predicted microRNAs and luciferase constructs. The CCND1 3'-UTR sequences (3207 bp) is based on NM_053056. Three microRNAs identified to be positive to CCND1 in this study are indicated in green with relative positions. Those previously validated microRNAs are indicated in red. See Table 2 for detail positions.

PP01-31

Acute myeloid leukemia with RAM immunophenotype: Distinct or Hazy?

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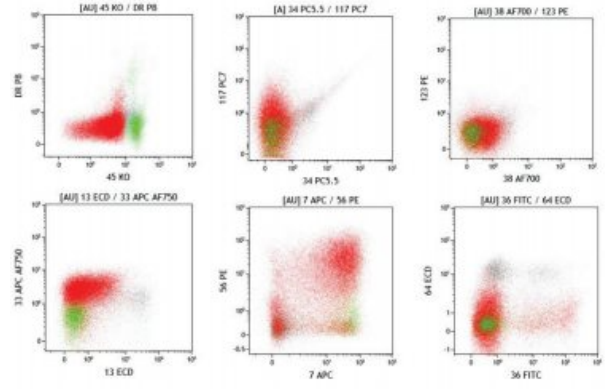
Background : A new subtype of Acute Myelogenous Leukaemia (AML), with a distinct immunophenotype at diagnosis, referred to as RAM immunophenotype was identified as high-risk type AML by Eidenschink Brodersen et al in 2016. It is characterized by bright CD56 positivity, dim-to-negative CD45 and CD38, and a lack of HLA-DR expression. [1] It is observed that RAM immunophenotype AML cases are distinct from other CD56 positive leukaemia and around 40% cases of RAM immunophenotype have acute megakaryocytic leukemia immunophenotype (AMKL). Complete remission (CR) is significantly lower and minimal residual disease (MRD) positive rate is higher with lower three-year event free survival (EFS) and relapse in patients who achieve CR.

Method : We evaluated 5 AML patients which had immunophenotypic profile similar to RAM phenotype as described by Eidenschink Brodersen et al in 2016 in their COG study. The age of patients ranged from 7-71 years (Mean age- 39.8 years) and male to female ratio was 4:1. Fever was the most common symptom, followed by weakness. Other symptoms observed were gum hypertrophy, backache, and decreased appetite. Mean haemoglobin (Hb) among the patients was 8.2gm/dl (range:5.6-10.3g/dl), mean total leukocyte count (TLC) 52284/mm3 (range:5900-99700/mm3) and platelet counts 71200/mm3 (range:10000-249000/mm3). Peripheral blood blast percentage ranged between 52%-95% (mean-81.4%). Symptoms, age, and complete blood count (CBC) and blast percentage of each case has been listed in Table 1.On flowcytometric immunophenotyping the blasts were bright for CD56, CD38 dim to negative, HLA-DR dim to negative [Figure 1]. All these patients had immunophenotypic profile like RAM phenotype as described by Eidenschink Brodersen et al. Immunophenotypic profile of each case has been listed in Table 2. All the 5 AML patients were started on 3+7 induction protocol followed by HiDAC consolidation. Post-induction MRD was negative in all patients. Two Patients relapsed after 7 and 9 months of treatment free interval (TFI). They received a second cycle of chemotherapy (3+7 induction and HiDAC consolidation) and then underwent allogenic stem cell transplantation. One of the patients relapsed again after a TFI of 2.5-years and was put on hypomethylating agents. He achieved remission status by induction with cytarabine and idarubicin and then underwent a second allotransplant. This patient relapsed for the third time and presented with severe anaemia, fatigue, gum hypertrophy and hepatosplenomegaly. At 3rd relapse he also developed complications like febrile neutropenia, oral mucositis, and fungal pneumonia. Patient was given induction one more time, but he finally succumbed to the disease. Rest of the 4 patients responded well to the therapy and are doing well and are on follow up.

Results : Risk stratification in AML is based on molecular and cytogenetic markers. [2] High risk patients have monosomy 7, deletion 5q, monosomy 5, or FLT3-ITD with a high allelic ratio (>0.4) and those with inv (16) (including t (16;16) variants), t (8;21), a CEBPA mutation, or an NPM1 mutation are classified as low risk. Rest of the AML patients with known cytogenetics are labelled as standard-risk group. [3] Some recent studies have also proposed to include immunophenotype as a risk stratification tool in cases of AML. [4,5] Acute myeloid leukaemia (AML) with RAM immunophenotype is a newly described subtype characterized by a unique immunophenotype and a poor prognosis. It is a standard risk type AML which is comparable to the de novo AML with poor prognostic features such as FLT3-ITD and high-risk cytogenetics. [1] In the original study by Eidenschink Brodersen et. al. around 38% of AML patients with RAM phenotype were acute megakaryoblastic leukaemia (AMKL) or M7. Similarly, in their case report Miriam Conces et. al. described a case of AML with RAM phenotype having AMKL where they described morphological and immunophenotypic features in detail.[6] According to them the myeloid blasts of RAM phenotype were present in cohesive clumps and showed nuclear moulding which is an unusual feature for cases of AML. [7,8]

Conclusion : There is paucity of literature describing clinical course, morphology, immunophenotype and cytogenetics of RAM phenotype cases but most of them discuss about the unique immunophenotype, age of presentation and extremely poor prognosis of the disease characterized by resistance to treatment, induction failure and high relapse rate. Contrary to the available text and findings of few of the studies our RAM phenotype cases were of adult age group and none were morphologically AMKL and only one patient had a poor clinical outcome. This study emphasizes that we need to study this entity in much detail and incorporate many patients having such unique immunophenotype. This would help us in timely and accurate diagnosis with formulating appropriate treatment guidelines.

Keyword : Acute Myeloid Leukemia, RAM Immunophenotype, Flow Cytometry



PP01-32

Impact of COVID-19 on the treatment of acute myeloid leukemia: A systematic review

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Background : The disease (COVID-19) novel coronavirus pandemic has so far infected millions resulting in the death of over a million people as of December 2020. More than 90% of those infected with COVID-19 show mild or no symptoms but the rest of the infected cases show severe symptoms resulting in significant mortality. High dose consolidation chemotherapy in patients with acute myeloid leukemia (AML) cause severe and prolonged granulocytopenia with increased risk of severe infections, particularly of bacterial or fungal origin. Respiratory virus infections can also occur, particularly during seasonal outbreaks, but their clinical impact in Acute Myeloid Leukemia (AML) has been generally considered as less relevant. Therefore, an increasing number of patients with different hematologic malignancies, including AML, is expected to present with concomitant COVID-19 either at diagnosis or during disease course. This study aims to delineate the possible impact of the current COVID-19 pandemic on patients with AML in terms of treatments, supportive measures and targeted therapies, as well as ways to mitigate it.

Method : Data obtained from secondary data on 21 articles journal evaluated by searching in PubMed, EMBASE, and the Cochrane Library database that have been carried out in the last 5 years (2016-2020) to identify reports of patients with hematologic malignancy and COVID-19.

Results : The literature describe that on hospitalised patients with hematological cancers resulted SARS-COV-2 positive, describing a more severe disease and a higher case fatality rate. However, no specific mention was done about AML patients who are at higher risk of infections compared to other hematological cancers. Nevertheless, other research shows the patients affected by hematological malignancies, including AML cases were found SARS-CoV-2-positive by nasopharyngeal swab. COVID-19 required hematological treatment modifications in symptomatic patients. Treatment for COVID-19 depended on the policy of the center and included to different options which are currently available. COVID-19 infection has a substantial impact on AML patient survival as well as on the possibility of receiving optimal planned treatment. Other studies shows AML patients are at a higher risk of severe complications for several reasons. As the presenting symptoms can be similar, health care practitioners should imperatively keep the possibility of AML in mind. Targeted therapies could potentially be used. However, physicians should be aware of their interactions with other drugs used to treat SARS-CoV-2-related infections/ complications such as antibiotics, anti-viral drugs and various other drugs that prolong QTc or impact targeted-therapy pharmacokinetics. They should be considered in all patients with AML in order to best tailor individual therapeutic decisions and, whenever possible, mitigate the impact of the pandemic.

Conclusion : It can be concluded that COVID-19 infection has a substantial impact on the survival of AML patients. To manage COVID-19 AML patients by hematologists in strict collaboration with pneumologists and intensivists in dedicated units. Alternatively, a single room with negative pressure in the hematology ward can be considered.

Keyword : COVID-19, Impact, Treatment, Acute Myeloid Leukemia

PP01-33

Repeated and sustained remissions with decitabine therapy in an elderly male with acute myeloid leukemia

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Background : Elderly patients with acute myeloid leukemia (AML) have a generally poor prognosis, with treatment options being limited by overall medical fitness to undergo intensive treatment. Decitabine, a hypomethylating agent, is an option offered to patients who prefer or are candidates for less intensive chemotherapy. It can induce remission in as much as 27% of patients and can offer a median overall survival of around 8 months.

Method : Herein, we report a case of an elderly male with AML who has achieved repeated and sustained remissions with decitabine chemotherapy over 4 years and counting.

Results : Initially presenting with pancytopenia, he was diagnosed with AML at 66 years of age and was given decitabine as first-line treatment. Due to resource constraints, chemotherapy cycles were given in 2-to-3-month intervals instead of the usual monthly interval, with each cycle given as a 5-day course. This setup afforded him sustained periods of transfusion independence. Cytopenias recurred whenever he missed treatment for prolonged periods and improved towards normalization whenever treatment was resumed. Interim bone marrow aspirate flow cytometry revealed a disease remission status every time. Recently, he has been restarted on decitabine chemotherapy due to the recurrence of cytopenias, after missing his treatment due to the community restrictions imposed by this current pandemic.

Conclusion : In certain patients with AML, decitabine can induce repeated and sustained remissions and can provide transfusion independence for several years. It remains a viable option for less intensive chemotherapy in elderly patients.

Keyword : AML, Acute Myeloid Leukemia, Elderly, Decitabine, Disease Remission, Chemotherapy

PP01-34

A rare case of acute promyelocytic leukemia with BCR-ABL1 rearrangement

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Background : Acute promyelocytic leukemia (APL) is an acute myeloid leukemia characterized by predominating abnormal promyelocytes and PML-RARA fusion or its variants. BCR-ABL1 translocation is an oncogenic event mainly observed in chronic myeloid leukemia but also in acute lymphoblastic leukemia, acute myeloid leukemia (non-APL) as well as in healthy individuals. However, APL with concurrent PML-RARA and BCR-ABL1 fusion genes has been rarely reported.

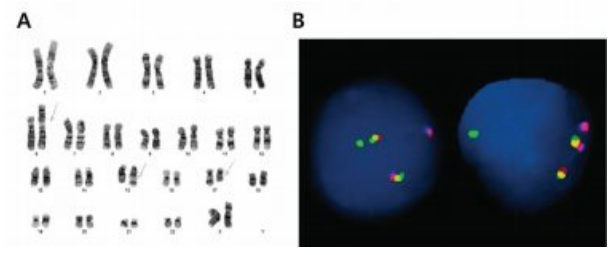
Method : A 46-year-old woman was referred to our hospital for the evaluation of leukocytosis and disseminated intravascular coagulopathy. Her complete blood count on admission was white blood cells 64,800/μL, hemoglobin 6.9 g/dL and platelet 27,000/ μL. Bone marrow examination show hypercellular marrow with 10% of blasts and 80% of abnormal promyelocytes. The blasts and abnormal promyelocytes were positive for MPO, CD13, CD33, CD117, CD34, CD2 and CD56 in flow cytometric analysis. Her karyotype was 46,XX,der(6)t(6;8)(p23;q13),t(15;17)(q24;q21)[20] (Figure 1A). Muliplex reverse transcriptase PCR showed concurrent presence of PML-RARA and BCR-ABL1 fusion genes in the BM. Quantitative reverse transcriptase PCR showed PML-RARA fusion gene of 1.06 PML-RARA/ABL1 and BCR-ABL1 fusion gene of 0.0131 BCR-ABL1/ABL1. Fluorescence in situ hybridization showed 5 cells with BCR-ABL1 translocation out of 500 interphase cells (Figure 1B).

Results : The patient was diagnosed with APL and treated with all-trans retinoic acid combined with idarubicin. She achieved complete hematological remission 38 days after the initial treatment. Post-induction bone marrow examination demonstrated normal karyotype of 46,XX[20] and reduced PML/RARA of 0.00322 PML-RARA/ABL1, whereas BCR-ABL1 was not detected. Followed by consolidation therapies, molecular remission of PML-RARA was also achieved. She is well tolerating maintenance therapy up to date, 10 months since initial therapy.

Conclusion : There are only 5 cases reported with concurrent of PML-RARA and BCR-ABL1 fusion genes. Three of them had co-existing PML-RARA and BCR-ABL1 fusion genes in each leukemic cell. The other 2 had only a minor population of BCR-ABL1 fusion gene harbouring cells, and only one of them proved BCR-ABL1 existed in cells without PML-RARA fusion gene. It is uncertain that ours is either an APL case in an individual with underlying BCR-ABL1 observed in normal individuals or an APL case with BCR-ABL1 observed in acute myeloid leukemias. The benefit of additional tyrosine kinase inhibitor therapy in cases with concurrent PML-RARA and BCR-ABL1 fusion genes is unclear yet and more cases should be reported to establish a proper therapeutic strategy for such cases.

Keyword : Acute Promyelocytic Leukemia, BCR-ABL1, PML-RARA

Figure 1. Cytogenetic analysis of bone marrow sample at diagnosis
(A) Chromosomal analysis showing 46,XX,der(6)t(6;8)(p23;q13),t(15;17)(q24;q21) in 20 metaphase cells; (B) fluorescence in situ hybridization FISH with probes targeting *BCR* (green) and *ABL1* (red) loci showing 2 yellow fusion signals in 5 out of 500 interphase cells.



PP01-36

Nonleukemic myeloid sarcoma involving the ileum, duodenum, lungs, mesentery, posterior cul-de-sac and multiple lymph node groups: A case report

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Background : Myeloid sarcoma is a rare extramedullary tumor often associated with acute myeloid leukemia. Myeloid sarcoma in the absence of acute myeloid leukemia is even rarer.

Method : Herein, we report a case of a young adult female diagnosed with nonleukemic myeloid sarcoma involving the ileum, duodenum, lungs, mesentery, posterior cul-de-sac and multiple lymph node groups.

Results : She initially presented with an ileal mass causing gut obstruction, and underwent laparotomy, ileal resection and end-to-end anastomosis. The initial histopathologic impression was non-Hodgkin lymphoma, but no immunohistochemistry or further treatment was pursued. A few months later, the symptoms of gut obstruction recurred. Imaging studies revealed masses at the mesentery and posterior cul-de-sac, a lung nodule, and enlargement of diaphragmatic, retroperitoneal, and mesenteric lymph nodes. Duodenal thickening was also seen and biopsied during an upper gastrointestinal endoscopy. Histopathologic and immunohistochemistry studies of the previously resected ileal mass and of the duodenal mucosa all revealed a diagnosis of myeloid sarcoma. Bone marrow studies did not show leukemic involvement. She underwent acute myeloid leukemia-type of induction chemotherapy and subsequent consolidation chemotherapy, and achieved clinical and radiologic resolution of the disease.

Conclusion : Myeloid sarcoma can form at any anatomic site outside the bone marrow. It can also disseminate to multiple sites even in the absence of leukemic involvement. Clinching the diagnosis, especially in nonleukemic cases, remains challenging but is imperative for proper definitive management. As such, a high index of suspicion and timely histopathologic and immunohistochemical studies are essential.

Keyword : Myeloid Sarcoma, Nonleukemic Myeloid Sarcoma, Ileum, Duodenum, Mesentery, Acute Myeloid Leukemia

PP01-37

Analytical performance of the oncomine myeloid research assay testing for myeloid neoplasms

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Background : A wide range of genes related to myeloid neoplasm have been discovered using high throughput testing. Targeted next-generation sequencing (NGS) for myeloid neoplasm might be an efficient strategy to capture diagnostic decision and clinically actionable mutations. In this study, we validated and optimized the Ion Torrent S5 XL platform using the OncomineTM Myeloid Research Assay (OMA, Thermo Fisher Scientific) for routine diagnostic targeted gene panel testing in myeloid neoplasms.

Method : DNA reference materials, RNA reference material and clinical samples were used, including 29 genomic DNA and 20 RNA samples. Certified DNA controls were HD752 (Tru-Q0), HD728 (Tru-Q1), HD731 (Tru-Q4) (Horizon), and SeraSeq Myeloid mutation DNA mix (SeraCare). Certified RNA control was SeraSeq Myeloid fusion RNA mix (SeraCare). Sequencing was performed using the OMA on Ion S5 XL sequencers. The OMA uses amplicon-based semiconductor sequencing technology to cover 40 DNA genes recurrently mutated in myeloid malignancies (23 hotspots and 17 full coding), 29 RNA fusion driver genes and 10 gene expression targets. Bioinformatics pipeline was Oncomine Myeloid Research 530 w3.0.3. Sequencing data were analyzed using Torrent Suite, Torrent Variant Caller, Ion Reporter (v.5.3.-5.10.). The OMA included Ion Reporter "Oncomine filter" and we also added the "SNV-INDEL filter". Genetic variants including single nucleotide polymorphism (SNP), small insertion and deletion were validated. Limit of detection (LOD) was evaluated by mixing reference material and clinical samples in DNA. Validated LOD ranged 15%, 10%, 5%, 2.5% of VAF.

Results : All reactions passed the quality control criteria of sequencing and bioinformatics pipelines. A total of 41 variants verified by DNA control material were detected using OMA showing 100% accuracy. A total of 40 variants in 25 clinical samples were detected using OMA except one (one ASXL1). Missense mutations (n=52) were most commonly comprised, followed by frameshift mutation (n=18), inframe insertion (n=10), and nonsense mutation (n=3). A total of 9 variants identified in RNA control were detected using OMA. A total of 9 fusion transcripts identified RT-PCR in 19 clinical samples were detected. Analytical sensitivity was 4% and analytical specificity was 100%. Validated LOD was 4.0%.

Conclusion : Targeted NGS panel assay for myeloid neoplasm can identify the clinically actionable variants and provide the reliable results for detection of variants.

Keyword : Next Generation Sequencing, Myeloid Neoplasm

PP02-01

Screening of dysplastic neutrophils using cell population data by automated hematology analyzer

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Background : It is a long-standing goal to obtain accurate diagnostic clues of myelodysplastic syndrome (MDS) by detecting PB abnormalities using an automated analyzer. This study evaluated the diagnostic utility of complete blood cell (CBC) and automated cell population data (CPD) parameters, especially information about morphology of neutrophils and monocytes, to screen MDS using PB

Method : The hematology automated analyzer Sysmex XN-1500 were used and neutrophil-FSC (NEFSC), neutrophil-SSC (NESSC), neutrophil-SFL (NESFL), monocyte-FSC (MOFSC) and monocyte-SSC (MOSSC) and other CPD were analyzed. Dysplastic neutrophil was defined by microscopic findings including nuclear hypolobulation (pseudo-Pelger-Huet anomaly), hypersegmentation, bizarre lobulation, clumping, cytoplasmic hypogranularity and pseudo-Chediak-Higashi granules and small size.

Results : A total of 390 participants were enrolled (63 with MDS and 327 as controls; mean age, 51.6 ± 17.9 years) during May and July 2018. The number of the sub-classification of MDS in this study were as follows: MDS with single lineage dysplasia (n =1), MDS with multi-lineage dysplasia (n =14), MDS with excess blasts (n =47), and unclassifiable MDS (n =1). In multiple regression analysis, RBC count (P=0.0001), platelet count (P=0.0001), NEFSC (P=0.0002), NESSC (P=0.0138), QFlag(Blasts) (P=0.0002), PB-blast(%)(P=0.0002) and IPF count (P=0.0002) were independently associated with MDS. The area under curve (AUC) for RBC count (0.942), platelet count (0.881), NESSC (0.876), and NEFSC (0.865) showed higher diagnostic power with acceptable sensitivity and specificity in receiver operation characteristic curves (ROC) analysis. When using combinations of'NESSC and NEFSC and RBC count and platelet count, the positive predictive value (PPV) markedly increased to 100.0% (100%), however, the sensitivity decreased to 50.8%. Overall, if combination criteria satisfying one of four CPD cut-off criteria were used, all 64 MDS patients could be detected (sensitivity 100%).

Conclusion : This study demonstrates that CPD representing cell volume (decreased NEFSC) and complexity of neutrophils (decreased NESSC) may be useful for screening MDS using PB. The existing known markers, low RBC count and platelet count showed highest diagnostic efficiency in screening MDS. The combination of these four markers markedly improved sensitivity of MDS detection. These parameters are convenient and objective markers obtained from the automated analyzer with the CBC test. This could help to suspect the presence of MDS rapidly without additional cost.

Keyword : Cell Population Data, Sysmex-XN, Dysplastic Neutrophil, Myelodysplastic Syndrome

Table 1. The sensitivity and positive predictive values of the combination of CPDs for the predicting myelodysplastic syndrome

	(A) The number of subjects fulfilling cut-off criteria*	(B) The number of MDS patients among (A) subjects. (Sensitivity†)	Positive predictive value‡	*P*-value
NESSC or NEFSC	71	54 (84.4%)	76.0%	<0.0001
RBC count or platelet count	112	63 (98.4%)	56.3%	<0.0001
NESSC or NEFSC or RBC count or platelet count	126	64 (100.0%)	50.8%%	<0.0001
NESSC and NEFSC and RBC count and platelet count	34	34 (53.1%)	100%	<0.0001

Abbreviations: MDS, myelodysplastic syndrome; NESSC, neutrophil-side scatter light; NEFSC, neutrophil-forward scatter light.
*Number of patients meeting the cut-off criteria for each parameter of the cell population data from the receiver operation characteristics curve analysis (top four parameters), i.e., positive patients with a combination of tested CPD.
† Sensitivity = the number of MDS patients in (A) subjects/ total 64 MDS patients
‡ Positive predictive value = (B) (true positive)/ (A) (test positive)

PP02-02

TET2 mutation and high miR-22 expression as biomarkers to predict clinical outcome in myelodysplastic syndrome patients treated with hypomethylating therapy

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Background : The driver genes frequently mutated in myelodysplastic syndrome (MDS) include DNA methylation, chromatin modification, RNA splicing, transcription, signal transduction, DNA repair, and other discrete functional pathways. Loss of TET2 function is caused by genetic mutations, miRNA interference, and metabolites such as 2-hydroxyglutarate accumulating in IDH1/2 mutations. Cheng et al. identified > 30 miRNAs that inhibit TET2 expression and forced expression of TET2-targeting miRNAs in vivo disrupts normal hematopoiesis, leading to hematopoietic expansion and/or myeloid differentiation bias. Song et al. reported that the oncogenic microRNA miR-22 also targets the TET2 tumor suppressor to promote hematopoietic stem cell self-renewal and transformation. Theoretically, loss of TET2 is a good candidate for HMT. Indeed, some studies reported that functional loss of TET2 predicts response to HMT.

Method : In this study, we evaluated whether TET2 mutation and miRNA-22 expression are predictive markers of response to HMT. We evaluated TET2 mutation status and miRNA-22 expression level in BM samples of MDS patients and assessed their relationship with responsiveness to HMT and other clinical characteristics such as age, risk stratification, leukemic transformation,and survival.

Results : Responsiveness to HMT was not affected by both TET2 mutation (Odds ratio [OR] 0.720, P=0.729) and high miR-22 expression (OR 1.238, P=0.819). There was a tendency for TET2 mutation to be associated with lower risk based on IPSS (P=0.073), lower leukemic transformation (OR 0.181, P=0.048) and longer survival (Hazard ratio 0.363, P=0.066). Although high miR-22 expression also showed similar tendency, this tendency was weaker than that of TET2 mutation.

Conclusion : Both TET2 mutation status and miR-22 expression status are not thought as good biomarkers for predicting response to HMT. Loss of TET2 function, including both TET2 mutation and high miR-22 expression, may be associated with lower risk based on IPSS, lower leukemic transformation and longer survival.

Keyword : TET2, miR-22, Hypomethylating Therapy, Myelodysplastic Syndrome

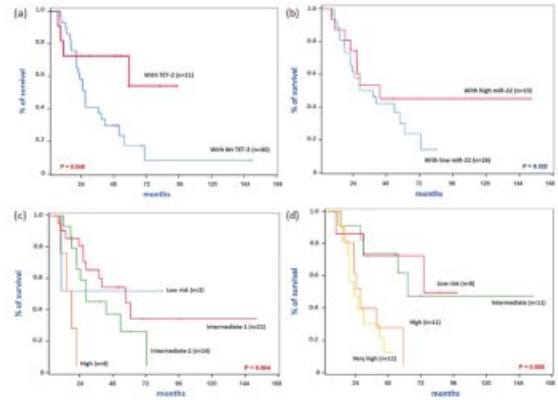

Figure 2. Kaplan-Meier survival curves according to various clinical factors.
Abbreviations: TET2, ten-eleven-translocation 2. * P-values were calculated using log-rank test.

PP02-03

Molecular profile in adult myelodysplastic/myeloproliferative neoplasms highlighting diagnostic ambiguity in certain cases

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Background : Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) are a heterogeneous group of myeloid neoplasms that exhibit overlapping features of MDS and MPN. Although the classification of these diseases relies largely on clinical features and hematopoietic cell morphology, the routine use of next-generation sequencing (NGS) testing has helped in accurate classification, risk stratification and establishment of treatment strategies. However, given their hybrid nature, none of molecular biomarkers is disease specific, but they are shared by different myeloid neoplasms. In this study, we presented cases showing diagnostic ambiguity due to a discrepancy between the genotype and the clinicopathologic features in patients with WHO-defined MDS/MPN.

Method : We retrospectively searched 34 adult patients with MDS/

MPN from the bone marrow archive of Asan Medical Center from 2018 to 2020. Medical chart review was conducted to collect their clinical information and sequencing data. The mutation profile was based on targeted NGS panel assay of 61 genes. We intentionally selected 7 cases with a diagnostic ambiguity from the pathologists' point of view.

Results : Study patients included chronic myelomonocytic leukemia (CMML) in 18, atypical chronic myeloid leukemia (aCML) in 9, MDS/MPN unclassifiable in 4, and MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) in 3. Categorization and clinicopathologic characteristics of selected cases were summarized in Table.

Conclusion : Molecular profiling raises a certain degree of ambiguity in pathologic diagnosis according to WHO criteria in a subset of adult MDS/MPN. These cases may represent either a spectral nature or a true gray zone of neoplasms.

Keyword : Myelodysplastic/Myeloproliferative Neoplasms, Molecular Profile, Diagnostic Ambiguity

Table. Clinicopathologic characteristics of selected patients presenting with diagnostic ambiguity

Category	Case No.	WHO diagnosis	Karyotype	Mutation (VAF, %)
Genotype-phenotype discrepancy	UPN 26[a]	MDS/MPN-U	46,XY[20]	*SF3B1* p.K666T (36.5); *JAK2* p.V617F (13.1)
	UPN 34[b]	aCML	45,XY,der(3;4)(q10;q10),del(5)(q12),-7,inv(12)(p13q14),?add(20)(q12.1),+mar[20]	*TP53* c.376-2A>C (50.1); *TP53* p.Y234H (47.3); *TP53* p.I232N (46.3); *DNMT3A* p.H506R (45.5)
Molecular biomarkers of AML[c]	UPN 14	CMML	46,XY,t(11;19)(q23;p13.1)[20]	None
	UPN 18	CMML	46,XY[20]	*CEBPA* p.V308_E309insAS (47.5); *CEBPA* p.H24fs (39.8)
	UPN 21	CMML	46,XX[20]	*ASXL1* p.E453fs (44.9); *FLT3* p.Y597_P606dup (19.2)
Subclones associated with other hematologic cancers	UPN 13[d]	CMML	46,XY[20]	*TET2* p.Q1603* (48.0); *TET2* p.P29R (44.4); *KRAS* p.G12S (33.1); *NRAS* p.A146T (2.1), *ZRSR2* p.C172Y (85.3), *RB1* p.R455* (33.6); *CALR* p.L367fs (9.1)
	UPN 31[d]	MDS/MPN-RS-T	46,XY[20]	*SF3B1* p.K700E (48.0); *TET2* p.H1380Y (52.8); *TET2* p.R1216* (21.7); *RAD21* p.R584* (27.5); *CXCR4* p.S338* (3.4); *MYD88* p.L265F (2.1)

[a]Co-existence of *SF3B1* and *JAK2* V617F mutations strongly supports the diagnosis of MDS/MPN-RS-T. [b]Molecular profiles indicate high-risk myelodysplastic syndrome rather than aCML. [c]These biomarkers (11q23 rearrangement in UPN 14, biallelic mutations of *CEBPA* in UPN 18, and *FLT3* internal tandem duplication in UPN 21) are known to have a role in leukemogenesis of acute myeloid leukemia. [d]*RB1* mutations have been reported in cases of chronic lymphocytic leukemia or blastic plasmacytoid dendritic cell neoplasm. *CALR* L367fs is a well-known driver mutation of Ph-negative myeloproliferative neoplasms. [e]Two subclonal mutations (*CXCR4* S338* and *MYD88* L265P) were strongly associated with lymphoplasmacytic lymphoma.
Abbreviations: AML, acute myeloid leukemia; No, number; VAF, variant allele frequency; MDS/MPN-U, MDS/MPN unclassifiable; aCML, atypical chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS/MPN-RS-T, MDS/MPN with ring sideroblasts and thrombocytosis.

PP03-01

Germline and somatic mutations in Korean patients with ALL

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Background : B-cell and T-cell acute lymphoblastic leukemia/lymphoma (B-ALL, T-ALL) are two of the most common malignancies in children. ALL can be classified by genetic alterations, which are various and heterogeneous. In addition to somatic mutations, germline genetic predisposition to hematologic malignancies is an emerging area of research interest. In this study, we investigated genetic alterations in Korean acute lymphoblastic leukemia/lymphoma (ALL) patients using targeted gene panel sequencing.

Method : Eighty-one well known genes associated with 23 predisposition syndromes were included in the gene panel. In addition to sequence variants, gene-level copy number variants (CNVs) were investigated. Annotated variants were classified by automated algorithm software, DxSeq Analyzer (Dxome, Seoul, Korea), by applying the standards and guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. An R package, ExomeDepth (1.1.10), was used to detect exon- and gene-level CNVs in target regions, followed by visualization using a base-level read depth normalization algorithm implemented in DxSeq Analyzer (Dxome, Seoul, Korea). We selected paired initial-diagnosis and complete remission (CR) bone marrow samples from patients diagnosed with ALL at Samsung Medical Center from 2008 to 2012. To detect germline mutations, bone marrow slides obtained when the patients were in CR were used. We enrolled 65 pediatric (<20 years old) ALL patients and 28 adult ALL patients, including 12 T-cell ALL patients (seven children, five adults). Differences in survival according to mutation group were analyzed using Kaplan-Meier estimates. A P-value of <0.05 was considered statistically significant. All statistical analyses were performed in PASW Statistics 20.0. The Institutional Review Board at Samsung Medical Center approved this study (IRB No. 2015-11-053) and informed consent was obtained from all participants.

Results : We identified 197 somatic sequence variants and 223 somatic CNVs. NOTCH1, IL7R, FBXW7, and NRAS were the most common variants overall in T-ALL. NRAS, FLT3, SETD2, and KRAS were the most common variants overall in B-ALL. Lymphoid development and differentiation and the cell cycle and p53 signaling pathway were the most common CNVs overall. The IKZF1 alteration had an adverse effect on OS (overall survival) and RFS (relapse free survival) in childhood B-ALL. Only one patient (male, 18 years old, B-ALL-NOS) had a known CNV, CASP10 (deletion of exon 6-exon). This same CNV was previously found in a patient with systemic juvenile idiopathic arthritis with incomplete penetrance.Only one TP53 variant was identified. The TP53 NM_000546.5: c.733G>A variant was identified in a B-ALL, NOS patient. The TP53 NM_000546.5: c.733G>A variant was previously reported in Li-Fraumeni syndrome patients (multiple cancers, including breast cancer, liver cancer, and lung cancer). Nine PID-associated gene variants were identified in eight patients (8.6%). Apart from MEFV (Familial Mediterranean fever, AR or autosomal dominant - AD), all the others were heterozygous autosomal recessive (AR) PID associated variants. Three variants (IL12RB1, CTC1, LPIN2) have not been published while the other variants (JAK3, ADA, MEFV, TYK2, LIG4) were known variants.

Conclusion : We found recurrent somatic alterations in Korean ALL patients while the probability of germline mutation predisposition in unselected sporadic Korean ALL patients was low. However, our study suggest further comprehensive studies on carrier state of PID-associated genes in leukemia, considering that the prevalence

of these PID-associated germline variants is very low in the general population of Korea and other countries.

Keyword : Acute Lymphoblastic Leukemia/Lymphoma, Somatic, Germline, NGS, Korea

Table 1. PID-associated germline sequence variants identified in Korean ALL patients

ID	Age/ Sex	Gene	Nucleotide/ Amino acid	% Variant	dbSNP	gnomAD	Global (ExAC)	Genome Asia	Korea1K	Korean (KRGDB)	Diseases	PMID
ALL0009	51/F	*JAK3*	c.1503G>T/ p.Glu501His	51.3	rs201283129	0.00001988	0.00002825	0.0003	0.0027	0.0032154	SCID, AR, T-negative/ B-positive type, AR	18397343
ALL0011	63/M	*ADA*	c.715G>A/ p.Gly239Ser	50.8	rs777820729	0.00002386	0.00003766	-	-	-	ADA deficiency, partial, AR, SM; SCID due to ADA deficiency, AR, SM	14499267
ALL0011	63/M	*MEFV*	c.1508C>G/ p.Ser503Cys	50.5	rs190705322	0.00007555	0.000115	0.0009	-	0.0008039	FMF, AD; FMF, AR	19531756
ALL0090	3/F	*JAK3*	c.1503G>T/ p.Glu501His	52.3	rs201283129	0.00001988	0.00002825	0.0003	0.0027	0.0032154	SCID, AR, T-negative/ B-positive type, AR	18397343
ALL0077	10/M	*TYK2*	c.209_212del/ p.Cys70Serfs6Ter21	40.2	rs770927552	0.000048	0.00006591	-	0.0027	-	Immunodeficiency 35, AR	17088085
ALL0053	2/M	*IL12RB1*	c.1897G>T/ p.Glu633Ter	50.7	rs772340282	-	0.00001967	-	-	-	Immunodeficiency 30, AR	-*
ALL0060	40/M	*LPIN2*	c.480_483del/ p.Lys160AsnfsTer23	44.0	-	-	-	-	-	-	Majeed syndrome, AR	-*
ALL0071	2/F	*CTC1*	c.2249dupt/ p.Gly751Argfs5ter40	47.0	-	-	-	-	-	-	Dyskeratosis congenital, AR	-*
ALL0021	2/M	*LIG4*	c.1271_1275del/ p.Lys424Argfs5ter20	42.6	rs772226399	0.000156	0.000148	0.0003	-	-	LIG4 syndrome, AR	26762768

*Likely pathogenic by ACMG/AMP guideline; PVS1- Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon, single or multi-exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease, PM - Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes or ExAC.
Abbreviations; AD, Autosomal dominant; ADA, Adenosine deaminase; AR, Autosomal recessive; dbSNP, The Single Nucleotide Polymorphism Database; ExAC, Exome Aggregation Consortium; F, Female; FMF, Familial Mediterranean fever; gnomAD, The Genom Agregation Database; KRGDB, Korean Reference Genome Database; M, Male; PMID, PubMed identifier; SCID, Severe combined immunodeficiency; SM, Somatic mosaicism.

PP03-02

Spectrum of genetic mutations detected by next-generation sequencing in pediatric acute lymphoblastic leukemia

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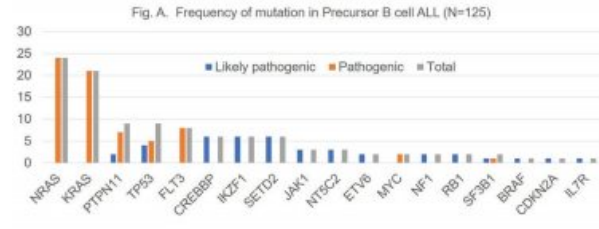
Background : Recent development of molecular biology has led to the classification of pediatric ALL incorporating genetic mutations related to prognosis, and next-generation sequencing is improving the understanding of pathogenesis of ALL by allowing various genetic aberrations to be identified. In this work, we studied the mutational spectrum in pediatric acute lymphoblastic leukemia (ALL), and its impact on the clinical prediction factors and clinical outcomes.

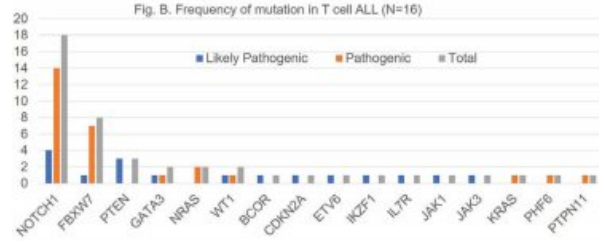
Method : Targeted next-generation sequencing was used to analyze 67 genes in children with ALL. Samples and clinical information were collected from 141 children who were diagnosed with de novo or relapsed ALL consecutively between April 2018 and October 2020. Selected mutations were interpretated according to the Joint consensus recommendation of Association for molecular pathology, American Society of Clinical Oncology and College of American pathologists, and classified to Pathogenic (P), Likely pathogenic (LP), Variants of Unknown significance or Benign.

Results : Among the 141 patients, 125 patients (88.7%) were B cell precursor ALL (BCP-ALL) and 16 patients (11.3%) were T-cell ALL (T-ALL). Thirty patients had relapsed and 111 patients were diagnosed with de novo ALL. A total of 86 patients (61%) harbored at least one genetic mutation which seemed either likely pathogenic (LP) or pathogenic (P). The number of P or LP mutations was 153 and the median number of these mutation was 1 (range, 0-10) per sample. Thirty-four patients (24%) harbored more than 1 mutation. In BCP-ALL, 70 patients (56%) had P or LP mutations and 22 patients had more than 1 mutation (range, 1-6). The mean number of P and LP mutations in patients with ETV6-RUNX1 fusion gene was significantly lower than in patients with high hyperdiploidy (0.32±0.64 vs.1.39±1.40). The mutation number was significantly high in relapsed patients but there was no relationship with the risk-group, steroid response and initial WBC counts. The most frequently mutated genes were NRAS and KRAS, which was followed by PTPN11, TP53, FLT3, CREBBP, SETD2, NT5C2 and IKZF1 in BCP-ALL. In T-ALL cases, all patients had P and LP mutations and the median number of mutations was 2 (range, 1-10). The most commonly mutated gene was NOTCH1 (81.3%, n=13) which was followed by FBXW7 (37.5%, n=6). RAS pathway mutations and NOTCH pathway mutations had no relation to disease relapse in BCP-ALL and T-ALL respectively. Mutations of the NT5C2 (relapsed in 3 of 3), PTEN (2 of 2), CDKN2A (2 of 2), TP53 (4 of 8) and CREBBP (3 of 6) genes seemed to be related with disease relapse.

Conclusion : In our study, we showed genetic mutation profiles in pediatric ALL, involving various signaling pathways, and found that the profiles were different between B-ALL and T-ALL. The dominant mutations were enriched in the RAS pathway (KRAS, NRAS, PTPN11, FLT3) and Notch pathway (NOTCH1, FBXW7) in BCP-ALL and T-ALL. We also identified mutations with potential prognostic significance. However, it is difficult to conclude due to the small number of patients harboring these mutations in this study. Our results should be further validated with a larger number of cases and long-term follow-up.

Keyword : Acute Lymphoblastic Leukemia, Mutation, Next-Generation Sequencing





PP03-04

Minimal residual disease status of patients with B-cell precursor acute lym-

phoblastic leukemia in South Korea

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Background : In recent decades, most patients with acute lymphoblastic leukemia (ALL) have achieved complete remission (CR) after treatment. However, 20% of children and 40-50% of adults with ALL still experience relapse during consolidation chemotherapy or after allogeneic hematopoietic cell transplantation. Minimal residual disease (MRD) has been shown to be an important predictor of relapse in both children and adults with ALL. Therefore, MRD-directed risk stratification and treatment approaches have been performed in Europe and the United States. However, data from Asian populations are still limited. Here, we generated real-world MRD data to to develop MRD-directed treatment strategies in Korea.

Method : This was a retrospective study in Seoul St. Mary's Hospital, from Jan 1, 2018 to Mar 31, 2019. Inclusion criteria were the followings: (1) patients with newly diagnosed B-cell precursor (BCP)-ALL or those with relapsed/refractory BCP-ALL; (2) patients who achieved hematologic CR after induction or salvage treatments; (3) patients who had baseline MRD data at the point of study enrollment; (4) patients who had MRD data at the end of induction or salvage treatments. For MRD assessment, high-throughput sequencing for clonal rearrangements of the immunoglobulin gene (LymphoTrack® IGH FR1/2/3 assay panel, InVivoScribe Technologies) was used for Philadelphia chromosome (Ph)-negative ALL. For Ph-positive ALL, MRD monitoring was evaluated by real-time quantitative PCR for the BCR-ABL1 transcript. Patients were treated with induction, consolidation, and salvage therapies according to our institutional protocol. The primary endpoint was estimation of MRD-positive rate in patients who achieved hematologic CR at the end of induction or salvage treatments. MRD positivity was defined as >0.01% leukemic cells.

Results : During the study period, 99 patients with BCP-ALL (66 adults and 33 children; median age, 32 years [range, 2-70 years]) who achieved hematologic CR and had available MRD data after induction (n=82) or salvage (n=17) treatments, were included in the final analysis reported here. In total, 44 patients (44.4%) were MRD-positive after induction (36/82 [43.9%]) or salvage (8/17 [47.1%]) treatments. Fifteen of 33 children (45.5%) and 29 of 66 adults (43.9%) were MRD-positive. Twenty-five of 56 patients (44.6%) with Ph-positive ALL and 19 of 43 patients (44.2%) with Ph-negative ALL had detectable MRD. After consolidation treatment, MRD was still detected among 15 of 64 evaluable patients (23.4%). At this time point, MRD-positive rates for children and adults were 12.0% and 30.8%, respectively. Twelve of 41 Ph-positive ALL patients (29.3%) and 3 of 23 Ph-negative ALL patients (13.0%) were MRD-positive.

Conclusion : This is the first study to examine the MRD-positive rate in CR for BCP-ALL in real-world setting in Korea. Our data provide preliminary evidence to estimate the size of the MRD-positive population at risk of relapse, which is essential for BCP-ALL treatment in Korea. Based on these results, an MRD-directed treatment strategy would be developed at an earlier phase of treatment for BCP-ALL in the future.

Keyword : Minimal Residual Disease, Acute Lymphoblastic Leukemia

PP03-05

Prognosis of pediatric acute lymphoblastic leukemia treated by SCCLG-ALL 2016 protocol - A single institutional experience

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Background : To analyze the clinical features and prognosis of 220 children with acute lymphoblastic leukemia (ALL) treated with SCCLG-ALL 2016.

Method : To investigate clinical data of 220 children with acute lymphoblastic leukemia (ALL) who were newly diagnosed from October 1, 2016 to August 31, 2019. The clinical features, efficacy and prognostic factors were evaluated.

Results : Among the 220 children enrolled, there were 127 males (57.7%) and 93 females (42.3%), with a male to female ratio of 1.37:1. The median age was 4 years and 4 months (7 months to 14 years 7 months old). The median follow-up time was 22.9 months (0.9 to 44.9 months). The complete remission rate on d15 and d33 evaluations were 77.7% (171/220) and 99.5% (215/216), respectively. The median relapse time was 20.2 months (11.7 to 22.1 months) after complete remission, among them there were 5 cases died with the mortality rate of 2.3%. The median time of death is 4.5 months after diagnosis (1˜7.6 months). All were treatment-related deaths due to severe infection after bone marrow suppression of chemotherapy. Three-year overall survival (OS) rate was (97.6±2.2)% while the events-free survival (EFS) rate was (95.0±3.1)%. Low risk, intermediate risk and high risk cases accounted for 41 (18.6%), 130 (59.1%) and 49 (22.2%), respectively. Three-year EFS were (97.4±4.9)%、(95.8%±3.7)% and (90.3±9.0)%, and there was not statistically significant (X =3.445,P=0.179). Univariate analysis indicated male (P=0.031), age <1 years or >10 years of age (<0.001), T immunophenotype (P=0.002), WBC count at diagnosis>50 109/L(P=0.002) and chromosomal structural abnormality (P=0.017) were risk factors for inferior outcomes. Multivariate analysis showed that gender was male (HR=0.107,95.0% CI 0.012~0.922, P=0.042), age<1 year or >10 years old (HR=31.574,95.0% CI 3.164~315.042,P=0.003) and chromosomal structural abnormality (HR=0.093,95.0% CI 0.017˜0.501,P=0.006)were independent risk factors affecting prog-

nosis in children with ALL.

Conclusion : SCCLG-ALL 2016 protocol has a high survival rate and significant efficacy in the treatment of pediatric acute lymphoblastic leukemia. Abnormal chromosomal structure may indicate poor prognosis, and we should pay attention to karyotype for the initial diagnosis.

Keyword : Pediatric, Acute Lymphoblastic Leukemia, Prognosis

PP03-06

Clinicopathological and immunophenotypic profile of T-cell acute lymphoblastic leukaemia

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Background : T-cell Acute Lymphoblastic Leukaemia (T-ALL) is a neoplasm of lymphoblasts committed to the T-cell lineage, with > 25% blasts in bone marrow. Patients typically present with high WBC count and mediastinal mass. According to 1995 EGIL criteria, T-ALL is subtyped into 4 categories: pro T-ALL, pre T-ALL, cortical T-ALL and mature T-ALL. In 2009, the early T-cell precursor ALL subtype (ETP-ALL) was introduced and WHO 2016 classification mentions that most cases of pre and pro T-ALL fall under the criteria for ETP-ALL. In addition, near ETP-ALL are defined as leukaemias expressing "brighter or more uniform CD5" but otherwise meeting criteria of ETP-ALL.

Method : This is a 4 year retrospective study (October 2016 - September 2020) in which 37 cases of T-ALL were analysed on flow cytometry using a 6/8 colour panel of monoclonal antibodies, which included T-cell, B-cell, myeloid and non-lineage markers like CD34 and HLA-DR. Cases were categorized as ETP-ALL, near ETP-ALL, cortical T-ALL and medullary T-ALL. Relevant clinical history and laboratory data were retrieved from patient case files.

Results : 37 T-ALL cases were analysed during the study period. The patient age ranged from 1 to 64 years, with median age being 13 years. 23 patients were below the age of 18 years. Male to female ratio was 2.1: 1. The most common clinical presentation was fever, seen in 70.3% cases (n=26). 35.1% cases (n=13) were documented to have mediastinal mass and 67.6% cases (n=25) had palpable splenomegaly. Mean haemoglobin level was 8.6 g/dl, mean platelet count was 73,800 /microlitre. Total WBC count ranged from 700 – 502,900/ microlitre with mean of 175,700/ microlitre. Blast percentage in peripheral blood ranged from 39-98%, with mean of 84.8%. Most of the cases were classified as medullary T-ALL, constituting 37.8% cases (n=14). 21.6% cases (n=8) were ETP-ALL, 13.5% cases (n=5) were near ETP-ALL and 24.3% cases (n=9) were cortical T-ALL. One case could not be definitely assigned to a specific category. 5 cases (2 ETP-ALL and 3 Near ETP-ALL) were previously subtyped as pre, pro or medullary T-ALL and were reclassified according to newer guidelines. The table attached denotes the frequency of expression of different immunophenotypic markers. 32.4% cases (n=12) were CALLA+ (CD10+). The aberrant expression of B-cell marker (CD79a) was observed in 5.4% cases (n=2).

Conclusion : This study reflects the difficulties encountered in subtyping of cases due to antigenic overlap and/or due to lack of an extended panel of secondary markers. Hence, a wider panel of markers is required to categorize the T-ALL cases, which has potential prognostic and therapeutic implications.

Keyword : Immunophenotype, T-ALL, Flow Cytometry, Blasts

Number and percentage of cases showing positivity for various markers

S.no	Marker	Number of cases showing positivity	Percentage of cases positive (%)
1	CD7	37	100
2	Cytoplasmic CD3	37	100
3	Surface CD3	24	64.9
4	CD5	33	89.2
5	CD2	34	91.9
6	CD1a	10	27.0
7	CD10	12	32.4
8	CD4	17	45.9
9	CD8	14	37.8
10	TCR αβ	5	13.5
11	CD34	20	54.1
12	CD13	3	8.1
13	CD33	4	10.8
14	HLA-DR	6	16.2
15	CD79a	2	5.4

PP03-07

Treatment response to targeted immunotherapy in adult ALL with isolated extramedullary relapse after previous allogeneic HCT

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Background : Relapsed or refractory acute lymphoblastic leukemia (R/R-ALL) has a poor prognosis. Recently introduced immunotherapeutic agents have shown high complete remission (CR) rate and safe bridging to allogeneic hemopoietic cell transplantation (allo-HCT). Although several data showed the results were not as promising in patients with extramedullary relapse (EMR), other data revealed immunotherapeutic agents such as blinatumomab or inotuzumab ozogamicin (INO) were effective in isolated EMR without bone marrow relapse (BMR).

Method : We analyzed treatment outcomes in 9 consecutive patients with isolated EMR after previous allo-HCT from 2017 to 2020 who were treated with blinatumomab or INO for first- or second-line salvage treatment, and subsequent allo-HCT was planned

if CR was achieved. Response was evaluated with PET-CT, and bone marrow (BM) was also examined.

Results : In seven patients who were treated with blinatumomab for first-line salvage, 4 (57.1%) achieved CR, 2 switched to INO (1 CR,1 PR), and 1 switched to standard multiagent chemotherapy which led to CR. In 2 patients treated with INO for first-line salvage, one showed partial response (PR) and the other achieved CR. Overall response was achieved in 8 (88.9%) patients (6 CR, 2 PR) and 5 (56%) patients proceeded to second allo-HCT in CR after those novel immunotherapeutic agents. Median overall survival after relapse was 27.8 months.

Conclusion : In the present study, blinatumomab and INO both novel agents showed good response and bridging role to successive allo-HCT in ALL patients with isolated EMR. Clinical differences between isolated EMR and EMR with BMR remains to be elucidated with more subjects in future clinical trials.

Keyword : Acute Lymphoblastic Leukemia, Relapsed, Blinatumomab, Inotuzumab Ozogamicin, Hematopoietic Stem Cell Transplantation

Table 1. Characteristics and treatment outcomes of the 9 patients

Case No.	Sex/Age (years)	CR Duration after Prior HCT (months)	Sites of iEMR	Salvage Regimen	Response	Time to HCT (months)	HCT after Salvage	Cause of Death	Survival after Relapse (months)
1	F/49	87.2	BONE, KIDNEY, LIVER, UTERUS	BLIN	CR	6.7	MUD	VOD	8.2
2	M/44	20.5	BONE, SKIN	BLIN → MEC	NR → CR	39.0	FMT	ALL progression	44.6
3	F/33	24.7	BONE, BREAST, LN	BLIN	CR	3.8	MUD	ALL progression	27.8
4	F/51	24.6	BONE, MUSCLE, SKIN	BLIN → INO	PR → N/A	N/A	N/A	VOD	20.6
5	M/20	15.7	PNS(RADIAL NERVE)	BLIN	CR	N/A	N/A	Alive	20.3
6	M/30	8.3	BONE, HEART, LN, MESENTERY, TESTES	BLIN → INO	NR → CR	8.0	DCBT	Infection	9.8
7	F/60	29.4	BONE	BLIN	CR	4.4	MUD	Alive	6.7
8	M/24	43.9	BONE, HEART, TESTES	INO	PR	N/A	N/A	Alive	24.2
9	F/59	23.5	CNS, KIDNEY, PANCREAS	INO	CR	N/A	N/A	Alive	10.2
	TOTAL 9		BONE 7; HEART, KIDNEY, LN, SKIN, TESTES 2; BREAST, CNS, LIVER, MESENTERY, MUSCLE, PANCREAS, PNS, UTERUS 1	7 BLIN (2 BLIN → INO) (1 BLIN → MEC) 2 INO					Median Overall Survival 27.8 months

Abbreviations: CR, complete remission; HCT, hematopoietic cell transplantation; iEMR, isolated extramedullary relapse; BLIN, blinatumomab; MEC, mitoxantrone, etoposide, and cytarabine; INO, inotuzumab ozogamicin; NR, no response; PR, partial response; N/A, not applicable; MUD, matched unrelated donor; FMT, familial mismatched transplantation; DCBT, double-unit cord blood transplantation; VOD, veno-occlusive disease; ALL, acute lymphoblastic leukemia

PP03-08

Strategies to prevent and manage complications of acute lymphoblastic leukaemia in young people in Bihar

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Background : Thrombotic events cause significant morbidity and mortality in chil-dren and young people treated for acute lymphoblastic leukaemia(ALL). There is a lack of evidence-based guidance for the preventionand management of thrombosis in this setting and a survey was conducted

Method : A survey was sent to the 30 centres participating in the trial. 72% of centre shave a protocol for the management of thrombosis in children/young people with ALL. Most stop COCP in females and few per-form thrombophilia screening prior to treatment. Timing of centralvenous line (CVL) insertion varies between centres: for individuals receiving regimen A, 33% place a line prior to induction while ther emaining defer until end of induction; for regimen B, 62% insert aline prior to induction.

Results : CVL remains in situ until end of intensive block in 28% and end of treatment in 28%. Antithrombin levels are not routinely monitored during/prior to anticoagulation. 40% treatthrombotic events with twice-daily low molecular weight heparin(LMWH), 66% monitor anti-factor Xa activity levels and 40% (inline-associated thrombosis)/63% (in cerebral sinovenous thrombosis(CSVT)) transfuse platelets to maintain platelet count >50 9 109/l inpreference to interrupting therapeutic anticoagulation. 56% remove the CVL in line-associated thrombosis, usually after 48–72 hoursanticoagulation. Therapeutic anticoagulation is commenced immedi-ately for CSVT in the presence of intracranial haemorrhage in 66%while 49% withhold anticoagulation pending interval imaging

Conclusion : This survey has identified significant variation in practice between centres. In the absence of high quality evidence consensus guidelines may be helpful and provide a basis for future research strategies

Keyword : Leukaemia

PP03-09

A case controlled study on digital dermatoglyphic patterns among children with acute lymphoblastic leukemia in Guyana

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Background : Dermatoglyphic patterns are the skin epidermal ridges seen on the surface of the palm, sole & digits which play an important role in predicting the various medical disorders. Recent association of the dermatoglyphic traits and specific chromosomal aberrations has established a predicting tool and a diagnostic aid. Acute lymphoblastic leukemia (ALL) is a malignancy of the lymphoid line of blood cells which in most cases are of unknown origin

and is highly prevalent in the current perspective. The early diagnosis of such a fatal disorder is beneficial to undertake preventive measures and hence reduce the mortality rate. Fingerprints develop in the embryonic stage at the same time as the angiogenesis and hematopoiesis from mesodermal tissue, therefore insults to the embryo that may cause leukemic changes in the hemopoietic cells may also result in aberrant palmar crease patterns. This research aims to study the association between acute lymphoblastic leukemia (ALL) and dermatoglyphic trait to assess the value of dermatoglyphics as a screening tool to detect leukemia in high-risk groups. The study also reviews systematically and appraise available literature that evaluates an association of different dermatoglyphic variables with hematological disorders.

Method : A case-controlled study conducted at the Georgetown Public Hospital Corporation(GPHC), a tertiary care hospital under the Ministry of Public Health, Georgetown, Guyana in 2019. The children suffering from acute lymphoblastic leukemia were included in the study. Fingerprints of the affected children were analyzed in both hands and compared with the fingerprint patterns of age and sex-matched controls. An intense systematic literature search was also conducted using keywords 'Dermatoglyphics', 'Acute Lymphoblastic Leukemia' etc, from PUBMED, Medline, Google Scholar, EBSCO, HINARI etc. The review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Qualitative dermatoglyphics patterns like whorls, loops, arches, and quantitative parameters like angles(atd, dat, adt), absolute finger ridge count (AFRC), total finger ridge count (TFRC), a-b ridge count, mainline index and pattern index line were studied.

Results : Our research signifies an association between dermatoglyphic features and ALL. The mean ab–ridge count, and the mean atd angle were observed to be higher in cases while the mean dat angle was found to be lower in cases than controls. An increase in the frequency of whorls and a decreased frequency of loops in children suffering from ALL were noted. The quantitative analysis of patterns, mean pattern intensity index (PII) was found to be significantly higher in cases than controls.

Conclusion : The findings of the present study suggest a possible trend and an association of dermatoglyphic features with children suffering from ALL. Such studies can be useful in forensic cases where the linkage of dermatoglyphic features with certain diseases is to be established. Fingerprint studies provide a simple, inexpensive, anatomical, and non-invasive means of determining the diseases with genetic linkage and can be employed as a method of screening the acute lymphoblastic leukemia of the high-risk population on early detection, thus reducing morbidity and mortality. Future studies can be done considering the limitations of earlier studies, reanalyzing the existing data in the literature, and therefore ensure the findings of dermatoglyphic research in the medical field.

Keyword : Dermatoglyphics, Acute Lymphoblastic Leukemia, Quantitative and Qualitative

PP03-10

Wearble technology to assess the sleep quality of patients with acute lymphoblastic leukemia after treatment with chemotherapy

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Background : In the case of Acute Lymphoblastic Leukemia, patients were treated with chemotherapy and suffer with poor sleep. Disturbances in sleep are not a common problem and not charcterised in patient, beyond this it is observed. The aim of present study is to analyse the practicability of quality of sleep in the patients with Acute Lymphoblastic Leukemia with the help of actigraphy device (wearble watch)

Method : 42 participants were participated in the current design study. We used the wearable watch Actigraph GT3X to measure latent time of sleep, total sleep hour, sleep onset after sleep, onset sleep in this awakening number and patient sleep efficiency after treated with chemotherapy in patients with Acute Lymphoblastic Leukemia/. Pittsburg sleep quality parameter were measured by self reported by pateint

Results : Out of 42 patients, only 35 respondents were completed the actigraphy study and measurements of PSQI, to determine the practicability. Respondents receive and wear the watch for the 10 days with mean and SD (17.87), that refers to bad sleep of patients. Respondents showed sleep awakening time of 7.21 (median) with the sleep onset after awakenings of 5 and latent time of sleep median is 9.5min. Efficiency of sleep was higher with median of 0.89 that indicates patients with Acute Lymphoblastic Leukemia had sleep disorder, because of interruptions during sleep for example supplementation of drugs, insomnia, disturbances factors and bad dream.

Conclusion : It was concluded from current study that patients wore a watch that is feasible device to asseses the sleep. It was observed that patient with Acute Lymphoblastic Leukemia have bad sleep and needs a special treatment and supportive care. More research is required to improve the quality of sleep duration in patients with Acute Lymphoblastic Leukemia.

Keyword : Wearble, Device, Actigraphy, Sleep

PP03-11

Methotrexate mitigates leukemia by targeting toll/NF-kB pathway in both in vivo and in vitro model systems

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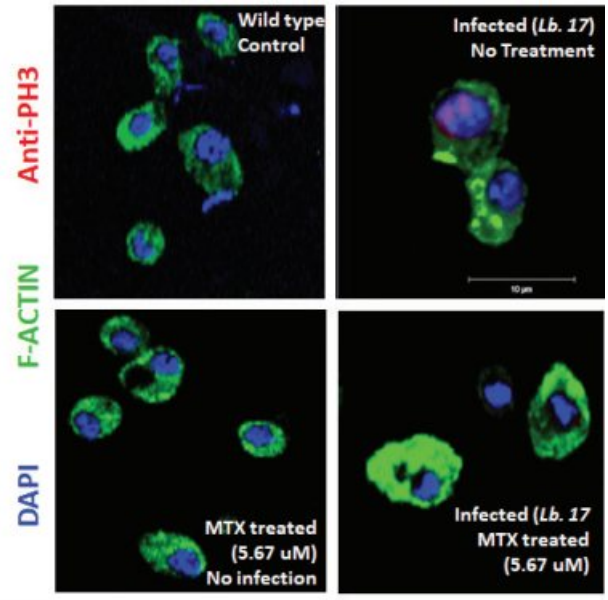
Background : Leukemia is a type of cancer associated primarily with bone marrow cells. Methotrexate (MTX) is a folate antagonist used in the treatment of leukemia, lymphoma, lung cancer, breast cancer etc. It exhibits common side effects (nausea, increased risk of infection, dizziness etc.) and some severe side effects (bone marrow damage, leukopenia, hepatotoxicity, and kidney related disorders). MTX is known to inhibit JAK/STAT pathway that intrigued us to further understand its effects on other important hematopoietic pathways. Successful treatment of acute leukemia using MTX needs further research in understanding its role in targeting the key hematopoietic signaling pathways

Method : Current study is focused on using an in-vivo (Drosophila) and in-vitro (K562 leukemic cell-lines) model systems to decipher the effect of MTX on cancerous blood cells through two important hematopoietic signaling. We studied the effects of MTX on Toll/NF-κB and RAS pathway from whole animals and specifically in the blood cells of wild type, wasp infested and Ubc9-/- mutants (Ubc9 is a negative regulator of Toll pathway). Immunofluorescence assay, qRT-PCR and western-blot analysis were performed to examine different components of hematopoietic pathways. We analyzed protein localization of the NF-κB and its inhibitor Ik-B in the immune cells using immunofluorescence.

Results : Toll/NF-κB pathway is involved in both proliferation and inflammation of blood cells in Drosophila and mammals. Earlier studies showed that MTX inhibit NF-kB pathway (in-vitro, 10 μM in Jurkat cells, Hela and U937 up-to 60 minutes). We observed that MTX inhibits wasp induced encapsulation response thereby inhibiting the penetrance and the expressivity of the encapsulated bodies in host larva accompanied with a reduction in the mitotically active blood cells (Cyclin-A, Cyclin-B and Anti-PH3). MTX significantly inhibits nuclear localization of NF-κB by retaining it in the cytoplasm in the immune tissues (hemocytes, lymph gland and fat body) of Drosophila. Positive regulator (SPE) and the readout of the pathway (Drosomycin) showed reduction in their expression along with their protein levels whereas negative regulator Iκ-B of the pathway showed up-regulation after MTX treatment. Similar observation was found in the RAS pathway components (EGFR and Ras-GTPase) as well. While in-vivo (Drosophila) MTX is shown to down-regulate NF-κB pathway, surprisingly we found that prolonged treatment with MTX in-vitro in leukemia cells (K562) showed up-regulation of the NF-kB pathway. We noted that the read outs not only the TLR-2 but also COX1 showed up-regulation upon prolonged treatment.

Conclusion : We determined that MTX treatment suppresses blood cell proliferation in animals with defective hematopoiesis. Our results establish that MTX inhibits Toll/NF-κB and RAS pathway along with reduction in the number of associated blood tumors. We understand from our results a role of MTX in modulating these important hematopoietic pathways in cancerous cells. We further conclude that longer treatment of MTX has a reverse effect on NF-kB pathway in leukemia cells (K562) thereby revealing an opposite role of MTX on modulating NF-kB signaling. This study underscores the importance of MTX in regulating cancerous cells with its hold on hematopoietic signaling.

Keyword : Methotrexate, NF-kB, Blood, Tumor, Proliferation



PP03-12

Anti-leukemic effects of Ibrutinib on B-cell acute lymphoblastic leukemia cells

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Background : The incorporation of tyrosine kinase inhibitors in the treatment of Philadelphia-positive Acute lymphoblastic leukemia (ALL) significantly improved treatment outcomes, but the treatment of B-cell ALL is still challenging. Recently introduced kinase inhibitors targeting B-cell receptor (BCR) proteins showed impressive results in mature B-cell malignancy. The signaling pathway of the precursor B-cell receptor (pre-BCR) is similar to the mature BCR pathway. We investigated anti-leukemic effects and the mechanism of action of ibrutinib in B-cell ALL cells.

Method : B-cell ALL cells (KASUMI-2, TOM-1, RCH-ACV, NALM-20, and REH) were used for this study. Cell lines were validated by flow cytometry with the pre-BCR-specific monoclonal antibody (HSL2). Cell viability and cell doubling time were performed using Celltiter-glo luminescent cell viability assay (Promega, WI). The proteins signal transduction and apoptosis were detected with immunoblot assay using specific primary antibodies.

Results : Ibrutinib caused a dose-dependent inhibition of various B-cell ALL cells. According to the viability test, KASUMI-2 (pre-BCR+) was most sensitive to 1 uM of ibrutinib, followed by TOM-1 (pre-BCR-), RCH-ACV (pre-BCR+), and NALM-20 (pre-BCR-). Pre-BCR- RCH was resistant to ibrutinib. All of these cells expressed BTK, there was

no difference in cell survival and BTK expression. After exposure to 1uM of Ibrutinib in 96 hours, the immunoblotting showed decrease of phosphorylation of AKT and ERK protein, and there was no phosphorylation of SYK protein in KASUMI-2 cell. On the other hand, the other B-cell ALL cells including pre-BCR+ RCH-ACV, showed no difference in phosphorylation of SYK protein. Survivin protein was decreased in KASUMI-2 cell, there was no significant change in the other apoptotic proteins.

Conclusion : Our preclinical studies revealed the anti-leukemic effect of Ibrutinib in B-cell ALL cells. Phosphorylation of SYK protein may induce resistance to ibrutinib. Inhibition of BTK and SYK can be a potential therapeutic option for B-cell ALL.

Keyword : Acute Lymphoblastic Leukemia, BTK, SYK

PP03-13

Anti-proliferative and apoptotic effect of zeaxanthin on different malignant cell lines

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Background : Zeaxanthin is one of the most common carotenoid alcohols found in nature. The beneficial effect of zeaxanthin from fruits and leafy green vegetables on a variety of chronic diseases and particularly its association with decreased incidence of prostate and breast cancer seems to be well established. It has been reported that higher intake and higher blood levels of zeaxanthin appear to be associated with a lower risk of occurrence of prostate and breast cancer. The aim of the study was to examine anti-proliferative and apoptotic effect of zeaxanthin on other malignant cell lines.

Method : Cells of the following lines were incubated with 1.0, 2.0, and 4.0microM of zeaxanthin: human colon carcinoma (HuCC), B chronic lymphocytic leukemia (EHEB), human erythroleukemia (K562) and Raji, a prototype of Burkitt lymphoma cell line.

Results : The results showed that zeaxanthin exerted a significant dose-dependent effect on the proliferation capacity of K562, Raji and HuCC lines, whereas this effect was observed in EHEB cells only with the highest dose used in the study. Increased apoptotic rate was found after incubation of HuCC cells with 2.0 and 4.0microM of zeaxanthin and in Raji cells following incubation with 2.0microM.

Conclusion : The findings point out that the anti-proliferative effect of zeaxanthin on tumor cells and its effect on the apoptotic rate depends on its dosage and on the type of the malignant cells, suggesting that zeaxanthin may be a promising agent to be explored for the prevention and treatment of malignant cells. These studies are consistent with epidemiological studies that show inverse relationships of these carotenoids with prostate cancer.

Keyword : Tumor Cells , Prostate Cancer, Zeaxanthin, Carotenoids

PP03-14

Anti-leukemia effect of solid lipid nanoparticles of hesperidine against the benzene induced leukemia via regulation of growth factors and inflammatory mediators

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Background : The incidence of deadly diseases world widely is alarming and one of the deadliest disease currently killed to animal and human is cancer. Leukaemia has been characterized as a cancer of bone marrow or blood affecting haemopoietic stem cells, described by uncontrolled accumulation and proliferation of malignant leukocytes in peripheral blood and bone marrow usually results from mutation in DNA. The aim of the current investigation to explore the antileukemic effect of solid lipid nanoparticles of hesperidine (SLN-HP) on benzene induced leukemia bearing rats.

Method : Double emulsion solvent displacement method was used for the preparation of SLN-HP. Intravenous injection of benzene (0.2 ml) was used for the induction of leukemia. The rats were divided into different groups and received the SLN-HP and cyclophosphamide. Body wright, hematological, antioxidant and pro-inflammatory parameters were estimated, respectively. Spleen and liver tissues were macroscopically and microscopically evaluated.

Results : Surface methodology suggests the 170 2 nm particle size and 0 360 poly-dispersity index for SLN-HP. SLN-HP significantly altered the hematological parameters such as RBC (45.5%), WBC (48.4%), neutrophils (43.4%), lymphocytes (49.3%), eosinophils (53%), basophils (38.3%), monocytes (37.6%) and monocytes (45.5%), respectively. SLN-HP also increased the level of SOD (45.6%), GSH (42.3%), CAT (48.3%) and reduced the MDA (69.8%) level. The pro-inflammatory cytokines such as TNFα (38.4%), IL-1β (43.4%), IL-6 (65.5%) and inflammatory mediators such as iNOS (57.4%), GM-CSF (50.3%) and VEGF (48.5%), respectively. Macroscopically, benzene induced group showed the enlargement of spleen and liver tissue and SLN-HP treated group reduced the spleen and liver tissue.

Conclusion : The current study suggested anti-leukemia effect of SLN-HP via reverses the leukaemic effect induced by benzene in the experimental rats via inflammatory mechanism.

Keyword : Leukaemia, Benzene, Nanoparticle, Nanoparticle, Inflammation

PP03-15

Anti-leukemic effect of ajwain oil against DMBA induced leukemic rat

model: Possible mechanism of action

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Background : Leukemia is a malignant blood disease induced by the over-generation of huge number of immature blood cells that enter the peripheral blood. Leukemia considered as the 9 th most common cancer in men and 12 th rank in women. Its etiologic factors such as environmental, genetic alteration, viruses, alcohol consumption, immune deficiency and chemicals. Available treatment for the disease are chemotherapy, allogeneic cell transplantation and radiation therapy with side effects. Due to side effect associated with the treatment, medicinal herbs treatment having the more attraction to treat the leukemia. The aim of the current study to scrutinize the antileukemic effect of ajwain oil against the 7, 12-dimethyl benza[a]anthracene (DMBA) induced leukemia in rats and explore the possible mechanism of action.

Method : DMBA was used for the induction of leukemia in experimental rats. The rats were divided into different groups and body weight, haematological parameters, DNA fragmentation and cell cycle regulatory parameter were also estimated. RT-PCR was used for the estimation of mRNA expression of sphingosine-1-phosphate receptor-1.

Results : Ajwoin oil treated rats showed the increased body weight as compared to other groups. Moreover, ajwoin oil decreased the blasts(56%) in leukemic rats. Its also altered the hemotological parameters such as WBC (35%), lymphocytes (43%), neutrophils (41%), monocytes (38%), esnophills (46%), basophils (42%) and monocytes (54%), respectively. Ajwoin oil treated rats showed the increased level of p21 and p53 and reduced level of cyclins D1 and E. RT-PCR showed the up-regulated of mRNA expression of sphingosine-1-phosphate receptor-1 of ajwoin oil treated group rats as compared to other groups.

Conclusion : The current study, showed the anti-carcinogenic effect of ajwain oil and highlights the possibility of its use in leukemia to minimize the side effect of the usual therapy.

Keyword : Leukemia, DMBA, Medicinal Herbs, Cytotoxicity, Sphingosine-1-Phosphate Receptor 1, Gene Expression

PP03-17

Association MTHFR gene polymorphisms in promotor-677C/T with risk for adult acute lymphoblastic leukemia in Asia population: An update meta-analysis

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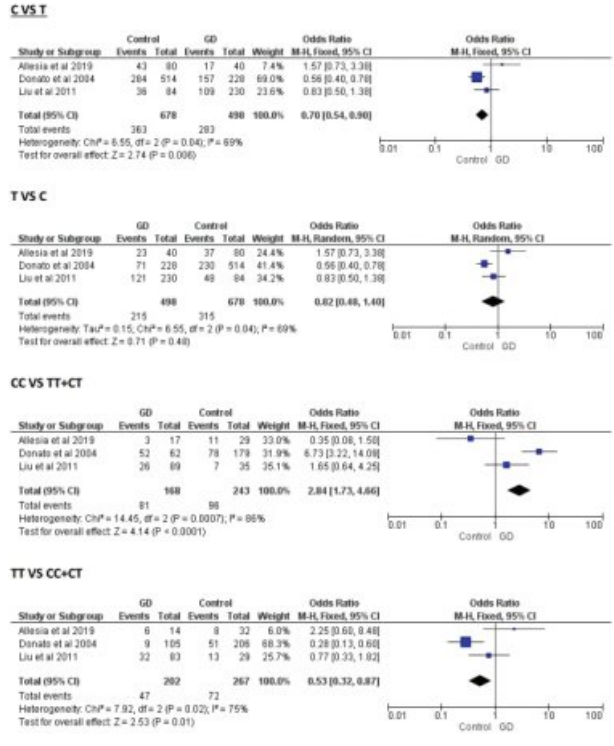
Background : Genetic polymorphisms in methylenetetrahydrofolate reductase (MTHFR) gene have been associated with the development of acute leukemias. MTHFR is a key enzyme in folate metabolism involved in DNA methylation which is a predominant circulatory form of folate. Folate deficiency results in uracil mis-incorporation during DNA replication, inducing strand breaks resulting in chromosomal translocations and deletions associated with increased risk of leukemia.

Method : This Meta-analysis is accordance with the PRISMA guidelines. Literature search from Pubmed and EMBASE are conducted until December 2020. Literature are limited to English. Included studies in this meta-analysis determine its quality using the Newcastle Ottawa (NOS) scale. The relationship between promotor-677C/T in MTHFR gene polymorphism with a risk of incidence of Acute Lymphoblastic Leukemia (ALL) in adult ASIA population are counting pooled by OR and 95% CI.

Results : 3 studies met the inclusion criteria. From the results obtained polymorphism - 677C/T in the MTHFR gene was associated with an increased risk (CC vs TT + CT, OR 95% CI =2.84 [1.73 – 4.66], p=0.0001) and decreased risk of ALL (C vs T, 95% OR =0.70 [0.54 - 0.90], p=0.006; T vs C, OR 95% CI =0.82 [0.48 – 1.40], p=0.48; TT vs CC + CT, OR 95% =0.53[0.32-0.87], p=0.01).

Conclusion : MTHFR Gene Polymorphisms in Promotor-677 C/T has association with risk of adult ALL in ASIA population

Keyword : ALL, MTHFR, Promotor-677 C/T



PP03-18

Factors related to quality of life of children with acute lymphoblastic leukemia who undergo chemotherapy

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Background : Acute Lymphoblastic Leukemia (also called ALL or Acute Lymphocytic Leukemia) is a cancer of the blood and bone marrow. This type of cancer usually gets worse quickly if it is not treated. ALL is a type of leukemia that is most prevalent among children which is around 75-80%. The progress of chemotherapy for ALL has increased the survival rate for this cancer. Chemotherapy is the treatment of cancer with a long period of time and most often done which can cause side effects that interfere with the function of physical and psychosocial function. This study aimed to identify factors that are related to the quality of life of children with acute lymphoblastic leukemia who undergo chemotherapy in several hospitals in Indonesia.

Method : The method used was studying secondary data from published journals. Of the several journals collected, 12 articles were selected. The search for articles included the following criteria; the articles must be published in the last 8 years (from 2010-2018) and the ALL patients conducted in Indonesia.

Results : Based on the dependent variable, the length of life of the patients is often not accompanied by the better quality of life due to chemotherapy side effects towards patients' physical and psychosocial conditions. In Indonesia the ALL is the highest ranked cancer in children that causes of death in children. The results showed that there was correlation between chemotherapy phases and nurses roles with generic quality of life.

Conclusion : It is recommended for health care provider to improve outreach to the community, especially about the associated factors of ALL. Thus, there is a need to improve nurses' roles through education and training regarding chemotherapy management and its side effects for ALL.

Keyword : Chemotherapy Phases, Quality of Life, Acute Lymphoblastic Leukemia, Indonesia

PP03-19

Identification of acute lymphoblastic leukemia (ALL) cells in peripheral blood smear image based on morphology of white blood cells (WBC) with classification technique using support vector machine (SVM)

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Background : Acute lymphoblastic leukemia (ALL) is a type of leukemia (white blood cell cancer) that generally occurs in children. The highest incidence rate is around 80% of sufferers aged 1-4 years and their malignancy develops rapidly, if not treated immediately it can be fatal to the patient's condition within a few months. Early detection is very important for more effective treatment steps. This research proposes a system for Acute Lymphoblastic Leukemia (ALL) cell identification in the peripheral blood smear image based on morphological characteristics.

Method : Data in the form of ALL blood smear images were obtained from Fabio Scotti, University of Milan, Crema, Italy which consisted of two versions namely ALL_IDB1 and ALL_IDB2. The algorithm used includes several steps: pre-processing, image segmentation, feature extraction, and classification. K-means clustering algorithm based on color segmentation is used to separate the peripheral blood smear image into four areas: background, WBC nucleus, WBC cytoplasm, and RBC. Nuclei are overlapping then separated by applying the watershed transform method. In this study, identification of Acute Lymphoblastic Leukemia (ALL) cells based on morphological characteristics was carried out. Color-based segmentation can work to separate components from blood smear images, but it needs to be considered in the process of coloring the slides. Because the quality of coloring affects this process. The application of median filters, K-means clustering, and morphological operations prior to the watershed transform can avoid over-segmentation.

Results : The Support Vector Machine method gives promising results on the classification of normal white blood cells and ALL cells. The accuracy of the introduction of this method to all test images was 96.45%.

Conclusion : The conclusion in this study obtained a very good classification close to perfect value because the accuracy value shows that the system is built capable of identifying ALL cells and normal white blood cells with very satisfactory performance.

Keyword : ALL Identification, Blood Smear Image, Support Vector Machine (SVM), White Blood Cells (WBC)

PP03-20

Acute lymphoblastic leukemia with lytic lesions

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Background : Acute Lymphoblastic Leukemia(ALL) is a well known hematologic malignancy. Approximately 75-80% cases are of B cell origin whereas 15-20% of cases are of T-lineage. ALL is rarely associated with lytic lesions in bone. Here we are presenting such a unique case.

Method : The case was selected from Leukemia clinic of our hospital.

Results : The patient was 66 years of male with pain in left hip,-weight loss,and fever for 3 months.He was diabetic and hypertensive for more than 5 years. Laboratory investigations showed Hemoglobin 9.2 gm%, platelet count-31000/cmm and Total Leukocytes Count(TLC) 8600/cmm. Peripheral blood smear showed 41% blasts. Bone marrow aspiration showed 90-95% blasts. On immunophenotyping by flowcytometry (blood sample), it showed 40% blasts which were positive for cCD79, CD34,CD33, CD45,HLA-DR,CD19,CD38,CD10 and TdT and negative for MPO, CD3, CD13,CD20,CD22,CD23,CD5;B-ALL was suggested. The patient was having a soft tissue mass in left iliopsoas muscle, which on biopsy showed infiltration by abnormal lymphoid cells positive for CD20 and TdT and negative for CD3.Low grade Non Hodgkin Lymphoma(NHL) was suggested. Radiology showed focal lytic lesions in multiple dorso-lumbar vertebrae and pelvic bones. On further work-up, Lymphoma and Myeloma was excluded and ALL with lytic lesions was considered and managed accordingly.

