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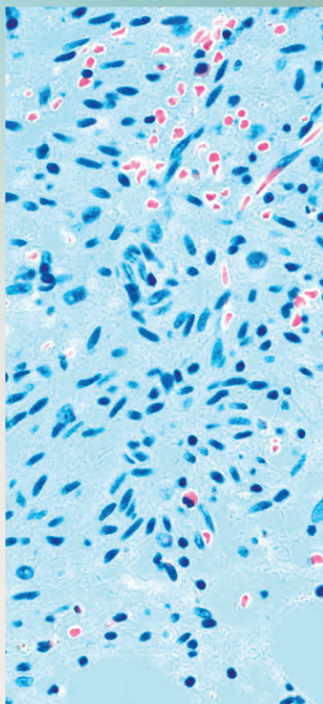
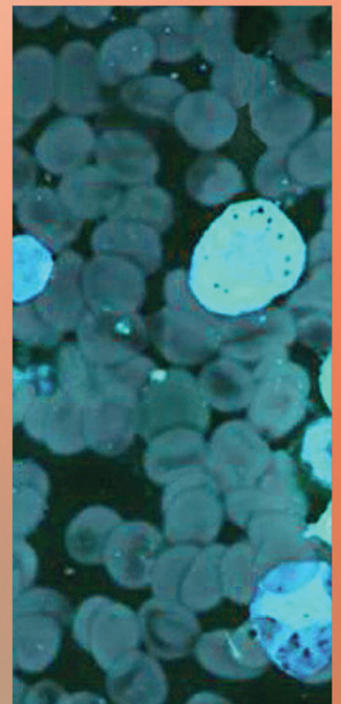
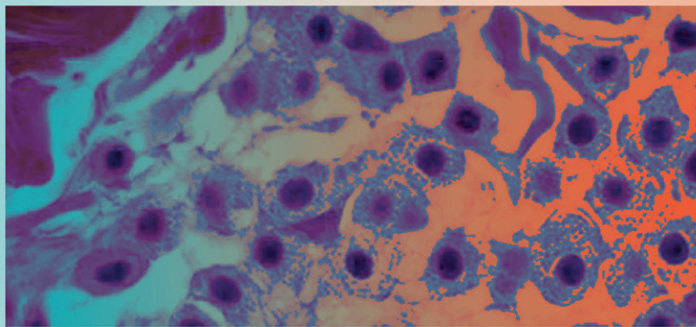
# LEUKEMIA RESEARCH

CLINICAL AND LABORATORY STUDIES

Supplement

Abstracts of the  
IXth International  
Eurasian Hematology  
Oncology Congress

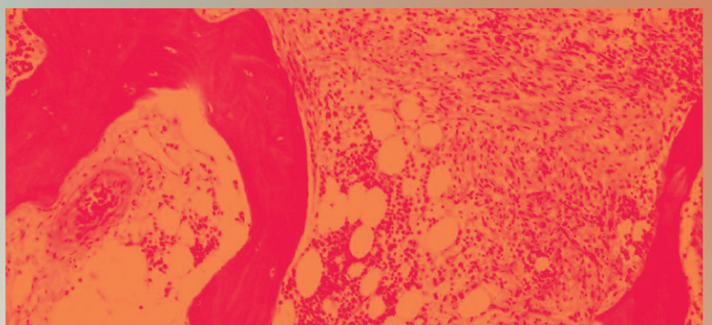
17–20 October 2018  
Istanbul, Turkey



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# *Leukemia Research*

**CLINICAL AND LABORATORY STUDIES**

Supplement

**Abstracts of the  
IXth International Eurasian Hematology Oncology Congress**

**17–20 October 2018, Istanbul, Turkey**



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# Leukemia Research

## CLINICAL AND LABORATORY STUDIES

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### Aims and Scope

*Leukemia Research* is an international journal which brings comprehensive and current information to all health care professionals involved in basic and (or) applied clinical research in leukemias, lymphomas, multiple myeloma and other hematologic malignancies. The editors encourage the submission of articles relevant to normal and leukemic hemopoiesis, biochemistry, cell biology, immunology and molecular biology as well as epidemiologic and clinical studies.

Specifically, of major interest will be articles that encompass the application of oncogenes, growth factors, cell markers, cell cycle and differentiation agents, novel therapeutics and clinical trials in both the acute and chronic leukemias as well as the myelodysplastic syndromes. In addition, we solicit selected articles on the rapidly increasing specialty of marrow or stem cell reconstitution after high dose therapy with curative attempt in patients with a wide range of neoplasms.

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# Leukemia Research

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## Welcome Address

Distinguished Colleagues,

The Hematology Specialist Association has been expanding its borders to the Americas, Asia, Middle East and Africa with a brand new concept named EHO (Eurasian Hematology Oncology Congress).

Hematologists and Oncologists within these continents will gather for the IXth International Eurasian Hematology Oncology Congress which will be held in Istanbul at the Hilton Istanbul Bosphorus between 17–20 October 2018.

This year's scientific program will also include the oncology program for the first time parallel to the adult hematology and the extended pediatric hematology sessions.

A great number of abstracts and case reports were submitted to the congress which has been evaluated by an international reviewing committee. There will be nine Meet the Expert sessions and nine oral presentation sessions within the main agenda and three poster walks.

We would like to thank all of our colleagues for their participation and attribution, the authors for their contributions, and our sponsors for their invaluable support in our growth targets.

Sincerely yours,



Prof. Birol Güvenç, MD  
*President of Hematology Specialist Association*

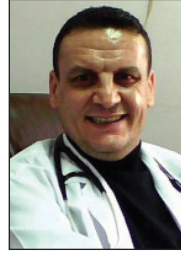
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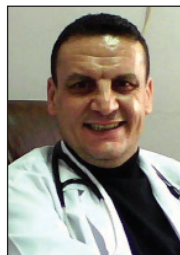
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## HEMATOLOGY PROGRAM

### 17 OCTOBER 2018

13.00-13.15	<b>OPENING REMARKS - Birol Güvenç and Giuseppe Saglio</b>
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	<b>SESSION I - PROF. ELIEZER RACHMILEWITZ SESSION</b>	<b>CHAIRS: Osman İlhan, Serdar Bedii Omay</b>
13.15-13.25	How Hematology Changed During the Days in the Life of Eliezer Rachmilewitz	Giuseppe Saglio
13.25-13.45	Lessons Learned From CML (Inaugural Lecture Dedicated to Eliezer Rachmilewitz)	Robert Gale
13.45-14.05	Von Willebrand Disease, Laboratory Issues	Pierre Toulon
14.05-14.25	Tumor Evolution in Genomic Era and Darwin	Emin Kansu
14.25-14.45	The Role of T Cell Immunotherapy in the Management of Aggressive Lymphomas	Hanan Hamed
14.45-15.00	Best Abstract Presentation (Eliezer Rachmilewitz Prize) - Analysis of Genetic Abnormalities in Newly Diagnosed Acute Lymphoblastic Leukemia Patients at King Faisal Specialist Hospital & Research Centre	Osamah Khojah

15.00-15.30	<b>COFFEE BREAK</b>
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	<b>SESSION II - PROF. EKREM MÜFTÜOĞLU SESSION - MYELOYDYSPLASTIC SYNDROME</b>	<b>CHAIRS: Tapan Kadia, Zahit Bolaman, Orhan Ayyıldız</b>
15.30-16.00	Paroxysmal Nocturnal Hemoglobinuria	Hanan Hamed
16.00-16.30	Prognostic Molecular Markers in MDS	Mustafa Çetiner
16.30-17.00	New Therapies in MDS	Tapan Kadia
17.00-17.30	Current Treatment of MDS	Tapan Kadia

17.30-18.00	<b>COFFEE BREAK</b>
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	<b>SESSION III - PROF. ATILLA YALÇIN SESSION - CHRONIC MYELOPROLIFERATIVE DISORDERS</b>	<b>CHAIRS: Tariq Mughal, Ferit Avcu, Fahri Şahin</b>
18.00-18.30	Current Treatment of Myeloproliferative Neoplasms	Haifa Kathrin Al-Ali
18.30-19.00	Jak2 Inhibitors and What Comes Next for Patients with BCR-ABL1- Negative Myeloproliferative Neoplasms	Tariq Mughal
19.00-19.30	Molecular Markers and New Prognostic Scores in MPNs	Tariq Mughal

19.30-20.30	<b>POSTER PRESENTATIONS SESSION 1</b>	<b>CHAIRS: Ahmet İfran, Ahmet Öztürk, Ozan Salim</b>
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### 18 OCTOBER 2018

07.30-08.15	<b>MEET THE EXPERT SESSION &amp; ORAL PRESENTATIONS</b> ROOM 1 - Angelo Maiolino (MM)/ROOM 2 - Tapan Kadia (MDS)/ROOM 3 - Nitin Jain (ALL)	<b>CHAIRS: Emin Kaya, Mahmut Töbü, Pervin Topçuoğlu</b>
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	<b>SESSION IV - MULTIPLE MYELOMA</b>	<b>CHAIRS: Angelo Maiolino, Levent Ündar</b>
08.30-09.00	First Line Therapy for Multiple Myeloma	Guray Saydam
09.00-09.30	Treatments in Relapsed/Refractory Multiple Myeloma	Angelo Maiolino
09.30-10.00	New Drugs for Multiple Myeloma	Angelo Maiolino

10.00-10.30	<b>COFFEE BREAK</b>
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	<b>SESSION V - ACUTE MYELOID LEUKEMIA</b>	<b>CHAIRS: Alessandro Cignetti, Seçkin Çağırğan, Osman Özcebe</b>
10.30-11.00	AML Therapy: What is Essential and What is Investigational	Tapan Kadia
11.00-11.30	Molecular Characterization and Follow Up in AML, Practical Issues	Mehmet Yılmaz
11.30-12.00	APL: A Special Kind of AML with a Different Treatment	Alessandro Cignetti

12.00-13.00	<b>LUNCH BREAK</b>
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13.00-13.45	<b>Significant Milestones in CML Treatment - NOVARTIS SATELLITE</b>	<b>CHAIR: Birol Güvenç SPEAKER: Giuseppe Saglio</b>
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## HEMATOLOGY PROGRAM

### 18 OCTOBER 2018

SESSION VI - ACUTE LYMPHOID LEUKEMIAS		CHAIR: Dieter Hoelzer, Deniz Sargin, Mustafa Yenerel
13.45–14.15	ALL Therapy: Essential Elements for Proper Treatment	Dieter Hoelzer
14.15–14.45	Diagnostic And Prognostic Markers in ALL	Robin Foà
14.45–15.15	New Monoclonal Antibodies in ALL	Nitin Jain
15.15–15.35	Debate: Ph-Positive Acute Lymphoblastic Leukemia: Will We Still Need Chemotherapy and Stem cell Transplantation? Yes	Dieter Hoelzer
15.35–15.55	Debate: Ph-Positive Acute Lymphoblastic Leukemia: Will We Still Need Chemotherapy and Stem cell Transplantation? No	Robin Foà

**15.55–16.30 COFFEE BREAK**

SESSION VII - HEMATOLOGY SPECIALIST ASSOCIATION - HELLENIC SOCIETY OF HEMATOLOGY JOINT SESSION		CHAIRS: Panayiotis Panayiotidis, Birol Güvenç, Sehmus Ertop
16.30–17.00	New Therapeutic Options in CLL	Panayiotis Panayiotidis
17.00–17.30	New Biomarkers in CLL	Kostas Stamatopoulos
17.30–18.00	Future Goals in CLL Therapy	Robin Foà

18.00–19.00 POSTER PRESENTATIONS SESSION 2		CHAIRS: Oktay Bilgir, Sami Kartı, İsmet Aydoğdu
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### 19 OCTOBER 2018

07.30–08.15 MEET THE EXPERT SESSION & ORAL PRESENTATIONS ROOM 1 - Carmino de Souza (NHL)/ROOM 2 - Tariq Mughal (CMD)/ROOM 3 - Dieter Hoelzer (ALL)		CHAIRS: Gülsüm Özet, Atilla Özkan, Düzgün Özatlı
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SESSION VIII - APHERESIS SESSION		CHAIRS: Robert Weinstein, Fevzi Altuntaş
08.30–09.00	Apheresis in the Management of Hematological Disorders Using the Therapeutic Apheresis Guidelines of the American Society for Apheresis	Joseph Schwartz
09.00–09.30	Medical Decision Making in Apheresis Medicine: When the Guidelines Do Not Cover Your Patient's Condition	Robert Weinstein
09.30–10.00	Recent Advances in the Management of Thrombotic Thrombocytopenic Purpura (TTP) and Their Effect on the Role of Apheresis in Its Treatment	Ravi Sarode