Conclusion : ALL is relatively uncommon in adults. When it is associated with soft tissue mass and bony lytic lesions, it becomes a case of severe diagnostic dilemma. Soft tissue lesion is common in AML as Myeloid Sarcoma, but extremely rare in ALL, although IHC markers of the mass are matching with B-ALL. Evaluation of M-band, immunofixation and beta-microglobulin in serum as well as urine are required for exclusion of myeloma. Determination of cause of lytic lesions is warranted for adequate management.

Keyword : Acute Lymphoblastic Leukemia, Lytic Lesions, CML

PP03-21

A case illustrating therapy-related acute lymphoblastic leukemia eventually progressed to therapy-related myelodysplastic syndrome with clonal branching evolution

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Background : Therapy-related acute lymphoblastic leukemia (t-ALL) has been recently emerged as a distinct entity due to the rarity of the disease, whereas therapy-related myeloid neoplasms (t-MNs) are well-characterized complications of cytotoxic chemotherapy and/or radiation therapy. We present the clinical, pathologic and molecular features of a case with prior treatment for breast cancer who developed t-ALL and subsequently therapy-related myelodysplastic syndrome (t-MDS) with a distinct pattern of clonal changes.

Method : The medical chart review was conducted for the case, focusing on past medical history, blood and bone marrow pathology, cytogenetics and mutation data.

Results : A 59-year-old women presented with circulating blasts and prior history of breast cancer and lung metastasis treated with chemotherapy regimen (doxorubicin, cyclophosphamide and paclitaxel, 15 years ago; docetaxel, 5 years ago) and radiotherapy 15 years ago. The blasts were 83.8% of bone marrow cells and expressed CD34, TdT, CD10, CD19, cytoplasmic CD22, CD33 and CD13. These findings were consistent with B-lymphoblastic leukemia. Chromosomal analysis showed a normal female karyotype. Next-generation sequencing assay revealed DNMT3A p.R736H (variant allele frequency [VAF] 43.4%) and PTPN11 p.G60V (VAF 33.7%). She achieved remission after induction chemotherapy including cyclophosphamide, vincristine, doxorubicin, and dexamethasone. She remained remission for 1.7 years when bicytopenia (hemoglobin, 8.4 g/dL; platelet count, 38 x 109/L) developed. Bone marrow examination showed multilineage dysplasia with 5.8% of myeloblasts supported by immunohistochemical positivity for CD34 and CD117. Chromosomal analysis showed a complex karyotype (46,XX,-5,del(7)(q11.2),del(9)(q22q32),-18,+2mar[17]/46,XX[3]). NGS assay detected DNMT3A p.R736H (VAF 5.0%) and TP53 p.N131fs (VAF 9.2%). She was diagnosed with t-MDS and underwent supportive therapy. This case illustrated that t-ALL could be considered as one of the therapy-related hematologic cancers as well as t-MNs could be considered as one of the complications during the clinical course of ALL. Moreover, NGS assay found genetic evolution with stable mutation (DNMT3A), gained mutation (TP53), and lost mutation (PTPN11), which is called branching evolution.

Conclusion : We report a unique case of t-ALL and subsequently progression to t-MDS in the setting of clonal hematopoiesis (CH). DNMT3A is a representative mutated gene in CH. Dominance and stability of this mutation indicates a triggering role of CH mutations in therapy-related hematologic cancer caused by cytotoxic damage and rapid hematopoietic stem cell expansion.

Keyword : Therapy-related ALL, Therapy-Related MDS, Clonal Hematopoiesis, Branching Evolution

PP03-22

Mixed phenotype acute leukemia - A pathologist's nightmare

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Background : Mixed phenotype acute leukemia (MPAL) is a heterogeneous category in WHO classification that comprises acute leukemia with discrete admixed populations of myeloid and lymphoid blasts or with extensive coexpression of myeloid and lymphoid markers in a single blast population. It comprises 0.5-1% of all the acute leukemia cases.

Method : A 36 year old male patient presented with neck swelling for 1-2 months.On examination he had bilateral massive cervical and inguinal lymphadenopathy but no organomegaly.

Results : Laboratory investigations showed Hb of 10 g/dl, total count of 36.2X103/µl, platelet count of 129.0X103/µl. Peripheral smear showed 90% blasts. Flow cytometric analysis revealed 2 population of blasts one expressing MPO with aberrant expression of CD7 & CD56 but cCD3 negative and other expressing T cell antigens but MPO negative. Immunohistochemistry on lymph node showed positivity for CD3,CD5,CD34,Tdt suggestive T lymphoblastic leukemia. MPO was negative on the lymph node.Molecular studies were sent to outside lab.Reports awaited.

Conclusion : Mixed phenotype acute leukemia poses to be a diagnostic dilemma unless a thorough laboratory evaluation is offered. A broad folwcytometry panel and molecular studies in conjunction with morphology is a must to confirm the diagnosis in such cases.

Keyword : Mixed Phenotype, Acute Leukemia, Flow Cytometry, T Lymphoblast

PP 04-01

Pulmonary hypertension in newly diagnosed and tyrosine kinase inhibitor-treated chronic myelogneous leukemia patients: A single center retrospective analysis

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Background : Dasatinib, a tyrosine kinase inhibitor (TKI), is well known to induce pulmonary hypertension (PH) in patients with chronic myelogenous leukemia (CML), which is usually reversible by discontinuing the agent. However, this is based mainly on case reports and small-sized case series. In addition, it remains unclear whether other TKIs, such as imatinib or nilotinib, are also linked to PH. Furthermore, there have been few reports on PH in newly diagnosed CML patients. In this study, we analyzed the prevalence of PH and its clinical implications in both newly diagnosed and TKI-treated CML patients.

Method : Patients and Methods: The medical records of newly diagnosed CML patients who underwent transthoracic echocardiographic examination (TTE) at diagnosis and TKI-treated patients who underwent TTE at least once during treatment at Chungnam National University Hospital from January 2003 to June 2020 were analyzed retrospectively. TTE results were reviewed by two cardiologists and a diagnosis of PH was made when the PH probability was "high" according to the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines.

Results : Of 189 CML patients diagnosed and/or treated during the study period, 57 (30.2%) and 112 (59.3%) underwent TTE at the time of CML diagnosis and during TKI treatment, respectively; thus, enrolled in the study. The majority of patients underwent planned TTE for screening for PH; i.e, only 7 (12.3%) of the 57 newly diagnosed patients and 11 (9.8%) of the 112 TKI-treated patients underwent TTE duet to cardiopulmonary symptoms. Among the 57 newly diagnosed patients, 4 (7.0%) had PH. All the 4 patients with PH had palpable splenomegaly and high Sokal score. PH was resolved in 3 (75.0%) of the 4 patients after the TKI treatment (imatinib in 2 patients and nilotinib in 1 patient). PH was lasted for 8 years in a male patient (61-year old at CML diagnosis) despite changing TKI (imatinib, nilotinib and dasatinb in order). Time receiving any TKI(s) was a median of 40.4 months (range: 0.1-167.2 months) in TKI-treated patients. PH was found in 12 (10.7%) patients among the 112 TKI-treated patients. PH was most frequently detected in the dasatinib-treated patients: 3 (7.5%) of 40 imatinib-treated group, 1 (3.1%) of 32 nilotinib-treated group, and 8 (21.6%) of 37 dasatinb-treated group had PH. In multivariate logistic regression analysis, age > 60years (odds ratio 12.3; 95% CI, 1.1-142.1, P=0.044), dasatinib treatment (odds ratio 8.2; 95% CI, 1.3-50.6, P=0.026), and positive cardiopulmonary symptoms/signs at the time of undergoing TTE (odds ratio 36.1; 95% CI, 5.3-247.3, P=0.001) were statistically significant risk factors for developing PH. PH was resolved in 5 (62.5%) of the 8 dasatinib-treated patients after discontinuation of the agent. On the other hand, PH was persistent in 3 patients: 1 have had PH since CML diagnosis and 2 retained PH despite discontinuing dasatinib. Among them, 1 patient had symptoms relevant to PH. All the 3 imatinib-treated patients recovered from PH: 1 after changing TKI and 2 despite continuing imatinib. One nilotinib-treated patient also recovered from PH after changing TKI.

Conclusion : PH is common in CML patients who are treated with dasatinib; however, it is also noted in patients treated with imatinib or nilotinib and even in newly diagnosed patients. Careful screening for PH, not only during dasatinib treatment but also at the time of diagnosis and during any TKI treatment, is warranted in patients with CML.

Keyword : Chronic Myelogenous Leukemia, Pulmonary Hypertension, Tyrosine Kinase Inhibitor, Dasatinib

PP 04-02

Clinically diagnosed chronic myeloid leukemia in hyperleukocytosis complicated by acute respiratory distress syndrome from SARS-CoV-2 (COVID-19)

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Background : Symptomatic hyperleukocytosis in CML is a medical emergency characterized by extremely elevated blast cell count and symptoms of decreased tissue perfusion. Immunosuppression among patients with malignancy is a risk factor for susceptibility to develop COVID-19. We present a case of a clinically diagnosed CML in hyperleukocytosis complicated by ARDS from COVID-19.

Method : Case Report

Results : A 48-year-old female presented with a ten-day history of cough with dyspnea. She was tachypneic, tachycardic and hypoxemic. Pertinent physical examination revealed bibasal crackles and splenomegaly. Diagnostics revealed bilateral pneumonic densities; CBC showed anemia (Hgb 102 g/L) and hyperleukocytosis (WBC 390 x 109/L) with left shift; elevated inflammatory markers (D-dimer, CRP, Ferritin and LDH); ABG showed PF ratio: 115 and ROX index: 7.82. She was placed on high-flow nasal cannula, given oral cytoreduction (Hydroxyurea), aggressive IV hydration and tumor lysis syndrome prophylaxis. Piperacillin-Tazobactam and Azithromycin were started. FISH for BCR-ABL was not facilitated due to enhanced community quarantine restrictions. On the second hospital day, she developed ARDS. Repeat workups revealed progression of pulmonary infiltrates, further increase in WBC count (512 x 109/L), ABG showed PF ratio: 57 and ROX index: 3.92. Her symptoms progressed and she eventually succumbed to the disease. Postmortem, RT-PCR (oropharyngeal swab) was positive for SARS-CoV-2.

Conclusion : Patients with hematologic malignancy are at increased risk for severe COVID-19. Acute pulmonary complications among these patients should raise also suspicion for leukostasis. Factors that may have contributed to disease progression were cytokine storm from SARS-CoV-2, severe tissue hypoxia from leukostasis and overwhelming sepsis.

Keyword : Chronic Myeloid Leukemia, COVID-19, ARDS, Hyperleukocytosis

PP 04-03

A case of e1a2 (Minor, P190) BCR-ABL1-positive chronic myeloid leukemia in Korea

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Background : The Philadelphia chromosome, resulting from the chromosomal translocation t(9;22), contains the BCR-ABL1 fusion gene, which is the hallmark of CML. Over 95% of CML patients are BCR-ABL1-positive. Depending on the breakpoint in the BCR gene, the fusion gene product varies in size: major p210, minor p190, and micro p230. The most common form, the major BCR-ABL1 rearrangement, is mostly observed in CML patients, whereas the minor BCR-ABL1 rearrangement is more common among patients with acute lymphoblastic leukemia (ALL). Minor BCR-ABL1-positive chronic myeloid leukemia (CML) is very rare that only 1–2% of patients with CML have this fusion gene as a sole rearrangement.

Method : To the best of our knowledge, of the several cases in the literature, only one has been reported in Korea so far. Here, we report a second case of minor BCR-ABL1-positive CML in Korea. Through this case, we intend to remind readers about the unique characteristics of minor BCR-ABL1-positive CML, which may confound physicians into a misdiagnosis, and warn about its less favorable prognosis despite the use of tyrosine kinase inhibitor (TKI) therapy.

Results : An 81-year-old male was referred to the Division of Hematology-Oncology of National Health Insurance Service of Ilsan Hospital due to marked leukocytosis. The complete blood count (CBC) at referral indicated anemia, leukocytosis, and thrombocytopenia. The WBC differential count showed left shift in granulocytes and monocytosis (Fig. 1). His bone marrow was hypercellular, with an estimated cellularity of 70-90% with granulocytic proliferation. The number of megakaryocytes and dwarf megakaryocytes was increased. Approximately 5.3% of all nucleated cells (ANCs) were counted as blasts, while the population co-expressing CD34(+), CD117(+), and myeloperoxidase, corresponding to myeloblasts, were 2.28% of total events according to the flow cytometry (FCM) results. Monocytes accounted for 17.1% of ANCs, which was consistent with the FCM results of 17.4%. Conventional chromosome analysis using BM cells showed 46, XY, t(9;22)(q34;q11.2)[20]. Reverse transcriptase-polymerase chain reaction (PCR) showed minor (P190) BCR-ABL1 transcripts of the e1a2 type. No major (P210) and micro (P230) BCR-ABL1 transcripts were detected. The patient was diagnosed with minor BCR-ABL1-positive CML, in chronic phase.

Conclusion : This is the second minor BCR-ABL1-positive CML case reported in Korea, in addition to the several similar reports overseas. Our case matches the description of these prior reports in that CML with minor BCR-ABL1 is associated with significant monocytosis. The patient did not undergo TKI therapy immediately after diagnosis due to the presence of a ureter stone complicated by infection that required surgery. On November 26th, the patient was started on dasatinib, a second-generation TKI. Thus, it was too early (< 1 month) to predict treatment response. Nevertheless, minor

BCR-ABL1-positive CML has been correlated to a poor prognosis. CML patients with a minor BCR-ABL1 fusion gene respond more slowly to TKI treatment and are less likely to achieve a major molecular response. Therefore, a less favorable outcome can be expected in our patient compared with that of a patient with a typical major BCR-ABL1-positive CML.

Keyword : Monocytosis, e1a2 BCR-ABL1, Chronic Myeloid Leukemia, Tyrosine Kinase Inhibitor

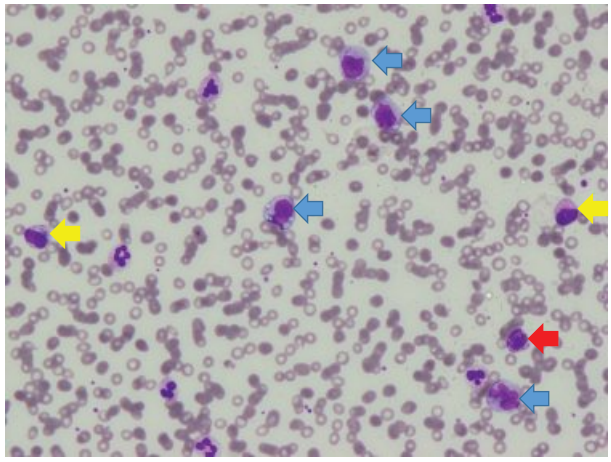

Fig. 1 The peripheral blood smear showed leukocytosis with monocytosis (blue arrows), basophilia (red arrow) and left shift (yellow arrow) (white blood cell 37.59 × 10^9/L with monocytes 19% and basophils 4%; Wright-Giemsa, ×400).

PP04-04

Measuring health related quality of life of chronic myeloid leukemia patients on newer generation TKIs using the Filipino version of the FACT-Leu questionnaire

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Background : Significant attention has been placed on recognizing impact of symptom burden and treatment-related toxicities on patients' health-related quality of life (HRQoL) since these would have an effect on treatment tolerability and adherence. In the Philippines, the only locally available TKIs are Imatinib and Nilotinib. Access and sustainability for the newer TKIs such as Dasatinib, Ponatinib and Bosutinib as second- or third-line agents is made possible with the help of The Max Foundation via their Max Access Solutions (MAS). There is paucity of published local data on HRQoL outcomes on Filipino CML patients treated with newer-generation tyrosine kinase inhibitors (TKIs). This study determined the HRQoL of Chronic Myeloid Leukemia (CML) patients on newer-generation TKIs using the Filipino-version of the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) Questionnaire©.

Method : A single-center, cross-sectional study included CML patients, aged ≥ 19, with stable comorbidities, taking newer-generation-TKIs as second-or-third line treatment (Dasatinib, Ponatinib and Bosutinib) for ≥ 3 months. HRQoL was assessed using the Filipino-version of the FACT-Leu© questionnaire. Descriptive statistics was used to summarize patients' demographic and clinical characteristics. Independent sample T-test and one-way analysis of variance was used to test significant difference between groups. STATA 13.1 was used for data analysis.

Results : All 33 patients were in chronic-phase. Newer-generation TKIs used were: Dasatinib (54.55%), Bosutinib (30.30%) and Ponatinib (15.15%). Mean scores: Trial Outcomes Index (106.15 + 12.27), FACT-G score (94.79 + 10.74) and FACT-Leu score (151.58 + 17.25) showed good HRQoL. There was no significant difference between HRQOL with sex, marital status, educational attainment, employment, adverse drug event with concomitant dose adjustment and newer-generation TKI used (p-value 0.786, 0.764, 0.764, 0.944, 0.864, 0.554); and insufficient evidence to conclude a correlation between overall FACT-Leu score to age, CML and treatment duration (p-value 0.7389, 0.4738, 0.6984).

Conclusion : HRQoL evaluation is a vital part of disease management. This study demonstrated that Filipino CML patients using newer-generation TKIs as second or third-line therapy showed good HRQoL regardless of age, sex, marital status, educational attainment, employment, CML duration, treatment duration, presence or absence of adverse drug event with concomitant dose adjustment and newer-generation TKI used.

Keyword : Quality of Life, Chronic Myeloid Leukemia, Protein Kinase Inhibitors

PP05-01

Outcome of non-Hodgkin lymphoma: A single center experience

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Background : Outcomes of pediatric Non-Hodgkin Lymphoma (NHL) are linked to its subtype and stage. Here, we describe treatment outcome of children with NHL at our center.

Method : We retrospectively collected data regarding presentation, type & stage and treatment outcome of 19 children with NHL diagnosed at our center between from Jan 2014 to Jan 2019.

Results : The mean age was 11.7 years (6 years to 18 years). The

male to female ratio was 18:1. Types of NHL were lymphoblastic lymphoma-8/19 (42%) (T cell-5 and B cell-3), anaplastic large cell lymphoma (ALCL)-4/19 (21%), Burkitt lymphoma was present in -3/19 (15%), Diffuse Large B-Diffuse Large B cell Lymphoma (DLBCL)-2/19 (10.5%), primary mediastinal B cell lymphoma-2/19 (10.5%). Staging showed Stage I-0, Stage II-1, Stage III-1 and Stage IV-17. Presentation at admission showed mediastinal mass -7/19 (37%), abdominal mass -7/19 (37%) bone metastasis-6/19 (32%) and superior mediastinal syndrome -5/19 (26%). One child had underlying Lynch syndrome and he presented with twin malignancies- B-cell NHL and metastatic adenocarcinoma of colon. The protocol used were ALCL99, LMB96, DA R-EPOCH and BFM 95.Treatment abandonment was high-7/19 (31.57%). Of the remaining 12 children 10 (83%) achieved complete remission (CR). Two had refractory disease and one relapsed in brain and all three died. The overall survival was 75% and disease free survival was 75% at median follow-up of 2.83 years.

Conclusion : In our small cohort, mediastinal mass was a common presentation and most children had Stage 4 disease. Abandonment rate was high and those who completed therapy had good outcomes.

Acknowledgements- Our deep appreciation and thanks to Mr. Indra Bhushan Pandey, our database manager, for retrieving the data.

Keyword : Non Hodgkin Lymphoma, Subtypes, Outcomes

PP05-02

Small extracellular vesicle-derived messenger RNA for liquid biopsy-based biomarker research in non-Hodgkin lymphomas

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Background : Non-Hodgkin lymphoma (NHL) is the most common form of blood cancer, and basically curable disorder by chemotherapy. However, a substantial number of NHL patients still experience relapses even after radiological imaging studies demonstrate completely disappeared tumor lesions at the end of treatment. Thus, the detection of treatment-resistant clones and minimal residual disease (MRD) during or after chemotherapy could help to develop the risk-driven treatment approach for NHL patients. Liquid biopsy has received huge attention during the past decade because it is a minimally invasive and convenient repeatable way to detect tumor-derived materials in blood or other body fluids. In particular, much progress has been made in the blood-based tumor diagnosis and surveillance using circulating tumor cells or tumor-derived DNA. Indeed, circulating tumor DNA (ctDNA)-based assessment of tumor genetic profiles in plasma or serum has been developed to serve as a diagnostic tool of MRD detection for monitoring of disease status in NHL patients. However, ctDNA might not exactly reflect disease status because a proportion of ctDNA derives from apoptotic dying cells rather than viable tumor cells. Extracellular vesicles (EVs) are highly abundant in almost all human biological fluids, including blood. Thus, EVs have been thought to hold tremendous potential as non-invasive biomarkers because intercellular communication via secreted EVs has a critical role in the pathogenesis of multiple disorders and the information within EVs could reflect their originating cells. Although diverse types of EVs could exist based on their size, origin and biogenesis, 'small extracellular vesicles (sEV)', also known as exosomes, are the smallest EVs having a dimeter of 30–150 nm. Tumor cells could constitutively release sEV into blood, and circulating tumor-derived sEV could contribute to tumor growth and metastasis through the transfer of sEV cargo including proteins, DNAs, messenger RNAs (mRNA), and microRNA. Thus, tumor-derived sEV as biomarkers through liquid biopsy has been widely explored such as the analysis of sEV cargo because sEV cargo could be used for the identification of tumors which sEV is originated. Although most previous studies have mainly focused on protein and microRNA cargo, the analysis of sEV mRNA also might provide the information representing the genomics of primary tumor cells. However, there is few study about the feasibility of sEV cargo mRNA as biomarkers for NHL patients. Therefore, this study analyzed whether serum-derived sEV mRNAs in NHL patients could predict treatment outcomes, and compared the clinical relevance of sEV mRNA profiles with that of ctDNA to validate their role as biomarkers for monitoring disease status.

Method : This study was aimed to explore the feasibility of serum derived sEV mRNA expression profiles as biomarkers for NHL patients. Thus, we isolated sEV from archived serum samples of NHL patients, and performed mRNA sequencing using RNA extracted from sEV cargo. Then, we analyzed the association of sEV mRNA expression profiles at diagnosis with primary tumor mutation profiles and treatment outcomes. Then, we compared serial changes of sEV mRNA expression with that of ctDNA mutation profiles in terms of predicting relapse. Patients were from our prospective lymphoma cohort study where blood sampling was taken from lymphoma patients at diagnosis, during and after the primary treatment, and at the time of relapse or progression after written informed consents. Out of patients enrolled into the prospective cohort study, the samples of 33 patients were analyzed in this study according to the following inclusion criteria: (1) patients were treated with curative intent; (2) patients had available data for treatment response and survival outcome; (3) patients had archived serum samples that obtained at the baseline, interim, end of treatment and/or relapse/progression; (4) patients had the data for ctDNA mutation profiles. We isolated sEV from serum samples using ultracentrifugation, and extracted RNA from isolated sEV. RNA sequencing was perfomed, and the TPM (transcripts per million) values for each gene were generated for the normalization of RNA sequencing data and comparison of sEV mRNA expression among patients.

Results : A total of 33 patients with NHL that were the study pop-

ulation of this study: diffuse large B-cell lymphoma (DLBCL, n =17), intravascular B-cell lymphoma (IVL, n =1), primary mediastinal large B-cell lymphoma (PMBL, n =4), follicular lymphoma (FL, n =3), mantle cell lymphoma (MCL, n =3), and extranodal NK/T-cell lymphoma (ENKTL, n =5). With the median follow-up of 38.9 months (95% Confidence Interval: 34.4 – 43.4 months), 20 patients died due to disease relapse or progression whereas the remaining 13 patients including two patients with relapse were alive at the time of analysis. The concentration of sEV was variable across subtypes of NHL, however, there was no significant difference among them. The size and morphology of sEV were not significantly different, either. The vesicular surface expression of CD81, CD63, and CD9 confirmed the quality of sEV samples isolated from each subtype. Considering the presence of sEV derived from non-tumor cells in patients' serum samples, we analyzed the proportion of CD20-positive sEV in patients with B-cell lymphoma including DLBCL and that of CD56-positive sEV in patients with ENKTL. Although the proportion of CD20 and CD56-positive sEV were variable, we found the presence of CD20- or CD56-positive sEV in the sEV samples isolated from patients' serum. The RNA concentration extracted from patients' serum-derived sEV samples was sufficient to perform RNA sequencing, and the RNA concentration was not significantly different across NHL subtypes. The mRNA expression was detected in sEV of 26 cases from baseline serum samples collected prior to treatment (79%, 26/33) and the remaining seven cases with less than 50 ng of RNA library failed to enter the RNA sequencing. The performance of sEV mRNA sequencing was not different across subtypes, and not significantly associated with stage, either. The analysis of sEV mRNA expression profiles of 25 patients with newly diagnosed NHL showed the presence of sEV mRNA expression at baseline sample was associated with poor progression-free survival (P=0.027). The OS also showed similar pattern although it failed to show statistical significance (P=0.057). The comparison of sEV mRNA expression with ctDNA mutation profiles between matched patients showed significant difference and sEV mRNA expression profiles detected genes compared to ctDNA mutation profiles although the number was small. The extent of mRNA expression was represented by TPM values, and the TPM values of relapsed patients with DLBCL and PMBL were higher than that of newly diagnosed patients although its difference was not statistically significant. The serial changes of TPM values of sEV mRNA expression profiles showed increase of TPM values at the end of treatment even though they achieved response in imagining studies, and they all relapsed at the time of analysis.

Conclusion : Our study demonstrated the feasibility of sEV mRNA expression profiles as a biomarker for NHL patients, and compared its performance as a liquid biopsy with ctDNA mutation analysis using matched patients' samples. Although this study has limitations, including a relatively small number of patients, our results may provide the rationale for the continuation of studies to explore the potential of sEV mRNA as a biomarker in NHL patients. Further study should be warranted to validate and confirm our results.

Keyword : Lymphoma, Exosome, Prognosis, Biomerker, RNA, Blood

PP05-03

Bone marrow involvement in lymphoma: Flow cytometry verusus bone marrow biopsy; The gold standard?

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Background : The most common extra nodal site of involvement in lymphoid malignancies is Bone Marrow. However, the frequency of its involvement varies among different lymphoma subtypes. (1). Routine staging in Non-Hodgkin's Lymphomas thus includes evaluation of bone marrow involvement as this serves important information affecting both prognosis and treatment. (2) Bone marrow biopsies are also routinely performed in post treatment assessment of Non-Hodgkin Lymphoma. Flow cytometric immunophenotypic analysis is long known essential technique for the diagnosis and classification of many hematologic disorders. Besides leukemia, FCM also has a key role in staging of Non-Hodgkin's Lymphoma by assessing bone marrow for involvement or by detecting relapse. FCM on peripheral blood smear also serves as an excellent screening tool for detecting leukemic presentation of lymphoma and thus guide in prognostication, risk stratification and treatment plan. The utility of flow cytometric analysis in routine staging of NHL has been evaluated by previous studies (4), however sufficient data and standardization protocols are lacking.

Method : 159 flow cytometry samples of bone marrow aspirates/PBS, and 427 BMA slides were received for staging or diagnosis of lymphoma over a period of 1 year between 1st February 2018 to 28 February 2019 at Laboratory Oncology Unit, Dr B.R.A.I.R.C.H, AIIMS, New Delhi. Each was evaluated for the presence of lymphoma , and if present the lymphoma was typed on based on IHC and other markers

Results : BMA morphology V/S FCM -66 bone marrow aspirate flow was run and results were concordant with morphological assessment in 87.8 % (58/66 cases). Results between morphological assessment of bone marrow aspirate and flow cytometry were discordant in 12.1% (8/66). PBS morphology V/S FCM 88 PB samples were evaluated by flow cytometry and results were concordant with morphological assessment of peripheral blood in 97.8 % (86/88) cases. Discordance was seen in 2 cases BMBx v/s FCM Among 66 FCM samples results were concordant in 56 /66 (84.84%) and discordant in 15.15%. 8 cases were picked up on FCM and were negative on BMBx wheras in 2 cases FCM was unable to pick up cells.BMA v/s BMBx Results were disconcordant in 87/372 (23.3%) with 17 cases being posistive on spirate and negative on biopsy and 72 cases positive on biopsy and negative on BMA.

Conclusion : We would like to conclude that flow cytometry, BMA and BMB are all useful methods for assessing bone marrow in NHL staging with each complementing the other. Although BMA and FC are not a substitute for BMB, they do play an important and complementary role in detecting a small portion of lymphoma cells in small subsets of patient as FC enables more specific gating of abnormal populations

Keyword : Lymphoma, Bone Marrow Aspirate, Flow Cytometry

		FCM(BMA)	BMA	
GROUP 1	47	+	+	
GROUP 2	4	+	-	2 Cases of DLBCL, 2 cases of diluted BMA slides
GROUP 3	4	-	+	1 case of hematogones, and 3 cases of? B-NHL
GROUP 4	11	-	-	

		FCM(PB)	PB(morphology)	
GROUP 1	80	+	+	
GROUP 2	2	+	-	1 mantle cell leukemia, 1 HCL
GROUP 3	0	-	+	
GROUP 4	6	-	-	

PP05-04

Diagnostic accuracy and prognostic relevance of immunoglobulin heavy chain rearrangement and 18F-FDG-PET/CT compared with unilateral bone marrow trephination for detecting bone marrow involvement in patients with diffuse large B-cell lymphoma

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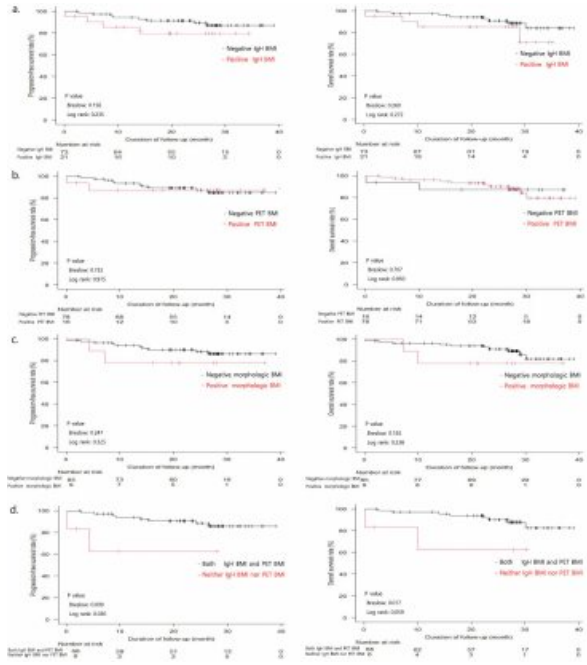
Background : In diffuse large B-cell lymphoma (DLBCL), bone marrow involvement (BMI) has the important clinical implication as a component of the Ann Arbor staging and clinical risk-stratification index including the International Prognostic Index (IPI). For many years, unilateral bone marrow (BM) trephination has been regarded as the gold standard for the evaluation of BMI in patients with DLBCL. The extent of lymphoma cell infiltration in the BM is a highly significant negative prognostic factor. However, BM trephination biopsy has some limitations, namely, low sensitivity to patchy or focal lymphomatous BM involvement, inter-observers'flexibility, and technical problem such as inappropriately obtained specimens. This study aimed to determine whether molecular analysis of immunoglobulin heavy chain (IgH) genes and 18F-FDG positron emission tomography-computed tomography (PET/CT) could increase the diagnostic accuracy and prognostic significance of BMI compared with bone marrow trephination biopsy.

Method : Over 94 de novo DLBCL patients (2017–2018 from a single institution) underwent 18F-FDG PET/CT, polymerase chain reaction (PCR) test for detection of IgH gene rearrangement, and unilateral BM trephination at the time of rituximab-containing treatment. BM trephination section biopsy and aspirate smears from DLBCL patients who had positive morphologic BMI (mBMI) were retrospectively reviewed by experienced hematopathologist in accordance to the WHO criteria. All patients underwent 18F-FDG PET/CT, and PET BMI was classified as either focal or diffuse according to the BM FDG uptakes on PET/CT by nuclear medicine physicians. The clonality of B-cell neoplasms was examined by conducting a BIOMED-2 clonality assay, while the IgH clonal gene rearrangements were detected using the IdentiClone IGH Gene Clonality Assay (Invivoscribe Technologies, San Diego, CA, USA) following the manufacturer's instructions.

Results : Among 94 patients with DLBCL, 9 (9.6%) were found to have morphologic BMI (mBMI) via BM trephination biopsy. Over 21 patients (22.3%) were confirmed to have IgH monoclonality (IgH BMI) based on the results of IgH gene rearrangement PCR assessment, while 16 (17%) had BMI based on the results of 18F-FDG PET/CT (PET BMI). The diagnostic accuracy of PET/CT was 81.8%, and the sensitivity, specificity, and NPV were 44.4%, 85.9%, and 93.3%, respectively. Moreover, the combined IgH rearrangement and PET/CT assessment increased a diagnostic accuracy of 88.0% with an 91.7% of NPV. A significant difference was observed in the PET BMI status between patients with stage I–III (3 of 70 patients; 4.2%) and those with stage IV (13 of 24 patients; 54%, P<0.001). A significant correlation was also found between detection of PET BMI and IPI risk groups (P=0.001). Moreover, a significant difference was observed in the IgH BMI status between patients with Stage I–II (5 of 47 patients; 10.6%) and those with stage III–IV (16 of 47 patients; 30.0%, P=0.017). IgH BMI was significantly increased in high-risk patients, depending on the IPI risk classification (IPI non-high risk vs high risk, P=0.039) The median duration of follow-up was 25.34 months (range: 0–39.1) at the time of analysis. After the follow-up period, 18 patients (19.1%) had disease progression and 12 (12.8%) died. In the whole population, the estimated 2-year PFS was 88.7 ± 3.4%, while the estimated 2-year OS was 87.8 ± 3.7%. Although the difference was not statistically significant, patients with BMI confirmed by BM trephination biopsy or PET/CT or IgH gene rearrangement PCR individually showed shorter progression free survival (PFS) and overall survival (OS) than those without BMI (P>.05, Figure 1a,1b,1c). The survival of patients with both PET BMI and IgH BMI were significantly worse than that of patients with either PET BMI or IgH BMI (2-year PFS: 62.5% vs 90.6%, P=0.009, 2-year OS: 62.5 vs 90.1% P=0.017; Figure 1).

Conclusion : The study results suggested that the combination of PET/CT assessment and IgH rearrangement could accurately identify a BMI compared with IgH or PET/CT alone. These noninvasive techniques can be used to determine the clinical factors for detecting BMI as an important part of the prognosis.

Keyword : Immunoglobulin Heavy Chain, FDG PET/CT, Bone Marrow Involvement, Diffuse Large B Cell Lymphoma



PP05-05

Role of FDG-PET/CT in the management of pediatric burkitt lymphoma

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Background : Burkitt lymphoma (BL) is highly FDG-avid even though its usefulness in the management of pediatric patients with BL is still controversial.

Method : We analyzed the role of positron emission tomography/computerized tomography (PET/CT) in staging and evaluation of tumor response in newly diagnosed children with BL receiving LMB 96 protocol. A total of 180 PET/CTs were performed in 94 patients (94 at diagnosis and 91 at time of evaluation). Involved areas were prospectively compared with those observed in contrast enhanced CT. Residual lesions in both PET/CT and contrast-enhanced CT were correlated with patient outcome at one year after end of treatment.

Results : A total of 199 disease sites were detected at PET/CT, while 172 sites were detected at contrast-enhanced CT and bone marrow biopsy (BMB). PET/CT showed improved detection of nodal lesions (P <0.0001) (Kappa value =0.633), extranodal lesions (P <0.0001) (Kappa value =0.632) and bone marrow (P <0.0001) (Kappa value =0.728) compared to contrast enhanced CT and BMB. PET/CT had upstaged 15 cases (16%) and downstaged 4 cases (4.3%) (P <0.001) (Kappa value =0.649). Among the upstaged 15 cases, 10 patients (10.9%) were upstaged from stage II to III, based on residual in PET/CT not seen in contrast enhanced CT after abdominal mass excision. Four patients (4.3%) were upstaged from stage III to IV based on bone marrow uptake in FDG-PET without positivity in BMA or BMB. Regarding response assessment, sensitivity was 60% for PET and 80% for contrast-enhanced CT (p=0.56). Specificity was 100% for PET and 65% for CT (p< 0.0001). Positive predictive value for PET was 100%, while was 12% for CT scan (p< 0.0001). Negative predictive value for both PET and CT was 98% (p=0.82). Five patients had 2nd biopsy to confirm viability of the residual lesions, 4 lesions were negative in pathological examination (all of them were metabolic negative in PET/CT; Deauville score below 4). One lesion was positive in pathological examination (was positive in PET/CT; Deauville score of 4).

Conclusion : PET/CT detected additional sites compared with contrast-enhanced CT and resulted in changing stage of disease. PET scan is significantly more specific than CT in the management of children with Burkitt lymphoma.

Keyword : FDG-PET/CT, Burkitt Lymphoma , Pediatric

Correlation between results of FDG-PET/CT and CIM & BMB and outcome at 6 months Follow up.

PP05-06

Clinical outcomes of early-progressed follicular lymphoma in Korea: A multicenter, retrospective analysis

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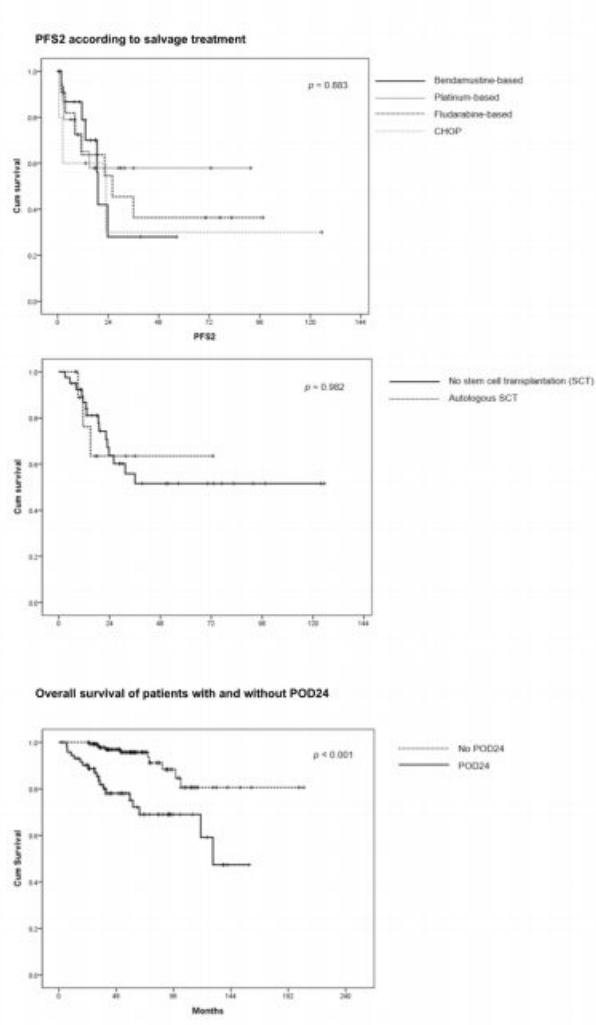
Background : While the expected survival of patients with follicular lymphoma (FL) almost reaches that of the normal population, the outcomes of patients who experience early progression within 24 months, that is, POD24 is dismal. To define outcomes and treatment patterns FL with POD24 in daily practice, we performed a multicenter, retrospective analysis.

Method : The clinical data of the patients who met following criteria were collected retrospectively, 1) Histologically confirmed diagnosis of FL grade 1, 2, and 3A; 2) Documented progression within 24 months after initiation of induction chemotherapy; 3) Available medical records including clinicopathologic characteristics and clinical outcomes. The primary endpoint was overall survival (OS) from the first diagnosis of FL, and OS was compared with our historical cohort of 147 FL patients without POD24.

Results : From 2007 to 2019, a total of 73 cases were eligible for analysis. Median age at diagnosis was 53 (range, 28 – 83) and 45 patients (61.6%) were male. Most patients had an advanced disease at diagnosis (I~II 11, III~IV 62). In terms of FLIPI-1 risk group, 14 (19.2%), 24 (32.9%), and 35 (47.9%) patients were categorized as low-, intermediate-, and high-risk group, respectively. Sixty-two patients (84.9%) had received rituximab as the induction treatment, and 11 patients (15.1%) had not. CVP (cyclophosphamide, vincristine, and prednisone) was the most commonly used regimen (N =40, 54.8%), followed by CHOP (CVP plus doxorubicin, N =26, 35.6%). Forty-four patients (60.3%) had received maintenance treatment with rituximab and 29 patients (39.7%) had not. The best responses during or after the front-line were complete response (CR) in 32 patients (43.8%), partial response (PR) in 32 patients (43.8%), stable disease in 3 patients (4.1%), and progressive disease in 6 patients (8.2%). POD24 was documented after a median duration of 11.6 months (95% CI 9.8 – 13.4). For salvage treatment, rituximab was administered in 19 patients (26.0%), and platinum-based combinations (N =23, 31.5%) were the most commonly used backbone treatment followed by bendamustine (N =15, 54.8%) and fludarabine-based combinations (N =12, 5.5%). A CR was observed in 28 patients (38.4%), and a PR in 23 patients (31.5%). Progression free survival (PFS) from the first progression was 23.7 months (95% CI 7.8 – 39.6). The estimated median OS was 128.9 months, with the 5-year being 75.2% (95% CI 69.4 – 81.0). OS did not significantly differ by the re-induction regimen, use of rituximab, or stem cell transplantation. When we compared these patients with our previous cohort in which 147 FL patients without POD24 were included, the 5-year survival rate was significantly inferior in the current cohort (75.2% vs. 95.7%, p < 0.001).

Conclusion : Our analysis for FL patients with POD24 revealed that they have poor outcomes, in agreement with the findings of previous studies. No particular treatments including ASCT demonstrated improved outcomes.

Keyword : Follicular Lymphoma, Relapse or Refractory, Transplantation



PP05-07

Long-term clinical outcomes of gastric MALT lymphoma: A single-center experience of 207 patients in Catholic Hematology Hospital

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Background : Gastric mucosa-associated lymphoid tissue (MALT) lymphoma accounts for approximately 40% of gastric lymphomas, and its incidence is increasing. Its pathogenesis is often related to Helicobacter pylori infection (HPI), and the presence of HPI determines the therapeutic approach. The prognosis is known to be favorable, and the eradication of H. pylori is recommended as the initial treatment for HPI-positive gastric MALT lymphoma. Both radiation and chemotherapy are suitable alternatives for HPI-negative, relapsed/refractory, or high-grade gastric MALT lymphoma.

Method : We included 207 patients diagnosed as having gastric low-grade MALT lymphoma from September 2001 to August 2020 at St Mary's Hospital, Seoul, South Korea. Among them, 180 patients (87.0%) had early-stage MALT lymphoma (Ann-Arbor Stage IE), and 151 patients (72.9%) showed HPI. We also used endoscopic ultrasound (EUS) for more accurate diagnosis, staging, and prognosis prediction. Helicobacter pylori eradication was performed in all early-stage gastric MALT lymphoma patients with HPI. After the initial treatment, endoscopic follow-up with multiple biopsies was performed regularly at three-month intervals for 1 year and at six-month intervals thereafter. We identified residual presence or no regression of mucosal lesions based on endoscopic findings and pathological review at six months. For delayed responders, we watched and waited for an additional six months without further treatment.

Results : In the median follow-up period of 51.6 months (range, 3.0–230.4 months), the cumulative incidence of relapse (CIR) was 11.9% (95% CI, 7.1–17.9), non-relapsed mortality was 2.5% (95% CI, 0.4–4.1), overall survival was 98.5% (95% CI, 94.1–99.7), and progression-free survival (PFS) was 85.1% (95% CI, 78.0–90.1). Among 156 H. pylori eradication group patients, 119 (76.3%) achieved complete remission. Furthermore, 16 (10.3%) and 21 (13.5%) patients showed endoscopic findings indicative of either no regression or residual disease, consistent with resistance to HPI treatment for up to one year after treatment, respectively. In addition, 10 of 119 (8.4%) patients who achieved remission presented with relapse during the follow-up period. Among the 67 patients who underwent EUS in this group, the depth of lymphoma infiltration in the gastric wall was mucosa in 40 cases (59.7%) and submucosa or beyond in 27 cases (40.3%). The HPI treatment response-related invasion depth of submucosa or beyond was more likely to cause treatment failure and warrant salvage therapies. The 51 patients diagnosed as having advanced-stage gastric MALT or absence of HPI underwent radiation therapy (47.1%) or chemotherapy (39.2%) or both (3.9%). Among these patients, 49 (96.1%) achieved complete remission, but two patients showed progressive disease on CT scans and FDG-PET. In this study, HPI positivity was significantly associated with superior PFS (90.2% vs. 68.1%, p=0.007) and CIR (8.5% vs. 24.7%, p=0.042) compared to HPI negativity, and compared with stages II to IV, stage IE was associated with better PFS (88.0% vs. 65.6%, p=0.087).

Conclusion : The real-world clinical outcomes of gastric MALT lymphoma treated with different therapeutic modalities were presented in this long-term, retrospective, single-center study with sufficient patients. Initial EUS workup to define regional lymph nodes and depth of mucosal invasion is recommended, particularly in early-stage IE patients with HPI because locally advanced-stage patients are more likely to experience eradication treatment failure.

Keyword : Gastric, Lymphoma, Helicobacter Pylori Infection, EUS

PP05-08

Long-term clinical outcome of R-CVP chemoimmunotherapy in treatment-naïve patients with orbital adnexal MALT lymphoma: A single-center experience

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Background : Ocular adnexal mucosa-associated lymphoid tissue (MALT) lymphoma (OAML) is the most common type of ocular lymphoma with a prevalence that is high in Asia and increasing steadily. The choice of primary treatment for OAML depends on the extent of

tumor spread. As most OAMLs are in a limited-stage of progression, despite ophthalmic complications, radiotherapy (RT) is commonly used as first-line therapy because of good clinical outcomes and relatively superior local control efficacy. However, there is no consensus regarding the initial therapeutic strategy for OAML.

Method : We present a large single-center retrospective analysis on OAML diagnosed by the Catholic University Lymphoma Group between January 2004 and February 2020. The analysis included real-world data focused on treatment outcomes of 302 patients followed for up to 237 months to investigate the role of RT and its dose as frontline or salvage therapies, comparing the outcomes and complication profiles of systemic chemotherapy, especially in limited-stage OAML.

Results : During a median follow-up of 69.0 months (range, 3.0–237.0) in 302 patients with primary OAML, the overall survival and progression-free survival at 19 years were 97.2% and 81.1%, respectively. The majority of the patients (83.4%) presented with stage I disease, and 82.8% of the treated patients achieved a complete remission (CR) after first-line therapy regardless of its treatment modalities. Of the 179 patients who underwent RT as first-line therapy, 88.8% achieved CR, treated by either ≥ 3000 cGy (49.2%) or < 3000 cGy (50.8%). Chemotherapy was used to treat 107 OAML patients, of which 60 (56.1%) were limited-stage OAML possessing adverse prognostic factors such as bilateral or beyond-conjunctival involvement, especially of the orbit. The majority (86.9%) of the chemotherapy group patients achieved CR, and 13.1% achieved a partial response. With respect to adverse events, radiation-related, permanent, ophthalmic complications, including dry-eye syndrome (38.5%) and cataract (25.7%), caused a persistent decline in the quality of life (QoL). However, the most significant chemotherapy-related complications were Grade 3 or 4 neutropenia (36.4%) and peripheral neuropathy (13.1%), which were manageable and transient.

Conclusion : OAML patients were predominantly female (59.6%) and relatively young (median age 48 years), and RT as a first-line therapy was more likely to lead to persistent complications, resulting in lower QoL. However, chemotherapy demonstrated more durable efficacy with tolerable toxicities than RT and no delayed adverse events. Hence, it could be recommended as an alternative first-line therapy for younger, limited-stage OAML patients, while RT could be reserved for elderly chemotherapy-ineligible patients

Keyword : OAML, Primary Therapy, Orbit, Radiotherapy, Cataract

PP05-09

CNS involvement in relapsed mantle cell lymphoma

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Background : Mantle cell lymphoma (MCL) is a specific clinicopathologic subtype comprising 7-8% of all Non Hodgkin's Lymphoma. It is characterized by t(11;14) and overexpression of cyclin D1. MCL frequently presents with extranodal involvement like CNS, although incidence, risk factors and outcome are still controversial.

Method : The case was retrieved from ongoing hospital services in Leukemia/ Lymphoma Clinic.

Results : A 64 year female presented with itching & decreased appetite for six months. There was no history of fever, weight loss or night sweat. Associated comorbidities were Diabetes Mellitus and Hypertension for more than 5 years. CBC showed hemoglobin (Hb) 9.5gm% with normal TLC & platelet count. Bone marrow aspiration smear showed 20% abnormal lymphoid cell, which was confirmed by biopsy. USG and CECT Neck demonstrated generalized lymphadenopathy. Lymph node biopsy showed abnormal lymphoid cell infiltration positive for CD 20, CD 5, Bcl-2 and Cyclin D1 and negative for CD 23, CD3 and Bcl-6. MCL stage IV was considered and managed with 6# Bendamustine – Rituximab (BR) regimen. Follow up PET showed no evidence of metabolically active disease. Patient showed complete response to the therapy. She spent 'Treatment Free Interval (TFI)' for 3 months. Maintenance therapy was given as further management. Later she complained of fever and loose stool with no relief from oral antibiotics. She had splenomegaly & lymphadenopathy, which was confirmed by CT scan. CBC showed Hb 8.9 gm% and Platelet count 60000/cmm and blood film showed few atypical lymphoid cells. Bone marrow biopsy showed CD20, cyclin D1 positive and CD3 negative cells, suggesting Relapsed MCL. She was managed with 4# VR-CAP and clinical remission (CR) was achieved. After some days she developed neurological symptoms, backache radiating to legs, loss of vision, diplopia, motor weakness in all 4 limbs. CSF Cytology was positive for lymphoma cells. MRI showed Grade 1 Retrolisthesis involving l1-l4 vertebra. Looking Performance status 4, chemotherapy was stopped and lastly succumbed to death.

Conclusion : CNS involvement was noticed during the course of therapy, which may be an indicator of the case not responding to therapy, although the patient spent 3 months of TFI. At the time of diagnosis of MCL, work-up for CNS lesion should be an important component to achieve a prolonged disease free survival.

Keyword : MCL, CNS Involvement, Relapse

PP05-10

Efficacy and safety of ibrutinib in mantle cell lymphoma patients: Real world experience in a single center, retrospective analysis

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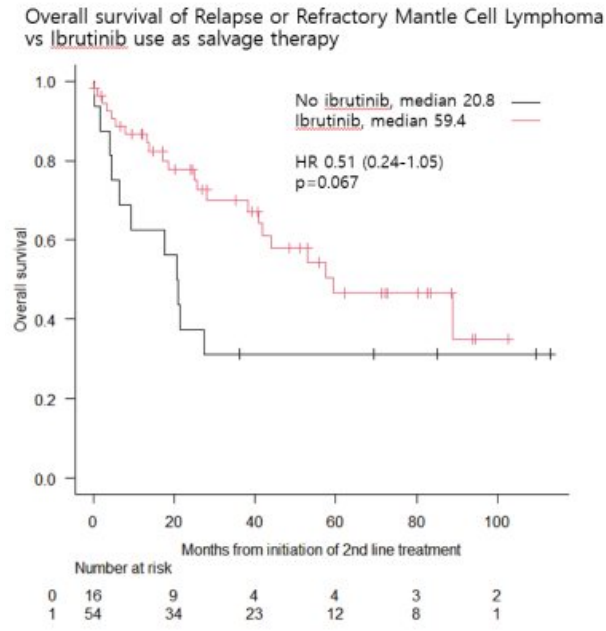
Background : Ibrutinib is the first clinically approved Bruton's tyrosine kinase inhibitor against relapsed or refractory mantle cell lymphoma (MCL). It is available in oral form and well tolerated in elderly patients but is designed to continue the drug indefinitely until progression. Well known adverse events related to ibrutinib include cytopenia, infection, bleeding and atrial fibrillation. However, there is no reported data yet regarding safety of ibrutinib in Korean patients. We report a single-center, retrospective analysis to evaluate the efficacy and safety of ibrutinib in Korean patients with MCL.

Method : We analyzed medical records of MCL patients treated with ibrutinib in Seoul St. Mary's Hospital between 2013 and 2020. Kaplan-Meier method was used to estimate overall surival (OS), progression free survival (PFS). Response evaluation was based on Lugano response criteria for non-hodgkin lymphoma. Grading of adverse events (AEs) were based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Hypogammaglobulinemia was determined based on the reference values provided from the department of diagnostic medicine at our hospital.

Results : 56 patients were included in the analysis. Ibrutinib was administered as 1st line therapy in 2 patients, as 2nd line in 28, as 3rd line in 12 patients. The median follow up period of patients currently on ibrutinib (n=24) was 24.5 months (range 2.0-93.8). Median OS and 5-year OS after initiation of ibrutinib was 32.7 months (95% confidence interval (CI) 21.1-not available(NA)) and 41.2% (95% CI 24.1-57.5), respectively. Median PFS and 5 year-PFS was 32.5 months (95% CI 12.6-NA) and 40.2% (95% CI 23.8-56.0). Overall response rate (ORR) was 66.1%. When compared with our hospital cohort, patients with relapsed or refractory MCL, although not statistically significant, show longer median OS when treated with ibrutinib as salvage therapy than chemotherapy without ibrutinib (Median OS after 2nd line therapy: 59.4 months vs 20.8 months, p=0.067) Of 32 (57.1%) patients that has stopped ibrutinib, 3 (5.4%) patients has undergone upfront stem cell transplantation (1 autologous, 2 allogeneic) after reaching complete remission while 19 (33.9%) patients have had progressive disease. Other patients either discontinued ibrutinib due to recurrent infection (n =1, 1.9%) died during treatment (n =3, 5.6%), were lost to follow-up (n =4, 7.4%). Two patient developed acute kidney injury of unknown etiology and died. One patient has developed acute myeloid leukemia and proceeded to leukemia treatment, and eventually died during allogeneic stem cell transplantation due to sepsis. Most common adverse events were infection (n =18, 32.1%) with 9 patients (16.1%) greater than grade 3. The most common sites of infections were lower respiratory tract, skin and soft tissue. Hypogammaglobulinemia was found in 20 patients (35.7%) and its association with severe infection (greater than grade 3) was significant (chi square test, p=0.046). Cytopenia occurred in 10 patients (16.1%) with neutropenia (n=9) more common than thrombocytopenia (n=2). Major bleeding (grade >=3) events did not occur in our cohort while minor bleeding occurred in 2 patients (3.6%). Atrial fibrillation was newly developed in only one patient. While no other AEs of grade 3 or more occurred in our patients, other AEs included renal failure (n=3, 5.4%, including two cases mentioned above), elevated serum aminotransferase level (n=2, 3.6%), diarrhea (n=2, 3.6%) and rash (n=2, 3.6%). Five cases of secondary malignancies occurred in three patients (5.4% rectum 2, bladder 1, kidney 1, acute myeloid leukemia 1), which could be attributed to factors other than ibrutinib, such as previous cytotoxic chemotherapy and age. Six patients have reduced ibrutinib dose from 560mg to 480mg, due to one or many of following reasons: persistent cytopenia, recurrent infection, existing renal disease, diarrhea, elevated serum aminotransferase level and general weakness.

Conclusion : We present a real-world experience of adverse effects during ibrutinib treatment in Korean mantle cell lymphoma patients. Though a limited number of patients are included in the analysis, safety of ibrutinib on Korean patients show similar profile as other large studies. However, our data suggests decreased immunoglobulin levels may be associated with severe infection. Careful monitoring and management of adverse effects may be beneficial for patients on ibrutinib.

Keyword : Mantle Cell Lymphoma, Ibrutinib, Hypogammaglobulinemia, Adverse Effect



PP05-11

Long-term real-world results of R-CHOP chemoimmunotherapy in 479 previously untreated elderly patients with diffuse large B-cell lymphoma: A single-center experience at Catholic He-

matology Hospital

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Background : The incidence of aggressive non-Hodgkin lymphoma such as diffuse large B-cell lymphoma (DLBCL), increases with age, yet outcomes among elderly patients remain significantly suboptimal among younger patients in the rituximab era. Although differences in tumor biology may play a partial role, the management of those patients is strongly influenced by preexisting comorbidities and various geriatric syndromes. Therefore, elderly DLBCL patients need particular attention and thorough evaluation regarding whether they are fit for standard chemotherapy (R-CHOP) or palliative treatment.

Method : We characterized real-world treatment patterns in 1,020 DLBCL patients and stratified the elderly into three age groups (60–69 years, 70–79 years, and >80 years) receiving standard R-CHOP chemotherapy. Four hundred and seventy-nine of the 1,020 R-CHOP-treated patients who were ≥60 years were included in this analysis with a median follow-up of 41.5 months (range 0.2–171.1). For enrolled elderly patients, careful dose modification schedules were applied in cyclophosphamide, doxorubicin, and vincristine based on the patients' initial hematological, liver, renal function, and limited drug-specific toxicities during treatment. No dose reductions were re-escalated in subsequent cycles.

Results : Significantly poorer overall survival (OS) and progression-free survival (PFS) were observed in patients with increasing age (<60s, 60s, 70s, >80s OS rate: 76.7% vs. 72.0% vs. 60.4% vs. 54.1%, respectively; $p < 0.001$ and PFS rate: 56.8%, 51.7%, 46.4%, and 41.6%, respectively; $p < 0.001$). Treatment-related mortality (TRM) also showed more inferior outcomes by increasing age subgroup (<60s, 60s, 70s, >80s TRM rate: 5.1% vs. 9.2% vs. 17.6% vs. 47.4%, respectively; $p < 0.001$). The patients who received a suboptimal dose (<75%) with reducing at least two regimens of R-CHOP (cyclophosphamide, doxorubicin, and vincristine) because of relatively multiple comorbidities, lower performance status, and expected toxicities, showed significantly inferior survival outcomes (OS: 77.1% vs. 61.3%; $p < 0.001$ and TRM 4.3% vs. 20.6%; $p < 0.001$). The suboptimal dose R-CHOP treatment in elderly patients did not lead to a higher relapse rate but the inferior OS, PFS, and TRM. Elderly patients who received eight cycles of R-CHOP as compensation for dose-reduction showed lower TRM but higher relapse rates than those who received six cycles of R-CHOP.

Conclusion : This retrospective analysis of a real-world patient population with DLBCL presented that the judicious selection of elderly patients who are intolerant of full-dose R-CHOP and that proper dose-modification is essential. Survival outcomes for elderly DLBCL patients progressively worsen with age. Elderly patient age-associated fragilities and poor survival outcomes are closely related to older persons' functional ability, physical health, comorbidities, and cognition. Furthermore, the dose-reduction R-CHOP schedule and supportive care itself did not effectively optimize the clinical outcomes for the elderly. Therefore, a large cohort prospective study for pretreatment with comprehensive geriatric assessment is necessary to predict the survival and treatment-related toxicities to guide overall treatment decisions.

Keyword : Diffuse Large B Cell Lymphoma, Elderly, R-CHOP, Long-Term Survival

PP05-12

Role of upfront ASCT in patients with bone marrow involvement by immunoglobulin gene rearrangement of diffuse large B-cell lymphoma

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Background : Bone marrow (BM) involvement is poor prognostic factor for diffuse large B-cell lymphoma (DLBCL). The purpose of this study was to investigate the incidence and clinical impact of histologic BM involvement and immunoglobulin gene rearrangement (IgR) from BM aspirates, and to find out if upfront ASCT could overcome the poor prognosis of BM involvement or clonal IgR.

Method : We included 624 DLBCL patients who have BM biopsy results. One hundred twenty-three of 624 (19.7%) patients have histologic BM involvement, 88 of 624 (14.1%) patients had clonal IgR with negative histologic BM involvement.

Results : Patients with histologic BM involvement or clonal IgR were related with aggressive clinical features, and high IPI scores. OS and PFS was inferior in patients with BM involvement or clonal IgR compared to both negative patients (P=0.05, P=0.001 and P <0.001, P=0.006, respectively). Total 82 (13.1%) patients received upfront ASCT as con-

solidation, upfront ASCT showed superior OS and PFS in patients with histologic BM involvement or clonal IgR (P=0.004, P=0.009). There was no survival difference according to the BM involvement or positive IgR in patients who received upfront ASCT, but patients who did not receive upfront ASCT still have poor prognosis in case of histologic BM involvement or positive IgR. Among the patients who did not receive upfront ASCT, elevated LDH, and positive IgH and/or IgK are the prognostic factors for inferior OS and PFS. These factors did not affect the survival the patients with receiving upfront ASCT.

Conclusion : This study suggested that clonal IgR as well as BM involvement was associated with inferior survival in the newly diagnosed DLBCL patients. This poor prognosis could be overcome by the upfront ASCT.

Keyword : Diffuse Large B-cell Lymphoma, Bone Marrow Involvement, Autologous Hematopoietic Stem Cell Transplantation, Immunoglobuline Gene Rearrangement

PP05-13

Long-term follow-up of limited-stage ocular adnexal lymphoma patients treated with chemoimmunotherapy

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Background : Systemic chemoimmunotherapy may be an alternative frontline therapy for the limited-stage ocular adnexal mucosa-associated lymphoid tissue lymphoma (OAML) with adverse factors which are bilaterality, nonconjunctival location, and nodal involvement. However, there are limited data on the treatment outcome of chemoimmunotherapy in those patients.

Method : We followed the study patients long-term who were enrolled in a multicenter, phase II study of R-CVP treatment for the limited-stage OAML patients with bilateral or beyond-conjunctival involvement (Clinical trial registration: NCT01427114). A total of 33 study patients had been enrolled from 2011 to 2013 and followed up until the end of 2020.

Results : All but one of the study patients achieved a complete response after treatment. At a median follow up of 66.0 months, eight patients had progressed eventually. Six patients relapsed at the same site as at the time of diagnosis and two patients relapsed at the other sites. Progression-free survival and overall survival at 5 years was 81.1% and 100%, respectively. Those at 8 years was 55.3% and 100%.

Conclusion : Systemic chemoimmunotherapy is an alternative treatment option for limited-stage OAML patients but delayed relapse is still problematic in patients with the adverse prognostic factor. Long-term follow-up is necessary although patients achieve complete remission after the treatment.

Keyword : Ocular Adnexal Lymphoma, Mucosa-Associated Lymphoid Tissue Lymphoma, Chemoimmunotherapy, Rituximab

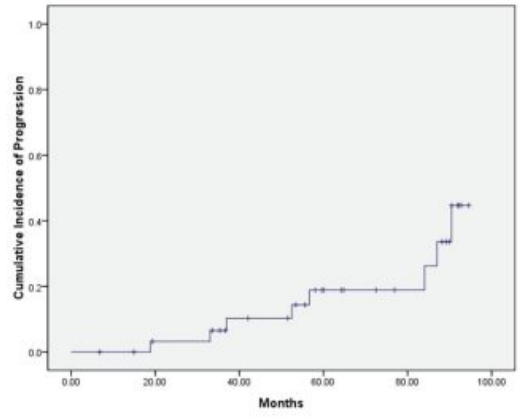

Figure. The cumulative incidence of progression in the limited-stage OAML patients with adverse prognostic factors

PP05-14

Use of high dose methotrexate in patients with primary CNS lymphoma without therapeutic drug monitoring of methotrexate levels: Challenges & outcome

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Background : High Dose Methotrexate (HDMTx) based chemotherapy in the mainstay of treatment for patients with Primary CNS Lymphoma. However, delivering HDMTx in resource limited settings,

especially without help of therapeutic drug monitoring, is difficult. We share our experience of treatment of patients with PCNSL at our center over a 10-year period with local adaptations made to deliver HDMTx without using methotrexate level estimation

Method : We analysed the case records of patients diagnosed with a PCNSL treated over the course of 10 years from 2010-2020 with an emphasis on finding methotrexate toxicity and treatment abandonment rate in a clinical setting with limited access to therapeutic drug monitoring

Results : Fifty-five patients received therapy for newly diagnosed PCNSL. Thirty-six patients received Modified De-Angelis protocol ± Rituximab with curative intent. Fourteen of these patients were unable to complete the protocol with the most common cause being development of methotrexate toxicity. Patients unable to complete the designated 5 cycles of HDMTx had a poorer PS and higher probability of having a high IELSG score at baseline. Nineteen patients were given non HDMTx based therapy either due to advanced age or poor performance status Twenty-nine patients (52.7%) were able to achieve a complete response. The most common cause of mortality was relapse/progressive disease. The Median EFS and OS of the cohort was 29 months and 40 months respectively.

Conclusion : The higher than usual rate of toxicity and treatment interruption in our study indicate that delivering HDMTx based therapy, without therapeutic drug monitoring is not the optimal method of treating PCNSL. Yet, for a curable malignancy like PCNSL, it is favourable to deliver HDMTx based regimen in centres without access to therapeutic drug monitoring of methotrexate using more stringent hydration, urine alkalinisation, and leucovorin rescue.

Keyword : High Dose Methotrexate

Study	Omuro et al	DeAngelis et al	Nagle et al	Morris et al	Podder et al	Patekar et al	**Our study**
Rx protocol	R-MPV f/b ASCT	MVP f/b WBRT f/b Cytarabine	Rituximab + HDMTx + Temozolomide	R-MVP + WBRT/ WBRT (reduced dose)	Modified DeAngelis protocol	Modified DeAngelis protocol	Modified DeAngelis protocol + Temozolomide based therapy
No. of patients	32	98	27	52	29	99	57
Median Age (in years)	57 (23-67)	56.5	61 (21-85)	60 (30-79)	55 (14-71)	50 (13-70)	50 (22-85)
Median PFS	NR	24 months	22 months	3.3 years	NR	20.4 months	29 months
Median OS	NR	36.9 months	55.3 months	6.6 years	NR	31.7 months	40 months
CR rate	66%*	58%*	70%*	79%*	73.1%*	46.8%*	52.7%*
OR rate	94%*	94%*	81%*	95%*	96.1%*	81.8%*	56.3%*

PP05-15

Efficacy and safety of high-dose etoposide cytarabine as consolidation in transplant ineligible primary central nervous system lymphoma

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Background : High dose chemotherapy with autologous stem cell transplantation is proven efficacy in young and fit patients. Consolidation with chemotherapy should considered for transplant ineligible patients, but there is no established consolidation regimen. We evaluated the role of high-dose etoposide cytarabine (EA) as consolidation chemotherapy for transplant ineligible patients.

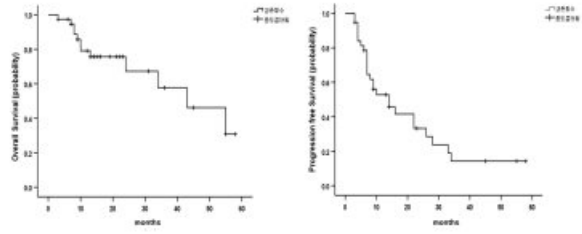
Method : Total 80 newly diagnosed PCNSL patients over 50 years were included.

Results : Median age was 70 years (range: 53-79 years). After high-dose methotrexate based chemotherapy, 46 (57.5%) patients achieved complete response (CR), 25 (31.3%) patients were partial response (PR) and 11.3% progressed. Thirty-eight patients who achieved CR or PR received EA consolidation chemotherapy. The median overall survival 14 months, and progression free survival was 9 months. Most toxicities were hematological, all patients were experienced grade III-IV neutropenia, anemia and thrombocytopenia. Thirty-one patients experienced febrile neutropenia during consolidation chemotherapy, one patient died due to treatment related mortality.

Conclusion : This study demonstrates that EA consolidation might be a valuable option for transplant ineligible PCNSL patients, but more effective treatment strategies with less toxicities using new agents should be investigated.

Keyword : Primary CNS Lymphoma, Consolidation Chemotherapy

Overall survival and progression free survival in patients with primary CNS lymphoma treated with EA consolidation



PP05-16

Effect of systemic intravenous methotrexate administration on CNS relapse in patients with primary intraocular lymphoma

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Background : Primary intraocular lymphoma (PIOL) is a subset of primary central nervous system (CNS) lymphoma characterized by intraocular involvement without evidence of another disease in the brain or cerebrospinal fluid. Any disease causing choroidal, retinal, subretinal, or vitreous chamber infiltration could mimic or be mimicked by PIOL. Therefore, PIOL diagnosis and management remain challenging. This study aimed to identify factors indicative of PIOL, describe treatment outcomes, and determine modalities to prevent relapse.

Method : The subjects were 24 consecutive patients with PIOL who were diagnosed and followed up between October 2013 and March 2020. PIOL was diagnosed based on the combined results of several tests, cytopathology with immunohistochemical staining, flow cytometry, PCR to assess monoclonality, and IL-10/IL-6 level analysis via ELISA using vitreous samples. All 24 patients underwent vitrectomy and local intravitreal methotrexate (IV-MTX) injection for vitreous opacity in Seoul St. Mary's Hospital. Clinical outcomes of PIOL, including treatment response and relapse, of patients receiving IV-MTX alone or IV-MTX with systemic high-dose methotrexate (HD-MTX), were compared.

Results : Overall, 29.2% of patients were diagnosed via confirmative cytology and immunohistochemical staining, and 58.3% were diagnosed via additional flow cytometry or molecular studies. There were 12 ophthalmological and 10 CNS relapse cases within a median of 20.3 and 12.1 months, respectively. A significantly higher number of patients who received IV-MTX and HD-MTX had concurrent CNS lesions, low Eastern Cooperative Oncology Group performance status scores at diagnosis, and CNS relapse than those receiving IV-MTX alone. Furthermore, patients demonstrated rapid elevations in the vitreous fluid IL-10/IL-6 cytokine ratio before relapse.

Conclusion : PIOL diagnosis should be based on clinical signs and assisted by vitrectomy, cytologic, and molecular studies. Primary treatment with IV-MTX without systemic therapy is recommended for isolated PIOL because systemic HD-MTX by itself did not show significant clinical benefits; in particular, it did not prevent or delay CNS relapse. To prevent CNS relapse of PIOL efficiently, prospective trials with large numbers of patients and advanced therapeutic regimens are necessary. Furthermore, regular clinical follow-up is crucial, and the IL-10/IL-6 ratio can help evaluate relapse more promptly.

Keyword : PIOL, PCNSL, Intravitreal Methotrexate, Relapse

PP05-17

GIT DLBCL in hospital Malacca, Malaysia

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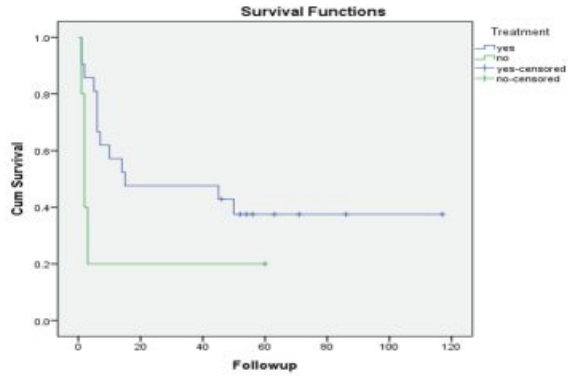
Background : Gastrointestinal tract (GIT) is the commonest extranodal site involved by lymphoma, majority being non-Hodgkin lymphoma, especially diffuse large B cell lymphoma (DLBCL). GIT lymphoma is usually secondary to widespread nodal disease. The most frequent involved sites are stomach followed by small intestine and ileocecal region. The optimal therapy is still poorly defined and controversial. Surgery, chemotherapy, radiotherapy and radioimmunotherapy can be applied in different combination. Nonetheless, the optimal therapy is still poorly defined. We present our experience in clinical characteristics, treatment and outcome of DLBCL of GIT in Malacca Hospital, Malaysia.

Method : This is a retrospective study, and data was collected from year January 2012 to December 2015 in Melaka Hospital, with all patients diagnosed with GIT DLBCL. A total of 26 patients were identified and analysed. All patients were followed up till December 2019.

Results : From year 2012 to 2015, total of 268 NHL were diagnosed in our centre. 26 out of 268 (9.7%) were GIT DLBCL. There was equal gender distribution, with the mean age of presentation at 54.9 years (range from 28-80 years). Median follow-up time was 12 months (range from 1-117 months). Ileocaecal junction being the commonest involved site (12, 46.2%), followed by stomach (11, 42.3%) then small intestine (3, 11.5%). Eight (30.8%) with revised International Prognostic Index (R-IPI) 3 or more, whereas majority were 2 (9, 34.6%). Twenty one (80.8%) of them received either surgical resection or chemotherapy as first line treatment. Twenty (76.9%) of them received chemotherapy, with 15 (75%) of them received Rituximab-based regime, namely R-CHOP regime for curative intention and five (25%) of them received oral chemotherapy for palliative intention. Eight (38%) received surgical resection with systemic chemotherapy, two (9.5%) received surgical resection, systemic chemotherapy with involved field radiotherapy. Only one (4.7) received surgical resection followed by systemic chemotherapy and autologous stem cell transplant. Among the cohort, only nine patients (34.6%) achieved complete remission with curative intention. The overall 5-year survival rate was 38%.

Conclusion : Up to now, there is no consensus on the optimal treatment because lack of large-scale prospective randomized studies on this disease. My cohort did not confer significant survival advantage in Rituximab-based chemotherapy in addition to surgical resected intestinal DLBCL. However, from this small scale analysis showed that only treatment that render complete remission will improve OS.

Keyword : GIT, DLBCL, Outcome



PP05-18

Subcutaneous mosunetuzumab shows promising safety and encouraging efficacy in relapsed or refractory B-cell lymphoma: Initial results from dose escalation

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Background : More effective, less toxic, and more convenient treatments are needed for patients (pts) with relapsed/refractory (R/R) B-cell lymphoma (B-NHL). Mosunetuzumab (Mosun), a full-length, fully humanized IgG1 CD20/CD3 bispecific antibody, redirects T cells to engage and eliminate malignant B cells. In GO29781 (NCT02500407), an ongoing Phase I/Ib, open-label, multicenter dose-escalation and expansion study, step-up intravenous (IV) Mosun dosing showed promising efficacy and manageable safety in pts with R/R B-NHL (Bartlett, et al. ASCO 2019, Schuster, et al. ASH 2019). Cytokine release syndrome (CRS) is a significant adverse event (AE) related to T-cell engaging immunotherapies. As well as reduced healthcare resource utilization and increased convenience, subcutaneous (SC) administration of Mosun has the potential of minimizing CRS risk. Clinical data with Mosun SC in R/R B-NHL are presented here.

Method : On Day 1 of each 21 day Cycle (Q3W), pts received single-agent Mosun SC. Treatment continued for 8 cycles in pts with complete response (CR) and up to 17 cycles in pts with partial response or stable disease. Dose escalation used a standard 3+3 design, assessing doses from 1.6 to 20 mg. Tolerability, best objective response (per Cheson 2007 criteria), and maximum tolerated dose (MTD) were the key outcome measures.

Results : As of January 21, 2020, Mosun SC was administered to 23 pts (diffuse large B-cell lymphoma, n=10; follicular lymphoma [FL], n=5; marginal-zone lymphoma [MZL], n=3; primary mediastinal large B-cell lymphoma, n=2; transformed [tr] FL, n=1; trMZL, n=1; tr nodular lymphocyte-predominant Hodgkin lymphoma, n=1). Pts received a median of 4 (range: 1–8) prior systemic therapies; five pts (22%) received prior chimeric antigen receptor T-cell therapy. Thirteen (57%) and 16 (70%) pts were refractory to last prior therapy and prior anti-CD20 therapy, respectively. At 1.6 mg, one dose-limiting toxicity (Grade [Gr] 4 neutropenia; resolved) was observed, but the MTD was not reached at all dose levels assessed up to 20 mg. Twenty-two (96%) of the 23 safety-evaluable pts experienced ≥1 AE; no AEs resulted in treatment discontinuation. CRS (n=8, 35%), headache (n=5, 22%; all Gr 1) and injection site reaction (n=5, 22%; all Gr 1) were the most common (>20%) Mosun-related AEs. With SC dosing, all CRS events were Gr 1 (n=6, 26%) or Gr 2 (n=2, 9%) per Lee criteria (Lee, et al. Blood 2014); no Gr 2 CRS occurred at doses <13.5mg (unlike IV fixed-dosing, where 15% of pts experienced Gr 2 CRS at doses 0.05–2.8mg). All CRS events occurred during Cycle 1, and resolved without tocilizumab treatment, intensive care unit admission or use of vasopressors; one pt required low-flow oxygen. Among the efficacy-evaluable population (n=22), in indolent NHL patients, the overall response rate (ORR) was 86% (6/7) and the CR rate was 29% (2/7). In aggressive NHL patients, the ORR and CR rates were 60% (9/15) and 20% (3/15), respectively. After a median 6.9 (range: 1.3–22.1) months on study, amongst the SC cohort, all but one CR pt remained in remission at data cut-off. The pharmacokinetic (PK) profile of Mosun SC is characterized by a slow absorption rate evidenced by a delay of Tmax (at 72 hours post-dose) and ~70% reduction of Cmax versus IV fixed dosing. Furthermore, high bioavailability (>75%) was observed, supporting the use of SC dosing for CRS mitigation. With SC dosing, peak IL-6 levels had delayed onset and decreased magnitude compared with fixed-dose Mosun IV.

Conclusion : In heavily pretreated R/R B-NHL pts, Mosun SC demonstrated a manageable safety profile, promising efficacy and a favorable PK. CRS events were mild and transient (no Gr ≥3 CRS), required minimal intervention, and were confined to the first Cycle. Compared to the IV fixed-dosing cohort, less frequent Gr 2 CRS events were observed with SC dosing despite the fact that 7-fold higher Mosun doses were used. These data support continued development of Mosun SC in R/R B-NHL. Updated clinical, PK and biomarker data, will be presented, including about 20 pts from an interim expansion cohort.

Keyword : Follicular Lymphoma, Mosunetuzumab

PP05-19

Treatment outcomes of involved-field radiotherapy in elderly patients with high-grade or recurrent non-Hodgkin lymphoma

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Background : The purpose of this study was to evaluate the usefulness and efficacy of involved-field radiotherapy (IFRT) in elderly patients with high grade or recurrent non-hodgkin lymphoma (NHL).