**10.00–10.30 COFFEE BREAK**

SESSION IX - CHRONIC MYELOID LEUKEMIAS		CHAIRS: Rudiger Hehlmann, Ridvan Ali, Burhan Turgut
10.30–11.00	Impact of High-Risk Additional Chromosome Aberration on Survival and Blast Crisis	Rudiger Hehlmann
11.00–11.30	Are the Results that We Can Obtain with Imatinib All the Same in the World?	Katia Pagnano
11.30–12.00	Treatment Discontinuation in Chronic Myeloid Leukemia, When and How ?	Giuseppe Saglio
12.00–12.30	Response Monitoring in Chronic Myeloid Leukemia in the TFR Era	Naem Chaudhri

12.30–13.15 New Era with Carfilzomib in the Treatment of Relapsed/Refractory Multiple Myeloma - AMGEN SATELLITE		CHAIR: Ali Ünal SPEAKER: Güray Saydam
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**13.15–14.15 LUNCH BREAK**

14.15–15.00 New Treatment Approaches in ALL Treatment - BMS SATELLITE		CHAIR: Birol Güvenç SPEAKER: Mehmet Ali Özcan
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SESSION X - SPECIAL TOPICS FOR NHL		CHAIRS: Carmino de Souza, Burhan Ferhanoglu
15.00–15.30	State of the Art of NHL Therapy	Carmino de Souza
15.30–16.00	A Translational Perspective on Diffuse Large B-Cell Lymphoma	Yücel Erbilgin
16.00–16.30	New Approaches in Marginal Zone Lymphoma	Catherine Thieblemont
16.30–17.00	Mantle Cell Lymphoma, Blastic Variant; Diagnosis, Treatment	Tayfur Toptaş

**17.00–17.30 COFFEE BREAK**

## HEMATOLOGY PROGRAM

### 19 OCTOBER 2018

<b>SESSION XI - AGGRESSIVE AND INDOLENT NH LYMPHOMAS</b>		<b>CHAIRS: Catherine Thieblemont, Tayfur Toptaş</b>
17.30–18.00	Essential Treatments of NHL	Carmino de Souza
18.00–18.30	First-Line Treatment of Hodgkin Lymphoma	Massimo Federico
18.30–19.00	Transplant in NHL; When? To Whom?	Elif Birtaş Ateşoğlu
19.00–20.00	<b>POSTER PRESENTATIONS SESSION 3</b>	
		<b>CHAIRS: Oral Nevruz, İhsan Karadoğan, Güven Çetin</b>

### 20 OCTOBER 2018

<b>MEET THE EXPERT SESSION &amp; ORAL PRESENTATIONS</b> ROOM 1 - Panayiotis Panayiotidis (CLL)/ROOM 2 - Massimo Federico (NHL)/ROOM 3 - Alessandro Cignetti (AML)		<b>CHAIRS: Salih Aksu, Cengiz Ceylan, Mehmet Sönmez</b>
		<b>SESSION XII - CHRONIC LYMPHOCYTIC LEUKEMIAS AND INDOLENT LYMPHOMAS</b>
		<b>CHAIRS: Mehmet Turgut, Hakan Göker, Nilgün Sayınalp</b>
08.30–09.00	CLL Treatment Landscape in R/R CLL Patients in Scope of BCL-2 Inhibition	Mehmet Ali Özcan
09.00–09.30	Chronic Lymphocytic Leukemia Old and New Treatments	Panayiotis Panayiotidis
09.30–10.00	When and Why Chemo-Free Regimens in Mantle Cell Lymphoma	Burhan Ferhanoğlu
10.00–10.30	<b>COFFEE BREAK</b>	
		<b>SESSION XIII - STEM CELL TRANSPLANT AND CELLULAR THERAPY</b>
		<b>CHAIRS: Jean-Francois Rossi, Filiz Vural</b>
10.30–11.00	Cancer Immunotherapy: Monoclonal antibodies from laboratory reagents to therapy	Vera Donnerberg
11.00–11.30	Single cell surface proteomics for discovery of therapeutic targets	Albert Donnerberg
11.30–12.00	Impact of Posttransplant Hypomethylating Agents on Cumulative Incidence Risk of Relapse After Allogeneic Transplants for Myeloid Malignancies	Khalid Halahleh
12.00–12.30	From Allogeneic Transplantation to Precision Immune Therapy: The Role of Effector Cells	Jean-Francois Rossi
12.30–13.00	Antifungal Management in Febrile Neutropenia	Ömür Uzun
13.00	<b>CLOSING</b>	

## ONCOLOGY PROGRAM

### 17 OCTOBER 2018

SESSION I - COLORECTAL CANCER		CHAIR: Şuayip Yalçın
13.30–14.00	Is Shortening the Duration of Adjuvant Treatment is Eligible in Early Staged Colon Cancer?	Gökhan Demir
14.00–14.30	Is Tumor Sideness, Biomarkers or Molecular Subtype Classification More Predictive for the Treatment of Unresectable Metastatic Colon Cancer?	Şuayip Yalçın
14.30–15.00	Systemic Therapy for Potentially Resectable Metastatic Rectal Cancer	Ece Esin

15.00–15.30	<b>Prolonging a Life is an Art, Paint with OPDIVO - BMS Satellite</b>	<b>CHAIR: Berksoy Şahin SPEAKERS: Ahmet Gül, Berksoy Şahin</b>
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SESSION II - NON-SMALL CELL LUNG CANCER		CHAIR: Mustafa Erman
15.30–16.00	Sequencing Agents in the Management of EGFR Mutation Positive Non-Small Cell Lung Cancer	Meral Günaldı
16.00–16.30	Management of ALK Non-Small Cell Lung Cancer Through First and Subsequent Lines of Therapy (Immunology Konusu)	Çiğdem Usul Afşar
16.30–17.00	Immunotherapy in Small and Non-small Cell Lung Cancer; The Role of Immune Checkpoint Inhibitors in Frontline and Beyond Frontline Therapy	Mustafa Erman

17.00–17.30	<b>COFFEE BREAK</b>	
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SESSION III - EARLY BREAST CANCER		CHAIR: Erdem Göker
17.30–18.00	Challenging Adjuvant Therapy in HER2+ Breast Cancer: Escalating or De-escalating ?	Gül Başaran
18.00–18.30	Evolving Approaches in Systemic Therapy for Triple-Negative Breast Cancer in Neoadjuvant and Adjuvant Settings	Özlem Er

SESSION IV - URO-ONCOLOGY		CHAIR: Sevil Bavbek
18.30–19.00	What is the Role and Best Sequencing of the New Generation Hormonal Agents in the Treatment of Both Hormone Sensitive and Resistant Metastatic Prostate Cancer?	Mustafa Erman
19.00–19.30	How to Treat the Patients with Platin Ineligible Metastatic Bladder Cancer?	Nuri Karadurmuş
19.30–20.00	Perioperative Systemic Therapy for Localized Renal Cell Carcinoma: To Treat or Not to Treat	Sevil Bavbek

### 18 OCTOBER 2018

SESSION V - MELANOMA		CHAIR: İsmail Çelik
08.30–09.00	Practice-Changing Developments in Stage III Melanoma: (neo-)Adjuvant Targeted Therapy and Immunotherapy	İsmail Çelik
09.00–09.30	Systemic Treatment of Stage IV Melanoma: Sequencing of Therapies, Biomarkers and the Cancer Immunogram	Bülent Orhan
09.30–10.00	Different Combinations of Systemic Therapy for Melanoma Brain Metastases	Burçak Karaca

10.00–10.30	<b>COFFEE BREAK</b>	
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SESSION VI - NON - COLORECTAL GIS TUMORS		CHAIR: Gökhan Demir
10.30–11.00	New (neo-)adjuvant Standarts of Care in Gastro-esophageal Cancer	Timuçin Çil
11.00–11.30	What is Changed in the Treatment of Biliary Tract Cancer?	Tülay Akman Demir
11.30–12.00	Has Sorafenib Still Been the Real Winner Against New Generation TKIs and Immune Checkpoint Inhibitors in HCC?	Çağatay Arslan

SESSION VII - ADVANCED / METASTATIC BREAST CANCER		CHAIR: Berna Öksüzöğlü
12.00–12.30	Optimizing Therapy for ER-Positive Metastatic Breast Cancer	Berna Bozkurt Duman
12.30–13.00	Overcoming Resistance in HER2+ Metastatic Breast Cancer	Berna Öksüzöğlü
13.00–13.30	Shining Side of the Moon; PARP Inhibitors in the Treatment of Advanced Triple Negative Breast Cancer	Ömer Dizdar

13.30–14.30	<b>LUNCH BREAK</b>	
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## ONCOLOGY PROGRAM

### 18 OCTOBER 2018

#### SESSION VIII - SARCOMA

CHAIR: Berksoy Şahin

14.30–15.00	Controversies in Adjuvant/Neoadjuvant Chemotherapy in Localized Soft Tissue Sarcoma	Sema Sezgin Göksu
15.00–15.30	Can We Ever Have a Specific Treatment for Every 50 Subtypes of Soft Tissue Sarcoma?	Berksoy Şahin

15.30–16.00

COFFEE BREAK

#### SESSION IX - HEAD AND NECK CANCER

CHAIR: Musa Altun

16.00–16.30	New Staging and New Treatments in Surgery for Head and Neck Cancer	H. Hakan Coşkun
16.30–17.00	Recent Advances in Nazofarınigal Carsinoma	Musa Altun
17.00–17.30	p16-Negative Advanced Head and Neck Cancer Treatment	Cemil Bilir

### 19 OCTOBER 2018

#### SESSION X - IMMUNO-ONCOLOGY

CHAIR: Jean-Francois Rossi

08.30–09.00	Precision Immune Therapy For Cancers	Jean-Francois Rossi
09.00–09.30	Long-term Results of the Treatments with Immune Checkpoint Inhibitors in Solid Tumors	Oğuz Kara
09.30–10.00	CART therapy for solid tumors	Xiao Yang

10.00–10.30

COFFEE BREAK

#### SESSION XI - PRECISION ONCOLOGY

CHAIR: Fulden Yumuk

10.30–11.00	The Bio-Informatics of Precision Cancer Medicine	Serdar Ceylaner
11.00–11.30	How Do Molecular Panels Help Me Make Clinical Decisions About My Patients?	Atıl Bişgin
11.30–12.00	Is Liquid Biopsy Success Story in the Manegenment of NSCLC ?	Fulden Yumuk

12.00

CLOSING



## PEDIATRIC HEMATOLOGY PROGRAM

### 18 OCTOBER 2018

SESSION I - HEMOPHILIA		CHAIRS: Kaan Kavaklı, Murat Söker
08.30–09.00	Practical Approach to Utilizing Extended Half-Life Products in Hemophilia	İlgen Şaşmaz
09.00–09.30	Emerging Nonfactor Therapies for Hemophilia	Alphan Küpesiz
09.30–10.00	Gene Therapy for Hemophilia	Bülent Antmen

10.00–10.30	COFFEE BREAK	
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SESSION II - SICKLE CELL DISEASE		CHAIR: Yurdanur Kılınc
10.30–11.00	Gene Therapy in Sickle Cell Disease	Selin Aytaç Eyüboğlu
11.00–11.30	A Better Understanding Towards Sickle Cell Trait	Salam Al - Kindi
11.30–12.00	New Therapies in Sickle Cell Disease	Maria N. Dimopoulou
12.00–12.30	Blood Transfusion - How to Avoid Alloimmunization in Sickle Cell Disease ?	Göksel Leblebisatan

12.30–13.30	LUNCH BREAK	
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SESSION III - THALASSEMIA		CHAIRS: Maria Domenica Cappellini, Leyla Ağaoğlu
13.30–14.00	Update on Management of Iron Overload	Maria Domenica Cappellini
14.00–14.30	Non-Transfusion-Dependent Thalassemia: An Update on Complications and Management	Zeynep Karakaş
14.30–15.00	Gene Therapy in Beta Thalassemia	Samantha Scaramuzza

15.00–15.30	COFFEE BREAK	
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SESSION IV - LEUKEMIA		CHAIRS: Lebriz Yüksel Soycan, Ümran Çalışkan
15.30–16.00	Pediatric AML in 2018: Advances in Clinical Practice.	Vassilios Papadakis
16.00–16.30	Novel Therapy for Childhood Acute Lymphoblastic Leukemia	Sinan Akbayram
16.30–17.00	The What, When and How of CAR T-Cell Therapy for Acute Lymphoblastic Leukemia	Fatma Visal Okur

### 19 OCTOBER 2018

SESSION V - BONE MARROW TRANSPLANTATION I		CHAIRS: Atilla Tanyeli, Savaş Kansoy
08.30–08.50	MUD, Cord Blood or Haplo-identical Transplantation in the Future	Francesco Saglio
08.50–09.10	Haploidentical Stem Cell Transplantation in Thalassemia	Akif Yeşilipek
09.10–09.30	Allogeneic Transplantation for Refractor Leukemia in Pediatric Patients	Volkan Hazar
09.30–10.00	Haplo-transplant in high-risk pediatric AL	George Mentkevich

10.00–10.30	COFFEE BREAK	
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SESSION VI - BONE MARROW TRANSPLANTATION II		CHAIRS: Sema Anak, Gülyüz Öztürk
10.30–11.00	Stem Cell Transplantations in Pediatric Osteopetrosis	Adalet Meral Güneş
11.00–11.30	Prevention and Treatment of Cytomegalovirus Reactivation in Haploidentical and MUD Stem Cell Transplantations	Gülsün Karasu
11.30–12.00	Viral Infections Except Cytomegalovirus in Pediatric Stem Cell Transplantations	Yöntem Yaman
12.00–12.30	The Different Type of Haploidentical Stem Cell Transplantation in Pediatric Patients	Musa Karakükçü

12.30–13.30	LUNCH BREAK	
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## PEDIATRIC HEMATOLOGY PROGRAM

### 19 OCTOBER 2018

SESSION VII - RED CELLS, THROMBOCYTE AND NEUTROPHILS		CHAIR: Ömer Devecioğlu
13.30-14.00	Pediatric PNH and Treatment	Şule Ünal
14.00-14.30	The Approach and Diagnosis of Coombs Negative Hemolytic Anemia	Achilles Iolacson
14.30-15.00	The New Treatment Modalities of Pediatric ITP	Sinan Akbayram
15.00-15.30	Congenital Neutropenias and Treatment Approach	Gül Nihal Özdemir

15.30-16.00

#### COFFEE BREAK

SESSION VIII - PEDIATRIC LYMPHOMAS & SOLID TUMORS - RHOA & HSA JOINT SESSION		CHAIRS: Bülent Antmen, Irina Poddubnaya
16.00-16.30	Current Approaches in Transplantation in Medulloblastoma	George Mentkevich
16.30-17.00	Autologous Transplantation for Neuroblastoma	Serap Aksoylar
17.00-17.30	High Dose Chemotherapy with Autologous SCT in Pediatric HL	Alexandr Popa

17.30

#### CLOSING

## NURSING PROGRAM

### 17 OCTOBER 2018

10.30-10.40

#### OPENING REMARKS - Serpil Vieira and Medine Yılmaz

SESSION I - ESSENTIALS OF TRANSPLANT		CHAIRS: Fatih Erbey, Medine Yılmaz
10.40-11.00	Hematology and SCT Experiences	Serpil Vieira
11.00-11.20	The Role of the Transplant co-ordinator	Serpil Vieira
11.20-11.40	GVHD Management and Nursing Care	Havva Dulda
11.40-12.00	Infection Prevention Issues in Transplant Patients	Medine İlksen Kılıç

12.00-13.00

#### LUNCH BREAK

SESSION II - TRANSPLANT COMPLICATIONS AND NEW TREATMENT OPTIONS		CHAIRS: Barbaros Şahin Karagün, İlgen Şaşmaz
13.00-13.20	Nursing Care of Patients Receiving CAR-T Cells	Rose Ellard
13.20-13.40	CMV Reactivation / Treatment/ Nursing Role	Iris Agreiter
13.40-14.00	Haemorrhagic Cystitis/ JC & BK Virus	Marie Waller

14.00-14.30

#### COFFEE BREAK

SESSION III - TRANSPLANT CARE		CHAIRS: Rose Ellard, Demet Çekdemir
14.30-14.50	Late Effects and Living with and Beyond in Transplant Patient Care	TBA
14.50-15.10	Haploidentical Transplant and Nursing Care	Esra Bayrak
15.10-15.30	Neutropenia and Why Sepsis is Important in a Neutropenic Patient and Prophylactic Approaches	Zhanna Sharoyan
15.30-15.50	Patients and Families Social and Physiological Issues Before During and Post Transplantation	Emine Kılıç

15.50-16.20

#### COFFEE BREAK

SESSION IV - TRANSFUSION PRACTICE AND COMPLICATIONS IN BMT		CHAIRS: Bülent Antmen, Hayriye Mavruk
16.20-16.40	Transfusion Practice in Transplant Patients	Şule Menziletoğlu Yıldız
16.40-17.10	Transfusion Complications and Its Treatment in Transplant Patients	Pınar Yüzer

17.10

#### CLOSING

## Speaker biographies

### Robert Peter Gale

D.Sc. (hc) State University of New York at Buffalo; FRCP, Royal College of Physicians, London, UK



Prof. Robert Peter Gale is an expert in several medical fields including the biology and therapy of leukemias, bone marrow transplants and therapy of victims of nuclear and radiation accidents. His accomplishments include basic and clinical sciences and public policy. For example, in 1974 at UCLA he and Prof. Martin Cline reported on the use of cytarabine and daunorubicin to treated acute myeloid leukaemia (AML). Gale and his colleagues

from the Center for International Blood and Marrow Research (CIBMTR) at the Medical College of Wisconsin have analyzed and published data on recipients of more than 450,000 haematopoietic cell transplant recipients in more than 200 publications. Serval of these analyses provided the 1<sup>st</sup> convincing evidence of the efficacy of immune therapy in humans. Also, in 1983 at the Weizmann Institute of Science, Gale and Prof. Eli Canaani molecularly-cloned the *BCR/ABL1* gene which causes chronic myeloid leukaemia (CML) setting the stage for the 1<sup>st</sup> targeted therapy of cancer in humans.

Beginning in 1985 Gale has assisted the governments of the Soviet Union (Chernobyl), Japan (Fukushima; Tokaimura) and Brazil (Goiana) and others in dealing with victims of nuclear and radiation accidents and is regarded an expert in nuclear terrorism preparedness.

Prof. Gale received his AB degree with high honors in biology and chemistry from Hobart College in 1966, his MD from the State University of New York at Buffalo in 1970 and his PhD in microbiology and immunology from the University of California, Los Angeles (UCLA) in 1976). From 1973–1993, Gale was on the faculty of the UCLA School of Medicine and remains on the UCLA Ronald Regan Medical Center Medical Staff. In 1983 he was the Meyerhoff Visiting Scholar at the Weizmann Institute of Science in molecular biology. From 1980–1997, Gale was Chairman of the Scientific Advisory Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR), 1989–2003 he chaired the Scientific Advisory Board of the Center for Advanced Studies in Leukemia. From 1986–1993, he was President of the Armand Hammer Center for Advanced Studies in Nuclear Energy and Health, and 1985–1990 he was the Wald Scholar in Biomedical Communications at UCLA.

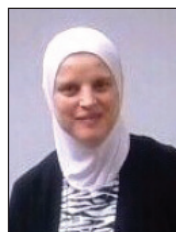
Gale is currently Visiting Professor of Haematology at the Haematology Research Centre, Division of Experimental Medicine, Department of Medicine, Imperial College London. He is the Editor-in-Chief of *Leukemia*, Associate Editor of *Clinical Transplantation*, Executive Editor of *Bone Marrow Transplantation* and a reviewer for many scientific journals in haematology, oncology, immunology, transplantation, radiation biology and internal medicine.

Gale has published about 1000 scientific articles and 25 books on medical topics, nuclear energy and weapons and politics of US-Russian relations with articles for the New York Times, Los Angeles Times, Washington Post, USA Today, *Der Spiegel*, the Wall Street Journal and others. Dr Gale has also written popular books on Chernobyl and radiation and screenplays for and/or appeared in several movies and received an Emmy award. His latest book "Radiation: What it is, what you need to know" with Eric Lax was published in 2013.

Awards for his scientific achievements include the Presidential Award, New York Academy of Sciences, Scientist of Distinction Award, Weizmann Institute of Science, Distinguished Alumni Award, Hobart College and Intra-Science Research Foundation Award. He holds honorary degrees including DSc from Albany Medical College and the State Univ. of New York at Buffalo, LHD from Hobart College and DPS from MacMurray College. He lives in Los Angeles with his wife Laura.

### Hanan Hamed

Ain Shams University, Egypt



Professor of Internal Medicine and Clinical Hematology Faculty of Medicine Ain Shams University from October 2004 to present.

Member of Hematology Board at Faculty of Medicine Ain Shams University.

Member of Bone Marrow Transplantation Board at Faculty of Medicine Ain Shams University.

Head of Internal Medicine Department at Ain Shams University Specialized Hospital ASUSH Cairo – Egypt.

#### Qualifications

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|------|--|
| 1983 | MB Bch, Faculty of Medicine Ain Shams University   |
| 1988 | MSc Internal Medicine, Faculty of Medicine Ain Shams University  |
| 1994 | MD Internal Medicine, Faculty of Medicine Ain Shams University   |
| 1994 | Full training program in "Medical Response to Nuclear Accidents" in collaboration with Radiation Emergency Assistance Centre/ Training Site REACTS - Oak Ridge Institute of Science 1994 |

#### Member of

- American Society of hematology ASH
- European Hematological Association EHA
- International Society of Hematology ISH
- International Union of Angiology IUA
- Pan-Arab hematology association
- Egyptian Hemato-oncology group EHOG
- Egyptian Society of Hematology ESH
- Egyptian Group of Hemostasis and Thrombosis
- Egyptian Society of Oncology
- Egyptian Society of Vascular Diseases and Surgery

### Haifa Kathrin Al-Ali

Associate Professor of Hematology and Internal Oncology and the head of the Krukenberg Cancer Center at the University Hospital of Halle (Saale), Germany



Her main clinical and research interests are myeloid malignancies (MPN, AML, MDS).

Research articles have been published in journals such as *The New England Journal of Medicine*, *Blood*, and *Leukemia*.

### Alessandro Cignetti

University Division of Hematology and Cell Therapy, A.O. Ordine Mauriziano and University of Torino, Turin, Italy



#### Education and Training

- |      |   |
|------|---|
| 1990 | Medicine - Degree in Medicine and Surgery at the University of Turin  |
| 1994 | Haematology - Specialization in Haematology at the University of Turin Specialization in Haematology at the University of Turin |
| 1998 | Immunotherapy of acute leukemia - PhD in Human Oncology at the University of Turin  |

**Professional Experience:**

- 1989 National Cancer Institute, Bethesda, Surgery Branch (Head: Dr S.A. Rosenberg): training on the isolation and expansion of Tumor Infiltrating Lymphocytes
- 1990-1997 Clinical trainee in Hematology (1990-1994) and PhD Student in Oncology (1994-1997) in the Laboratory of Tumor Immunology (Head: Prof R. Foà) at the Department of Biomedical Science and Human Oncology, University of Turin, Italy.
- 1990 Research training at the Institut fur Immunologie, University of Berlin, Laboratory of Dr T. Blankenstein (Topic: cytokine gene transfer technologies into tumor cells).
- 1996 Department of Medicine, Division of Oncology, University of Washington, Seattle, Laboratory of Dr. M.A. Cheever (Topic: isolation and characterization of T cell clones directed against primary acute myeloid leukemic cells).
- 1997-1999 Postdoctoral fellow in the Department of Immunology (Head: K. Grabstein; Mentor: M.A. Cheever) of Corixa Corporation, Seattle, USA (Topic: differentiation of acute leukemia cells into dendritic cells).
- 1999-2003 Clinical Assistant in the University Division of Clinical Immunology and Hematology (Head: Prof. F. Caligaris-Cappio), Ospedale Mauriziano Umberto I, Torino, Italy and Institute for Cancer Research and Treatment, Candiolo, Italy.
- 2004-2005 Research Associate of the Division of Medical Oncology (Head: Prof. M. Aglietta), Institute for Cancer Research and Treatment, Candiolo, Italy.
- 2006-2009 Research Scientist of the Laboratory of Cancer Immunology, Institute for Cancer Research and Treatment, Candiolo, Italy.
- 2010-2014 Attending Physician at the University Division of Hematology and Cell Therapy at the Mauriziano Hospital of Turin (Head: Prof. C. Tarella)
- 2014-2016 Head of the Inpatient Unit at the Division of Hematology and Cell Therapy at the Mauriziano Hospital of Turin (Head: Prof. M. Massaia in 2015, Prof G. Saglio from 2016 to date)
- 2010 to date Research Scientist at the Molecular Biotechnology Center/ University of Turin (Head: Prof. L. Silengo)

**Previous participation in clinical trials and publications:**

Involved in many national and international clinical trials in hematology according to GCP ICH principles. Many scientific publications (44 listed in pubmed) are the results of studies on tumor immunotherapy and in particular immunotherapy of hematological malignancies

**Robin Foà**

*Sapienza University, Rome, Italy*



Robin Foà is Professor of Hematology and Head of Hematology at the Sapienza University of Rome. He earned his medical degree in Turin, Italy, and specialized in pediatrics and in hematology. He worked at the MRC Leukaemia Unit, Royal Postgraduate Medical School and Hammersmith Hospital of London between 1976 and 1979. He took a sabbatical at Memorial Sloan-Kettering Cancer Center, New York, between 1991 and 1992.

His main interests have been the biologic characterization of acute and chronic lymphoproliferative disorders, the role of molecular biology in the diagnosis and monitoring of hematologic malignancies, the role of cytokines in lymphoid malignancies, gene profiling, microarray analyses and next generation sequencing in acute and chronic leukemias, as well as the design of innovative therapeutic strategies for hematologic neoplasms.