Method : We analyzed the treatment outcomes of 14 patients who had received IFRT between January 2014 and August 2018 at a single institution. IFRT was defined as the involved-site radiotherapy with/without adjacent nodal-station irradiation (ANI) to high risk areas. The median age of study population was 75 (range, 65-83) years and 7 (50%) patients were male. Tumor histology was diffuse large B-cell lymphoma in 10 (71.4%), NK/T-cell lymphoma, nasal type in 2 (14.3%), high-grade follicular lymphoma in 1 (7.1%) and recurrent nodal marginal zone lymphoma in 1 (7.1%) patient, respectively. The treatment sites were neck/nasal cavity in 9 (64.3%), neck/abdomen in 1 (7.1%), chest in 1 (7.1%), axilla in 1 (7.1%), neck/chest in 1 (7.1%) and abdomen/pelvis in 1 (7.1%), respectively. ANI was selectively accomplished in 7 patients with neck and axilla origins. The ECOG performance status was 0 in 1 (7.1%), 1 in 10 (71.4%) and 2 in 3 (21.4%) patients, respectively. The majority of the patients (n=10, 71.4%) had aging-related multiple comorbidities.

Results : The median follow-up duration was 11 (range, 2.2-56.2) months and 7 (50%) patients were dead at the time of this analysis. Although upfront chemotherapy was employed in 10 (71.4%) patients before IFRT, 5 patients did not complete the entire course of chemotherapy schedule. Among 10 patients who had received IFRT as a consolidation treatment after chemotherapy, 8 (80%) patients maintained major infield responses during follow-up. Infield and outfield progression occurred in 2 and 2 patients, respectively (both infield and outfield progression in one patient). Among the remaining 4 patients who had received IFRT as a curative or salvage aim, all 4 patients achieved major infield responses and 1 patient experienced multiple outfield progression. Among the entire study cohorts, all 3 outfield progression occurred from patients who received no or incomplete chemotherapy. Major causes of death and worsening of general condition were pulmonary infections and aging-related illnesses. In 7 dead patients, the median survival duration after IFRT was 6 (range, 2.2-12.3) months. There was 6 (42.9%) long-term (≥ 1 year) survivors after IFRT and their median survival duration was 35.7 (range, 23.6-56.2) months.

Conclusion : Although limited with small sample sizes, IFRT was efficacious and well tolerated in elderly high grade or recurrent NHL patients. Although durable response and long-term survival was achieved in medically healthy population, watchful surveillance is necessary to avoid deaths from cancer-unrelated causes (infections/comorbidities).

Keyword : Elderly, High-Grade Lymphoma, Radiotherapy, Recurrent Lymphoma

PP05-20

ECHELON-2: 5-year results of a phase 3 study of frontline brentuximab vedotin + CHP vs CHOP in patients with CD30-positive peripheral T-cell lymphoma

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Background : The phase 3 ECHELON-2 study (NCT01777152) established the superiority of frontline brentuximab vedotin + cyclophosphamide, doxorubicin, and prednisone (A+CHP) vs cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for patients (pts) with systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCLs) (Horwitz, Lancet 2019). At the primary analysis, risk of progression-free survival (PFS) per blinded independent central review (primary endpoint) and overall survival (OS) events favored A+CHP over CHOP. A+CHP was the first treatment regimen to increase OS compared with CHOP in this population. We report the 5-year data from ECHELON-2.

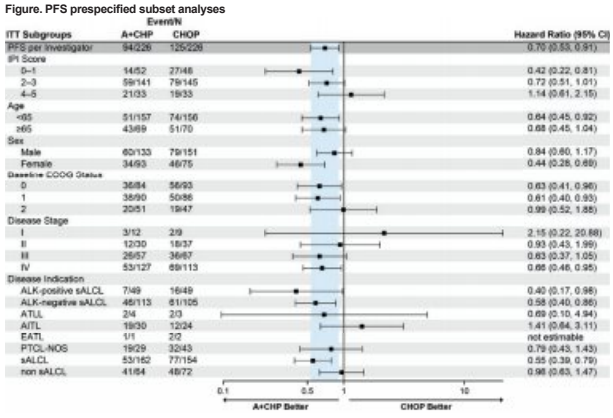
Method : ECHELON-2 is a randomized, double-blind, double-dummy, placebo-controlled, active-comparator, multicenter study. Adults with untreated CD30-positive PTCL (targeting 75% ± 5% with sALCL) were randomized 1:1 to receive 6–8 cycles of A+CHP or CHOP. Pts were stratified by histological subtype and international prognostic index (IPI) score. We report PFS per investigator (INV) and the following key secondary endpoints: OS, PFS in sALCL, complete remission (CR) rate, and objective response rate (ORR) in re-treated pts. Brentuximab vedotin-based subsequent therapies were allowed.

Results : Of 452 pts enrolled, most had sALCL (n=316 [70%]; 218 [48%] anaplastic lymphoma kinase [ALK]-negative, and 98 pts [22%] ALK-positive) and had advanced disease (27% Stage III, 53% Stage IV; 78% IPI ≥2). At data cutoff, median follow-up was 47.6 months for PFS and 66.8 months for OS. Hazard ratios (HRs) for PFS per INV (0.70 [95% confidence interval [CI]: 0.53, 0.91], p=0.0077) and OS (0.72 [95% CI: 0.53, 0.99], p=0.0424) favored A+CHP over CHOP. Median PFS was 62.3 months (95% CI: 42.0, not evaluable) and 23.8 months (95% CI: 13.6, 60.8) for A+CHP and CHOP, respectively. Estimated 5-year PFS was 51.4% (95% CI: 42.8, 59.4) with A+CHP vs 43.0% (95% CI: 35.8, 50.0) with CHOP. Median OS was not reached in either arm. Estimated 5-year OS was 70.1% (95% CI: 63.3, 75.9) for A+CHP vs 61.0% (95% CI: 54.0, 67.3) for CHOP. PFS in prespecified subgroups was generally consistent with overall PFS (Figure). In pts with sALCL, the HR for PFS (0.55 [95% CI: 0.39, 0.79]) also favored A+CHP over CHOP, with an estimated 5-year PFS of 60.6% (95% CI: 49.5, 69.9) for the A+CHP arm vs 48.4% (95% CI: 39.6, 56.7) for the CHOP arm. A total of 29 pts (13%) in the A+CHP arm (sALCL [n=19]; PTCL not otherwise specified [n=5], angioimmunoblastic T-cell lymphoma [n=5]), and 54 pts (24%) in the CHOP arm received subsequent systemic therapy with brentuximab vedotin. In the A+CHP arm, median time to retreatment was 15.0 months (range, 3–64); 17 pts (ORR: 59%) had CR (n=11) or partial remission (n=6) after retreatment with brentuximab vedotin monotherapy (n=25) or a brentuximab vedotin-containing regimen (n=4). Treatment-emergent peripheral neuropathy (PN) occurred in the A+CHP (n=117) and CHOP arms (n=124), of which, 72% and 78% had resolved or improved in the A+CHP and CHOP arms, respectively. In pts with ongoing events at last follow-up (A+CHP [n=47] vs CHOP [n=42]) PN was grade 1, 2 and 3 in 70% vs 71%, 28% vs 26% and 2% vs 2%, respectively.

Conclusion : At 5 years' follow-up, frontline A+CHP continued to provide clinically meaningful improvements in PFS and OS vs CHOP, including ongoing remission in 59% of re-treated pts with sALCL, with a manageable safety profile, including continued resolution or improvement of PN.

Keyword : Brentuximab Vedotin, Peripheral T-Cell Lymphoma, Systemic Anaplastic Large Cell Lymphoma, Previously Untreated

Figure. PFS prespecified subset analyses



AITL, angioimmunoblastic T-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; EATL, enteropathy-associated T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.

PP05-21

Prognostic effect of C-reactive protein-to-albumin ratio in peripheral T-cell lymphoma

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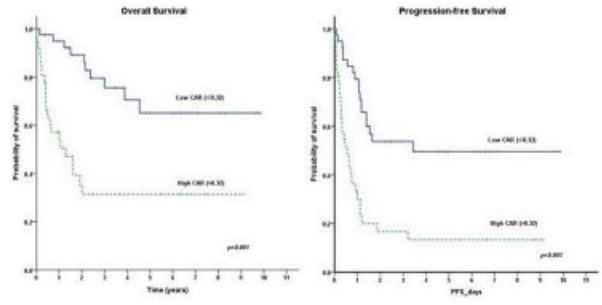
Background : Peripheral T cell lymphoma (PTCL) is a category of aggressive T-cell lymphoid malignancies consisting of heterogeneous groups. There have been many suggested prognostic indexes such as International Prognostic Index (IPI), Prognostic Index for PTCL-unspecified (PIT), and T cell score developed by the international T cell project network, but risk assessment for PTCLs is complex and not fit for all PTCL subtypes. C-reactive protein (CRP)-to-albumin ratio (CAR) has been proposed as one of easily-accessible parameters in diverse cancers, but its value has never been assessed in PTCL.

Method : This study reviewed 76 patients who were diagnosed with PTCL including angioimmunoblastic T cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL), and PTCL, not otherwise specified (NOS), retrospectively. All patients were histologically confirmed and received at least one cycle of chemotherapy between 2007 and 2020. Patients for whom initial laboratory values of CRP and albumin were inaccessible were excluded. The value of 0.32 was appointed as the most discriminative point of CAR, with which the survival difference was maximized. Clinical outcomes including response rate, overall survival (OS), and progression-free survival (PFS) were assessed between high (>0.32) and low (≤0.32) group.

Results : In our patients group, PTCL, NOS was the most common diagnosis (n=31, 40.8%) followed by AITL (n=24, 31.6%), ALK(-) ALCL (n=12, 15.8%), and ALK(+) ALCL (n=9, 11.8%). More than half of patients (n=46, 60.5%) received CHOP(E)-based 1st line chemotherapy. Others were treated with ICED (n=19, 25.0%), IMEP (n=9, 11.8%), and ESHAP (n=2, 2.6%). Of all patients, 36 were classified as high CAR group, 40 as low CAR group in comparison. In terms of IPI, 24 (66.6%) patients in high CAR group presented ≥3, while 12 (33.4%) in low CAR group (p<0.001). In low CAR group, complete response (CR) was achieved in 33 patients (82.5%) after induction chemotherapy, whereas only 14 (38.9%) in high CAR group showed CR (p=0.003). In terms of overall response including CR and partial response, high CAR group revealed significantly inferior result (50.0% vs. 87.5%, p=0.003). There was no significant difference of overall response according to induction regimen (69.0% for CHOP(E), 63.2% for ICED, 66.7% for IMEP, p=0.254). Of 47 patients who achieved CR upfront autologous stem cell transplantation was performed in 11 patients (23.4%), without significant difference between high and low CAR group (21.4% vs. 24.2%, p=1.000). During the median follow-up of 54 months, high CAR group revealed significantly worse 5-year PFS (13.4% vs. 49.6%, p<0.001) and 5-year OS (31.4% vs. 65.1%, p<0.001) (Figure 1). In univariable Cox analysis, high CAR was significantly associated with inferior PFS (HR: 3.382, 95% CI: 1.860-6.149, p<0.001) and OS (HR: 4.193, 95% CI: 1.966-8.945, p<0.001). With adjustment for IPI (≥3), high CAR remained as a significant prognostic factor for PFS (HR: 2.810, 95% CI 1.521-5.193, p=0.001) and for OS (HR: 2.958, 95% CI: 1.351-6.478, p=0.007). Infection was the most common cause of death (n=14), followed by disease progression (n=13) and others (n=5).

Conclusion : Elevated CAR was associated with worse response to treatment and survival in patients with PTCL. CAR might play a complementary role to predict prognosis in patients with PTCL considering its simplicity, objectivity, and easy accessibility.

Keyword : Peripheral T-Cell Lymphoma, C-Reactive Protein, Albumin, Prognosis



PP05-22

Cutaneous T cell lymphoma in Asian patients: A multinational, multicenter, prospective registry study in Asia

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Background : Cutaneous T-cell lymphomas (CTCLs) are group of mature T-cell lymphomas with low and heterogeneous in their incidence. Since its indolent characteristics in early stage, there is still no established treatment strategies for advanced and relapsed or refractory CTCLs. We conducted a study to estimate the relative incidence of CTCLs in Asia and share the therapeutic outcomes according to various treatment strategies currently used in the clinic for advanced CTCLs.

Method : In a part of multinational, multicenter, prospective registry study of adult patients with peripheral T-cell lymphomas (PTCLs) whichwas conducted across Asian countries and territories, we performed subgroup analysis for the patients with CTCLs only.

Results : Among the 486 patients who were registered in the study of PTCLs, 37 patients (7.6%) were identified between April 2016 and February 2019. The median age of patients was 56 years (range of 16 – 84 years) and majority of patients had good performance status. Unlike in Western, Primary cutaneous anaplastic large cell lymphoma, ALK-negative (ALCL, n=13, 35.1%) was the mos common subtype, followed by subcutaneous panniculitis T-cell lymphoma (SPTCL, n=9, 24.3%), mycosis fungoides (MF, n=5, 13.5%), cutaneous PTCLs (C-PTCLs), rare subtypes (n=4, 10.8%), primary cutaneous CD30 positive T-cell lymphoproliferative disorders (n=3, 8.1%) and Sezary's syndrome (SS, n=3, 8.1%). Of identified 37 patients, total 32 patients received any kind of treatment. 3 patients with local therapy only, 7 patients with combination of local and systemic therapy and 22 patients with systemic therapy alone. During the median follow-up periodof 32.1 months, estimated the median progression-free survival (PFS) and overall survival (OS) were 53.5 months (95% CI,0.0 - 122.5) and not reached, respectively. Survival analysis according to the inclusion of anthracycline in chemotherapy did not show the significant differnces. After first-line chemotherapy, 14 patients (48.2%) underwent subsequent treatment but the overall response rate (ORR) was only 20% and the median PFS was inferior to first-line systemic treatment, 2.2 months (95% CI,0.3-4.0). Among patients who underwent systemic treatment, 6 patients performed autologous stem cell transplantation (Auto-SCT) as upfront or salvage treatment but Auto-SCT did not present better PFS (P-value =0.40).

Conclusion : This multinational, multicenter registry study estimated the relative incidence of CTCLs of Asian countries, and the survival outcomes according to the therapeutic strategies currently used in clinic. In our study, primary cutaneous anaplastic large cell lymphoma, ALK-negative was reported as the most common subtype of CTCLs. The most commonly selected first-line systemic treatment was anthracyline-based chemotherapies. Additional studies are needed on standard care treatment of advanced or refractory and relapsed CTCLs.

Keyword : Lymphoma, T-Cell, Cutaneous, Asia, Incidence, Therapy

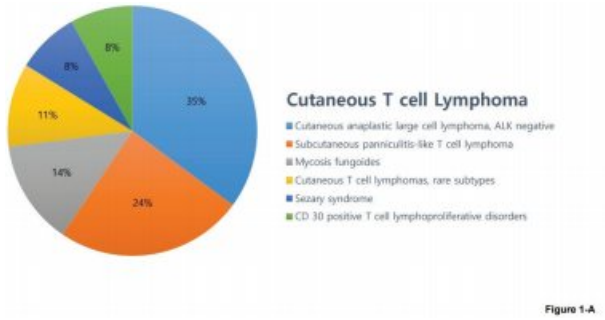


Figure 1-A

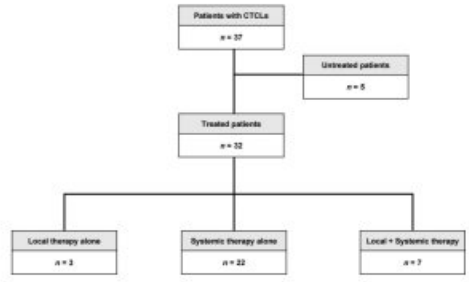


Figure 1-B

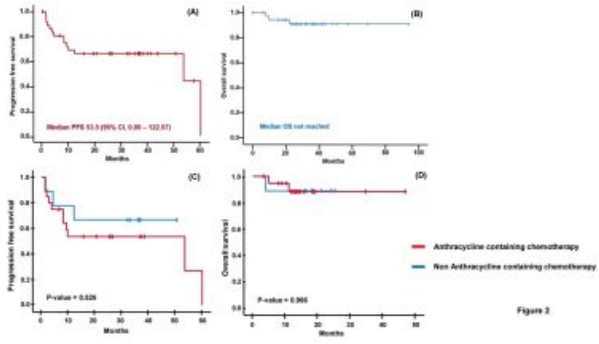


Figure 2

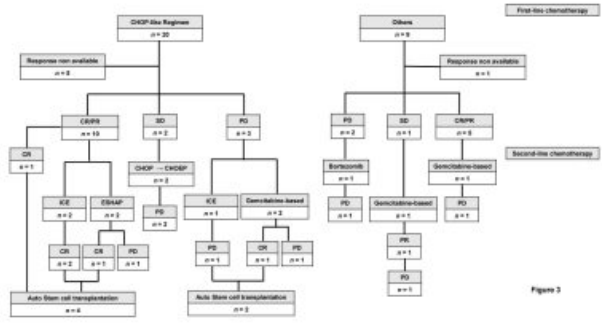
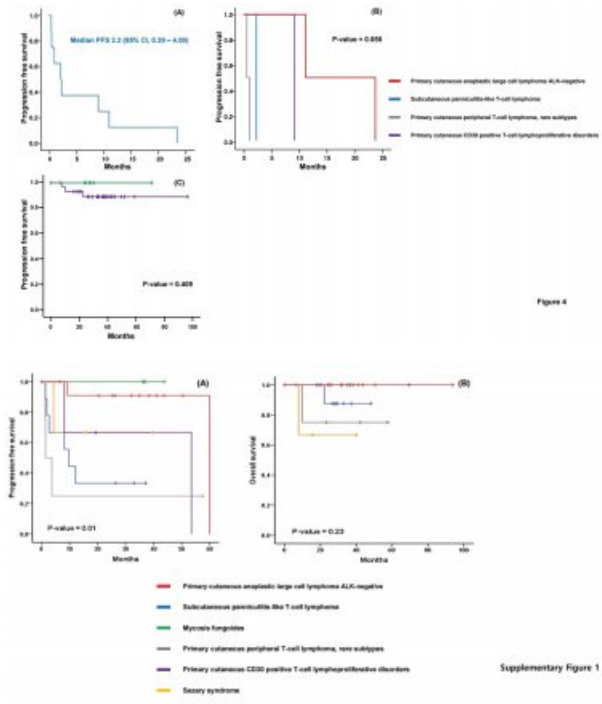


Figure 3



PP05-23

Long-term clinical outcome of of Pro-MACE-CytaBOM regimen with sandwiched radiotherapy in newly diagnosed patients with localized extranodal NK/T-cell lymphoma, nasal type

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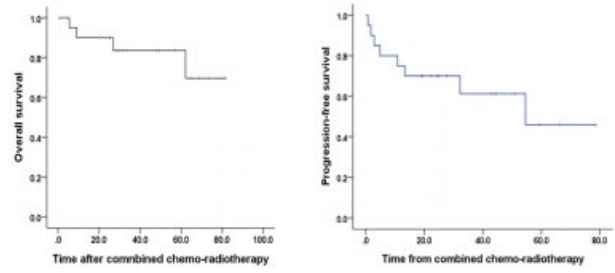
Background : On the basis of the characteristics of extranodal natural killer T (NK/T)-cell lymphoma (ENKTL) which is predisposed to have the multidrug resistance phenotype and radiosensitivity, combined chemotherapy-radiotherapy is one of the effective options in localized early-stage, ENKTL, nasal type. However, frequent severe myelosuppression (grad 3/4 cytopenia), grade 3 radiation-related mucositis, and local/systemic relapse is a major obstacle. So we evaluated the proMACE-cytaBOM (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, and methotrexate) as a slightly less intense regimen with sandwiched radiotherapy (36 Gy).

Method : From July 2005 to December 2019, Fifty-one patients with newly diagnosed, stage IE to IIE, nasal type ENKTL were analyzed retrospectively. 35 patients received the chemoradiotherapy sandwiched method: Initially 3 cycles of proMACE-cytaBOM, followed by radiotherapy of 36 Gy, after sandwiched radiotherapy and additional 3 cycles of proMACE-cytaBOM were administered. The other 16 patients were treated with following: seven patients received the frontline autologous hematopoietic stem cell transplantation, two patients were treated with sequential chemoradiotherapy as VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone) followed by radiation of 50 Gy. four patients received the chemotherapy alone (4 to 6 cycles of proMACE-cytaBOM).

Results : In 35 patients with completely proMACE-cytaBOM and sandwiched radiotherapy schedule, median age was 50-year (range 26 to 79), with male-dominant (85%). A median of 6 (range, 4-6) cycles of proMACE-cytaBOM were administered, and sandwiched radiotherapy was received with a median 36 Gy (range 34.5 to 36). Interim analysis after 3 courses of proMACE-cytaBOM showed that an overall response rate (ORR) of 82.6%, with complete remission (CR) and partial remission (PR) achieved in 73.9% and 8.7%, respectively. On treatment completion with chemotherapy and sandwiched radiotherapy, the ORR was increased to 90.0%, with CR rate increased to 85%. One patient experienced disease progression, and the other one was within stable disease during therapy. With a median follow-up of 61 months (range 5.5 to 120.4), the 5-year overall survival and progression-free survival were 89.6% (95% CI, 69 to 95 %) and 51.9% (95% CI, 45 to 95%), respectively. Grade 3/4 neutropenia developed in 14% (n=5) of patients and grade 3 radiation-related mucositis in 6% (n=2). There was no regimen treatment-related mortality (TRM).

Conclusion : The proMACE-cytaBOM regimen with sandwiched radiotherapy (36 Gy) could be a promising and feasible option in the treatment of newly diagnosed localized ENKTL due to its favorable efficacy and tolerable low toxicities including of low radiation-related mucositis and no TRM.

Keyword : Extranodal NK/T Cell Lymphoma, Sandwich Method, Promace-Cytabom Regimen, Outcome



PP05-24

A novel ICOS gene mutation in a patient with common variable immunodeficiency and T large granular lymphocyte leukemia

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Background : Common variable immunodeficiency (CVID) is the most well-defined PID and is diagnostically by reduced total serum IgG and IgA and/or IgM levels in the presence of impaired vaccination responses and recurrent bacterial infections. T large granular lymphocyte leukemia (T-LGL) is a rare hematological tumor that is caused by the clonal proliferation of T lymphocytes and presents as an inert or invasive process. The clinical manifestations of T-LGL are recurrent infection, anemia and splenomegaly. Here, we introduce a patient diagnosed as CVID complicated with T-LGL, with a novel ICOS gene mutation.

Method : A patient was admitted to a hospital due to 5 months of interrupted fever. Bone marrow cytology showed granulocytopenia and lymphocytosis. Immunofluorescence analysis showed that 17.5% of lymphocytes had abnormal immunophenotypes, including CD3+, CD7+, CD8+, CD57+, TCRαβ+. CD3+CD57+ T-LGL cells accounted for 26.05% of lymphocytes. We collected blood samples from all family members to identify the gene mutation. The ICOS mRNA expression was measured. T and B cell development and function in the patient and 15 HCs was tested. We also predicted the protein structure of the mutant gene.

Results : WGS found out the homozygous ICOS mutation (c.279dupTp.L96Sfs*20) of the patient. Sanger sequence confirmed 6 blood relatives had heterozygous mutaton of ICOS. It is worth noting that the proband and his parents do not conform to Mendel's law of heredity (Figure 1A,1B). We reviewed the HGMD professional database and the mutation was not reported in CVID. The Q-PCR analysis showed dramatically reduced of ICOS mRNA in the patient. Also, the patient lacked ICOS on the surface of activated T cells (Figure 1C,1D). The patient had significantly reduced naive and memory B cells (Figure 2). The serum Ig concentrations were severely decreased in the patient (Table 1). The percentage of CD3+ T cells was low, with an untypical distribution of CD4+ and CD8+ T cell subsets (Figure 3). Th1, Th2 and Th17 cells were reduced and Tregs were specifically increased in the patient. We observed a reduction in CD8+CCR7+CD45RO+ central memory T cells (TCMs) and CD8+CCR7-CD45RO+ (TEMRO) in the patient (Figure 3). This reduction was counterbalanced by an increased frequency of CD8+CCR7-CD45RO- (TEMRA). Our prediction suggests that the mutation forms a new protein structure (Figure 4).

Conclusion : Due to a homozygous frameshift mutation of ICOS gene, the patients were unable to express ICOS and result impaired T cell help for B cells. ICOS-deficient patients develop an adult-onset immunodeficiency characterized by low numbers of B cells, lack of memory B cells and low serum immunoglobulins. The low number and imbalance of T cells may be caused by T-LGL. Whether the occurrence of TLGL is related to CVID remains to be further explored.

Keyword : ICOS, CVID, T-LGL, Frameshift Mutation

Table 1. Immunoglobulin levels of the family members

	Proband II:2	I:1	I:2	II:1	II:3	II:4	II:5	II:6	II:7	II:8	III:1	III:2	IV:1
IgG(7-16g/L)	2.71	12.2	15.3	15.3	11.4	17.1	15.5	11.1	15.6	13.6	13.3	9.36	8.56
IgA(0.7-4g/L)	<0.28	4.42	2.06	3.07	2.77	3.41	3.36	3.14	2.22	2.3	2.6	2.24	1.19
IgM(0.4-2.3g/L)	0.218	1.09	1.64	1.64	0.763	0.835	1.5	1.24	1.55	0.995	2.540	0.893	1.570

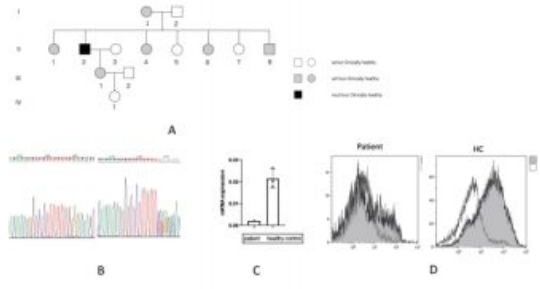

Figure 1. Defective ICOS expression in CVID patients. A. Pedigree of familial NFKB1 case. B. ICOS mRNA expression of the patient and healthy control. C. Sanger sequencing of the patient and healthy control. D. ICOS expression on T cells from affected and healthy family members

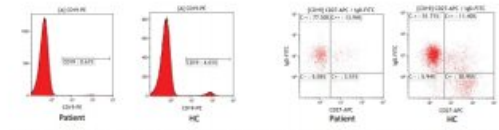

Figure 2. Reduced B cell numbers and lack of switched memory B cells in ICOS-deficient patients

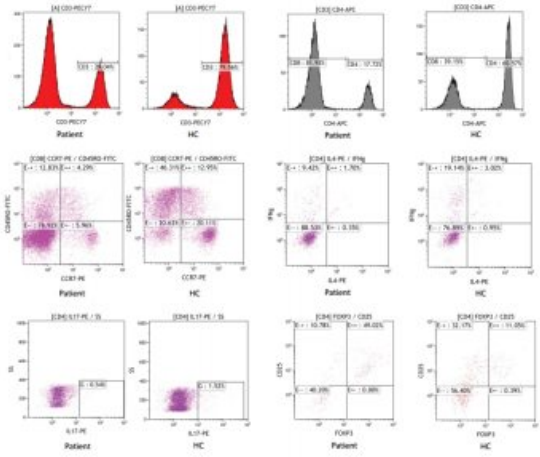

Figure 3. Decrease in memory T cells in ICOS-deficient patients

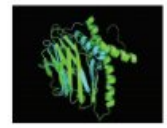

Figure 4. Part of tertiary structure predictions of wild-type and mutant NFKB1. The wild type is shown in green and the mutant in blue

PP05-25

Brentuximab vedotin with chemotherapy for previously untreated, stage III/IV classical Hodgkin lymphoma: 5-year update of the ECHELON-1 study

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Background : Based on historical data, most relapses in classical Hodgkin lymphoma (cHL) occur within 5 years of treatment (Radford et al, BMJ 1997). In the phase 3 ECHELON-1 study (NCT01712490), treatment with brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) significantly improved modified progression-free survival (PFS) per independent review facility in patients (pts) with newly diagnosed Stage III/IV cHL compared with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) (Connors et al, NEJM 2018). Durable PFS per investigator (INV) benefits were seen with A+AVD vs ABVD in the intent-to-treat (ITT) population, and across most key pt subgroups, after 3 and 4 years' follow-up (Straus et al, Blood 2020; Bartlett et al, Blood 2019); improvements were seen irrespective of interim positron emission tomography (PET) scan status, disease stage, and baseline disease risk factor score. We report updated efficacy and safety results after 5-years' follow-up.

Method : Pts with previously untreated Stage III or IV cHL were randomized 1:1 to receive up to 6 cycles of A+AVD (n=664) or ABVD (n=670) intravenously on days 1 and 15 of a 28-day cycle. Pts were required to have an interim PET scan after cycle 2 (PET2). Analyses were performed after extended follow-up (cutoff date September 18, 2020) to assess PFS per INV. Resolution and improvement (improvement by ≥1 grade from worst grade as of the latest assessment) of peripheral neuropathy (PN) in pts with ongoing symptoms at the end of treatment (EoT) were monitored throughout the extended follow-up period. The rate of secondary malignancies, and the incidence and outcomes of pregnancies among pts and their partners were also assessed.

Results : After a median follow-up of 60.9 months (95% confidence interval [CI] 55.2–56.7), estimated 5-year PFS per INV rates were 82.2% (95% CI 79.0–85.0) for A+AVD and 75.3% (95% CI 71.7–78.5) for ABVD. PFS per INV favored A+AVD over ABVD (hazard ratio [HR] 0.681; 95% CI 0.534–0.867; p=0.002) (Table). Estimated 5-year PFS with A+AVD vs ABVD in the ITT population was 84.9% vs 78.9% in PET2-negative pts (HR 0.663; 95% CI 0.502–0.876; p=0.004) and 60.6% vs 45.9% in PET2-positive pts (HR 0.702; 95% CI 0.393–1.255; p=0.229). In the A+AVD and ABVD arms, 85% and 86% of pts with treatment-emergent PN had complete resolution or improvement of symptoms, respectively. Median time to complete resolution of PN events ongoing at EoT was 34 weeks (range 0–262) in the A+AVD arm and 16 weeks (range 0–267) in the ABVD arm; median time to improvement was 49 weeks (range 8–270) and 12 weeks (range 2–70), respectively. In the A+AVD arm, 29% of pts had ongoing PN with maximum severity of grade 1 (17%), grade 2 (9%), grade 3 (3%), and grade 4 (<1%). In the ABVD arm, PN was ongoing in 21% of pts; maximum severity was grade 1 (14%), 2 (6%) or 3 (1%). In total, 150 pregnancies were reported; the proportion of ongoing pregnancies or live births was similar in both arms (92% and 85% in the A+AVD and ABVD arms, respectively).

Conclusion : At 60.9 months' median follow-up, sustained PFS benefit was observed with A+AVD vs ABVD, which was independent of disease stage and PET2 status. In addition, treatment adaptation by interim PET2 status is not required for

A+AVD and bleomycin exposure is avoided. The durable and robust treatment benefit with A+AVD is coupled with a manageable safety profile; these results suggest that A+AVD is an attractive treatment option for all pts with previously untreated Stage III or IV cHL.

Keyword : Classical Hodgkin Lymphoma, Brentuximab Vedotin, Previously Untreated

Table: PFS per INV at 60.9 months by PET2 status and age in the ITT population

Group, % (95% CI)	A+AVD	ABVD	HR (95% CI) p-value
All pts	n=664	n=670	0.681 (0.543–0.867)
	82.2 (79.0–85.0)	75.3 (71.7–78.5)	0.002
PET2-negative	n=588	n=578	0.663 (0.502–0.876)
	84.9 (81.7–87.6)	78.9 (75.2–82.1)	0.004
PET2-positive	n=47	n=58	0.702 (0.393–1.255)
	60.6 (45.0–73.1)	45.9 (32.7–58.2)	0.229
Pts aged <60 years	n=580	n=568	0.665 (0.505–0.876)
	84.3 (81.0–87.1)	77.8 (74.0–81.1)	0.003
PET2-negative	n=521	n=493	0.675 (0.492–0.927)
	86.6 (83.3–89.3)	81.5 (77.7–84.7)	0.014
PET2-positive	n=42	n=50	0.702 (0.370–1.331)
	63.1 (46.4–75.9)	49.3 (34.7–62.3)	0.274
Pts aged ≥60 years	n=84	n=102	0.820 (0.494–1.362)
	67.1 (55.1–76.5)	61.6 (50.9–70.7)	0.443
PET2-negative	n=67	n=85	0.720 (0.401–1.292)
	71.9 (59.0–81.3)	64.9 (53.5–74.2)	0.268
PET2-positive	n=5	n=8	0.923 (0.229–3.715)
	40.0 (5.2–75.3)	25.0 (3.7–55.8)	0.910

PP05-26

Influence of DNA repair and TLR4 gene variants on response to ABVD regimen in South Indian patients with Hodgkin lymphoma

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Background : Hodgkin Lymphoma (HL) is an uncommon B-cell malignancy which is currently being treated with ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) regimen. With the current treatment strategy, 5-year overall survival in the early stage favourable disease is around 90% but in the advanced stage, it is around 60-70%. In addition to the clinical prognostic factors, genetic polymorphisms involved in drug metabolism pathways could be used as prognostic markers in HL response. The present study aimed to investigate the influence of XPC rs2228000, rs2228001, PMAIP1/Noxa rs809376 (DNA repair) and TLR4 rs1554973 variants on response to ABVD regimen in patients with Hodgkin Lymphoma.

Method : After obtaining institutional ethics committee approval, 78 cases with HL receiving ABVD regimen were recruited from the Medical Oncology outpatient department. Response assessment was done using 5-point scale (Deauville) criteria. From the study participants, 5ml of blood was collected for DNA extraction. Genotyping was performed using TaqMan assay kits by real-time PCR. Statistical analysis was done using SPSS v19.

Results : Three-year overall survival was 88% and three-year relapse-free survival was 87% in 78 HL patients who completed treatment with ABVD regimen. Eight (10%) patients relapsed and 8 (10%) patients died. We found that in univariate analysis CT genotype of variant XPC rs2228000 was associated with 4.9 times increased risk of relapse in HL patients. In multiple logistic regression analysis, the proposed variants did not influence treatment outcome in HL patients receiving ABVD regimen.

Conclusion : The results suggest that XPC rs2228000, rs2228001, PMAIP1/Noxa rs809376 and TLR4 rs1554973 variants did not influence treatment outcome in HL patients receiving ABVD regimen. Although studies with a larger cohort are needed to confirm this finding.

Keyword : TLR4, PMAIP1/Noxa, XPC, Polymorphisms, Hodgkin Lymphoma

PP05-27

Multicenter, retrospective analysis of patients with chronic lymphocytic leukemia in Korea

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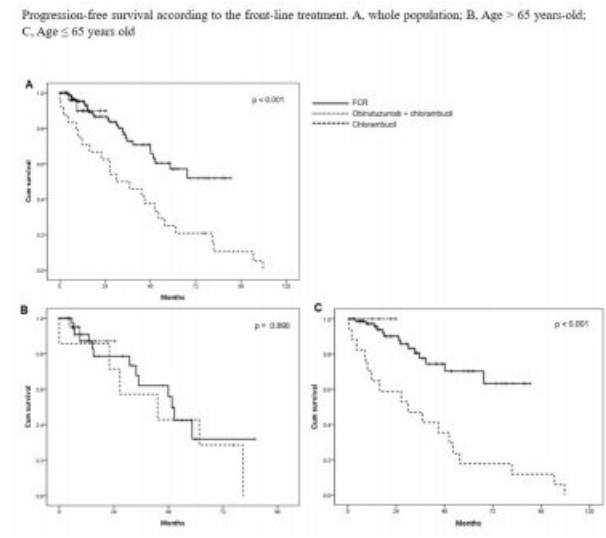
Background : Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western countries. However, it is rare in East Asia. Due to the paucity of the disease, lack of feasibility of novel agents and the laboratory prognostic tools, there has been limited data dealing with clinical outcomes of this disease in Asia. To further elucidate the current status, we have carried out a multicenter, nation-wide, retrospective analysis of Korean CLL patients.

Method : A retrospective study of patients with CLL who were treated with either alkylating agent, purine analog, or anti-CD20 monoclonal antibody was carried out in 18 tertiary institutes in Korea. Medical records were reviewed for clinical characteristics, treatment courses, and outcomes.

Results : Between 2008 to 2019, a total of 192 cases were eligible for the analysis, and all patients were Asians. Median age at treatment was 63 (range, 34 – 87) the Rai stages at treatment were as follows; 0-1(0.5%), I-46 (24.0%), II-46 (24.0%), III-50 (26.0%), and IV-49 (25.5%). The Binet stages were as follows; A-22 (11.5%), B-76 (39.6%), and C-94 (49.0%). Most of molecular analysis have not been carried out. FISH test for 17p has been done in 46 cases (23.9%) of which 7 cases (15.2%) were positive. TP53 mutation analysis was done in 66 cases (34.3 %) of which 10 cases (15.2%) were positive. IgHV analysis was done in 10 cases and none of them had mutation. The front-line treatment regimens were as follows; Fludarabine/Cyclophosphamide/Rituximab (FCR) 117 (52.7%), Obinutuzumab/Chlorambucil (GC) 30 (13.5%), Chlorambucil monotherapy 24 (10.8%), other fludarabine-based combinations 16 (8.3%), and others 5 (2.6%). The complete response rate was 54.7% (N =105), and the partial response rate was 26.6% (N =51). And the overall response rate of FCR arm, GC arm, chlorambucil arm were 89.7%, 70.0%, and 58.3%, respectively. With the median follow-up duration of 60.5 months (95% CI 53.6 – 67.4), the median PFS was 55.6 months (95% CI 40.4 – 70.7), and the 2-year PFS rate was 80.3 ± 3.4%. Although several molecular features, such as del(17p), and TP53 mutation, could discriminate the PFS, other known prognostic factors including del(13q), del(11q), stages or age could not. In addition, the PFS out of either FCR or GC was not significantly different, but chlorambucil was associated with significantly inferior PFS ($p < 0.001$). The overall survival was 136.3 months (95% CI 100.1 – 172.5) with the 5-, 10-year OS rates were 82.0 ± 3.3%, and 57.4 ± 10.7%, respectively.

Conclusion : This is one of the largest studies from Korean CLL patients. Although patients had been treated with less favored agents, the outcomes were not different from the Western studies. To elucidate the role of ethnicity in this 'orphan' disease in Asia, further studies incorporating novel agents are warranted.

Keyword : Chronic Lymphocytic Leukemia, Treatment Outcome



PP05-28

Possible correlation of torque teno virus/torque teno-like minivirus and human herpes virus-8 in kikuchi-fujimoto disease

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Background : Kikuchi-Fujimoto disease (KFD) is idiopathic lymphadenitis with possible connection to viral infectious agents because of its febrile, self-limiting clinicopathologic characteristics. In our previous metaanalysis, none of most common infectious pathogens were related to KFD except human herpesvirus-8 (HHV-8) despite of relatively limited evidence. On the other hand, we have recently found that Torque Teno virus/Torque Teno Minivirus (TTV/TTMV) is significantly increased in KFD patients suggesting the transient immune suppression and possible relationship to high HHV-8 in KFD. Here we designed a case control study to reconfirm the relationship of HHV-8 to KFD and to find possible association of TTV/TTMV and HHV-8 using larger samples

Method : We performed RT-PCR specific to TTV/TTMV and HHV-8 with formalin-fixed paraffin-embedded tissue of 64 KFD patients and 25 randomly selected, matched normal controls. We compared the positivity and analyzed the its correlation with other clinicopathologic characteristics.

Results : The mean average age of KFD cases was 22 years, with 19 males and 45 females. TTV/TTMV was positive in 51 out of 64 KFDs and 6 out of 25 normal controls, respectively (79.7% vs. 25%, p<0.05). HHV8 was positive only in 2 cases of KFD (2/64, 3.1% vs. 0/25, 0.0%, p<0.05) with being all cases TTV/TTMV-positive KFDs (2/51, 3.9% vs. 0/13, 0.0%, p<0.05).

Conclusion : In this study, we found that HHV8 was significantly associated to KFD than controls and HHV8 positivity is related to TTV/TTMV positivity in KFD. This results suggest the another evidence of possible association of HHV8 and TTV/TTMV in KFD pathogenesis. Future study is needed to investigate the mechanism to cause KFD using cell culture or animal models.

Keyword : Kikuchi-Fujimoto Disease, Histiocytic Necrotizing Lymphadenitis, Human Herpesvirus-8 Torque Teno Virus, Torque Teno Like Minivirus, Polymerase Chain Reaction

PP06-01

Clinical study on risk-stratified treatment in children with HLH

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Background : To investigate the therapeutic effect and side effects of risk-stratified treatment for children with hemophagocytic lymphohistiocytosis (HLH).

Method : A prospective historical comparison analysis was performed on the newly diagnosed HLH children, who were treated in Beijing Children's Hospital affiliated with, Capital Medical University from July 2017 to July 2019 with risk-stratified treatment. The results were compared with those children treated with HLH-04 in our hospital from 2008 to 2013. According to the protocol, the children were divided into low-risk group, high-risk group and system autoinflammatory disorders (SAIDs) associated-HLH group. The first-line treatments included giving low-risk group only hormone therapy, giving high-risk group hormones combined with etoposide (VP-16) and giving SAIDs-HLH group hormones combined with cyclosporine. The second-line treatment was comprised of DEP, L-DEP and/or Ruxolitinib (Ru). And hematopoietic stem cell transplantation (HSCT) was performed on refractory and recurrent HLH and primary HLH. The clinical data, laboratory examination, treatment and prognosis were collected. The events included recurrent, disease activity, death and abandoning treatment.

Results : 1) Basic character : a total of 122 patients were enrolled in this study. There were 60 boys and 62 girls. The median age at disease onset was 2.4 (0.17-16.9) years, of which 59% patients were younger than 3 years old. There were 21 patients with primary HLH (17.2%), 55 with EBV-HLH (45.1%), 25 with SAIDs-HLH (20.5%), 16 with non-EBV infections associated HLH, which included 9 bacterial infection cases (7.4%), 3 cytomegalovirus infection (2.5%), 3 mycoplasma infection (2.5%), and 1 herpes simplex virus infection (0.8%). And 5 cases had unknown etiology.

2) Treatment and prognosis: according to the stratification criteria, 38 patients were in the low-risk group, 84 in the high-risk group and 25 in SAIDs-HLH group. In the 8th week after first-line treatment, the remission rate (CR+PR) was 69.7%. 26 cases accepted second-line treatment, 7 cases with Ruxolitinib, 3 cases with L-DEP regimen, 6 cases with RU-DEP regimen, and 10 cases with RU-L-DEP regimen. The remission rate of second-line treatment was 57.7%. 15 patients accepted HSCT, and only one patient died. The median follow-up time was 12 (0.25-27) months, and the overall survival (OS) rates in the 1st, 2nd, 12th and 24th month were 91.0%, 85.2%, 82.8% and 82.8% respectively. The event-free survival (EFS) rate in the 1st, 2nd, 12th and 24th months were 77.0%, 68.0%, 64.3% and 56.7% respectively. There was no significant difference in survival rates among different subtypes. Compared with the children who accepted HLH-04 protocol in our hospital, the 2-year OS of the risk-stratified treatment increased significantly (58.6% vs. 82.8%, P<0.001) and the mortality due to severe infections was significantly decreased (48.8% vs. 4.8%, P=0.009).

3) Side-effect: 27 cases (36.5%) developed varying degrees of myelosuppression, including 2 cases in grade 1 (7.4%), 4 cases in grade 2 (14.8%), 12 cases in grade 3 (44.4%), and 9 cases in grade 4 (33.3%). The myelosuppression recovered after 7 (3-11) days. 21 cases (17.2%) complicated with infection during the treatment, mainly with pneumonia (90.5%) and septicemia (4.8%). Pancreatic damage occurred in 5 cases (4.1%), with myocardial damage in 8 cases (6.6%), and renal function damage in 2 cases (1.6%). Compared with the patients treated with HLH-04 protocol in our hospital, the incidence of infection and myocardial damage decreased (P=0.040 and 0.003).

Conclusion : 1) Risk stratification therapy provided individualized treatment for HLH patients, which significantly improves the survival rate and reduces infection-related mortality. 2) Ruxolitinib and L-DEP/DEP were effective for patients with recurrent and refractory HLH, which improves the remission rate and earns chance for hematopoietic stem cell transplantation.

Keyword : Hemophagocytic Lymphohistiocytosis, Stratified-Treatments, Clinical Manifestation, Prognosis

PP06-02

Clinical analysis of chronic active EBV infection with coronary artery dilatation and a matched case-control study

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Background : Epstein-Barr virus (EBV) belongs to the gamma–herpesvirus family, which consists of double-stranded DNA viruses. The primary infection mainly invades B lymphocytes and can cause infectious mononucleosis (IM) and EBV-associated hemophagocytic lymphohistiocytosis (HLH). EBV can also occasionally infect T lymphocytes and/or natural killer (NK) cells, resulting in EBV-driven T/NK-cell lymphoproliferative diseases, such as chronic active EBV infection (CAEBV). The diagnosis of CAEBV is based on clinical manifestations and evidence of EBV in tissues or peripheral blood samples. In CAEBV, EBV-infected T or NK cells clonally proliferate and infiltrate multiple organs, leading to their failure. CAEBV has two characteristics: systemic inflammation and neoplastic disease. The main clinical finding of CAEBV is inflammation, which is characterized by fever, lymphadenopathy, liver dysfunction, hepatosplenomegaly, and an abnormal hemogram3. CAEBV causes vasculitis due to the direct invasion of the infected cells, which can lead to the development of vascular aneurysms. However, CAEBV combined with coronary artery dilatation (CAD) has been rarely reported. To date, there is no unified and effective chemotherapy regimen for CAEBV. The only effective treatment strategy is allogeneic HSCT. According to Sawada's report, a 3-step strategy including allogeneic HSCT for the treatment of CAEBV was proposed. The 3-year overall survival rate (3y-OS) was 87.3 ± 4.2%. Here, we report 10 cases of pediatric patients diagnosed with CAD secondary to CAEBV.

Method : Children with CAEBV associated with CAD hospitalized at Beijing Children's Hospital, Capital Medical University from March 2016 to December 2019 were analyzed. Children with CAEBV without CAD were selected as the control group and matched by sex, age, treatment and admission time. The clinical manifestations, laboratory and ultrasound examinations, treatment and prognosis of the children were collected in both groups.

Results : There were 10 children with CAEBV combined with CAD, including 6 males and 4 females, accounting for 8.9% (10/112) of CAEBV patients in the same period, with an onset age of 6.05 (2.8-14.3) years. The median follow-up time was 20 (6-48) months. All the patients had high copies of EBV-DNA in whole blood [1.18x107 (1.90x105-3.96x107) copies/mL] and plasma [1.81x104 (1.54x103-1.76x106) copies/mL], and all biopsy samples (bone marrow, lymph nodes or liver) were all positive for Epstein-Barr virus-encoded small RNA. Among the 10 children, 8 had bilateral CAD, and 2 patients had unilateral CAD. After diagnosis, 7 children were treated with L-DEP chemotherapy in our hospital. After chemotherapy, four patients underwent allogeneic hematopoietic stem cell transplantation (HSCT). The others were waiting for HSCT. At the time of the last patient follow up record, the CAD had returned to normal in 3 patients, and the time from the diagnosis of CAD to recovery was 21 (18-68) d. LDH, serum ferritin, TNF-α and IL-10 levels were statistically significantly different between the two groups (P=0.009, 0.008, 0.026 and 0.030). There were no significant differences in survival rate between the two groups (P=0.416).

Conclusion : The incidence of CAEBV with CAD was low. CAEBV with CAD did not influence the prognosis. Patients who had high LDH, serum ferritin, TNF-α, and IL-10 levels early in their illness were more likely to develop CAD.

Keyword : Epstein-Barr Virus, Coronary Artery, Clinical Characteristics, Pathogenesis

PP06-03

Outcome of langerhans cell histiocytosis: A single center experience

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Background : Langerhans cell histiocytosis(LCH) is a rare childhood disorder which can have varied presentation (single system SS or multi-system MS)and outcomes. Outcomes are linked to risk organ (RO)(hematologic system, liver and spleen) involvement.Here, we describe outcomes of children treated with LCH at a single center.

Method : We retrospectively analyzed data of treatment and outcome of 14 children diagnosed with LCH at our hospital from April 2015 to Aug 2019.

Results : The mean age was 6.35 years(0.9 years- 19 years). Majority 12/14 (86%) had SS-LCH while 2/14 (14%) had MS-LCH.Both children with MS-LCH had RO involvement.Amongst children with SS-LCH all had skeletal involvement only(Multi-ostotic in 2 and Mono-ostotic in 10).Diagnosis was biopsy proven in all. All cases were CD1a positive. Both children with MS-LCH showed poor response to LCH III protocol and required salvage cladribine based chemotherapy. First case achieved complete remission (CR) and is at present on maintenance therapy for last 1 year.Other patient had sclerosing cholangitis, lung, and bone marrow involvement and remained refractory to chemotherapy.She was positive for BRAF mutation and was given Vemurafenib after which she achieved partial remission and was taken for living donor liver transplant.Post liver transplant developed bilateral pneumothorax and died of sepsis.Among SS-LCH, three with mono-ostotic disease needed curettage only and no chemotherapy was given.Seven children with mono-ostotic disease(Vertrebral-1,Diabetes insipidus-1,Hip joint-1,Jaw-2,Skull-2) and 2 with Mutli-Ostotic were treated as per LCH III protocol. All responded to therapy except 1 who required salvage therapy (vincristine and cytarabine)and achieved CR. After 6 weeks of induction therapy 67% and at 12 weeks 73% were in CR.The overall survival was 93% and event free survival was 93% at median follow-up of 13 months.

Conclusion : LCH without risk organ involvement is highly curable in children.Children with risk organ involvement and poor response to therapy have high risk of mortality.

Acknowledgements- Our deep appreciation. and thanks to Mr. Indra Bhushan Pandey, our database manager, for retrieving the data.

Keyword : Langerhans Cell Histiocytosis, Risk Organ Involvement, Outcomes

PP06-04

Clinical analysis of pediatric systemic juvenile xanthogranulomas: A retrospective single-center study

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Background : To investigate the clinical characteristics, treatment, and prognosis of children with juvenile xanthogranuloma (JXG).

Method : Children with JXG who were hospitalized in Beijing Children's Hospital, Capital Medical University, from January 2012 to December 2019 were retrospectively analyzed. Data relating to the clinical manifestations, laboratory values, treatment, and prognosis of the children were extracted from medical records. Patients underwent vindesine +prednisone as the first-line treatment and cytarabine + vindesine + dexamethasone +/- cladribine as the second-line treatment.

Results : Ten patients, including 8 males and 2 females, with an onset age of 1.95 (0.80-7.30) years, exhibited multi-system dysfunction. The median age of diagnosis was 2.45 (1.30-12.10) years. The most common location of extracutaneous lesions was the central nervous system (6 cases), followed by the lung (5 cases) and bone (4 cases). Nine patients underwent first-line chemotherapy, and 6 patients underwent second-line chemotherapy, including 5 patients with poorly controlled disease after first-line treatment. The median observation time was 20 (3-106) months. Nine patients survived, whereas one patient died of respiratory failure caused by pulmonary infection. By the end of follow-up, 7 patients were in an active disease (AD) state but better (AD-better), and 2 patients were in an AD-stable state. Three patients had permanent sequelae, mainly, central diabetes insipidus. The first-line treatment response rate was 40.0%, and the second-line treatment response rate was 66.7%.

Conclusion : The chemotherapy protocol for Langerhans cell histiocytosis (LCH) was effective for patients with systemic JXG, which also resulted in good outcomes. Central nervous system involvement did not impact overall survival, but serious permanent sequelae remained.

Keyword : Juvenile Xanthogranuloma, Clinical Characteristics, Treatment, Prognosis

Table 1 General information

Pt	Onset age (years)	Diagnosis age (years)	Sex	Biopsy sites	Involved location			
					Skin	CNS	Lung	Liver	Others
1	0.8	1.5	F	skin	+	pituitary gland	+	-	-
2	5.7	6.0	M	testis	-	-	+	+	kidney, eye, parotid gland, salivary gland, testis
3	1.4	1.5	M	skin + liver	+	-	-	+	blood, spleen
4	2.2	2.5	M	femur	-	Multiple	-	-	femur, vertebra
5	7.3	7.3	M	skin	+	Multiple	+	-	eye, parotid gland, pancreas, testis
6	1.1	1.4	M	skin	+	-	+	-	Bone
7	1.2	1.3	F	femur	-	-	-	-	thyroid gland, bone
8	1.7	2.4	M	skin + liver +bone marrow	+	Multiple	+	+	bone marrow, spleen, bone
9	7.2	7.8	M	muscle	-	Multiple	-	-	soft tissue, muscle
10	5.1	12.1	M	skin +conjunctiva	+	pituitary gland + multiple	-	-	eye, blood

Note: Pt: patient, F:femal, M:male, CNS: central nervous system

Table 2 Treatment and prognosis

Pt	Treatment			Duration of follow-up (month)	Disease status at last follow-up	Permanent sequelae
	First-line (week)	Second-line (cycle)	Other treatment			
1	12	-	-	106	AD-B	central diabetes insipidus
2	6	2B	-	70	AD-S	-
3	2	1B	-	3	Dead	-
4	25*	-	-	23	AD-B	-
5	5	4B+2A	-	21	AD-S	-
6	52*	-	-	19	AD-B	-
7	25*	-	-	9	AD-B	-
8	-	1A	liver transplantation	9	AD-B	liver cirrhosis, liver failure
9	12	3B	-	9	AD-B	-
10	52*	4B+4A*	-	28	AD-B	movement disorders, central diabetes insipidus, diminution of vision, abnormal thyroid dysfunction

Note: Pt: patient, A: Cytarabine + VDS + Dexamethasone, B: Cytarabine + VDS + Dexamethasone + Cladribine, AD-S: AD-Stable, AD-B: AD-Better. *: treatment course finished, *: this patient accepted first-line treatment in other hospitals for 1 year

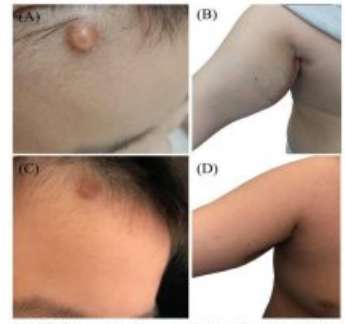

Fig. 1 JXG: soft tissue mass (case 9): a round mass in the head(A) and right axilla(B) of the onset, tough, no tenderness. (C) and (D) showed the mass after treatment.

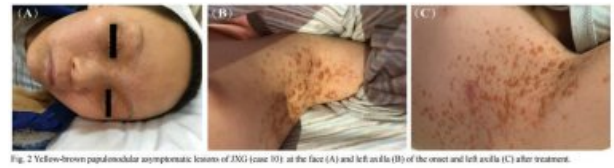

Fig. 2 Yellow-brown papulonodular asymptomatic lesions of JXG (case 10): at the face (A) and left axilla (B) of the onset and left axilla (C) after treatment.

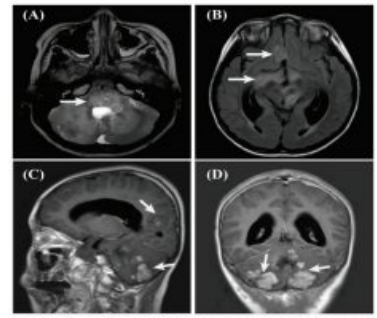

Fig. 3 Head MRI (case 10): Brainstem (A), optic pathway, sellar region, anterior middle cranial fossa (B) and cerebellum (C, D), multiple space occupying lesions with slightly longer T2 signal, high signal intensity on FLAIR image, and uneven signal intensity of the lesion.

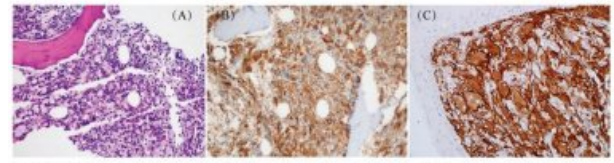

Fig. 4 Pathological changes about skin in JXG: A: HE staining: X200 (case 9); B: Special staining: CD68(+)(case 9), C: Special staining: CD163(+)(case 3).

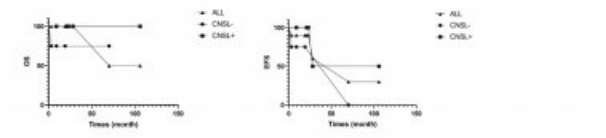

Fig. 5 In comparison, systemic IXG with and without central nervous system involvement had no significant difference in 5-year overall survival rate (100.0% vs. 75.0%, Log-rank test, P=0.2207), and there was no significant difference in 2-year event-free survival rate between the two groups (50.0% vs. 75.0%, Log-rank test, P=0.3636). ALL: all the patients; OS: overall survival; EFS: event-free survival.

PP07-01

Generation of potent dendritic cells using interleukin-15 in multiple myeloma

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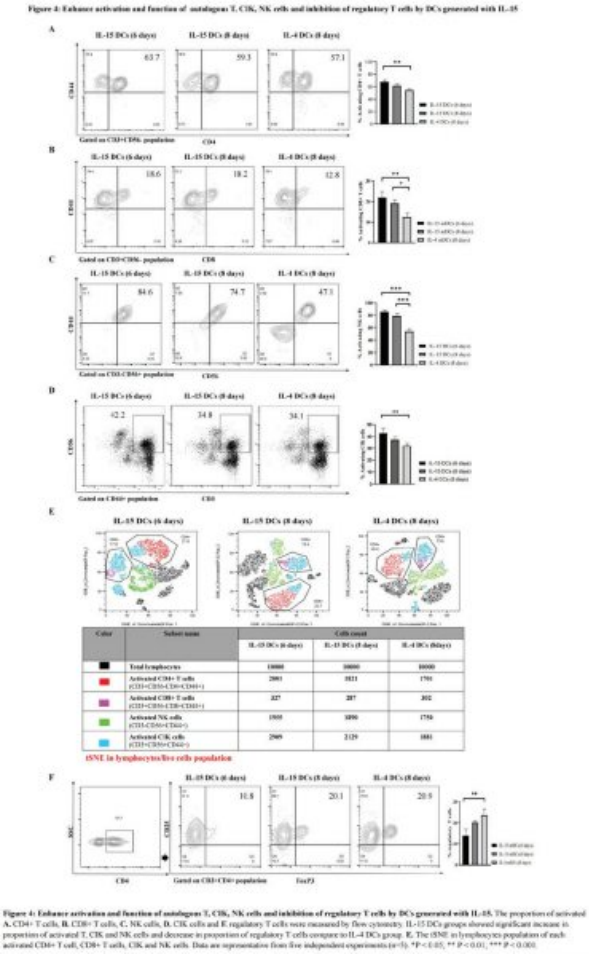
Background : The dendritic cell (DC) is the most potent antigen-presenting cell, which has been exploited in clinical, including cancer vaccines. However, the effect of DCs vaccines is still limited, thus a novel way to develop effective DCs vaccines are highly desirable. In this study, we set out to investigate whether the generation of human monocytes derived DCs in addition of interleukin 15 (IL-15) have the stronger capacity to stimulate immune cells, in comparison with conventional IL-4 DCs.

Method : We collected CD14+ cells from peripheral blood of multiple myeloma (MM) patients, then cultured DCs in addition to GM-CSF and IL-4 with or without IL-15 ex vivo. We checked DC morphology, cytokines secretion of DCs, along with function and cytotoxicity of activated lymphocytes by DCs against ARH77, IM9 and K562 cancer cells line, patient's autologous primary myeloma cells.

Results : Our data showed that IL-15 matured DCs had a stronger expression of stimulation and migration receptors, importantly, secreted much higher IFN-γ compare to IL-4 matured DCs. Activated T cells by IL-15 mDCs showed higher polarization toward T1 helper, a higher proportion of activated CD4+, CD8+ T cells, and interestingly, CIK and NK cells, strong cytotoxicity toward specific target cancer cell lines and patient's autologous primary myeloma cells.

Conclusion : DCs generated in addition of IL-15 from MM patients resulted in outstanding T cells, CIK cells and NK cells activation and strong cytolytic activity against both cancer cell lines and patient' primary myeloma cells. Thus, our finding serves as a cornerstone of cancer immunotherapy in MM.

Keyword : Anti-Cancer Immunity, Dendritic Cells, Interleukin-15



PP07-02

Relationship between number of plasma cells with monoclonal protein levels in myeloma multiple patients

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Background : Multiple myeloma is a neoplasm of the B cell that is characterized by abnormal proliferation of plasma cells. Plasma cells will form monoclonal proteins (antibodies). These monoclonal proteins enter the circulation which can be detected in serum and urine electrophoresis. Measurement of monoclonal protein in circulation is a standard of diagnosis, prognosis, and management of multiple myeloma. Many role of monoclonal proteins in multiple myeloma, so information is needed about relationship between plasma cells and monoclonal proteins. The aims of this study was

to know relationship between plasma cell counts to monoclonal protein levels in multiple myeloma patients.

Method : This study used analytic observational retrospective design. Subjects of this study were inpatient medical records in Sardjito Hospital with diagnosis of multiple myeloma during 2017. Diagnosis is based on International Myeloma Working Group 2002 criteria. Monoclonal protein calculation is calculated from percentage of monoclonal protein to total protein that forms monoclonal gammopathy in gamma, alpha, and beta regions. Monoclonal gammopathy is determined by looking ratio between weight to width 4: 1 to differentiate from polyclonal gammopathy. If there is no monoclonal gammopathy, monoclonal protein is calculated from percentage of gamma globulin to total protein. Data were analyzed by linear regression.

Results : Thirty subjects were obtained in this study. Gender is dominated by males with 21 subjects (70%). Median value of plasma cells is 21% (1% -86%). Mean monoclonal protein level was 4,287 (± 2,375) gr / dL. The smallest monoclonal protein content is 0.7 gr / dL and the highest is 9.4 gr / dL. Monoclonal protein was obtained in the alpha-2 region by 2 subjects (6.66%), beta-1 1 subjects (3.33%), beta-2 2 subjects (6.66%), and gamma 25 subjects (83%). Mean level of monoclonal protein in each region is alpha-2 of 2,365 gr / dL, beta-1 2,5 gr / dL, beta-2 3,59 g / dL, and gamma 4,51 gr / dL. Linear regression analysis obtained correlation between the number of plasma cells with monoclonal protein levels (p=0.038; r =0.38).

Conclusion : A positive correlation was obtained between the number of plasma cells and monoclonal protein in multiple myeloma

Keyword : Multiple Myeloma, Monoclonal Protein, Plasma Cells

PP07-03

Galectin-3 in multiple myeloma in residents of Gomel region of Belarus

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Background : Galectin-3 belongs to the lectin family and is involved in a variety of biological processes including apoptosis, cell proliferation, and tumor progression. However, its diagnostic value in MM is not fully understood.

Method : The study included 17 MM patients from Gomel region of Belarus The observation period was 8 months. The median age -58 years. Females - 52.9%. Immunophenotypic markers CD56, CD200, CD117, and CD95, CD20 in MM patients were evaluated and the relationship with increased expression of galectin-3 was studied. Results were evaluated at the time of diagnosis.

Results : Increased expression of galectin-3 was detected in 5 out of 17 patients (29.4%). When studying the expression of galectin-3, an increase in its level was not associated with sex, age, type of immunoglobulin, the amount of M-protein; however, increased expression was observed in patients with the secretion of light chains of immunoglobulins (p=0.018), more often kappa (p=0.049). Also, all patients with increased expression had an increase in the level of β2-microglobulin more than 3 mg/l. All patients with increased expression of galectin-3 had damage to the kidneys. Of these, signs of disease progression during the observation period appeared in 3 patients (60%). In a study in 100% of patients with increased expression of galectin, 3 showed an excess of the level of the immunophenotypic marker CD56 and 80% of patients - the level of CD117, and it was also found a correlation between high expression of galectin-3 and the expression of these immunophenotypic markers CD56 (p=0.014) and CD117 (p=0.013).

Conclusion : Our study revealed that galectin-3 is strongly overexpressed in patients with newly diagnosed myeloma with kidney damage. We observed a relation of increased expression of galectin-3 with immunophenotypic markers CD56 and CD117. These results also suggest a key role for galectin-3 in tumor progression in MM in patients with kidney damage. And it is possible that galectin-3 can be used as an indicator for the differential diagnosis of MGRS of tumor origin and kidney damage of non-tumor origin.

Keyword : Galectin-3, Multiple Myeloma, Progression

PP07-04

Translational data supporting the rational combination of iberdomide with proteasome inhibitors

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Background : In a phase 1/2 dose-escalation study for relapsed/refractory multiple myeloma (MM) (CC-220-MM-001; NCT02773030), iberdomide (IBER; CC-220), a potent, novel cereblon (CRBN) E3 ligase modulator (CELMoD) agent is under investigation. IBER modulates CRBN to induce ubiquitination and proteasome-dependent degradation of Ikaros/Aiolos, resulting in anti-myeloma and immunomodulatory activity. IBER binds to CRBN with 20-fold higher affinity than immunomodulatory drugs (IMiDs) and is more efficient at degrading Ikaros/Aiolos, and can overcome IMiD drug resistance. We compared the preclinical activity of IBER versus IMiD drugs + proteasome inhibitors (PIs), and assessed IBER pharmacodynamic (PD) activity in patients (pts) receiving IBER+dexamethasone (DEX), IBER+DEX+bortezomib (BORT), and IBER+DEX+carfilzomib (CFZ).

Method : MM cell lines from healthy volunteers were treated with PIs (BORT; CFZ), pulsed with drug for 1 h, followed by treatment with clinically relevant concentrations of lenalidomide (LEN; 1 μM), pomalidomide (POM; 300 nM), or IBER (20 nM). PD analyses were performed on blood samples of pts enrolled in the IBER+DEX, IBER+DEX+BORT, and IBER+DEX+CFZ cohorts of CC-220-MM-001 using peripheral blood flow cytometry for immunophenotyping and degradation of Ikaros/Aiolos. Analyses were completed at Cycle (C) 1 Day (D) 1, pre-dose, and post IBER/IBER+PI dose for substrate degradation and at C1D1, C2D15, C4D1, and C4D15 for immune profiling.

Results : Substrate degradation by IBER was minimally affected by 1 h pulse treatment with PIs and was more potent than LEN or POM. These results correlate with synergistic antiproliferative activity and more potent tumoricidal activity in cell lines treated with IBER+PI than IMiD+PI combinations. Ex-vivo treatment of PBMCs with IBER+PIs minimally affected cytokine induction by IBER. Analysis of pt samples from CC-220-MM-001 confirmed preclinical observations showing minimal inhibition of IBER PD with addition of PIs to the treatment regimen. In pt T cells, Ikaros/Aiolos protein levels decreased by >50%/>70%, with IBER+DEX, and by >30%/>45% (at lower IBER doses) with IBER+DEX+BORT or IBER+DEX+CFZ. In all cohorts, the nadir of substrate expression was determined to be 6 h. After repeated dosing (mid-C1) pts treated with IBER+PIs showed >70% decreases in both Ikaros/Aiolos expression. Immune profiling of pts showed that addition of PIs to the IBER treatment regimen did not inhibit immune-stimulatory activity of IBER, including induction of natural killer (NK) and T cell proliferation.

Conclusion : In combination with PIs, IBER induced substrate degradation and substantially increased tumoricidal activity in vitro. Deeper substrate degradation and increased apoptosis were also observed when PIs were combined with IBER versus IMiD drugs. Clinically, IBER led to rapid decreases in substrate levels, even in the presence of PIs, and levels were reduced further with repeated dosing, suggesting concurrent administration of PIs minimally affects proteasomal degradation of substrates mediated by IBER. Increases in NK and T cell proliferation in IBER-treated pts were consistent regardless of also receiving a PI, further confirming that IBER has immune-stimulatory activity in combination with PIs. These data support continued clinical development of IBER in combination with PIs for the treatment of MM.

Keyword : Multiple Myeloma, Immune Cells

PP07-05

Adaptive natural killer cells facilitate effector functions of daratumumab in multiple myeloma

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Background : To investigate the different roles of heterogeneous natural killer (NK) cell subpopulations in multiple myeloma (MM) and to identify NK cell subsets that support the robust anti-myeloma activity of daratumumab via antibody-dependent cellular cytotoxicity (ADCC).

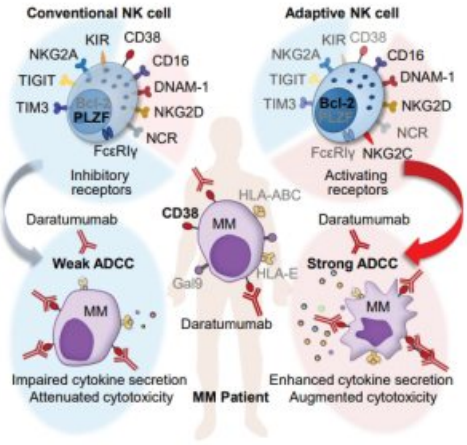
Method : We performed single-cell RNA sequencing of NK cells from newly diagnosed MM (NDMM) patients and delineated adaptive NK cells in their bone marrow (BM). We further characterized the distinct immunophenotypic features and functions of adaptive NK cells by multicolor flow cytometry in 157 NDMM patients.

Results : Adaptive NK cells exhibit a significantly lower level of CD38 expression compared with conventional NK cells, suggesting that they may evade daratumumab-induced fratricide. Moreover, adaptive NK cells exert robust daratumumab-mediated effector functions ex vivo, including cytokine production and degranulation, compared with conventional NK cells. The composition of adaptive NK cells in BM determines the daratumumab-mediated ex vivo functional activity of BM NK cells in NDMM patients. Unlike conventional NK cells, sorted adaptive NK cells from the BM of

NDMM patients exert substantial cytotoxic activity against myeloma cells in the presence of daratumumab.

Conclusion : Our findings indicate that adaptive NK cells are an important mediator of ADCC in MM and support direct future efforts to better predict and improve the treatment outcome of daratumumab by selectively employing adaptive NK cells.

Keyword : Multiple Myeloma, Daratumumab



Characteristic features of adaptive NK cells compared with conventional NK cells from patients with MM and their distinct responsiveness after daratumumab treatment. Schematic images depicting the immunophenotypic differences between conventional NK cells and adaptive NK cells and their distinct responsiveness to anti-CD38 antibody daratumumab. Adaptive NK cells have attenuated expression of NK inhibitory receptors KIR, NKG2A, TIGIT, and TIM3, in addition to differential expression of activating receptors, including natural cytotoxicity receptors (NCRs) NKp46 and NKp30. After daratumumab treatment, adaptive NK cells exhibit augmented effector functions with enhanced cytotoxicity against myeloma cells compared with conventional NK cells.

PP07-06

Translational data supporting the rational combination of iberdomide with CD38- and SLAMF7-directed monoclonal antibodies

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Background : In a phase 1/2 dose-escalation study in relapsed/refractory multiple myeloma (MM) (CC-220-MM-001; NCT02773030), iberdomide (IBER; CC-220), a potent, novel cereblon (CRBN) E3 ligase modulator (CELMoD) agent is under investigation. IBER modulates CRBN to induce ubiquitination and proteasome-dependent degradation of Ikaros/Aiolos, resulting in anti-myeloma and immunomodulatory activity. IBER binds to CRBN with 20-fold higher affinity than immunomodulatory drugs (IMiDs) and is more efficient at degrading Ikaros/Aiolos, and can overcome IMiD drug resistance. Here, we evaluate the preclinical activity of IBER in combination with monoclonal antibodies (mAbs) and assess immune pharmacodynamic changes of IBER+daratumumab (DARA) among patients (pts) in the CC-220-MM-001 study.

Method : Peripheral blood mononuclear cells (PBMCs) and MM cell lines from healthy volunteers, were treated with clinically relevant concentrations of lenalidomide (LEN; 1 μM), pomalidomide (POM; 300 nM), and IBER (20 nM). Preclinical analyses and combination experiments were performed with DARA or elotuzumab (ELO). Immune profiling data were obtained by flow cytometry from blood samples of pts enrolled in IBER+dexamethasone (DEX) and IBER+DARA+DEX cohorts of the CC-220-MM-001 study.

Results : IBER treatment of CD3-stimulated PBMCs showed a more potent increase in cytokine secretion compared with IMiD drugs. Natural killer (NK) cell proliferation and NK cell numbers increased (>30%) in cultures. Immune-mediated killing of MM cell lines was enhanced, and pretreatment of MM cell lines for 48 h followed by washout sensitized cells to immune-mediated clearance. Treatment of MM cells with IBER increased protein expression of CD38, but had no effect on SLAMF7 expression. IBER+DARA or ELO enhanced the immune-mediated killing of MM cell lines and resulted in deeper cell killing compared with LEN or POM in combination with the same mAbs. An immune-stimulatory effect was observed via immune profiling of pts treated with IBER+DEX demonstrated, including increased proliferation of NK and T cells. Pts who received a regimen containing DARA showed depleted NK cell counts, which rebounded by nearly 2-fold after 1 cycle of IBER+DEX. The effects of IBER on T and NK cell proliferation were similar in pts treated with IBER+DEX+DARA and IBER+DEX, except for overall reduction in CD38-expressing NK and T cells in pts receiving DARA.

Conclusion : MM cells treated with IBER were sensitized to immune-mediated clearance. IBER also induced immune-stimulatory activity more potently than LEN or POM, with enhanced cytokine release and NK cell proliferation. These findings suggest IBER may enhance

the activity of biologics with anti-malignant activity through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In the CC-220-MM-001 trial, IBER induced an immune-stimulatory effect on NK and T cells. The effect of IBER on NK cells was also greater in pts whose last regimen contained DARA, suggesting IBER may contribute to NK cell recovery after DARA treatment. Immune changes observed by the addition of DARA to IBER+DEX were similar, suggesting IBER was the primary agent promoting immunomodulation in this triplet therapy. These data support continued clinical development of IBER combined with CD38- and SLAMF7-directed mAbs as well as other immune-directed therapies for MM treatment.

Keyword : Multiple Myeloma, Immunotherapy, Antibodies

PP07-07

Clinical implication of next-generation flow cytometry based minimal residual disease assessment in patients with multiple myeloma

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Background : With advances in therapy, minimal residual disease (MRD) provides a deeper treatment response in patients with multiple myeloma (MM). EuroFlow-based next-generation flow cytometry (NGF) is one of the gold standard methods for evaluating MRD, and in this study, we evaluated the clinical implication of NGF-based MRD assessment in a heterogeneous MM patient population.

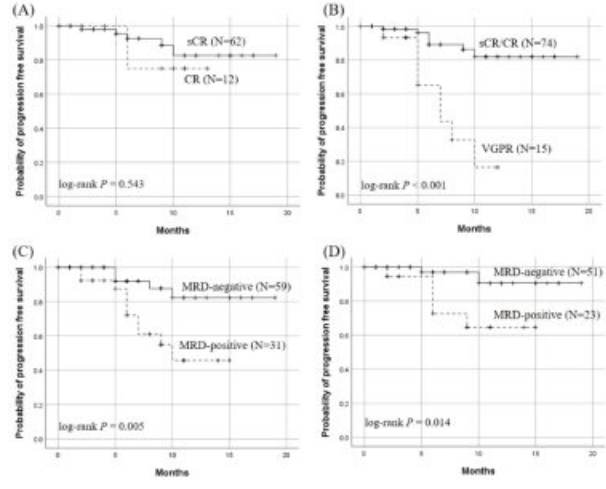
Method : Among the patients undergoing follow-up after or during treatment of MM, 91 patients suspected of morphologic remission were prospectively enrolled for MRD assessment from February 2019 to October 2020. Disease response at the time of MRD assessment was determined as stringent complete response (sCR), complete response (CR), and very good partial response (VGPR) according to the consensus criteria of International Myeloma Working Group (IMWG). NGF-based MRD assessment was performed according to the EuroFlow protocol as the following. After RBC bulk lysis, BM samples were stained in eight-color two-tubes: tube 1 with CD45-PerCPCy5.5, CD38-FITC, CD138-BV421, CylgKappa-APC, CylgLambda-APCC750, CD19-PECy7, CD27-BV510, and CD56-PE, and tube 2 with CD45-PerCPCy5.5, CD38-FITC, CD138-BV421, CD117-APC, CD81-APCC750, CD19-PECy7, CD27-BV510, and CD56-PE antibodies. Minimum 5 x 106 cells per each tube were acquired using the FACSLyricTM flow cytometer (Becton Dickinson, San Jose, CA, USA), and data were analyzed using Infinicyt software (Cytognos, Salamanca, Spain). Progression free survival (PFS) was determined from the time of last MRD assessment to disease progression or last follow-up.

Results : Total 108 BM samples from 90 patients were included, excluding one BM samples who did not achieve the morphologic remission. MRD was positive in 34 (31.5%) of 108 samples. Median MRD level was 0.015% (interquartile range [IQR], 0.006%-0.072%), and samples with less than 0.01% of MRD were 6 (17.6%) out of 34 MRD-positive samples. There were no significant differences in response status and follow-up duration between MRD-negative and MRD-positive patients (all P > 0.05). Samples with sCR showed a lower MRD-positive rate (25%) than CR (43%) and VGPR (53%), but they did not differ significantly (P=0.051). Median MRD levels also tended to increase to 0.009% (IQR, 0.004%-0.046%), 0.014% (0.007%-0.072%), and 0.066% (0.009%-0.135%) for sCR, CR, and VGPR, respectively, although not significantly different (P=0.284). In survival analysis, while no significant difference was observed between patients with sCR and CR (log-rank P=0.543), patients with VGPR showed inferior PFS than others with sCR and CR (log-rank P < 0.001) (Fig. 1). In the analysis according to MRD status, PFS was significantly inferior in MRD-positive patients than in MRD-negative patients (log-rank P=0.005). And even for patients other than VGPR, MRD-positive patients persistently showed inferior PFS than MRD-negative (log-rank P=0.014).

Conclusion : This study demonstrated the usefulness of NGF-based MRD assessment for predicting PFS in a real clinical setting, especially in MM patients with sCR and CR. Regardless of the timing of assessment, NGF-based MRD test might provide valuable information in predicting progression in patients with remission.

Keyword : Multiple Myeloma, Minimal Residual Disease, Next-Generation Flow Cytometry

Figure 1. Survival analysis. Progression free survival between patients with sCR and CR (A) and between patients with sCR/CR and VGPR (B). Progression free survival according to the MRD status in (D) all patients and (D) in patients with sCR and CR.
Abbreviations: MRD, minimal residual disease; sCR, stringent complete remission; CR, complete remission; VGPR, very good partial response



PP07-08

Association between vitamin D recep-

tor (VDR) gene polymorphisms and multiple myeloma susceptibility: A systematic review and meta-analysis

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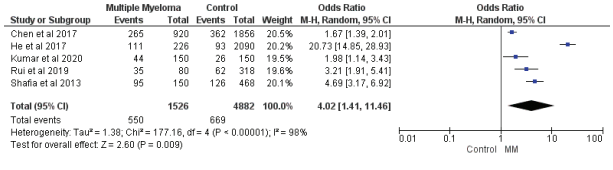
Background : Recently, studies of the association between Vitamin D receptor (VDR) polymorphisms and myeloma multiple (MM) have been investigated but the result still inconclusive. Therefore, this study aimed to investigate the association between VDR gene polymorphisms and MM susceptibility.