Over the years, Professor Foà has received support from many national and international sources. He is part of the European Leukemia Network and referee for national and international funding agencies. He was chairman of the Scientific Committee of the 4th EHA (European Hematology Association) Congress, Barcelona in 1999, councilor of EHA until December 2002, and a

member of the Education Committee of EHA until December 2005. Has been President-Elect, President and Past-President of EHA during the years 2007-2013. He is currently chairman of the Education Committee and Outreach Unit of EHA.

He has been a member of the National Committee for Health Research for the Ministry of Health (Italy) until December 2010. He is chairman of the GIMEMA Working Party for chronic lymphoproliferative disorders and member of the board of the Working Party for acute leukemias.

Professor Foà has authored, co-authored, and edited over 600 papers, reviews, and books. He has been co-editor of *Leukemia and Lymphoma*, and associate editor of the *British Journal of Hematology* and of *The Hematology Journal*. He has also been editor-in-chief of *The Hematology Journal* up to December 2004 and of *Haematologica* from January 2005 to February 2008.

**Joseph (Yossi) Schwartz**

*Professor of Pathology and Cell Biology at the College of Physician and Surgeons of Columbia University; Director of the Transfusion Medicine & Cellular Therapy Service at the Columbia University Medical Center Campus of the New York Presbyterian Hospital*



Joseph (Yossi) Schwartz MD, MPH is a Professor of Pathology and Cell Biology at the College of Physician and Surgeons of Columbia University and the Director of the Transfusion Medicine & Cellular Therapy Service at the Columbia University Medical Center campus of the New York Presbyterian Hospital. As the Director of the Transfusion Medicine & Cellular Therapy Service, Dr. Schwartz oversees the Blood Bank, The Apheresis unit and the Cell Therapy facility. As a major tertiary

& transplantation center, those facilities collect, receive & process blood products for transfusion in variety of indications such as patients with Sickle Cell Disease, complex cardiac surgery, Hematopoietic Progenitor Cell transplantation, and all types of solid organ transplantation. He is currently the President of the American Society for Apheresis and until recently was the chair of the FACT-JACIE international standards for cellular therapy.

**Robert Weinstein**

*University of Massachusetts*



Dr. Weinstein is a Phi Beta Kappa, Magna Cum Laude graduate of Brandeis University, Waltham, Massachusetts, where he majored in chemistry. After graduating from the New York University School of Medicine in New York City, he completed an internship and residency in Internal Medicine at the University of Miami Affiliated Hospitals program in Miami, Florida. He returned to New England as a fellow in hematology at the Beth Israel Hospital, Boston, where he stayed

after completing his fellowship, as Assistant Professor of Medicine at Harvard Medical School. In 1985 he joined the Division of Hematology/Oncology at St. Elizabeth's Medical Center of Boston, a Tufts Medical School affiliate, where he established a program in therapeutic and donor apheresis. He later directed the Hematology and Transfusion Medicine section of the Division and became Professor of Medicine at Tufts. In 2006 he became the founding Chief of the Division of Transfusion Medicine at the UMass Memorial Medical Center, and University of Massachusetts Medical School, Worcester, Massachusetts, where he is Professor of Medicine, Pathology and Nursing and, among other duties, he is co-Director of the "Host Defense and Blood" course in the first-year medical school curriculum.

Dr. Weinstein has served as chair of the Hemapheresis Committee of AABB and chair of the Committee on Practice of the American Society of Hematology. He is past-president of the American Society for Apheresis, and of the World Apheresis Association. He served as Editor-in-Chief of the *Journal of Clinical Apheresis* from 2004 to 2015. He currently serves on the Board of Directors of the World Apheresis Association as Vice President for the Americas.

**Katia B. Barbosa Pagnano**

*Hematology and Hemotherapy Center, University of Campinas (UNICAMP), Campinas, SP, Brazil*



Katia Pagnano is a Hematologist and Researcher of the Hematology Division of the Hematology and Hemotherapy Center at the University of Campinas, Campinas, SP, Brazil. Dr. Pagnano received her medical degree from the University of Campinas, where she also completed her medical training in Hematology and received her Ph.D. In 1998 did a split fellowship at University of Pennsylvania, Philadelphia, USA. Her clinical interests include chronic myeloid leukemia, Ph-negative myeloproliferative neoplasms, acute myeloid leukemia and lymphomas. Her research interest focus is molecular diagnosis and monitoring of minimal residual disease in hematological neoplasms. Dr. Pagnano has participated in several clinical trials, focusing on the treatment of chronic myeloid leukemia, acute myeloid leukemia and lymphomas. She has published in peer-reviewed journals and presented her research in meetings from the American Society of Hematology, European Hematology Association and Brazilian Congress of Hematology.

**Giuseppe Saglio**

*Full Professor of Internal Medicine, University of Turin, Turin, Italy*

**Professional experience:**

1975 Degree in Medicine, University of Turin  
 1975–1980 Residency in Internal Medicine, University of Turin  
 1980–1983 Residency in Hematology, University of Milan  
 1983–1990 Assistant Professor in Internal Medicine, University of Turin

1990–present Full Professor in Internal Medicine – University of Perugia (90/91), University of Turin in Novara (91/98), University of Turin in Turin (98–present)  
 1996–1999 Director of the I School in Internal Medicine of the University “Amedeo Avogadro” of Eastern Piedmont (formerly University of Turin in Novara)  
 1996–1999 Coordinator of the PhD program in Molecular Medicine of the University “Amedeo Avogadro” of Eastern Piedmont (formerly University of Turin in Novara)  
 2000–2004 Vice-Dean of the Faculty of Medicine of the University of Turin  
 2001–2006 President of the II School of Medicine of the University of Turin

**Present appointments:**

Director of the Department of Internal Medicine of the San Luigi University Hospital of Turin

Director of the Division of Hematology at the San Luigi Hospital, University of Turin

**Honors:**

President (1996–98) and past-president (1998–2000) of the Italian Society of Experimental Hematology (SIES)

Member of the Academy of Medicine of Turin

Member permanent of the SAG Oncology Board of EMEA (London)

**Research activity:**

Focused in molecular biology applied to clinical medicine in haematology. More than 350 peer reviewed publications with a total IF of >2000. HI 49

**Editorial activity:**

- Editorial Board of Journal of Clinical Oncology;
- Referee for Journal of Clinical Oncology, Blood, British Journal of Hematology, Leukemia, Bone Marrow Transplantation, European Journal of Hematology, Haematologica and others;

- Reviewer for grants for the Leukemia Research Fund (UK), for MIUR, CNR and several Italian and European Universities (Padova, Siena, Jerusalem, Southampton, Salamanca, Cordoba etc.)

**Yücel Erbilgin**

*Post Doctoral Researcher, Istanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Genetics, Vakif Gureba Cad. 34093, Capa-Fatih/Istanbul, Turkey*

**Education**

2008–2015 Ph.D. in Genetics, Istanbul University, Institute of Experimental Medicine, Department of Genetics. Thesis Title: “Whole genome analysis in relapsed childhood acute leukemia patients”  
 2005–2008 M.Sc. in Genetics, Istanbul University, Institute of Experimental Medicine, Department of Genetics. Thesis Title: “Analysis of NOTCH1 mutations in T-ALL patients”  
 2001–2005 B.S. in Medical Biology, Istanbul University, Cerrahpaşa Medical Faculty, Department of Medical Biological Sciences Graduation Project Title: “Mechanisms of cancer metastasis”

**Work Experience**

2009–present Teaching and Research Assistant, Istanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Genetics

**Catherine Thieblemont**

*Professor of Haematology in the Paris VII- University, France*



Catherine Thieblemont is Professor of Haematology in the Paris VII University, France, and the head of the Hemato-Oncology Department in the Hospital Saint-Louis, Paris, France since December 2009.

She trained as a Hemato-oncologist in Lyon from 1990 until 1995. She stayed 2 years in the department of Hemato-Pathology (Doctor Elaine Jaffe) at the National Cancer Institute - Bethesda (MD), USA. She became Assistant-Professor in 2003 in Lyon and moved in

Paris in 2007 for the position of head of the Hemato-Oncology Department, focalised in the management of patients with lymphoma, at the Hospital Saint-Louis, Paris, France.

She is an active member of the Lymphoma Study Association (LYSA), a cooperative group of French, Belgian physicians interested in the treatment of lymphomas. Within the LYSA, she is one of the members of the steering committee and the scientific committee, and she is coordinating the subcommittee of the marginal zone lymphoma. She is an active member of the International extranodal Lymphoma study group (IELSG) and participates as one of the members of the board directors. She participates to the coordination of several randomized trials for the treatment of lymphoma patients.

Her major interest is the biological and clinical features of lymphomas. She is biologically involved in programs developing genomic and metabolomic studies on low and high grade lymphomas, particularly marginal zone lymphomas, but also refractory high grade lymphomas, using integrative genomics to determine biological key targets for new therapies.



### Carmino Antonio De Souza

*Professor Doutor da UNICAMP Especialista em Hematologia*



Prof. Carmino Antonio De Souza, graduated in Medicine in 1975, Medical Residence in Internal Medicine and Hematology in 1979, Doctorate in 1987, Free Professor in 1996 and Full Professor in 2001 at Internal Medicine Department from University of Campinas, Brazil. Post Doctorate at Department of Hematology, San Martino Hospital from University of Genoa-Italy in 1997-1998 supported by FAPESP. Onco-hematologist acts, particularly, in the Malignant Lymphomas, Chronic Myeloid Leukemia and Bone Marrow Transplantation. He has about of 330 published papers mainly in English and Portuguese; more than 1000 abstracts presented in national and international Congresses; 24 books' chapters most in Portuguese and 34 coordinated theses in post graduated university program. In August 2018, the h-index is 47 and h-10 index is 181 (Google Scholar) and the number of citations in the international literature is about of 10000. Health Secretary of São Paulo State in 1993-1994. Currently is the Health Secretary of Campinas City - São Paulo State and Director of Hematology and Hemotherapy Brazilian Association (ABHH). Is an active member of American Society of Hematology (ASH), European Hematology Association (EHA) and European Bone Marrow Transplantation Group (EBMT) and founder member of the LALNET (Latin America Leukemia Net) and AIBE (Italian Brazilian Hematology Association).

### Burhan Ferhanoglu

*Professor of Medicine, University of Koc, Department of Internal Medicine, Division of Hematology, Istanbul, Turkey*



2012–present	Koc University School of Medicine, Department of Hematology
1998–present	V.K.V. American Hospital, Chair of Department of Hematology
1994–2012	Professor of Hematology, Cerrahpasa Medical school
1993–1994	Associate professor of Cerrahpasa Medical School
1992–1993	Fred Hutchinson Cancer Center, Bone Marrow Transplantation Experience
1991–1992	Cerrahpasa Medical School, Associate Professor
1990–1991	University of Texas, Health Science Center, Department of Hematology, Research Fellow, Basic Science Research
1988–1990	Associate professor of Hematology, Cerrahpasa Medical School
1986–1988	Cerrahpasa Medical School, Department of Internal Medicine, Hematology Fellow
1984–1986	Corum State Hospital, Department of Internal Medicine
1982–1984	Military work at Bursa Military Hospital, Department of Internal Medicine
1978–1982	Istanbul University, Medical School, Department of Internal Medicine, Resident
1978	University of Istanbul Medical School
1972	Vefa High School, Istanbul

- Çetiner M, Sucak G, Aydın F, Birtaş E, Yozgatlıgil C, Kalaça S, Akı Z, Kalaycıoğlu-Beşışık S, Ferhanoglu B, Gülbaş Z, Uzay A, Kaygusuz I, Fıratlı-Tuğlular T, Bayık M. Evaluation of Life Quality in Hematopoietic Stem Cell Transplantation Patients (Hematopoyetik Kök Hücre Nakli Yapılan Hastalarda Yaşam Kalitesinin Değerlendirilmesi). "Clinical Hematology" award in Turkish Society of Hematology 33rd National Hematology Congress, Ankara, October 16–19, 2007.
- Demirsoy ET, Ar MC, Öngören Ş, Üre Ü, Başlar Z, Ferhanoglu B, Aydın Y, Tüzüner N, Ülkü B, Aktuğlu G, Soysal T. Prognostic Significance of Serum Vascular Endothelial Growth Factor in Chronic Lymphocytic Leukemia (Kronik Lenfositik Lösemide Serum Vasküler Endotelial Büyüme Faktörü Düzeyinin Prognoz Değeri). "Schering Lymphoproliferative Disorders"

second rank award in Turkish Society of Hematology 32nd National Hematology Congress, Antalya, 2006.

- Özbalak M, Yürüyen M, Tüzüner N, Ar MC, Güner Şİ, Çetin G, Öngören Ş, Üre Ü, Başlar Z, Soysal T, Aydın Y, Ülkü B, Demir G, Saçlı FS, Ferhanoglu B. Response rates of germinal center and non-germinal center subtypes of DLBCL to R-CHOP chemotherapy in newly diagnosed diffuse large B cell lymphoma evaluated by immunohistochemistry (Yeni Tanı Almış Diffüz Büyük B Hücreli Lenfomada İmmünohistokimya Aracılığıyla Değerlendirilen Doku Microarray Yöntemi ile Germinal Merkez ve Non-Germinal Merkez Tiplerinin R-Chop Kemoterapisine Yanıtları). Roche Non-Hodgkin Lymphoma award. (Turkish Society of Hematology Roche Industry Award) in Turkish Society of Hematology 32nd National Hematology Congress, Antalya, 2006.
- Ar MC, Sırma S, Hatırnaz Ö, Öngören Ş, Üre Ü, Başlar Z, Aydın Y, Ferhanoglu B, Özbek U. Re-evaluation of Minimal Residual Disease by PCR IG/ TCR and Follow-up of Minimal Residual Disease by Detection of Translocation in patients with Acute Lymphoblastic Leukemia: Preliminary Results (Erişkin Akut Lenfoblastik Lösemili Hastalarda Minimal Residüel Hastalığın PCR IG/ TCR Yeniden Yapılanması ve Translokasyon ile Tesbiti ve İzlenmesi: Ön Sonuçlar). "TSH Clinical Laboratory Hematology" award in Turkish Society of Hematology 30th National Hematology Congress, Istanbul, 2003.

*Referee for:*

- Journal of Istanbul Faculty of Medicine
- Journal of Osmangazi Faculty of Medicine
- Journal of Cukurova Faculty of Medicine
- Turkish Journal of Hematology
- Journal of Clinical Evolution

*Membership of Scientific Societies:*

- Turkish Society of Hematology
- International Society of Hematology
- American Society of Hematology
- European Bone Marrow Transplantation Society
- European Hematology Association

### Jean-François Rossi

*Professor at the University*



He participated to the creation of 4 start-ups. In addition, he is an active member of the Scientific Advisory Boards for 3 start-ups such as Urodelia and Beta Innov.

With Nutriprevent, he developed programs on microbiota modulation through preventive nutrition particularly focused on inflammatory process. With E-Sana as a co-founder with Pr Kalle Levon (Polytechnic Institute of NYU, Brooklyn, USA) and Césaire Massart,

he participates to new programs based on innovative technology for tests including in-Home and biological monitoring, with dynamic follow-up.

Nowadays, based on different patents on NK cells from Umbilical Cord Blood, he participates to new therapeutic strategies, including vaccine programs developed by URODELIA Inc. France).

A new bio-clinical platform for patients is developed with different Healthcare centers.

Dr Jean-François Rossi has over 30 years of experience in medicine and was certified in Rheumatology, Medical Oncology, Hematology, Immunology and Internal Medicine.

He received his MD and PhD degrees in Hematology Immunology at the University of Montpellier and had post-doc at the Universities of Arizona (Tucson) and San Antonio (Texas) in the domain of multiple myeloma and bone research.

He was associate professor at the University of Suzhou (China) for more than 10 years. He is member of 7 international scientific societies and the Scientific Advisory Board of the Castleman Disease Collaborative Network (CDCN).

Beginning at the Internal Medicine department, he was in charge of Medical Oncology for 5 years in Montpellier Cancer Center. Then, he became the head



of the Hematology Department during 14 years and he developed 1) with Professor Bernard Klein the Biotherapy Saint-Eloi site (Immunotherapy-Regenerative Medicine (Chu/Inserm/ University), 2) wellbeing concept using Art as a language for coming back to normal life with a "COMMANDE Publique d'Etat".

He was granted 3 patents and has 195 scientific PUBMED publications. He is particularly active in Immunotherapy for cancer and programs on crossed information analysis developing decision algorithms including epigenetics with microbiota and nutrition influence. He participated or activated different clinical or bio-clinical research programs with pharmaceutical companies (more than 150) or with academic institutes (national or international, including CLiNK, from EEC on NK Lymphocytes). He obtained an AWARD from the AMERICAN ASSOCIATION for CANCER RESEARCH on April 2017 for his work on inflammatory process and interleukin 6 (<http://aacrjournals.org/content/j-f-rossi-bio> and *The Best of the AACR Journals*).

He was a consultant for different BIG PHARMA for more than 20 years, including Celgene, Roche, J&J (Centocor) for siltuximax development, Serono Merck for TACI-Ig FC5, Innate Pharma for IPH1101, LFB for the anti-CD20 LFB-R603, Petrovax Pharm LLC for polyoxidinium (ongoing), in-home biology for Horiba Medical and for Biotherapy with Marc Cluzel when he was the General Director of Sanofi Research.

### Ece Esin

University of Health Sciences Dr. A. Y. Ankara Oncology Education and Research Hospital Department of Medical Oncology, Ankara-Turkey



#### Education

2011–2016 Fellowship and MD position:  
Hacettepe University Cancer Institute,  
Medical Oncology Department

2013–2014 Research Fellowship:  
Multidisciplinary Approach to  
Gastrointestinal Malignancies at  
University of Maryland, Baltimore,  
United States

2013–2016 Master of Science in Cancer Epidemiology, Hacettepe University Cancer Institute, Preventive Oncology Department

2006–2011 Residency: Hacettepe University Medical Faculty, Internal Medicine Department

1999–2006 University: Hacettepe University Medical Faculty (English)

*Special Training*

2016 ESMO Leaders Generation Programme, alumni

2014 ESO-ESMO Eastern Europe and Balkan Region Masterclass in Medical Oncology Brdo, Slovenia

2013 Advanced Good Clinical Practice (GCP) Training Course

2011 Good Clinical Practice (GCP) Training Course

*Examinations and Awards*

2014 ESMO Medical Oncology Board Examination

2014 Turkish Society of Medical Oncology Board Examination

1996 Ranked 2nd in Highschool Entrance Examination of Turkey

1999 Ranked 49th degree in University Entrance Examination of Turkey

2003 Şeref Zileli (University of Hacettepe) Best Student Award

2010 Şeref Zileli (University of Hacettepe) Best Resident Award

### Ömür Berna Öksüzöğlü

Dr. A. Yurtaslan Ankara Oncology Training and Research Hospital, Turkey



Ö. Berna Öksüzöğlü, MD, is currently Professor of Medical Oncology at Erzincan University School of Medicine and still working as Head of Medical Oncology in Dr. A. Yurtaslan Ankara Oncology Training and Research Hospital, Turkey.

Dr. Öksüzöğlü attended Hacettepe University, School of Medicine and graduated in 1991. She received her internal medicine specialist qualifications at

the Ankara Numune Training and Research Hospital. From 1997 through 1999 she served as a internal medicine chief resident. She completed her fellowship programme in medical oncology at Hacettepe University, Institute of Oncology, Ankara in 2002.

Dr. Öksüzöğlü is an active member of many professional organizations including ESMO (European School of Medical Oncology), TOG (Turkish Oncology Group), TTOD (Society of Turkish Medical Oncology) and Ankara Society of Breast Diseases. She was on duty of the Medical Oncology Board of Directors of Turkey between 2011 and 2012.

She is author and co-author of more than 50 scientific publications in peer-reviewed journals.

Her focus is clinical oncology and research interests are clinical studies and practice on breast cancer.

### Salam Al Kindi

Department of Haematology Sultan Qaboos University, Muscat Oman



Following my graduation from Trinity college, Dublin Ireland, in 1993, I have completed my general medicine as well as haematology/oncology training in Dublin, Ireland as well as the Fred Hutch cancer centre in Seattle USA, where I did my training in Bone marrow transplant. In 1999 I have joined Sultan Qaboos University and in 2005 I was appointed as head of department of haematology for 10 years. Previously also I held the position of deputy director of Sultan Qaboos university hospital for clinical affairs (clinical director in effect) for about 5 years. Research interests include sickle cell disease, chronic leukaemia and autoimmune disorders with more than 80 articles published in international peer reviewed journals.

### Zeynep Karakas

Pediatric Hematology-Oncology, Istanbul Medical School, Istanbul University, Turkey



Prof Dr Zeynep Karakas was born in 1959 in Gaziantep. She graduated from Istanbul Medical Faculty in 1982. She worked as a general practitioner in Konya and worked in Pediatrics at the Department of Pediatrics, Faculty of Medicine, Dicle University. From 1994 to 1998 she trained subspeciality for hematology oncology at Istanbul Medical Faculty, Pediatric Hematology/Oncology. She is married and has a son and daughter. She is currently a professor of Pediatric

Hematology/Oncology. She studied haematopoietic stem cell transplantation for 1 year. Erythrocyte diseases and hemoglobinopathies are the main topics of Prof. Karakas. Since 2003, she has participated in international clinical studies in hematology, especially hemoglobinopathies. She is also responsible for the Hemoglobinopathy Center, Istanbul Medical Faculty, which was founded in 2007.

### Vassilios Papadakis

Pediatrics-Hematology-Pediatric Hematology Oncology



Dr Vassilios Papadakis was born in 1961 and was brought up in Pireaus, Greece. He graduated Ionidios Lyceum with honors, first in order in 1979 and enrolled the Medical School of the National and Kapodistrian University of Athens eight in order. He obtained his MD degree with summa cum laude in 1986, following elective training in the summer of 1985 in Pediatric Gstrenerology in the USA Professor Lebenthal, Buffalo, NY).

Residency in Pediatrics (1987–1990) was completed at St Luke's/Roosevelt Medical Center of the Columbia University of Physicians and Surgeons (New York City, USA). Full Fellowship in Pediatric Hematology-Oncology

was completed at Memorial Sloan-Kettering Cancer Center and NYH Cornell Medical Center (1990–1993, NYC). The following year (7/1990–6/1994) he was a Special Fellow in Bone Marrow Transplantation (BMT) at Memorial Sloan-Kettering Cancer Center, NYC. Research activities involved the pathophysiology of bone marrow engraftment and failure following BMT, CNS tumor megatherapy/ transplantation and late effects of cancer treatment, all with relevant publications.

Dr Vassilios Papadakis is Board Certified in Pediatrics and in Pediatric Hematology Oncology in the USA and holds the Specialty Title of Pediatrics and Hematology in Greece.

Following military and civil medical service in Greece he worked as Senior Attending in Pediatrics at Thiva General Hospital in Greece. Since, 1997, he was appointed at the Department of Pediatric Hematology – Oncology at Agia Sofia Children's Hospital in Athens, Greece, where he is still working, as Director.

A PhD Degree has been obtained following successful completion of research from the Medical School of the University of Crete. The thesis involved long term outcome of growth, development and gonadal function in children treated for Hodgkin's Lymphoma.

Current research interest involves the treatment of Neuroblastoma, Leukemias, Lymphomas and Histiocytic Syndromes in children.

Clinical practice involves the full spectrum of Pediatric Hematology – Oncology.

Dr. Papadakis is a founding member of the SIOPEN European Neuroblastoma consortium and he has served at the SIOPEN Executive Committee (2006–2000, 2012–2016). He is a member of Hellenic and International Scientific Committees and he is currently the Vice President of the Hellenic Society of Pediatric Hematology – Oncology (2012 to present, ΕΕΠΑΟ Ελληνική Εταιρεία Παιδιατρικής Αιματολογίας Ογκολογίας). He also enjoys being a member of the Board (Medical Doctor) of the Make-A Wish Foundation Greece.

Since 2016, Dr Papadakis serves on the Board of the Second Chapter of the National Medicinal Organization of Greece (Εθνικός Οργανισμός Φαρμάκων ΕΟΦ [www.eof.gr/](http://www.eof.gr/)) for the approval of biological and blood products in the country.

He is currently co-Principal Investigator of the “European Low and Intermediate Risk Neuroblastoma. A SIOPEN Study”, an currently open study, (EudraCT number: 2010-021396-81) and National Principal Investigator for the High Risk Neuroblastoma Study 1.5 of SIOPEN-Europe (SIOPEN) (EudraCT number: 2006-001489-17).

In parallel, he is married and has grown two boys, aged 24 and 27 years old, both graduates of the Metsovion National Technical University of Athens, but he cannot allocate enough time to his hobbies: music and photography.

### Francesco Saglio

*Oncoematologia Pediatrica Centro Trapianti Cellule Staminali e Terapia Cellulare, Ospedale Infantile Regina Margherita, AOU Città della Salute e della Scienza di Torino, Italy*



Born 23 August 1982

2001–2007 Medical School, Università' degli Studi di Torino (Turin, Italy)  
2009–2014 Residency in Pediatrics at Facoltà' di Medicina e Chirurgia Università' degli Studi di Torino (Turin, Italy)  
2011–2012 Visiting Post Doctoral Fellow, Center for Cell and Gene Therapy, Baylor College of Medicine (Houston, TX, US)

2014–present PhD Program in Biomedical Sciences and Oncology, Università degli Studi di Torino (Turin, Italy)

2014–present Attending Physician Oncoematologia Pediatrica Centro Trapianti Cellule Staminali e Terapia Cellulare

Ospedale Infantile Regina Margherita- AOU Città della Salute e della Scienza di Torino

### Georgiy Mentkevich

*National Cancer Research Center N.N. Blokhin, Moscow, Russian Federation*



Deputy Director for Science, Institute for Pediatric Oncology,  
Head Department of Chemotherapy and Bone Marrow Transplantation  
National Cancer Research Center N.N. Blokhin, Moscow, Russian Federation

### Yöntem Yaman

*Department of Pediatric Hematology Oncology, Medipol University, İstanbul, Turkey*



Dr Yaman was born on July 26, 1972, in Tekirdağ. He graduated from Galatasaray High School in 1991. He graduated from Istanbul University Cerrahpaşa School of Medicine (English program), İstanbul, Turkey in 2000. He received his speciality in child health and disease in 2005 at Zonguldak Karaelmas University School of Medicine. He made first compulsory service and military training in Mardin and Adana between 2005–2008. He completed fellowship in Pediatric

Hematology Oncology in 2013 at İzmir Dr Behçet Uz Children's Hospital, İzmir, Turkey. He made his second compulsory service in Kahramanmaraş University School of Medicine Pediatric Hematology Oncology department between 2013–2015. He is working as faculty member in Medipol University School of Medicine Pediatric Hematology Oncology department and stem cell transplantation unit as an assistant professor since 2015. He has more than 25 articles published in SCI or SCI-E journals. He is a member of Turkish Society of Hematology and Turkish Society of Pediatric Hematology Association.