Method : The literature search was performed using databases such as PubMed and EMBASE until December 2020. Studies included in this meta-analysis were accessed using The Newcastle Ottawa Score (NOS). The association between VDR polymorphisms and the risk of MM was evaluated using pooled odds ratios (ORs) and 95% confidence intervals (CIs).

Results : Six studies (895 cases/1233 controls) were included in this meta-analysis. In FokI, T vs C (OR 95%CI =4.02 [1.41 – 11.46], p=0.009) and TT vs CC + CT (OR 95%CI =2.44 [1.80 – 3.29], p=<0.00001) had significant association with the susceptibility of MM, while CC vs CT + TT (OR 95%CI =0.56 [0.46 – 0.67], p=<0.00001) was associated with reduced risk of MM. In ApaI, T vs G (OR 95%CI =1.34 [1.15 – 1.56], p=0.0002) and TT vs GG + GT (OR 95%CI =1.63 [1.17 – 2.27], p=0.004) was associated with MM risk, while GG vs GT + TT was associated with the decrease risk of MM (OR 95%CI =0.73 [0.59 – 0.89], p=0.002). In BsmI, AA genotype was associated with reduced risk of MM (OR 95%CI =0.70 [0.58 – 0.87], p=0.002). In contrast, AG genotype had significant association with the susceptibility of MM (OR 95%CI =1.26 [1.01 – 1.57], p=0.04). In TaqI, TT vs TC + CC was associated with reduced risk of MM (OR 95%CI =0.56 [0.35 – 0.89], p=0.01), while TC vs TT + CC was associated with the increase risk of MM (OR 95%CI =1.71 [1.07 – 2.73], p=0.03).

Conclusion : In summary, our meta-analysis suggested that a significant association between VDR gene polymorphism and MM susceptibility was detected in some genetic models of VDR gene

Keyword : Myeloma Multiple, Vitamin D Receptor Gene, Single Nucleotide Polymorphisms, Hematology Malignancy



PP07-09

Immunomodulatory drugs increase the risk of serious infections in multiple myeloma patients: A meta-analysis

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Background : Immunomodulatory drugs like thalidomide, pomalidomide and others are commonly used for the management of multiple myeloma. Epidemiological evidence showed variable findings. So, this meta-analysis is aimed to understand the association of immunomodulatory drugs use and risk of infections.

Method : PubMed and Embase electronic databases were searched by independent investigators. Only those observational studies qualified for inclusion which reported the association between any of the immunomodulatory drug use and risk of serious infections. The primary outcome of this study was to investigate the rate of infections in multiple myeloma patients treated with immunomodulatory drugs. Secondary outcomes include risk based on different types of immunomodulatory drugs. All the analysis was done with RevMan software.

Results : This meta-analysis was 3224 patients from all the included studies with a mean age range from 54 years to 75 years. Included studies reported infections incidence from 1.54% to 21.88%. Due to significant heterogeneity, a random effect model was applied. Pooled incidence of infection due to immunomodulatory agents was 8.80% (95% CI: 6.90% - 10.70%). The pooled incidence of serious infection among pomalidomide users with relapsed and refractory cases was 11.80% (95% CI: 6.50% - 17.10%). Thalidomide user has a higher incidence in multiple myeloma patients on induction therapy 8.70% (95% CI: 5.40% - 11.90%). Where the pooled incidence was lower in maintenance therapy in thalidomide user 2.70% (95% CI: 0 – 6.70%).

Conclusion : Higher risk of infections was observed in multiple myeloma patients receiving immunomodulatory therapy. Preventive management is essential for patients.

Keyword : Infections; Immunomodulatory Drugs, Multiple Myeloma, Pomalidomide, Meta-Analysis

PP07-10

Diagnostic impact of non-CRAB myeloma-defining events in multiple myeloma

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Background : The diagnosis of multiple myeloma (MM) requires the presence of one or more myeloma defining events (MDE) in addition to evidence of either clonal bone marrow plasma cells of ≥10% or a biopsy-proven plasmacytoma. In addition to typical CRAB symptoms (hypercalcemia, renal insufficiency, anemia, and

osteolytic bone lesions), the 2014 revised International Myeloma Working Group criteria for the diagnosis of MM included three additional MDE parameters, which are clonal bone marrow plasma cell percentage (BMPC) ≥60%, involved:uninvolved serum free light chain ratio (rFLC) ≥100, and >1 focal lesions on magnetic resonance imaging (MRI) studies. We investigated the diagnostic impact of non-CRAB MDE in MM patients.

Method : We retrospectively reviewed 278 patients diagnosed with MM between January 2016 and June 2020. Clinical and laboratory findings at the time of diagnosis were investigated, which include CRAB, BMPCs, rFLC, and MRI results.

Results : A total of 14 (5.0%) MM patients without CRAB were identified, which would have been classified as smoldering multiple myeloma (SMM) by the previous criteria. The cases without CRAB showed BMPCs ≥60% group 28.6% (4/14), rFLC ≥100 group 76.9% (10/13), and >1 focal lesions on MRI group 40.0% (2/5), respectively. Regardless of the presence of CRAB, total subjects revealed BMPCs ≥60% group 17.6% (49/278), rFLC ≥100 group 30.8% (85/276), and >1 focal lesions on MRI group 49.6% (64/129), respectively.

Conclusion : The 2014 new definition of MM led to a shift of high-risk SMM to MM. This study shows the facilitating roles of non-CRAB MDE for the correct diagnosis of multiple myeloma.

Keyword : Multiple Myeloma, CRAB, Myeloma-Defining Events

PP07-11

Determinant factors for early mortality in newly diagnosed multiple myeloma patients

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Background : In the recent years we have observed a great improvement in the survival of patients with multiple myeloma (MM), because of the novel treatments and drugs. But the challenge still remains for the survival of about 10% of MM patients who die very fast after the disease diagnosis. In this study we try to investigate the associated factors for early mortality in MM patients.

Method : We evaluated 315 newly diagnosed MM patients from the registry of Alzahra Hospital between 2006 and 2017. Early mortality (within 2 month of diagnosis) were detected among those patients and disease history and baseline characteristics and laboratory data were used in univariate and multivariate analysis to find the independent factors which are associated with the early mortality.

Results : Thirty six patients (11.4%) experienced early mortality. In the univariate analysis male gender, Hemoglobin less than 10 g/dL, platelet less than 150,000/μ, serum albumin less than 3.5 g/dL, corrected serum calcium more than 12 mg/dL, serum creatinine more than 2 mg/dL, lactate dehydrogenase (LDH) more than 250 U/L and serum beta 2 microglobulin more than 5500 md/L were associated with early mortality (all p values less than 0.05). Multivariate analysis showed that male gender (OR=3.2, CI=2.8-4.9), having the serum albumin less than 3.5 g/dL (OR=2.2 CI=1.5-6.1), corrected serum calcium more than 12 mg/dL (OR=1.3, CI=1.1-3.6), LDH more than 250 U/L (OR=1.7, CI=1.3-5.2) had independent effects on the early mortality when controlling for other risk factors.

Conclusion : We can conclude that male MM patients with serum albumin less than 3.5 g/dL, corrected serum calcium more than 12 mg/dL and LDH more than 250 U/L have a greater risk for the early mortality.

Keyword : Multiple Myeloma, Mortality, Serum Albumin Level, Lactate Dehydrogenase

PP07-12

The clinical characteristics and survival outcomes of multiple myeloma patients aged 80 or over

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Background : Multiple myeloma (MM) is largely a disease of older adults. Although effective novel agents and supportive care have substantially improved outcome, studies for extremely older MM patients are limited. In this study, we retrospectively analyzed the clinical features and survival outcomes of MM patients aged ≥80 years.

Method : This multicenter retrospective study was conducted to investigate clinical characteristics, treatment patterns and outcomes of patients aged ≥80 years who were newly diagnosed with MM at 5 academic hospital in Daegu, Korea between 2010 and 2019.

Results : A total 127 patients, median age 83 years (range, 80-93 years) were included in this analysis. Of these, 52 patients (40.9%) had a poor performance status (ECOG 3-4), 84 (66.1%) had an International Staging System (ISS) stage III disease, and 93 (73.2%) had a Charlson comorbidity index score of 5 or more. Chemotherapy was given in 86 (67.7%) patients. Bortezomib based chemotherapy was given in 27 (31.4%) patients, lenalidomide based chemotherapy in 17 (19.8%) patients, other chemotherapy (MP or CP) in 42 (48.8%) patients. The median number of chemotherapy cycles was three (range 1-54). Median overall survival of all patients was 13.8 months. Ninety and three patients died with median overall survival of 9.25 months. Median overall survival was

15.97 months in the patients who received chemotherapy and 1.67 months in the best supportive care group (p<0.001). In the univariate analysis, significant prognostic factors for overall survival were age (80-83 vs. >83, p=0.017), ECOG performance status (0-2 vs. 3,4, p<0.001), ISS stage (I, II vs. III, p=0.005), treatment (chemotherapy vs. best supportive care, p<0.001), hypercalcemia (p=0.007) and thrombocytopenia (p=0.007). In multivariate analyses using the significant prognostic variables from univariate analysis, overall survival was affected by ECOG performance status, ISS stage, and treatment. Event free survival according to first line chemotherapy regimen was 11.44 months in bortezomib-based regimen, 8.23 months in lenalidomide-based regimen, and 9.25 months in alkylating agents, but it was confirmed that these values did not have statistical significance.

Conclusion : Even in extremely older MM patients aged 80 years or over, chemotherapy can result in better survival outcomes than the best supportive care. Age 80 years or over itself should not be a contraindication of treatment.

Keyword : Multiple Myeloma, Aged 80 or Over, Survival

PP07-13

Addition of cyclophosphamide to pomalidomide/dexamethasone has a benefit in refractory multiple myeloma?: The comparison with pomalidomide-based chemotherapy in Asian patients

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Background : The third-generation immunomodulatory drug, pomalidomide, has potent anti-myeloma effects in patients with multiple myeloma (MM). However, data for pomalidomide-based therapy in Asian patients are limited. We compared pomalidomide/dexamethasone (pom/dexa) alone and with added cyclophosphamide in patients with relapsed/refractory MM in Korea.

Method : This retrospective, single center study of patients with relapsed/refractory MM who were treated with pom/dexa or pom/dexa + cyclophosphamide was performed at Seoul National University Hospital.

Results : One hundred-three patients were enrolled between February 2015 and April 2020. They were previously treated with bortezomib (98.1%) or lenalidomide (100%) and pomalidomide was administered as median 4th line of therapy. Fifty-seven (55.3%) and 46 (44.7%) patients were treated with pom/dexa or pom/dexa+cyclophosphamide, respectively. The 2-year progression-free survival (PFS) and overall survival (OS) rates for all patients were 30.6±5.7% and 51.4±5.8%, respectively. The overall response rate (ORR) was 58.1%. We found a significantly better ORR in the cyclophosphamide-added (75.6%) vs. the pom/dexa (41.7%) group (P=0.001), but no significant differences for PFS or OS. Subgroup analysis revealed that younger age, high-risk myeloma, and lower numbers of previous treatment lines (<4) groups had superior ORRs when addition of cyclophosphamide, but no significant survival outcome differences. Pomalidomide-based therapy was discontinued in five patients due to intolerance or adverse events, but there was no mortality during treatment.

Conclusion : A pomalidomide-based regimen was a beneficial option for Asian patients with MM, even in heavily-treated settings.

Keyword : Multiple Myeloma, Relapsed, Refractory, Pomalidomide, Cyclophosphamide

PP07-16

Primary plasma cell leukemia with long term survival - A report of two cases

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Background : Plasma cell leukemia (PCL) is the rare and most aggressive form of plasma cell dysplasia. Diagnostic criteria for PCL include presence of clonal plasma cells in the peripheral blood with absolute plasma cell count of $2X10^9$ / L or more than 20% of the differential count. However, many recent studies have suggested that a diagnosis of PCL can be made at lower values to make an early diagnosis of PCL. PCL is characterized by poor prognosis despite of chemotherapy. We are introducing two case reports of patients who have survived for more than 2 years with the use of conventional chemotherapy.

Method : We describe 2 cases of PCL diagnosed at AIIMS, New Delhi between 2008 to 2014.

Results : Case 1. 54-years male presented with fatigue and ear discharge in December 2008 at Bombay hospital. On Peripheral blood examination was found to have 34% plasma cells. Bone marrow aspiration showed hypercellular aspirate with 76% plasma cells. Bone marrow cytogenetics showed heterozygous p53 del in 10%, heterozygous del of 11q23 in 5% of cells. Serum M band was 0.9 g/dl. Serum free light chain showed kappa chain restriction with kappa light chain of 710mg/dl, lambda light chain of 43mg/dl and kappa to lambda ratio of 16.511. A diagnosis of Plasma cell Leukemia was made. Patient was started on Bortezomib, dexamethasone and thalidomide. Patient developed adverse reactions with this combination so he was started in Bortezomib and Lenalidomide for 5 cycles. Patient was doing well for around 9 months. After which on regular follow-up serum protein was found to 0.8gm/dl. Peripheral

blood examination showed 45% plasma cells. Bone marrow aspiration showed near total replacement by plasma cells. 24-hour urine protein loss was 5439mg/3000ml. A diagnosis of Plasma cell Leukemia Relapse was made. After which patient was started on4 cycles of Bortezomib, Adriamycin and Dexamethasone. On follow up patient was doing well till June 2013 after which he lost to follow-up. Case 2. A 64-year male presented to us in January 2014 with complaints of pain in upper abdomen, weight loss, cough with expectoration. Complete blood count showed hyperleukocytosis with total count of 41360/cumm and thrombocytopenia with platelets approximately 70000/cumm. On bone marrow aspirate, plasma cells were around 70% of total cellularity and 20% of total leukocyte on peripheral blood. On examination, liver was 13cm below costal margin and tip of spleen was palpable. Bilateral wheeze was present. CECT of lung showed bilateral pleural effusion with ground glass opacity. Urine protein electrophoresis showed a narrow M-band however pleural fluid electrophoresis showed dense M-band. Urine protein was 15.4mg/dL. Serum free light chain assay showed kappa light chain of 664.4mg/L and lambda light chain of 5.98mg/L. Kappa to lambda ratio of 111.11. A diagnosis of Plasma cell Leukemia was made and patient was started on 4 cycles of Bortezomib, Adriamycin and Dexamethasone. After 5 months, on regular follow-up patient relapsed with bone marrow aspirate findings of 50-60% plasma cells of all hematopoietic cells and focally formingaggregates. Therapy was revised with 6 cycles of Bortezomib, Adriamycin and Dexamethasone. On repeat bone marrow aspirate, plasma cells were around 2% and peripheral blood showed neutrophilia and adequate platelets. There was no M-band on urine protein electrophoresis and free light chain ratio was 2.62. Patient was on follow up and doing well till 2016 after which he lost to follow up.

Conclusion : PCL are usually associated with short term survival. This study demonstrated that these two cases with exceptionally long-term survival. Study of genetic mutations associated with these long-term survival needs to be worked up.

Keyword : Long Term Survival, PCL, Plasma Cell Leukemia

PP07-17

Analysis of overall survival in plasma cell leukemia

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Background : Plasma cell leukemia (PCL) is a rare & aggressive form of plasma cell dyscrasia.

Method : Eleven cases (6 males & 5 females) were retrieved from hospital record in last 3-4 years.

Results : We had 9 primary & 2secondary cases. Most of the cases presented with low back pain, bony lesions & renal failure for more than 3-4 months. They had fever, cough with pleural effusion and easy fatigability. Positive M-band was seen in serum & urine in 9/11 cases, whereas 2/11 showed positivity in urine only indicating light chain disease. One case with pleural effusion showed M band in pleural fluid too. Hepato-splenomegaly was also seen in one case, which had dyspnoea with lung consolidation in Radiology.

Relapse was seen in one case of pPCL (primary PCL) after two years of diagnosis. Immunofixation: 1/11 case showed isotype class switch after relapse. It showed kappa light chain at presentation. After therapy and progression free survival for one year it relapsed with IgG heavy chain with kappa restriction. In rest of the cases, IgG kappa was the most common isotype (5/10) followed by lambda light chain (LC) 3/10. IgG lambda & kappa LC was seen in one case each. Stem cell transplant was done in 2 cases, one for pPCL & the other for secondary PCL (sPCL), 4.5 years after the diagnosis of MM, which later developed PCL. Flowcytometry was done in 3 cases; showed positive CD 38 & CD138 and negative CD 19 & CD56. CD45 expression was variable. PAD (Bortezomib, Doxorubicin & Dexamethasone) regimen was given in all cases.

Overall survival: Out of 11 cases, 5 cases died within 4 months, 2 within 8 months, 2 in 2 years & 5 years respectively. One case discontinued the follow up. One case is still alive for more than 7 years.

Conclusion : Organomegaly was seen in one of our cases, which had associated pulmonary ailments (pneumonia, pleural effusion). So, in this case possibly organomegaly was due to lung pathology. Relapse is rare in PCL, as it is itself aggressive (1). Isotype switch in plasma cell dyscrasia is extremely rare (2,3). 7/11 (63.6%) cases died within a year, which shows the severity of disease. 2/11 cases responded well and spent 2 years & 5 years respectively. Decoding the ways to have prolonged survival needs further study, possibly molecular one. Diagnosis needs 20% plasma cell in blood film, but needs immediate management. pPCL responds early with standard therapy, but resistance and relapses are common. Therapeutic resistance is common in sPCL.

Keyword : Plasma Cell Dyscrasia, Immunophenotyping, Multiple Myeloma

Table 1: cases of plasma cell leukemia describing signs, symptoms, M- band, Immunofixation & overall survival

Case No.	Symptoms	Electrophoresis M-band +	Immunofixation	Overall survival
1	Fever-2 months	Serum + urine	Kappa; on relapse IgG kappa	5 & ½ yrs
2	LBP- 4 months,	----do----------	kappa	Alive
3	LBP 8 months	----do----------	IgG lambda	3 months
4	Fever 4 months	----do----------	IgG kappa	7 months
5	LBP 2 months	Urine only	lambda light chain	3 months
6	LBP 2 months fever, wt loss	Serum + urine	IgG Kappa	Not traceable
7	LBP 2 months	----do----------	IgG Kappa	8 months
8	LBP 1 months	----do----------	IgG Kappa	4 months
9	Pain abdomen, dyspnoea (Pneumonia) , Liver/ spleen +	----do---------- Pleural fluid +	IgG Kappa	2 yrs
10	Easy fatiguability - 4 months	Serum + urine	Lambda light chain	16 days
11	LBP +- 1 Year	Urine only	Lambda light chain	3 months

LBP: Low back pain

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PP07-18

Multiple myeloma in man 32 years old with metachronous soft tissue sarcoma. A multiple primary malignant tumors with successfull chemotherapy medication

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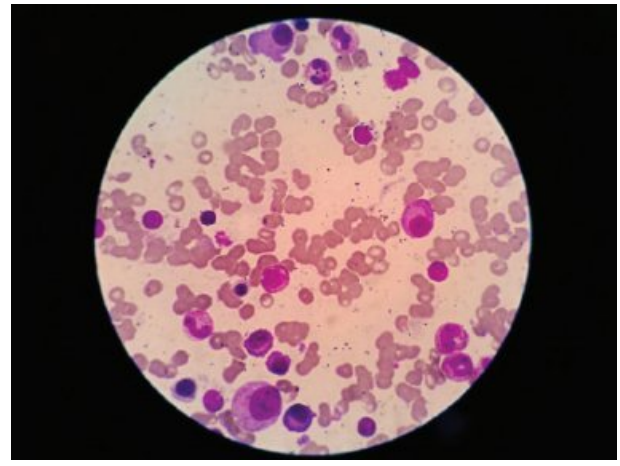
Background : Multiple Primay Malignant Tumors (MPMTs) are defined two or more histologically distinct malignancies in one individual, the occurance of MPMTs is a rare clinical entitiy. The association between a solid malignancy with a hematological neoplasm is even rare.

Method : It is Case report. we follow the patient from the initial diagnosis of multiple myeloma untill diagnosis with soft tissue sarcoma, treatment and evaluated untill now.

Results : We present a case of a 32 years old Indonesian male who was known case of Multiple Myeloma and on regular chemotherapy medication (vincristin, doxorubicin, and dexamethason) since 2018, was admitted with a lump in his back with size 6x10cm since 6 months before admission, initially it was a small size but its getting bigger slowly. Patients did not complained about pain or numbness in his back. From the imaging studies, MSCT we found soft tissue mass originates from the left spinal rectus as high as the left thoracal 7 to the left 12 thoracal,the mass infiltrates the left pleura and subcutaneous fat with no visible destruction of ribs and impression of malignancy. When we did core biopsy, we found proliferated tissue consist of development mass or tumor cells with oval cell and from imature fatty cells (lipoblast) with conculsion is liposarcoma and differential diagnosed round cell rhabdomyosarcoma. We managed the patient with chemotherapy treatment, because the mass was unresectable and the patient itself did not want to undergo surgery. We give the ifosfamide, mesna and etoposide regimen for the soft tissue sarcoma. After 3 cycle, evaluated imaging MSCT have done and the lump was disappear, there were no visible left thoracal region soft tissue mass, intrapulmonary metastases was not seen, there was no visible destruction of the ribs or thoracal vertebrae.

Conclusion : The case described represents a rare clinical condition called multiple primary malignant tumors, through the metachronous occurance of multiple myeloma and soft tissue sarcoma. The lack of studies on this metachronous association, as well as the few reported cases in the literature, inhibits a greater clarifications of the involved pathogenesis. However, soft tissue sarcoma was disappear when we did chemoteraphy treatment, further observation from the patients was necessary.

Keyword : Multiple Myeloma, Soft Tissue Sarcoma, Multiple Primary Malignant Tumors, Chemotherapy Medication



PP08-01

Thrombotic and hemorrhagic events in 2016 who-defined Philadelphia-negative myeloproliferative neoplasms

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Background : Thrombosis and hemorrhage are the main clinical manifestations of Philadelphia chromosome-negative myeloproliferative neoplasms (Ph- MPNs). The diagnostic criteria for Ph- MPNs have been continuously revised. Thus, some patients with early essential thrombocythemia (ET) diagnoses are now classified as prefibrotic/early primary myelofibrosis (pre-PMF) or polycythemia vera (PV), which necessitates the revision of early data on vascular events associated with MPN subtypes. In this retrospective study, we analyzed thrombotic and hemorrhagic events in 2016 WHO-defined MPNs.

Method : Patients who were diagnosed with ET, PV pre-PMF, or PMF based on 2016 WHO diagnostic criteria from January 1996 to July 2020 at Chungnam National University Hospital were enrolled, and their medical records were reviewed. Thrombotic events included cerebrovascular, coronary, splanchnic, and peripheral thromboembolism. Hemorrhagic events were defined as any acute bleeding requiring red cell transfusion or admission.

Results : A total of 335 patients (139 ET, 42 pre-PMF, 124 PV, and 30 PMF; 192 male and 143 female) with a median age of 64 years (range 15-91 years) were enrolled. They were followed up for a median of 4.6 years (range 0.1-26.5 years). Of the 335 patients, 112 (33.4%) experienced a total of 126 thrombotic events. Cerebrovascular

thrombosis (N =63, 18.8%) was the most common initial event, followed by coronary heart disease (N =34, 10.1%) and splanchnic (N =5, 1.5%) and peripheral thrombosis (N =5, 1.5%). Arterial thrombosis was predominant compared to venous thrombosis (N =105, 31.3% vs. N =7, 2.1%, P=0.001). Thrombotic events were most frequent in PV patients (39.5%), followed by patients with pre-PMF (38.1%), ET (30.9%), and PMF (13.3%). Ischemic stroke was the most common initial event across MPN subtypes other than PMF (23.4% in PV, 19.0% in pre-PMF, 12.9% in ET, and 0% in PMF). Acute coronary syndrome was the next most common event (5.6% in PV, 2.4% in pre-PMF, 7.2% in ET, and 6.7% in PMF). Deep vein thrombosis occurred in only two (0.6%) patients. Of the 112 patients who experienced thrombotic events, 53 (47%) and 39 (33.9%) experienced them before and at the time of MPN diagnosis, respectively. ET patients with thrombosis were older (67.6 ± 12.8 years vs. 57.2 ± 15.2 years, P=0.000), predominantly male (66.7% vs. 43.3%, P=0.011), and exhibited higher positivity for JAK2V617F (81.3% vs. 63.5%, P=0.045) compared with those without. No differences were observed in demographic features or laboratory findings between PV patients with and without thrombosis. Overall, age > 60 years (OR 1.88, 95% CI 1.09-3.02, P=0.022), male sex (OR 2.11, 95% CI 1.29–3.48, P=0.003), and hypertension (OR 2.05, 95% CI 1.25-3.34, P=0.004) were independent risk factors for thrombosis in MPN patients. Of the 335 patients, 27 (8.1%) experienced 29 hemorrhagic events. Gastrointestinal bleeding (N =20, 6.0%) was the most common initial event, followed by soft tissue bleeding (N =4, 1.2%), central nervous system bleeding (N =2, 0.6%), and genitourinary bleeding (N =1, 0.3%).

Conclusion : The pattern of thrombotic vascular events in this study cohort differed from those reported in Western countries in some respects. Arterial thrombosis was far more prevalent than venous thrombosis, whereas deep vein thrombosis was far less prevalent. The majority of thrombotic events occurred before or at the time of MPN diagnosis, which highlights the importance of early detection of MPNs.

Keyword : Essential Thrombocythemia, Polycythemia Vera, Prefibrotic/Early Primary Myelofibrosis, Primary Myelofibrosis, Thrombosis, Hemorrhage

PP08-02

Effect of CALR mutant type and allele burden on the phenotype of BCR/ABL1-negative myeloid proliferative neoplasms

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Background : Somatic CALR mutations have been identified in about 70% of JAK2 mutation-negative essential thrombocythaemia (ET) and primary myelofibrosis (PMF). Type 1 mutation (c.1099_1150del) and type 2 mutation (c.1154_1155insTTGTC) are most frequent CALR mutations, and the different clinical effects of different CALR mutant subtypes are well known. However, there are limited data on the effect of CALR mutant allele burden on disease phenotype. In this study, we evaluated the clinical implication of CALR mutant type and allele burden in BCR/ABL1-negative myeloproliferative neoplasm (MPN).

Method : We retrospectively reviewed the results of CALR mutation analysis performed between July 2015 and May 2020. CALR mutation analysis was performed by fragment analysis and direct sequencing, using the genomic DNA isolated from peripheral blood or bone marrow aspirates. CALR mutant allele burden (%) was calculated as area of mutant allele/[area of mutant allele + area of wild- type allele])x100, and each CALR mutation was classified as Type 1-like or Type 2-like mutation based on predicted effect of CALR mutation on calreticulin C-terminal. For CALR-mutated patients, their clinical and laboratory findings were compared according to the CALR mutation type and allele burden.

Results : Among total 510 patients, CALR mutations were detected in 49 patients (9.6%). Among them, 67% (33/49) of patients were ET, and others (33%; 16/49) were PMF. According to the CALR mutant subtypes, type 1-like mutation and type 2-like mutation were detected in 40.8 % (20/49) and 44.9% (22/49) of patients, respectively, and 14.3 % (7/49) of patients had other mutations. In two patients, CALR mutations were only detected in fragment analysis, not in Sanger sequencing. Platelet counts were significantly higher in patients with Type 2-like mutation (893x109/; interquartile range [IQR], 705-1336x109/L) than those in Type 1-like mutation (491x109/L; IQR, 210-790x109/L) (P=0.000), and lactate dehydrogenase (LDH) was higher in patients with Type 1-like mutation (580.5 IU/L; IQR, 425.5-1112.0 IU/L) than those in type 2-like (413.0 IU/L; IQR, 267.5-482.5 IU/L) (P=0.020). There were no significant differences in mutant allele burden, presence of fibrosis and the specific diagnosis of MPN according to the mutant subtypes (P=0.503; P=784; P=0.051, respectively). In the analysis according to the CALR mutant allele burden, median mutant allele burden in patients with PMF was 45.4% (IQR, 39.7-47.3%), which was significantly higher than those with ET (33.8%; IQR, 17.7-40.4%) (P=0.001). Especially, among 27 patients with mutant allele burden < 40%, 85.2% (23/27) were patients with ET, and among 12 patients with mutation allele burden ≥ 45%, 83.3% (10/12) were PMF. Mutant allele burden also showed a positive correlation with white blood cell count (WBC) (r=0.333; P=0.019) and absolute neutrophil counts (ANC) (r=0.356; P=0.012), and showed a negative correlation with hemoglobin (Hb) (r=-0.389, P=0.006).

Conclusion : This study showed that higher CALR mutant allele burden was associated with disease phenotype of PMF, higher WBC and ANC, and lower Hb level. Assessment of CALR mutant allele burden would help to understand the disease phenotype and differential diagnosis of ET and PMF.

Keyword : CALR, Allele Burden, Myeloproliferative Neoplasm, Essential Thrombocythemia, Primary Myelofibrosis

PP08-03

Impact of MPNs on quality of life: Korean landmark survey

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Background : Patients with polycythemia vera (PV), myelofibrosis (MF), and essential thrombocythemia (ET) in myeloproliferative neoplasms (MPNs) experience various symptoms that negatively impact their quality of life (QoL), but there is a lack of data on Korean patients.

Method : This Landmark health survey is a multi-center, cross-sectional survey of patients diagnosed with MPN (MF, PV, or ET) and treating physicians in Korea. The survey consisted of two stages. The first stage was done internationally, and we added the results of Korea to the results of the second stage. The first stage was conducted by both patients and physicians recruited via local field agency from Oct 2018 to Dec 2018 in 6 countries (China, Russia, Saudi Arabia, Korea, Taiwan, and Turkey). The second stage was conducted only by patients in routine clinical practices from May 2020 to August 2020 in Korea. The results assessed patients' understanding of diagnosis, self-awareness of symptoms, and current treatment options compared to physicians' perceptions.

Results : A total of 105 patients (MF, n=39; PV, n=25; ET, n=41) completed this survey. The median disease duration for respondents was four years in all subgroups. Most MF patients experienced symptoms before diagnosis for six months to a year (n=23, 60.53%), and PV patients presented shorter duration that was less than six months (n=10, 45.45%). The majority of patients scored their risk as low (42.11%) in MF, while the intermediate-risk was the most common in PV (62.5%) and ET (38.46%) patients. Among the MPN-Symptom Assessment Form 10 symptoms, 'fatigue or tiredness' was the most reported symptom, especially in MF and ET patients (mean severity score: overall, 4.63±2.39; MF, 4.99±2.36; ET, 5.00±2.26). Itching was the most common and severe symptom (mean severity score, 4.29±3.24) in PV patients. The MPN-SAF Total Symptom Score was 16.84±14.67 in MF, 14.87±10.15 in PV, and 13.59±12.14 in ET patients without statistical significance between subgroups (p=0.504 from Kruskal-Wallis test). Patients reported that doctors proactively ask how they feel (40%) or specifically ask about the most important symptoms (37.78%). Of note, none of the patients reported that they were asked to fill a symptom checklist before the review of each symptom, while half of the physicians reported that they request their patients to fill out some symptom checklist. Most patients reported 'strongly agree' or 'somewhat agree' to the question of MPN-related QoL reduction experience in MF (94%), PV (68%), and ET (63%), while MF patients affected more (p=0.0004 from Fischer's exact test), and they worried about their condition would get worse (sometimes, 19.23%; often, 11.54%; a great deal, 16.35%). On the patient's report of the current state of health, overall respondents reported they are fair (59.05%). However, respondents with PV reported a poor health status (36%). Although the major treatment goals are aligned with patients and physicians, there are differences with the priorities, and the gap was more obvious in PV. The unmet needs to achieve the goal of the treatment from the physicians' perspective were effective drugs/therapy (42.31%) and cure (30.77%) in MF, cure (33.33%), effective drugs/therapy and decrease/replace phlebotomy treatments (25%, respectively) in PV, and cure (53.33%), effective drugs/therapy (26.67%) in ET.

Conclusion : Our Korean Landmark survey confirmed that PV, ET patients experienced as many disease-related symptoms as MF patients, and there are differences between patients and the treating physicians' perspective on symptom burden and treatment goal.

Keyword : Quality of Life, Myeloproliferative Neoplasm, Myelofibrosis, Polycythemia Vera, Essential Thrombocythemia

Table 1. MPN-SAF 10 symptoms within the last 12 months

	MF		PV		ET		All	
	Mean Score	Incidence, n (%)	Mean Score	Incidence, n (%)	Mean Score	Incidence, n (%)	Mean Score	Incidence, n (%)
Fatigue or tiredness	4.89±2.36	30 (76.92)	3.44±2.41	13 (52.00)	5.00±2.26	32 (78.05)	4.63±2.39	75 (71.43)
Abdominal discomfort	2.33±2.17	8 (20.51)	2.50±3.02	2 (8.00)	3.07±2.63	9 (21.95)	2.63±2.48	19 (18.10)
Night sweats	3.38±2.90	8 (20.51)	3.07±2.89	9 (36.00)	1.80±2.94	5 (12.20)	2.84±2.90	22 (20.95)
Filling up quickly when eating (early satiety)	3.56±2.71	10 (25.64)	2.67±3.24	5 (20.00)	2.75±3.02	4 (9.76)	3.08±2.89	19 (18.10)
Bone pain (diffuse/not joint pain or arthritis)	1.67±1.95	4 (10.26)	2.00±1.95	7 (28.00)	1.67±1.97	3 (7.32)	1.76±1.91	14 (13.33)
Inactivity	3.54±2.45	16 (41.03)	3.15±2.61	8 (32.00)	3.77±3.14	6 (14.63)	3.50±2.64	30 (28.57)
Itching (pruritus)	2.75±2.35	7 (17.95)	4.29±3.24	15 (60.00)	2.70±1.87	12 (29.27)	3.23±2.58	34 (32.38)
Unintentional weight loss	3.50±3.42	5 (12.82)	1.86±3.76	0 (0.00)	1.58±3.09	3 (7.32)	2.39±3.38	8 (7.62)
Problems with concentration	3.83±2.50	15 (38.46)	2.64±2.84	8 (32.00)	2.81±2.40	7 (17.07)	3.24±2.55	30 (28.57)
Fever	2.08±2.61	6 (15.38)	1.33±2.18	3 (12.00)	1.30±1.95	3 (7.32)	1.61±2.25	12 (11.43)
MPN-SAF TSS mean±SD	16.84±14.67		14.87±10.15		13.59±12.14		15.18±12.73	
median (range)	11.00 (0.00, 56.00)		11.00 (2.00, 36.00)		9.00 (0.00, 53.00)		11.00 (0.00, 56.00)	

PP08-04

Characteristics of hydroxyurea-resistant or intolerant polycythemia patients in Korea

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Background : Six to twelve percent of Polycythemia Vera (PV) patients are resistant to a frontline cytoreductive agent, hydroxyurea (HU), and around 10% of patients are intolerant to the drug. Recent studies revealed that inadequate hematologic control was associated with a high risk of thrombosis and the HU-resistant patients showed unfavorable clinical outcomes in terms of disease progression and thrombosis-free survival.

Method : We reviewed PV patients who received hydroxyurea as a frontline treatment in 6 centers in Korea based on medical records and analyzed HU-resistant or intolerant patients retrospectively.

Results : A total of 425 PV patients was observed in this study and we found 29 patients (6.8%) were resistant and 16 patients (3.8%) were intolerant to HU. The median age of resistant or intolerant patients was 65.6 (range, 40-80) years. Cumulative incidence of thrombosis was 5.6% at 4 years after developing resistance or intolerance and that of disease progression was 24.2%. Overall survival of those patients was 93.1% at 4 years after developing resistance or intolerance. Univariate analysis indicated higher LDH level and history of thrombosis at the time of diagnosis was associated with disease progression-free survival.

Conclusion : A substantial portion of PV patients developed HU resistance or intolerance in Korea like in western countries. The resistant or intolerant PV patients experienced disease progression within a relatively short period after developing resistance or intolerance, so that close monitoring is necessary for those patients. The effect of second-line drugs on lowering the risk of disease progression in those patients should be studied in the future.

Keyword : Polycythemia Vera, Hydroxyurea, Resistance, Intolerance

PP08-05

The risks and benefits of hydroxyurea in children and young adults with essential thrombocythemia and polycythemia vera

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Background : Myeloproliferative neoplasms (MPNs) are a rare, heterogeneous group of clonal hematopoietic stem cell disorders, characterized by aberrant proliferation of one or more myeloid lineages leading to an overproduction of both mature and immature cells.Three major components of classical BCR-ABL1-negative are MPNs polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Patients with MPNs have a high risk of complications including thrombotic or hemorrhagic events, and transformation to either secondary myelofibrosis (SMF) or secondary acute myeloid leukemia (SAML). In addition, second primary malignancies (SPMs) can occur during follow-up. Even though young patients with MPNs constitute a distinct, steadily growing subpopulation, there is a significant diagnostic challenge given the lack of an objective clonal marker in children. Further, due to the small number of young MPN patients, few reports have described the disease characteristics and outcomes in this group.

Method : We conducted an epidemiological study to elucidate the clinical course of ET and PV in children and young adults under the age of 39 years, focusing on thromboembolic events (TE), and SPMs by analyzing the Health Insurance Review and Assessment Service (HIRA) database, which includes almost all hospital-based patients'information in Korea from 2008 to 2017.

Results : Among 5,028 patients selected as patients with BCR-ABL1-negative MPNs, 990 patients were diagnosed with ET or PV aged 1-39 years. ET was a more common MPN (643 patients, 64.9%) than PV (347 patients, 35.1%). The incidence was 2.53 per 1,000,000 for ET (643 patients; 276 male patients; median 31 years) and 1.37 per 1,000,000 for PV (347 patients; 309 male patients; median 32 years). Three ET patients developed secondary acute myelogenous leukemia and three developed secondary myelofibrosis. The 5-year cumulative incidence of TE was 14.2% in ET and 21.3% in PV. Thus, the incidence was higher in PV; in particular, arterial TE (ATE) was evidently higher in PV than in ET. The 5-year cumulative incidence of SPMs was 2.5% in ET and 2.6% in PV. While the use of both aspirin and hydroxyurea reduced the incidence of ATE, hydroxyurea significantly increased the incidence of SPMs.

Conclusion : This is the first population-based epidemiological study in Korean children and young adults with ET and PV. The incidence of ET and PV was very low in this age group and ET was more common than PV. Transformations of ET to fibrosis or AML, and occurrence of SPMs, were found in a small number of patients. The incidence of thrombosis, especially ATE, was significantly higher in PV than in ET. This suggests that children and young adults with ET and PV should also focus on thrombosis prevention and treatment. However, since hydroxyurea appears to increase SPMs, the risks and benefits should be considered. Further research is necessary in this patient group, including studies involving genetic

variations affecting MPNs.

Keyword : Child, Young Auldts, Essential Thrombocythemia, Polycythemia Vera, Second Primary Malignancy, Thromboembolism

PP08-06

Radiologic splenomegaly in patients with essential thrombocythemia and prefibrotic/early primary myelofibrosis

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Background : Previously, palpable splenomegaly was present in up to 50% of patients with essential thrombocythemia (ET) at diagnosis and was controversially thought to impose thrombotic risk. Currently, palpable splenomegaly is unusual in ET patients, possibly due to early diagnosis facilitated by lowering the diagnostic threshold of platelet counts from ≤ 600 × 109/L to ≤ 450 × 109/L and defining prefibrotic/early primary myelofibrosis (pre-PMF). Despite these changes, non-palpable splenomegaly has seldom been addressed. In this retrospective study, we evaluated radiologic splenomegaly in patients with 2016 WHO-defined ET and pre-PMF.

Method : Patients who were diagnosed with ET or pre-PMF and underwent abdominal computed tomography (CT) at diagnosis from January 1996 to July 2020 at Chungnam National University Hospital were enrolled, and their medical records were reviewed. In patients diagnosed with ET prior to 2017, the diagnosis was revised based on 2016 WHO diagnostic criteria. Two radiologists reviewed abdominal CT images and measured spleen volume using volumetry software. The spleen volume of each patient was adjusted for the age and body surface area of the patient, and the degree of splenomegaly was classified as follows: no splenomegaly, borderline volumetric splenomegaly, overt volumetric splenomegaly, and palpable splenomegaly.

Results : Seventy-six ET patients with a median age of 62.5 years (range 29–88 years) and 19 pre-PMF patients with a median age of 65 years (range 22–88 years) were enrolled. The ET and pre-PMF patients were followed up for a median of 2.4 years (range 0.1–17.6 years) and 4.2 years (range 0.2–19.6 years), respectively. Spleen volume was significantly larger in pre-PMF than in ET patients (377.9 ± 92.2 cm3 vs. 224.9 ± 115.2 cm3, P=0.000). No, borderline volumetric, overt volumetric, and palpable splenomegaly were found in 42 (55.3%), 24 (31.6%), 10 (13.2%), and 0 (0%) ET patients, respectively, and in 0 (0%), 8 (42.1%), 19 (52.6%), and 1 (5.2%) pre-PMF patient(s), respectively (P=0.000). Spleen volume did not correlate with white blood cell counts, monocyte counts, hemoglobin levels, platelet counts, LDH levels, or overall JAK2V617F allele burden. ET patients with overt volumetric splenomegaly exhibited lower JAKV617F positivity (76.3% vs. 25.0%, P=0.022) and lower allele burden in positive cases (17.7 ± 19.4% vs. 6.2 ± 11.5%, P=0.050) compared with those without splenomegaly. By contrast, CALR mutation was more frequent in patients with overt volumetric splenomegaly (63.5% vs. 0.0%, P=0.001). The degree of volumetric splenomegaly did not affect thrombosis-free survival (TFS) (3-year TFS: 63% vs. 80% vs. 83%, respectively, for no, borderline, and overt volumetric splenomegaly, P=0.225) or overall survival (OS) (10-year OS: 88% vs. 100% vs. 100%, P=0.543) in ET patients. In pre-PMF patients, JAK2V617F positivity or allele burden did not differ between patients with borderline or overt volumetric splenomegaly, nor did the degree of volumetric splenomegaly affect TFS (3-year TFS: 100% vs. 56%, P=0.540) or OS (10-year OS: 100% vs. 75%, P=0.392).

Conclusion : Spleen volume in patients with 2016 WHO-defined pre-PMF was significantly higher than that in patients with ET. No ET patients had palpable splenomegaly, whereas no pre-PMF patients had a normal-sized spleen. Radiologic splenomegaly did not confer thrombotic risk in either ET or pre-PMF patients.

PP08-07

Clinical predictors in diagnosing essential thrombocytosis: A correlational study

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Background : The objective is to correlate the following clinical predictors to diagnose essential thrombocytosis: A. Presence or absence of splenomegaly, B. Number of times with thrombocytosis, C. Age, D. Gender, E. Absence or presence of thrombotic event.

Method : ThE study employed retrospective cross-sectional method wherein out-patient charts of patients with essential thrombocytosis (cases) and polycythemia vera (controls) were reviewed in the University of Santo Tomas Hospital Benavides-Cancer Institute (BCI). Descriptive statistics included mean, standard deviation, frequency, and percentage, while correlation analysis involved Pearson Correlation and binary logistic regression. All significant clinical predictors were identified and included in the diagnostic parameters. Diagnostic performance was determined using the area under the curve receiver operating characteristic (AUC-ROC) curve. The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were also estimated. The overall prevalence of essential thrombocytosis was estimated using chi-square test exact binomial with a 95%

confidence interval (95% CI).

Results : Among cases, it can be noted that the mean age was 54.52 years old (18.62) and majority were 60 – 75 years old (36.00%), males (60.00%), had more than 3 episodes of thrombocytosis (68.00%), did not have splenomegaly (96.00%), and had no thrombotic events (76.00%). Results showed that 80.00% of the cases and 89.47% of the control were positive for the Janus Kinase – 2 (JAK-2) test. Among the different predictors, times of thrombocytosis and history of thrombotic event significantly predicted essential thrombocytosis. In particular, three or more episodes of thrombocytosis increases the odds of developing essential thrombocytosis by 128.00 times (p=0.001) than fewer episodes of elevated platelet count. Similarly, results indicated that a history of thrombotic event increases the odds of essential thrombocytosis by almost four-folds (p=0.001).

Conclusion : Among the different predictors, times of thrombocytosis and history of thrombotic event significantly predicted essential thrombocytosis.

Keyword : Predictors of Essential Thrombocytosis, Correlation of Predictors with Essential Thrombocytosis

PP08-08

Soluble ST2 for prediction of bone marrow fibrosis

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Background : Soluble suppressor of tumorigenicity 2 (sST2) is a novel biomarker for heart failure and inflammation that are related to underlying fibrosis. We explored whether sST2 is related to bone marrow fibrosis (BMF).

Method : In a total of 98 BM specimens, BMF was graded into BMF0/1 (n =70) and BMF2/3 (n =28) on reticulin stains, and in the paired plasma samples, sST2 levels were measured using ichroma ST2 assay (BODITECH MED INC., Chuncheon, Korea). sST2 levels were analyzed in relation to BMF grades, using the receiver operating characteristic (ROC) curve and logistic regression analyses.

Results : Median sST2 levels between BMF0/1 and BMF2/3 differed significantly (19.8 ng/mL vs. 32.3 ng/mL, P=0.015). With the cut-off of 23.1 ng/mL, sST2 level could predict BMF2/3 (area under the ROC curve =0.66, 95% confidence interval [CI] =0.56 - 0.75) with 71.4% of sensitivity and 64.3% of specificity. In the logistic regression, the level of sST2 > 23.1 ng/mL was associated with BMF2/3 (odd ratio =4.5, 95% CI =1.7 - 11.6, P=0.001).

Conclusion : This is the first study that analyzed sST2 level for predicting BMF. sST2 level seems to be related to BMF and could be a useful biomarker to predict it.

Keyword : Soluble ST2, Biomarker, Bone marrow, Fibrosis, Prediction

PP08-09

Coexistence of JAK2 and CALR mutations in a patient with myelofibrosis

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Background : CALR mutation was known to exist mutually exclusively with other diagnostic mutations in myeloproliferative neoplasms (MPNs) such as JAK2 or MPL mutations. However, as next generation sequencing (NGS) tests, which can detect mutations more sensitively, have been widely used in clinical laboratory, cases of JAK2 V617F/CALR double mutations have been reported [1]. The clinical features and prognosis of the JAK2 V617F/CALR double mutant group in MPNs have not been clearly identified. Therefore, the authors report a case of JAK2 V617F/CALR double mutation found in a patient diagnosed with myelofibrosis.

Method : Case report

A 79-year-old Russian woman was admitted to hospital because of a brain tumor. The patient was referred for checking the bone marrow status before surgery, because she had a history of being diagnosed with MPN in 2004, but differential diagnosis of MPN and clinical details were not clear at that time in Russia. At admission, complete blood count results were as follows: Hb, 116 g/L (120–160 g/L); platelet count, 456×109/L (130–450×109/L); and white blood cell count (WBC), 8.6×109/L (4.0–10.0×109/L) and myeloblasts were 2% of the total nucleated cells. Bone marrow (BM) cell count through BM aspirate smears was not possible due to dry-tapped, and myelofibrosis was measured as grade 4 in reticulin stains and Masson's trichrome stains of BM biopsy (Fig. 1A-D). As CALR exon 9 mutation (c.1099_1150del, p.Leu367Thrfs*46) was found in the Sanger sequencing, it was presumed that the initial diagnosis was essential thrombocythaemia, and then progressed to post-essential thrombocythaemia. The possibility that the initial diagnosis was primary myelofibrosis (PMF) cannot be ruled out. However, the NGS results, reported one month later, showed mutations in JAK2 along with CALR (JAK2 V617F mutation, allelic frequency 5.41%; CALR mutation, allelic frequency 32.3%) (Fig. 1E-G).

Results : Discussion

As molecular genetic tests with higher sensitivity have been used for diagnosis, the frequency of JAK2 V617F/CALR double mutations has gradually increased [1]. In MPNs, the JAK2 V617F/CALR double mutant group tend to have a higher platelet count and increase the risk of thrombotic complications than the CALR alone mutant group [1-3], so the mutations of MPNs should be considered clinically important. It was considered that JAK2 V617F/

CALR double mutations were usually present in subclones by clonal evolution [4, 5]. In addition, the possibility that JAK2 V617F mutation was independently acquired regardless of the presence of CALR mutation should also be considered, since the JAK2 V617F mutation is a representative age-related clonal hematopoiesis (AGCH) mutation [6, 7].

Conclusion : The JAK2 V617F/CALR double mutant group is likely to have clinical significance as a characteristic subgroup of MPNs in the future, when data on the clinical features and prognosis are accumulated. Therefore, when differential diagnosis of MPN is performed, mutation detection using a more sensitive method than Sanger sequencing is required.

Keyword : JAK2 V617F/CALR Double Mutation, Myeloproliferative Neoplasm, Age-Related Clonal Hematopoiesis, Sanger Sequencing, Next Generation Sequencing

Figure legend

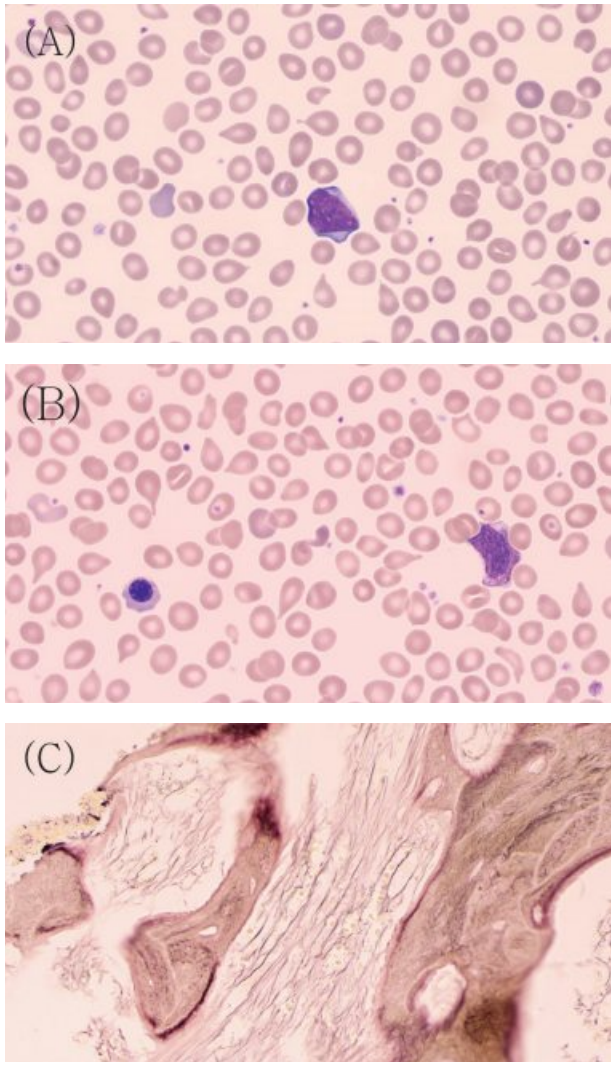

Figure 1. Microscopic findings of myelofibrosis and identification of the CARL and JAK2 V617F gene mutation by cytogenetic tests.

(A, B) Peripheral blood smear showing myeloblasts, leukoerythroblastic feature, and tear drop cells (Wright-Giemsa stain, ×1,000). (C, D) Bone marrow biopsy showing fibrosis of grade 4 (Reticulin stain, ×400, Masson's trichrome stain, ×200). (E) Sanger sequencing showing mutation of CALR (c.1099_1150del, p.Leu367Thrfs*46; The blocks indicate mutation site.) (F, G) Next generation sequencing showing the presence of the CALR (c.1099_1150del, p.Leu367Thrfs*46, allelic frequency 32.3%) and the JAK2 V617F (c.1849G>T, p.Val617Phe, allelic frequency 5.41%) mutation.

PP08-10

Immune gene signature distinguishes overt primary myelofibrosis from other myeloproliferative neoplasms

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Background : The Philadelphia-negative myeloproliferative neoplasms (MPNs) are clonal hematopoietic disorders characterized by an overproduction of differentiated hematopoietic cells, including the three major subcategories i.e., polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF). The excessive myeloproliferations of the MPNs are driven by mutations in JAK2, CALR, MPL, and uncommon variants. More recently, the biological basis on acquisition of somatic mutations have been accumulated, which may silence several immune-related genes in tumor and tumor microenvironment and contribute to the immune dysregulation. Moreover, there are increasing evidences that inflammation have a key role in promoting MPN initiation and influencing disease evolution. However, to date the bone marrow immune microenvironment of MPNs remains unclear exactly. Here, we carried out immune-related gene expression profiling of bone marrow aspirates (BMAs) from 33 MPN patients (6 PV, 6 ET, 6 early PMF, and 15 overt PMF) using nCounter Immunology Panel.

Method : BMA samples collected at diagnosis using EDTA-coated tubes. Those samples were processed within 24 hours from collection to obtain mononuclear cells by density centrifugation using Ficoll-Paque. NanoString analysis using a 594-gene nCounter Immunology panel (Human v2 - nanoString) was performed on RNAs extracted from 33 MPN bone marrow aspirates.

Results : First, to investigate whether there are distinct gene expression signatures of immune cells between three subcategories of MPNs, we compared gene expression profiles (GEPs) between ET, PV, and overt PMF. Using a P-value cutoff of ≤0.05 and fold-change ≥ 2, 10 upregulated and 32 downregulated differentially expressed genes (DEGs) were identified in ET than PMF, and 9 upregulated and 11 downregulated DEGs were identified in PV than PMF, while we found no significant DEGs between ET versus PV, except seven genes. We then questioned differences in GEPs between early PMF and overt PMF. Thirty-two downregulated and 4 upregulated DEGs were identified in early PMF than overt PMF. Gene set analysis revealed that the expression of genes related to almost processes decreased in early PMF than overt PMF. Next, we computed relative abundances of immune cell subpopulations, estimated based on expression counts from the entire panel of surveyed genes, and compared them between the subcategories of MPNs. The abundance measurement of exhausted CD8+ T cell genes were significantly lower in ET and PV, compared with overt PMF, suggesting T cell exhaustion was distinct in overt PMF, compared to ET and PV.

Conclusion : The results demonstrated that immune microenvironment signature was distinguishable in the subcategories of MPNs. In addition, inflammatory signature was enriched in the bone marrow of overt PMF and exhausted CD8+ T cell genes were distinct in overt PMT. Further investigation is warranted to determine the immunological factors critical for potential therapeutic targets to alleviate progress to myelofibrosis.

Keyword : Polycythemia Vera, Essential Thrombocythemia, Primary Myelofibrosis, Immune Microenvironment

PP08-11

A case of atypical chronic myeloid leukemia with concomitant CSF3R T618I and JAK2 V617F variants

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Background : Atypical chronic myeloid leukemia (aCML) is a rare and fatal myelodysplastic/myeloproliferative neoplasm (MDS/MPN). Due to the absence of specific genetic aberration and overlapping features with MDS and MPN, diagnosis of aCML has sometimes been challenging. In aCML, CSF3R variant that support the diagnosis of chronic neutrophilic leukemia has been reported with varying frequencies from 0% to 40%, and the JAK2 V617F variant is rare. Here, we report a rare case of aCML with concomitant CSF3R T618I and JAK2 V617F variants.

Method : A 75-year-old male without known underlying medical history was referred for incidentally found leukocytosis. Complete blood cell count (CBC) was as follows: hemoglobin, 7.1 g/dL; white blood cells, 136.82x109/L (absolute neutrophil count, 95.77x109/L); and platelets, 480x109/L, and differential counts were as follows: blasts, 1%; myelocytes, 8%; metamyelocytes, 7%; band neutrophils, 7%; segmented neutrophils, 63%; lymphocytes, 6%; monocytes, 3% ; eosinophils, 5%; and basophils, 1%. Splenomegaly was not noted on physical examination. Bone marrow (BM) examination, cytogenetic studies and targeted next-generation sequencing (NGS) were conducted for further evaluation of hematologic malignancy.

Results : BM showed hypercellular marrow with 80-90% cellularity, and increased granulocytes and megakaryocytes were noted with dysplasia of tri-lineage hematopoietic cells. Chromosome study revealed normal karyotype, and fluorescent in situ hybridization (FISH) for BCR/ABL1, PDGFRA/FIP1L1, PDGFRB and FGFR1 rearrangement were all negative. On targeted NGS, five variants

from four genes were detected: ASXL1 (p.R693*, 47.3%), CSF3R (p.T618I, 10.5%), JAK2 (p.V617F, 35.6%), and TET2 (p.H839fs, 47.5%; p.Y1659fs, 65.6%). Based on the morphologic findings of BM and CBC and cytogenetic results, this patient was finally diagnosed as aCML, and has been administered hydroxyurea and ruxolitinib, a JAK2 inhibitor.

Conclusion : We identified a patient with aCML carrying two oncogenic variants of CSF3R and JAK2 associated with JAK-STAT signaling. In this patient, targeted therapy with JAK2 inhibitor may particularly benefit. Although MPN should be considered when JAK2 V617F is identified, this case clearly illustrates JAK2 variant is not definite evidence for exclusion of aCML.

Keyword : Atypical Chronic Myeloid Leukemia, JAK2 V617F, CSF3R

PP08-12

Reslizumab treatment in a Korean adolescent patient with hypereosinophilic syndrome: A case report

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Background : Hypereosinophilic syndrome (HES) is a group of heterogeneous rare disorders characterized by eosinophilia ≥ 1.5 x 109/L in peripheral blood and evidence of end organ manifestations associated with eosinophilia. The causes of the eosinophilia in HES can be myeloid origin, lymphocyte-driven, or unknown. Although corticosteroid is a first-line therapy for most forms of HESs, long-term corticosteroid use causes several complications in the patients. Here we introduce an adolescent Korean patient who was diagnosed as lymphocyte variant HES (L-HES) and also showed phenotypes of episodic angioedema with eosinophilia (EAE, Gleich syndrome), who has been treated with reslizumab.

Method : We report about an eighteen years-old adolescent patient with L-HES treated with reslizumab for over 1 year. This patient showed the findings corresponding to L-HES and also had clinical features of EAE. This study was approved by the Institutional Review Board of Keimyung University Dongsan Hospital (approval No. 2018-02-006-001) and was conducted according to the tenets of the Declaration of Helsinki. Informed consent was obtained from the patient and patient's parents before the study.

Results : A four-year female patient was transferred to the pediatric hematologic clinic due to generalized edema, weight gain, wheal of skin, hepatosplenomegaly, and eosinophilia. She had been taking oral corticosteroid prescribed for 4 months in the local clinic. In the laboratory test, complete blood cell count showed white blood cell (WBC) count 24.84 × 103/μL, eosinophil count 11,377 cells/μL (45.8% of WBC), hemoglobin (Hb) 115 g/L, and platelet count 46 × 103/μL. The peripheral blood smear film showed normocytic normochromic erythrocytes. Leukocytes were increased in number with neutrophilia and absolute eosinophilia. Platelets are adequate in number without abnormal form. There was no evidence of secondary or reactive eosinophilia including drugs, parasite/bacterial/viral infections, underlying autoimmune diseases, inflammatory bowel disease, adrenal insufficiency or malignant neoplasm. The bone marrow aspirate smear film showed hypercellular marrow particles for their age with increased M/E ratio. Myeloid series were increased in number with eosinophilia and increased eosinophilic precursors (30.3%). Erythroid series were relatively decreased in number and morphology. Other cell lines are unremarkable. Malignant cell was not found in this smeared film. Other laboratory tests showed IgG 1,778.4 mg/dL (reference range, 800–1,700 mg/dL), IgA 273.6 mg/dL (reference range, 68–378 mg/dL), IgM 826.9 mg/dL (reference range, 60–263 mg/dL), and IgE 192.0 mg/dL (reference range, < 100 mg/dL). Lymphocyte phenotyping by flow cytometry, an aberrant CD3–CD4+ T-cell population was detected. The FIP1L1-PDGFRA fusion was not found in her peripheral blood by fluorescence in situ hybridization. These findings of the patients listed above correspond to EAE among L-HES. She had distinct symptoms (periodic generalized edema and weight gain every 1 month) corresponding to EAE. And an increased IgM level was also consistent with the diagnosis of EAE. However, the patient's symptoms (thrombocytopenia or hepatosplenomegaly) were much more severe than those of EAE that have been reported to date. Her symptoms did not improve spontaneously, thus prolonged corticosteroid administration was needed for several years.

At her age of 15 years, mepolizumab, the targeted agent blocking IL-5, became available in Korea. To reduce corticosteroid use, 100 mg mepolizumab was administered subcutaneously every 4 weeks for the patients. At first, eosinophil count was decreased below 100–200 cells/μL and she didn't need corticosteroid. However, her eosinophil count increased gradually despite of mepolizumab injection, thus mepolizumab was stopped after 6 months of treatment. At her age of 17 years, we decided to change the medication to reslizumab, another monoclonal antibody against IL-5. She has been receiving 3 mg/kg of reslizumab intravenously every 4 weeks for more than a year so far. After reslizumab treatment, her eosinophil count has been consistently in normal range and corticosteroid was stopped. After stopping corticosteroid, her short stature (< 3 percentile) was improved and her height is now in normal range (25 percentile).

Conclusion : In conclusion, intravenous reslizumab injection every 4 weeks is effective in this Korean adolescent patient with HES. Since this patient shows clinical manifestations of L-HES as well as EAE, periodic examination is required for the possibility of developing lymphoma or leukemia.

Keyword : Hypereosinophilic Syndrome, Reslizumab, Mepolizumab, Episodic Angioedema and Eosinophilia, Gleich's Syndrome

PP09-01

Evaluation of the efficacy of CsA combined with recombined human erythropoietin in the treatment of patients with chronic aplastic anemia

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Background : Aplastic anemia (AA) is a bone marrow failure disease with decreased hematopoietic function. AA consists of severe (SAA) and non-severe aplastic anemia(NSAA), which is also known as chronic aplastic anemia (CAA). Compared with immunosuppressant alone, rhEPO in combination with G-CSF and immunosuppressant (CsA + ATG) promotes better recovery of hematopoietic function, and shorten the time of transfusion dependency in the treatment of SAA. However, there is no report about the efficacy of rhEPO combined with immunosuppressant in the treatment of CAA yet. For CAA with transfusion dependency, immunosuppressive therapy is feasible. However, due to the price and side effects, the widely used therapy in Chinese CAA patients is CsA combined with androgen and G-CSF. The overall response rate (ORR) of CsA in the six months ranges from 30%-46%, and the ORR in the first year can reach 50%-60%. Because CAA patients often present as anemia and may have severe transfusion dependency, the rapid improvement of anemia can enhance the quality of life of patients. Therefore, in this study, we aim to compare the efficacy and safety of CsA and the combination of CsA and rhEPO for CAA patients.

Method : Data from 79 patients with CAA between January 2016 and June 2018 was collected, retrospectively. Among them, 45 patients were treated with CsA+rhEPO, and the other 34 patients with compatible baseline characteristics were treated with CsA alone. All enrolled patients were treated with CsA for at least 1.5˜2 years and were followed for at least one year. The efficacy, side effects, long-term outcomes were compared between the two groups, and factors that may influence the efficacy were analyzed as well.

Results : For patients treated with CsA+ rhEPO, there were 14 males and 31 females, with a median age of 43 (19˜73) years old. The median CsA treatment duration was 26 (12˜38) months and the median duration of rhEPO treatment was 4 (3˜6) months. Patients were followed up for a median of 24 (12˜42) months. In terms of patients treated with CsA alone, there were 16 males and 18 females with a median age of 36 (16˜85) years old. The median CsA treatment duration was 24 (12˜40) months and the median follow-up time was 25 (12˜40) months. There was no statistical difference in baseline characteristics between the two groups (P>0.05). There was no statistical difference in CR, PR, and OR rate between the two groups after 3 and 12 months of treatment and at the end of follow-up (P>0.05), apart from that CsA+ rhEPO group had a higher OR rate (55.6% vs 31.3%, P=0.040) and PR rate(53.3% vs 25.0%, P=0.019) compared with CsA alone group after 6 months of treatment. Similarly, the hemoglobin level at the sixth month for CsA+ rhEPO group was higher than CsA alone group (102.6g/L vs 90.3g/L, P=0.047). However, no significant difference was found between the two groups at other time points. A total of 11.1% (5/45) patients in the CsA+ rhEPO group reported soreness at the injection site. The rate of the clonal revolution was similar during the follow-up period with no death in either group. No clinical characteristic was found to predict the efficacy of CsA+ rhEPO.

Conclusion : CsA+ rhEPO treatment has a better OR rate and higher hemoglobin level at the sixth month with compatible side effects compared with CsA alone.

Keyword : Chronic Aplastic Anemia, Recombined Human Erythropoietin, Cyclosporin A, Efficacy, Side Effects

Table Comparisons of response between group A and group B [number of cases (%)]

Group	3 months			6 months			12 months			End of follow-up		
	CR	PR	OR	CR	PR	OR	CR	PR	OR	CR	PR	OR
Group A	0	15(33.3)	15(33.3)	1(2.2)	24(53.3)	25(55.6)	6(13.3)	20(44.4)	26(57.8)	7(15.6)	11(37.9)	18(62.1)
Group B	0	8(23.5)	8(23.5)	2(6.3)	8(25.0)	10(31.3)	3(9.4)	15(46.9)	18(56.3)	4(12.5)	11(36.7)	15(50.0)
χ^2	–	0.902	0.902	0.930	6.280	4.456	0.326	0.008	0.001	1.135	0.009	0.871
P	–	0.454	0.454	0.567	0.019	0.040	0.726	1.000	0.920	0.333	1.000	0.435

PP09-02

The outcome of hematopoietic stem cell transplantation in children with Shwachman-Diamond syndrome

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Background : Shwachman-Diamond syndrome (SDS) is an autosomal recessive, multisystem disorder characterized by exocrine pancreatic dysfunction, bone metaphyseal dysostosis, bone marrow failure, and high risk of leukemia. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only currently available curative treatment for bone marrow failure and leukemia in SDS patients. Only small case series of patients with SDS undergoing HSCT have been reported, which generally show a poor outcome compared with other inherited bone marrow failure syndrome Risk factors predicting outcome are unavailable in SDS. The aim was to describe the outcome of HSCT in a Canadian cohort of patients with SDS.

Method : The Canadian Inherited Marrow Failure Registry (CIMFR) is a multicenter registry that includes tertiary centers that care for IBMFS patients across all Canadian provinces. Patients with SDS who were enrolled in CIMFR and underwent HSCT between January 2001 and December 2019 were included. HSCT data were extracted from the CIMFR database.

Results : Among the 62 patients with SDS enrolled in the CIMFR, 9 underwent HSCT. Six patients were male. The median age at presentation and diagnosis was 0.17 years (range: 0 to 0.57 years) and 1.12 years (range: 0.22 to 2.34 years). The median age at HSCT was 7.14 years (range; 2.48-15.39 years). Median follow up time from HSCT was 6.66 years for five survivors (range; 1.04 to 10.53 years) and 0.82 years for four non-survivors (range; 0.16 to 1.64 years). Among nine transplanted patients, seven patients had SBDS mutations and two patients had DNAJC21 mutations. Eight patients had pancreatic insufficiency at the time of HSCT. Transplanted patients with SDS were hematologically characterized by refractory cytopenia including aplastic anemia (AA) (n=4), myelodysplastic syndrome (MDS) (n=2) and acute myeloid leukemia (AML) (n=2). One patient had a diagnosis of Diamond-Blackfan anemia at the time of transplant, but was reclassified as having SDS after finding a SBDS mutation by next generation sequencing. One patient with AML and one with MDS received over 20 units of red blood cells and platelets before HSCT. Two patients had a fully-matched sibling donor, three had a fully-matched unrelated donor, three had a mismatched alternative donor, and one had no data on donor matching. The 5-year overall survival (OS) was 45.7±18.9%. Of the five patients who received reduced-intensity conditioning (mainly busulfan-fludarabine), four survived. Among three patients who received myeloablative conditioning (busulfan-cyclophosphamide), two patients deceased. Two of eight patients from whom engraftment data was available experienced graft failure; both received unrelated cord blood (two of three cord blood transplantation). One of these two patients died from infection associated with graft failure. The second patients received a second and third HSCT and survived. One patient who received stem cells from a mismatched family donor and a myeloablative regimen died from post-transplant lymphoproliferative disorder two months after HSCT. The patient with AML relapsed 9 months after HSCT and died 10 months later. The patient who underwent HSCT as having DBA, but later was diagnosed as having SDS died for unknown cause 17 months after HSCT.

Conclusion : The outcome of HSCT in patients with SDS is about 50%. Reduced-intensity conditioning regimen and bone marrow as stem cell source may confer better outcome, but larger studies are required to replicate these results.

Keyword : Shwachman-Diamond Syndrome, Hematopoietic Stem Cell Transplantation, Outcome

PP09-03

A predictive scoring system for severe aplastic anemia patients treated with antithymocyte globulin and cyclosporine

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Background : There is increasing unmet needs for the optimized application of immunosuppressive therapy with rabbit antithymocyte globulin (rATG) and cyclosporin A (rATG-CsA) in patients with severe aplastic anemia. This study aimed to speculate risk factors for failure of rATG-CsA, and establish a scoring system to predict treatment failure using consecutive 170 adult SAA patients treated rATG-CsA.

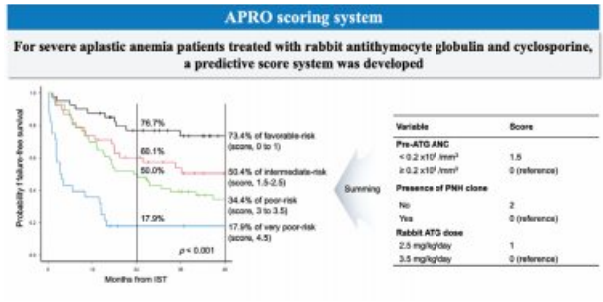
Method : Failure-free survival (FFS) is a composite endpoint that measures survival free of death, no response, relapse, or clonal evolution after rATG-CsA.

Results : With a median follow-up of 55.4 months, the 2-year cumulative incidences of overall response (OR) and complete response (CR), and probabilities of overall survival and FFS were 54.8%, 27.3%, 89.3%, and 51.2%. In multivariable analysis, three parameters, including a lower ANC at baseline (< 0.2 x109 /mm3), no presence of paroxysmal nocturnal hemoglobinuria clone, a higher dose of rATG (3.5 mg/kg/day rather than 2.5 mg/kg/day), were independently associated with achieving FFS. Based on these

three factors, four risk groups (2-year FFS: 76.7% in favorable-risk, 60.1% in intermediate-risk, 50.0% in poor-risk, and 17.9% in very poor-risk; p < .001) were identified by developed scoring system. The scoring system also provides discriminative differences of achievement OR as well as CR according to risk groups (all p < 0.001).

Conclusion : Conclusively, the probability of failure of rATG-CsA could be predicted by a scoring system, and it could help clinicians to consider risk-adapted selection of treatment for SAA.

Keyword : Rabbit, Antithymocyte Globulin, Dose, Aplastic Anemia, Immunosuppressive Therapy, Thymoglobulin



PP09-04

Long-term outcome of allogeneic hematopoietic stem cell transplantation from HLA-matched sibling donor in young patients with severe acquired aplastic anemia

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Background : Severe aplastic anemia (SAA) is a rare multi-lineage bone marrow failure disorder and matched related hematopoietic stem cell transplantation (HSCT) is the treatment of choice especially in young patients (age < 40 years old). We retrospectively analyzed patients who received HLA-matched sibling allogeneic HSCT (MSD allo-HSCT) at our institution.

Method : The clinical data of 15 acquired aplastic anemia (AA) patients received MSD allo-HSCT from 2011 to 2020 were analyzed retrospectively. Six patients were male and nine were female. Median age was 23.3 (4 – 40) years old. Eight patients had transfusion-dependent intermediate aplastic anemia (AA), six had SAA and one had very severe aplastic anemia (VSAA). Six (40%) patients received more than 20 units of transfusions (red blood cells and/or platelets) and two (13.3%) patients failed to respond to the previous immunosuppressive therapy. The median time from diagnosis to HSCT was 3 (range: 1.5 – 17) months. All patients received allogeneic peripheral blood stem cell (PBSC) transplantation (allo-PBSCT). Some various conditioning regimens were used such as cyclophosphamide (CY) + horse anti-thymocyte globulin (h-ATG) (10 patients), CY + h-ATG + Fludarabine (FLU) (3 patients), CY + FLU (1 patient), CY (only one patient). Fifteen patients received prophylaxis for graft-versus-host disease (GVHD) with cyclosporine (CSA) plus short-term methotrexate (MTX).

Results : The median number of infused CD34(+) cells and MNC were 7.31 (5.76 – 7.90)×106/kg and 6.83 (4.50 – 9.70)×108/kg in allo-PBSCT, respectively. Engraftment was observed in all patients. The median time to neutrophil (ANC) recovery and to platelet (PLT) recovery were 12 (range: 9 - 20) days and 12 (range: 8 - 28) days, respectively. Six (40%) patients developed acute GVHD (aGVHD) and all of them had grade I-II aGVHD. One patient suffered from chronic GVHD (cGVHD) which was well managed with corticoid. CMV reaction occurred in 5 (33.3%) patients and was controlled with Ganciclovir. Of two patients who had secondary graft rejection, one patient successfully received second stem cell transplantation and the other achieved partial response following with h-ATG + Cyclosporin. Median follow-up time was 27 (5.3 - 127) months. Three-year estimated overall survival (OS), disease free survival (DFS), GvHD-free relapse-free survival (GRFS) was 100%, 93% (95% CI: 79% – 100%) and 83% (95% CI: 64% - 100%) respectively. Early complications after transplantation included febrile neutropenia (11 patients), severe pneumonia (2 patients), platelet transfusion refractory (2 patients), multi-drug resistant sepsis (2 patients). Chronic renal failure, hypothyroidism, cataract, femoral head avascular necrosis were the most common late complications. At report time, 93.3% of patients were alive with normal hematologic parameters and most patients really did experience good levels of quality of life (QOL) during 5 years after transplantation.

Conclusion : MSD allo-HSCT is an effective therapy for young patients with acquired AA. The outcome of allogeneic HSCT in patients with acquired AA at our institution was comparable to the results of the other previous studies.

Keyword : Severe Acquired Aplastic Anemia, HLA-Matched Sibling Donor, Transplantation

PP10-01

Authenticating a common NGS-detected ASXL1 codon 646 mutation using Sanger sequencing

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Background : Mutations in the ASXL1 gene occur frequently in

myeloid malignancies, aplastic anemia, and age-related clonal hematopoiesis. The most common, accounting for half such mutations, is a guanine nucleotide duplication at position 1934 that produces a frameshift and premature stop codon (c.1934dupG; p.Gly646fs). Previous studies have shown that ASXL1 mutations negatively impact the prognoses of patients with myeloid malignancies, particularly those with myelodysplastic syndromes and acute myeloid leukemia. However, it has been suggested that this mutation is not somatic but rather an artifact of next-generation sequencing (NGS) owing to its location in an eight base-pair guanine mononucleotide repeat, and that its frequency is therefore overestimated. In this study, we used Sanger sequencing to investigate whether the ASXL1 codon 646 variant is a true mutation or a sequencing artifact.

Method : Amplicon-based NGS was performed on 120 clinical samples from patients with various hematological malignancies and on the Myeloid DNA Reference Standard HD829 (Horizon Discovery Ltd., Cambridge, United Kingdom) using a 54-gene TruSight Myeloid panel that included ASXL1 exon 12 (Illumina, San Diego, CA, USA) and a MiSeqDx system (Illumina). Sanger sequencing was performed on 109 available clinical samples, one clinical sample exhibiting a high allele frequency (AF) of the ASXL1 codon 646 variant, and various reference material dilution ratios.

Results : The expected and measured AFs of the ASXL1 codon 646 mutation within the reference material were 40.00% and 18.65%, respectively. The measured AFs of reference materials serially diluted at 1:1, 1:2, 1:4, and 1:8 were 9.09%, 5.82%, 1.92%, and 2.87%, respectively (y =0.4391x + 0.8642; r2 =0.9846). When diluting both the clinical sample exhibiting a high AF (18.73%) and the reference material, Sanger sequencing was able to confirm the variant with an NGS AF as low as 3.75%. The AF, depth, and quality score of the 109 samples using NGS were 3.77% (range 0.00–22.48%), 2951 (51–7868), and 100 (21–100), respectively. The variant was observed in six of these samples (5.5%); their AF, depth, and quality score using NGS were 14.61% (range 7.36–22.48%), 1884.5 (53–4265), and 100 (70–100), respectively. The NGS-derived AF, depth, and quality score of the remaining 103 samples (94.5%), in which the variant was not observed with Sanger sequencing, were 3.71% (range 1.74–22.48%), 3013 (80–7868), and 21 (70–100), respectively; the AFs of 93 of them (90.3%) were less than 5%. Moreover, a known variant, c.1954G>A (p.G652S; rs3746609), and a novel variant, c.1926delA (p.G642Gfs*60), were observed in 29 (26.6%) and 1 (0.9%) of the samples, respectively.

Conclusion : The measured AFs of the ASXL1 codon 646 variant in the serially diluted reference material were approximately half their expected values, suggesting difficulties in detecting the variant using NGS. Sanger sequencing confirmed the variant at AFs as low as 3.75%. The AF, depth, and quality score were higher in the samples in which the variant was confirmed by Sanger sequencing than in those in which the variant was not observed using this method, even though there was substantial overlap in all three parameters between the two groups. None of the samples with a Sanger sequencing-confirmed ASXL1 codon 646 variant showed an AF of less than 5% using NGS; however, the majority of the samples in which the ASXL1 codon 646 variant was not confirmed by Sanger sequencing showed AFs of less than 5% using NGS.

Keyword : Allele Frequency, ASXL1, Mutation, Next-Generation Sequencing, Sanger Sequencing

PP10-02

HTLV-1 viral oncoprotein HBZ protects cells from pro-apoptotic stress by up-regulating stabilization of HAX-1

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Background : Human T-cell leukemia virus type-1 (HTLV-1) is an oncogenic retrovirus and its infection causes adult T-cell leukemia (ATL) in 2-5 % of carriers after a long latent period. The HTLV-1 bZIP factor (HBZ) gene was identified and this protein expression is consistently observed in all ATL cells. Thus HBZ may play a critical role in the development of ATL, but these mechanisms remain unclear. In this study, we searched for cellular factors that interact with HBZ by yeast two-hybrid screening system. Consequently, we identified HCLS1-associated protein X-1 (HAX-1), a substrate of Src family tyrosine kinases, known as a potent antiapoptotic protein.

Method : We performed an yeast two-hybrid screen using HBZ as a bait and identified HAX-1. Interaction between HBZ and HAX-1 was investigated in mammalian cells and binding regions both of them were determined. To observe subcellular localization, coexpression of HBZ with HAX-1 in cells were examined confocal microscopic. Also, we investigated whether HBZ regulated the stability of HAX-1 and the effect on apoptosis induced by staurosporine (STS), which is known to induce the intrinsic caspase-9-dependent pathway of apoptosis.

Results : We confirmed that HBZ and HAX-1 interacted in mammalian cells by co-immunoprecipitation (Co-IP) assay. N-terminal region of HBZ bound to N-terminal region of HAX-1. And when we use a nuclear export signal (NES) mutant of HBZ that can't export to cytoplasm from nucleus, the interaction with HAX-1 disappeared. However, in the case using HBZ-NES-mut-PKI that can be exported to the cytoplasm, the association appeared again. The ubiquitination level of HAX-1 was significantly reduced by the expression HBZ in cells and the cytoplasmic export of HBZ was required for the inhibitory effect on HAX-1 ubiquitination. Stabilization of HAX-1 by HBZ might be contributing to the inhibition of staurosporine (STS)-induced apoptosis.

Conclusion : Our results suggested that HBZ may have influence on HAX-1-mediated cellular function(s) and help us to understand the role of HBZ in ATL development.

Keyword : HTLV-1, ATL, HBZ, HAX-1, Ubiquitination, Caspase-9

PP10-03

Complete blood count and cell population data parameters are useful in differentiating myelodysplastic syndromes from other forms of cytopenia

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Background : Myelodysplastic syndromes are clonal myeloid neoplasms characterized by morphologic dysplasia, cytopenia and having propensity for acute leukemic transformation. However, dysplasia is determined by morphology and may be present in reactive conditions. If there are cell population data that can discriminate cytopenic patients with MDS by other conditions, it may facilitate diagnosis and also become a reliable feature that would be reproducible in many laboratories.

Method : The patient cohort (n=183) included 40 samples from patients with MDS, 143 samples from patients with other forms of cytopenia (iron deficiency, aplastic anemia, immune thrombocytopenia, hematological malignancies, etc.). Hematological parameters, measured by the Abbott Alinity hq analyzer and the Sysmex XN-2000 analyzer, were compared between the two cytopenic groups by the Mann-Whitney test. The effectiveness of individual standard and research CBC parameters to differentiate MDS for other forms of cytopenia was assessed by ROC analysis. Patients who have received RBC transfusion in the past eight weeks were excluded from the analysis.

Results : Several CBC parameters demonstrated significant differences between MDS and other cytopenia patients. From the RBC parameters, % MAC (Macrocytic RBCs), % HPR (hyperchromic RBCs), and hemoglobin distribution width (HDW) from the Abbott Alinity analyzer were higher in MDS than in other cytopenia and showed the largest difference between the two groups with an area under the curve (AUC) with 0.767 (0.687 - 0.847), 0.700 (0.615 - 0.785), 0.762 (0.681 - 0.843), respectively. From the Sysmex XN analyzer, mean corpuscular volume (MCV), red cell distribution width-standard deviation (RDW-SD), macrocytic RBC ratio (MacroR) and HYPER-He were higher in MDS, showing the largest difference between the two groups with AUC of 0.735 (0.644 - 0.825), 0.799 (0.724 - 0.874), 0.798 (0.716 - 0.881), 0.731 (0.637 – 0.825), respectively. Regarding the white blood cell parameters, Sysmex analyzer showed differences with neutrophil scattergram, NE-WX, NEU-WY and NEU-WZ. The lateral, fluorescent and forward scattered light distribution width of the MDS patients were higher than other cytopenic patients with AUC of 0.868 (0.791 -0.945), 0.816 (0.7430-0.889) and 0.799 (0.701-0.897), respectively. For the platelet parameter, platelet distribution width from the Abbott Alinity analyzer was higher in MDS with a AUC of 0.741 (0.662 – 0.821).

Conclusion : Several standard and research CBC and cell population data from the hematology analyzers have demonstrated significant differences between MDS and other forms of cytopenia. The differences likely reflect the dysplastic erythropoiesis and thrombopoiesis and consequential morphological abnormalities. These results demonstrate the clinical utility of cell population data and hematology parameters in the differential diagnosis of MDS.

Keyword : Myelodysplastic Syndrome, Cell Population Data, Abbott Alinity Hq, Sysmex Xn Analyzer

PP10-04

Comparison of hematology profile between recovery and death group of COVID-19 patient in Jember, East Java, Indonesia: Preliminary study

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Background : Novel coronavirus disease (COVID-19) resulted various clinical outcomes. Searching for instrument that can predict the prognosis of COVID-19 patient is valuable. One of prognostic factor that can be used in limited healthcare facilities is hematology profile. It can be done through minimal facilities in laboratory services without high cost needed. The aim of our study is to compare routine hematology profile between death and recovery group of COVID-19 patient as preliminary research of prognostic tools.

Method : We collected medical records from COVID-19 patients who were hospitalized in three hospitals between April and November 2020 in Jember Regency, Indonesia. Inclusion criterias were confirmed cases of COVID-19 with a positive PCR result and discharged from hospital due to death or recovery. Any patient with incomplete medical record was excluded. There were 181 patients who met the criteria. The sample was divided into death group (n=29) and recovery group (n=152). The parameter of routine hematology profile assessed were hemoglobin, hematocrit, thrombocyte, leukocyte, eosinophil, neutrophil,

lymphocyte, monocyte, neutrophil-lymphocyte ratio (NLR), derived neutrophil-lymphocyte ratio (d-NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR). We also included age, sex, number of co-morbidities, and severity. All variables were compared between the two groups. The continuous variable was analyzed with Mann Whitney, and the categorical variable was analyzed with Chi Square or Kruskal Wallis under SPSS v.22.

Results : Our patients composed of 97 males and 84 females, with a mean age of 42.19 years. A total of 124 (68.5%) confirmed patients had no comorbidity, and 89 (49%) patients were hospitalized at a moderate level. Age, number of co-morbidities, and severity level between the two groups were significantly different with p-value <0.001. In routine hematology profile, we found that almost all variables were significantly different, such as hemoglobin (p=0.005), hematocrit (p=<0.001), leukocytes (p=0.01), eosinophil (p=0.001), neutrophil (p=<0.001), lymphocyte (p=<0.001), and thrombocyte (p=0.048). Other inflammatory predictors included in this study also revealed significant findings between two groups, such as NLR (p=<0.001), d-NLR (p=<0.001), TLR (p=0.048) and LMR (p=<0.001). Other inflammatory predictors included in this study also revealed significant findings between two groups, such as NLR (p=<0.001), d-NLR (p=<0.001), TLR (p=0.048) and LMR (p=<0.001).

Conclusion : Routine hematology profile between recovery and death group are significantly different. Further analysis is needed to determine hematology factor which affect mortality and predict the prognosis of COVID-19 patient.

Keyword : COVID-19, Indonesia, Routine Hematology

Table 1. Patient Characteristic and Hematology Laboratory Profile Covid-19 Patient

	Total	Recovery Group (n=152)	Death Group (n=29)	Statistic test
Patient Characteristic				
Age (M±SD)	42.19 ± 16.99	39.82 ± 16.26	54.62 ± 15.477	Z =-4.54, p=<0.001
Sex (M/F)	97/84	80/72	17/12	X^2 =0.351, p=0.553
No. of Comorbidities (0/1/2)	124/40/17	118/24/10	6/16/7	X^2 =36.61, p=<0.001
Severity (Mild/Moderate/Severe)	80/89/12	80/69/3	0/20/9	K =39.06, p=<0.001
Laboratory Profile				
Hb (M±SD)	13.6 ± 1.88	13.91 ± 1.74	12.58 ± 2.24	Z =-2.805, p=0.005
Hematocrit (M±SD)	39.19 ± 5.39	39.87 ± 5.00	35.65 ± 6.10	Z =-3.352, p=<0.001
Leucocyte (M±SD x 10^3)	8.793 ± 5,41	8.57 ± 5.63	9.98 ± 3.90	Z =-2.580, p=0.010
%Eosinophil (M±SD)	1.0 ± 1,64	1.23 ± 1.73	0.27 ± 0.53	Z =-3.235, p=0.001
%Neutrophil (M±SD)	66.78 ± 13	64.84 ± 12.48	76.97 ± 10.86	Z =-4.657, p=<0.001
%Lymphocyte (M±SD)	25.35 ± 11.76	27.16 ± 11.30	15.86 ± 9.50	Z =-4.932, p=<0.001
%Monocyte (M±SD)	6.7 ± 3.26	6.78 ± 3.32	6.72 ± 2.96	Z =-0.257, p=0.797
Thrombocyte (M±SD x 10^3)	167.66 ±128.17	156.11 ± 109.37	228.23 ± 191.25	Z =-1.976, p=0.048
NLR (M±SD)	3.98 ± 3.92	3.30 ± 3.11	7.53 ± 5.57	Z =-4.929, p=<0.001
d-NLR (M±SD)	2.67 ± 2.09	2.36 ± 1.84	4.37 ± 2.54	Z =-2.805, p=<0.001
TLR (M±SD)	167.53 ± 128.31	155.96 ± 109.55	228.23 ± 191.25	Z =-1.976, p=0.048
LMR (M±SD)	4.54 ± 3.03	4.80 ± 2.98	3.22 ± 4.49	Z =-4.723, p=<0.001

PP10-05

Benign variants associated with hematologic malignancy in the catalogue of somatic mutations in cancer

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Background : The presence of benign variants in mutation databases is one of the well-documented pitfalls when interpreting clinical variants associated with hematologic malignancy. The aim of this study is to investigate the frequency of benign or likely benign (B/LB) variants associated with hematologic malignancy in the Catalogue of Somatic Mutations in Cancer (COSMIC), which is one of the most commonly used databases for cancers.

Method : A total of 12,149,816 coding variants were downloaded from the COSMIC (release v91, April 2020) and 123,211 variants in 99 genes associated with hematologic malignancy were used for the analysis. The genes were selected according to the criteria recommended by the World Health Organization classification and National Comprehensive Cancer Network guideline. The variant classification was done based on the standardized interpretation guidelines.

Results : The frequency of B/LB variants was 3.2% (3,890/123,211) of COSMIC variants. In addition, 44.9% (1,748/3,890) of B/LB variants were recurrently observed in at least two cancer samples. In terms of drug response and cancer susceptibility, 2.9% (112/3,890) of B/LB variants were clinically-significant.

Conclusion : Interpretation and reporting of somatic mutations in cancer databases need to use with caution. We found that a significant number of B/LB variants associated with hematologic malignancy have been registered in COSMIC. In addition, a number of B/LB variants were clinically-significant in terms of drug response and cancer susceptibility. This study highlights the importance of the reinterpretation of cancer variants reported from mutation databases and could be a good starting point for in-depth review of somatic mutation essential for precision oncology.

Keyword : Catalogue of Somatic Mutations in Cancer (COSMIC), Mutation, Benign Variants, Hematologic Malignancy, Actionable Variants

PP10-06

Novel factor VII gene mutations in six families with hereditary coagulation factor VII deficiency

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Background : Hereditary human coagulation factor VII (FVII) deficiency is an inherited autosomal recessive hemorrhagic disease involving mutations in the F7 gene. The sites and types of F7 mutations may influence the coagulation activities of plasma FVII (FVII:C) and severity of hemorrhage symptoms. However, the specific mutations that impact FVII activity are not completely

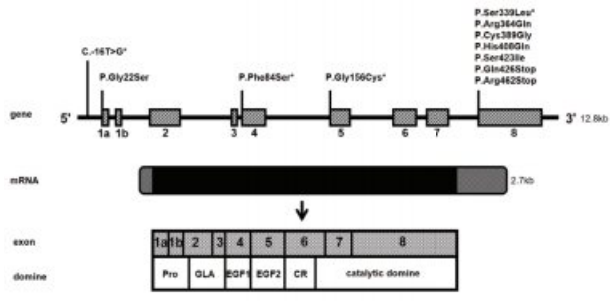
known. The further exploring of the possible pathogenic mutations of hereditary coagulation FVII deficiency contributes to the diagnosis and treatment of the disease in the future.

Method : We tested the coagulation functions and plasma activities of FVII in seven patients recruited from six families with hereditary FVII deficiency, and sequenced the F7 gene of the patients and their families. Then, we analyzed the genetic information from the six families and predicted the structures of the mutated proteins.

Results : In this study, we detected 11 F7 mutations, including 4 novel mutations, in which the mutations p.Phe84Ser and p.Gly156Cys encoded the Gla and EGF domains of FVII, respectively, while the mutation p.Ser339Leu encoded the recognition site of the enzymatic protein and maintained the conformation of the catalytic domain structure. Meanwhile, the mutation in the 5´ untranslated region (UTR) was closely associated with the mRNA regulatory sequence.

Conclusion : We have identified novel genetic mutations and performed pedigree analysis that shed light on the pathogenesis of hereditary human coagulation FVII deficiency and may contribute to the development of treatments for this disease.

Keyword : Hereditary FVII deficiency, Factor VII, Gene Mutation, Pedigree Analysis, Protein Structure



PP10-07

Red blood cell deformability and distribution width in patients with hematologic neoplasms

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Background : Despite increasing evidence that red blood cell (RBC) deformability is impaired in pathologic conditions, little research has been done on RBC deformability in hematologic diseases. The authors measured RBC deformability in patients with various hematologic diseases, including hematologic malignancies.

Method : A total of 568 patients who underwent bone marrow (BM) examination for initial diagnosis were enrolled. We collected the subjects' age, sex, diagnosis of BM examination, and complete blood count results. The RBC deformability, which was quantified by an elongation index, was measured by a microfluidic ektacytometer.

Results : RBC deformability was lower in primary myelofibrosis, acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), and acute lymphoblastic leukemia (ALL) from least to greatest. When the correlation between red blood cell distribution width (RDW) and RBC deformability was analyzed for 370 subjects in hematologic neoplasms, the correlation coefficients of RDW was –0.2974 ($P < 0.01$). When comparing MDS and aplastic anemia (AA), the deformability of MDS was significantly lower than that of AA. RBC deformability was decreased in leukemic diseases such as AML, MDS, CML, and ALL compared to control, and RDW showed a negative correlation with deformability.

Conclusion : RBC deformability was decreased in leukemic diseases such as AML, MDS, CML, and ALL compared to control, and RDW showed a negative correlation with deformability. Also, we found the possibility that RBC deformability as a complementary differential diagnostic test for MDS and AA.

Keyword : RBC Deformability, RDW, Blood Rheology, Leukemia, Hematologic Malignancy, Myelodysplastic Syndrome, Aplastic Anemia

Table. RBC deformability and other blood test results of all subjects

Diagnosis	Case Number (total: 568)	Male/Female ratio	RBC deformability (elongation index)		RBC parameters										WBC count (X10³/μL)		Platelet count (X10³/μL)	
					Hemoglobin (g/dL)		Reticulocyte (%)		MCV (fL)		MCH (pg)		MCHC (g/dL)		RDW (%)			
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
IDA	14	0.4	0.2540	0.0389	8.5	1.4	1.18	0.47	73.3	7.6	23.1	1.9	30.5	2.7	19.5	3.3	6.6	5.4	226.4	188.9
HA	18	2.0	0.2653	0.0504	7.6	1.9	6.24	6.48	100.7	9.0	33.3	3.1	33.1	1.5	18.8	3.8	6.7	4.3	222.3	162.4
PMF	9	2.0	0.2713	0.0216	7.2	1.3	1.34	1.03	90.5	8.3	29.5	2.6	32.7	1.6	18.2	4.0	24.4	31.3	180.7	127.5
AML	80	1.5	0.2718	0.0327	8.5	1.6	0.76	0.88	94.6	8.0	32.9	3.8	34.8	2.0	16.5	2.0	23.3	37.5	78.8	80.6
MDS	36	3.9	0.2739	0.0302	9.1	1.7	1.25	1.05	95.4	13.0	32.1	5.7	33.4	2.5	19.1	4.2	5.1	11.1	149.1	205.7
CML	25	1.9	0.2748	0.0355	11.0	2.6	1.60	0.57	91.5	4.8	30.9	2.4	33.8	2.9	15.7	1.9	121.6	106.2	575.7	366.3
ALL	32	3.1	0.2783	0.0315	9.4	2.1	1.19	2.24	86.0	7.9	29.8	2.5	34.7	1.0	15.6	2.1	32.4	45.5	92.3	62.7
BMI	23	2.7	0.2870	0.0295	9.6	2.1	1.08	0.97	90.5	7.7	30.8	2.6	34.1	1.2	15.6	2.5	6.8	5.7	136.0	78.7
PRCA	7	0.5	0.2908	0.0279	8.5	1.4	0.31	0.38	91.8	6.1	32.2	2.2	35.0	0.8	17.1	3.1	6.8	3.5	233.2	100.2
PV	19	0.6	0.2928	0.0326	17.5	2.0	2.25	0.44	79.6	8.7	25.4	4.2	31.8	2.1	16.6	2.6	14.1	6.1	704.8	385.7
AA	38	1.2	0.2931	0.0304	9.2	2.3	0.59	0.77	95.0	8.9	32.7	2.9	34.4	1.2	15.3	2.7	2.9	1.6	68.0	53.5
PCN	67	1.5	0.3025	0.0239	9.7*	2.4	1.17	0.65	93.1	5.8	31.4	2.3	33.7	1.3	15.7	2.8	7.0	2.9	222.7	116.7
ITP	67	1.1	0.3041	0.0230	13.1	2.2	1.67	0.61	88.4	8.3	30.4	2.9	34.3	1.5	14.0	2.2	6.8	3.0	53.0	38.4
CLL	12	2.0	0.3043	0.0166	10.5*	2.0	1.29	0.65	95.3	9.6	31.9	2.6	33.5	0.8	14.7	1.6	42.0	55.2	164.3	88.2
ET	22	1.3	0.3047	0.0355	14.0	1.4	1.92	0.32	86.4	7.5	29.0	2.5	33.5	1.1	14.5	2.5	10.6	4.1	1163.9	459.6
Control	99	1.7	0.3116	0.0203	13.5	1.5	3.93	20.20	89.1	6.7	30.5	2.4	34.2	1.1	13.2	1.6	7.3	2.9	259.5	78.2

Abbreviations: RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; WBC, white blood cell; IDA, iron deficiency anemia; HA, hemolytic anemia; PMF, primary myelofibrosis; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; ALL, acute lymphoblastic leukemia; BMI, bone marrow involvement; PRCA, pure red cell anemia; PV, polycythemia vera; AA, aplastic anemia; PCN, plasma cell neoplasm; ITP, immune thrombocytopenic purpura; CLL, chronic lymphocytic leukemia; ET, essential thrombocythemia

PP10-08

Establishment of reference intervals in Malaysia: A performance evaluation and comparison of haematological parameters between Sysmex XE5000 and XN3000

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Background : The Sysmex XN-3000 is a new automated haematology analyzer designed to improve the accuracy of cell

counts and the specificity of the flagging events. By comparing the previous Full blood count (FBC) reference intervals in Malaysia for Sysmex XE-5000, we determined a reference interval for all parameters measured by the Sysmex XN-3000 for the Malaysia population.

Method : Three hundred ninety-seven healthy adults comprising all ages, both genders and three principal races were recruited through voluntary participation. FBC was performed on the two analyzers. Qualified healthy adults were screened using questionnaire followed by determination of reference intervals, measures of central tendency and dispersion with point estimates for each subgroup.

Results : Complete data was available in 397 subjects comprising of 227 women and 170 men, which were included in the reference interval calculation. Compared to other populations there were significant differences for haemoglobin, red blood cell count, platelet count including Immature platelet fraction (IPF) in Malaysians. XN-3000 showed excellent precision and linearity results. Within- and between-run precisions, were met for all parameters tested, except for immature platelet fraction. Less than or equal to 0.5% carry-over was seen for all parameters tested. Comparison studies showed an acceptable correlation with both XN-3000 and XE-5000.

Conclusion : XN-3000 showed good analytical performance and may be a solution for laboratories with medium to high workload with evolving clinical needs. Our data also confirms the importance of population specific haematological parameters and supports the need for local guidelines rather than adoption of generalized reference intervals.

Keyword : Reference Intervals, Haematological Parameters, Sysmex XN-3000, Reference Intervals in Malaysia

PP10-09

Label-free rapid differential diagnosis of lymphocyte and leukemic blast using optical diffraction tomography

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Background : It is difficult to clearly distinguish between normal lymphocytes, lymphoblasts and myeloblasts only by morphological analysis of peripheral blood smears. However, rapid cell discrimination is essential to determine the diagnosis and treatment direction. ODT (Optical Diffraction Tomography) microscopy can capture images by reconstructing refractive index (RI) of living cells without staining. It can also measure the RI of cells as well as volume, surface area, dry mass, protein concentration, sphericity, and projected area. The aim of this study is to determine whether three types of cells can be identified through ODT microscopy.

Method : The study included residual samples from patients who had undergone medical examination and those diagnosed with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) in bone marrow examination at Asan Medical Center. Peripheral blood was collected from a total of 23 patients in EDTA tubes (BD, Franklin Lakes, NJ, USA); 8 healthy individuals, 5 ALL patients and 10 AML patients. ODT microscope (HT-1S, Tomocube Inc., Korea) was used to capture all live cells and it was completed within 24 hours after blood collection.

Results : Analysis of data from 48 lymphocytes, 100 lymphocytes, and 220 myeloblasts showed that volume, dry mass, surface area, projected area, sphericity and threshold RI were statistically significant. Most interestingly, when visualized in 3D, the nuclei of mature lymphocytes were clearly visible, but in the nuclei of leukemic blasts were not well distinguished from the cytoplasm. In the case of lymphocytes, the distinction between the nucleus and cytoplasm was clear except for 2.1%, but not in 74% of lymphoblasts and 94.5% of myeloblasts. In all three cells, the RI of the nucleus was higher than that of the cytoplasm, but in particular, the mean RI value of the lymphocyte nucleus was much higher than that of the blast nucleus ($p<0.001$).

Conclusion : This study confirmed that the three cells could only be distinguished by imaging live cells without further staining using an ODT microscope. It is generally known that during cell maturation, nuclear membrane loose plasticity and rise stiffness due to heterochromatin formation. Therefore, it is thought that blast nuclear envelope has a high plasticity than lymphocyte, result in a little difference in the mean RI value from the cytoplasm. Further study is needed to distinguish RI differences in highly proliferative malignant cells, and it would be able to differentiate leukemic cells rapidly.

Keyword : Label-Free, Optical Diffraction Tomography, Refractive Index, Lymphocyte, Leukemic Blast

Table. Comparison of parameters measured by optical diffraction tomography microscope

Parameters	Lymphocyte	Lymphoblast	Myeloblast	*P* value
No. of measured cells	48	100	220	
Volume (μm³)	320.62 ± 59.31	397.36 ± 171.55	541.74 ± 213.72	<0.001
Dry mass (pg)	45.39 ± 7.07	54.14 ± 14.90	78.25 ± 27.27	<0.001
Surface area (μm²)	279.51 ± 40.10	314.42 ± 95.25	392.89 ± 115.01	<0.001
Projected area (μm²)	64.79 ± 14.39	72.53 ± 28.85	92.22 ± 29.34	<0.001
Sphericity	0.8100 ± 0.0286	0.8226 ± 0.0269	0.8118 ± 0.0335	<0.05
Threshold RI	1.3448 ± 0.0013	1.3445 ± 0.0014	1.3445 ± 0.0015	<0.05
Mean RI	1.3610 ± 0.0039	1.3611 ± 0.0051	1.3618 ± 0.0043	0.339
Protein concentration (pg/μm³)	0.1439 ± 0.0204	0.1444 ± 0.0269	0.1479 ± 0.0226	0.335
3D visualized image				

PP10-10

Determination of reference range (Based on CLSI) leukocyte parameters for Indonesian subject

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Background : Complete blood count is a basic test required in almost all clinical cases and important for making the diagnosis. Each laboratory is recommended to establish the reference range locally due to the variation of population characteristics and geographic areas. This study aims to determine the reference range for leucocyte and differential count of leucocyte parameters in Indonesian adult subjects.

Method : This is a cross-sectional observational study. Samples were obtained from general check-up patients in Dr. Sardjito General Hospital. Blood samples were collected in K2-EDTA tubes. All samples were analyzed using automatic hematology analyzer CELL-DYN Ruby, which had been validated before. Subjects who had exclusion criteria or became outliers were removed. The reference range was analyzed using Medcalc software according to the CLSI C28-A2 recommendation.

Results : A total of 265 subjects (130 men and 135 women) aged 21 – 40 years old included in this study. There is significant differences between men and women group at the level of neutrophil, lymphocyte, eosinophil, and basophil (p< 0,05), but no significant differences at the level of leucocyte and monocyte (p> 0,05). Reference ranges for each men and women were stated respectively: Neutrophil (43,74-74,32; 48,43-77,95)x10^3 µ/L, lymphocyte (14,81-44,39; 14,05-41,54)x10^3 µ/L, eosinophil (0,25-8,49; 0,27-5,77)x10^3 µ/L, and basophil (0,26-1,73; 0,35-2,03)x10^3 µ/L. The reference range for leukocyte and monocyte were same, namely 4.54-11.15x10^3 µ/L and 3.24-9.46x10^3 µ/L.

Conclusion : This study has determined the reference range for leucocyte parameters in Indonesian adult subjects using automatic hematology analyzer CELL-DYN Ruby

Keyword : Reference interval, CELL-DYN Ruby, Leucocyte Parameters

Parameter	Number of Subjects	Mean ± SD	95%CI for mean	Median (Min-Max)	Range	2.5th-97.5th	p
Leksoit							0.0991*
- Total	242	7.849 ± 1.6852	7.636 - 8.062	7.665 (4.53 - 12.4)	4.5462-11.1520	5.008 - 11.600	
- Men	125	7.686 ± 1.6298	7.397 - 7.974	7.47 (4.53 - 12.1)	4.6977-10.8932	5.049 - 11.600	
- Women	117	8.024 ± 1.7324	7.706 - 8.341	7.93 (4.75 - 12.4)	4.6282-11.4191	4.869 - 11.600	
Neutrophil							0.0022*
- Total	240	4.791 ± 1.3492	4.620 - 4.963	4.6 (2.39 - 9.12)	1.9900-7.3712	2.630 - 7.550	
- Men	123	4.51 ± 1.1974	4.297 - 4.724	4.42 (2.39 - 7.24)	2.2245-7.2638	2.543 - 7.038	
- Women	117	5.086 ± 1.4392	4.823 - 5.350	4.81 (2.43 - 9.12)	2.0295-7.8614	2.779 - 8.631	
Neutrophil %							0.0004**
- Total	245	60.997 ± 8.2271	59.961 - 62.032	61.1 (38.8 - 79.1)	44.8719-77.1216	44.263 - 75.800	
- Men	127	59.229 ± 8.301	57.771 - 60.687	59.9 (38.8 - 75.6)	46.0593-75.4055	43.735 - 74.328	
- Women	118	62.899 ± 7.7399	61.488 - 64.310	62.25 (44.6 - 79.1)	47.7292-78.0691	48.435 - 77.955	
Lymphocyte							0.1181**
- Total	236	2.203 ± 0.5264	2.135 - 2.270	2.24 (0.977 - 3.68)	1.1709-3.2342	1.152 - 3.186	
- Men	124	2.253 ± 0.5396	2.158 - 2.349	2.305 (0.977 - 3.68)	1.2879-3.2750	1.136 - 3.218	
- Women	112	2.146 ± 0.5078	2.051 - 2.241	2.12 (1.07 - 3.28)	1.1509-3.1414	1.222 - 3.177	
Lymphocyte %							0.0093**
- Total	243	29.244 ± 6.7429	28.392 - 30.097	29.3 (13.2 - 47)	16.0286-42.4603	16.445 - 41.670	
- Men	125	30.333 ± 6.7718	29.134 - 31.532	29.8 (16.1 - 47)	17.0486-42.5886	18.100 - 44.988	
- Women	118	28.092 ± 6.5449	26.898 - 29.285	27.55 (13.2 - 41.9)	15.2638-40.9192	15.790 - 40.555	
Monocyte							0.2934*
- Total	244	0.501 ± 0.1516	0.482 - 0.520	0.481 (0.191 - 1.02)	0.1872-0.7912	0.252 - 0.821	
- Men	128	0.517 ± 0.1711	0.487 - 0.547	0.485 (0.193 - 1.02)	0.1961-0.8022	0.230 - 0.912	
- Women	116	0.484 ± 0.1251	0.460 - 0.507	0.48 (0.191 - 0.797)	0.2383-0.7287	0.269 - 0.729	
Monocyte %							0.1386**
- Total	243	6.348 ± 1.587	6.148 - 6.549	6.24 (2.38 - 10.3)	3.2379-9.4588	3.493 - 9.421	
- Men	125	6.495 ± 1.5794	6.215 - 6.775	6.47 (2.38 - 10.1)	3.5047-9.4878	3.064 - 9.344	
- Women	118	6.193 ± 1.5869	5.904 - 6.482	5.835 (2.95 - 10.3)	2.7491-9.2223	3.629 - 9.489	
Eosinophil							0.0185*
- Total	222	0.133 ± 0.08183	0.122 - 0.143	0.116 (0.004 - 0.368)	0-0.2877	0.0192 - 0.330	
- Men	115	0.145 ± 0.08459	0.129 - 0.161	0.124 (0.004 - 0.368)	0.03652-0.2228	0.0205 - 0.343	
- Women	107	0.119 ± 0.07694	0.105 - 0.134	0.103 (0.015 - 0.331)	0-0.2669	0.0191 - 0.288	
Eosinophil %							0.0063*
- Total	224	1.713 ± 1.0195	1.579 - 1.847	1.585 (0.02 - 4.6)	0-3.6363	0.300 - 4.074	
- Men	115	1.879 ± 1.016	1.691 - 2.066	1.73 (0.02 - 4.6)	0.3416-3.0027	0.262 - 4.009	
- Women	109	1.539 ± 0.9984	1.349 - 1.728	1.29 (0.2 - 4.37)	0-3.4459	0.301 - 3.988	
Basophil							0.2001*
- Total	242	0.0744 ± 0.0257	0.0712 - 0.0777	0.072 (0.027 - 0.153)	0.02407-0.1248	0.0321 - 0.138	
- Men	128	0.0774 ± 0.02843	0.0724 - 0.0824	0.073 (0.027 - 0.153)	0.02616-0.1172	0.0331 - 0.142	
- Women	114	0.0711 ± 0.02187	0.0670 - 0.0751	0.0715 (0.03 - 0.125)	0.02822-0.1140	0.0311 - 0.114	
Basophil %							0.0065**
- Total	236	0.932 ± 0.2924	0.895 - 0.970	0.906 (0.281 - 1.8)	0.3216-1.4810	0.410 - 1.666	
- Men	125	0.981 ± 0.3263	0.923 - 1.039	0.934 (0.281 - 1.8)	0.3920-1.4266	0.453 - 1.724	
- Women	111	0.878 ± 0.2386	0.833 - 0.923	0.881 (0.352 - 1.4)	0.4102-1.3454	0.397 - 1.367	

PP10-11

Blood smear pitfall of platelet count confirmation examination: A case study

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Background : Manual platelet estimation is one of the methods used when automated hematology analyzer result showed that platelet counts are very low or very high. Confirmation is necessary to ensure the results issued by the automatic blood counts. Some recommendations recommend using a blood smear that is stained with Wright-Giemsa stain. This case shows the failure of this stain in detecting platelets

Method : This case shows the discrepancy between the results of examining platelet numbers using an automated hematology analyzer with a manual method with blood film stained with Wright-Giemsa stain. Automated hematology analyzer used are Sysmex XN-1000, Sysmex XN-550, Ruby, and ADVIA 2120. Examination conducted using appropriate tool usage instructions. The manual technique used are painting wright and platelet count manually with Rees Ecker method.

Results : A 34-year-old female patient came to Dr. Sardjito Hospital to carry out surgery. The patient's blood is drawn for surgery. The complete blood count results with Sysmex XN-1000 showed a platelet number of 572 x 10^3 cells / µL. Peripheral blood films were obtained and stained with Wright-Giemsa stain. The results obtained

an estimate of 76 x 10^3 cells / μL. This discrepancy is then followed up by repeated checks with another hematology analyzer, Ruby. The results obtained value 566 x 10^3 cells / μL. Repeated blood smears were performed to ensure manual results. The results obtained are similar values that are 88 x 10^3 cells / μL. Examination using Sysmex XN-550 showed 543 x 10^3 cells / μL. Confirmation of the results is done using another hematology analyzer Advia 2120 at the same time to see the function of other platelets. The results obtained value of 513 x 10^3 cells / μL. Manual calculation using the Rees Ecker method yields a platelet count of 599 x 10^3 cells / μL.

Conclusion : The difference in these results is possible because the Wright-Giemsa stain is not able to enter and color all platelets. The results of hematology analyzer showed conformity to the platelet manual calculation method with the Rees Ecker Technique

Keyword : Automatic Hematology Analyzer, Platelet, Discrepancies, Rees Ecker

PP10-12

Effectivenes of quality assessment program for blood smear examination

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Background : Blood smear analysis is one of the most basic testing methods and is used widely around the world. It is an essential tool for diagnosis and management of various hematological disorders, among others. On the world, External Quality Assessment Scheme (EQAS) for blood smear examination has been widely deployed, especially in Europe. However, in Viet Nam, there is still no unification about the technique and results, especially at provincial hospitals and private health laboratories. Therefore, if we do not have quality control system, error is possible. To develop a laboratory quality system, the Ministry of Health has issued regulations that require laboratories to control their quality through internal and external quality control. External quality assessment is the assessment of laboratory quality in a schematic way through an external agency by using material of known value but undisclosed results. It measures the accuracy of the results, detects the error, defines the cause, corrects the error. In additions, EQA also brings many benefits to laboratories, clinicians, patients as well as regulatory and legal agencies.

Method : Describe series of intervention/adjustment cases.
Step 1: Conduct quality control, evaluate the uniformity and stability of the external control samples before sending to the participating laboratories.
Step 2: Each participating laboratory will receive 2 samples (EH01 and EH02)
Step 3: Randomly group the laboratory
Step 4: Collect result table to evaluation statistics.
Step 5: Statistics the percentage of matching results of the white blood cell EH01 sample based on z-score, then classify the laboratory, filter out inconsistent results of the laboratories, impact monitoring and intervention assistance (EH01).
Step 6: Evaluate results of EH02 sample about red blood cell morphology and platelets against the standard value, then, filter out inconsistent results of the laboratories, impact monitoring and intervention assistance.
The standard value is determined based on the uniformity results of advisory board, the central specialist and the laboratories participate in the interlaboratory comparison. We do not use a general consensus from participating laboratories because it leads to systematic bias in the evaluation of results where the majority of laboratories misjudge the same morphological index or percentages cell.

Results : Evaluation of leukocyte series results: the percentage of results achieved of leukemia components increased gradually from 89.29% to 90.48% at the end of 2018 and reached completely in cycle 1 of 2019. Assessing the results of erythrocyte series results: the ratio of the results of increase and decrease is not stable over the first 4 cycles but by the end of 2018 this rate has a positive improvement and achieved completely in cycle 1 of 2019. Evaluation of platelet series results: the proportion of consistent results increased or decreased unstable over the first 4 cycles and has a positive improvement in cycle 1 of 2019.

Conclusion : Compared with the supportive impact of the program, the results of the peripheral blood smear had improved and improved, the rate of "very good" rating increased (increased to 14.29% after 6 cycles and 26.32% in the first cycle of 2019), the rate of "failing" rating dropped sharply (to 9.52% after 6 cycles and 0% in the first cycle of 2019).

Keyword : Peripheral Blood Smear, Exterior Control, Quality Control, Blast

PP10-13

A meta-analysis on the role of the -308 G/A polymorphism of the TNF-α gene with malaria susceptibility

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Background : Previous studies have focused on the effect of the -308

G/A polymorphism of the TNF-alpha gene on the development and severity of malaria. However, the results obtained were varied and conflicting. This meta-analysis was conducted to further elucidate the role of the said polymorphism on malaria susceptibility.

Method : A literature search for relevant studies written in English was conducted in Pubmed using the key terms "TNF-alpha gene," "polymorphism," and "malaria" as of April 11, 2020. Obtained from the included studies were case-control data, genotypic frequencies, and other pertinent information. Pooled odds ratios (OR) and 95% confidence interval (CI) were computed using Review Manager 5.3. Subgroup analysis was also performed based on the type of malaria and the genotyping method used.

Results : Six studies, providing a total of 1321 participants (676 with malaria and 645 without malaria) were included in this meta-analysis. With the removal of one outlier study after analysis using Galbraith's plot, results showed homogeneity in the genotypic and allelic models and identifying significant associations for the co-dominant (OR: 0.31; 95% CI: 0.14-0.69; p=0.004) and recessive (OR: 0.25; 95% CI: 0.12-0.54; p=0.004) models. Similar observations were also noted for subgroup outcomes in terms of the type of malaria, studies within the HWE, and the method used for SNP determination.

Conclusion : Our meta-analysis suggests that -308 G/A SNP in the TNF-α gene reduces an individual's susceptibility to malaria. Though these findings are promising, additional studies are needed to confirm and establish the results of the research in order to better understand the development and pathogenesis of malarial infections.

Keyword : Malaria, -308 G/A Polynorphism, TNF-Alpha, Meta-Analysis

PP11-01

Hemoglobin polygenic risk score as a tool in elucidating the causal role of elevated iron status on cardiometabolic outcomes in Taiwan Han Chinese

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Background : Epidemiological studies have implicated elevated iron levels with higher risk and onset of cardiometabolic diseases presumably via production of free radicals and oxidative stress. Cardiometabolic syndrome (CMS) is a disease entity mainly characterized by insulin resistance, impaired glucose tolerance, dyslipidemia, hypertension, and central adiposity - all of which can lead to major cardiovascular events. There has been a continuous increase in the prevalence of CMS in both men and women in all age groups globally due to genetic susceptibility and environmental risk factors. However, it is not completely clear whether iron homeostasis causally influence its development and progression.

Method : In this study, we carried out Mendelian Randomization (MR) analyses in determining the causal effect of iron excess in predicting the risk for CMS and cardiovascular and metabolic outcomes among the Han Chinese of Taiwan. With the use of Taiwan Biobank (TWB) data that comprised of complete genetic, physical, biomedical, and health information of around 70,000 adult participants, we constructed gender-specific polygenic risk scores from hemoglobin-associated SNPs (i.e., Hb-GRS) and utilized them as instrumental variables for iron status in risk prediction.

Results : Ninety-two (92) and 96 SNPs were used as genetic instruments for Hb in male and female Taiwan Han Chinese, respectively. The corresponding mean calculated Hb-GRS were 0.033 and 0.025 g/dL. In our MR analyses, we found modest evidence to support the causal association between tertiles of Hb-GRS and risks for (1) elevated triglyceride and hypertriglyceridemia, (2) high diastolic blood pressure and hypertension, (3) impaired fasting blood sugar and diabetes mellitus, (4) combined overweight and obesity,(5) hyperuricemia and gout, and (6) CMS ($p<0.05$) using multivariate logistic regression models. However, we did not detect any statistically significant associations with cardiovascular events in general using initial data, which warrants further investigations.

Conclusion : Our findings confirm the role of elevated iron levels in the pathophysiology of metabolic dysfunctions among the Han Chinese of Taiwan. Our future works will include the conduct of sensitivity analyses and cross-validation in a different ethnic group (i.e., UK Biobank data).

Keyword : Hemoglobin, Iron Status, Genetic Risk Score, Mendelian Randomization, Cardiometabolic Syndrome, Taiwan Han Chinese

PP11-02

Association of the V736A polymorphism in the TMPRSS6 gene with the risk of developing iron deficiency anemia: A meta-analysis

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Background : Iron deficiency anemia is considered as the most common type of anemia worldwide. It is mostly associated with a decrease in dietary iron intake, malabsorption, and chronic bleeding. Several studies suggested that mutations in the TMPRSS6 gene affect hepcidin, the body's iron-regulating hormone, which may lead to anemia. The present study was undertaken to evaluate the possible correlation of the V736A polymorphism in the TMPRSS6 gene with the development of iron deficiency anemia.

Method : The key terms "TMPRSS6", "polymorphism," and "iron deficiency anemia" were used in conducting the electronic search for potential studies in PubMed. Selected data regarding the genotypic and allelic frequencies of the target polymorphism, as well as other general information on the participants, were extracted from the included studies. Data analysis was subsequently performed using Review Manager 5.3. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed using either the fixed- or random-effects model.

Results : A total of 3105 participants (1544 cases/1561 controls) from five studies were included in the meta-analysis. Pooled ORs using the random-effects model indicate that the presence of the V736A polymorphism in the TMPRSS6 gene is associated with the risk of developing iron-deficiency anemia in the dominant model after removing outlier studies and those studies that deviated from the Hardy-Weinberg equilibrium. Other models of the analysis showed no significant association. Our results suggest that the presence of the polymorphism is correlated with an increased risk of developing IDA.

Conclusion : To our knowledge, this is the first meta-analysis conducted to determine the association of the V736A polymorphism in the TMPRSS6 gene as a risk factor in the development of iron deficiency anemia. Generally, our results suggest that the presence of the mutant variants of the polymorphism is associated with a higher risk of developing iron-deficiency anemia. Further studies among the Filipino population may be done to confirm the applicability of these findings in our population.

Keyword : TMPRSS6 Gene, V736A Polymorphism, Iron-Deficiency Anemia, Meta-Analysis

PP11-03

Sickle cell anemia: A risk factor for craniofacial abnormalities and dental malocclusion– A systematic review

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Background : Sickle cell anemia (SCA) is an autosomal recessive hemoglobinopathy predominant among Afro-descendants, and has been categorized as a public health issue as it affects a significant percentage of the world's population expansion. The phenomenon of red cell sickling decreases the plasticity of erythrocytes reducing their ability of diapedesis and resulting in increased blood viscosity and consequent vascular occlusion, causing ischemia and local infarction. Malocclusion in sickle cell disease patients is due to Bone marrow hyperplasia, and compensatory expansion of medullar spaces manifest as mid face protrusion and maxillary expansion. The most common craniofacial bone abnormalities are turricephaly, jaw protrusion and the formation of a large trabecular pattern. They can determine the existence of dental malocclusion and the developmental of abnormalities of the teeth and arches, which cause aesthetic discomfort in the mildest cases and functional disorders or disabilities, in the most severe cases.

Method : PubMed, EBSCO, COCHRANE and Google Scholar were searched for articles published between 1980 and 2020 with keywords malocclusion, Maxillofacial Abnormalities, and Angle Class I, Angle Class II and Angle Class III malocclusions in association with sickle cell disease. Initially 106 articles were downloaded from which 13 articles were selected according to the inclusion criteria (only English language articles with full text available). Screening of all the articles was performed by a single examiner who initially read the abstracts and then for selected abstracts full text was screened. The data, including information on authorship, year of publication, study site, study design, purpose, sampling technique, sample size, ethnical background, age, method of orthodontic diagnosis craniofacial bony changes and malocclusion were tabulated. For the selected 13 articles; relevance was determined by examining the title and abstract of the articles and were assessed using STROBE checklist. Articles scored more than 18 points on STROBE checklist were included in the study for analysis.

Results : The most common craniofacial bone abnormalities in SCA individuals reported in the literature were maxillary protrusion, overjet, overbite, spacing of the previous segment in both arches, retrusion of mandible and large trabecular bone. Increased over jet among sickle cell disease population had been reported in studies as one of the most common malocclusion traits. Another significant aspect found in this review is that there was a higher prevalence of Blacks with SCA. This can be attributed to selection bias, as the samples of all the selected studies were mostly composed of Afro-Brazilians.

Conclusion : It was concluded that despite the high frequency of craniofacial bone abnormalities and malocclusion among patients with sickle cell anemia with sufficient scientific proof that this disease causes malocclusion. It is recommended that SCA patients should have access to orthodontic treatment associated with phonoaudiologic support in order to alleviate or prevent these conditions. These results suggest a need for public health policies in relation to the implementation of community programs for early diagnosis and appropriated treatment of dental malocclusion in this population, in order to provide a better quality of life to these individuals, who already suffer due to their disease.

Keyword : Malocclusion, Craniofacial Abnormalities, Sickle Cell Anemia, Orthodontics, Phonoaudiologic

PP11-04

The prevalence of thalassemia in Bangladesh: Evidence from a molecular study

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Background : Thalassemia, a common autosomal recessive blood disorders widely scattered around the world and Bangladesh as well. Approximately, 3% of people in Bangladesh are carriers of β-thalassemia while almost 4% of people are suffered from HbE-β-thalassemia. Unfortunately, a huge number of people of Bangladesh do not have any prior knowledge about the genetic basis of this disorder. This study updates and expands an earlier profile of β-thalassemia mutations among the Bangladeshi population.

Method : A simple polymerase chain reaction (PCR) approach and flow-through hybridization technique were designed and performed to investigate β-thalassemics. A total of 40 patients samples were tested.

Results : Four common mutations were detected finally, while IVS I–5 (G>C) were in the top, accounting for (60%), Cd 26 (G>A)/HbE (27.5%), Cd 41/42 (–TTCT) & -28 (A>G) found the least common mutation in this study, both were (2.5%). Moreover, some mutations were still uncharacterized (7.5%) finally.

Conclusion : It is not possible to uproot β-thalassemia completely but may possible to reduce the percentage of spreading to generation to generation through out the population. The findings of this study may help the government and policy-makers of Bangladesh to create public awareness; as a result, the percentage of thalassemic patients will be reduced in the near future.

Keyword : β-thalassemia, Bangladesh, Polymerase Chain Reaction, Mutation

PP11-05

A comprehensive study of prevalence and distribution of anaemia among OPD patients visiting Integral Institute of Medical Sciences Research & Hospital, Lucknow

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Background : Studies have also shown an association between nutrition, education and family income with anaemia. Education influences not the only the outcome of anaemia but also influences the attitude about anaemia. Studies have shown that educated parents are more likely to be aware of the causes and consequences of nutritional anaemia. It has been found that women who have children and women who are working have more awareness about the nutritional anaemia and subsequently are found to be more health-conscious. Socio-demographic factors like education, type of family, parity, spacing and different trimesters significantly determine maternal anaemia. Anaemia is a major public health problem affecting economic and social development. WHO defines anaemia as haemoglobin concentration <12gm/dl in females and 13 gm/dl in men. Anaemia is multifactorial with widespread negative consequences on health. It is more common in developing countries. It has a negative influence on the social and economic development of the country. Thus need of the hour is to work on programs which look beyond the traditional approach of evaluating the effectiveness of programs in terms of increase in life expectancy or disability-adjusted life years. Since anaemia is multifactorial and also includes socio-demographic factors, thus it is important that a holistic and inclusive approach be followed. Results of a recent study show a high prevalence of anaemia in Lucknow. Prevalence of anaemia is an indicator of poor nutrition and health. It has the potential to negatively affect the social and economic development of the Nation. Keeping in view the public health importance of anaemia, its consequences and long term health effects the present study was undertaken. The objective was to analyse the burden of anaemia in subjects belonging to various socioeconomic and education class.

AIMS

1. To find out the prevalence of anaemia in patients visiting the different OPDs of IIMS&R.
2. To study causative factors of anaemia which may be socioeconomic, demographic or environmental.
3. A detailed analysis of socioeconomic, demographic and environmental factors affecting anaemia patients

Method : The present study was a cross-sectional study conducted between January to June 2017 in the Department of Physiology and the various OPD'S of Integral Institute of Medical Sciences and Research, Lucknow. 385 subjects were enrolled from various OPD'S of Hospital after following inclusion (18-60 years of age, those attending OPD and willing to participate in the study) and exclusion criterion (anaemic patients already taking medication, not giving consent, suffering from chronic diseases, less than 18 years of age and greater than 60 years of age and pregnant females). Blood Samples were collected under the aseptic condition from the various OPD's by using a disposal syringe in an EDTA vial. The samples were analysed using Automated Analyser (Beckman Coulter) in the central pathology lab of IIMS&R, Lucknow. The study was approved by Institutional Research and Ethical Committees 385 subjects of 18-60 years, attending various OPD'S of Medicine, Surgery, Orthopaedics, ENT of Integral institute of Medical Sciences and Research, Lucknow were included. A detailed clinical history including age, gender, socio-economic status, education and type of diet, was elicited from the patient and they were made to undergo relevant investigations. This study included 211 anaemic and 174 non-anaemic subjects. Age, gender, socioeconomic status, dietary habits and education was enquired about and

haematological parameters were analysed. Data were analysed using appropriate tests. Statistical Analysis The data were analysed using the Statistical Package for Social Science software (21.0). Statistical tests Chi-Square and unpaired t-test were used to analyse the data. p-value <0.05 was taken as significant.

INCLUSION CRITERIA

1) Subjects attending IIMSR OPDs
2) Subjects willing to participate in the study.

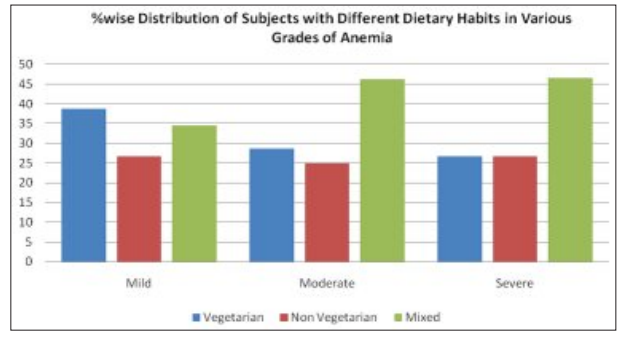
EXCLUSION CRITERIA

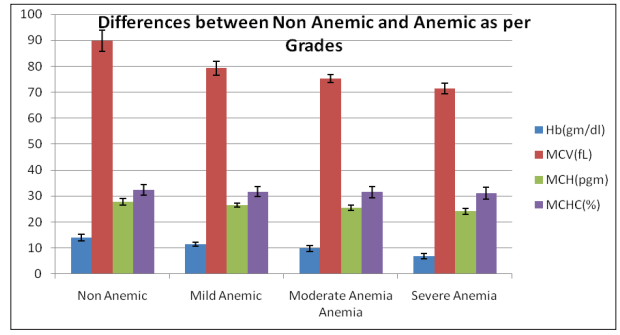
1) Anaemic patients on medication
2) Subjects not giving consent
3) Subjects suffering from chronic diseases
4) Subjects less than 18 and greater than 60 years of age.
5) Pregnant females

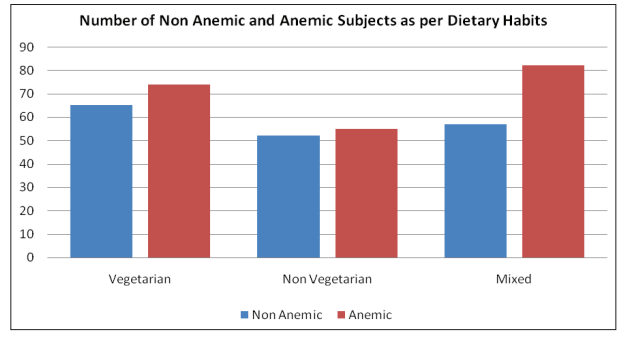
Results : Out of 385 subjects, 211(54.80%) were anaemic and 174(45.20%) were non-anaemic. Mean age of the anaemic group was 34.32 ±12.65 years and that of the non-anaemic group was 32.72 ±12.63 years. The difference was statistically non - significant at p=0.217 54.8% of patients attending OPD's were found to be anaemic. It was higher in females (65%) than males (41.2%). As per WHO classification, mild, moderate and severe anaemia was present in 54.98%, 37.91% and 7.11% subjects respectively. 63.99% anaemic subjects belonged to upper to the middle class and 36.01% belonged to the lower-middle and lower class. Anaemia was higher in subjects belonging to the middle to lower classes and those belonging to low education class like high school to illiterate class. Not much difference was found on the basis of dietary preferences. However, the percentage of anaemic subjects with mixed dietary habits was slightly higher. Out of a total of 385 subjects, anaemia was present in 211 i.e. 54.8% and absent in 174 i.e.45.2%. 68/165(41.2%) males and 143/220(55%) females were anaemic. Similarly, 97/165(58.85) males and 77/220(35%) females were non-anaemic. Out of a total of 211 anaemic patients, 68/211(32.23%) were males and 143/211(67.77%) were females. Similarly, out of a total of 174 non-anaemic patients, 97(55.75%) and 77(44.25%) were males and females respectively) Amongst the anaemic group, 116/211(54.98%) had mild anaemia, whereas 80/211(37.91%) and 15/211(7.11%) subjects had moderate and severe anaemia respectively. The difference between haematological parameters between the non-anaemic and anaemic group as per grades was found to be statistically significant. Out of total of 385 subjects mild, moderate and severe anaemia was present in 116(30.13%), 80(20.78%) and 15 (3.90%) subjects respectively). Out of total of 165 male subjects, mild and moderate anaemia was present in 47(28.50%) and 21(12.73%) subjects respectively. Similarly, out of total of 220 females mild, moderate and severe anaemia was present in 69(31.36%), 59(26.82%) and 15(6.82%) females respectively. Out of total 116 mild anaemic subjects, 47(40.52%) were males and 69(59.48%) were females respectively. Similarly, 21/80(26.25%) males and 59/80(73.75%) females were having moderate anaemia. All the patients with severe anaemia were found to be females i.e. 15/15(100%). The difference was significant between males and females when haematological parameters namely Hb, MCV, MCH and MCHC were compared (p<0.001).

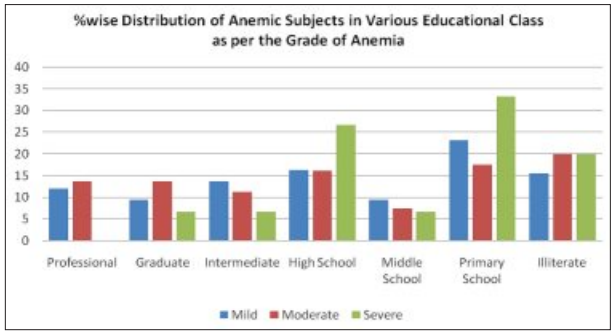
Conclusion : In the present study percentage of vegetarian, non-vegetarian and mixed dietary habit subjects in the non-anaemic group were found to be 37.36%, 29.88% and 32.76% respectively. In anaemic group 35.07% subjects were vegetarian, 26.07% were non-vegetarian and 38.86% subjects were of mixed dietary habit. Generally, education, culture and family practices influence dietary habits. Dietary preferences may also change over a period of time. Dietary patterns are influenced by older siblings (not in a positive manner) and the education of their grandparents as well as their parents. Anaemia is more common in females than in males. Advancing age also makes the subject prone to anaemia by causing and hormonal imbalance in the body apart from other factors. Low socioeconomic status and low education are also risk factors as they directly or indirectly influence the awareness about health and hygiene and make the subject more vulnerable to risk factors. Dietary preferences also influence the prevalence of anaemia.

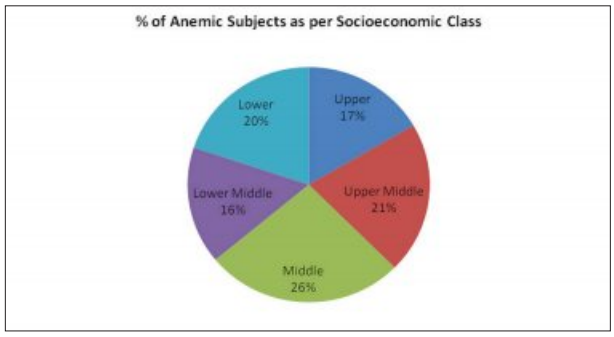
Keyword : Anaemia, Demographic, Socioeconomic, Nutrition, Education, Environmental











PP11-06

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 questionnaire 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=0.0000)

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 : Iron Deficiency Anemia, Knowledge Attitude Practices, Filipino Teens

PP11-07

The characteristics of anemia among patients with diabetic foot infection admitted to Dr. Hi. Abdul Moeloek General Hospital, Lampung, Indonesia

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Background : Foot infection is a common and serious complication that may affect patients with diabetes mellitus. All comorbidities affecting wound healing must be identified and promptly managed for optimal outcomes. This includes the identification and management of anemia. This study aims to assess the prevalence of anemia in Dr. Hi. Abdul Moeloek General Hospital, Lampung, Indonesia.

Method : This study is a cross-sectional study with retrospective method. Laboratory data of DFI patients admitted to Dr. Hi. Abdul Moeloek General Hospital in 2017-2019, which met the inclusion criteria, was taken from medical records. Anemia is defined as a Hb level of below 12 g/dL.

Results : 79 patients had DFI and were included in this study. The mean hemoglobin (Hb), red blood cell (RBC) count, and mean corpuscular volume (MCV) were 9.40±1.76 g/dL, 3.35±0.65 million/mm3, and 82.93±5.29 fL, respectively. The median of erythrocyte sedimentation rate (ESR) and random blood glucose level was 63.04 mm/h and 233 mg/dL, respectively. 75 (94.9%) of the patients had anemia. Among the patient with anemia, 12 (15.2%) had mild anemia, 45 (57%) had moderate anemia, and 18 (22.8%) had severe anemia. Based on MCV value, 19 (25.3%) had microcytic anemia, and 56 (74.7%) had normocytic anemia. There was a negative correlation between Hb (p=0.001) and RBC count (p=0.001) with ESR.

Conclusion : Anemia is a prevalent problem in subjects with DFI. Identification of the exact cause and prompt treatment of the anemia is crucial to achieve optimal outcomes for DFI patients.

Keyword : Anemia, Diabetes, Diabetic Foot Infection, Hemoglobin

PP11-08

Protein, iron, and vitamin C intake with anemia in adolescent girls in Yogyakarta city

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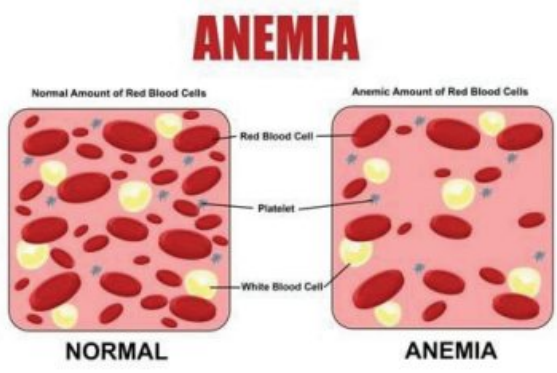
Background : Adolescent girls are a population at risk for iron deficiency due to an increased need for iron in its infancy. The high prevalence of anemia among adolescents will continue into adulthood if not treated properly. Anemia contributes greatly to maternal mortality, premature birth, and low birth weight infants. This study is conducted to determine the correlation of protein, iron, and vitamin C intake with anemia incidence in adolescent girls in Yogyakarta City.

Method : This research is an analytic survey research with a cross-sectional study design. The subject is adolescent girls aged 12-18 years in Yogyakarta. Measurement of hemoglobin level, MCV, MCH, and MCHC were measured using Hematoanalyzer KX-21 with Sodium Lauryl Sulphate method. Protein, iron, and vitamin C intake were measured using the Semi Quantitative-Food Frequency Questionnaire (SQ-FFQ) of the last three months.

Results : The prevalence of anemia among adolescent girls in this study was 13.13%. 45.96% of adolescent girls have lower protein intake; 54.5% lower vitamin C intake; 86.36% lower iron intake. In this study there was no significant correlation between protein intake with anemia incidence in adolescent girls of Yogyakarta (OR 1.439; CI 95% 0.638-3.242); P=0.386), there was no significant correlation between iron intake with the incidence of anemia (OR 4.452; CI 95% 0.577-34.30; P=0.152), there was no significant correlation between vitamin C intake with the incidence of anemia in adolescent girls of Yogyakarta (OR 2.05; CI 95% 0.862-4.860;P=0.106).

Conclusion : The intake of adolescent girls is low, so education at schools about balanced nutrition and breakfast habits is required. For adolescents, it is necessary to increase iron consumption, especially during menstruation and the collaboration between the school, the education office and the health department, such as making posters about nutrition and healthy food at schools.

Keyword : Protein, Iron, Vitamin C, Adolescent, Anemia, Yogyakarta



PP11-09

Screening of MT-CO3 gene mutations for sickle cell anaemia in tribes from Tamil Nadu, South India

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Background : Sickle Cell Anaemia (SCA) is a blood disorder commonly occurring in people. In this condition, the number of red blood cells decreases and their oxygen-carrying capability becomes inadequate to meet the physiological desires of the body. It has both environmental and genetic risk factors. The abnormal hematologic parameters in anemic patients lead to many disorders in mitochondrial genome. MTCO3 or mitochondrially encoded cytochrome c oxidase III gene is located in the respiratory complex IV. Hence the aim of this study is to evaluate the mitochondrial DNA (MT-CO3) influence on SCA, among tribal population in Tamil Nadu.

Method : Totally 40 blood samples were collected from tribal population of Tamil Nadu, including 20 SCA patients and 20 healthy people. Mitochondrial DNA was isolated, after which PCR and Sanger sequencing has been conducted on the MTCO3 gene.

Results : DNA sequence analysis showed mutation in MTCO3 gene in SCA subjects. The T9540C mutation in MTCO3 gene was detected in nine tribal people from the SCA subject group. In mutated individuals, Thymine (T) nucleobase is replaced by Cyanine (C) nucleobase in the base position 9540 of MTCO3 gene.

Conclusion : To the best of our knowledge this would be the first of its kind study to be conducted in Tamil Nadu, were the tribal population with SCA were analysed. Further studies should be carried out using advanced molecular techniques in genetic research to study the exact reasons behind genetic variation and also to find the genetic pattern in SCA from the tribal population of Tamil Nadu, South India.

Keyword : Sickle Cell Anaemia, MT-CO3 Gene Mutations, Tribes, Sanger Sequencing

PP11-10

Identifications of β-globin gene mutations among the sickle cell anaemia patients from the tribes of Coimbatore, Tamil Nadu

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Background : Sickle Cell Anaemia (SCA) is a common blood disorder which occurs in people of all age group. In this condition, the amount of oxygen becomes inadequate to meet the physiologic desires of the body due to decreased number of Red Blood Cells (RBCs). Low haemoglobin (Hb) concentration or iron deficiency is the most common cause of SCA. Human haemoglobin, a tetramer containing two α globins and two β globins, is responsible for oxygen transportation in the body. SCA disease is one of the most common autosomal recessive disorders caused by mutations in the β-globin gene. Hence the aim of this study was to evaluate the β-globin gene mutations and its influence on SCA disease, among tribal population in Tamil Nadu.

Method : For the present study, totally 40 samples were recruited from various tribal populations in Tamil Nadu. Blood samples from 20 SCA patients and their age and sex matched 20 controls were obtained from the study area. In this study, DNA was extracted and PCR was performed on β-globin gene. The PCR amplified products were gel purified and sequenced to analyse for any specific mutations.

Results : Higher degree of β-globin gene mutation was prominent in the SCA subjects than compared to the controls. We found that 11 SCA patients had similar type of mutations (T<C) at the 753 region of the β-globin gene. This had proved that transitions of nucleotides in β-globin gene could be a causative agent for this disease.

Conclusion : Thus, the present study concludes that mutations in β-globin gene may contribute to the inter – individual susceptibility to SCA disease, but the present study is the first to evaluate the mutation frequency of this gene in Coimbatore patients. This study serves as a basis for much needed future research on SCA.

Keyword : Sickle Cell Anaemia, β-Globin, Sanger Sequencing, Tribal Population

PP11-12

Risk factor for anemia in infancy: A literature review

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Background : Prevalence of anemia among infants is still high especially in developing countries. Long term consequences of anemia in infancy has been shown to delay cognitive and psychomotor development. Therefore, the objective of this study was to identify the risk factors for anemia in infants.

Method : The method used in this study is literature review by taking journals that have been published online consisting of Indonesian and English journals. The criteria for sampling were in accordance with the key words, namely "anemia", "risk factor", "infant", and "children". The inclusion criteria were primary research, English, Indonesian, and publications in the last 10 years. There are 15 articles as the final article for further analysis.

Results : Risk factors causing anemia in infants were infants who did not receive exclusive breastfeeding, infections (malaria. diarrhea), socioeconomic status (low family income, crowded living conditions, parent education), mother's nutritional status (maternal anemia status), addition of infant formula, minimum feeding frequency, formula milk feeding, malnutrition, Low birth weight, more siblings, age, vitamin A insufficiency, stunting, source of drinking water, and inappropriate complementary food introduction significantly increased the risk for infant.

Conclusion : Suggestions for the community health centers in the area to Improving the quality of health centers ANC primarily related to maternal nutrition during pregnancy to prevent maternal anemia that can affect newborn anemia.Beside that, need to regularly check the anemia status of the infant.

Keyword : Anemia, Infant, Risk Factor

TITTLE	RESULT
Prevalence and risk factors of anemia among children aged 6-23 months in Huaihua, Hunan Province	Mother and father of Miao ethnicity (OR = 1.23 and 1.31), diarrhea in the previous 2 weeks (OR = 1.35), breastfeeding in the prior 24 h (OR = 1.50), and caregivers able to identify the optimum timing of complementary feeding (OR = 1.15) had positive correlations with anemia.
Risk factors for anemia in infants aged 6-12 months from rural areas of southern Shaanxi Province, China	Breastfeeding after birth (lack of scientific supplementary food) increased the risk of anemia in infants (OR=1.768, P<0.01). Addition of supplementary food which met the criteria for minimum feeding frequency recommended by WHO (OR=0.779, P<0.05) and formula milk feeding (OR=0.658, P<0.01) were protective factors against anemia in infants.
Anemia, malnutrition and their correlations with socio-demographic characteristics and feeding practices among infants aged 0-18 months in rural areas of Shaanxi province in northwestern China: a cross-sectional study	Anemia was significantly associated with malnutrition (underweight, OR: 2.42, 95%CI: 1.50-3.88; stunting, OR: 1.65, 95%CI: 1.05-2.61; wasting, OR: 2.89, 95%CI: 1.45-5.76). Low birth weight, more siblings, less maternal education, low family income, crowded living conditions, and inappropriate complementary food introduction significantly increased the risk for infant anemia.
Anemia and feeding practices among infants in rural Shaanxi Province in China	We find that children still breastfed over 6 months of age had lower Hb concentrations and higher anemia prevalence than their non-breastfeeding counterparts (p < 0.01), and that children who had ever been formula-fed had significantly higher Hb concentrations and lower anemia prevalence than their non-formula-fed counterparts (p < 0.01).
Stunting and anemia among children 6-23 months old in Damot Sore district, Southern Ethiopia	Independent variables of anemia were early initiation of complementary feeding (AOR = 2.96, 95% CI: 1.23-4.85), poor dietary diversity (AOR = 2.95, 95% CI: 1.78-4.91), poor breast feeding practice (AOR = 2.94, 95% CI: 1.63-5.32) and stunting (AOR = 3.65, 95% CI: 2.15-6.19)

PP11-13

Compliance of consuming iron tablets and anemia cases in pregnant women

Nuraliah Nuraliah

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Background : Anemia is biggest public health problem in the world, especially the group of women reproductive age. Nearly half or as many as 48.9% of pregnant women lack of blood or anemia based on Basic Health Research data 2018. Giving iron tablets is one of the government's efforts in preventing and controlling anemia and it is expected that pregnant women can consume more than 90 iron tablets during pregnancy. However, the high number of not

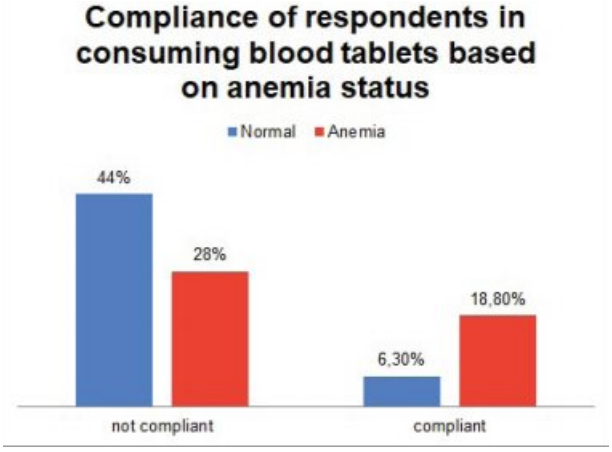
compliant of pregnant women consuming iron tablet is also still a problems faced in Indonesia.

Method : This cross sectional study was conducted using an online questionnaire. The questionnaire was distributed online to the group of pregnant women. The number of samples was 31 pregnant women chosen by convenience. The analysis used is univariat and bivariat using distribution tables.

Results : Most (65%) of gestational age were in the third trimester with an average Hemoglin level of 10.9 grams /dl. The lowest hemoglobin level was 8.1 gram / dl. Based on compliance of onsuming iron tablet, pregnant women who are not compliant were 26% and pregnant women who have anemia with Hb levels <11 grams / dl that was 48%. Pregnant women who are not compliant in consuming iron tablets and have anemia which is 23%.

Conclusion : 2 out of 10 pregnant women has anemia with non-compliant behavior in consuming iron tablets. Intervention among pregnant women is needed to encourage compliance to consume iron tablets to prevent anemia.

Keyword : Anemia, Compliance, Iron Tablet, Pregnant Women



PP11-14

Coping strategy in preventing anemia: Case study of Indonesian pregnant women on WhatsApp groups

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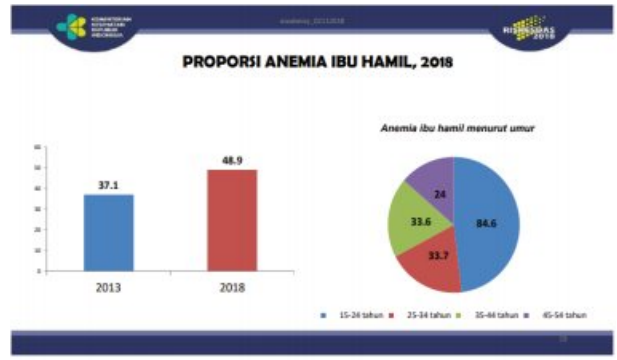
Background : Pregnant women is one of a sufferer of anemia in Indonesia. Based on Riskesdas (Basic Health Research) in 2018, pregnant women cases were 48.9 %. This study aims to learn the behavior of the pregnant women in preventing anemia by exploring Orami groups (community of pregnant women from variuos provinces in Indonesia on social media). The authors learned the ways and motivations of pregnant women to protect and prevent the anemia.

Method : This study used a qualitative method with nethnographic approach. The authors collected data through observation and documentation on social media especially in WhatsApp Groups of Orami, where there are approximately 300 persons following and joining in these groups. The authors also did in dept interview to some of group members to know how coping strategies of them in preventing anemia during pregnancy.

Results : The results of this study indicated that; 1) The coping strategies of pregnant women in preventing anemia used more treatments. They use both modern medicine and traditional medication. 2). Personal health behavior of them was influenced by the communication each other, where they support each other by asking and sharing informations about how to prevent anemia and use alternative medical treatments like taking and consuming herbs.

Conclusion : Communication on social media how to enhance hemoglobin (HB) was one of the coping strategies of pregnant women. The experience and knowledge of member groups became an important element to them to prevent anemia.

Keyword : Anemia, Coping Strategies, Pregnant Women



PP11-15

Relationship of economic status with the occurrence of anemia in the third trimester of pregnant women at Caile Health Center, Bulukumba Regency, South Sulawesi

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Background : Anemia in pregnancy is an indicator of poor health where inadequate food intake is based on family income. This

study aims to look at the relationship of economic status with the incidence of anemia in the third trimester of pregnant women.

Method : This research uses an analytic design with a cross-sectional approach. The target population in this study were all of the pregnant women in the Caile Region. The sample in this study was the third trimester of pregnant women who came to the Caile Health Center, Bulukumba Regency who had fulfilled the inclusion and exclusion criteria with a total of 87 people. In this study using univariate analysis in the form of frequency distribution and bivariate analysis with the chi-squared test.

Results : The results of the analysis of the relationship between economic status and the incidence of anemia in the third trimester of pregnant women showed that there were 25 out of 39 people (61.0%) of mothers whose income was < PMW (Provincial Minimum Wage) had anemia, while among pregnant women earning ≥ PMW there were 16 of 47 people (39.0%) had anemia. Chi-squared statistical test results showed that the value of p=0.005 (p≤0.05), RP 3.460 (95% CI =1.421 - 8.425), it can be concluded that mothers with income < PMW increase the incidence of anemia by 3.4 times compared with the mothers with income > PMW. The third trimester of pregnant women with low economic status are more at risk of anemia. This relates to people's purchasing power. Counseling provided is to increase compliance with the Fe tablet and to choose foods that contain a high protein at a low price.

Conclusion : Based on the results of the research, the researcher concluded that economic status plays an important role in the incidence of anemia in the third trimester of pregnant women.

Keyword : Anemia, Pregnant Women, Economic Status, Caile Health Center

PP11-18

The influence of health and socio-economic factors on prevalence of anemia among children in six countries based on income

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Background : Anemia among children under 5 years old is one of the most important diseases to pay attention, because it affects the growth of children. The high rate of anemia among children in the world has become focus of this study.

Method : This study analyzes the effect of health indicators (stunting, prevalence of overweight, prevalence of undernourishment) and Socio-Economic indicators (literacy rate of adult women, GDP per capita and the participation rate of women working) in six country categories based on income (high income, low income, lower middle income, low and middle income, middle income an upper middle income). Secondary analysis is done by using panel data with fixed effect method. Data from World Indicator Index for the period 2010-2016.

Results : The results of the graph show that anemia in children is a concern because it affects the growth and development of children. The results show that countries in the high income and upper middle income categories have a prevalence rate of anemia among children below 30 percent but it has increased. Low income countries have the highest anemia rate compared to other categories, which is more than 60 % but has decreased from year to year. Lower middle income, low-middle income and middle income categories have a prevalence rate among children between 40-58% with a decreasing percentage from year to year. Meanwhile, the results of the regression show that stunting, prevalence of overweight, undernourishment, GDP per capita and has a positive and significant effect on anemia in the children. The higher the percentage of stunting, overweight, undernourishment, GDP per capita and the level of literacy and working women, the higher the anemia rate in children under 5 years of age. However, the literacy rate of adult women negatively affect anemia in children under 5.the higher the literacy rate of adult women, the lower anemia in children under 5.

Conclusion : It is expected that the government try to increase the GDP per capita, the level of education of female to decrease anemia of the children, and the need for special attention regarding women working, stunting and nutrition. It is highly recommended that women read a lot to reduce the incidence of anemia in children under 5 years of age.

Keyword : Anemia, Children under 5, Stunting, Undernourishment, Socio-Economic

	(1) Fixed Effects	(2) Random Effects
stunting	1.272***	0.442***
	(0.0481)	(0.0847)
overweight	1.688***	-2.692***
	(0.298)	(0.539)
adultliteracy	-0.236***	-0.453**
	(0.0535)	(0.170)
gdppercapita	0.00207***	0.00219***
	(0.000121)	(0.000471)
femaleworker	0.247***	-0.669***
	(0.0518)	(0.0737)
undernourishement	0.430**	1.254*
	(0.138)	(0.517)
_cons	0.117	78.20***
	(7.645)	(18.05)
N	28	28

Standard errors in parentheses
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

PP11-19

Effect of lavandula officinalis leaves ethanolic extract on hematological and biochemical parameters in male rats

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Background : Lavandula officinalis, known as lavender, consists of geraniol, linalool, linalyl acetate, valerianic acid, and luteolin flavonoids. It has wide range of anti-inflammatory, cognitive enhancer, protective, effects thus may be advantageous in the treatment of metabolic disease.

Objective : This study aims to elucidate the effects of Lavandula officinalis leaves ethanolic extract (LOE) on hematological and biochemical parameters in rats.

Method : Sixty male Wistar rats were randomly assigned into three groups. Group 1 was control, while groups 2 (100 mg/kg) and 3 (300 mg/kg) received LOE extract orally once daily for 30 days. Complete blood count was done using an automatic counter.

Results : The group 3 (LOE 300 mg/kg) had significantly higher red blood cell (RBC) counts, packed cell volume (PCV), hemoglobin (Hb), and platelet counts as compared with the control and group 2(LOE 100 mg/kg). No significant changes were observed in the total white blood cell (WBC) count of the three groups, but significantly (P<.05) lower lymphocyte and higher neutrophil counts were observed in the group 3 compared with the group 2. The mean platelet volume (MPV), platelet-large cell ratio (P-LCR), and platelet distribution width (PDW) were significantly reduced in the higher dose compared with the low dose of LOE group. The mean corpuscular volume (MCV) and RBC distribution width-standard deviation were significantly lower in the group 3 than in control. No significant changes were observed in levels of mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and RBC distribution width-coefficient of variation among the groups.

Conclusion : We conclude that oral administration of LOE increases RBC, PCV, Hb, platelet count, and neutrophils and also leads to a decrease in platelet indices.

Keyword : Red Blood Cell, Lavandula Officinalis, Platelet, Blood Indices

PP11-20

Study of punica granatum (pomegranate) seed oil extract in phenylhydrazine induced-anemia in albino rats

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Background : Pomegranate (Punica granatum) seed oil extract is rich in phytoestrogen and antioxidant compounds. The present study is designed to investigate the protective effects of Pomegranate seed oil extract (SOE) on haematological and biochemical parameters in phenylhydrazine induced-anemia albino rats

Method : The experimental animals were randomly grouped into five groups of six rats each – group 1 (non--anemic control), group 2 (anemic control), group 3 (100 mg/kg of SOE), group 4 (300 mg/kg of SOE) and group 5 (DMSO control). Phenylhydrazine was administered once at a dose of 80 mg/kg b.w. to induce hemolytic anemia. After 30 days of SOE administration, rats were sacrificed and the serum collected was used for biochemical analysis.

Results : In the acute toxicity study, the LD50 was found to be above 500 mg/kg body weight. Packed Cell Volume (PCV) values, Red Blood cell (RBC) and haemoglobin (Hb) concentrations decreased ($p < 0.001$) significantly after 48 hours of phenylhydrazine induction, but after 30 days of administering SOE, PCV values, RBC and Hb increased ($p < 0.001$) significantly. There were significant decreases in cholesterol, triacylglycerol, and LDL cholesterol concentrations in the SOE-administered groups relative to the anemic control. There was a significant increase in HDL-cholesterol concentrations in the extract groups relative to the non-anemic control.

Conclusion : The results of our study suggest that SOE treatment showed excellent protective effects in reversed anemic conditions, improved the lipid profile in a phenylhydrazine-induced rats.