### Achille Iolascon

*Department of Molecular Medicine and Medical Biotechnologies, University Federico II, Naples, Italy & CEINGE-Advanced Biotechnologies, Via Gaetano Salvatore 482 – 80145 Naples*



#### Education

1972–1978 M.D. University of Naples  
1978–1981 Post-graduate school in Pediatrics  
1982–1985 Post-graduate school in Oncology  
1986 Ph.D. in Pediatrics

#### Post-graduate training

1979 Intern in Medicine, University of Naples, Department of Pediatrics  
1981–1993 Assistant physician in Pediatrics

1994–2000 Associate professor of Pediatrics  
2000–2003 Professor of Pediatrics and Chairman of the Institute for Pediatrics, University of Foggia (Italy)  
2004–2010 Adjunct professor of Medicine, Department of Biology, Temple University College, Philadelphia  
2004– Professor of Medical Genetics- University Federico II, Naples

#### Faculty appointments

Professor of “Pathology” at the Nursing School of Naples University  
Professor of Pediatric Therapy  
Professor of Pediatrics  
Professor of Medical Genetics

#### Hospital and Administrative appointments

1980 Research investigator  
1982–1989 Genetic counselor at USL 39-Napoli  
1990–1993 Assistant physician in Pediatrics

1990–1994	Head of Molecular Biology Unity and Medical Genetics of Pediatrics Dpt. of University of Bari
1999–2004	Chairman of the CISME- Interuniversity Center for the Studies on Hereditary Diseases of Evolutive Age
2000–2004	Chairman of the University Pediatric Division at Policlinico of Foggia
2004	Chairman of Div. of Medical Genetics- Dpt. Molecular Medicine and Medical Biotechnologies

#### Specialty Certification

1978	Italian Board of Internal Medicine
1981	Italian Board of Pediatrics
1985	Italian Board of Oncology

#### Memberships of Professional and Scientific Societies

Italian Society of Pediatrics (SIP)
Italian Association of Pediatric Hematology-Oncology (AIEOP)
Italian Society of Hematology (SIE)
European red cell membrane study group (EHA)
American Society of Hematology (ASH)
Italian Society of Human Genetics (SIGU)

#### Academic Committee

1986	Member of the board committee of Italian Society of Pediatrics
1988	Member of the Italian molecular biology group in Oncology
1990	Chairman of the Italian study group on “hemolytic anemia” of the AIEOP
2011–2014	Member of the scientific committee on Red Cell Biology of the American Academy of Hematology
2014–2017	Chairman of the Scientific Working Group of the European Society of Hematology

#### Scientific interests

Since 1978	Thalassaemia and haemoglobinopathies
Since 1986	Oncogenes in pediatric tumors genetic disorders of the red cell membrane
Since 1995	Stomatocytosis and related diseases, dyserythropoietic anemias
Since 1998	Hereditary thrombocytopenias
Since 2000	Molecular medicine
Since 2004	Iron metabolism in red cells

#### Iris Agreiter

Staff Nurse at The Haematology and Oncology Day Care of St. James's Hospital in Dublin, Ireland



Iris Agreiter, RN, works actually as staff nurse at the Haematology and Oncology Day Care of St. James's Hospital in Dublin, Ireland. She has worked for 6 years at the Haematology and BMT Unit San Maurizio Regional Hospital in Bolzano, Italy, previously for 4,5 years at the Infectious Diseases Department of the same hospital. She focuses on infection control, multidrug-resistant organisms and is link nurse of the EBMT Infectious Diseases Working Party. In July

2018, she graduated at a Master in Psychology, therefore, she has also an interest in Psychological issues. She has presented several posters and oral communications at national and international congresses.

#### Naeem Arshad Chaudhri

Professor, College of Medicine, Alfaisal University; Director, Research Unit, Oncology Centre; Consultant, Adult Hematology/HSCCT; King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia



Dr. Chaudhri is a Consultant in Hematology and Hematopoietic Stem Cell Transplantation at KFSH&RC. He is board certified in Internal Medicine, Medical Oncology and Hematology from American Board of Internal Medicine and he completed his fellowship in Hematology and Medical Oncology in 1995 at Lombardi Cancer Center, Georgetown University Hospital, Washington D. C. He joined King Faisal Specialist Hospital and Research Centre in 1996.

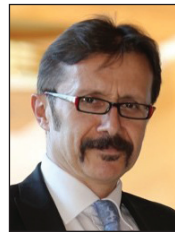
KFSH&RC is the major tertiary care referral centre in Saudi Arabia and Middle East with Oncology Centre being accredited by the World Health Organization (WHO) as a Collaborating Centre for Cancer Prevention and Control.

His main interest is Malignant Hematology, specifically Acute and Chronic Leukemia as well as Hematopoietic Stem Cell Transplant.

Dr. Chaudhri is also the Director/Head of Research Unit overseeing clinical research in the Oncology Centre at KFSH&RC. He is the principal investigator of the South West Oncology Group (SWOG) for KFSH&RC and principal investigator of numerous ongoing clinical trials. He is an Associate Editor-in-chief of Annals of Saudi Medicine and an Editorial Board of other journals. He has around 130-140 publications and abstracts in peer-reviewed journals. At the same time, Dr. Chaudhri is the Congress Chairman of the annual conference of the Critical Reviews in Hematological Malignancies in Riyadh, Saudi Arabia and also a member of organizing and scientific committees of numerous national and international meetings. He is invited speaker on national and international scientific meetings.

#### Ismail Celik

Hacettepe University Cancer Institute, Ankara



Prof. Ismail Celik is an internist and medical oncologist. He also has MS degree in cancer epidemiology.

He worked as a visiting NCI scholar in the Johns Hopkins University, School of Public Health, Cancer Epidemiology Program between 2006–2007.

He is the director of the “Turkish Immunotherapy and Oncology Association”. His field of interests are melanoma and immunotherapy and he currently works at the Hacettepe University Cancer Institute, Ankara.

#### Nitin Jain

Associate Professor in the Department of Leukemia at MD Anderson Cancer Center in Houston, Texas, USA



Nitin Jain, M.D., is an Associate Professor in the Department of Leukemia at MD Anderson Cancer Center in Houston, Texas, USA. He earned his medical degree from All India Institute of Medical Sciences, New Delhi in 2002. He then moved to the United States and completed his internal medicine residency training at the Medical College of Wisconsin, Milwaukee. He then completed a year of clinical fellowship in leukemia at MD Anderson Cancer Center

followed by another year of leukemia research fellowship at the Memorial Sloan-Kettering Cancer Center in New York. He then pursued hematology/oncology fellowship from the University of Chicago. After completed his medical training, he was recruited as a faculty member in the Department of Leukemia at MD Anderson in 2012. Dr. Jain clinical interests focus on new drug development for patients with leukemia, especially chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL). Dr. Jain is PI of several investigated-initiated phase I-II clinical trials, including checkpoint



inhibitors in CLL, combination targeted therapies (ibrutinib and venetoclax) in CLL, and a trial with JAK2 inhibitor in Ph-like ALL. He has published papers in prominent journals including Journal of Clinical Oncology, Blood, Clinical Cancer Research, Cancer, Leukemia Lymphoma, Leukemia Research and others. He has won many awards during his career including Sardari Lal Kalra Gold Medal in Microbiology and Merit Award from the American Society of Clinical Oncology (ASCO). He received High-Impact Clinical Research Support Award from MD Anderson Cancer Center in the year 2014 and 2016. He has served as a faculty on American Society of Hematology CRTI workshop for year 2017 and 2018. He is recipient of Sabin Family Foundation Award in 2018.

### Rüdiger Hehlmann

Chief of Medicine at the Mannheim Medical Faculty of Heidelberg University



Prof. Dr. med. Dr. h. c. Rüdiger Hehlmann, chief of medicine at the Mannheim Medical Faculty of Heidelberg University until 2007, founded in cooperation with his colleagues the German CML Study Group in 1982, the German Competence Network for Acute and Chronic Leukemias in 1997 and the European LeukemiaNet (ELN) in 2002. He is past president of the German Society of Hematology and Oncology, past Dean of his faculty and past

Secretary General of the International Association of Comparative Research on Leukemia and Related Diseases (IACRLRD). He is honorary member of the Polish and German Societies for Hematology and Oncology. He completed his last randomized CML study (CML Study IV) in 2017 and currently manages the ELN Foundation in support of ELN.

#### 10 Selected Publications (2016–2018)

- Barbui T, Tefferi A, Vannucchi AM, Passamonti F, Silver RT, Hoffman R, Verstovsek S, Mesa R, Kiladjian JJ, Hehlmann R, Reiter A, Cervantes F, Harrison C, Mc Mullin MF, Hasselbalch HC, Koschmieder S, Marchetti M, Bacigalupo A, Finazzi G, Kroeger N, Griesshammer M, Birgegard G, Barosi G. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. *Leukemia*. 2018 May;32(5):1057-1069. doi: 10.1038/s41375-018-0077-1. Epub 2018 Feb 27.
- Saussele S, Hehlmann R, Fabarius A, Jeromin S, Proetel U, Rinaldetti S, Kohlbrenner K, Einsele H, Falge C, Kanz L, Neubauer A, Kneba M, Stegelmann F, Pfreundschuh M, Waller CF, Oppliger Leibundgut E, Heim D, Krause SW, Hofmann WK, Hasford J, Pfirrmann M, Müller MC, Hochhaus A, Lauseker M. Defining therapy goals for major molecular remission in chronic myeloid leukemia: results of the randomized CML Study IV. *Leukemia*. 2018 May;32(5):1222-1228. doi: 10.1038/s41375-018-0055-7. Epub 2018 Feb 26.
- Hehlmann R. Advancing a field by building consortia: The example of the European LeukemiaNet. *Cancer*. 2018 Mar 15;124(6):1100-1104. doi: 10.1002/cncr.31199. Epub 2018 Feb 16.
- Hehlmann R, Lauseker M, Sauße S, Pfirrmann M, Krause S, Kolb HJ, Neubauer A, Hossfeld DK, Nerl C, Gratwohl A, Baerlocher GM, Heim D, Brümmendorf TH, Fabarius A, Haferlach C, Schlegelberger B, Müller MC, Jeromin S, Proetel U, Kohlbrenner K, Voskanyan A, Rinaldetti S, Seifarth W, Spieß B, Balleisen L, Goebeler MC, Hänel M, Ho A, Dengler J, Falge C, Kanz L, Kremers S, Burchert A, Kneba M, Stegelmann F, Köhne CA, Lindemann HW, Waller CF, Pfreundschuh M, Spiekermann K, Berdel WE, Müller L, Edinger M, Mayer J, Beelen DW, Bentz M, Link H, Hertenstein B, Fuchs R, Wernli M, Schlegel F, Schlag R, de Wit M, Trümper L, Hebart H, Hahn M, Thomalla J, Scheid C, Schafhausen P, Verbeek W, Eckart MJ, Gassmann W, Pezzutto A, Schenk M, Brossart P, Geer T, Bildat S, Schäfer E, Hochhaus A, Hasford J. Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. *Leukemia*. 2017 Nov;31(11):2398-2406. doi: 10.1038/leu.2017.253. Epub 2017 Aug 14.
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### Serpil Vieira

Sister/Deputy Manager the London Clinic, London - United Kingdom



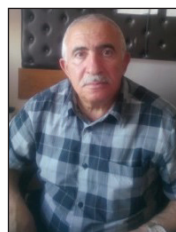
2002–Present Sister/Deputy Manager the London Clinic, London, United Kingdom

- Set up and running the nurse lead “Late effect Clinic” service for Transplant recipient to screen the quality of life post-transplant. In this clinic, conduct a physical examination, blood test and consultation to explore existing problem.
- Deputy Transfusion Practitioner, responsible from training and competency assessment of all the medical staff in The London Clinic, provide support all other transfusion champions
- Conducting clinical audits on regular basis
- Preparing /conducting research, data collection for EBMT on regular basis
- To educate and train all members of the clinical unit team in the development of skills that have been specifically identified for the role in the accordance with most up-to-date JACIE standards.
- Writing/reviewing SOPs for JACIE
- Staff training and competency assessment in all clinical activities
- Training of super users in other ancillary department
- Heavily involved and take part as a core member in creating a new medical software “Meditech 6.0”
- Involved in developing chemotherapy pathways for haematology /BMT patients
- Deputised the unit manager in administrative work
- To be able to defrost and administer stem cells/bone marrow, and to teach junior members of staff this process once stem cell competency has been achieved.
- To be able to administer fresh allogeneic cells, DLI
- To have relevant knowledge to care for and access central venous catheters (e.g. PICC, Hickman, Groshong, Vascath, and Portacath).
- To perform venepuncture and cannulation once appropriate training has been given.
- To recognise and appropriately deal with neutropenic sepsis, by recognising safe parameters and acting quickly on adverse.
- To interpret and act upon blood results including electrolytes and clotting disorders.
- To administer cytotoxic drugs, intravenous antibiotics and supportive therapies, including all necessary blood products e.g. FFP, platelets (single, pooled and HLA matched donors).
- To check intrathecal chemotherapy once Trust training has been taken.