Keyword : Phenylhydrazine Induced-Anemia Albino Rats, Pomegranate (Punica granatum) Seed Oil Extract, Acute Toxicity, Triacylglycerol

PP11-21

Anemia in pregnancy: Risk factors influencing age and level of education among mothers in Sawangan health-care center

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Background : Anemia is a red blood cells disorder is not sufficient to meet the physiological need of the body. Reproductive age women and pregnant are high risk of anemia, which can lead to maternal morbidity and mortality. Anemia in pregnancy is a public health problem, especially in developing countries, and it is associated with adverse pregnancy outcomes. World Health Organization (WHO) has defined anemia in pregnancy if haemoglobin concentration of less than 11g/dl. Incidence of anemia is a significant indicator of health. A 2013 study showed a higher prevalence of anemia in developing

countries (43%). Maternal mortality is one of the key indicators of performance in a country's health care and anemia during childbirth is one of the major causes of maternal mortality (Nivedita et al, 2016). Anemia during pregnancy has a negative effect on maternal and child health and increases the risk of maternal and perinatal death (Allen, 2000). The main causes of anemia are nutrition and infection. Among the nutritional factors that contribute to anemia are iron deficiency. This is because food consumption is not varied, but is rich in substances that inhibit the absorption of iron (phytates) so that iron cannot be utilized by the body. Iron deficiency can also be made worse by nutritional status. The need for iron during pregnancy can increase twice the requirement before pregnancy. This happens because the volume of blood during pregnancy increases by 20-30% so that more iron is needed to form hemoglobin. In addition, the rapid growth of the fetus and placenta also requires a lot of iron (Cunningham, 2013). Anemia during pregnancy has a negative effect for mother include fatigue, poor working ability, compromised immune function, increase risk of heart disease and mortality. Anemia affecting approximately 32 million women worldwide and at least half of all pregnant women in middle and low-income coutries. The global data showed that in low and middle income countries 56 percent of women have anemia/ Africa has the highest prevalence of anemia (57%), followed by Shoutheast Asia (48%), and the lowest prevalence in South America (24,1%) (WHO, 2008). The increasing number of anemia sufferers in pregnant women has become one of the problems in the working area of the Sawangan II Healthcare Center. Based on the background of the above problems, encourage researchers to conduct research by taking the title "Risk Factors Influencing Age and Level of Education Among Mothers in Sawangan Healthcare Center".

Method : This study is descriptive observational with design cross sectional study. This study take place in Sawangan, Magelang, Indonesia. Data collected by medical record in Sawangan II Healthcare Center from January until November 2018. Population of this study is pregnant women in third trimester from Januari until November 2018. Inclusion criteria of this research is pregnant women without any complication. Exclusion criteria of this research is pregnant women with infection disorder, cancer, and another blood disorder. This research is using total sampling population. There are 204 pregnant women include in this study. Independent variable of this study is incidence of anemia in pregnant women in third trimester at Sawangan II Healthcare Center between January-November 2018. dependent variable of this study is age and level of education. Data processing and analysis using SPSS software version 23. Data from the research results will be presented in table. The analysis plan that will be used is Chi Square analysis to determine the relationship between the independent variables and the dependent variables.

Results : Table 1 shows demographic data for third trimester pregnant women recorded in the working area of the Health Care Center Sawangan which checks hemoglobin (Hb) levels. The number of samples included in this study were 204 people from January to November 2018. Of those 204 pregnant women aged <21 years as many as 31 people (15.2%), aged 21-30 years were 96 people (47.1 %), aged 31-40 years were 71 people (34.8%), and aged 40-50 years were 6 people (2.9%). A total of 20 people were in elementary school (9.8%), 86 were in junior high (46.2%), 78 were in high school (38.2%), and 20 were in college (9.8%) %). The 204 samples, 108 (52.9%) had anemia during the third trimester of pregnancy, while 96 (47.1%) had no anemia. Relationship between age and anemia in third trimester pregnant women Table 2 shows the causal relationship with the incidence of anemia in pregnant women. There was a significant relationship between high-risk age and the incidence of anemia (p <0.05) with OR 1.86; 95% CI (1,067-3,252), which means the risk of anemia in trimester 3 pregnant women in pregnant women who have an age at risk 1.86 times greater than pregnant women aged 21-30 years. According to Ristica (2013) shows that the mother's age during pregnancy <20 years and> 35 years has a 2 times risk of suffering from anemia compared to pregnant women aged 20-35 years during pregnancy. Age of pregnant women is related to reproductive organs. Biologically female reproductive organs, if the mother's age during pregnancy if too young or too old will affect pathological things in pregnancy and childbirth. According to the Department of Nutrition and Public Health (2007), pregnant women over 30 years tend to experience anemia, this is due to the decrease in Fe reserves in the body. Relationship between level of education and anemia in third trimester pregnant women In table 3 shows the relationship between the level of education with the incidence of anemia in pregnant women third trimester. There is a significant relationship between the level of education with the incidence of anemia (p <0.05) with an OR 2.82; 95% CI (1,598-4,981) which means the risk of anemia in 3rd trimester pregnant women in pregnant women with low education levels (elementary school and junior high school) has a risk of 2.82 times greater than pregnant women with high education levels (senior high school and college). Fitriasari (2017) explaining that as many as 44.4% of pregnant women have low levels of education having moderate anemia, while as many as 7.7% of pregnant women with high education have severe anemia. This shows that highly educated pregnant women are more likely to experience mild anemia. Ristica (2013) said that low education can cause anemia in pregnant women 2.4 times compared to higher education (95% CI: OR =1.24-4.50). Anemia is most common in the group of pregnant women with low education. This is due to the lack of access to anemia information and how to overcome it. A person's level of education greatly influences awareness of the importance of one's health. The level of education will also affect awareness to behave in healthy living. Someone who is highly educated will take rational decisions and be more open so they can accept changes or new things. The level of education of pregnant women will affect their behavior, the higher education or education of the mother, the higher the awareness to prevent anemia.

Conclusion : Risk factors for anemia in third trimester pregnant women in the Sawangan Health Care Center for the period January to November 2018 include age and education level. More younger or older the mother during pregnancy has the risk of anemia. The lower the level of education of pregnant women has the risk of anemia.

Keyword : Anemia, Risk Factor, Pregnancy

PP11-22

Automatic anemia identification based on machine learning on red blood cell image

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Background : In general, laboratory tests to identify anemia are done by manually counting the number of red blood cells, which is called the Complete Blood Cell (CBC) method, and automatically using a device called a blood analyzer. Manual calculation of the number of red blood cells in a blood sample under a microscope by a doctor takes a relatively longer time than an automatic examination. However, automatic inspection is relatively expensive. This research work proposes a computerized algorithm to perform an efficient and low-cost anemia identification.

Method : Our algorithm consists of three main phases, namely image processing, feature extraction, and identification. The image processing phase is done in two steps, the image pre-processing and segmentation steps. The feature vector of all images is constructed based on the pixel intensity values of the segmented images. The constructed feature vector becomes the input of the identification phase, which is performed using the K-Means method. The proposed algorithm is applied on 92 red blood cell images, consist of 52 and 40 anemia and non-anemia images, respectively.

Results : The identification results are validated by comparing them to those of the medical staff. The achieved accuracy for the validation process is 95%, indicating that our proposed algorithm is able to identify anemia and non-anemia effectively.

Conclusion : In this study, the results obtained with very good accuracy so that the system is able to detect very well.

Keyword : Anemia, Machine Learning, Red Blood Cell Image

PP11-23

Pregnant women, health crisis and hemogoblin detect in the age of COVID-19 in Indonesia

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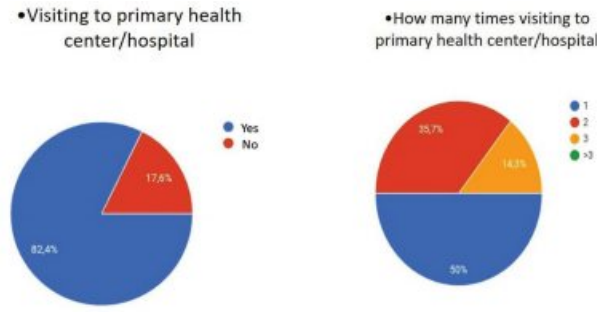
Background : During the pandemic, the pregnancy in Indonesia have risen. More activities at home causes a wide range of increases pregnancy. Result of research have provided a new insight into the pregnant women's experience in detecting Hemoglobin (Hb)in the Age of COVID-19. To know it, the authors surveyed expectant mother groups in social media especially WhatsApp groups. This study aims to describe pregnant women's experience to detect Hb in the Age of COVID-19. The phenomenon that is learned from these groups is behavior of pregnant women who check (pregnancy) in order to determine its accuracy, quality, or condition of the Hemoglobin.

Method : An online questionnaire survey among pregnant women conducted via social media and email newsletters.

Results : The COVID-19 pandemic has reduced the intensity of visiting pregnant women to primary health center (Puskesmas) and hospital. During the pandemic, pregnant women rarely check for hemeglobin. Commonly, they check for just 3 times. They consume more herbs such as honey and dates to avoid anemia.

Conclusion : There are still pregnant women who experience anemia but some of them do not check Hemoglobin because of COVID-19. However, it needs socialization from health workers to pregnant women to carry out routine checks at the hospital while adhering to health protocols of COVID-19.

Keyword : Anemia, COVID-19, Hemogoblin Detect, Pregnant women



PP11-24

A case of acute intermittent porphyria in a young woman with epilepsy

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Background : The porphyrias are rare metabolic disorders caused by altered activities of enzymes within the heme biosynthetic pathway. Acute intermittent porphyria (AIP) is one of the porphyrias which causes predominately neurovisceral symptoms including neuropathies, abdominal pain, constipation and seizures. In AIP, the porphyrin precursors, porphobilinogen and amino-levulinic acid (ALA), accumulate. A number of factors precipitate or exacerbate attacks, including starvation, poor intake of carbohydrates, alcohol, smoking, stress, infections, medications like metoclopramide, rifampicin, and anti-epileptic drugs. We report a case of AIP precipitated by urinary tract infection and carbamazepine, in a patient with epilepsy.

Method : Case Presentation
A 27 year old woman with epilepsy admitted with central colicky abdominal pain and psychotic symptoms associated with fever and dysuria. She had been diagnosed to have epilepsy for six years, for which she had been taking Carbamazepine. As she had recurrence of seizures despite of treatment, Carbamazepine dose had been increased recently. Examination revealed and average built woman, febrile, irritable and in distress due to pain .There was no neck stiffness and neurological examination was normal including the fundi. The abdomen was slightly tender without guarding or rigidity. There was no organomegaly. Pulse rate was 120 beats per minute with elevated blood pressure of 190/130 mmHg.

Results : Investigations revealed normal hematological (FBC: Hb-13.9g/dl, WBC- 13.1/cumm, platelets – 349000/cumm, ESR-26mm/1st hour) and biochemical parameters (RBS- 140mg/dl, serum amylase-65u/l , serum creatinine -65umol/l, urine metanephrine- normal) with normal imaging of abdomen(USS of abdomen and pelvis- normal). But urine porphobilinogen was positive (Figure 01) and urine analysis was suggestive of urinary tract infection (Pus cells- moderately field full, RBC- moderately field full, No casts). Thus the diagnosis of AIP precipitated by urinary tract infection and Carbamazepine was made. The patient was markedly improved with treatment for urinary infection, withdrawal of precipitating drugs and carbohydrate loading, although Intravenous hemin, the ideal treatment was not available. After full recovery she was discharged following health education. A plan was made for further follow up and family screening.

Conclusion : Acute porphyria usually presents with abdominal pain and neurovisceral manifestations which are common to many other medical and surgical conditions. Therefore, the possibility of acute porphyria should be considered in patients with these symptoms that does not have a clear explanation.

Keyword : Acute Intermittent Porphyria, Abdominal Pain, Epilepsy, Carbamazepine

PP12-02

A delayed presentation of neonatal alloimmune thrombocytopenia (NAIT): A case report

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Background : Neonatal thrombocytopenia (NT) is a condition with platelet count less than 150,000/uL. It can be divided into early onset (within 72 hours after birth) and late onset (after 72 hours after birth) (1). Causes of early onset NT include infection, perinatal asphyxia, autoimmune, and alloimmune thrombocytopenia. Late onset NT can be caused by sepsis, necrotizing enterocolitis among others (1). Neonatal alloimmune thrombocytopenia (NAIT) accounts for 1 in 350 to 1000 live births and is due to transplacental passage of maternal alloantibodies directed against the fetal platelet antigens (2). Among Caucasians, 75-80% are due to antihuman platelet antigen (HPA) 1a followed by antiHPA-5b.

Method : Descriptive study: Case report

Results : A term baby boy was delivered via spontaneous vaginal delivery with good birth weight and Apgar score. Antenatally, his mother had mild anaemia but no history of bleeding disorder with platelet count of 266,999/uL. At day 19 of life, he developed low grade fever and petechiae rashes for 2 days duration. Otherwise, he was active and tolerating feeding well. He had no significant history of ill contact. Physical examination revealed petechiae rashes over his face and multiple bruises over all four limbs. Otherwise, he was active, afebrile, and hemodynamically stable. There was no active mucosal bleeding or hepatosplenomegaly. Follow-up management: Initial investigation included full blood count which revealed severe thrombocytopenia (1,000/uL) with moderate anemia (hemoglobin: 10.3g/dl). Full blood picture excluded pseudothrombocytopenia and no abnormal or blast cell was seen. Ultrasound cranium showed no intraventricular hemorrhage. He was treated as neonatal sepsis and started on intravenous antibiotic. However, further investigations showed negative C-reactive protein and blood culture. Viral screening included TORCHES (toxoplasma, rubella, cytomegalovirus, herpes, syphilis) and parvovirus screening were negative. In view of severe thrombocytopenia, he was transfused with platelet (10ml/kg). However, his platelet count did not raise as expected. Since NAIT with refractory thrombocytopenia was suspected, he was given intravenous immunoglobulin (IVIg) (0.8g/kg) daily for 2 days. He demonstrated a transient improvement of platelet counts but the response did not sustain. Subsequently, he was started with oral prednisolone (2mg/kg/day) but withheld due to superimposed septicemia and supported with antibiotic and matched platelet transfusion. He gradually improved with his platelet count recovered prior to discharge. His NAIT screening result returned and supported the diagnosis of NAIT with both he and his paternal platelet HPA phenotype was 3a3b, while his maternal platelet HPA phenotype was 3b3b. AntiHPA-3a alloantibodies was detected in his mother.

Conclusion : This case illustrates a delayed presentation of NAIT

involving an uncommon platelet HPA3 phenotype comparing to known literature. A high index of suspicious is necessary for accurate diagnosis and timely treatment to prevent undesired complications. Cross-matched compatible platelet transfusion, IVIg, and corticosteroid are among few options available in treating patients with NAIT.

Keyword : Neonatal Alloimmune Thrombocytopenia, Bleeding, Platelet

PP12-03

Treatment outcomes and profile of patients with immune thrombocytopenia at a tertiary hospital: The TOP-IT study

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Background : Immune thrombocytopenia (ITP) is the most common cause of isolated thrombocytopenia in clinical practice. However, there is insufficient published data on the prevalence and incidence of ITP in low-income countries such as the Philippines. We aim review the clinical profile and survival outcomes of newly-diagnosed, adult ITP patients seen at our institution.

Method : This retrospective cohort study included all patients who consulted at our institution from 2011 to 2015. Survival rates were measured, and differences among treatment regimens were analysed using the Kaplan-Meyer method.

Results : In the 214 patients included in the study, majority were <40 years old, and female. The most common chief complaint was gum bleeding. The most common first-line treatment used was prednisone. Mean time to loss of response is longer with first-line steroid therapy compared to other treatments. Gender had a borderline significant association with loss of response to treatment.

Conclusion : In this 5-year study, ITP accounts for the 2-5% of the patients in hematology service of our institution. Among the different therapeutic modalities used, prednisone remains the initial treatment of choice.

Keyword : Platelets, Steroid, Thrombocytopenia

Logistic regression of loss of response with possible associated variables (n = 196)

Variable	Odds ratio	p-value
Treatment group	2.15	0.472
Age	1.01	0.551
Gender	3.27	0.054
Alcoholic beverage drinking	0.68	0.708
Smoking	0.76	0.839
Illicit drug use	2.78	0.510
Presence of co-morbidities	0.62	0.585
Number of treatments	1.12	0.871

PP12-05

A study on the association of immune thrombocytopenia with viral infection through public health data analysis

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Background : The most common cause of thrombocytopenia in children is immune thrombocytopenic purpura (ITP), with an estimated incidence of 4.2 per 100,000. The highest incidence rate is observed in children between the ages of 2 and 5 years, but ITP may occur in all pediatric age groups. In 50–60% of pediatric patients, ITP is preceded by an upper respiratory tract infection 1–4 weeks before its onset. Recent studies have provided insights into the epidemiologic association of ITP with specific viruses, such as the Epstein–Barr virus and rotaviruses; however, information on its association with common respiratory and enteric viruses remains insufficient. In this study, we investigated the relationship between the outbreak of ITP and virus in children and adolescents using the Health Insurance Review and Assessment (HIRA) Open Access Big Data Platform and public health data from Korea Disease Control and Prevention Agency.

Method : We extract patient data from HIRA during 2015 to 2018, then analyzed monthly incidence patterns and seasonal trends. Virus positive detection rate (PDR) datas for the following viruses was extracted from the Korea Disease Control and Prevention Agency on a weekly/monthly basis. These data were collected from 2010 to 2018: human adenovirus (HAdV), human parainfluenza virus (HPIV), human respiratory syncytial virus (HRSV), influenza virus (IFV), human coronavirus (HCoV), human rhinovirus (HRV), human bocavirus (HBoV), human metapneumovirus (HMPV), rotavirus, norovirus, and astrovirus. For statistical analyses, the crude incidence rate (incidence per 100,000 people) was calculated using the number of patients diagnosed with each disease in the numerator, and the Korean population by age per year for the denominator. The virus PDR seasonal trend data was analyzed by time series through ARIMA modeling. The ITP diagnostic data and the prevalence of the virus 1 and 2 months prior were analyzed using the Granger test.

Results : From 2015 to 2018, 19,166 patients were diagnosed with ITP, with an average of 399 new diagnoses each month. The age range of 0–5 years accounted for 4,365 (22.8%) ITP diagnoses, 5.1–18 years accounted for 2,122 (11.1%) diagnoses, and >18 years accounted for 12,679 (66.2%) diagnoses. The female to male ratio was approximately 1.29:1, with 10,794 female (56.3%) patients developing ITP. The annual cumulative cases per month were the highest in July and lowest in February. Most patients were diagnosed with ITP in the summer (27%). The PDR for rotavirus (p=0.035) at <5 years of age and HRSV and astrovirus (p=0.030 and p=0.029, respectively) at 5.1–18 years of age were related to prevalence of ITP after 1 month. HRV and rotavirus (p=0.015 and p=0.050) from birth to 1 year of age, rotavirus (p=0.031) at <5 years of age, and HPIV (p<0.001) at >18.1 years of age were related to prevalence of ITP after 2 months.

Conclusion : This study showed that among common respiratory and enteric viruses, rotavirus infection positively affected the diagnosis of ITP after 2 months. In addition, HRSV, HRV, and astrovirus infections were also shown to influence the diagnosis of ITP in some age groups. We expect additional insights into the causative factors associated with ITP to be elucidated through long-term, multi-faceted, epidemiological data analysis

Keyword : ITP, Thrombocytopenia, Virus, HRSV, HRV, Rotavirus

PP12-06

Efficacy of Helicobacter pylori eradication for the treatment of chronic or persistent immune thrombocytopenia patients with moderate thrombocytopenia: multicenter prospective randomized phase 3 study

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Background : The standard treatments such as steroid, splenectomy are not recommended in patients with immune thrombocytopenia (ITP) presenting with moderate thrombocytopenia because of toxicities, compliance, and cost-effectiveness according to the long-term treatment. However, the platelet responses were reported after eradication in some Helicobacter pylori (H.pylori)-positive ITP patients. We conducted a multi-center, phase III study to evaluate the efficacy and safety of eradication for H.pylori-positive ITP patients with moderate thrombocytopenia.

Method : Persistent or chronic ITP patients with platelet ranges of 30,000~80,000/uL and confirmed active H. pylori infection were randomly assigned to the eradication or the control group. The eradication group received 10-day sequential therapy consisting of 40 mg pantoprazole b.i.d and 1 g amoxicillin b.i.d for 5 days followed by 40 mg pantoprazole b.i.d, 500 mg clarithromycin b.i.d and 500 mg metronidazole t.i.d for 5 days and the control group was observed without treatment till 3 months, and then they also received same eradication regimen. Eradication was assessed by urea breath test (UBT) 3 months after treatment. Platelet counts were monitored serially after treatment and the response was assessed by International Working Group Criteria.

Results : Of the 28 H.pylori-positive ITP patients, 17 were randomized to the treatment group and eradication was achieved in 15 (88.2%) of them at 3 months. Of the 11 control patients, 4 withdrew consent, and 7 patients participated in the study. There were statistically significant differences in platelet response rates between the eradication group (9/15, 60%) and the control group (0%) (p=0.008) at 3 months. Six patients in the control group were treated with the same eradication regimen at 3 months after enrollment and 3 patients showed negative conversion of UBT and one of them acquired the platelet response. Regardless of the randomized group, the platelet response rate at 3 months after treatment was 55.6% (10/18) in patients with successful H. pylori eradication. No significant differences were found in clinical factors between the responders and the non-responders.

Conclusion : In this phase 3 study, it was verified that H. pylori eradication is an effective ITP treatment in patients with H. pylori-associated moderate ITP who were not previously indicated for standard treatment. In addition, this sequential regimen, not been reported for ITP treatment until now, showed not only high H. pylori eradication rate and tolerable side effects but also remarkable efficacy for the treatment of ITP.

Keyword : Immue Thrombocytopenia, Helicobacter Pylori, Eradication, Platelet Response

PP12-07

Clinical outcomes after splenectomy for relapsed or refractory immune thrombocytopenia according to first-line intravenous immunoglobulin response

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Background : As a second-line therapy for chronic immune thrombocytopenia (ITP) patients who were refractory or relapsed to first-line therapies, splenectomy is still considered although thrombopoietin receptor agonists and other novel agents are widely introduced these days. However, there has been a tendency to avoid surgical management and recently modified guidelines suggest delaying splenectomy for at least 12 to 24 months from diagnosis of chronic ITP especially in patients who are reluctant for surgery. We tried to identify the long-term treatment outcome of splenectomy as second-line therapy in relapsed/refractory chronic ITP, according to first-line intravenous immunoglobulin (IVIG) responses.

Method : We retrospectively identified 52 consecutive adult patients (median age 38 years old, range 25-72) treated with splenectomy as second-line therapy for chronic ITP from 2009 to 2019. The responses to first-line IVIG administration before splenectomy were investigated and we classified patients who did not respond to IVIG as non-responders, patients who showed IVIG response but not lasting longer than 4 weeks as poor-responders, and patients who responded to IVIG for a longer period with stable platelet counts as stable-responders. The response and relapse rates after splenectomy, relapse-free survival, post-splenectomy complications according to three groups were analyzed.

Results : Of the total 52 patients, 10 patients were IVIG non-responders, 34 were poor-responders and the rest 8 were stable-responders. The median platelet counts prior to splenectomy in three groups were 41.5x10^9/L (range: 5-102), 93.5x10^9/L (range: 31-352), and 123.5x10^9/L (range: 57-241), respectively (P=0.0004). Overall, 7 (13.5%, 5 non-responders and 2 poor-responders) were refractory even after splenectomy. Response to splenectomy was observed in 5 (50.0%) IVIG non-responders, 32 (94.1%) poor-responders and 8 (100%) stable-responders (P=0.0030). Among the 45 (86.5%) who responded to splenectomy, 23 (51.1%) relapsed subsequently, and a significantly low relapse rate in the stable-response group was noted (in non-responder, poor-responder, stable-responder, 3 out of 5 (60.0%), 19 out of 32 (59.4%), and 1 out of 8 (12.5%), respectively. P=0.0220). Totally 30 (57.7%) were refractory or relapsed to splenectomy and salvage therapy showed another response in 21 (70.0%), and 7 (33.3%) of the responders (3 IVIG non-responders, 4 poor-responders) finally stopped all treatments.

Conclusion : Our data showed that splenectomy is a feasible second-line therapy for relapsed or refractory chronic ITP, but refractoriness or subsequent relapse was observed in a significant number of patients, especially in non or poor first-line IVIG responders. IVIG response is suggested as a useful predictive factor for response to splenectomy.

Keyword : Immune Thrombocytopenia, Intravenous Immunoglobulin, Splenectomy, Refractory, Salvage Treatment

Table 1. Splenectomy outcomes of patients

Variables	Total (N=52)	Non responder (N=10)	Poor responder (N=34)	Stable responder (N=8)	P
Type of op.					0.3462
Open (N, %)	1 (1.9)	1 (10.0)	0 (0)	0 (0)	
Laparoscopic (N, %)	51 (98.1)	9 (90.0)	34 (100)	8 (100)	
PLT on op. day (Median, range)	85 (5-352)	41.5 (5-102)	93.5 (31-352)	123.5 (57-241)	0.0004
<50 (N, %)	10 (19.2)	8 (80)	2 (5.9)	0 (0)	
≥50 ~ <100 (N, %)	21 (40.4)	1 (10)	17 (50)	3 (37.5)	
≥100 (N, %)	21 (40.4)	1 (10)	15 (44.1)	5 (62.5)	
Response					0.0030
No response (N, %)	7 (13.5)	5 (50.0)	2 (5.9)	0 (0)	
Response (N, %)	45 (86.5)	5 (50.0)	32 (94.1)	8 (100)	
Relapse					0.0683
No relapse (N, %)	22 (48.9)	2 (40.0)	13 (40.6)	7 (87.5)	
Relapse (N, %)	23 (51.1)	3 (60.0)	19 (59.4)	1 (12.5)	
Post op. 1month max PLT (Median, range)	284 (32-1152)	179.5 (32-600)	304 (75-960)	393.5 (128-1152)	0.0583
<150 (N, %)	8 (15.4)	4 (40)	3 (8.8)	1 (12.5)	
≥150 ~ <300 (N, %)	19 (36.5)	4 (40)	14 (41.2)	1 (12.5)	
≥300 (N, %)	25 (48.1)	2 (20)	17 (50)	6 (75)	
Relapse free survival (median weeks, 95% CI)	137 (10.4-NA)	4.57 (0.71-NA)	118.43 (10.43-NA)	NA	0.0439
2-year relapse free (%, 95% CI)	55.6 (43.6-70.9)	40.0 (18.7-95.5)	52.9 (38.6-72.7)	87.5 (67.3-100)	
Complications					
Ischemic heart disease	1 (1.9)	0	1 (2.9)	0	1.000
Venous thrombosis	3 (5.8)	1 (10.0)	2 (5.9)	0	0.7292
Sepsis	1 (1.9)	0	1 (2.9)	0	1.000
Others	2 (3.8)	0	2 (5.9)	0	1.000
Death (N, %)	4 (3.8)	2 (20)	2 (5.9)	0 (0)	0.2651

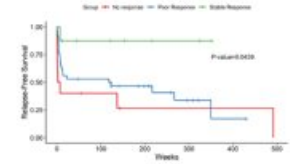

Figure 1. Relapse-free survival after splenectomy according to IVIG response group

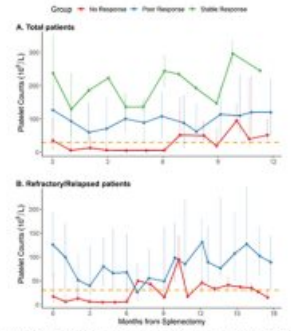

Figure 2. Median platelet counts flow after splenectomy, grouped by IVIG response

PP12-08

An escalating treatment strategy for children with severe chronic immune thrombocytopenia: The preliminary report from a single-center

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Background : Childhood immune thrombocytopenia (ITP) is a disease that usually runs a benign, self-limiting course. First-line treatments are usually sufficient for those in need of management, yet approximately 20% of those patients do not respond well to first-line therapy and consequently develop chronic ITP.To analyze the effect of a novel second-line escalating treatment strategy (high-dose dexamethasone (HDD), low-dose rituximab to eltrombopag) for children with severe chronic immune thrombocytopenia (SCITP).

Method : This study was a single-center, retrospective cohort study. The data of children SCITP who received escalating treatment strategies in our center were collected between June 2017 and August 2019. The second-line escalating strategy included 3 steps: Step I (6 courses high-dose dexamethasone: HDD), Step II (HDD combined

with low-dose rituximab), and Step III (eltrombopag).

Results : A total of 30 cases (18 males and 12 females) were included; the median age was 8.83 (1.42-13.9) year-old, the duration time of ITP was 20.5 (12.0-96.0) months, and the platelet counts were 15 (3-29) ×109/L. After the median 14 (12-37) months' treatment, the remission rate was 36.7% (11/30), and the sustained response (SR) rate was 68.2% (15/22). The distribution (remission rates) from step I to III were: 30.0%, 9/30 (33.3%, 3/9); 13.3%, 4/30 (50%, 2/4); 56.7%, 17/30 (29.4%, 5/17), respectively. In eltrombopag (step III) cases, 47.5% (8/17) maintained platelet ≥50×109/L, 37.5% (3/8) dose tapering, and 25% (2/8) were successfully discontinued from medication. The number of patients at 12th, 24th, and 36th months was 30, 7, and 2, with the total response (TR) and remission rates of 80% (36.7%), 57.1% (28.6%), and 50% (50%), respectively. The total relapse rate was 26.7% (8/30), three cases(75%, 3/4)from Step II and 5 cases (41.7% ,5/12)from Step III, none in Step I.

Conclusion : The new second-line escalating strategy for children SCITP has an effective improving rate with 36.7% remission and 68.2% SR; 30% could benefit and retain stable response from HDD treatment. Combined treatment with eltrombopag can reduce the relapse rate of low-dose rituximab.

Keyword : Second-Line Treatment

PP12-10

An intronic variant at a splice-site (c.5170+5G>A) of VWF gene causes exon 29 skipping in a patient with von Willebrand disease

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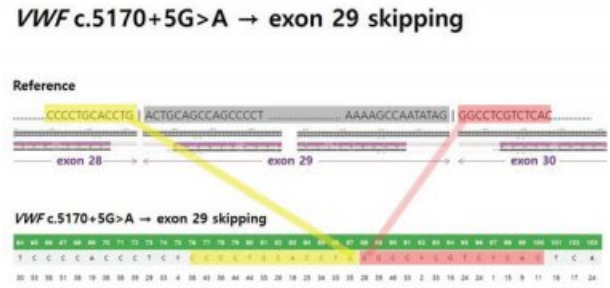
Background : Von Willebrand disease (vWD) is a most common inherited coagulation disorder, with a prevalence from 1:100 to 1:10,000 depending on the criteria. Generally, type 1 vWD is estimated about 75–80% of cases, and type 2 vWD 20–25%, and type 3 vWD is very rare. However, when diagnosing using genetic methods, the incidence of each subtypes varies; type 1 vWD accounts for 25%, type 2 vWD 66% (type 2A 18%, type 2M 17%, and type 2N 19%), and 1% are of undetermined type. In other words, clinical diagnosis of vWD without genetic testing may be inaccurate.

Method : We conducted targeted exome sequencing for exact genetic diagnosis and rule out another bleeding disorders. Library preparation was performed with TruSight One Sequencing Panel (Illumina, San Diego, CA, USA) and massively parallel sequencing was conducted with NextSeq (Illumina). For RNA purification, QIAamp Blood RNA Mini Kit (Qiagen, Hilden, Germany) was used. Reverse transcription was applied using Hemavision Multiplex RT [DNA Diagnostics] and Transcriptor Reverse Transcriptase [Merck KGaA, Darmstadt, Germany]). To separate 2 bands from the gel and purification, AccuPrep(TM) PCR/Gel DNA Purification kit (Bioneer, Daejeon, South Korea), and sequenced using same primer set that used in PCR amplication step.

Results : A 10-year-old boy visited the hospital because of frequent epistaxis. His grand-mother, his father, and his father's older brother also had bleeding tendency. His platelet count was 237,000 /μL but the bleeding time by Duke method was prolonged as 6 minutes (reference, 1–3 minutes). The closing time by PFA-100 (epinephrine) was prolonged as >202 sec (reference, 81-192 sec) and the closing time by PFA-100 (ADP) was also prolonged as >217 sec (reference, 61-110 sec). The activated partial thromboplastin time was prolonged as 41.1 sec (reference, 23.2–39.4 sec). The von Willebrand factor (vWF) antigen was 39.4% (reference, 47–197 sec), and multimeric assay of vWF showed abnormal pattern with decreased high molecular weight form. By targeted exome sequencing, an intronic variant of unknown significance, NM_000552.3: c.5170+5G> A, heterozygote of VWF gene was found. This variant was also found in the family members with same phenotype; but it was not found in the normal population. This variant was suggested to cause splicing error by the in-silico prediction (SSF: 81.43→0, MES: 5.56→0). Finally, it was confirmed to result exon 29 skipping by mRNA study (Fig. 1). Therefore, according to the 2015 ACMG/AMP classification, the variant was upgraded from VUS to Pathogenic.

Conclusion : In conclusion, although vWD is a common bleeding disorder, there is a strong possibility that clinical diagnosis without genetic analysis is incorrect. Further, genetic confirmation using DNA-based next-generation sequencing and RNA-based study are necessary for a definite diagnosis.

Keyword : Von Willebrand Disease, Next-Generation Sequencing, Ribonucleic Acid, Exon Skipping



PP12-12

Performance evaluation of coaguchek pro II in comparison with CoaguChek XS Plus and STA-R Max Analyzer

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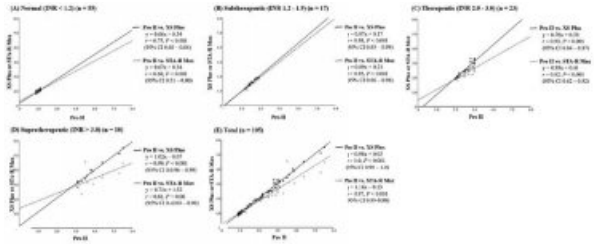
Background : We evaluated the analytical performance of CoaguChek Pro II (Roche Diagnostics GmbH, Mannheim, Germany), a new point-of-care device measuring the international normalized ratio (INR) values, in comparison with CoaguChek XS Plus (Roche Diagnostics GmbH) and STA-R Max using STA-Neoplastine CI Plus (Diagnostica Stago SAS, Asnières-sur-Seine, France).

Method : The precision of Pro II was analyzed, according to the Clinical and Laboratory Standards Institute guidelines (CLSI POCT14-A2 and EP15-A3). In 105 clinical samples, the Pro II INR values were compared with those of XS Plus and STA-R Max using STA-Neoplastine CI Plus (CLSI EP09-A3 and EP35). We also compared the Pro II INR values between capillary blood (CB) and venous blood (VB; CLSI EP35).

Results : The precision of Pro II was acceptable (within-run and between-run CV%: 2.71% and 3.28% at normal level; 1.52% and 4.47% at an abnormal level, respectively). The Pro II INR values showed a very high correlation and almost perfect agreement with those of XS Plus and STA-R Max using STA-Neoplastine CI Plus (r =.97 and κ =.94; r =.95 and κ =.91). The mean difference between Pro II and STA-R Max using STA-Neoplastine CI Plus increased as INR values increased, with 60% of samples showing differences >0.5 in the supratherapeutic range. The Pro II INR values showed a very high correlation between CB and VB (r =.98).

Conclusion : Pro II INR values are accurate and reliable using both CB and VB; however, they should be confirmed by laboratory analyzers in the supratherapeutic range.

Keyword : Capillary Blood, CoaguChek Pro II, Comparison, International Normalized Ratio, Performance, Point-Of-Care Devices, Venous Blood



PP12-13

Promotion of platelet production by cotransplatation of tonsil-derived mesenchymal stem cells in allogeneic bone marrow transplantation mouse model

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Background : Therapeutic strategies that can promote platelet production is in demand to enhance clinical outcomes of hematopoietic stem cell transplantation. Our research group has been studied on human tonsil-derived mesenchymal stem cells (T-MSCs) and their effectiveness in promotion of bone marrow engraftment in a mouse model of bone marrow transplantation (BMT). In this study, we analyzed the effects of T-MSCs on platelet production using BMT mouse model and ex vivo MegaCult assay.

Method : Preconditioning of mouse bone marrow (BM) was performed by administration of busulfan and cyclophosphamide (Bu-Cy; 20 mg/kg Bu for 4 days and 100 mg/kg Cy for 2 days) in BALB/c recipient mice. Donor BM cells (BMCs) were isolated from C57BL/6 mice and transplanted to the recipient mice via tail vein with or without T-MSCs. Mice were sacrificed on day 21 post BMT and numbers of blood cells were counted using an auto hematology analyzer. Paraffin-embedded femur sections were immunohistochemically stained with CD41 antibody to analyze megakaryocytes in the bone marrow. Growth factor secretion form MSCs were analyzed using the Quantibody Human Growth Factor Array. MegaCult assay was performed to investigate the effects of a candidate molecule on megakaryopoiesis.

Results : T-MSC cotransplantation increased a percentage survival from 50% to 70% compared to the group transplanted BMCs only. Body weights of mice cotransplanted with T-MSCs showed a trend higher than BMC only group. Blood cell numbers were counted on 3 weeks after BMT. The number of platelets were significantly lower in BMC only group while T-MSC cotransplantation recovered the circulating platelet number to the levels similar to the normal control group. The numbers of red blood cells and white blood cells were not significantly different between experimental groups. The numbers of megakaryocytes were determined in the mouse femurs. Results demonstrated that the number of CD41+ megakaryocytes were significantly reduced in Bu-Cy and BMC groups, but T-MSC cotransplantation augmented the megakaryocyte number in bone marrow. Placental growth factor (PlGF) secretion from T-MSCs were identified and effects of PlGF secreted from T-MSCs on megakaryopoiesis was investigated. Promotion of megakaryopoiesis by T-MCS conditioned medium was determined whilst this effect was disrupted by the presence of the anti-PlGF blocking antibody.

Conclusion : In this study, we have demonstrated the effectiveness of T-MSCs cotransplantation in promoting megakaryopoiesis and platelet production after BMT. These findings highlight the potential therapeutic relevance of T-MSCs for prevention of thrombocytopenia after BMT.

Keyword : Bone Marrow Transplantation, Mesenchymal Stem Cell, Megakaryopoiesis, Platelet, Placental Growth Factor

PP12-14

Extended platelet parameters on COVID-19

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Background : Currently, COVID-19 is a life-threatening disease and is still a challenge around the world. Hemostasis abnormality or coagulopathy is one of the causes of death. The role of platelet quantity and quality is not well known. Extended platelet parameters are relatively new platelet parameters that can be checked using a routine, inexpensive and practical hematology tool. Currently, it is not known how the extended platelet parameters or platelet indices are described in COVID-19 patients, whether there is a difference between non- COVID-19 and COVID-19 cases, severe and not severe, and survive and not survive. This study aims to know the extended platelet parameter profile in COVID-19 patients.

Method : This is the first report of an ongoing study funded by Dr. Sardjito Hospital. This is an observational analytic cross-sectional study. The subject of this study was that inpatients had confirmed COVID-19 for the first time (with the rtPCR test) at Dr. Sardjito hospital, age> 18 years, male and female. Patients were classified as severe and not severe, survive and not survive. The variables measured: demographics, complete blood count, extended platelet parameters: mean platelet volume (MPV), platelet distribution width (PDW), mean platelet component (MPC), mean platelet mass (MPM), plateletcrit (Pct), severity, and mortality. The study sample used 1 ml EDTA blood and was examined for complete blood using an automatic hematology analyzer ADVIA 2120

Results : In this study, the MPV, PDW, MPC, and MPM values were not significantly different in all groups, while the platelet and plateletcrit counts were lower in the not survive group. It appears that there is a response of platelet activity to the decreasing platelet count with increasing MPM which reflects increased platelet mass due to the formation of pseudopods and increased volume (MPV). Platelet degranulation occurs when there is platelet activation which then results in MPC which represents a decreased platelet density, followed by a decrease in MPM.

Conclusion : This research is still ongoing, so this conclusion is still tentative. The results showed that most of the extended platelet parameter values did not differ between severe and not severe patients, as well as survive and not survive. Platelet and plateletcrit counts were lower in deceased patients. There is a relationship between platelet count, volume, mass, and platelet degranulation. Platelets may play a role in the pathomechanism of COVID-19.

Keyword : Platelet Parameter, COVID-19, MPV, MPM

	Negative PCR Result (n = 43)	Positive PCR Result (n = 39)	P
Hb (g/dL)	10.12 ± 2.46	12.3 ± 2.05	0.004
Leucocyte count (x 10^9/L)	10.47 (0.47 - 150.8)	9.6 (3.1 - 36.18)	0.306
Platelet count (x 10^9/L)	227 (10 - 669)	268 (57 - 785)	0 .163
MPV (fL)	10.35 (8.8 - 15)	10.7 (8.5 – 14.8)	0.297
PDW (%)	45.7 (13.9 - 70.9)	48.6 (34.4 – 62.1)	0.669
Pct (%)	0.25 (0.04 – 0.71)	0.27 (0.05 – 0.77)	0.305
MPC (g/dL)	21.49 ± 1.73	21.09 ± 1.95	0 .325
MPM (pg)	2.17 (1.85 - 2.91)	2.13 (1.79 – 2.76)	0.718
	Not Severe (n = 10)	Severe (n = 29)	P
Hb (g/dL)	12.15 (10.8 – 15)	12.6 (8.7 – 16.5)	0,950
Leucocyte count (x 10^9/L)	8.56 (4.34 – 11.8)	10.55 (3.6 – 36.18)	0.011
Platelet count (x 10^9/L)	260 ± 54.06	288 ± 166.5	0.433
MPV (fL)	10.25 (8.5 – 12)	10.7 (9.3 - 14 .8)	0.059
PDW (%)	43,31± 6.19	48.37 ± 7.92	0.274
Pct (%)	0.255 (0.18 – 0.35)	0.28 (0.05 – 0.77)	0.784
MPC (g/dL)	21,96 ± 1.86	20.7 ± 1.92	0.111
MPM (pg)	2.12 ± 0.25	2.19 ± 0.044	0.652
	Survive (n = 24)	Not Survive (n = 15)	P
Hb (g/dL)	12.629 ± 1.8348	11.773 ± 2.3255	0.2092
Leucocyte count (x 10^9/L)	9.169 ± 3.4917	14.704 ± 8.6738	0.0081
Platelet count (x 10^9/L)	288.5 (168 - 563)	156 (57 - 785)	0.0193
MPV (fL)	10.513 ± 0.9575	11.287 ± 1.6075	0.0665
PDW (%)	46.017 ± 7.2464	50.113 ± 7.6203	0.1006
Pct (%)	0.31 (0.18 - 0.59)	0.2 (0.05 - 0.77)	0.0186
MPC (g/dL)	21.267 ± 1.9789	20.82 ± 1.9527	0.4950
MPM (pg)	2.137 ± 0.2074	2.195 ± 0.2359	0.4200

PP13-01

Low survival rate in patients with veno-occlusive disease whose creatinine levels have already begun to increase when defibrotide is administered

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Background : Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is one of the most fetal complication that occurs in the early stage of hematopoietic cell transplantation (HCT). The mortality rate is more than 80% in

severe VOD/SOS patients. In the past, since there was no effective therapeutic agent for severe VOD/SOS, more strict diagnostic criterias were applied. However, with the use of defibrotide in severe VOD/SOS patients, the importance of early diagnosis in treatable patients is emphasized. We conducted this study to confirm the survival rate of VOD/SOS patients diagnosed in Korea and the treatment results of defibrotide.

Method : Patients diagnosed with VOD/SOS after allogeneic HCT at 9 hospitals in Korea from January 2003 to February 2020 were enrolled. Of the 124 patients, a total of 110 patients satisfied the modified Seattle criteria within 50 days after transplantation, and 37 patients were treated with defibrotide. We investigated day +100 survival rates and associated risk factors of patients who satisfies modified Seattle criteria at diagnosis and patients treated with defibrotide.

Results : The mean age was 41.7±16.0 years old, and 58.2% were male. The diagnosis was acute lymphoblastic leukemia in 34.5%, acute myeloid leukemia in 32.7%, and myelodysplastic syndrome in 15.5%. The mean VOD/SOS diagnosis day was 11.1±7.5 days after HCT, and 65.5% of patients satisfied the Baltimore criteria at diagnosis. According to revised EBMT criteria for severity grading, mild, moderate, severe, and very severe patients were 20.9%, 54.5%, 19.1%, and 5.5%, respectively. The number of patients with multi-organ dysfunction was 44.5%. The day +100 survival rate after HCT of 110 patients was 65.3%. The survival rates of patients who did not meet the Baltimore criteria and those who satisfied were 86.8% and 53.7%, respectively (p=0.001). According to the severity, the survival rates of mild, moderate, severe and very severe were 91.3%, 68.3%, 29.8% and 50.0%, respectively (p>0.001). The survival rate of patients with multi-organ dysfunction was as low as 46.1% (vs 80.3%, p<0.001). The day+100 survival rate of patients treated with defibrotide was 50.5%. The survival rates of patients with defibrotide administration within 1 day and after 2 days after diagnosis were 64.7% and 37.4%, respectively (p=0.106). In patients receiving defibrotide, creatinine levels at the time of administration were investigated. The survival rate of patients whose creatinine level was more than 1.2 times the baseline value was significantly lower at 26.7% (vs 67.6%, p=0.014). In multivariate regression analysis, the factors affecting the day+100 survival rate in 110 patients were age, satisfaction of Baltimore criteria at diagnosis, and severity grading. The hazard ratio (HR) of satisfaction of Baltimore criteria at diagnosis was 4.83 (95% confidence interval (CI); 1.79-13.01, p=0.002). In patients treated with defibrotide, the factors affecting survival rate were age and creatinine elevation at administration of defibrotide. The HR was 11.22 (95% CI; 1.56-80.75, p=0.016) when creatinine was more than 1.2 times baseline when administered.

Conclusion : The day+100 survival rate was significantly lower when the Baltimore criteria were satisfied when VOD/SOS was diagnosed, and when there was an increased in creatinine at administration of defibrotide. The use of highly sensitive diagnostic criteria and administration of defibrotide before renal dysfunction improved survival rate.

Keyword : Hepatic Veno-Occlusive Disease, Hematopoietic Stem Cell Transplantation, Risk Factors, Survival Rate

PP13-02

ABO incompatibility and outcomes of allogeneic hematopoietic stem cell transplantation

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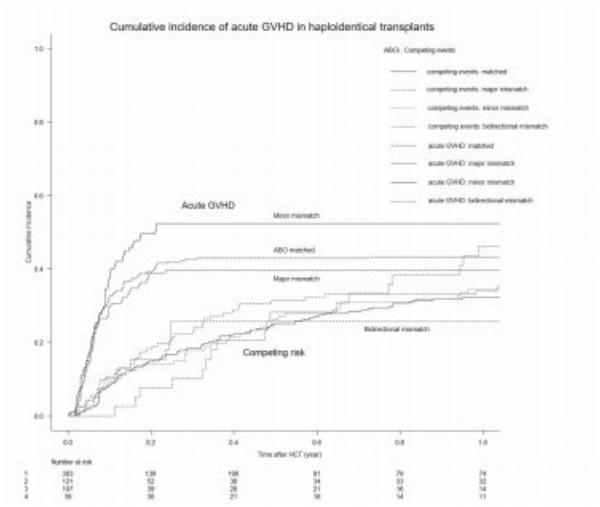
Background : Previous research about impact of ABO mismatch on outcomes of allogeneic hematopoietic stem cell transplantation (HCT) had mixed results. A few studies reported ABO incompatibility had negative influence on non-relapse mortality, engraftment, incidence of acute graft-versus-host disease, while other studies demonstrated no significant relationship between ABO mismatch and outcomes of transplantation.

Method : We analyzed influence of ABO mismatch on outcomes of 2,062 consecutive allogeneic HCT recipients transplanted over period of 28 years (December 1993 – May 2020), with median follow up duration of 5.72 years. Outcomes of HCT included overall survival (OS), event-free survival (EFS), non-relapse mortality (NRM), relapse, incidence of acute and chronic graft-versus-host disease (GVHD), engraftment by cell lineage, and rate of primary and secondary graft failure.

Results : Presence of any ABO mismatch was associated with higher NRM, 1year cumulative incidence 0.177 vs 0.144, p=0.0298, but type of ABO incompatibility did not lead to difference. In major and bidirectional ABO mismatched HCT, there was significant delay in time required for reticulocyte ratio rise to ≥ 1% (median 16 vs 28 days, p<0.0001) and red cell transfusion independence. Other outcomes of HCT, such as OS, EFS, relapse rate, incidence of acute and chronic GVHD, leukocyte/platelet engraftment rate, and incidence of graft failure, there was no significant difference by ABO incompatibility. In haploidentical transplants (28.2%), there was higher incidence of acute GVHD in minor ABO mismatch group (day 180 cumulative incidence 0.523 vs 0.256-0.429 varied by ABO mismatch status, p=0.0197), higher trend in NRM (1 year cumulative incidence 0.310 vs 0.132-0.176 by ABO status, p=0.082). There was no statistically significant difference in other outcomes of HCT in haploidentical transplant group.

Conclusion : ABO mismatch has negative impact on NRM after HCT, and particularly minor ABO mismatch was related with increased incidence of acute GVHD in haploidentical HCT.

Keyword : ABO Mismatch, Hematopoietic Stem Cell Transplantation, Haploidentical Transplantation



PP13-03

DEFIFrance registry study: Defibrotide treatment of veno-occlusive disease/ sinusoidal obstruction syndrome after hematopoietic cell transplantation

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Background : Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially fatal complication that occurs after hematopoietic cell transplantation (HCT) conditioning. In its most severe form, VOD/SOS is associated with multi-organ failure (MOF) and a mortality rate of >80% if untreated. Defibrotide is approved for the treatment of severe hepatic VOD/SOS post-HCT in patients aged >1 month in the European Union and the Republic of Korea, and to treat hepatic VOD/SOS with renal or pulmonary dysfunction post-HCT in adult and pediatric patients in the United States. The DEFIFrance study collected real-world data on the safety and effectiveness of defibrotide in France. This analysis presents final primary data on the subgroup of DEFIFrance patients who received defibrotide for the treatment of severe/very severe VOD/SOS post-HCT.

Method : This post-marketing study collected retrospective and prospective real-world data on patients receiving defibrotide at 53 HCT centers in France from July 15, 2014 to March 31, 2020. VOD/SOS severity was categorized using EBMT criteria (adults) or study steering committee member adjudication (pediatric patients). The primary endpoints included Kaplan-Meier (KM)–estimated Day 100 (post-HCT) survival and Day 100 complete response (CR; total serum bilirubin <2 mg/dL and MOF resolution per investigators' assessment) in patients with severe/very severe VOD/SOS post-HCT. Secondary endpoints included evaluation of adverse events (AEs) of interest, such as hemorrhage, coagulopathy, injection-site reactions, infections, and thromboembolic events, irrespective of their relationship to treatment.

Results : Of the 775 defibrotide-treated patients included in the study analysis, 250 received defibrotide for the treatment of severe/very severe VOD/SOS post-HCT (severe: 119 [48%]; very severe: 131 [52%]). The median patient age was 45 years (range: 5 months, 74 years) and 52 (21%) patients were less than 18 years of age. A total of 219 (88%) patients had received allogeneic HCT and 95 (38%) patients had an unrelated donor. The Day 100 KM-estimated survival was 58% (95% confidence interval [CI]: 52%, 64%) in patients with severe/very severe VOD/SOS post-HCT. The estimated Day 100 survival rate was higher in patients with severe (74% [95% CI: 65%, 81%]) versus very severe (43% [95% CI: 35%, 52%]) VOD/SOS. Among patients with severe/very severe VOD/SOS post-HCT, the CR rate at Day 100 was 53% (95% CI: 47%, 59%). The Day 100 CR rate was higher in patients with severe (68% [95% CI: 60%, 77%]) versus very severe (39% [95% CI: 30%, 47%]) VOD/SOS. Treatment emergent AEs of interest occurred in 41% of patients with severe/very severe VOD/SOS, with infection (23%) and bleeding (17%) being the most commonly reported.

Conclusion : The DEFIFrance study represents the largest collection of real-world data on the use of defibrotide. The effectiveness and safety observed in this study build upon prior studies supporting the utility of defibrotide for treating severe/very severe VOD/SOS post-HCT in a real-world setting. Among patients receiving defibrotide for VOD/SOS post-HCT, outcomes were better in patients with severe versus very severe disease, highlighting the importance of early diagnosis and treatment of VOD/SOS before patients reach the most severe stage of VOD/SOS.

Keyword : Defibrotide, Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome, Hematopoietic Cell Transplantation, Effectiveness, Safety, DEFIFrance

PP13-04

Haploidentical hematopoietic stem cell transplantation for malignant infantile osteopetrosis and intermediate osteopetrosis : A retrospective analysis of a single-center

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Background : Osteopetrosis, which is also called Marble bone disease, refers to a heterogeneous group of rare inherited skeletal dysplasia. Inheritance can be divided into autosomal recessive, autosomal dominant or X-Link1. The most severe cases are almost autosomal recessive and are termed malignant infantile osteopetrosis (MIOP). The prognosis of MIOP is very poor and death in the first decade is common without appropriate therapy. HSCT is the only effective treatment for MIOP. Intermediate osteopetrosis (IOP) is mostly autosomal dominant inheritance of abnormal CLCN7 gene. There are no clear guidelines for transplantation in this kind of patients. Here, we report the long-term survival of 27 cases of haploid hematopoietic stem cell transplantation (haplo-HSCT) in the treatment of MIOP and IOP in Beijing Children's Hospital affiliated to Capital Medical University. In order to further explore the safety and feasibility of haplo-HSCT in the treatment of osteopetrosis.

Method : Children with MIOP and IOP who underwent haplo-HSCT in Beijing Children's Hospital, Capital Medical University, from January 2010 to May 2018 were retrospectively analyzed. Data relating to the clinical manifestations, engraftment, and prognosis of the children were extracted from medical records.

Results : Twenty-seven patients, including 18 males and 9 females, with an onset age of 12 (0.04-72) months, were enrolled in this study. The median time from diagnosis to transplantation was 4 (1-23) months. All patients received haplo-HSCT with myeloablative conditioning regimen (including fludarabine, busulfan, and cyclophosphamide). The graft versus host disease (GVHD) prophylaxis was based on, anti-human T lymphocyte porcine immunoglobulin /anti-human thymus globulin, methotrexate, and mycophenolate mofetil. The median observation time was 55.2 (0.3-126.2) months. By the end of follow-up, twenty patients survived and seven patients died. The five years overall survival (OS) rate was 73.9%, and the five years OS of MIOP and IOP were 73.9% and 100.0% respectively. Acute GVHD degree I-II was observed in 20 patients, degree III in 1 patient and without degree IV. Chronic GVHD was observed in 11 patients (40.7%). It was controlled by anti-GVHD therapy.

Conclusion : Haplo-HSCT was effective for MIOP and IOP, with high survival rate and significantly improved of clinical symptoms. For the patients with vision impairment before HSCT, the improvement was slow after transplantation. The incidence of GVHD was high but mild, and could be effectively controlled after appropriate treatment. These data provided that haplo-HSCT was feasible in the treatment of MIOP and IOP.

Keyword : Malignant Infantile Osteopetrosis, Intermediate Osteopetrosis, Haploidentical Hematopoietic Stem Cell Transplantation, Prognosis, Graft Versus Host Diseases

Table 1 General information

Total patients	27	
Gender（%）	Male	18(66.7)
	Female	9(33.3)
Age at transplant（median）	12months（range：4-107）	
Gene（%）	TCIRG1 compound heterozygosity	18（66.7）
	CLCN7 compound heterozygosity	2（7.4）
	CLCN7 heterozygous mutation	4（14.8）
Visual impairment	26/27	
Hearing impairment	5/27	
Splenomegaly	10/27	
Abnormal hemogram	27/27	

Table 2 Engraftment and GVHD

Overall survival(%)	73.9%	
Engraftment source	Father	19（70.4）
	Mother	8（29.6）
HLA-matched	5/10（3/6）	18（66.7）
	6/10	2（7.4）
	7/10	4（14.8）
	5/6	2（7.4）
	9/10	1（3.7）
Conditioning	TBI（12）+Cy（120）	1
regimen	Flu（120-150）+Bu（16-19.2）+Cy（200）	26
Blood type	matched	12
	mismatched	15
Stem cell infused	MNC $x10^8$/kg	23.12（10.04-51.90）
	$CD34^+$ $x10^6$/kg	10.22（5.96-24.88）
aGVHD(%)		21/27（77.8）
	I-II°	20
	III°	1
	IV°	0
cGVHD(%)		11/27（40.7）
Infection	CMV infection（dead/alive）	0/15
	EBV infection, reactived	10
	bacterial	12
Hemorrhagic cystitis		3
HVOD（%）		5（18.5）
Engraftment failure		0

Note: TBI total body irradiation; Cy cyclophosphamide; Flu fludarabine; Bu busulfan; GVHD graft versus host diseases; HVOD hepatic veno-occlusive disease

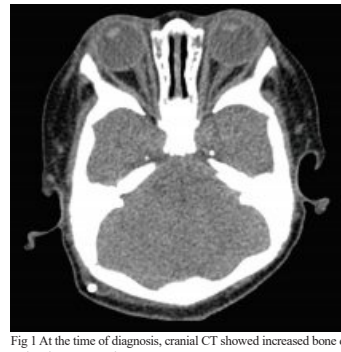

Fig 1 At the time of diagnosis, cranial CT showed increased bone density, thickening of plate barrier and stenosis of bilateral optic nerve canal.

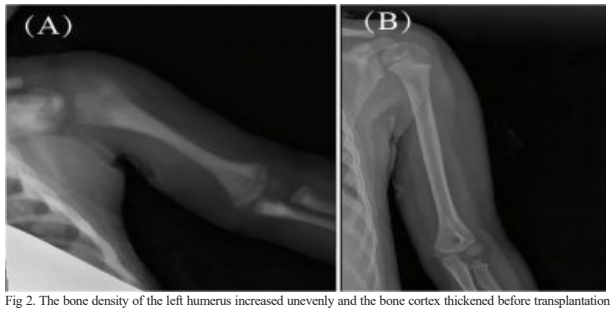

Fig 2. The bone density of the left humerus increased unevenly and the bone cortex thickened before transplantation (A): Four years after transplantation, the bone mineral density decreased and the bone marrow cavity was clear (B).

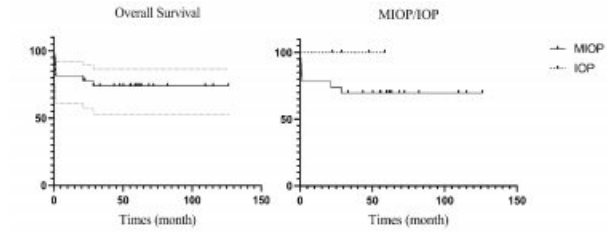

Fig. 3 The 5-year overall survival (OS) was 73.9% in our cohort of 27 patients. Compared with MIOP and IOP, there was no statistically significant between them (73.9% vs. 100.0%, P=0.2444).

PP13-05

Outcome of allogenic hematopoietic stem cell transplantation in chronic granulomatous disease: A single center experience of 31 patients

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Background : Chronic granulomatous disease (CGD) is a primary immunodeficiency caused by genetic defects leading to impaired function of phagocyte. Patients with CGD suffer from life-threatening infections and dysregulated hyperinflammation, and as a result, only about 50% of patients can survive over three decades. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is known for curative option for CGD, but the indication and optimized protocol for transplantation are not established.

Method : We retrospectively analyzed 31 patients who underwent allogenic hematopoietic stem cell transplantation in Seoul National Children's hospital for CGD from January 2010 to December 2020. Targeted busulfan-based myeloablative conditioning using intensive pharmacokinetic monitoring was used uniformly.

Results : The median age at transplantation was 13.8-year-old (range 2.4-30.2). The median follow-up duration was 2.9 years (range 0.5-10.2). The pattern of inheritance was X-linked (19/31, 61.3%) and autosomal recessive (6/31, 19.4%), and the rest (6/31, 19.4%) were not evaluated. Transplants were performed from matched related (7/31, 22.6%), unrelated (14/31, 45.2%), and haploidentical (10/31, 32.3%) donors. Four of unrelated donors had 1 human leukocyte antigen (HLA) allele mismatch. Peripheral blood or bone marrow was used for stem cell source in 21 (67.7%) and 10 (32.3%) of 31 patients. The 3-year overall survival (OS) and event-free survival (EFS) were 82.9% and 73.3%, respectively. The 3-year EFS and OS were not significantly different among related, unrelated, and haploidentical donor transplant, at 71.4%, 83.6%, and 60.0% for EFS (p-value 0.396), and 85.7%, 90.9%, and 70.0% for OS (p-value 0.319). Comparing two groups, haploidentical HSCT and the others, EFS and OS were not significantly different. Age at transplantation and stem cell source did not make significant difference in OS and EFS. Graft failure occurred in 5 patients (5/31, 16.1%). Among 5 patients with graft failure, primary and secondary graft failure were 2 and 3 patients, respectively. Two patients died from infections and others were alive after second allo-HSCT. Three other mortalities occurred from 2 cases of severe chronic lung graft-versus-host disease (GvHD) and a case of pneumonia. Acute GvHD grade II to IV and moderate to severe chronic GvHD occurred in 8 patients (25.8%) and 7 patients (22.6%), respectively. Age at transplantation, donor type, and stem cell source did not influence cumulative incidences of acute and chronic GvHD. Transplantation with peripheral blood was related with prolonged admission compared to bone marrow (p-value 0.030).

Conclusion : We report a promising outcome of allo-HSCT in CGD. Haploidentical donor transplantation, which risk was not evaluated in CGD, tended to have lower survival rates and more complications, but the differences were not significant due to the small number of patients. Despite using myeloablative conditioning, overall graft failure rate was high. Further research is needed to improve engraftment.

Keyword : Hematopoietic Cell Transplantation, Chronic Granulomatous Disease

PP13-06

Benefit of leukemia induction treatment and allogeneic stem cell transplantation for blastic plasmacytoid dendritic cell neoplasm

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Background : Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare aggressive hematologic neoplasm which originates from the professional type I interferon-producing cells or plasmacytoid monocytes. The prerequisite for its diagnosis is the CD4+ and CD 56+ co-expression without common lymphoid or myeloid lineage markers. Recently, targeted therapy with Tagraxofusp (SL-401), an IL-3 fusion protein which binds to CD123, has proved its efficacy with an overall response rate (ORR) of 90% in 32 untreated and 67% in 15 previously treated BPDCN patients. Although several retrospective and small case series has been published so far, there is few population-based study on BPDCN classified after 2008 WHO classification in Asian population.

Method : Data of 35 patients who were diagnosed with BPDCN from April, 2002 to February 2019 in 11 centers of South Korea were retrospectively collected and analyzed. Pathologic slides were reviewed in the central lab by the 2 pathologic experts and were finally confirmed for diagnosis. Overall survival was defined by the period from the date of the initial diagnosis to death by any cause or follow-up loss.

Results : The median age of the patients was 54.5 years (range, 17 - 84 years) with a male preponderance of 71.4% (25 of 35). 5 patients were preceded with hematologic malignancies. The most common initial presenting site was skin followed by lymph nodes, bone marrow, spleen, and liver. 32 of the included patients proceed to treatment with acute lymphoblastic leukemia (ALL)-like regimen (19 patients), acute myeloid leukemia (AML)-like regimen (5 patients) and lymphoma-like regimen (8 patients) (Table 1). Baseline characteristics of age ≥ 65 years, liver involvement and induction chemotherapy with lymphoma-like regimens expected worse prognosis in both univariate and multivariate analysis (Table 2). Among the 32 patients who received induction chemotherapy, 11 cases proceeded to allogenic stem cell transplantation (SCT) and 3 received autologous SCT. With a median follow-up of 16.60 months (range, 0.53-79.73 months), patients who had been treated with leukemia-like induction regimen compared with lymphoma-like induction regimen (39.30 vs. 6.33 months, P=0.005) and allogeneic SCT compared with autologous SCT (54.13 vs. 7.70 months, P=0.015) showed markedly prolonged overall survival (Figure 1 and 2)

Conclusion : Induction treatment with leukemia-like regimen and proceeding to allogeneic stem cell transplantation can prolong overall survival in Asian patients with BPDCN.

Keyword : Blastic Plasmacytoid Dendritic Cell Neoplasm, Allogeneic Stem Cell Transplantation

PP13-07

Evaluation of the bacterial and fungal infection status in hematopoietic stem cell transplantation patients in HCMC blood transfusion and hematology hospital

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Background : Bacterial and fungal infection are the major threat to hematopoietic stem cell transplantation (HSCT) patients and is one of the main causes that contribute to the increased complication and mortality. The aim of this study is to investigate the characteristics of bacterial and fungal infection and isolated pathogens in hematopoietic stem cell transplantation at our institution.

Method : This study is retrospective descriptions of 113 hematopoietic transplantation recipients from 1/2017 to 3/2020 at HCMC Blood Transfusion and Hematology Hospital, both autologous and allogeneic HSCT. We collected and analyzed the data about conditioning regimens, number of infection episodes, the date when infection occured, isolated pathogens and antibiotic / antifungal susceptibility within first 100 days after transplant.

Results : The median age at the time of transplantation was 44 (range, 4-66). There were 64 autologous (56.6%) and 49 allogeneic (43.4%) patients. The most common indication for HSCT was hematologic malignancies such as multiple myeloma (31.9%), acute myeloid leukemia (24.8%), non-Hodgkin Lymphoma (17.7%). There were 20 patients receiving nonmyeloablative HSCT. 108/113 patients (95.5%) were infection following HSCT with 166 infection episodes. Most infections occurred during the neutropenic period. About one-third of patients had two or more infection episodes. There were 17 patients with positive blood culture, including 3 fungal and 14 bacterial bloodstream infections. 26 infection episodes (15.6%) had isolated pathogen. Gram-negative bloodstream infection was more frequent than Gram-positive (50.4% vs 34.5%). On the other hand, the rate of fungal bloodstream infection was 15.3%. We considered that 50% of Gram-negative bacteria were resistant to Carbapenem and Amikacin. Gram-positive pathogens were still sensitive to both Vancomycin and Teicoplanin. The rate of Amphotericin B susceptibility in fungal infection was 75%. Transplant-related mortality (TRM) at day 100 after transplantation was 4%.

Conclusion : The incidence of bloodstream infection was still high,

especially during neutropenia. These results will help guide initial antibiotic treatment and develop strategies to prevent bacterial and fungal infection in the future.

Keyword : Infection, Hematopoietic Stem Cell Transplantation

PP13-08

Outcome of BK virus induced hemorrhagic cystitis in children undergoing haploidentical stem cell transplant with post transplant cyclophosphamide

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Background : BK virus (BKV) reactivation can present as asymptomatic viruria, hemorrhagic cystitis and BKV nephropathy post allogenic stem cell transplant (SCT). Here we describe our outcomes of BKV induced hemorrhagic cystitis (BKV-HC) in children undergoing haploidentical SCT with post-transplant cyclophosphamide (PTCy).

Method : We retrospectively analyzed data from February 2017 to March 2020 of 85 consecutive children who underwent haploidentical SCT with PTCy at our center for BKV-HC.

Results : A total of 11/85 (13%) children developed BKV-HC (mean age 8 +3.54 years). All had blood clots in urine and 4 required catheterizations. All except 1 were male. Diagnosis were Fanconi anemia (FA)-3, thalassemia major-3, leukemia-3 and aplastic anemia (AA)-2. Total body irradiation (TBI) based conditioning was given to 55%. The stem cell source was peripheral blood stem cells (PBSC) in all patients. The donor sex was female in 63%. Nine patients engrafted. Two patients had primary graft failure (thalassemia-1, AA-1) and both died post second haploidentical SCT (adenovirus with BKV-HC-1 & BKV-HC with multi-drug resistant E. coli sepsis-1). The mean stem cell dose infused was 10.76 million CD34 positive cells/kg. Neutrophil engrafted among remaining 9 patients at median of 18 days (13 to 40) and platelet engrafted in 7 patients at median of 20 days (11 to 38). Overall incidence of acute graft vs. host disease (GVHD) 36% (grade III-IV-27%). Overall incidence of chronic extensive GVHD was 18 %. BKV activation occurred at median of 26 days post SCT (12 to 116). BK virus levels by quantitative PCR in blood ranged from 990 to 76,70,880 copies/ml and median levels were 10,000 copies/ml. CMV reactivation was also seen in 72%. Prophylactic ciprofloxacin treatment was given to all patients. Mefloquine was given to 64% patients and Cidofovir to 18 %. The chimerism was fully donor in 82%. Another 4 patients (FA-2, thalassemia-1, leukemia-1) died post engraftment (GVHD grade III with BKV induced thrombotic microangiopathy-1, BKV encephalitis with intracranial bleed-1, Human Corona virus pneumonia-1, BKV & Adenovirus induced thrombotic microangiopathy with Candida Auris sepsis-1). Five patients (45.45%) are alive and disease free at median follow-up of 1.6 + SD 0.88 years.

Conclusion : BKV-HC continues to be serious cause of morbidity and mortality among children undergoing haploidentical SCT with PTCy. BKV-HC was frequently associated with PBSC graft, CMV co-infection, female donor, TBI based conditioning, GVHD and rejection. Acknowledgements- We thank Mr. Indra Bhushan Pandey, our database manager, for retrieving the data

Keyword : BKV Induced Hemorrhagic Cystitis, Haploidentical Stem Cell Transplant, Post Transplant Cyclophosphamide

PP13-09

Predictive model by machine learning through repetitive internal validation for hepatic SOS/VOD and early death after allogeneic-HCT

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Background : We have previously analyzed the risk factors and treatment outcomes of hepatic SOS/VOD after allogeneic-HCT in a large single center cohort by traditional statistical methods. The data revealed the incidence of 3.4%, and male gender, busulfan with myeloablative dose, other than matched sibling donor (MSD), and very high disease risk index scores were in relation with development of SOS/VOD. In this cohort, we attempted to use machine learning algorithms and tried to make a prediction model for SOS/VOD development and early death using pre-HCT parameters, and finally recommendation model was made after repetitive 5-fold cross-validation.

Method : From 2009 to 2018, 2572 consecutive allogeneic-HCT cases were analyzed with various disease, transplantation, and patient related factors by using a boosting tree model (XGBoost) for the prediction of SOS/VOD development (all grades, severe to very severe based on EBMT stratification) and early death within 100-day post-HCT. With SHAP (SHapley Additive exPlanations) values from the tree model, we found significantly affecting 11 immutable and 5 adjustable (SOS/VOD prophylaxis, busulfan or TBI dose, conditioning regimen toxicity, and stem cell source) and finally made a recommendation model which was internally verified by repetitive

5-fold cross validations.

Results : Calculated SHAP values suggested that male gender, busulfan-containing regimen, and young age were significant factors for all SOS/VOD, and male gender, busulfan-containing regimen, and history of liver disease were significant for severe to very severe SOS/VOD, and higher disease risk index, and EBMT or PAM score were significant for early death. Area under Receiver Operation Characteristic curve (AUROC) of our prediction model for the development of all SOS/VOD was 0.759, severe to very severe SOS/VOD was 0.790, and early death was 0.732. One recommendation model for single feature was validated in two subgroups divided into group 1 who followed the model's recommendation, and group 2 who did not follow the recommendation, and the result showed regimen without busulfan or prophylaxis recommendation was the most effective for the prevention of VOD. The recommendation model for the adjustable feature set was validated in 3 subgroups divided into group 1 who corresponded 4~5 features to the recommended set, group 2 who corresponded 2~3 to the recommended set, group 3 who corresponded 0~1 to the recommended set, and showed significantly predictive power for SOS/VOD and early death.

Conclusion : Our recommendation model for SOS/VOD showed reproducibility in repetitive internal validation and possible personalized treatment recommendation, but its role should be validated in prospective research by external cohort when a sufficiently large data set becomes available.

Keyword : Allogeneic HCT, Hepatic SOS/VOD, Risk Factors, Machine Learning, Internal Validation, Recommendation Model

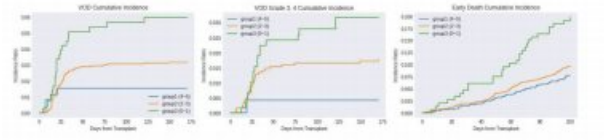

Figure Cumulative Incidence curve of (a) VOD, (b) severe VOD, (c) Early Death for each group 1 (patients who corresponded 4~5 features to the recommended set of the model), group 2 (patients who corresponded 2~3 features to the recommended set of the model), group 3 (patients who corresponded 0~1 features to the recommended set of the model)

PP13-10

Metabolic syndrome as a recognized complication after allogeneic haematopoietic stem cell transplantation: A single Asian institute experience

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Background : Metabolic syndrome (MS) is a disorder characterized by impaired fasting glucose, hypertension, dyslipidaemia and abdominal obesity. This study aims to evaluate the prevalence of MS, risk factors and outcome among patients who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) at a local stem cell transplant institute.

Method : The demographic data of patients who received allo-HSCT in between September 2013 and June 2020 at Hospital Pulau Pinang were collected retrospectively. From a cohort of 44 patients, only 23 patients with adequate clinical and laboratory data were available for analysis. Patients who were transferred to other hospitals, succumbed within 6 months of allo-HSCT and those with < 6 months of follow-up at the time of study were excluded. MS was defined using the Adult Treatment Panel (ATP) III criteria modified for an Asian population.

Results : Of 23 subjects, 11 (47.8%) were males and 12 (52.2%) were females. Nine (39.1%) patients received myeloablative (MAC) regimen while 14 (60.9%) had reduced-intensity conditioning (RIC). Two (8.7%) patients underwent second allo-HSCT for relapsed acute leukaemia. The median age at recruitment was 34.0 (19.0-59.0) years with a median follow-up duration of 35.0 (6.0-78.0) months. Eleven (47.8%) patients had hypertriglyceridaemia, 9 (39.1%) had low high-density lipoprotein (HDL), 8 (34.8%) had hypertension and elevated blood glucose respectively while 2 (8.7%) had abdominal obesity. Only 2 (8.7%) patients had pre-existing metabolic syndrome before allo-HSCT. From the cohort, 7 (30.4%) patients fulfilled the criteria for MS. The median duration from allo-HSCT to diagnosis was 10 (9.0-21.0) months. In subgroup analysis, the mean body weight was significant higher in patients with MS compared to those without this disorder (79.2 kg versus 56.3 kg; P=0.009). There was also a significant association between body mass index (BMI) of ≥ 25.0 kg/m^2 and MS (P=0.036). The mean BMI in MS and non-MS groups was 27.4 kg/m^2 and 22.0 kg/m^2 respectively (P=0.030). All patients with MS had underlying acute leukaemia but it was not statistically significant if compared to non-acute leukaemic cases (P=0.095). Otherwise, there was no significant association between MS and age, race, gender, conditioning regimen, serum creatinine, use of steroids or calcineurin inhibitor and presence of chronic graft-versus-host disease (cGVHD). There was also no difference in the survival outcome among patients with or without MS in our cohort.

Conclusion : With improvement in patient survival after allo-HSCT, MS has become an increasingly common complication in addition to cGVHD, infections and relapses. Early recognition and diagnosis of MS is important for early initiation of treatment. A larger sample size and longer follow-up are warranted to evaluate the impact of MS on survival outcome after allo-HSCT.

Keyword : Metabolic Syndrome, Allogeneic Haematopoietic Stem Cell Transplantation, Impaired Fasting Glucose, Hypertension, Dyslipidaemia, Abdominal Obesity

PP13-11

Efficacy of entecavir versus lamivudine prophylaxis in preventing hepatitis B virus reactivation in patients with allogeneic stem cell transplant

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Background : Immunosuppressive therapy has been the main stay of treatment in patients with hematological malignancies. Reactivation of occult hepatitis B infection (HBV), is commonly encountered with stem cell transplant recipients with anti CD20 agents, with history of resolved HBV infection. We aimed to find the efficacy of nucleos(t)ide analogues lamivudine(LVD) and entecavir(ETV) in preventing the HBV flare up when given prophylactically

Method : Patients who received allogeneic stem cell transplant were evaluated. Sixty patients, thirty in each group who received LVD or ETV prophylaxis were included in the study. All the baseline and post-transplant data was evaluated which includes anti –CD20 agent exposure, duration of prophylaxis of each drugs and clinical and virological follow up post transplantation. Serum ALT, HBsAg, anti HBs and HBV DNA were the parameters measured.

Results : The median clinical and virological follow up in each group was 24 months. LVD or ETV was given during the entire follow up period. There was no reactivation during the prophylaxis period, however 2 patients in LVD group showed detectable viral DNA post prophylaxis withdrawal.

Conclusion : The clinical outcome of both LVD and ETV reveals equal efficacy in preventing HBV reactivation. However screening is mandatory before chemotherapy. HBs Ag-negative/anti - HBc-positive patients require ALT monitoring during the entire chemotherapy

Keyword : Stem Cell Therapy, HBV

PP14-01

Single-cell characterization of hematopoietic stem and progenitor cells in immune thrombocytopenia

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Background : Primary immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by isolated thrombocytopenia. A growing body of emerging evidence indicates that abnormalities during any stage of thrombopoiesis and megakaryocytopoiesis can influence platelet production. Our study concentrated on the hematopoietic stem and progenitor cells (HSPCs) in ITP patients from the perspective of single cell transcriptome.

Method : CD34+ HSPCs were isolated from BM of four newly diagnosed ITP patients and 2 healthy adults as controls by fluorescence-activated cell sorter (FACS), and Single-cell RNA sequencing (scRNA-seq) data was collected using the recommended protocol for the 3' scRNA-seq 10X genomics platform.

Results : We perform scRNA-seq for 50,375 single CD34+ HSPCs, and detected over 3000 expressed genes per cell on average. We visualized the cells in 2D space using t-distributed stochastic neighbor embedding (tSNE) (Fig1. a and Fig1. c). Heatmap showed the scaled expression of top 10 differentially expressed genes in each cluster (Fig1. b). Cell clusters expressed established markers of hematopoietic populations, revealed diverse hematopoietic cell types and implied differentiation trajectories consistent with current views of hematopoiesis. We identified an unambiguous feature of HSPCs in ITP patients with the up-regulation of the metallothionein family genes (MT2A, MT1G, MT1X, MT1E and MT1F), which was most pronounced in megakaryocyte erythroid progenitor (Fig1. d). Metallothioneins (MTs), encoded by these genes, exhibit significant chelating properties and play a key role in trace elements homeostasis, protection against oxidative stress, and toxic heavy metals. Our study suggested that the metallothionein family genes were involved in the pathogenesis of ITP.

Conclusion : Using scRNA-seq, we revealed a hierarchically-structured transcriptional landscape of hematopoietic differentiation of BM CD34+ HSPCs. We observed a significantly increased expression of the metallothionein family genes in newly diagnosed ITP patients, which might relate with the generation of abnormal MKs and be a biomarker potentially using in diagnosis.

Keyword : Immune Thrombocytopenia (ITP), Single-cell RNA Sequencing, Hematopoietic Stem and Progenitor Cells (HSPCs)

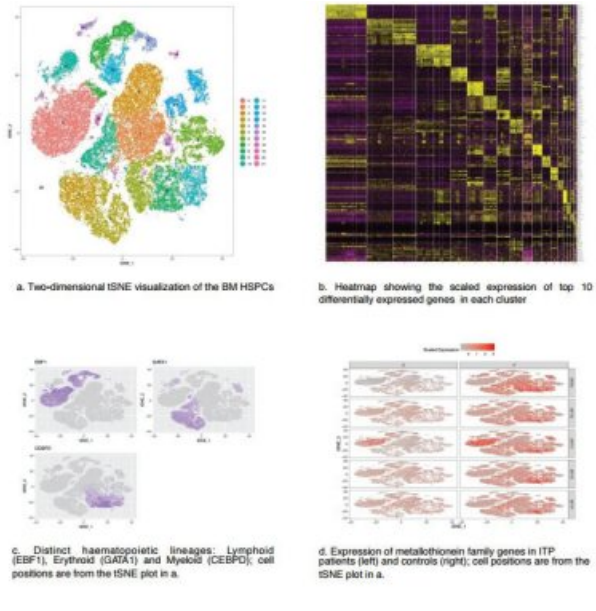

Fig1. ScRNA-seq analysis of the BM HSPCs from ITP patients and controls

PP14-02

SETDB1, histone methyltransferase maintains blood cell homeostasis by modulating the differentiation into cancerous blood cells

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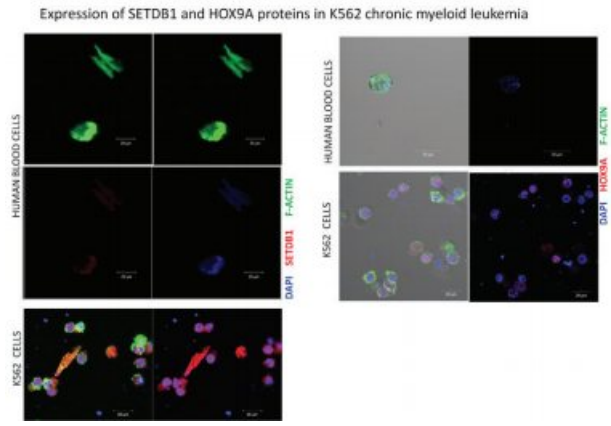
Background : Genome and epigenome regulation is crucial for normal functioning of cells. Role of epigenetic-regulators in suppressing tumor growth is well established. SETDB1 methylates histone-3 at lysine-9. In melanoma, colon-cancer and breast-cancer SETDB1 levels are amplified. We showed through earlier work that SETDB1-/- mutants exhibit hematopoietic defects with blood tumor formation and dysplasia of hematopoietic organ. Lack of SETDB1 in progenitors leads to differentiation of tumor forming blood cells, the lamellocytes. Through current work, we are understanding the differential expression of genes in both heterozygotes and mutants of SETDB1 using two model organisms, Drosophila and in human cancer cell lines (K562, U937, Jurkat).

Method : Through current work we first studied the differential gene expression in SETDB1-/- mutants. Genome wide studies (Microarray) were conducted using SETDB1-/- mutants (feeding third instar larvae) to examine differences in transcripts compared to wild-type animals. Using qRT-PCR the highly upregulated genes were validated. Through immunofluorescence and western blot the expression of SETDB1 protein in cytoplasm versus nucleus, and its target protein expression in both wild type and cancerous blood cells was determined.

Results : Microarray results revealed 653 genes were down-regulated and 598 genes were up-regulated. We found important hematopoietic genes were de-regulated (ex: ADB-A, ABD-B, Toll pathway genes, growth factors IDGF, and Notch). We next determined the levels of SETDB1 protein in blood cells of Drosophila and also human cancer cells (K562, U937, Jurkat). In Drosophila, we found that SETDB1 protein was lower in tumor forming blood cells i.e. the lamellocytes. Its expression was higher in progenitors compared to matured blood cells. While in human cancer cells (K562, U937, Jurkat), we found the expression to be higher compared to normal human blood cells. To our surprise, we found that cytoplasm showed higher levels of protein compared to nucleus. Expression of HOX genes are deregulated when SETDB1 expression is increased (Ceol et al., 20102). Consistently, we found HOX9A protein expression to be lower and strickingly nuclear in all the cancer cell lines (K562, U937, Jurkat).

Conclusion : It was evident from differential expression of HOX genes, Toll/NF-κB pathway genes, Notch and growth factors-IDGFs that SETDB1 modulates expression of these important hematopoietic regulators in wild-type animals. Results from this study will be instrumental in deciphering epigenetic mechanisms that are orchestrated by SETDB1 affecting hematopoietic signaling, HOX gene regulation and their link to blood cancer.

Keyword : SETDB1, Mutants, Tumor, Blood



PP14-03

CH223191, a potent aryl hydrocarbon receptor antagonist promotes the expansion of HPCs and megakaryocyte

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Background : Aryl hydrocarbon receptor (AhR) is widely used to manipulate human hematopoietic stem/progenitor cells (HSC/HPCs), but studies to see an effect on expansion of specific lineage-committed cells using AhR signaling have not been sufficiently conducted. AhR-mediated amplification of HSC/HPCs and specific cell populations are considered a promising approach to developing transplantation therapy thus are potentially important for the treatment of patients with abnormalities in blood homeostasis accompanied by the hematopoiesis hierarchy.

Method : In this study, we performed a multi-color immunophenotyping using the fluorescent-activated cell sorter (FACS) to analyze cord blood-derived cells. And the changes in the number of hematopoietic stem/progenitors (HSC/HPCs), and megakaryocyte population were assessed under treatment of AhR antagonists. For functional validation of expanded HSC/HPCs, we demonstrated the colony formation ability of cultured HSC/HPCs and infused short-term repopulating cells (STRCs) cultured

into the immune-deficient mice for the assessment of the in vivo engraftment efficacy. Transcriptome sequencing was performed with total RNA extracted from the HSC/HPCs cultured with or without AhR antagonists.

Results : AhR antagonism of CH223191 affects the HSC/HPCs and megakaryocyte (MK) lineage populations. CH223191 treated ex vivo culture expands the number of HSCs (Lin-CD34+CD38-CD90+CD45RA-) and myeloid progenitors of multipotent progenitors (MPPs, Lin-CD34+CD38-CD90-CD45RA-), lymphoid-primed multipotent progenitors (LMPPs, Lin-CD34+CD38-CD90-CD45RA+), and myeloid progenitor-like populations (Lin-CD34+CD38+CD45RA-). These four HSC/HPC fractions increased by 1.62-, 1.54-, 1.40-, and 1.56-fold, respectively by treatment-culture for 7 days, and the extended culture led to the increase in the number of four populations 2.17-, 1.63-, 1.56-, and 1.80-fold. CH223191 treatment showed great maintenance of their functionality. In the colony forming assay (CFA), the colony forming unit (CFU) count of each class was increased in the CH223191-treated group, compared to the control. Engraftment of short-term repopulating cells (STRCs) in the immune-deficient mice was significantly increased in the CH223191 treated group. CH223191 increased not only the absolute count of megakaryocyte-erythroid progenitors (MEPs) but also overall MK lineage cells including megakaryocyte progenitor (MKp, CD34+CD41+) populations. With this increase in progenitor level of megakaryocyte lineages, the treatment gives an excellent expansion in the absolute number of both immature MK (CD41+CD42b-) and mature MK(CD41+CD42b-) populations, including CD41+tetraploid (4N) MKs, which has a relatively high thrombopoiesis capacity. Differ from the SR1, CH223191 mediated AhR antagonism showed major contribution to the megakaryocyte/platelet-related signaling pathway (e.g. PF4, PPBP, SELP, and VWF) rather the regulating the AhR-responsive genes (e.g. FST, EPB41L3, FAM171A1, and TIPARP). Referring this transcriptome analysis, CH223191 was more likely to have intimate involvement with blood homeostasis and thrombopoiesis than SR1 treatment in hematopoiesis.

Conclusion : Taken together, this simultaneous effect on stem/progenitors and mature blood cells suggests that the possibility of AhR antagonist CH223191 to use as a therapeutic agent for the treatment of hematologic disorders. In addition, this might also contribute to the development of cord blood manipulation techniques that can be applied to adult cord blood transplantation (CBT) and platelet transfusion.

Keyword : Hematopoietic Stem Cell, Cord Blood, Aryl Hydrocarbon Receptor, Stem Cell Expansion, Megakaryocyte

PP14-04

Clonal hematopoiesis in cardio-cerebrovascular diseases

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Background : Clonal hematopoiesis is when hematopoietic stem cell starts making blood cells that all have the same changes in their DNA. The blood cells with the genetic mutation are different than the rest of blood cells. One of the surprising risk association is the connection between clonal hematopoiesis and cardiovascular disease. In this study, we investigated the mutations profiles using the next generation sequencing (NGS) in patients admitted to Busan Regional Cardio-cerebrovascular Center, Busan in Korea.

Method : NGS analysis was done in the form of targeted sequencing using DNA isolated from peripheral blood and Illumina MiSeqDx. The panel employed was myelodysplastic syndrome (MDS) panel including 49 prevalent genes. Somatic variants were correlated with clinical and laboratory findings.

Results : In acute coronary syndrome patients, tier 3 mutations were found in 66.7% and DNMT3A mutation was one of them. Interestingly in acute cerebral infarctions, also about 66.7% of patients showed at least tier 3 variants and 50% of them showed tier 1 variants in DNMT3A genes. In control group, there were no tier 1 variants identified.

Conclusion : The most frequently mutated genes in clonal hematopoiesis were reported to be DNMT3A, TET2, and ASXL1. The prevalence was much higher than expected. More thorough understanding of clonal hematopoiesis and associations with hematologic malignancies and cardiovascular diseases is warranted.

PP14-05

Sivelestat-loaded nanostructured lipid carriers modulate oxidative and inflammatory stress in human dental pulp and mesenchymal stem cells subjected to oxygen-glucose deprivation

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Background : Stroke remains the leading cause of morbidity and mortality. Stem cell-based therapy offers promising hope for survivors and their families. Despite the clinical translation of stem cell-based therapies in stroke patients for almost two decades, results of these randomized controlled trials are not very optimistic. In these lines an amalgamation of nanocarriers based drug delivery with stem cells holds great promises in enhancement stroke recovery.

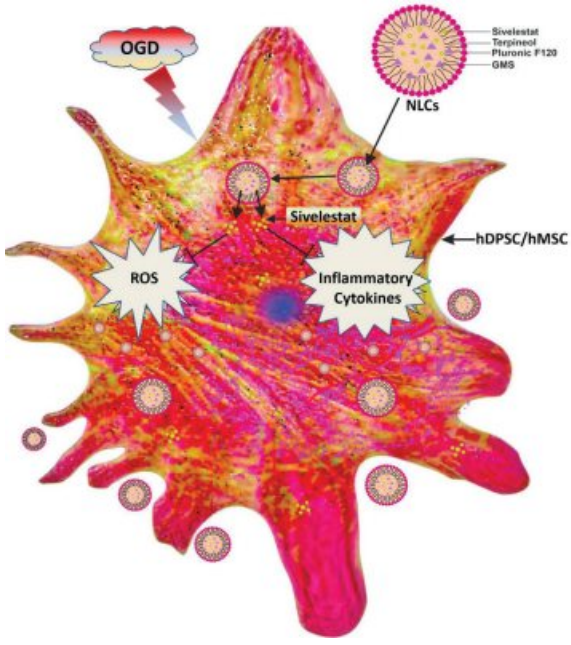
Method : In the present study, we employed Sivelestat loaded Nano Lipid Carriers to dental pulp stem cells and mesenchymal stem cells exposed to the oxygen-glucose treatment. Various physicochemical

limitations associated with sivelestat applications and its recent inefficacy in the clinical trials necessitates the development of novel delivery approaches for sivelestat. Therefore, to improve its efficacy on the survival of DPSCs and MSCs cell types under oxygen-glucose deprivation treatment, the current NLCs were formulated and characterized.

Results : Resulting NLCs exhibited a hydrodynamic diameter of 160 - 180 nm by DLS technique and possessed good PDI values of 0.2 - 0.3. Their shape size and surface morphology were corroborated with microscopic techniques like TEM, SEM, and AFM. FTIR and UV-Vis techniques confirmed nanocarriers' loading capacity, encapsulation efficiency of sivelestat, and its release behavior. Oxidative stress in DPSCs and MSCs was assessed by DHE and DCFDA staining, and cell viability was assessed by Trypan blue exclusion test and MTT assay. Results indicated that Sivelestat loaded NLCs protected the loss of cell membrane integrity and restored cell morphology. Furthermore, NLCs successfully defended human DPSCs and MSCs against OGD induced oxidative and inflammatory stress.

Conclusion : In conclusion, modulation of oxidative and inflammatory stress by treatment with sivelestat loaded nanocarriers in DPSCs and MSCs provides a novel strategy to rescue stem cells during ischemic stroke.

Keyword : Mesenchymal Stem Cells, Dental Pulp Stem Cells, Oxygen-Glucose Deprivation, Sivelestat, Nanostructured Lipid Carriers, Oxidative Stress and Inflammatory Stress



PP15-01

A combination of immunoadjuvant nanocomplex and dendritic cell vaccine in the presence of immune checkpoint blockade for effective cancer immunotherapy

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Background : Nanovaccines have emerged as a promising drug delivery platform and immunoadjuvants for cancer immunotherapy, particularly in combination with other anticancer therapies, which can modulate immune cells and tumor microenvironments

Method : In this study, we investigated the therapeutic efficacy of a combination treatment consisting of an immunoadjuvant nanocomplex, a dendritic cell (DC) vaccine, and PD-L1 blockade in a murine colon cancer model. The immunoadjuvant nanocomplex was formulated by complexing poly I:C with positively charged polysorbitol-co-polyethylenimine (PSPEI-PIC).

Results : We found that peritumoral administration of PSPEI-PIC combined with DC vaccination and PD-L1 blockade (PSPEI-PIC + DCs + PD-L1 blockade) triggered long-lasting systemic anti-tumor immune response, which inhibited of both treated and non-treated distant tumors in the murine colon cancer model. Additionally, PSPEI-PIC + DCs + PD-L1 blockade significantly inhibited various immunosuppressive factors and enhanced the activation of immune effector cells in the serum, spleen, and tumor microenvironment.

Conclusion : These findings suggest that the combination of the immunoadjuvant nanocomplex and DC vaccination with PD-L1 blockade exerts potent anti-tumor effects by synergistically inhibiting immunosuppressive cells and activating effector cells with superior polarization of Th1/Th2 balance in favor of tumor immune response. Hence, this new combinatorial therapeutic approach paves the foundation for the future development of immunotherapeutic modalities that inhibit tumor growth and restore systemic immune function.

PP15-02

Production and in vivo evaluation of chimeric antigen receptor (CAR)-γδ T cells

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Background : The chimeric antigen receptor (CAR) focuses the function of T cells on specific cell surface tumor antigen. CAR-T cell therapy has been used in cancer treatment and has an impressive response, especially to hematological cancers. The CAR directly recognizes cancer cell antigens and can attack regardless of the major histocompatibility complex (MHC) type. CAR-T cell therapy has been successful in clinics, but complications and side-effects hamper wide application. Gamma delta T (γδ T) cells are a distinct subset of unconventional T cells that represent about 1-5% of peripheral blood mononuclear cells (PBMCs). γδ T cells exhibit both adaptive and innate-like behaviors towards tumor cells. Unlike αβ T cells, they have the ability to recognize antigens without MHC restriction, which reduces the risk of graft-versus-host disease (GvHD). As well as T cells, CAR is introduced into immune cells with a cytotoxic ability such as gamma delta T cells and utilized in cell therapy.

Method : PBMC were isolated from healthy volunteers (IRB No. 2015-0307). Cell surface markers were characterized through flow cytometry. γδ T cells were cultured in the presence of 20 ng/mL IL-7 + 1 μg/mL PHA, 100 U/mL IL-2 + 50 ng/mL IL-15, or 100 U/mL IL-2 + 50 ng/mL IL-15 + 100 μM zoledronate (ZOL) for 2 weeks. Lentiviral vector to express CD19-CAR (FMC63-CD8 hinge) was transduced at day 10 in culture. Cytotoxicity was analyzed using 7-amino actinomycin D (7-AAD) and Annexin V in OCI-Ly7 cells, a human B cell lymphoma cell line. NSG mice were intraperitoneally injected (i.p.) with Carboxyfluorescein succinimidyl ester (CFSE)-labeled SU cells, and γδ T cells transduced with CD19-CAR were injected 30 minutes later. After 48 hours, peritoneal lavage was harvested and analyzed by flow cytometry.

Results : Vδ1 γδ T cells were expanded 10-fold in the presence of IL-2+IL-15, while Vδ2 γδ T significantly proliferated 114 in the presence of IL-2+ZOL+IL-15. γδ T cells were confirmed to express the activating (NKG2D, CD16, DNAM-1), cell death (TRAIL, FasL) and immune checkpoint (PD-1, BTLA) molecules. Except for PD-1, Vδ2 γδ T cells expressed the markers listed above approximately 1-2 fold more, compared with Vδ1 γδ T cells. In vitro, CAR-γδ T cells exhibited about 2-5% higher cytotoxicity than that of γδ T cells without CAR. In vivo, mice injected with ex vivo expanded CAR- γδ T cells showed 11 times lower levels of SU cells than mice injected with SU only.

Conclusion : This study shows γδ T cell expansion to be engineered with CAR under different conditions. As a result, γδ T cells transduced with CAR exhibited advanced tumor cell killing ability in vitro and in vivo without compromising the expression of multiple receptors.

Keyword : Chimeric Antigen Receptor (CAR), γδ T Cells, CAR-γδ T Cells, Immunotherapy

PP16-01

ABO blood groups may play a role in the development of dengue hemorrhagic fever: A meta-analysis

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Background : According to the World Health Organization (WHO), the global burden of dengue fever has grown dramatically all over the world. About 390 million dengue infections are manifested per year and the widespread presence of these cases are not only causing an endemic of multiple dengue virus serotypes, but are becoming an outbreak in different areas of the world. Today, because of the distribution trend of dengue worldwide, it is now an alarming and a serious global burden for it not only influences human health but also global and national economies. The dengue virus comes from the Flaviviridae family. Four distinct serotypes of the virus, DEN-1, DEN-2, DEN-3, and DEN-4, may cause any one of the scenarios: undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome or DSS (Kalayanarooj et al., 2007). The virus is vector-borne, primarily transmitted through a bite of an Aedes aegypti mosquito. Characteristics of a dengue fever does not limit on a severe, flu-like illness, but goes through having severe headache, joint pains, nausea, respiratory distress, and restlessness. Laboratory examinations of dengue patients reveal leukocytopenia and thrombocytopenia. Progression into DHF is characterized by an increased vascular permeability due to plasma leakage. The permeability of the blood vessels in DHF patients may be linked to the ABO blood group of patients since it ABO antigens are found to be confined to the endothelium of human tissues (Wang et al., 2013). The association of ABO blood groups with dengue fever and its severity has been cited in previous studies (Kalayanarooj et al., 2007; Khode, Ruikar, & Kabbin, 2013; Murugananthan et al., 2018; Sari et al., 2018; Sjafaraenan, Alvionita, Agus, & Sabran, 2018). Previous findings revealed that AB positive individuals were discovered to be 2.5 times susceptible to infection with dengue virus than other blood types (Murugananthan et al., 2018). This finding was supported by a related study which states that AB blood group individuals were more likely to develop dengue hemorrhagic

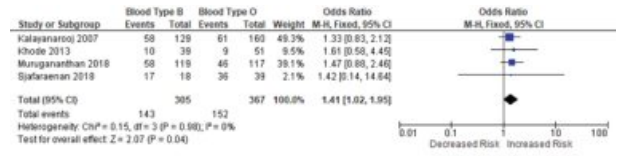
fever (Kalayanarooj et al., 2007). However, some studies contradict these findings through their conclusion that dengue infection is more common in persons with blood group O (Khode et al., 2013; Sjafaraenan et al., 2018). These contradicting data leaves a question unanswered regarding which blood type is most likely to develop or be associated with dengue fever and DHF. The purpose of this meta-analysis is to identify which ABO blood group is the most susceptible in contracting severe forms of dengue infection, specifically DHF. In addition, the possible role of ABO blood group antigens in the development of DHF is also included in this study.

Method : Search for related publication was carried out in PubMed using the following key search terms: "ABO blood group" and "dengue". An initial screening was done by checking the title and abstract of the resulting studies. After removal of irrelevant and duplicate studies, full texts of the articles were retrieved and were manually checked. Studies that contain the incidence of both dengue fever and dengue hemorrhagic fever, studies that grouped their participants based on their ABO blood type, and those written in English were included in the analysis. Cited reference from each text were also reviewed for possible additional studies. All studies were investigated independently by two of the authors (A Policarpio and IS Aguas). Two of the authors (A Policarpio and IS Aguas) independently extracted data and reached to a consensus on all the items. Any disagreement was resolved by a third author (RE Tiongco). For study included, the following information was extracted: (i) the first author's last name; (ii) year of publication; (iii) total number of participants included; and (iv) total number of participants with dengue fever and dengue hemorrhagic fever per ABO blood type. Statistical analysis for this study was carried out using Review Manager 5.3 (Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2014). The meta-analysis protocol used was based from the previous study of one of the authors (Tiongco et al., 2018). Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained and pooled using either the fixed- (absence of heterogeneity) or random-effects model (presence of heterogeneity) (DerSimonian & Laird, 1986; Mantel & Haenszel, 1959). Heterogeneity among the studies was investigated using a Chi-square based Q test (Lau, Ioannidis, & Schmid, 1997). The degree of heterogeneity was measured using I2 statistics (Higgins, Thompson, Deeks, & Altman, 2003). Due to the low power of the test, p-value (PH) for heterogeneity testing was set at <0.10 (Higgins & Thompson, 2002) whereas, p-value (PA) for association were two-sided with significance threshold set at <0.05. Sensitivity analysis determines the effect of the individual studies on the pooled ORs. This is done by systematic removal of one study at a time. This analysis determines the robustness of the overall outcomes. The study is robust if p-values for both association and heterogeneity remain the same all throughout. Publication bias was no longer performed due to the low sensitivity of the test when the number of studies is <10 (Ioannidis & Trikalinos, 2007).

Results : Overall, the total number of participants for the meta-analysis is 1,027. Diagnosis of DF was carried out through serological testing of dengue virus IgM/IgG in three of the included studies (Kalayanarooj et al., 2007; Khode et al., 2013; Murugananthan et al., 2018). As for the diagnosis of DHF, two studies utilized the WHO guidelines on DHF diagnosis. Standard hemagglutination method was used in all included studies for the determination of the ABO blood type of the participants. A total of four studies were included in the analysis of the association of the presence of ABO blood group antigens with DHF. In the fixed-effects model, non-blood type O (test group) was tested against blood type O (control group) achieve this objective. Overall analysis revealed that there is no significant heterogeneity (PH=0.98) among the included studies. No significant association was observed between the presence of ABO blood group antigens and DHF (OR: 1.26; 95% CI: 0.96-1.67; PA=0.10). Sensitivity analysis by omitting one study at a time did not alter the results of the analysis. Four studies were included in the analysis of the association of individual non-O blood groups with DF and DHF. In the fixed-effects model, each non-blood type O group (i.e. A, B and AB blood groups) was used as a test group while blood type O was utilized as the control group for the three comparisons. Among the three forest plots, only blood type B showed a significant association with DHF in comparison with the control group (OR: 1.41; 95% CI: 1.02-1.95; PA=0.04). As seen in Figure 4 (attached image), blood type B has an increased risk of developing DHF. Sensitivity analysis by omitting one study at a time did not alter the results of the analysis.

Conclusion : To the researchers' knowledge, this is the first meta-analysis conducted to determine the association of the presence of ABO antigens and individual ABO blood groups with DHF development. The results of this meta-analysis suggest that blood group B individuals with dengue fever are more likely to develop DHF in comparison with blood type O individuals. No significant association was observed in the analysis of the association of ABO blood group antigens with DHF. Based from the results generated in this study, further analysis of or case-control studies on the association of ABO antibodies with DHF development may help explain why type B dengue patients are more likely to progress into DHF. Doing so will provide additional knowledge and understanding on the pathophysiology of DHF. Thus, potentially improving the treatment and management of dengue patients. Lastly, more studies are needed to confirm the claims of our results. In addition, further studies in a Philippine setting are recommended.

Keyword : ABO, Dengue Hemorrhagic Fever, Meta-Analysis



PP16-02

Transfusion of the least-incompatible blood with intravenous immunoglobulin and steroid to a patient with anti-Fy(a)

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Background : Antibodies to high-incidence antigens is one of the most challenging issues in transfusion medicine. Some researchers have suggested strategies to prevent hemolytic transfusion reactions, such as the use of intravenous immunoglobulin (IVIG), steroids, plasma exchange, and so on. Transfusion of the least-incompatible red cell unit is a standard practice for dealing with the issue, resulting in unfavorable outcomes in some instances. In this case, we attempted to transfuse least-incompatible blood with IVIG and steroid to a patient with anti-Fy(a) antibody, which is a rare antibody resulting in difficulties in transfusion medicine in East Asia.

Method : A 39-year-old female patient with liver cirrhosis due to autoimmune hepatitis, systemic lupus erythematosus, and chronic kidney disease on hemodialysis was admitted for nausea, vomiting, and general weakness. Her hemoglobin level was 5.5 g/dL. Antibody identification tests showed anti-E, c, Jk(b), and Fy(a) alloantibodies. Since Fy(a) is a high-incidence antigen in East Asia, she was transfused with one unit of the least-incompatible RBC containing Fy(a) antigen, in conjunction with IVIG and hydrocortisone.

Results : Evidence of mild hemolysis was found on laboratory tests the following day: increased total bilirubin and plasma hemoglobin, decreased haptoglobin, and positive result on direct antiglobulin test. The hemoglobin level had increased to 7.3 g/dL, and this was sustained at 6.7 g/dL and 7.1 g/dL, respectively, 1 week and 2 weeks after the last transfusion.

Conclusion : We successfully administered the least-incompatible blood with IVIG and steroids. To our knowledge, this is the first case reporting the application of this strategy for treating a patient with anti-Fy(a) antibody.

Keyword : Duffy Blood-Group System, Intravenous Immunoglobulin, Steroid, Red Blood Cell Transfusion, Hemolytic Transfusion Reaction

PP16-03

The benefit of lekodepleted PRC transfusion for biliary patient after Kasai procedure

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Background : Patients with choledochal tract problems often needed surgery. The common procedure for this problem is Kasai portoenterostomy. However, some problems arising after surgery. Many patients encounter the bleeding problem that needed packed red cell (PRC) transfusion. This transfusion, which may increase the risk of transfusion reaction mediated by inflammatory cytokine. Accumulation of interleukin-8, one of the inflammatory cytokines produced by leukocyte contain in PRC, has been known to contribute to increasing transfusion reaction risk. Lekodepletion is an effort to decrease leukocyte number in PRC, give expectation to decrease IL-8 accumulation in PRC.

Method : The study is a quasi-experimental study. Subjects were biliary patients after Kasai Procedure who need PRC transfusion in Dr. Sardjito General Hospital Yogyakarta, after meet inclusion and exclusion criteria. The interleukin-8 level is measured using the ELISA sandwich method from mediana cubiti vein samples which are withdrawn just before and 1 hour after PRC transfusion. Delta IL-8 is obtained from the subtraction of IL-8 level one hour after transfusion with before transfusion. Statistical analysis was performed using the difference test to know significant differences of delta IL-8 mean value between lekodepleted and non-lekodepleted PRC.

Results : Total study subjects were 77 persons, most were women 52 (67,5%). There was no significant differences between group received lekodepleted with non-lekodepleted PRC transfusion based on age (p=0.484), gender (p=0.410). There was a statistically significant median difference in delta interleukin 8 between groups. Increased level of IL-8 value for group received lekodepleted PRC transfusion is less than group received non-lekodepleted PRC transfusion.

Conclusion : Lekodepletion PRC have potential benefit for biliary patients after Kasai procedure.

Keyword : Transfusion, Lekodepleted PRC, Biliary Patients

PP16-04

A comparative evaluation of effect of DTT and heat on ABO isoagglutinin titers in 2005 group O donors

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Background : ABO antibodies are known to play a major role in outcome of ABO incompatible grafts in case of solid organ as well as hematopoietic stem cell transplants. Anti-A and anti-B antibodies belonging to individuals of A and B blood group are predominantly IgM type while those of blood group O are predominantly IgG type. In order to determine the actual concentration of clinically significant IgG antibodies, there is a need to denature IgM antibodies; which can be performed by the use of DTT or heat. The aim of the present study was to compare the effect of DTT treatment and heat inactivation on ABO isoagglutinin titers performed by column agglutination technology (CAT) and conventional tube technique (CTT).

Method : This was a prospective, observational study conducted from October 2018 to March 2020. All consecutive O group donors were included. Serum from each donor was treated with DTT and heat and tests were performed by CTT and CAT before and after each treatment.

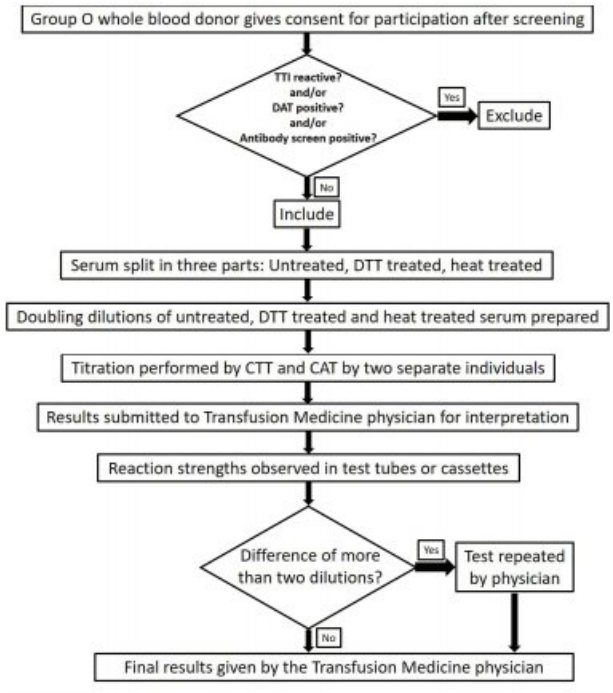
To reduce inter-observer bias for manual (CTT) and semi-automated (CAT) methods, each sample was given to two different personnel to perform the test.

Results : A total of 2005 group O donors were included. A total of 1916 (95.5%) were male and 89 (4.4%) were female. Mean age of the participants was 32.2±8.05 years. 401 (20%) samples had inter-observer variation by CTT and 69 (3.4%) had inter-observer variation by CAT. When performed by CAT, the range and mean of anti-A (HI: 2-4096, 312; DTT: 2-2048, 260) and anti-B (HI: 4-4096, 382; DTT: 4-1024, 294) titers were higher than anti-A (HI: 2-1024, 76; DTT: 1-256, 42) and anti-B (HI: 2-512, 80; DTT: 2-128, 48) titers performed by CTT. Median anti-A (CTT: 64, CAT: 256) and anti-B (CTT: 64, CAT: 256) IgG titer results showed a one to two-fold difference between CTT and CAT with titers reported by CAT being higher. Median titers post DTT treatment showed a two to three-fold decrease (anti-A: CTT-16, CAT-32; anti-B: CTT-16, CAT-64) whereas with heat inactivation, one-fold decrease (anti-A: CTT-32, CAT-128; anti-B: CTT-32, CAT-128) was observed. Concordance between post treatment (DTT and heat) titers was found to be poor. However, correlation between these categories was found to be strong.

Conclusion : This is the first study to compare effect of DTT and heat on ABO titers performed by two different methods on more than 2000 group O donors. The authors found that there is a definite overestimation of ABO IgG antibody titers due to presence of IgM antibodies and hence, estimation of ABO IgG titers after inactivation of IgM antibodies is strongly recommended. However, on comparing the two most commonly used methods, the authors found that DTT treatment was superior to heat inactivation in terms of efficiency in elimination of IgM activity.

Keyword : Immunohematology, ABO, Isoagglutinin Titer, DTT, CTT,

Figure 1: Algorithm for the study



PP16-06

Does Rh and Kell phenotyping of donor units complement type and screen method of compatibility testing?

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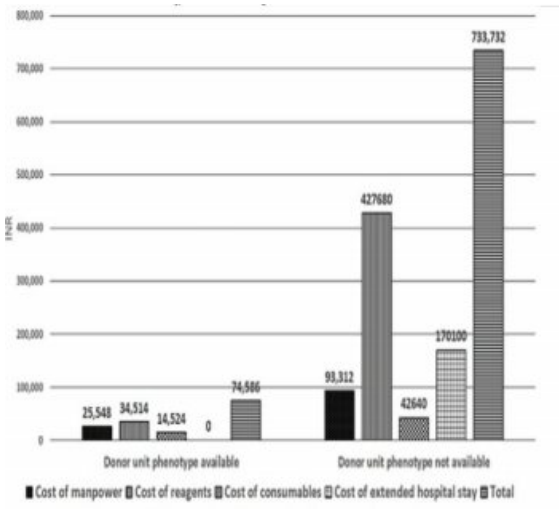
Background : Despite knowing benefits of extended phenotyping, a vast majority feel that phenotype matched units add to cost of blood banking. The purpose of this study was to discuss the advantages and disadvantages of performing Rh Kell phenotyping in Indian scenario by assessing:
a) Prevalence of C, c, E, e, K antigen frequency in donors and degree of patient and donor Rh-Kell phenotype matching
b) Prevalence of clinically significant Rh-Kell antibodies in patients
c) Follow-up of patients transfused prophylactically antigen matched red cell units for alloimmunization
d) Laboratory and cost benefit of performing Rh-Kell phenotyping in resource constraint settings

Method : This was a prospective, observational study conducted between July 2014 and February 2020. All consecutive donors and all consecutive patients whose samples were sent for Rh-Kell phenotyping were included for calculating antigen, phenotype and gene frequencies. For rate of alloimmunization in patients transfused with phenotype matched units, all patients who were given Rh-Kell phenotype matched transfusions were included in the prophylactic antigen matched (PAM) category and those who were given random units were included in the non-PAM category.

Results : A total of 37,588 donors and 258 patients were included for calculation of antigen, phenotype and gene frequencies. Percentage similarity of phenotypes between patient and donor populations was 67.69%. For rate of alloimmunization, results of a total of 31,991 patient samples revealed 0.94% prevalence of unexpected antibodies; highest against the Rh system (70.73%, 145 of 205). Of the 258 patients who were Rh-Kell phenotyped and followed up for alloimmunization, there were 151 patients in PAM category and 107 in the non-PAM category. A total of 439 and 372 units were transfused to patients belonging to PAM and non-PAM categories respectively. Three patients in the non-PAM category and one in the PAM category were alloimmunized during follow-up. Significant clinical and laboratory impact of phenotyping was observed in terms of reduced turnaround time and consumption of resources.

Conclusion : Rh-Kell phenotyping of donors can prevent alloimmunization, reduce cost burden on the patient and the laboratory, help the laboratory personnel in smooth routine testing and at the same time be cost effective even in a resource constraint setting.

Keyword : Rh, Kell, Extended Phenotype, Antigen Matched, Alloimmunization



PP16-07

Convalescent plasma therapy in severe to critical COVID-19 patients in the De La Salle University Medical Center: A case series

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Background : The number of affected COVID-19 patients continues to increase as well those who suffer significant morbidity and some even succumbing to the illness. Clinical trials are still underway for definitive data regarding definitive treatment strategies with proven benefit and efficacy for this novel coronavirus. Thus, it is crucial to find alternative treatment options especially among patients suffering from severe to critical illness. Convalescent plasma therapy (CPT) has been a promising option with good safety profile in the treatment for emerging viral illnesses such as COVID-19.

Method : Case series of 9 patients with laboratory-confirmed COVID-19, diagnosed using quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR) who presented with acute respiratory distress syndrome (ARDS) (defined as severe or immediately life threatening pneumonia with rapid progression; Pao2/Fio2 <300; and need for mechanical ventilatory support) were given convalescent plasma as compassionate use in combination with other investigational treatment (Remdesivir, Tocilizumab, steroid therapy, anticoagulation and hemoperfusion). Demographic and clinical characteristics of patients who received CPT were taken from review of medical records. Pulmonary function (Pao2/Fio2) and laboratory markers (CRP (mg/L) and Absolute Lymphocyte Count (cells/uL)) pre-and-post CP infusion were analyzed. This case series was conducted at the De La Salle University Medical Center, Philippines from June to August 2020.

Results : Patients were classified based on pneumonia severity: 5 patients had severe pneumonia and 4 had critical pneumonia. All patients who received CPT had underlying comorbid condition/s: obesity (2), Type II diabetes mellitus (3), chronic heart disease (7), chronic lung diseases (3), and thyroid disorder (1). The date of illness upon admission ranged from Day 3 to 14 (median of 9 days). Timing of convalescent plasma infusion to date of illness ranged from Day 8 to 19 (median of 13 days). Four out of five who were given convalescent plasma before the 14th day of illness showed improvement of PaO2/FiO2 and decrease in CRP levels while two out of five showed increase in absolute lymphocyte count. In contrast, for those who received CPT on or beyond 14th day of illness, three out of four patients had decreased CRP and all four patients had increase in PaO2/FiO2 post-transfusion. Out of the 9 patients who received CP infusion, five patients were discharged and four expired. There was a 40% mortality among patients who underwent CPT before 14th day of illness, and 50% mortality among patients who underwent CPT on or beyond 14th day of illness.

Conclusion : In this case series, we noted that early administration of CPT (before 14th day of illness) had decreased mortality compared to those receiving the infusion on or after the 14th day of illness. Moreover, there was notable decrease in CRP levels and improvement of PaO2/FiO2 in majority of patients post CP infusion regardless of CPT timing. However, the limited number of patients in this case series impede us in giving a conclusive statement about the overall efficacy and usefulness of CPT in patients with severe to critical COVID-19 infection. In addition, all patients were given other investigational treatment hence it is difficult to give a definite conclusion that the observed improvement in some patients could be attributed solely to CPT. Hence, it is recommended that further well-designed randomized clinical trials be done to evaluate these observations.

Keyword : Convalescent Plasma Therapy, COVID-19

PP16-08

Transfusion in coronavirus disease 2019 patients: A preliminary study in tertiary hospital in Daegu

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Background : Transfusion support is essential for patient care. COVID-19 can impact blood supply and transfusion needs significantly. We preliminarily investigated blood types and transfusion status among COVID-19 patients in a tertiary hospital in Daegu.

Method : We performed a retrospective study of ABO-Rh type, transfusion rate, unexpected antibodies, hemoglobin (Hb), platelet count (PLT), and blood component type among 315 patients with COVID-19 diagnosed at Yeungnam university medical center from February to May 2020.

Results : In a total of 315 patients, ABO-Rh types were reported in 14.9% (n =47); 6.3% of A+ (n =20), 3.8% of B+ (n =12), 3.5% of O+ (n =11), and 1.3% of AB+ (n =4). 3.2% (n =10) received transfusion; A+ (n =3), B+ (n =3), O+ (n =3), AB+ (n =1). In these patients, unexpected antibodies were not detected. Medan (interquartile range [IQR]) Hb and platelet counts were 80.0 g/L (IQR, 78.0- 88.5) and 32.5 ×109/L (IQR, 66.0 – 81.0) at transfusion. 2.9% (n =9), 0.6% (n =2), and 0.3 (n =1) received red blood cells (50 units), platelets (30 units), and plasma (four units), respectively.

Conclusion : This is the first study on blood types and transfusion status of COVID-19 in Korea. This study would be fundamental data for blood supply, transfusion strategy, and patient blood management in COVID-19.

Keyword : Blood Type, Transfusion, Coronavirus Disease 2019, Blood Supply, Transfusion Strategy, Patient Blood Management

PP16-09

Does ABO grouping have an association with severity and distribution of COVID-19? A cross sectional study

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Background : Blood groups are inherited traits affecting susceptibility/severity of disease. Various epidemiological and clinical characteristics, risk factors for mortality/morbidity and, predictors for susceptibility to SARS-CoV-2 have been reported. One early study at Central Hospital of Wuhan reported that ABO blood groups had an association with susceptibility to SARS-CoV-2. A clear relationship between COVID-19 and ABO blood grouping is yet to be established with various studies given varying results. Our study's aim was to demonstrate an association between the distribution and severity of COVID-19 with ABO blood grouping. In the presence of an overwhelmed healthcare system and the absence of an effective targeted therapy coupled with a yet-to-be widely studied vaccine, blood grouping will help effectively triage patients and frontline healthcare workers.

Method : Following Ethics approval (IEC 207/20), a cross-sectional study was conducted among hospitalized patients using in-patient records and via telephone call on a structured proforma and analyzed on SPSS-25. The reported most common blood type among COVID-19 patients is Blood type A. The proportion of Blood type A reported is 36.97%. Hence to estimate the prevalence of Blood type A among COVID-19 patients with an absolute precision of 5% and 95% confidence interval, the required minimum sample size was 358 patients. Chi-square tests were used for categorical data and Independent sample t-test/ Mann-Whitney U tests were used for continuous data. Multiple logistic regression was then done.

Results : The distribution of ABO blood groups in our study was comparable to the South Indian population indicating no association between distribution and ABO grouping. However, the AB blood group was significantly associated with lower ferritin ($p<0.05$), lower odds of antiviral usage (OR: 0.183, CI: 0.064-0.525), developing ARDS (OR: 0.326, CI: 0.109-0.973), sepsis (OR: 0.282, CI: 0.094-0.843) and septic shock (OR: 0.326, CI: 0.115-0.922). The O blood group was associated with significantly lower lymphopenia and leucocytosis. However, no clinical association was seen in O blood group.

Conclusion : Blood grouping is a novel and easy method of triaging patients. Our study has demonstrated that blood groups have a similar distribution amongst patients hospitalized with COVID-19 as in the South Indian population. Additionally, significantly lower risk of ARDS, sepsis, and septic shock has been found in the AB blood group. This contrast other studies where O blood group was found to have lesser association. This could be attributed to genetic differences seen in other diseases like Plasmodium falciparum malaria. Further studies are required to map out the genetic differences in severity and to develop targeted molecular therapy for patients affected with COVID-19

Keyword : COVID-19, ABO Blood Grouping

Relationship between AB blood group and outcomes

Characteristic	Estimate	P-value	OR	CI
ARDS	-1.122	**0.04**	0.326	0.109-0.973
Sepsis	-1.266	**0.02**	0.282	0.094-0.843
Septic Shock	-1.122	**0.03**	0.326	0.115-0.922
Use of antivirals	-1.696	**0.02**	0.183	0.064-0.525
Ferritin	0.001	0.129	1.001	1.000-1.002

PP17-01

Information is power: Hoax news and celebrity health prompt Indonesian audience into finding out more about leukemia

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Background : Leukemia was among the most prevalent non-solid tumor with more than 400 thousand new cases worldwide in 2018. With a high mortality rate, early detection of leukemia is

crucial. Today's technological advances have enabled the general population to access any information at their fingertips including leukemia. However, the motive behind the urge to learn more about leukemia might come from any sources. We sought after the motive behind this in the Indonesian population-based on Google Trends data.

Method : We evaluated Google Trends relative search volume (RSV) about leukemia and its top-grossing related search queries from September 2014-2019 originating from Indonesia. Among the top 25 related search queries, we selected queries relating to events that occurred in the past 5 years such as celebrity health and trending news. We used spearman test to assess the correlation between variables using R 3.6.2.

Results : Leukemia had an upward trend in the past 5 years. From the top 25 queries related to leukemia, 'plant causing leukemia' (R=0.18, p=0.003), 'denada's daughter' (R=0.33, p=0.000) and 'roman reigns' (R=0.24, p=0.000) were positively correlated to increased trend in leukemia searches. While 'plant causing leukemia' was the most popular query with 11 similar variations probably due to seasonal hoax news spread through social media, 'denada's daughter' achieve peak RSV at the same time as 'leukemia'. These searches lead to users looking for general topic about leukemia such as excessive white blood cell (R=0.30, p=0.000), leukemia symptoms (R=0.23, p=0.002), leukemia signs in children (R=0.35, p=0.000), difference between blood cancer (R=0.13, p=0.040), virus causing leukemia (R=0.24, p=0.000), and leukemia triggers (R=0.25, p=0.000).

Conclusion : Hoax news and celebrity health prompt Indonesian audience into finding out about leukemia related information. In the bigger picture, this could lead the user into seeking medical advice and improve the early management of leukemia. Partnership with celebrities might also beneficial in leukemia-related fundraising.

Keyword : Google, Trends, Leukemia

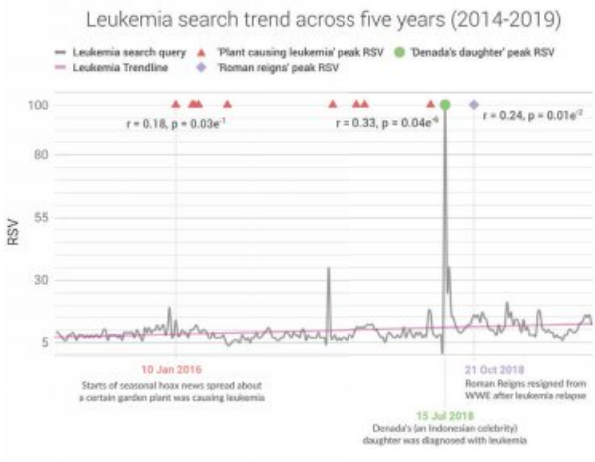

Figure 1. Leukemia search trends from September 2014-2019 with peak RSV of it's top-grossing related queries. RSV; relative search volume (0-100).

PP17-02

Clinical characteristic in cancer patients with febrile neutropenia at Sanglah General Hospital, Denpasar – Bali Indonesia

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Background : Febrile neutropenia is the most common leads to morbidity and mortality in patients with hematologic and solid organ malignancy receiving chemotherapy. Data showed neutropenia 10–50% of solid organ malignancy while 80% of hematologic malignancies with developing a fever. Lack of study in Indonesia so a future investigation is necessary. This study intends to describe descriptive data of febrile neutropenia in cancer patients either hematology or solid organ cancer.

Method : This study is an analytical study with a cross-sectional design. Samples were taken from the medical record installation room of Sanglah Hospital Denpasar. The data was taken by using a simple random sampling method for one year that is the year September 2019 until September 2020 according to inclusion and exclusion criteria. Febrile neutropenia was defined based on Infectious Diseases Society of America (IDSA), the occurrence of fever of a single oral temperature of >38.3 ºC (101 ºF) or a temperature of >38 ºC (100.4 ºF) sustained over a 1-h period with absolute neutrophil count (ANC) of <500 cells/mm3 or an ANC expected to decrease to <500 cells/mm3 in the following 48 hours. Statistical analysis was done by univariate, bivariate multivariate analysis using SPSS.

Results : Eighty-five patient sample data were used in this study with characteristics; female: male sex ratio 1.5, another baseline characteristic; mean age was 47.12 years old; 55 (66,7%) hematologic cancer patient. Nearly half with positive blood culture and prominent with streptococcus species (15.6%) specimen. Hematology parameter respectively Hematologic malignancy number (%) and solid was 0.17±0.15 vs 0.15±0.13 103/µL for absolute Neutrophile; 0.9(0.17-74.2) vs 0.63(0.58-1) 103/µL for WBC. Mann-Whitney analysis stated median of PLT have lower in hematologic malignancy 21.35(1.41-348.39) than solid organ malignancy group 89.41(3.31-523) with p=0.03. Febrile neutropenia was reported with a nearly equal frequency of positive (41.2%) and negative blood culture (58.8%). The ratio between gram-negative and gram-positive culture is 0.87.

Conclusion : The results of this study indicate a significant association between PLT and hematologic cancer, almost half of the patient with febrile neutropenia was positive blood culture. The nearly equal proportion between gram-negative and positive culture.

Keyword : Bacteremia, Blood Culture, Febrile Neutropenia, Hematologic Malignancy

Supplementary Data

Table 1.0 Baseline characteristic of sample (n=85)

	Number	%
Female:Male ratio	51/34 (1.5)	
Mean of age	47.12±16.95	
Hematologic malignancy	55	64.7
Positive blood culture	35	41.2
Negative Gram	13	15.6
Bacillus	1	1.2
Enterobacter	2	2.4
Escherichia coli	5	6
Pseudomonas	5	6
Klabsiella	5	6
Positive Gram	14	17.8
Streptococcus	13	15.6
Coagulase Negative Staphylococcus	1	1.2
Candida	3	3.6

Table 2.0 A comparison of patients with hematologic and solid organ malignancy who had febrile neutropenia

	Hematologic malignancy number (%)	Solid organ malignancy number (%)	P Value
Number	30 (35.29)	55 (64.7)	
Mean of age (years)	543.42±15.11	53.43±17.03	
Female	22 (73.3)	29(47.3)	0.7
Positive blood culture	23(41.8%)	13(43.3%)	0.54
Hematology Parameter			
Absolute Neutrophile Count(10^3/μL)	0.17±0.15	0.15±0.13	0.64
WBC (10^3/μL)	0.9(0.17-74.2)	0.63(0.58-1)	0.39
Neutrophile (%)	16.8(0.21-67.93)	16.23(1.72-60.08)	0.81
Lymphocyte(%)	61.21(6.48-96.96)	57.43(24.38-96.55)	0.50
Monocyte (%)	7.76(0.28-68.74)	15.92(0.17-42.91)	0.26
Basophile (%)	1.4(0-50.11)	1.52(0-6.4)	0.54
Eosinophile (%)	0.5(0.0-49.42)	0.71(0.0-14.37)	0.10
LDH	441.5(197-2236)	366(193-588)	0.31
PLT (10^3/μL)†	21.35(1.41-348.39)	89.41(3.31-523)	0.03
AST (U/L)	13.2(2.7-472.6)	24.7(5.6-83.2)	0.18
ALT (U/L)	18.1(5.9-243.5)	18.35(4.7-74.8)	0.82
Creatine serum (mg/dL)	0.75(0.39-1.94)	0.79(0.31-3.97)	0.46
Urid acid (mg/dL)	5.45(3.2-8.3)	4.9(1.6-8.4)	0.50
Kalium (mmol/L)	3.73(2.23-4.51)	3.78(2-4.9)	0.38

*All parameters are expressed as mean standard deviation for normally distributed data while not normally presented median (minimum to maximum), unless otherwise stated. Significance level was set at P < 0.05. †Significant different between other two groups. ALT, Alanine transaminase; AST, Aspartate amino transferase; LDH: Lactate dehydrogenase; PLT: Platelet.

PP17-03

COVID-19 infection in hematological patients: Results of a prospective cohort study

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Background : There is very little systematic data on the course and outcomes of COVID-19 infection in patients with hematological neoplasms. According to the existing data, cancer patients infected with SARS-CoV-19 have severe clinical manifestations and often poor outcomes comparing to general population. Objective of this prospective cohort study was to assess the course of COVID-19 infection in patients with hematological neoplasms as well as to estimate the predictors of adverse outcomes including fatal outcome.

Method : A prospective cohort study was carried out, including 66 patients with hematological neoplasms and a confirmed COVID-19 infection, who were treated from March to September 2020 at the Minsk Scientific and Practical Center for Surgery, Transplantology and Hematology. Verification of the infection, caused by SARS-CoV-2 was performed by real-time PCR of the oropharyngeal and nasopharyngeal swabs. The indications for diagnostic PCR for COVID-19 were: fever with signs of damage to the lung tissue (cough, shortness of breath, decreased oxygenation, etc.) or fever, unexplained by other reasons, loss of taste and smell. Diagnosis of COVID-associated lung disease was carried out using CT-scans. Outcome was determined as all-cause mortality.

Results : During the follow-up period, there were totally 66 hematological patients diagnosed with COVID-19 infection. The ratio of men (34) and women (32) was 1:1. The patients' age was from 21 to 88 years. Median age was 62.4 years. The most frequent range in which, along with hematological diseases, COVID-19 infection was confirmed is the age category of patients > 60 years. Also, the category of patients over the age of 60 had the highest case fatality rate. The courses of specific therapy with the use of various types of drugs, depending on the nosology of the underlying disease were prescribed accordingly - 42 (63.6%) patients received: proteasome inhibitors (combinations with bortezomib and/or lenalidomide) in patients with MM; courses with cytarabine; monoclonal antibodies (rituximab) in patients with CLL and NHL, hypomethylating agents (decitabine, azacytidine) in patients with MDS, and GCS. As a result of the study,aAge>60 years (HR 1.8; 95% CI 1.01-3.28) and the stage of progression of hematological disease (HR 2.8; CI 95% 1.9-4.0) were statistically significant factors of fatal risk in patients with hematological malignancies. Chronic kidney disease (CKD) at stages 4-5 was a statistically significant factor of a fatal outcome in patients with hematological disease and COVID-19 (P <0.05, Fisher's exact test 0.01). The presence of cardiovascular pathology, diabetes mellitus and other cancers did not affect the outcomes.

Conclusion : 1) In hematological patients COVID-19 infection is associated with a severe course and high mortality (48%).
2) The most common hematological diseases in our study, which was associated with COVID-19 infection was multiple myeloma (37.8% of patients).
3) The highest case fatality rate is observed in patients with multiple myeloma and acute leukemia (21% and 12%, respectively).
4) Risk factors for mortality of COVID-19 infection in patients with hematological malignancies are age> 60 (HR 1.8; 95% CI 1.01-3.28) and the stage of progression to hematological malignancies (HR 2.8; 95% CI ; 1.9-4.0).
5) Mortality in the groups of patients receiving PCT in the period from 1 to 3 months before the onset of COVID-19 infection and in the group of patients without PCT did not differ significantly.

Keyword : COVID-19, Risk Factors, Hematological Neoplasms

PP18-01

Vitamins: A cure for oral mucositis induced by cancer chemo/ radiotherapy – A meta-analysis of RCTs

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Background : Oral mucositis is a major, often dose-limiting toxicity in modern cancer-therapy, leading to dose reductions or delay in further cancer treatment. After chemotherapy, stem cell transplantation and radiotherapy, most of the patients suffer from stomatitis. It predisposes to life-threatening septic complication during aplasia and substantially reduces quality of life for cancer patients. Oral mucositis can affect nutritional status and the risk of infection, both local and systemic. Vitamins A, E, C seen to be beneficial for the prevention and therapy of both oral and gastrointestinal mucositis. Hence the objective of the study is to assess the effectiveness of various vitamins for prevention or treatment of patients with oral mucositis undergoing radiotherapy, chemotherapy or combination via meta-analysis.

Method : PubMed, EBSCO, COCHRANE and Google Scholar articles were searched for articles published between 1980 and 2020 with keywords vitamin A, vitamin E, vitamin B, vitamin C, Oral mucositis, Chemotherapy and Radiotherapy. A total of 447 articles were identified by the literature search; relevance was determined by examining the title and abstract of the articles. Total 45 original research studies met the inclusion criteria from which 15 articles scored more than 14 points on CONSORT checklist and were included in the study for analysis. All the articles were divided into three separate groups (Group 1- radiotherapy, Group 2- concurrent chemo radiotherapy, Group 3- chemotherapy) were analysed and data was extracted utilizing the eligibility, validity and design of the study. The data was tabulated into excel format which included number of patients, grading of mucositis, type of treatment, type of vitamin supplementation, outcome measures, gender and age distribution in each for all three groups separately. Using the random effects model, pooled Odds Ratio (OR) with 95% confidence intervals (CI) were calculated in measuring the incidence of improvement or resolution of oral mucositis.

Results : Among 325 subjects, there were 68% males and 32% females. Out of 15 studies, 4 were done among children and remaining 11 studies focussed on adult population. Meta-analysis performed regarding usage of various vitamins showed significant reduction in oral mucositis in vitamin A and E group ($p < 0.05$). There was reduced oral mucositis in a small group of patients with vitamin C and patients with vitamin D when compared to controls. The pooled rate of mucositis resolution was significantly higher in the group treated with Vitamin E (79.8% vs 42.8%), with an odds ratio of 5.45 (95% CI 1.42 - 11.25, $p < 0.05$) and Vitamin A (67.8% vs 39.5%), with an odds ratio of 3.87 (95% CI 1.8 - 9.65, $p < 0.05$). Heterogeneity between the studies was minimal (I2 0-20%). No severe adverse effects were reported in the studies with usage vitamin E, A, C & D and they were well tolerated.

Conclusion : Topical vitamin E had performed better on oral mucositis than other vitamins. Vitamin E and vitamin A (topical or oral) were significantly associated with higher rates of resolution of oral mucositis among cancer patients who underwent chemotherapy or radiotherapy. It is recommended that vitamin E and A can be considered a modest, non-toxic and effective method for prevention and treatment of oral mucositis. Though the effectiveness of vitamin C and vitamin D showed reduction in oral mucositis, it was evaluated in a very small sample which cannot be attributed to a larger sitting. Subgroup analysis based on type and dose of vitamin administration can be done in the future.

Keyword : Oral Mucositis, Radiotherapy, Chemotherapy, Vitamin, Leukemia, Lymphoma

Table: Odds ratio of various vitamins as a treatment for oral mucositis

Vitamin	Odds Ratio	Confidence Interval	p-value*
Vit. A	3.87	1.8-9.65	0.043
Vit. C	1.98	1.0-2.63	0.087
Vit. D	1.86	1.1-2.47	0.102
Vit. E	5.45	1.42-11.25	0.009

*significant if value<0.05

PP18-02

Self-care behavior: Support for improving a quality of life in patients thalassemia in Indonesia

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Background : Thalassemia has become a major global concern because it affects life expectancy and Quality of Life (QoL) of 100s of 1000s of individuals across the globe. The prevalence of thalassemia carriers in Indonesia is around 3 - 8%, until March 2009 cases of thalassemia in Indonesia have increased by 8.3% from 3653 cases recorded in 2006 (Wahyuni, 2008). Thalassemia patients experience physical and psychosocial changes. Physical changes include chronic anemia which can cause the patient to experience hypoxia, headaches, irritability, anorexia, chest and bone pain, and activity intolerance. Thalassemia patients also experience impaired growth and development of the reproductive system, these physical changes also have a psychosocial impact on patients (Hockenberry & Wilson, 2009). To minimize the impact, both physical and psychological, it takes the right management for thalassemia patients. One way that can be done is by self-care. Self-care is the core concept of health care and may be considered as one's stabilization, and restoration as well as the improvement of his/her health and well-being. Looking at the process of Self-care from patients' perspective who suffer from thalassemia may assist the nurses and health care providers to facilitate the health process. Quality of life becomes important as the life expectancy of thalassemia patients increases.

Method : Articles starting from 2000-2020 are collected from an electronic database. Then several selected articles were reviewed to answer the objectives of this study.

Results : Based on the findings of previous researchers, increasing self-care behaviorcan be done through the development of a structured educational program, increasing the competence of nurses in providing nursing care to Thalassemia patients related to self-care activities in Indonesia (Indanah et al., 2012). A source of

social support that plays a role in the self-care behavior of school age children is support from family and peers. Families play a psychosocial role by helping to control children's behavior by helping children regulate behavior towards changes that occur during illness (Indanah et al., 2016). Facilitating the process of self-care in patients with major thalassemia requires that they be helped so that their self-efficacy, influenced by real life conditions, might be strengthened in light of thalassemia. Increasing public awareness and social support may affect the recognition of individual, family and society (Pouraboli et al., 2017). Yang, et al., (2001) which revealed that knowledge is one of the factors that support daily self-care behavior, because with sufficient knowledge, a person will understand his physical condition and is expected to be able to show good self-care behavior to support efforts to maintain health. Maheri et al., (2020) self-care behaviour supportive programs aimed at improving the QoL in TDT patients. Research conducted at hospitals in Indonesia, states that bad self-care behavior can cause feelings of depression when diagnosing a disease, therapy that must be undertaken every month regularly, and having to not attend school because you have to undergo therapy (Aji et al, 2009). The result of the study indicate that there is an essential relationship between self care behaviour improving the quality of life of patients who have thalassemia will provide emotional support so that there is an increase in motivation by patients. Regarding functional self-care behaviour in school age children can improve their awareness of thalassemia early on so patients feels able to work, enjoy their life, accepted their illness and sleeping well. They're enjoying the thing they usually do for fun, and content with quality of their life right now. Functional self-care contributes to improving the quality of life of thalassemia in school age children.

Conclusion : It can be concluded that self-care behaviour as a supporting factors for improving the quality of live of school age children thalassemia patients.

Keyword : Quality of Life, School Age Children, Thalassemia, Indonesia

PP18-03

Epidemiological burden of anemia and its impact on the quality of life in diabetic kidney disease patients

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Background : In diabetic kidney disease (DKD) patients, anemia is responsible for morbidity and all-cause mortality. Anemia is associated with significant epidemiological, humanistic, and economic burden in Type 2 Diabetes Mellitus (T2DM) patients but scarce of evidence available on DKD patients. So, this study was aimed to determine the prevalence, predictors of anemia and its impact on health-related quality of life among diabetic kidney disease (DKD) patients.

Method : Patients with a confirmed diagnosis of Type 2 Diabetes Mellitus (T2DM), and had any stages of CKD (stage I to IV), based on their estimated glomerular filtration rate (eGFR) were enrolled in the study. Anemia was defined using the World Health Organization (WHO) criteria and quality of life was assessed using the EQ 5D scale. All the statistical analysis was performed using SAS v9.4.

Results : A total of 323 patients completed the study. The mean ± SD age of patients was 56 ± 11.25 years, and 51.7% were female. Mean duration of diabetes was 9.6 ± 4.57 years. A total of 227 (70.27%) had anemia as per the WHO criteria. Linear association was observed between the eGFR and hemoglobin. After controlling for the possible confounders in multivariate logistic regression analysis, older age (OR: 2.46 [95% CI: 1.16 to 5.28], p=0.021), diabetes duration (OR: 1.53 [95% CI: 1.04 to 2.25], p=0.022) and CKD stage III (OR: 3.63 [95% CI: 0.99 to 13.32], p=0.004) were found to be significantly associated with the anemia. Consistently lower EQ 5D index values were observed for the anemic group.

Conclusion : This study reported a high prevalence of anemia and impaired quality of life among DKD patients. Routine screening of anemia can be the most preventive measure to deal with this burdening comorbid condition.

Keyword : Anemia, Chronic Kidney Disease, Diabetic Kidney Disease, Epidemiology, Nephrology, Quality of Life

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조혈모세포 기증자의 채혈 시기 결정
CBC 동시검사로 빠르고 쉽게 검사 가능
(보험코드: CZ471)

Body Fluid

CSF를 포함한 다양한 체액검사의 자동화
정확하고 빠른 보고 가능

IPF (Immature platelet fraction)

혈소판 감소증 원인감별 및 치료 모니터링
조혈모세포이식, 항암제 치료 후 회복 예측

Malaria flag

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감염여부를 스크리닝

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VENCLEXTA™
venetoclax tablets

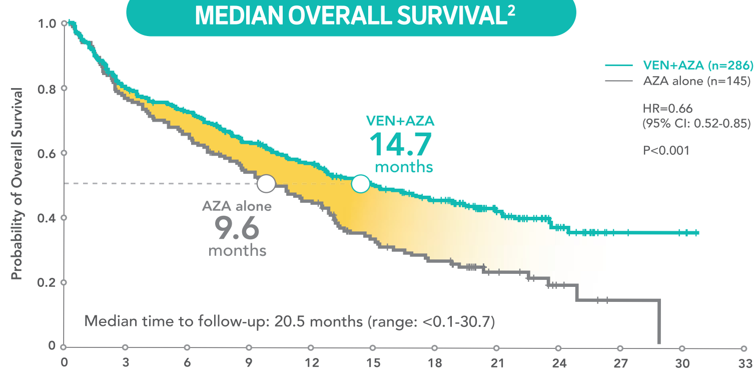
POWERED BY REMISSION V

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

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 종양부담(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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*프레비미스는 동종 조혈모세포 이식수술(HSCT)을 받은 성인 거대세포바이러스(CMV)-혈청 양성[R+] 환자에서 거대세포바이러스(CMV) 감염 및 질환의 예방을 목적으로 국내에서 허가받았으며, 1일 1회 용법으로 복용이 편리합니다.[1,2]

†[NCCN guideline] Consider letermovir as primary prophylaxis for CMV+allogeneic HCT recipients.

CMV, cytomegalovirus; **HSCT,** hematopoietic stem cell transplantation; **R+,** recipient positive.

References 1. 프레비미스정 제품설명서(개정년월일 2021.01.26). **2.** 프레비미스주 제품설명서(개정년월일 2021.01.26). **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.** 2020, 12/17/19 2019 National Comprehensive Cancer Network(NCCN) : Prevention and Treatment of Cancer-Related Infections.

프레비미스 주요 안전성 정보 (Selected Safety Information) [효능효과] 동종 조혈모세포 이식수술(HSCT)을 받은 성인 거대세포바이러스(CMV)-혈청양성[R+] 환자에서 거대세포바이러스(CMV) 감염 및 질환의 예방 **[용법용량]** 이 약 정제와 정맥주사 제형은 의사의 결정에 따라 서로 교차해서 투여할 수 있으며, 용량 조절은 필요하지 않다. 이 약의 정맥주사제는 히드록시프로필 베타덱스 성분을 함유하고 있으므로 경구 투여가 불가능한 경우에만 사용한다. 환자가 경구 투여가 가능해짐 경우 바로 정제로 교차하여 투여한다. **1. 성인 권장용량:** 이 약의 권장 용량은 1일 1회 480 mg이다. 동종 조혈모세포이식(allogeneic HSCT)을 받은 이후에 이 약의 투여를 시작해야 한다. 이 약은 이식 당일 및 이식 후 28일 이내에 시작할 수 있다. 이 약은 생착 전이나 후에 시작할 수 있다. 이식 후 100일까지 이 약을 계속 투여한다. 이 약은 사이클로스포린과 병용투여하는 경우 용량이 조절되어야 한다. **2. 성인에서의 용량 조절:** 이 약을 사이클로스포린과 병용투여하는 경우, 이 약의 용량을 1일 1회 240 mg으로 감량하여야 한다(사용상의 주의사항, 상호작용 항 참조) – 이 약의 투여를 시작한 이후에 사이클로스포린을 투여하는 경우, 이 약의 다음 용량은 1일 1회 240 mg으로 감량하여야 한다. – 이 약의 투여를 시작한 이후에 사이클로스포린의 투여를 중단한 경우, 이 약의 다음 용량은 1일 1회 480 mg으로 증량하여야 한다. – 사이클로스포린의 농도가 높아서 사이클로스포린의 투여를 일시적으로 중단한 경우, 이 약의 용량 조절은 필요하지 않다. **3. 신장애 환자:** 크레아티닌 청소율(CLcr)이 10 mL/min 이상의 신장애 환자에서 용량조절은 필요하지 않다. 투석 환자를 포함한 크레아티닌 청소율(CLcr)이 10 mL/min 미만의 말기 신질환 환자에서 이 약은 평가된 바 없다[4. 간장애 환자: 경증(Child-Pugh Class A)에서 중등증(Child-Pugh Class B)의 간장애에 따른 이 약의 용량 조절은 필요하지 않다. 중증(Child-Pugh Class C)의 간장애 환자에게는 이 약이 권장되지 않는다. 중등증 또는 중증의 신장애를 동반한 중등증의 간장애 환자에게는 이 약이 권장되지 않는다(사용상의 주의사항, 간장애 환자에 대한 투여 항 참조). **5. 투여방법:** 정제는 전체를 그대로 삼켜야 하며, 식사와 관계없이 투여할 수 있다. 정제는 쪼개거나, 부수거나 씹어서는 안된다. 주사제의 조제 및 투여 방법은 두 용량 모두 동일하다. 주사제는 투여 전에 희석이 필요하다(사용상의 주의사항, 11. 적용상의 주의 참조). **6. 복용을 잊었을 경우:** 환자가 이 약의 복용을 잊었을 경우, 이 사실을 기억한 즉시 복용하도록 설명한다. 다음 복용 시점까지 이 사실을 기억하지 못했을 경우, 누락한 용량은 생략하고 원래의 복용 스케줄에 따라 복용하도록 한다. 환자들이 다음 복용량을 2배로 늘리거나 1차분 용량 이상을 복용하지 않도록 안내한다. **[사용상의 주의사항] 1. 다음 환자에는 투여하지 말 것** 1) 이 약은 레테르모비르 또는 이 약의 성분에 과민한 환자에는 투여하지 않는다. 2) 피모짓(pimozide): 이 약과 병용투여할 경우, 레테르모비르에 의한 시토크롬 P450 (CYP3A) 억제로 인해 피모짓의 농도가 증가하여 QT 간격 연장과 Torsades de Pointes를 유발할 수 있다[3. 상호작용, 2) 이 약이 다른 약물에 미치는 영향 항 참조]. 3) 맥각 알칼로이드: 이 약과 병용투여할 경우, 레테르모비르에 의한 CYP3A의 억제로 인해 맥각 알칼로이드(에르고타민[ergotamine] 및 디하드로에르고타민[dihydro-ergotamine])의 농도가 증가하여 중독증을 유발할 수 있다[3. 상호작용, 2) 이 약이 다른 약물에 미치는 영향 항 참조]. 4)사이클로스포린과 병용시: 아토르바스타틴, 심바스타틴, 프라바스타틴 또는 로수바스타틴의 병용(이들 약물의 농도가 현저히 증가하여 근육병증이나 횡문근융해증을 유발할 수 있다.), 다비가트란의 혈중 농도를 증가시킬 수 있으며, 이는 출혈 위험의 증가와 관련될 수 있다. [3. 상호작용, 2) 이 약이 다른 약물에 미치는 영향 항 참조] **2. 이상반응:** 1) 임상시험에서의 경험– 성인 동종 조혈모세포이식(allogeneic HSCT)을 받은 성인 CMV–혈청양성[R+] 환자 – 이 약의 안전성은 제3상, 무작위배정, 이중맹검, 위약–대조 임상시험(P001)에서 평가되었는데, 565명의 대상자들을 무작위배정하여 이식 후 14주까지 이 약(N=373) 또는 위약(N=192)을 투여하고 이식 후 24주까지 안전성을 추적 관찰하였다. 이상반응은 이 약 투여 중 또는 투여 완료/중단 시점에서 2주 이내 평가되었다. 약물 관련성과 상관없이 심장 관련 이상반응 발생률은 위약(6%) 보다 이 약(13%)에서 더 높았다. 가장 흔한 심장 관련 이상반응은 빈맥(이 약 4%, 위약 2%) 및 심방세동(이 약 3%, 위약 1%)이었다. 한 가지 이상 심장 관련 이상반응을 경험한 환자 대부분은 경증 또는 중등증이었다. 이 약에서 10% 이상 발생하였고 위약보다 2% 이상 더 높은 빈도로 보고된 가장 흔한 이상반응 오심, 설사, 구토, 말초부종, 기침, 두통, 피로, 복통이었다. 전반적으로 이상반응으로 인한 투여중단은 두 군에서 유사하였다(이 약 13%, 위약 12%). 이 약 투여 중단을 유도한 가장 흔한 이상반응은 오심이었다(이 약 2%, 위약 1%). 이 약 투여 중단을 유도한 이상반응 중 중등증의 호흡곤란과 관련있는 과민성 반응이 이 약 경구투여에서 주사제로 교체후 이 약 정맥주사 시작후 한 명에서 보고되었다. 임상검사치 이상 – 전반적으로, 임상검사치(예, 혈액학, 화학, 신장 및 간 기능)에서 임상적으로 유의한 변화 가능성이 있는 대상자의 비율은 이 약 및 위약 투여군에서 유사하였다. 이 약과 위약 투여군 간에 생착률이나 생착시기에는 차이가 없었다. P001에 참여한 남성에서 고환 독성의 생물표지자(biomarker)를 평가하였다. 남성 성호르몬(혈청 inhibin B, 황체형성호르몬[LH]), 난포자극호르몬[FSH] 및 테스토스테론의 기저치로부터의 변화는 이 약 및 위약 투여군에서 유사하였다. **3. 일반적 주의:** 1) 거대세포바이러스(CMV) DNA 모니터링– 이 약의 안전성 및 유효성은 예방요법 시작 전 CMV DNA 검사 결과 음성인 환자에서 평가되었다. CMV DNA 는 이식 후 14일까지 매주, 이후 24주까지 격주로 모니터링되었다. 이 약의 예방요법 완료 후 CMV 재활성화에 대한 모니터링을 권장한다. 2) 약물상호작용으로 인한 이상반응 또는 치료 효과의 감소 위험– 이 약과 특정 약물을 병용투여 시 알려진 또는 잠재적으로 유의한 약물상호작용이 발생할 수 있으며, 그 중 일부는 다음과 같은 결과를 초래할 수 있다. – 병용 약물이나 이 약의 노출이 증가하여 임상적으로 유의한 이상반응이 발생할 수 있다. – 병용 약물의 혈장 농도가 현저히 감소하여 병용 약물의 치료 효과가 감소할 수 있다. 용량에 대한 권고사항을 포함하여, 이러한 알려진 또는 잠재적으로 유의한 약물상호작용을 예방하거나 관리하기 위한 조치에 관하여 표 2를 참조한다[1. 다음 환자에는 투여하지 말 것 항, **4. 상호작용,** 2) 이 약이 다른 약물에 미치는 영향 항 및 3) 확인된 및 기타 잠재적 약물상호작용 항 참조]. 이 약은 병용투여 시 CYP3A 기질의 혈장 농도를 증가시킬 수 있으므로, 좁은 치료범위를 가진 CYP3A 기질인 약물(예, 알펜타닐, 펜타닐 및 퀴니딘)과 주의하여 사용해야 한다. 병용투여된 CYP3A 기질의 면밀한 모니터링 및/또는 용량 조절이 권장된다[표 2, 4. 상호작용, 2) 이 약이 다른 약물에 미치는 영향 항 및 3) 확인된 및 기타 잠재적 약물상호작용 항 참조]. 4. 상호작용: 1) 다른 약물이 이 약에 미치는 영향 – 레테르모비르는 유기 음이온-수송 폴리펩타이드 1B1/3 (organic anion–transporting polypeptide, OATP1B1/3) 수송체의 기질이다. 이 약과 OATP1B1/3 수송체를 억제하는 약물을 함께 투여하게 되면 레테르모비르의 혈장 농도가 증가할 수 있다. 만약 이 약을 사이클로스포린(강력한 OATP1B1/3 억제제)과 병용투여할 경우, 이 약의 권장 용량은 1일 1회 240 mg이다[용법·용량, 2. 성인에서의 용량 조절 항 참조]. 2) 이 약이 다른 약물에 미치는 영향 – 이 약과 미다졸람을 병용투여 시 미다졸람의 혈장 농도가 증가하게 되며, 이는 레테르모비르가 중등도의 CYP3A 억제제임을 나타낸다. 이 약을 CYP3A 기질인 약물과 병용투여 시, 병용투여된 CYP3A 기질의 혈장 농도가 임상적으로 유의하게 증가할 수 있다[1. 다음 환자에는 투여하지 말 것 항 및 3. 일반적 주의, 2) 약물상호작용으로 인한 이상반응 또는 치료 효과의 감소 위험 항, 표 2 참조]. 레테르모비르는 OATP1B1/3 수송체의 억제제이다. 이 약과 OATP1B1/3 수송체의 기질을 병용투여할 경우 병용투여된 OATP1B1/3 기질의 혈장 농도가 임상적으로 유의하게 증가할 수 있다[표 2 참조]. 3) 확인된 및 기타 잠재적 약물상호작용 – 이 약의 투여로 인해 병용 약물의 용량을 조절하는 경우, 이 약의 투여를 완료한 후에 약물 용량을 재조절해야한다. 이 약을 사이클로스포린과 병용투여 시, CYP3A 기질에 대한 상호작용은 강력한 CYP3A 억제제와 유사할 수 있다. CYP3A 기질과 강력한 CYP3A 억제제의 병용투여에 관한 제품 정보를 참조한다. 이 약을 사이클로스포린과 병용투여 시, CYP3A와 OATP1B1/3 모두의 기질에 대한 상호작용은 이 약을 단독으로 투여하는 경우와 다를 수 있다. 병용 약물 및 사이클로스포린에 대한 제품 정보를 참조한다. 4) 이 약과 임상적으로 유의한 상호작용이 없는 약물 – 이 약을 P-당단백질(P-glycoprotein, P-gp) 억제제와 병용투여했을 때, 임상적으로 유의한 약물상호작용은 기대되지 않는다. 임상시험에서 이 약과 병용투여한 후, P-gp 기질인 디곡신 및 OAT3기질인 아시클로비의 혈장 농도에 임상적으로 유의한 변화는 없었다. 임상시험들에서 레테르모비르와 다음 열거된 약물 간의 상호작용이 연구되었다: 미코페놀레이트 모페틸, 플루코나졸, 포사코나졸 및 경구 피임약(에티닐 에스트라디올, 레보노르게스트렐). 이 약을 이러한 약물들과 병용투여 시 용량 조절은 필요하지 않다. **5. 임부, 수유부 및 가임여성에 대한 투여:** 1) 임부– 이 약이 임신 결과에 위험을 초래하는지 여부를 확인하기 위하여 사람에서 실시된 적절한 연구 자료는 없다. 랫드 및 토끼에서 배·태자 독성이 관찰되었다. 이 때 모체에서의 독성 전신 노출도는 사람에 대한 권장용량(RHD)에서의 노출도의 약 11배(랫드) 및 2배(토끼)였다. 랫드에서는 이 노출도에서 태자 기형이 관찰되었다. 랫드에서의 출생 전·후 발생시험(경구투여)에서 사람에 대한 권장용량(RHD)에서의 노출도의 약 2배에 해당하는 모체 노출도에서 총한배세끼 소실이 관찰되었다. 안전역을 계산하기 위해, 사람에 대한 권장용량(RHD)에서의 AUC는 480 mg IV를 투여한 HSCT를 받은 환자에서의 평균 AUC로 정의된다. 해당 집단에 대한 주요 선천적 장애 및 유산의 기저 위험은 알려져 있지 않다. 인간에 대한 잠재적인 위험 또한 알려진 바 없다. 2) 수유부 – 레테르모비르가 사람의 모유로 분비되는지, 모유 생성에 영향을 주는지, 또는 모유 수유 중인 유아에게 영향이 있는지는 알려져 있지 않다. 수유 중인 랫드에게 투여했을 때, 레테르모비르는 모유로 분비되었다. 수유부의 이 약에 대한 임상적 필요성 및 이 약 또는 산모의 기저 상태가 수유 중인 유아에게 미칠 잠재적인 부정적 영향과 함께 모유 수유가 발달 및 건강에 미치는 유익성을 고려하여야 한다. 3) 수태능 – 사람에서의 수태능 영향에 대한 자료는 없다. 랫드에서의 수태능시험에서 암컷 랫드의 수태능에는 영향이 없었으나 수컷 랫드에서 사람에 대한 권장용량에서의 노출도의 약 3배 이상 노출도에서 고환 독성에 따른 수태능 감소가 관찰되었다. 원숭이에서는 이러한 영향이 관찰되지 않았다. **6. 소아에 대한 투여:** 만 18세 미만 환자에서 이 약의 안전성과 유효성은 확립되지 않았다. **7. 고령자에 대한 투여:** 동종 조혈모세포이식을 받은 환자들을 대상으로 실시된 제3상 임상시험에서 만 65세 이상 고령자는 56명(15%)이 포함되었다. 이 임상시험에서 만 65세 이상의 고령자와 젊은 환자에서 전반적인 안전성은 유사하였다. **8. 신장애 환자에 대한 투여:** 크레아티닌 청소율(CLcr)이 10 mL/min 이상의 신장애 환자에서 용량조절은 필요하지 않다. 투석 환자를 포함한 크레아티닌 청소율(CLcr)이 10 mL/min 미만의 말기 신질환 환자에서 이 약은 평가된 바 없다[용법·용량, 3. 신장애 환자 항 및 4. 간장애 환자 항, 사용상의 주의사항, 9. 간장애 환자에 대한 투여 항 참조]. **9. 간장애 환자에 대한 투여:** 이 약은 경증(Child–Pugh Class A)에서 중등증(Child–Pugh Class B) 간장애에 대한 용량 조절이 필요하지 않다. 이 약은 중증(Child–Pugh Class C) 간장애 환자들에게 권장되지 않는다[용법·용량, 4. 간장애 환자 항 참조]. 이 약은 중등증의 간장애와 중등증 또는 중증의 신장애를 함께 가진 환자들에게 권장되지 않는다[용법·용량, 4. 간장애 환자 항 참조]. **10. 과량투여시의 처치:** 사람에서 이 약을 과량투여한 경험은 없다. 제1상 임상시험에서 86명의 건강한 성인들은 이 약 720 mg/일부터 1440 mg/일까지의 용량을 최대 14일간 투여받았다. 이상반응 양상은 치료용량(480 mg/일)에서 관찰된 것과 유사하였다. 이 약의 과량투여 시 특정한 해독제는 없다. 과량투여한 경우, 이상반응 및 적절한 증상 치료를 위해 환자를 모니터링하는 것이 권장된다. 투석으로 이 약을 체순환으로부터 유의하게 제거할 수 있는지 여부는 알려진 바 없다. **11. 보관 및 취급상의 주의사항:** 1) 어린이의 손이 닿지 않는 곳에 보관할 것 2) 이 약은 사용 전까지 원래의 포장 용기에 보관할 것

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Otsuka

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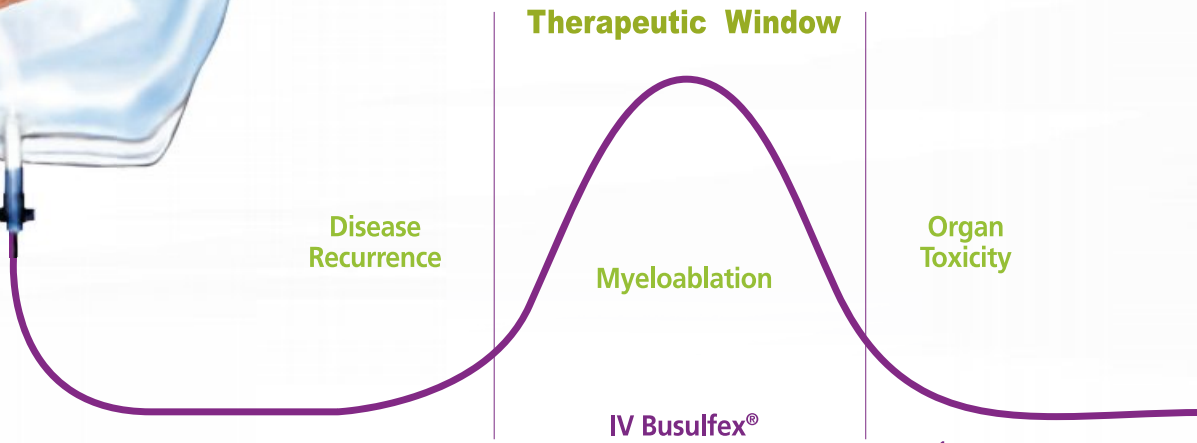
(busulfan) Injection

IV Busulfex (Busulfan)

- **IV Bu** formulation to **achieve absolute dose assurance** associated with its controlled administration[1]
- The combination of Cy with **IV Bu** administration appeared **safer compared with that of oral Bu.**[1]
- Significantly lower incidence of HVOD with **IV Bu** compared with oral Bu and a significantly lower day-100 TRM[1]

- **Cy** : Cyclophosphamide, **Bu** : Busulfan, **HVOD** : Hepatic veno-occlusive disease
  TRM : Treatment-Realted Mortality

Target AUCss with precision



IV Busulfex®
Therapeutic Window = 900-1500 μMol/min[1]
(Target AUC values)

Reference 1. Ciurea SO, et al. *Biol Blood Marrow Transplant.* 2009;15(5):523-536.