- To be aware of the side effects of any treatment in progress and adopt a problem-solving approach to minimise the potential adverse reactions.
  - Autograft, Allograft (sibling, matched unrelated donors and cord transplant)
  - To recognise and respond to all the side effects associated with high dose chemotherapy, total body irradiation and allograft or MUD transplantation including severe immune suppression, gross fluid imbalance (monitoring of CVP), electrolyte imbalance, Venous occlusive disease and TTP.
  - To liaise closely with the outreach nurses when a patient becomes aerodynamically unstable and to keep them informed of changes that may need further observation in the step-up unit.
  - To administer Ribavirin/Pentamidine nebuliser and to teach more junior staff the procedure.
  - In the absence of the ward manager follow up tissue typing and coordinate pre-transplant work ups for potential transplant patient's as well as attending to patient with the consultant.
  - To work closely with the nurses to ensure that clinical standards of care are achieved within the unit and to participate in the audit of clinical care.
  - To perform staff appraisals for junior members of staff.
- 2001–2002      *Adaptation Nurse, Cromwell Hospital, London (United Kingdom)*
- Adapting the nursing in UK
  - To learn differences in nursing in UK
- 1995–2001      *Staff nurse, Istanbul Medical Faculty Haematology & Bone Marrow Transplant Unit, Istanbul, Turkey*
- To look after patient with Haematological Malignancies
  - To transfuse blood products
  - Taking care of every type of central venous device (Hickman line, Vascath, Groshong)
  - Venepuncture & cannulation
  - Educating patient and families
  - Screening patient s for a potential Allogeneic transplant
  - Dealing with patient with post-transplant complications
  - Preparing & administering cytotoxic treatment, dealing with waste
- Screening patients' blood results and acting upon results
  - Coordinating patient care with the medical team
  - Training of Junior Staff
  - Taking part in national conferences on behalf of the unit
  - Dealing with side effects of chemotherapies
  - To be able to defrost and administer stem cells/ bone marrow, and to teach junior members of staff this process once stem cell competency has been achieved.
  - To be able to administer fresh allogeneic cells, DLI
  - To recognise and appropriately deal with neutropenic sepsis, by recognising safe parameters and acting quickly on adverse.
  - To check intrathecal chemotherapy once Trust training has been taken.
  - To be aware of the side effects of any treatment in progress, and adopt a problem-solving approach to minimise the potential adverse reactions.
  - To look after all transplant patients e.g. autograft, allograft (sibling, matched unrelated donors and cord transplant)

### Ümran Çalışkan

*Division of Child Health and Disease Selçuk University Konya, Turkey*



I was born in Yozgat in 1951. After completing my primary, secondary and high school, I enrolled Hacettepe University Medical School in 1972 and graduated in 1977. I began my pediatric residency in 1977 in the department of pediatrics in Hacettepe University Medical School, becoming a pediatrician in 1982. I am one of the founders of the department of pediatrics of Selçuk University in 1984. I got the title of associated professor in 1986 and professor in 1992. I am chief of the department of Pediatric Hematology and Oncology of Necmettin Erbakan University Meram Medical Faculty and still working at the same department. I am interested in hematologic and oncologic diseases of children. I am a member of Turkish Society of Hematology and Turkish Society of Pediatric Hematology. I am married and have 3 children.







## Abstracts of the IXth International Eurasian Hematology Oncology Congress 17–20 October 2018, Istanbul, Turkey

### Speaker Presentations – Hematology Program

#### SP-01

#### Can lessons learned from chronic myeloid leukaemia on targeted therapy and precision oncology be applied to other cancers

Robert Peter Gale

*Haematology Research Centre, Division of Experimental Medicine, Department of Medicine, Imperial College London, London, UK*

Therapy of chronic myeloid leukaemia (CML) is one of the recent success stories in cancer therapy and the poster child for targeted cancer therapy and precision oncology. As such, it is useful to consider what has been accomplished, how it was accomplished and implications for therapy of other cancers. The most important consideration and the reason CML was selected for detailed study is it is caused by 1 canonical mutation: *BCRABL1* associated with the Ph1-chromosome. Everyone with *BCRABL1* (in a cell biologically able to cause CML) has CML. Moreover, even if you have a disease resembling CML you don't have CML unless you have *BCRABL1*. This is an almost unique situation for a cancer in humans. For example, persons with acute myeloid leukaemia (AML) have a median of about 15 mutations whereas as those with pancreas cancer have a median of 75 mutations and those with lung cancer, >100 mutations. This uniqueness of CML facilitated identifying the gene product of *BCRABL1*, P210<sup>BCRABL1</sup>, a constitutively-activated tyrosine kinase and developing relatively specific biochemical inhibitors such as imatinib, dasatinib and nilotinib. Also, it was possible to accurately and precisely quantify numbers of CML cells in people by measuring *BCRABL1* mRNA levels using quantitative polymerase chain reaction (PCR). Not unexpectedly, mutations arose in *BCRABL1* (or were selected for) and had to be addressed by developing new tyrosine kinase-inhibitors (TKIs) such as ponatinib and bosutinib. Therapy with these drugs can produce deep, sustained molecular remissions but it is unlikely they eliminate the cell in which CML begins termed the CML stem cell. However, quite remarkably, TKI-therapy can be stopped in some persons without leukaemia recurrence. Also, persons receiving TKI-therapy have a life expectancy like age- and sex-matched normals, a situation termed operational cure. The question I will address is what are implications of these data for treating other cancers. Several are obvious. First, as indicated, most cancers in humans have 10s or 100s of mutations, not 1. Second, different persons with the same cancer (histologically) have different mutation topographies. For example, even in a relatedly mutational simple cancer such as AML no 2 persons have the same mutation topography. Third, although there are good data CML begins in a stem cell, it is less certain this concept applies to most cancers. Fourth, multiplicity of mutations in most cancer makes it unlikely targeting 1 gene product will result in cure, operational or real. For example, use of an inhibitor to the FLT3 gene product in AML (midostaurin) results in only a modest improvement in survival. The same is so for other TKI in diverse solid cancers. And there are many other important dis-similarities I will discuss. In summary, the good news is we can cure many

persons with CML. However, caution is needed apply concepts operating in CML to most other human cancers. But we can hope for progress.

#### SP-02

#### The role of T cell immunotherapy in the management of aggressive lymphomas

Hanan Hamed

*Professor of Internal Medicine and Clinical Hematology, Ain shams University, Cairo, Egypt*

The immune system is the body's main defense against infection and has been shown to harbor the potential to recognize and kill cancer cells. T cells have emerged as central players in the immune response to cancer [1,2].

The molecular understanding of T-cell lymphocyte activation and inhibition established the opportunity for cancer immunotherapy. Malignant cells influence the tumor microenvironment by altering immuno-regulatory cells that reduce host immunity [3]. Upon engagement of tumor cells by T cells expressing tumor antigen-specific T cell receptors (TCRs), the T cells are activated, undergo clonal proliferation to broaden the attack, and release cytokines that can enhance antitumor activity, ultimately leading to the lysis of tumor cells [4].

The field of cancer immunotherapy has rapidly progressed in the past decade as several therapeutic modalities have entered into the clinic. One such immunotherapy that has shown promise in the treatment of cancer is the use of chimeric antigen receptor (CAR)-modified T lymphocytes.

CARs are engineered receptors constructed from antigen recognition regions of antibodies fused to T-cell signaling and costimulatory domains that can be used to reprogram a patient's T cells to specifically target tumor cells. CAR T-cell therapy has demonstrated sustained complete responses for some patients with advanced lymphoid malignancies. CARs combine an antibody fragment with intracellular signaling domains, generating a single chimeric protein used to reprogram immune cells into "hunter cells" that target tumors [5]. CAR T-cell therapy combines the specificity of an antibody with the cytotoxic and memory functions of T cells [6].

An improved understanding of the interplay between malignant cells and the tumor microenvironment, as well as evasion of the host immune response, has led to identification of new targets in cancer therapy. The idea of harnessing the host immune system to combat cancer effectively has led to the development of agents that target immune checkpoint signaling pathways, enhance T-cell cytotoxic activity and subsequently induce tumor cell lysis. This groundbreaking immunotherapeutic approach has produced exciting results in different malignancies and many clinical trials are currently ongoing or underway to explore immune checkpoint inhibition (ICI) further [7].

Immune checkpoint inhibitors enhance the cytotoxic activity of host T cells by blocking inhibitory signals from tumor cells. Rather than targeting the cancer cell directly, these agents stimulate the host immune system

to exert an antitumor effect. The most clinically relevant checkpoints to date are cytotoxic T lymphocyte-associated antigen 4 (CTLA4; CD152) and programmed cell death 1 (PD-1; CD279). In lymphoid malignancies, these inhibitory pathways resemble their state in the native immune system, and differences may be mediated in part by the tumor microenvironment [8]. The PD-1 receptor and its ligands, PD-L1 and PD-L2, inhibit T-cell activation and proliferation. The PD-1 pathway is critical in regulating effector T-cell response in tissues by suppressing T-cell activity to limit tissue damage [9]. We enter a promising new era of immunotherapy to treat lymphoid cancers.

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#### SP-03

##### Paroxysmal nocturnal hemoglobinuria PNH

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PNH is a condition in which uncontrolled complement activity leads to systemic complications, principally through intravascular hemolysis and platelet activation. It arises through a somatic mutation of the phosphatidylinositol glycan A (PIG-A) gene in bone marrow stem cells [1,2], resulting in disruption to glycosylphosphatidylinositol (GPI) biosynthesis [3]. Among the deficient proteins are the complement regulatory proteins CD55 and CD59, resulting in increased complement sensitivity of PNH cells, intravascular hemolysis, promotion of inflammatory mediators, and systemic hemoglobin release [4]. Patients with PNH can present with multisystemic clinical manifestations due to intravascular hemolysis, thrombosis and bone marrow failure [5]. Symptoms are therefore often non-specific, ranging from loss of vision (due to retinal thrombosis), headache and nausea/vomiting (due to cerebral thrombosis), pulmonary hypertension (due to pulmonary embolism), anaemia, through to pain and swelling in the lower extremities (due to deep vein thrombosis), renal failure and other symptoms affecting different systems [6]. Thromboembolism is the most common cause of mortality in patients with PNH and accounts for approximately 40% to 67% of deaths of which the cause is known. Further, 29% to 44% of patients with PNH have been reported to have at least 1 thromboembolic event during the course of their disease, although the reason(s) a thrombotic event may suddenly occur remains an enigma [7–9]. Platelet activation, complement-mediated hemolysis, impaired nitric oxide (NO) bioavailability, impairment of the fibrinolytic system, and inflammatory mediators are all proposed mechanisms and thought to be responsible for the increased thrombotic risk in patients with PNH. Multiple factors are likely to contribute to any one thrombotic event in patients with PNH [10].

Therapeutic strategies include terminal complement blockade and bone marrow transplantation. Eculizumab, a monoclonal antibody complement inhibitor, is highly effective and the only licensed therapy for PNH [11].

The therapeutic anti-C5 antibody eculizumab (Soliris, Alexion) has proven effective in controlling intravascular hemolysis in vivo, leading to remarkable clinical benefit in a majority of PNH patients [12,13]. Yet, persistent C3 activation occurring during eculizumab treatment may lead to progressive deposition of C3 fragments on affected erythrocytes and subsequent C3-mediated extravascular hemolysis, possibly limiting the hematologic benefit of anti-C5 treatment [14,15]. Thus, upstream inhibition of the complement cascade seems an appropriate strategy to improve the results of current complement-targeted treatment [16,17].