INFORMATION

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 이틀간 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)를 15% 감소시킨다. 다른 항경련제를 사용하면 부설판의 혈장 AUC가 높아지므로 간정맥 폐쇄성질환(VOD) 또는 발작의 위험성이 높아진다. 다른 항경련제를 사용할 경우에는 혈장 부설판 노출을 모니터해야 한다. 5-HT3계열의 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 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.

KD Code : 649900341 **포장단위 :** 10ml x 1, 8바이알 **저장방법 :** 2~8℃보관, 밀봉용기 **사용기한 :** 제조일로부터 30개월

* 기타 상세한 사항은 최신제품설명서를 참조하시기 바랍니다.

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KRAMB0048_v1.0(2016.01.25)

AmBisome Injection (amphotericin B liposome for injection)

[Indications] Following systemic fungal infections sensitive to this drug: cryptococcosis, North American Blastomycosis, disseminated candidiasis, coccidioidomycosis, aspergillosis, mucormycosis and some cases of American mucocutaneous leishmaniasis Fever of unknown origin show in patients with neutropenia (Persistent fever of unknown origin which is not improved even after 96-hour treatment with antibiotics) Primary treatment of visceral leishmaniasis in immunocompetent adults and children Primary treatment of visceral leishmaniasis in immunocompromised patients (HIV-positive patients etc.) **[Dosage and Administration]** This drug should be administered via intravenous infusion for 30~60 mins. For doses greater than 5 mg/kg/day, intravenous infusion over 2 hour period is recommended. The recommended concentration in the intravenous infusion is 0.2~2.0 mg/mL of amphotericin B. The dosage of amphotericin B as AmBisome must be adjusted to the specific requirements of each patient. • Systemic fungal infections: Although 1.0 mg(titer)/kg/day is usually administered, the dosage can be gradually increased to 5.0 mg(titer)/kg/day, if required. • Fever of unknown origin show in patients with neutropenia: 1.0 mg(titer)/kg/day is administered as initial dose, which can be increased to 3.0 mg(titer)/kg/day according to symptoms. • Visceral leishmaniasis: 1.0~1.5 mg(titer)/kg/dayis administered for 21 days or 3.0 mg(titer)/kg/day for 10 days. Maintenance therapy or responsive therapy is performed if required due to the risk of recurrence. [Warnings] This drug is not used for common clinically inapparent fungal infections due to its strong activity. A positive skin serum test for fungus is not sufficient for administration. In addition, it is not used for bacterial infections or viral diseases due to no efficacy. In the treatment of fever of unknown origin, it is not used for fever caused by infections due to usual viruses, parasites or mycobacterium. **[Contraindications]** Patients with the hypersensitivity to this drug or any component of the drug **[General precautions]** It is recommended to check susceptibility for the prevention of the occurrence of resistant bacteria and to administer this drug for the minimum period required for the treatment. If a severe anaphylactic / anaphylactoid reaction occurs, the infusion should be immediately discontinued It was found that the incidence rates of increased serum creatinine, hypokalemia and hypomagnesemia were notably higher in the high dose groups. Patient management should include routine laboratory evaluation of hepatic, renal and hematopoietic function. Amphotericin B has nephrotoxicity. Patients with diabetes should bear in mind that each vial contains 900 mg of white sugar. This drug should not be given during the dialysis. [Adverse Reactions] The following adverse reactions may be caused by this drug. Their incidences were based on a clinical trial. (1) 10% : Fever, coldness/chills, hypokalemia, nausea, vomiting (2) 1~<10%: Elevations in creatinine and BUN, hypomagnesemia, hypocalcemia, hyperglycemia, hyponatremia, increased ALP, bilirubinemia, abnormal liver function test results, diarrhea, abdominal pain, dyspnea, flushing/vasodilation, hypotension, headache, low back pain, chest pain, rapid pulse rate (tachycardia) and rash (3) 0.1~<1%: Convulsion, bronchospasm, thrombocytopnea, anaphylactoid reaction, anemia and phlebitis (4) Frequency not known: anemia, anaphylactic reactions, hypersensitivity, cardiac arrest, arrhythmia, renal failure, renal insufficiency, angioneurotic edema, rhabdomyolysis(associated with hypokalemia) and musculoskeletal pain(described as arthralgia or bone pain) In post-marketing surveillance, anaphylactic reaction was uncommonly reported and angioedema was very rarely reported. Occasionally, there were cases of not severe hypersensitivity. Hematological changes, temporary hearing impairments, tinnitus, visual impairments, double vision, increase and decrease in blood pressure, arrhythmia, cardiac arrest, reversible increase of liver enzyme levels (transaminase), leukocytopenia, agranulocytosis, increase in leukocytes and eosinophil, and rarely reversible renal dysfunction may occur. Rhabdomyolysis accompanied by hypokalemia may be caused by amphotericin B. Therefore, if myalgia, feelings of burnout, increases in creatine kinase (CK, CPK) and increase of myoglobin in the blood and urine occur, administration should be discontinued and appropriate actions be taken. Interference with Phosphorous Chemistry Assays: False elevations of serum phosphate may occur when samples from patients receiving AmBisome are analyzed using the PHOSm assay. **[Use in pregnant women and nursing mothers & pediatric use]** The safety of this drug has not been established in pregnant women and nursing mothers. Safety and effectiveness in pediatric patients below the age of one month have not been established. **[Importer]** Gilead Sciences Korea (26 Eulji ro 5-gil, Jung-gu, Seoul,100-210, Korea, 02-6030-3330 [Distributer] yuhan Corp. (AMB-1605-01)

※ Please read full product information at www. gilead.co.kr or http://nedrug.mfds.go.kr before prescription.

References : 1. Boswell et al. J Clin Pharmacol 1998;38:583-592. 2. Wingard et al. Clin Inf Dis 2000;31:1155-1163. 3. Lipid formulations of amphotericin B. In: Sobel JD, Vazquez JA,editors.Contemporary Diagnosis and Management of Fungal Infections.Handbook in Healthcare, 2006:18-19. 4. Walsh et al. N Engl J Med 1999;340:764-771 5. Lass-Flörl et al. Antimicrob Agents Chemother 2008;52:3637-3641. 6. Cornely et al, for the AmBiLoad Trial Study Group. Clin Infec Dis 2007;44:1289-1297.

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베스폰사

References 1. Kantarjian HM, et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. New Engl J Med. 2016;375:740–53. 2. 베스폰사® 주 제품설명서(2020.12.04)

[Safety information²] 베스폰사®를 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(2% 이상) 중대한 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

[제품정보] 베스폰사® 주 (이노투주맙오조가마이신) **[유효성분]** 이노투주맙오조가마이신 **[효능·효과]** 재발 또는 불응성 전구 B세포 급성 림프모구성 백혈병(ALL) 성인 환자의 치료. 필라델피아 염색체 양성인 재발 또는 불응성 전구 B세포 급성 림프모구성 백혈병 환자는 1가지 이상의 티로신 키나제 억제제(TKI)에 실패한 적이 있어야 한다. **[용법·용량]** 1) 매 용량투여 전 예비투약한다. 2) 주기1에서, 이 약의 총 권장용량은 모든 환자에서 주기당 1.8 mg/m² 이며 총 3회로 나누어 제1일에 0.8 mg/m2, 제8일에 0.5 mg/m², 제15일에 0.5 mg/m²를 투여한다. 주기1의 투여 기간은 3주이지만, 환자가 CR(완전관해) 또는 CRi(불완전한 혈액학적 회복을 동반한 완전관해)를 달성한 경우 및/또는 독성을 회복 할 수 있도록 4주로 연장될 수 있다. 3) 이후 주기에서, •CR 또는 CRi를 달성한 환자의 경우, 이약의 총 권장용량은 주기 당 1.5 mg/m² 로서, 3회로 나누어 제1일, 제8일, 제15일에 각각 0.5 mg/m²씩 투여한다. 이후 주기의 투여 기간은 4주이다. 또는• CR 또는 CRi를 달성하지 않은 환자의 경우, 이 약의 총 권장용량은 주기 당 1.8 mg/m²으로써, 3회로 나누어 제1일에 0.8 mg/m², 제8일에 0.5 mg/m², 제15일에 0.5 mg/m²를 투여한다. 이후 주기의 투여 기간은 4주이다. 3주기 안에 CR 또는 CRi를 달성하지 못한 환자에서는 투여가 중단되어야 한다. 4) 조혈모세포이식(HSCT)을 시행하는 환자의 경우, 이 약의 권장 투여기간은 2주기이다. 2주기 투여 후 CR 또는 CRi를 달성하지 못하거나, MRD(미세잔존질환) 음성을 달성하지 못한 환자에서 세번째 주기가 고려될 수 있다. 5) HSCT를 시행하지 않는 환자의 경우, 추가적으로 최대 6주기까지 투여될 수 있다. **[사용상의 주의사항]** 1. 경고 1) 간독성(정맥폐쇄간질환/굴절관패쇄증후군(VOD/SOS) 포함): 약을 투여받은 재발성 또는 불응성 전구 B세포 급성 림프모구성 백혈병(ALL) 환자에서 치명적이고 생명을 위협하는 정맥폐쇄 간질환/굴절관패쇄증후군(VOD/SOS)을 포함하는 간독성이 발생하였다. 간 수치 평가결과 이 약의 일시중단, 감량, 영구적인 중단이 필요할 수 있다. VOD가 발생하였다면 이 약의 투여를 영구 중단해야 한다. 중증 VOD가 발생하였다면 표준의료행위에 따라 치료해야 한다. 2) 조혈모세포이식(HSCT) 후 비재발성 사망률의 위험 증가: 이 약을 투여받은 환자가 조혈모세포이식 후 100일 째 사망률을 평가했을 때 비재발성 사망률이 더 높았다. 2. 다음 환자에는 투여하지 말 것 1) 이 약의 주성분 또는 이 약의 구성성분에 과민증인 환자 2) 이전에 중증의 정맥폐쇄 간질환/굴절관패쇄증후군(VOD/SOS)를 경험했거나 진행 중인 환자 3) 심각한 간질환이 진행중인환자 (예, 간경변, 결절 재생 과다형성, 활성 간염) **[수입자]** 한국화이자제약㈜ **[개정연월일]** 2020년 12월 4일 **※제품에 대한 자세한 정보는 최신의 제품설명서를 참고하시길 바라며 홈페이지(www.pfizer.co.kr)를 통해 확인하실 수 있습니다.**

BeneFix® RT
Nonacog alfa
(Recombinant Coagulation Factor IX)

References 1. 베네픽스주® 제품설명서(최종변경허가일: 2021.02.17).

[주요 안전성 정보†] 이 약 투여 후 두통, 기침, 발열, 홍조, 구역, 발진, 그 외 알러지 증상 등의 반응이 일어날 수 있습니다. –IX인자를 함유한 제제로 치료받은 환자에게는 활성 중화항체(억제인자)가 발견될 수 있습니다. 이 약을 사용하는 환자에서 IX인자 억제인자가 발견되는지 모니터링 해야 합니다. –IX인자 억제인자를 지닌 환자의 경우 차후 IX인자 투여 시 아나필락시스의 위험성이 증가할 수 있습니다. 알레르기 반응이 나타난 환자에 대해서는 억제인자 생성 여부를 평가해야 합니다. –IX인자를 함유한 다른 제제에서 관찰된 혈전증과 파종성 혈관내응고(DIC), 혈전색전성 합병증을 유발할 가능성이 있으므로 간 질환자, 수술 후 환자, 신생아 또는 혈전색전증 및 파종성 혈관내 응고증(DIC)이 있는 환자에게 이 약 투여 시에는 주의해야 합니다.

베네픽스™주 제품요약정보 [제품명] 베네픽스™주 (노나코그-알파, 혈액응고인자IX(유전자재조합)) BeneFIX® Injection (Nonacog-alfa, Coagulation factor IX (Recombinant)) **[성분분량]** 1 바이알 중 노나코그-알파, 혈액응고인자 IX (유전자재조합) 표시역가 250IU /노나코그-알파, 혈액응고인자 IX (유전자재조합) 표시역가 500IU /노나코그-알파, 혈액응고인자 IX(유전자재조합) 표시역가 1000IU/노나코그-알파, 혈액응고인자 IX (유전자재조합) 표시역가 2000IU/노나코그-알파, 혈액응고인자 IX (유전자재조합) 표시역가 3000IU **[성상]** 환색의 동결건조물이 층진된 바이알에 등 주사제이며, 첨부용제로 용해시 입자가 없는 맑고 무색투명한 액 **[효능·효과]** 혈우병 B(선천성 IX인자 결핍증 또는 크리스마스병(Christmas disease)) 환자의 출혈 에피소드(episodes)의 억제 및 예방(외과적 수술 시 출혈억제 및 예방 포함) / 일상적 예방요법(routine prophylaxis)으로서 출혈 에피소드의 빈도 감소 **[용법·용량]** 이 약은 혈우병 B에 대한 치료경험이 있는 의사의 감독하에 투여하여야 합니다. 이 약을 포함한 모든 IX인자 제제는 각 개인에게 맞는 용량으로 투여하여야 합니다. 모든 IX인자 제제의 용량 및 투여 기간은 IX인자 결핍 정도, 출혈 부위 및 범위, 환자의 임상적 상태에 따라 결정됩니다. 이 약의 투여용량은 혈장 유래 IX인자 제제의 투여용량과 다를 수도 있습니다. 특히 수술의 경우, 요구되는 IX인자 활성농도를 확보하기 위해서는 IX인자 활성평가를 이용한 정확한 모니터링을 해야 합니다. 투여용량을 적절히 조절하기 위해서는 환자의 임상적 상태뿐만 아니라 IX인자 활성도도, 약력학적 인자(반감기 및 회복 수치)를 고려하여야 합니다. [용량계산식] IX 인자의 IU 요구량(IU) = 체중(kg) x 요구되는 IX인자 증가치(% 또는 IU/dL) x 측정한 회복 수치의 역수(IU/dL당IU/kg) 단, 억제인자가 존재할 경우는 더 많은 용량이 요구될 수도 있습니다. 예방적용량의 경우, 일반적인 이차예방에 대한 임상시험에서의 평균용량은 40IU/kg (13–78IU/kg범위)을 3–4일 간격으로 투여한 것이었습니다. 소아 환자의 경우에는 투여간격을 좀히기나 용량을 증가시킬 필요가 있습니다. 임상적 예방요법의 경우, 만 12세 이상에 대해 출혈을 장기적으로 예방하기 위해서는 주 1회 100 IU/kg투여요법이 권장됩니다. **[사용상의 주의사항]** 이 약을 포함하여 모든 IX인자 제제에 대해 아나필락시스를 포함한 알레르기 형태의 과민반응이 보고되었습니다. **[이상반응]** 이전 치료경험이 있는 환자 및 이전에 치료를 받은 적이 없는 환자에 대한 임상시험에서 보고된 이상반응과 시판 후 사용에서 확인된 이상반응은 두통, 기침, 구토, 발열, IX인자 억제, 과민반응, 어지러움, 저혈압, 홍조, 구역, 발진, 두드러기, 가슴불편감 등이 있습니다. **[저장방법]** 밀봉용기, 실온보관(2–30℃) ※제품에 대한 자세한 정보는 최신의 제품설명서를 참고하시기 바라며, 홈페이지(www.pfizer.co.kr)를 통해 확인하실 수 있습니다. 개정년월일: 2021.02.17 [수입판매원] 한국화이자제약㈜

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[제품명] 트룩시마주*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 WF분류중 B, C, D형) / 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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DOSAGE & ADMINISTRATION

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  Administer Antithrombin-III at 1,000~1,500 I.U. per day based on the degree of antithrombin-III consumption
- **Treatment**
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- **Treatment Period**
  Administer Antithrombin-III until the antithrombin-III plasma level becomed normal and all symptoms disappear.

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Reconstitude the freeze-dried powder in 10 mL of sterile water for injection and administer it by slow intravenous injection or drip infusion. For drip infusion, 5% human albumin solution in the most appropriate diluent; Ringer's lactate solution, normal saline solution, or glucose injection 5% may be used when diluted at up to 1:10.

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- ▸ Non-immunosuppressive, Non-invasive

Reference 1. 레볼레이드정 제품설명서(2020.03.18) **2.** Cheng G, et al. Lancet. 2011;377:393-402. **3.** Saleh MN, et al. Blood. 2013;121:537-45. **4.** Bussel JB et al. Haematologica 2016;101(s1) S517. **5.** Desmond R, et al. Blood. 2014;123(12):1818-1825. **6.** Koehrer S, et al. Leukemia. 2010;24(5):1096-1098. **7.** Olnes MJ, et al. N Engl J Med. 2012;367(1):11-9.

[레볼레이드정25mg, 50mg] 주성분: 엘트롬보파올라민 **효능효과: 1.** 코르티코스테로이드 또는 면역글로불린 또는 비장절제술에 충분한 반응을 보이지 않은 만성 면역성(특발성) 혈소판 감소증 환자에서의 저혈소판증 치료. 이 약은 출혈의 위험이 증가하는 임상적 상태의 저혈소판증을 갖는 환자에서만 사용한다. 혈소판 수를 정상화시키기 위한 목적으로 사용하지 않는다. **2.** 만성 C형 간염 환자에서 인터페론 기반 요법의 시작 및 유지를 위한 저혈소판증(투여 시작시 혈소판 수치가 75×109/L 미만) 치료. 이 약은 출혈의 위험이 증가하는 임상적 상태의 저혈소판증을 갖는 환자 또는 저혈소판증으로 인해 인터페론 기반 요법을 시작하지 못하거나 인터페론 기반 요법을 유지하는데 어려움이 있는 만성 C형 간염 환자에서만 사용한다. 혈소판 수를 정상화시키기 위한 목적으로 사용하지 않는다. **3.** 면역억제요법과 병용하여, 2세 이상 소아 및 성인 중증 재생불량성 빈혈 환자의 1차 치료 또는 면역억제요법에 충분한 반응을 보이지 않은 중증 재생불량성 빈혈의 치료 **용법용량:** 이 약의 투여 개시 전 및 투여 기간 동안 간 기능검사(ALT, AST 및 빌리루빈)를 모니터링하고 빌리루빈이 상승하는 경우에는 분획 검사를 실시한다. 또한 혈소판 수를 포함한 전 혈구 수를 모니터링하며, 모니터링 결과에 따라, 아래와 같이 용량 조절 또는 투약 중단을 결정한다. 이 약의 투여 중단 이후에는 최소 4주 동안 혈소판 수를 포함한 전혈구수를 모니터링한다. 공복(식사 1시간 전 또는 식사 2시간 후)에 이 약을 복용해야 한다. 이 약 과 다른 약제에, 제산제, 칼슘이 풍부한 음식(예, 우유제품 및 칼슘 보강 주스), 또는 철분, 칼슘, 알루미늄, 셀레늄, 아연과 같은 다가 양이온을 포함한 보충제를 복용하기 최소 2시간 전 또는 복용하고 최소 4시간 후에 이 약을 투여한다. **1. 만성 면역성(특발성) 혈소판 감소증** 출혈 위험을 감소시키기 위해 필수적인 혈소판 수(≥50×109/L)에 도달 및 유지를 위한 이 약의 가장 낮은 용량 25mg을 1일 1회 투여한다. 혈소판 수 반응에 따라 용량을 조절해야 한다. 그리고 이 약의 투여 개시 후, 출혈 위험을 감소시키기 위해 필수적인 혈소판 수(≥50×109/L)에 도달 및 유지를 위한 용량을 조절해야 한다. 1일 50mg을 초과해서는 안 된다. 이 약으로 치료하는 기간 동안 정기적으로 임상적 혈액 및 간 기능 검사를 모니터링 해야 한다. 이 약으로 치료하는 동안, 안정된 혈소판 수가 얻어질 때까지 매주 혈소판 수를 포함한 전혈구수를 평가해야 한다. 이후 매월 혈소판 수를 포함한 전혈구수를 측정해야 한다. 이 약의 1일 최대 용량 50mg으로 4주간 투여 후, 혈소판 수가 임상적으로 유의한 출혈을 막기 위한 충분한 수치로 증가되지 않는다면, 이 약의 투여를 중단해야 한다. **간장애 환자** 간장애(Child-Pugh 등급 A, B, C)가 있는 특발성 혈소판 감소증 환자의 경우, 이 약의 기대되는 이익이 문맥혈전증의 알려진 위험을 상회하는 경우에만 이 약을 투여한다. 간장애 환자(Child-Pugh 등급 A, B, C)의 경우 초기용량으로 25mg/일을 격일 투여한다. 간장애 환자(Child-Pugh 등급 A, B, C)의 경우 초기용량 또는 이후 용량 증가 후에는 3주 후부터 다음 용량으로 증가하는 것을 권장한다. **2. 만성 C형 간염** 페그인터페론 및 리바비린 항바이러스 요법을 시작 및 유지하기 위해 필요한 혈소판 수에 도달 및 유지를 위한 이 약의 가장 낮은 용량 25mg을1일 1회 투여한다. 혈소판 수 반응에 따라 용량을 조절한다. 항바이러스 요법을 시작하기 위한 목표 혈소판 수에 도달하기 위해 2주마다 25mg씩 용량을 조절한다. 항바이러스 요법을 시작하기에 앞서 매주 혈소판 수를 모니터링한다. 항바이러스 요법 중에, 페그인터페론을 감량하지 않도록 이 약의 용량을 조절한다. 이 약으로 치료하는 동안, 안정된 혈소판 수가 얻어질 때까지 매주 혈소판 수를 포함한 전혈구수를 평가해야 한다, 이후 매월 혈소판 수를 측정해야 한다, 1일 75mg을 초과해서는 안 된다. 이 약으로 치료하는 동안 정기적으로 임상적 혈액 및 간 기능 검사를 모니터링 해야 한다, 항바이러스 요법을 중단하면, 이 약의 투여를 중단하여야 한다. 혈소판 수의 과도한 증가 또는 중요한 간기능 검사 이상 시, 이 약의 투여를 중단해야 한다. **3. 중증 재생불량성 빈혈** [면역억제요법과 병용하여, 2세이상 소아 및 성인 중증 재생불량성 빈혈 환자의 1차 치료] 면역억제요법과 병용하여 이 약의 투여를 시작한다. 초기용량으로 성인 및 만 12–17세 청소년은 이 약 75mg을 6개월동안 1일1회투여한다. 만 6–11세 소아는 이 약 37.5mg을 6개월 동안 1일 1회 투여한다, 이 약 37.5mg을 1일 1회 투여하기 위해 이 약 25mg과 50mg을 격일로 투여할 수 있다. 만 2–5세 소아는 이 약 1.25mg/kg 용량으로 6개월 동안 1일 1회 투여한다, 이 약으로 치료하는 기간 동안 임상 혈액검사 및 간 검사를 정기적으로 수행해야 한다, 이 약의 전체 치료기간은 6개월이다. 혈소판 수의 과도한 반응 또는 특정 이상반응 발생시, 이 약의 투여를 중단해야 한다. [면역억제요법에 충분한 반응을 보이지 않은 중증 재생불량성 빈혈의 치료] 초기용량으로 25mg을 1일 1회 투여한다, 혈액반응은 일반적으로 100mg까지 용량 적정이 필요하고 복용시작 후 16주까지 소요될 수 있다, 필수적인 혈소판 수(50X109/L 이상)에 도달 및 유지하기 위해 2주마다 25mg씩 용량을 조절한다, 이 약으로 치료하는 동안 정기적으로 임상적 혈액 및 간 검사를 모니터링 해야 한다, 이 약으로 투여 16주 후에도 혈액학적 반응이 없어나지 않는 경우, 새로운 세포유전적 이상이 관찰되는 경우, 혈소판 수의 과도한 반응 또는 중요한 간 검사 이상 시, 이 약의 투여를 중단해야 한다. **경고:** 1) 간독성: 이 약은 간담도 검사 이상, 중증 간독성 및 잠재적으로 치명적인 간손상을 유발할 수 있다. 2) 만성 C형 간염 환자에서의 간 대상부전: 만성 C형 간염 환자에서 이 약과 인터페론/리바비린과 병용 시 간 대상부전의 위험을 증가시킬 수 있다. 간경변이 있는 만성 C형 간염 환자는 인터페론 알파 투여시, 간 대상부전 및 사망 위험이 있다. 이 환자들은 간 대상부전의 징후나 증상에 대해 면밀히 모니터링 되어야 한다. 3) 골수 그물세 및 골수섬유화의 위험 4) 혈전성/혈전색전성 합병증: 혈전색전성 이상반응은 특발성 혈소판 감소증 환자에서 나타날 수 있다. 5) 사망 위험성 및 골수 이형성 증후군(myelodysplastic syndrome, MDS)에서 급성 골수성 백혈병(AML)으로의 진행 위험성 증가 6) 혈청검사에 대한 영향: 이 약을 복용한 환자들로부터 일부 실험실 검사 (혈청 변색, 총빌리루빈 및 크레아티닌의 방해가 보고되었다. **다음 환자에게는 신중히 투여할 것:** 1) 간장애 환자 : 중등증 및 중증 간질환 환자에서는 이 약의 낮은 초기 용량을 투여해야 하고, 면밀히 모니터링 해야 한다. 특히 동아시아 간장애 환자에서 이 약의 안전성 및 유효성은 확립되어 있지 않으므로 임상의의 판단에 따라 신중히 투여해야 한다, 2) 골수 섬유화 등 혈구의 형태학적 이상 발생의 위험이 있는 환자 3) 혈전색전증의 위험요소(예, 혈액응고인자 Factor V Leiden, AT III 결핍, antiphospholipid 신드롬, 만성 간질환 등)가 있는 것으로 알려진 환자 4) 신장애 환자 **처방하시기 전, 상세 제품정보를 참조하시기 바랍니다.** (개정일: 2020년 3월 18일)

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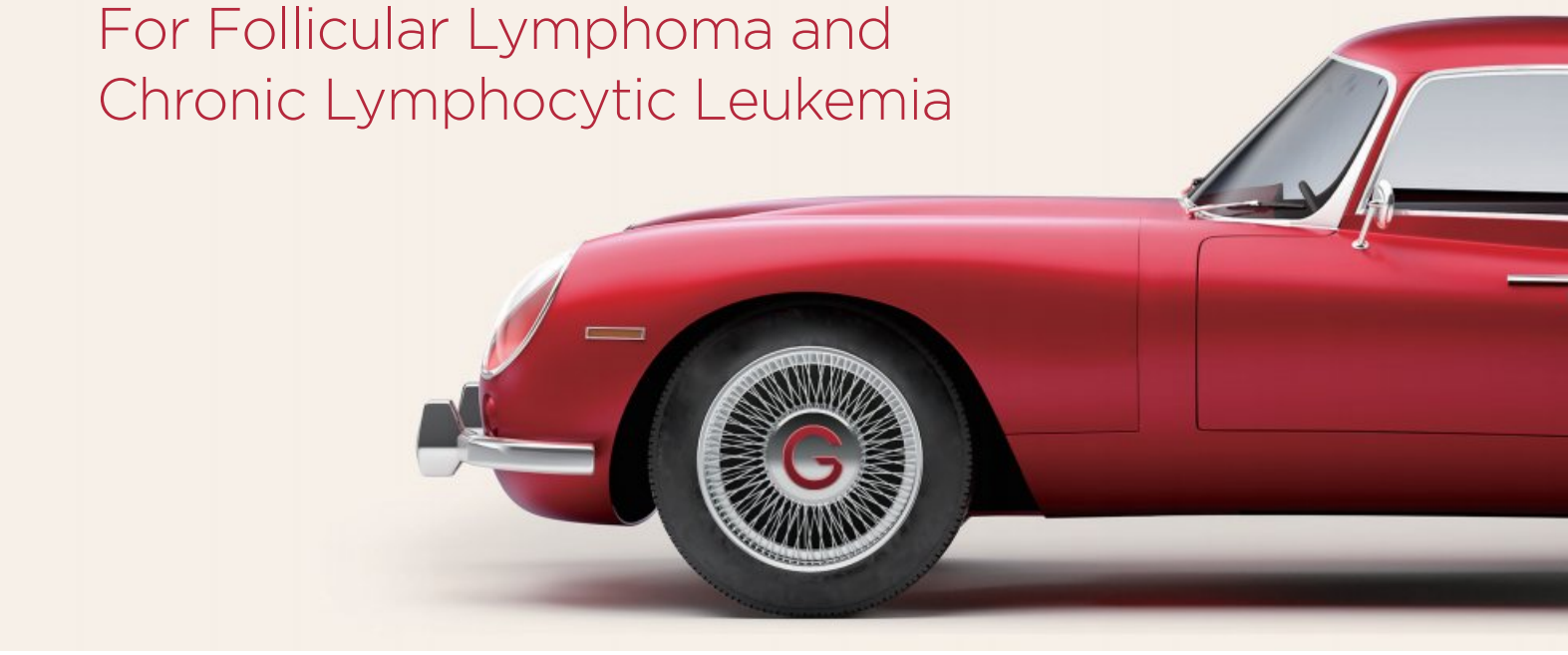

Prescribing Information

가싸이바주(오비누투주맙, 유전자재조합)

[효능.효과] ○ 만성 림프구성 백혈병 : 동반질환이 있으며 이전에 치료받은 적이 없는 만성 림프구성 백혈병에서 클로람부실과 병용투여 ○ 여포형 림프종 : 이전에 치료받은 적이 없는 stage II(bulky), III 또는 IV 여포형 림프종에서 화학요법과 병용투여 후 유지요법으로 단독 투여, 리툭시맙 단독요법 또는 리툭시맙이 포함된 병용요법에 반응하지 않거나, 투여 중 또는 투여 후에 질병이 진행된 여포형 림프종에서 벤다무스틴과 병용투여 후 유지요법으로 단독 투여

[용법.용량] 소생술이 즉시 가능한 환경에서 경험이 있는 의사의 면밀한 감독 하에 전용 라인을 통하여 정맥 점적주입(i.v. infusion)으로 투약하여야 한다. 이 약을 급속 정맥주입(i.v. push) 또는 정맥주사(i.v. bolus)로 투여해서는 안 된다. 등장성의 0.9% 생리식염주사액을 희석액으로 사용한다('사용상의주의사항'의 '8.적용상의 주의'항을 참고한다). **종양용해증후군(TLS)의 예방 및 전처치** : 종양 부하가 높고/또는 순환 림프구 수치가 높은(> 25 X 10^9/L)/또는 신장애(CrCl < 70mL/min) 환자는 종양용해증후군의 위험성이 높은 것으로 간주되어 예방조치를 받아야 한다. 표준 요법에 따라 이 약 투여를 시작하기 전에, 충분한 수분공급과 요산증치료제(예, 알로푸리놀) 또는 요산 산화효소(예, 라스부리카제)와 같은 적절한 대체제의 투여가 예방법으로 구성되어야 한다. 적절하다고 판단되면, 다음 약물을 투여하기 전, 예방조치를 계속 반복한다. **주입관련반응(IRR)에 대한 예방 및 전처치** : 주입관련반응의 위험을 감소시키기 위한 전처치('사용상주의사항'의 '1. 경고'항 참고)를 표 1에 요약하였다. 여포형 림프종 환자(FL)에 대한 코르티코스테로이드 전처치가 권장되며, 만성 림프구성 백혈병 환자(CLL)의 첫 점적주입 시에는 필수적이다. 아래에 설명된 대로 후속 주입 시의 전처치나 기타 전처치를 해야 한다. 주입 관련반응의 증상으로 정맥 점적주입시 저혈압이 나타날 수 있다. 따라서 이 약 투여 12시간 전과 투여 중 그리고 투여 후 1시간동안 항고혈압제 투여 보류를 고려해야 한다. ● **표준 권장 용량 : 1. 만성 림프구성 백혈병 (클로람부실과 병용투여)** : 1주기 이 약의 권장 용량은 첫 번째 28일 투여 주기에서 Day 1-2, Day 8과 Day 15에 1000밀리그램을 표 2와 같이 투여하는 것이다. 점적주입시 주입용 백을 두 개 준비한다(첫 번째 주입용 100밀리그램, 두 번째 주입용 900밀리그램). 100mg 용량을 점적주입 속도 변화나 중단 없이 투여한 경우, 점적주입동안 적절한 시간, 조건, 의학적 감독이 가능하다면 900mg 용량을 같은 날 투여할 수 있다(투약 지연 없이). 첫 번째 100밀리그램 투여시 점적주입 속도 변화나 중단이 있었다면, 900mg 용량은 반드시 다음날에 투여해야 한다(표 2 참고). 2-6주기 이 약의 권장 용량은 28일 투여 주기에서 매 Day 1에 1000밀리그램을 표2와 같이 투여하는 것이다. 투약일이 지났거나 투약을 놓친 경우(만성 림프구성 백혈병) 이 약의 투약을 놓친 경우에는 다음 계획된 투여까지 기다리지 말고, 가능한 빨리 투여해야 한다. 이 약의 계획된 치료 간격이 투여 간에 유지되어야 한다. **2. 여포형 림프종** : 이 약의 권장 용량은 1000mg을 표3과 같이 정맥으로 투여하는 것이다. 이전에 치료받은 적이 없는 여포형 림프종 : 이전에 치료받은 적이 없는 여포형 림프종 환자에게 유도요법으로 이 약을 다음과 같이 화학요법제와 병용투여한다. . 28일 투여주기의 벤다무스틴과 병용투여 6주기 또는, . 21일 투여주기의 시클로포스파미드, 독소루비신, 빈크리스틴, 프레드니손(CHOP)과 병용투여 6주기, 이후에 이 약 단독 투여 2주기 또는, . 21일 투여주기의 시클로포스파미드, 빈크리스틴, 프레드니손(CVP)와 병용투여 8주기. 이 약과 화학요법의 병용으로 완전 반응(complete response) 또는 부분 반응(partial response)을 보인 이전에 치료받은 적이 없는 환자는 유지요법으로서 2달에 한 번씩 이 약(1000mg)을 단독으로 질병 진행시까지 또는 최대 2년까지 지속한다. 투약일이 지났거나 투약을 놓친 경우(여포형 림프종)이 약의 투약을 놓친 경우에는 생략하거나 다음 계획된 투여까지 기다리지 말고, 가능한 빨리 투여해야 한다. 이 약과 화학요법의 투여 동안, 화학요법 주기 사이의 간격을 유지하도록 투여 일정을 조정해야 한다. 유지 요법 동안 원래의 투여 일정을 후속 투여에서도 지켜야 한다. **3. 재발성/불응성 여포형 림프종** : 리툭시맙이나 리툭시맙을 포함하는 요법 후에 재발하거나 불응한 여포형 림프종 환자들은 유도요법으로 이 약을 벤다무스틴과 병용하여 28일 투여주기로 6주기 동안 투여한다. 완전반응 또는 부분 반응, 또는 안정된 질환상태인 환자는 유지요법으로서 2달에 한 번씩 이 약 1000mg을 단독으로 질병 진행시까지 또는 최대 2년까지 지속한다. 투약일이 지났거나 투약을 놓친 경우(여포형 림프종) 이 약의 투약을 놓친 경우에는 생략하거나 다음 계획된 투여까지 기다리지 말고, 가능한 빨리 투여해야 한다. 이 약과 화학요법의 투여 동안, 화학요법 주기 사이의 간격을 유지하도록 투여 일정을 조정해야 한다. 유지 요법 동안 원래의 투여 일정을 후속 투여에서도 지켜야 한다. ● 치료 중 용량조절 (모든 적응증) 이 약의 감량은 권장되지 않는다. 증후성 이상사례(주입관련반응 포함)의 관리는 아래 표4와, '사용상의 주의사항'의 '1.경고'항을 참고한다. ● 특수 환자군 : 신장애 환자. 이 약은 주요 임상시험(pivotal trial)에서 크레아티닌 청소율이 70mL/min 미만인 환자에서 연구되었다. 경증 또는 중등도의 신장애 환자는 용량 조절이 필요하지 않다. 크레아티닌 청소율이 30mL/min 미만의 환자에서는 이 약은 연구되지 않았다.('사용상주의사항'의 '6. 5)신장애 환자'항 참고) **[사용상의 주의사항] 1. 경고** 1) 주입관련반응 (IRR) : 이 약을 투여받은 환자에서 가장 빈번하게 관찰된 약물이상반응(ADRs)은 대부분 최초 1000mg 주입시에 발생한 주입관련반응(IRR)이었다. 주입관련반응을 예방하기 위한 조치(적절한 코르티코스테로이드, 경구 진통제/항히스타민제 투여, 항고혈압 약물 치료제 보류)를 취한 만성 림프구성 백혈병 환자는 모든 등급의 주입관련반응 발생률 감소가 관찰되었다. 3-4등급 주입관련반응의 비율(상대적으로 적은 수의 환자에 근거한)은 완화조치를 시행하기 전과 후에 있어서 비슷하였다. 주입관련반응을 감소시키기 위해 완화조치를 따라야 한다('용법용량' 참고). 주입관련 증상의 발생률과 중증도가 최초 주입 이후 대체적으로 감소하였으며, 대부분의 환자는 추후 투여기간 동안 주입관련반응이 없었다('3. 약물이상반응'항 참고). 적응증과 상관없이 대부분의 환자에서는 주입관련반응이 경증 및 중등도였으며 1차 주입을 일시적으로 중단하거나 감속함으로써 조절이 가능하였다. 그러나 증상치료가 필요한 중증 및 치명적인 주입관련반응도 보고되었다. 주입관련반응은 면역글로불린E 매개성 알레르기반응(예, 아나필락시스)과 임상적으로 구분하기 어려울 수 있다. 종양부하가 높은 환자(예, 만성림프구성백혈병에서 말초혈액림프구 수치가 높은 환자(>25x10^9/L))는 중증 주입관련반응의 위험이 증가될 수 있다. 예방에 관한 정보는 '용법용량'을 참고하고, 반응 등급에 따라 주입관련반응을 조절하는 방법은 '용법용량' 표4. 주입관련 반응시 주입 속도 조절 가이드라인을 참고한다. 다음의 경우에는 이 약의 추가 주입을 중단해야 한다. ● 급성 치명적 호흡기 증상 ● 4등급 (예, 치명적) 주입관련반응 또는, ● (1차 주입을 재개한 이후 또는 다음 주입기간 동안) 3등급 주입관련반응이 2차로 발생한 경우(지속적/재발성) 기존에 심장 또는 폐 질환이 있는 환자는 주입기간 전체와 주입 이후에도 주의 깊게 모니터링 해야 한다. 저혈압이 이 약 투여 중에 일어날 수 있다. 그러므로 이 약의 매 주입 전 12시간부터 주입 후 1시간까지 고혈압 치료 보류를 고려해야 한다. 고혈압위기의 급성 위험이 있는 환자는 고혈압 치료제 보류에 따른 유익성과 위해성을 평가해야 한다. 2) 과민반응 : 즉시성(예, 아나필락시스) 및 후발성(예, 혈청병) 과민반응이 이 약을 투여한 환자에서 보고되었다. 주입하는 동안이나 주입 후에 과민반응이 의심되면(예, 전형적으로 이전에 노출된 후에 발생하고, 최초주입시에는 매우 드물게 나타남), 주입을 멈추고 치료를 영구적으로 중단해야 한다. 이 약에 대한 알려진 과민반응이 있는 환자에는 이 약을 투여하지 말아야 한다. 과민반응은 주입관련반응과 임상적으로 구분하기 어려울 수 있다. 3) 종양용해증후군(TLS) : 이 약을 투여한 환자에서 종양용해증후군이 보고되었다. 종양용해증후군의 위험이 있을 것으로 판단되는 환자(예, 종양 부하가 높고/또는 순환 림프구수치가 높은(>25x10^9/L)/또는 신장애(CrCl < 70mL/min) 환자)는 예방조치를 받아야 한다. '용법용량'항에 따라 이 약 주입 전에 충분한 수분공급과 요산증치료제(예, 알로푸리놀) 또는 요산 산화효소(예, 라스부리카제)와 같은 적절한 대체제의 투여가 예방법으로 구성되어야 한다. 위험하다고 판단되는 모든 환자는 투여 첫째 날에 신장 기능, 칼륨, 요산 수치에 특별히 집중하여 신중히 모니터링 한다. 표준 요법에 따른 추가 가이드라인이 있다면 따라야 한다. 종양용해증후군을 치료하기 위해서는, 전해질 이상을 바로잡고, 신기능 및 체액 평형을 모니터링하며, 투석을 포함한 지지요법을 투여한다. 4) 호중구감소증 : 열성 호중구감소증을 포함하는 중증이고 치명적인 호중구감소증이 이 약 치료기간동안 보고되었다. 호중구감소증을 경험한 환자는 소실될 때까지 정기적인 실험실 검사로 면밀히 모니터링 해야 한다. 치료가 필요하면 가이드라인에 따라 투여하고, 과립구집락 자극인자(granulocytes colony stimulating factors, G-CSF) 투여를 고려해야 한다. 동반 감염 징후는 적절하게 처치해야 한다. 후발성 호중구감소증 (late onset, 치료가 끝난 후 28일 후에 발생) 또는 지속적 호중구감소증(치료 완료/중단 후 28일 이상 지속)이 보고되었다. 5) 혈소판감소증 : 이 약의 치료기간 동안 급성 혈소판감소증(주입 후 24시간 이내 발생)을 포함해 중증이고 생명을 위협하는 혈소판감소증이 관찰되었다. 치명적인 출혈이 이 약을 투여하는 동안 1주기에서 보고되었다. 혈소판감소증과 출혈 사이에 명확한 인과관계는 확립되지 않았다. 특히 1주기 투여 동안, 혈소판감소증에 대해 환자를 면밀히 모니터한다. 정기적 실험실 검사를 경과가 소실될 때까지 실행하고, 중증이거나 치명적인 혈소판감소증의 경우 투여 연기를 고려한다. 관리체계에 따른 혈액제제 수혈(예, 혈소판 수혈)은 치료담당 의사의 재량에 따른다. 혈소판 억제제와 항응고제와 같이 혈소판감소증을 악화시킬 수 있는 모든 병용 요법의 투여는 특히 1주기에서 신중히 고려해야 한다. 6) 기존 심장상태의 악화 : 기저 심장 질환이 있는 환자에서 이 약으로 치료 시, 부정맥(심방세동 및 부정빈맥과 같은), 협심증, 급성 관상동맥 증후군, 심근경색증, 심장기능상실이 발생하였다. 주입관련반응의 일부로 발생하고 치명적일 수 있으므로, 심장질환 병력이 있는 환자는 면밀히 모니터링 해야 한다. 또한, 이러한 환자에서는 잠재적인 체액과부하를 방지하기 위해 주의하여 수분공급을 해야 한다. 7) 감염 : 활성 감염이 있는 경우에는 이 약을 투여해서는 안 된다. 재발 또는 만성 감염의 병력이 있는 환자에게 이 약 투여를 고려할 경우에는 주의가 필요하다. 이 약 치료 기간과 치료완료 후에 중증의 박테리아성, 진균성, 신규 또는 재활성 바이러스감염이 발생할 수 있다. 치명적인 감염이 보고되었다. 여포형 림프종 연구에서, 추적 방문을 포함한 모든 단계의 연구에서 높은 빈도로 감염이 관찰되었으며, 유지요법에서 가장 높은 빈도를 보였다. 추적 방문 단계에서, 유도요법으로 벤다무스틴과 이 약을 투여한 환자에서 3-5등급의 감염이 더 많이 관찰되었다. 8) B형 간염 재활성화 : 몇몇 경우에 전격간염을 일으키는 B형 간염 바이러스 재활성화, 간부전 그리고 사망이 이 약을 포함해 항CD20 항체를 투여받은 환자에서 발생할 수 있다. 이 약의 투여를 시작하기 전에 모든 환자들에 대해 B형 간염 바이러스 스크리닝 검사를 실시해야 한다. 최소한, HBsAg와 HBcAb 검사를 실시한다. 이는 가이드라인에 따라 적절한 표지로 보완될 수 있다. 활성 B형 간염 질환이 있는 환자에게 이 약을 투여해서는 안 된다. 혈청검사 결과 양성인 환자는 이 약을 투여하기 전에 간질환 전문가의 자문을 구하고, 간염 재활성화를 예방하기 위해 국내 치료표준지침에 따라 모니터링 및 관리한다. 9) 진행성 다초점 백색질뇌증(Progressive multifocal leukoencephalopathy, PML) : 이 약을 투여한 환자에서 진행성 다초점 백색질뇌증(PML)이 보고되었다. 신경학적 증상이 새롭게 나타난 환자는 PML의 진단을 고려해야 한다. PML의 증상은 특징적이지 않고, 영향 받은 뇌 부분에 따라 다양할 수 있다. 흔한 증상으로는 피질척수로 소견(예, 근육 약화, 마비 및 감각장애), 감각이상, 소뇌성 증상, 시야결손이 있는 운동증상이다. '피질로 간주되는 일부 징후/증상 (예, 언어상실증 또는 시공간 혼동)이 발생할 수 있다. PML 평가에는 신경전문의 자문, 뇌 MRI(magnetic resonance imaging), 요추천자(JC viral DNA에 대한 CSF testing) 등을 포함한다. 병용 화학요법 또는 면역억제치료의 중단 또는 감량을 고려해야 한다. PML의 평가와 치료를 위해서는 신경전문의의 자문을 받아야 한다. 10) 예방접종 : 이 약 투여 후 생백신 또는 약독화 바이러스 백신 사용의 안전성은 연구되지 않았다. 이 약의 치료기간과 B-세포 회복까지 생바이러스 백신의 접종은 권장되지 않는다. 이 약의 자궁 내 노출 및 영아에 대한 생바이러스 백신 접종: 임신 중 이 약에 노출된 모체의 영아에서 B 세포가 고갈될 가능성이 있으므로, 생바이러스 백신 접종의 안전성과 시점을 소아 의료전문가와 논의해야 한다. 임신 중에 이 약에 노출된 여성의 영아는 B 세포 농도가 정상 범위에 들어올 때까지 생백신 접종을 미루는 것을 고려해야 한다('6. 임부에 대한 투여'항 참고). **2. 다음 환자에는 투여하지 말 것** : 이 약 또는 구성성분에 대한 알려진 과민반응이 있는 환자

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Reference 1. Bahlis NJ, et al. *Leukemia* 2017;31:2435-42. **2.** NCCN clinical practice guidelines in oncology ver 4. 2020

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[전문의약품] [원료약품 및 그 분량] 레블리미드 2.5밀리그램 1캡슐 중, 레날리도마이드 수화물 (별규) 2.59 mg (레날리도마이드무수물로서 2.5 mg) 레블리미드 5밀리그램 1 캡슐 중, 레날리도마이드 수화물 (별규) 5.17 mg (레날리도마이드무수물로서 5 mg) 레블리미드 7.5밀리 그램 1캡슐 중, 레날리도마이드 수화물 (별규) 7.76 mg (레날리도마이드무수물로서 7.5 mg) 레블리미드 10밀리그램 1 캡슐 중, 레날리도마이드 수화물 (별규) 10.35 mg (레날리도마이드무수물로서 10 mg) 레블리미드 15밀리그램 1 캡슐 중, 레날리도마이드 수화물 (별규) 15.52 mg (레날리도마이드무수물로서 15 mg) 레블리미드 20밀리그램 1캡슐 중, 레날리도마이드 수화물 (별규) 20.70 mg (레날리도마이드무수물로서 20 mg) 레블리미드 25밀리그램 1 캡슐 중, 레날리도마이드 수화물 (별규) 25.87 mg (레날리도마이드무수물로서 25 mg) 첨가제 : 무수유당, 미결정셀룰로오스, 크로스카르멜로오스나트륨, 스테아르산마그네슘, 캡슐 **[성상]** 레블리미드캡슐 2.5밀리그램: 흰색의 가루가 든 상부 청녹색, 하부 흰색의 경질 캡슐 레블리미드캡슐 5밀리그램: 흰색의 가루가 든 상하부 흰색의 경질 캡슐 레블리미드캡슐 7.5밀리그램: 흰색의 가루가 든 상부 연노랑, 하부 흰색의 경질 캡슐 레블리미드캡슐 10밀리그램: 흰색의 가루가 든 상부 청녹색, 하부 연노랑의 경질 캡슐 레블리미드캡슐 15밀리그램: 흰색의 가루가 든 상부 청색, 하부 흰색의 경질 캡슐 레블리미드캡슐 20밀리그램: 흰색의 가루가 든 상부 청 녹색, 하부 청색의 경질 캡슐 레블리미드캡슐 25밀리그램: 흰색의 가루가 든 상하부 흰색의 경질 캡슐 **[효능·효과]** 1. 다발골수종 1)이전에 한 가지 이상의 치료를 받은 환자의 치료에 덱사메타손과 병용요법 2)새롭게 진단된 이식이 불가능한 환자의 치료에 덱사메타손과 병용요 법, 또는 멜팔란 및 프레드니솔론과 병용요법 3)새롭게 진단된 환자의 치료에 보르테조밉 및 덱사메타손과 병용요법 4)새롭게 진단된 자가 조혈모세포 이식을 받은 환자의 유지요법 2. 5q 세포유전자 결손을 동반한 International Prognostic Scoring System(IPSS) 분류에 따른 저 위험 또는 중등도-1-위험 골수형성이상증후군에서 수혈 의존적인 빈혈이 있는 환자의 치료 3. 이전에 한가지 이상의 치료를 받은 외투세포림프종 4. 이전에 치료를 받은 소포림프종(1-3a등급) 환자의 치료에 리툭시맙(항CD20항체)과 병용요법 **[용법·용량]** 이 약은 위해관리프로 그램 (사용상의 주의사항 중 '5. 일반적 주의사항 참조')에 규정된 사항을 따르는 것에 동의한 환자에게만 투여되어야 한다. 또한 이 약은 위해관리프로그램에 등록된 의사들에 의해서만 처방되어야 하고, 등록된 약사들에 의해서만 조제되어야 한다. 임신가능성이 있는 여성에게 처 방될 경우, 본 프로그램에서 정하고 있는 일정에 따라 지속적으로 임신테스트의 음성결과를 확인하여야 한다. 1. 다발골수종 1)이전에 한가지 이상의 치료를 받은 환자의 치료에 덱사메타손과 병용요법 절대호중구수 <1,000/㎕ 및/또는 혈소판수 <75,000/㎕이면 치료를 시작해서 는 안된다. 권장 초회 용량은 1일 1회 25mg이다. 28일 주기로 1–21일 동안 25mg 캡슐을 복용한다. 덱사메타손의 권장량은 28일 주기를 기준으로 하여 매 1, 8, 15, 22일에 1일 1회 40mg을 투여한다. 75세 이상의 경우 덱사메타손의 권장량은 28일 주기를 기준으로 하여 매 1, 8, 15, 22일에 1일 1회 20mg을 투여한다. 치료는 질병이 악화되거나 수용하기 어려운 독성이 나타 날 때까지 지속한다. 3) 새롭게 진단된 이식이 불가능한 환자의 치료에 멜팔란, 프레드니솔론과 병용요법 절대호중구수 <1,500/㎕ 및/또는 혈소판수 <75,000/㎕이면 치료를 시작해서는 안된다. 권장 초회 용량은 1일 1회 10mg이다. 28일 주기로 1–21일 동안 10 mg 캡슐을 복용 한다. 9주기까지 멜팔란은 28일 주기를 기준으로 하여 매 1–4일에 0.18mg/kg의 용량으로 경구투여하고, 프레드니솔론은 28일 주 기를 기준으로 매 1–4일에 2mg/kg의 용량으로 경구투여한다. 9주기를 완료하였거나 내약성 때문에 병용요법을 완료할 수 없는 환자의 경우 이 약 단독요법으로 1일 1회 10mg을 28일 주기의 1–21일 동안 질병이 악화될 때까지 복용한다. 4) 새롭게 진단된 환자의 치료에 보르테조밉 및 덱사메타손과 병용요법 (1) 새롭게 진단된 이식이 불가능한 환자의 치료에 보르테조밉 및 덱사메타손과 병용요법 절대호중구수 <1,000/㎕ 및/또는 혈소판수 <80,000/㎕이면 치료를 시작해서는 안된다. 이 약의 권장 초회 용량은 1일 1회 25mg으로, 21일 주기로 제1–14일 동안 복용한다. 보르테조밉은 체표면적 당 1.3mg/m2의 용량으로 21일 주기의 1, 4, 8, 11일에 피하주사로 투여한다. 덱사메타손의 권장량은 1일 1 회 20mg으로, 21일 주기를 기준으로 1, 2, 4, 5, 8, 9, 11, 12일에 복용한다. 환자들은 초기치료로서 8주기 (총 24주) 동안 치료를 받아야한다. 초기 치료 이후, 이 약 25mg을 덱사메타손과 병용하여 28일주기의 1-21일에 1일 1회 복용한다. 덱사메타손의 권장 용법용량은 28일 주기 의 1, 8, 15, 22일에 40mg을 1일 1회 복용한다. 75세 이상의 환자는, 덱사메타손의 시작 용량을 20mg로 하여 28일 주기의 1, 8, 15, 22일에 1일 1회 복용한다. 치료는 질병이 진행되거나 수용할 수 없는 독성이 나타날 때 까지 지속할 수 있다. (2) 새롭게 진단된 이식이 가능한 환자 의 치료에 보르테조밉 및 덱사메타손과 병용 유도요법 절대호중구수 <1,000/㎕ 및/또는 혈소판수 <80,000/㎕이면 치료를 시작해서는 안된다. 이 약의 권장 초회 용량은 1일 1회 25mg으로, 28일 주기로 제1–21일 동안 복용한다. 보르테조밉은 체표면적 당 1.3mg/m2의 용량으 로 28일 주기의 1, 4, 8, 11일에 피하주사로 투여한다. 덱사메타손의 권장량은 1일 1회 40mg으로, 28일 주기의 1-4, 9-12일에 복용한다. 환자들은 초기치료로서 6주기 (총 24주) 동안 치료를 받아야한다. 5) 새롭게 진단된 자가 조혈모세포 이식을 받은 환자의 유지요법 이 약의 유 지요법은 질병 진행의 증거가 없는 환자에서 자가 조혈모세포 이식을 받은 후 적절하게 혈액학적으로 회복된 후에 시작되어야 한다. 절대호중구수 <1,000/㎕ 및/또는 혈소판수 <75,000/㎕이면 치료를 시작해서는 안 된다. 권장 초회 용량은 1일 1회 10mg으로 28일 주기로 1–28 일 동안 10 mg 캡슐을 내약성이 없거나 질병의 진행이 있을 때까지 복용한다. 이 약의 유지요법을 3주기 진행한 후에 내약성이 있을 경우 1일 1회 15mg까지 증량할 수 있다. 2. 골수형성이상증후군 절대호중구수 <500/㎕ 및/또는 혈소판수 <25,000/㎕이면 치료를 시작해서는 안 된다. 권장 초회 용량은 1일 1회 10mg이다. 28일 주기로 1–21일 동안 10 mg 캡슐을 복용한다. 3. 외투세포림프종 권장 초회 용량은 1일 1회 25mg이다. 28일 주기로 1–21일 동안 25mg 캡슐을 복용한다. 4. 소포림프종 절대호중구수 <1,000/㎕ 및/또는 혈소판수 <50,000/㎕ 이 면 치료를 시작해서는 안 된다 (림프종이 골수에 침투하여 발생한 이차적인 경우는 제외). 권장 초회 용량은 1일 1회 20mg이다. 28일 주기로 1–21일 동안 20mg 캡슐을 복용한다. 최대 12 치료 주기까지 복용한다. 리툭시맙의 권장 초회 용량은 28일 주기를 기준으로 하며 1주기에 는 매주 375 mg/m2을 정맥 투여 한다(1, 8, 15, 22일). 2–5주기에는 28일 주기마다 매 1일에만 375 mg/m2을 정맥 투여 한다. **[사용상의 주의사항]** 1. 경고 1) 태아 위험 : 임신 중에 이 약을 사용하지 말 것 레날리도마이드(탈리도마이드 유사체)는 임신 원숭이의 배태자발생시험에 서 사지기형을 야기하였다. 탈리도마이드는 생명에 치명적인 인체의 선천성 결함을 야기하는 인체 최기형성 물질로 알려져 있다. 만약 이 약을 임신 중 복용하면 태아에게 선청성 기형 또는 유산을 유발할 수 있다. 임신 가능성이 있는 여성에서 이 약을 투여하기 전에 2번의 음성 임신 진단 검사 결과를 얻어야 한다. 가임기 여성의 경우 이 약 투여 중, 치료 후 4주까지의 기간 동안 이성간 성교를 삼가거나 적어도 적절한 피임법 중 최소한 두 가지 이상의 방법으로 피임을 해야한다. (적절한 피임법은 사용상 주의사항 중 '5. 일반적 주의' 항을 참조한다.) 2) 이 약은 위해관리프로그램에 등록한 의사와 약사만이 처방 및 조제할 수 있고, 이 프로그램에서 정하고 있는 사항에 동의하고, 서명한 환자에 한하여 처방할 수 있다. 환자들은 이 프로그램을 준수하여야 한다. 제조사로부터 동 프로그램에 대한 자세한 정보를 제공받아야 한다. **[사용기한]** 제조일로부터 36개월 **[저장방법]** 기밀용기, 실온보관(15-30℃) **[포장단위]** 7캡슐, 21캡슐/Pack

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- **GRASIN® PFS facilitates**
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The indications of GRASIN® PFS

1. Patients with cancers receiving myelosuppressive chemotherapy
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1. GRASIN is the only rhG-CSF product approved by FDA.
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XOSPATA

gilteritinib

First Approved* FLT3 Inhibitor Indicated for Adult Patients with Relapsed or Refractory FLT3m+AML¶,[1]

9.3 vs. 5.6 months[2]

median OS

XOSPATA® (95% CI: 7.7, 10.7)
vs. salvage chemotherapy (95% CI: 4.7, 7.3)

HR=0.64 (95% CI: 0.49, 0.83); *p*<0.001

34.0% (n=84/247)[2]

CR† / CRh‡

Risk difference (95% CI)
: 18.6 (9.8–27.4)

mDOR=11 months (4.6-NE)[2]

STUDY DESIGN

In an open-label, multicenter, randomized, phase 3 clinical trial, this study randomly assigned adults with relapsed or refractory FLT3-mutated AML patients in a 2:1 ratio to receive either gilteritinib (at a dose of 120 mg per day, n=247) or salvage chemotherapy (n=124). The two primary end points were overall survival and the percentage of patients who had complete remission with full or partial hematologic recovery. Secondary end points included event-free survival (freedom from treatment failure [i.e., relapse or lack of remission] or death) and the percentage of patients who had complete remission.

*XOSPATA® was market approved by the Ministry of Food and Drug Safety on March 6th, 2020.
¶FLT3 mutation status: *FLT3-ITD, FLT3-TKD*.[1]
†CR defined as normal marrow differential with <5% blasts, ANC ≥1.0x10⁹/L and platelets ≥100x10⁹/L, no evidence of extramedullary leukemia, and must have been RBC and platelet transfusion independent.[1]
‡CRh defined as marrow blasts <5%, partial hematologic recovery, ANC ≥0.5x10⁹/L and platelets ≥50x10⁹/L, no evidence of extramedullary leukemia, and could not have been classified as CR.[1]

AML=acute myeloid leukemia; **ANC**=absolute neutrophil count; **CI**=confidence interval; **CR**=complete remission; **CRh**=complete remission with partial hematologic recovery; **FLT3**=FMS-like tyrosine kinase 3; **HR**=hazard ratio; **ITD**=internal tandem duplication; **mDOR**=median duration of CR/CRh; **NE**=not be evaluated; **RBC**=red blood cell; **TKD**=tyrosine kinase domain; **m+**=mutation-positive.

REFERENCES 1. XOSPATA® Prescribing Information. The Ministry of Food and Drug Safety. **2.** Perl AE, Martinelli G, Cortes JE, *et al*. Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML. *N Engl J Med* 2019;381(18): 1728-1740.

Important Safety Information

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.

AKR-XSP-2020-02

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- **39% achieved CR within 2 treatment cycles** (n=27/70, 95% CI 27, 51)
- **In patients who achieved CR**, **
  - **52% complete MRD† response** (n=14/27, 95% CI 32, 71)
  - **48% received Allo HSCT** (n=13/27)

*the recommended dosage was 5 μg/m²/d for the first 7 days, followed by 15 μg/m²/d thereafter.
**CR was defined as no evidence of circulating blasts or extramedullary disease and < 5% blasts in bone marrow (M1)
†Complete MRD response was a prespecified exploratory endpoint, and defined as no detectable blasts as determined by flow cytometry.
ALL, acute lymphoblastic leukemia

Reference von Stackelberg A, et al. J Clin Oncol. 2016;34:4381-9.

블린사이토® 제품요약정보

제품명: 블린사이토주35마이크로그램(블리나투모맙,유전자재조합), **효능효과:** 성인 및 소아에서 재발 또는 불응성 전구 B세포 급성 림프모구성 백혈병의 치료, **용법용량:** 치료 과정은 이 약을 유도 요법으로 최대 2회 주기를 투여한 후 공고 요법으로 추가적인 3회 주기를 투여하고, 이후 지속 요법으로 최대 4주기를 추가로 투여하는 것으로 이루어져있다. 유도 또는 공고요법에서 이 약 투여의 단회 주기는 28일간의 연속적인 정맥투여와 이후의 14일간의 휴약기간으로 이루어져있다 (총 42일). 지속 요법에서 이 약 투여의 단회 주기는 28일간의 연속적인 정맥 투여와 이후의 56일간의 휴지 기간으로 이루어져있다 (총 84일). 체중 45kg 이상 환자의 경우 고정된 용량을 투여하고 (주기 1의 1–7일차: 9㎍/일, 주기 1의 8–28일차 및 이후 주기의 1–28일차: 28㎍/일), 45kg 미만 환자의 체표면적을 고려하여 용량을 설정한다. (주기 1의 1–7일차: 5㎍/m2/일, 주기 1의 8–28일차 및 이후 주기의 1–28일차: 15㎍/m2/일) 이 약은 24시간 동안 10mL/시간의 속도로 주입, 또는 48시간 동안 5mL/시간의 속도로 주입하여, 일정한 속도로 총 240mL이 주입된다. **경고:** 사이토카인 방출 증후군, 신경학적 독성, **다음 환자에게는 투여하지 말 것:** 블리나투모맙이나 이 약의 다른 성분에 과민반응이 있는 환자, **약물이상반응:** 재발 또는 불응성 급성 림프모구성 백혈병 환자를 대상으로 한 무작위배정, 공개–라벨, 활성 대조군 임상 시험 (TOWER 연구)에서 이 약 투여 후 가장 빈번하게 발생한 약물이상반응(≥20%)은 감염 (박테리아성 및 감염원 미확인), 발열, 두통, 점적투여 관련 반응, 빈혈, 발열성 호중구 감소증, 혈소판 감소증 및 호중구 감소증. 가장 빈번하게 발생한 중대한 약물 이상반응 (≥2%)은 열성 호중구감소증, 발열, 패혈증, 폐렴, 과량투여, 패혈성 쇼크, 사이토카인 방출 증후군(CRS), 박테리아성 패혈증, 기기 관련 감염 및 균혈증, **일반적 주의:** 감염증, 종양용해증후군, 호중구감소증 및 열성 호중구감소증, 운전 및 기계조작 능력에 대한 영향, 간 효소 증가, 췌장염, 백질뇌증, 조제 및 투여 실수, 예방접종, **임부 및 수유부:** 비임상 연구에서 임신한 생쥐에게 투여된 설치류 대리 분자는 태반 장벽을 통과하였다. 임산부에게 태아에 대한 잠재적인 위험성을 알려야 한다. 해당 모집단에서 주요 출생 결함과 유산의 발생률은 알려지지 않았다. 유즙 중 이 약의 존재 여부, 수유 시 영아에 미치는 영향, 유즙 생성에 미치는 영향에 대한 정보는 없으나 이 약으로 인해 수유중인 영아에서 B 세포 림프구감소증과 같은 중증 약물이상반응 발생 가능성이 있으므로, 이 약으로 치료 중이거나 치료 후 최소 48시간까지는 수유하지 않도록 권고해야 한다. **보관 및 취급상의 주의사항:** 차광 냉장 (2–8℃) 보관, 적용상의 주의–**주입을 위한 약액 재구성 및 조제: 투약 오류 (과량 투여와 소량 투여를 포함)를 최소화하기 위해서 제품에 첨부된 제품설명서의 조제(혼합)와 투여에 대한 설명을 엄격하게 지키는 것이 중요하다. 수입판매원:** 암젠코리아유한회사 (서울특별시 강남구 테헤란로 203, 서울인터내셔널타워 14층). **※제품을 처방하시기 전 상세 제품설명서를 참고하여주시기 바랍니다.**

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【DOSAGE FORMS AND STRENGTHS】 1. DOSAGE FORMS IMBRUVICA capsules contain 140 mg of ibrutinib, **2. STRENGTHS** White opaque, size 0, hard gelatin capsule marked with "ibr 140 mg" in black ink. **【Indications】 1. Mantle cell lymphoma (MCL) :** IMBRUVICA is indicated for the treatment of adult patients with MCL who have received at least one prior therapy. **2. Chronic lymphocytic leukemia (CLL) :** IMBRUVICA is indicated for the treatment of adult patients with CLL who have received at least one prior therapy **【Dosage and Administration】**IMBRUVICA should be administered orally once daily with a glass of water at approximately the same time each day. The capsules or tablets should be swallowed whole with water. Do not open, break, or chew the capsules. Do not break or chew the tablets. IMBRUVICA must not be taken with grapefruit juice. IMBRUVICA should continue until disease progression or no longer tolerated by the patient. **1. Mantle cell lymphoma (MCL)** The recommended dose of IMBRUVICA for MCL is 560 mg once daily. **2. Chronic lymphocytic leukemia (CLL)** The recommended dose of IMBRUVICA for CLL is 420 mg once daily **【Warnings and Precautions】** 1. Contraindications IMBRUVICA is contraindicated in patients who have known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to ibrutinib or to the excipients in its formulation 2. Adverse Reactions Isolated cases of leukostasis have been observed. **1) Mantle cell lymphoma** The most commonly occurring non-hematological adverse reactions for MCL (≥ 20%) were diarrhea, fatigue, nausea, angioedema, dyspnea, contusion, upper respiratory tract infection, vomiting. The most commonly occurring hematological adverse reactions for MCL (≥ 20%) were neutropenia, thrombocytopenia, anemia. **2. Chronic lymphocytic leukemia (CLL)** The most commonly occurring adverse reactions for CLL (≥ 20%) were diarrhea, musculoskeletal pain, upper respiratory tract infection, bruising, rash, nausea, pyrexia, neutropenia and anemia. **3. Precautions** 1) Bleeding-related events 2) Leukostasis 3) Infections 4) Cytopenias 5) Interstitial lung disease (ILD) 6) Cardiac arrhythmias 7) Tumor lysis syndrome 8) Non-melanoma skin cancer **4. Pregnancy, Breast-feeding and Fertility 1) Pregnancy** IMBRUVICA should not be used during pregnancy. **2)Breast-feeding** breast-feeding should be discontinued during IMBRUVICA treatment **3) Fertility** Men should be advised not to father a child while receiving IMBRUVICA, and for 3 months following completion of treatment **【COMPANY】** Janssen Korea * Please refer to full prescribing information for details.

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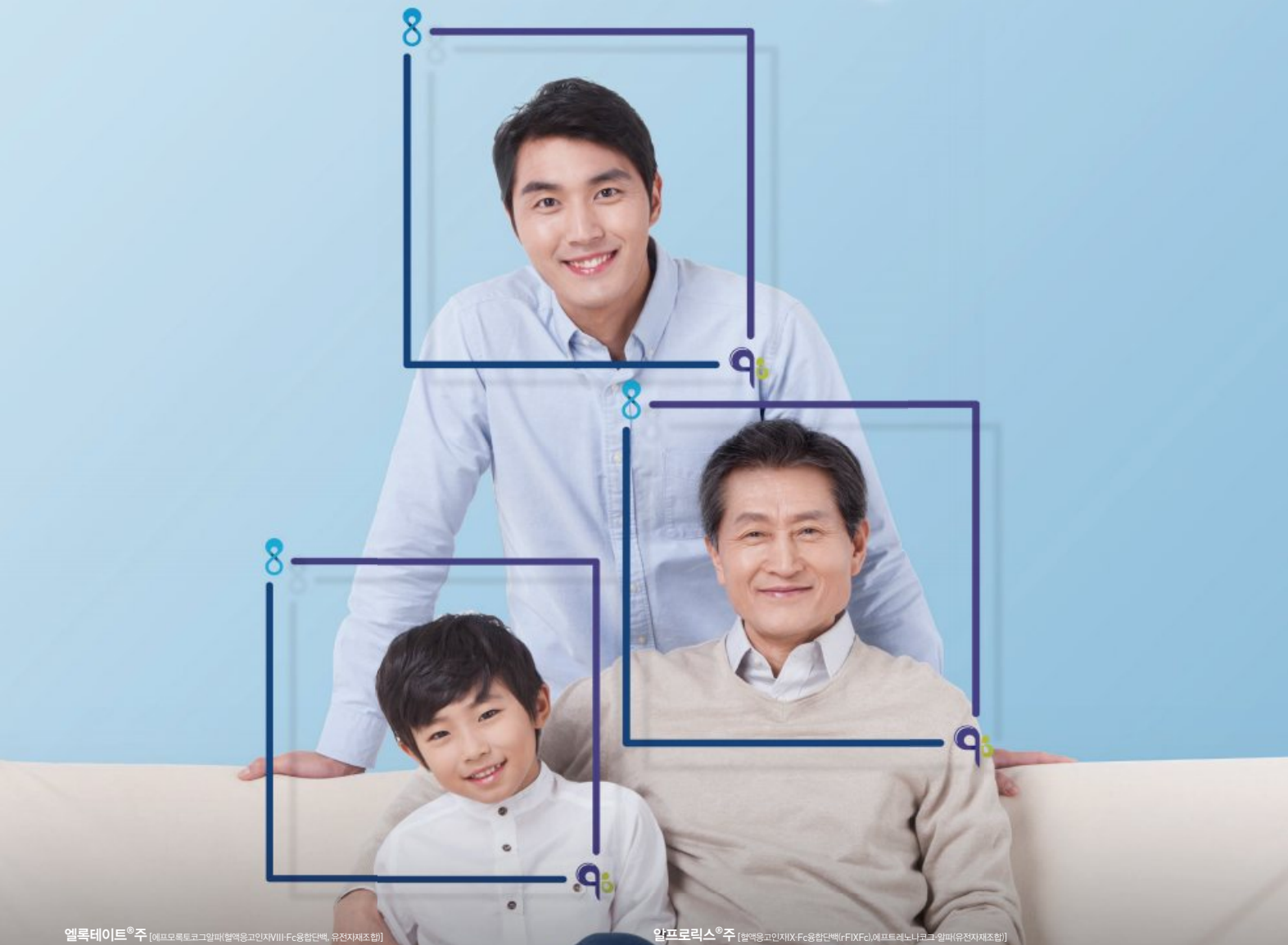

엘록테이트®주 [에프모록토코그알파(혈액응고인자VIII-Fc융합단백, 유전자재조합)]

[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 약은 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 저해제중화항체의 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) 사약 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)[2] 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, 감각이상, 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 연구로지 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

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정맥주사용 | 전문의약품

울토미리스 주 300 mg / 30 ml 라불리주맙

[원료약품 및 그 분량] 1바이알(30mL)중 유효성분 : 라불리주맙(별규)……300mg **[효능·효과]** 성인의 발작성 야간 혈색소뇨증 (PNH)의 치료 **[용법·용량]** 이 약은 환자의 체중에 따라 표1에 정한 용량으로 정맥 내 점적 투여한다. 초기 용량 투여 2주 후부터 8주 마다 한 번씩 유지 용량으로 투여한다. 투여일정은 예정된 투여일의 ±7일까지(이 약의 첫 번째 유지 용량 제외) 때때로 변경될 수 있지만, 그 다음 투여는 원래 일정에 따라 관리해야 한다. 에쿨리주맙 제제에서 이 약으로 바꾸는 경우, 에쿨리주맙 제제 마지막 투여 2주 후에 이 약을 환자의 체중에 따라 표1에 정한 용량(초기용량)을 투여하고, 이후 2주 후부터 8주마다 한 번씩 유지 용량으로 투여한다. (표 1은 제품설명서 전문 참고) **[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 더욱 활성화 될 수 있다. 결과적으로, 발작성 야간 혈색소뇨증(PNH)를 포함한 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 환자(단, 이 약 투여 지연에 따른 위험이 수막구균 감염 발생 위험보다 중대한 경우는 제외)(1. 경고 1) 중대한 수막구균 감염 항 참조) **3. 다음 환자에는 신중히 투여할 것 1) 기타 전신 감염** 활성 전신감염이 있는 환자를 이 약으로 치료 시 주의해야 투여해야 한다. 이 약은 말단 보체 활성을 차단하므로 환자들은 감염, 특히 *Neisseria* 균 및 피닝성 세균(encapsulated bacteria) 감염에 대한 감수성이 증가할 수 있다. 기타 말단 보체 억제제를 투여한 환자들에서 파종성 임균 감염을 포함하는 *N. meningitidis* 외의 Neisseria 종에 의한 중대한 감염이 보고되었다. 잠재적인 중대한 감염과 그 증상 및 징후에 대한 인식을 높이기 위하여 환자용 설명서를 제공해야 한다. 임질 예방에 관해 환자에게 조언해야 한다. **4. 약물이상반응** 가장 흔한 약물이상반응은 두통, 상기도감염, 비인두염이었다. 임상시험 환자 중 가장 중대한 약물이상반응은 수막구균 감염 및 수막구균 패혈증이었다. 임상시험에서 관찰된 약물이상반응 (표 1, ≥1% 발생한 이상반응 발췌): 매우 흔하게(≥1/10) - 상기도감염, 비인두염, 두통, 흔하게(≥1/100 - <1/10): 어지러움, 구토, 메스꺼움, 설사, 복부 통증, 소화불량, 발진, 가려움증, 요통, 관절통, 근육통, 근경련, 발열, 인플루엔자 유사 증상, 피로, 오한, 무기력 PNH 임상시험을 포함한 모든 임상시험에서 이 약으로 인한 가장 중대한 약물이상반응은 수막구균성 감염/패혈증이었다. 이 약으로 치료받은 환자에서 수막구균 감염은 수막구균성 패혈증으로 나타났다. 환자는 수막구균성 패혈증의 증상이나 징후에 대해 통보받아, 즉각적인 의학적 조치를 받을 수 있어야 한다. **[제조의뢰자]** Alexion Pharmaceuticals, Inc. **[제조자(완제의약품)]** Alexion Pharma International Operations Unlimited Company **[수입·판매자]** (주)한독 **[최종개정일]** 2020. 05. 21 **※ 보다 자세한 정보는 제품설명서를 참조하시기 바랍니다.**

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