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**SP-04****Current treatment of myeloproliferative neoplasms**

Haifa Kathrin Al-Ali

*Associate Professor of Hematology and Internal Oncology and the head of the Krukenberg Cancer Center at the University Hospital of Halle (Saale), Germany*

Myelofibrosis (MF), polycythemia vera (PV), and essential thrombocythemia (ET) typically affect people within a mid-advanced age group. The likelihood of survival for MF and thrombosis for PV as well as ET are the basis for risk-adapted treatment decision-making. Today, both a risk- and symptom-oriented approach need to be followed based on available data to the heterogeneity of symptoms within each myeloproliferative subtype which is sometimes independent of prognosis. In MF, treatment is directed to palliate symptoms in the majority of patients since there is no curative therapy other than allogeneic stem cell transplantation (SCT). Although randomized trials are lacking, eligible patients <65 years with advanced risk MF seem to have the best survival if offered SCT compared with conventional non-Janus kinase inhibitor therapies. Conventional therapies such as hydroxyurea (HU), thalidomide, and danazol have long been used to control some disease-related issues such as splenomegaly, anemia, and thrombocytopenia with limited success. Data suggest that these therapies provide little improvement in terms of splenomegaly, symptoms or quality of life as compared with placebo. The introduction of JAK-inhibitors in the last few years has changed the treatment landscape of MF. Ruxolitinib, the first in-class approved drug, resulted in improvements in splenomegaly and disease-related symptoms in two phase-III trials. Adverse events are mainly hematologic. Extended follow-up supports a survival benefit of ruxolitinib as compared with conventional therapies. Predictive factors for response are being identified. Exploration of factors accounting for a potential survival benefit warrant further research. Treatment options with other JAK-inhibitors and further drugs are being evaluated, though several studies have been terminated prematurely due to safety concerns.

On the other hand, conventional non-Janus kinase inhibitor therapies such as phlebotomy, HU, or interferon-based therapies in combination with low-dose aspirin yield satisfactory results in many patients with PV and ET. Yet, some patients are resistant to or intolerant of these treatment options. Data delineate that patients who are resistant/intolerant to HU are actually a heterogeneous group of PV and ET patients. JAK-inhibitors and Interferon are further options. Indeed, ruxolitinib has been approved based on a phase-III trial where ruxolitinib was superior, compared with best available therapy, to control hemoglobin, splenomegaly, and symptoms. Long-term follow-up data of response durability and safety are needed. Research is ongoing to explore the role of these drug classes and in combination therapies (eg, with epigenetic modifiers, androgens, and Hedgehog pathway inhibitors).

**SP-05****Treatment of relapsed or refractory multiple myeloma**Angelo Maiolino<sup>1</sup>, Marcia Garnica<sup>2</sup>*<sup>1</sup>Professor of Medicine, Department of Internal Medicine, Universidade Federal do Rio de Janeiro (UFRJ). Coordinator of Hematology, Americas Centro de Oncologia Integrado; <sup>2</sup>Assistant Professor of Medicine, Department of Internal Medicine, Universidade Federal do Rio de Janeiro (UFRJ)*

Survival in multiple myeloma (MM) patients had an important improvement in recent years. Median overall survival increased from 3 years in the 60s to 7 years nowadays [1]. The main reason for this improvement is the incorporation of the so called “new drugs” in MM treatment. There are three major classes of these drugs: Immunomodulatory (thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, ixazomib), and monoclonal antibodies (daratumumab and elotuzumab). This new therapeutic armamentarium has a significant importance in the scenario of relapsed or refractory patients [2]. In accordance to International Myeloma Working Group (IMWG), patients with MM relapse should receive a new line of treatment if there is a clinical relapse or if there is a significant biochemical relapse even without clinical manifestation [3]. There are three groups of factors that should be considered when selecting the new line of treatment:

factors regarding the disease, previous treatment and patient factors. For example: aggressiveness of current relapse, type of prior therapies and prior responses, age, frailty and performance status in the moment of relapse [4]. Since 2015, robust data regarding doublet versus triplet regimens has been published. The control arms of these trials consisted in combination of lenalidomide and dexamethasone or bortezomib and dexamethasone and were compared to combination of carfilzomib, lenalidomide and dexamethasone (ASPIRE trial) [5]; ixazomib, lenalidomide and dexamethasone (TOURMALINE trial) [6]; elotuzumab, lenalidomide and dexamethasone (ELOQUENT trial) [7]; daratumumab, bortezomib, dexamethasone (CASTOR trial) [8]; and daratumumab, lenalidomide, dexamethasone (Pollux trial) [9]. In all trials, results confirmed that triplet regimens are superior in terms of overall response rate and progression free survival. Extended follow-up of these trials has been published, and the benefits in terms of progression free survival has been sustained. For example, the extended follow-up from Pollux trial, reported an overall response rates of 93% vs. 76%, and complete remission rates of 55% vs. 23% in daratumumab, lenalidomide and dexamethasone arm versus control arm, respectively. In terms of progression free survival, the arm including daratumumab had not achieved the median progression free survival versus a PFS of 17.5 months in control arm after a median follow-up of 33 months (HR 0.44, p<0.001). Concluding, the actual knowledge supports that treatment of relapsed patients should be started as soon as possible; based in triplet regimens, and probable as a prolonged and continuous treatment.

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**SP-06****Maintenance treatment after autologous stem cell transplantation in patients with multiple myeloma – new drugs for multiple myeloma**Angelo Maiolino<sup>1</sup>, Marcia Garnica<sup>2</sup>*<sup>1</sup>Professor of Medicine, Department of Internal Medicine, Universidade Federal do Rio de Janeiro (UFRJ). Coordinator of Hematology, Americas Centro de Oncologia Integrado; <sup>2</sup>Assistant Professor of Medicine, Department of Internal Medicine, Universidade Federal do Rio de Janeiro (UFRJ)*

Autologous stem cell transplant (ASCT) increases overall response rate and progression free survival and contributes significantly to prolong overall survival in multiple myeloma (MM) patients. This benefit, although, is not enough to avoid progression of disease. To overcome progression,

consolidation or maintenance regimens have been validated in several clinical trials [1].

Previous maintenance trials were designed based on thalidomide. Thalidomide schedules varied from study to study, with doses ranging from 100 to 400 mg/day, combine or not with steroids, and with different durations of maintenance. Seven major trials were reported, all of them showed an improvement in PFS, but only two studies showed an overall survival benefit [2–8]. Systematic review of these data confirmed the benefit of maintenance after ASCT<sup>9</sup>. However, thalidomide is associated to serious adverse events, such as peripheral neuropathy and thromboembolism. These adverse events limit prolonged intake of the drug. Overcoming this limitation, lenalidomide has been applied as an interesting choice<sup>10</sup>.

Three recent trials, based on lenalidomide, consolidated the maintenance importance, demonstrating an improving of PFS in all. In one study, lenalidomide maintenance had also impact in overall survival [11–13]. A very recent Meta-analysis with pooled data from these studies reported that overall survival was significantly better in lenalidomide arm comparing to controls. Including more than 1200 patients, the analysis showed that in 7 years, 62% of patients in maintenance were alive versus 50% in control arm (HR 0.74; p<0.01) [14].

Lenalidomide benefits was seen in most subgroups, except in high-risk cytogenetics patients. Despite the low rate of neuropathy, an important adverse event reported in lenalidomide regimen is the increased incidence of second primary malignancies. This concerning is important but should be analyzed considering the significant improvement in overall survival with lenalidomide [15].

Nowadays, maintenance with lenalidomide is considered standard of care in evidence-based guidelines from Europe and USA [16].

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#### SP-07

#### Cellular immunotherapy of hematological malignancies – APL: a special kind of AML with a different treatment

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Tumor immunotherapy has shown demonstrable efficacy in patients with cancer. The most promising results have been with T-cell-based therapies. The first successful clinical application of cell therapy is represented by allogeneic hematopoietic stem cell transplant (HSCT). Although initially considered a method of bone marrow rescue after high-dose chemotherapy, it is now well known that HSCT generates a graft-versus-leukemia response, which can be further enhanced with donor lymphocyte infusion. HSCT is still the chosen therapeutic option for most hematologic malignancies, even though it remains a dangerous procedure with many complications. Improvements in conditioning, infectious disease monitoring and management, histocompatibility testing and graft selection have successively improved outcomes, primarily due to a reduction in non-relapse mortality. Unfortunately, disease relapse remains a significant cause of treatment failure in hematological patients after HSCT, especially in acute leukemias. Thus, cancer immunologists have sought additional approaches to stimulate anti-tumor immunity in order to activate the adoptive immune system, and recent years have given us several major breakthroughs. This includes the immune treatment modalities of chimeric antigen receptor (CAR) cells, immune checkpoint-blocking antibodies, bispecific antibodies, and vaccination therapy. For space constraint, we will focalize on CAR cells.

CARs are engineered receptors that graft a defined specificity onto an immune effector cell, typically a T cell, and augment T-cell function. T cells are collected from patients or healthy donors and genetically modified to express an artificial receptor. Patients then receive chemotherapy, prior to CAR-T cell infusion, which depletes immunosuppressive cells thereby aiding CAR-T cell expansion. The extracellular domain of the CAR derives from a monoclonal antibody (usually the single chain variable fragment) which binds to antigens on cancer cells. Binding initiates signaling in the intracellular domain, CD3 $\zeta$  (the downstream signaling component of a normal T-cell receptor) and a costimulatory domain (usually 4-1BB or CD28) that allows the T-cells to have sustained antitumor activity. Each CAR T cell can kill many tumor cells, and CAR T cells may promote immune surveillance to prevent tumor recurrence. CD19 was initially chosen as tumor antigen target not only because of its frequent expression in B-cell leukemias and lymphomas but also because of its broader and higher expression relative to other potential targets, such as CD20 or CD22. Its expression in normal tissues, which is confined to the B-cell lineage, predicted that on-target and off-tumor activity would be limited to B-cell aplasia, a side effect that can be mitigated with immunoglobulin-replacement therapy. Moreover, B-cell depletion may preempt a potential antibody response to the CAR, especially its murine components.

Adult B-acute lymphoblastic leukemia (B-ALL) patients relapsing post allograft have a median survival of ~7 months. Following CAR-T cell therapy >80% of relapsed and refractory patients achieved a complete remission (CR), resulting in 50–86% of patients being alive 1 year later. Similarly, B-cell lymphoma patients with chemorefractory disease have a median survival of



just ~6 months. More than 50% were in CR following CAR-T cells, with more than half alive 18 months post infusion. A proportion of patients are expected to achieve a long-term remission but a subset of patients still relapses and, in particular in B-ALL, the majority of the relapses are caused by the loss of CD19 on leukemic cells. Several mechanisms of CD19-targeted therapy resistance have been described, including convergence of acquired mutations of the CD19 gene, alternative CD19 splicing even if these known mechanisms do not explain all cases of CD19-negative B-ALL relapses. Nevertheless, the success of CAR-T cell therapy in B-cell malignancies is unprecedented, so that the first two CAR-T cell products were licensed by the FDA in 2017. Both licensed products target CD19: Tisagenlecleucel, brought to market by Novartis, and Axicabtagene Ciloleucel, developed by Kite Pharma/Gilead, are indicated for B-ALL and B-cell lymphoma respectively. The European Medicines Agency (EMA) are reviewing both products, and a decision is expected imminently. Treatment with CAR-T cells has potentially lethal side effects. The most significant, cytokine release syndrome (CRS) and CAR-T cell-related encephalopathy syndrome (CRES), require expertise from a range of medical specialties. Currently, it is known that some patients will succumb to these complications. There is a pressing need for improved understanding and management of these iatrogenic conditions. For this reason, hospitals delivering CAR-T cell therapy need to establish a multidisciplinary team, with an education program and expertise in managing the complications of this therapy. Centers will need to be JACIE (Joint Accreditation Committee-ISCT & EBMT) accredited bone marrow transplant (BMT) units.

The efficacy of CAR therapy against B-cell cancers has fueled the search of suitable targets for the treatment of other hematologic cancers. Several candidates for multiple myeloma have been explored pre-clinically; these include kappa light chain, CD138, Lewis Y antigen, BCMA, CS1 (cell-surface glycoprotein CD2 subset 1, also called signaling lymphocytic activation molecule F7 [SLAMF7] or CD319), CD38, and integrin  $\beta$ 7. Preliminary results of recent clinical studies on BCMA targeting by CAR T cells are encouraging and registration trials by several companies are ongoing. Several targets have also been suggested for acute myeloid leukemia: CD33, CLEC12A, CD44v6, EMR2, Tim3, CD70, Lewis Y antigen, CD123, and folate receptor  $\beta$ . Clinical trials that are designed to investigate the latter three targets have already been initiated. Although the mechanism is unclear, a fatal complication involving the capillary leak syndrome after administration of CD123 CAR T cells warrants deeper investigation on this target. Lacking targets with an expression profile as favorable as CD19, the targeting of two or more antigens (combinatorial targeting) may prove to be necessary to preempt antigen escape without exacerbating toxicity. To avoid toxicity and improve efficacy several efforts have been made to design smarter CAR T cells, but still more genetic and structural modifications of CAR are needed to increase the applicability and clinical outcomes of this adoptive immunotherapy approach. Since tumor microenvironment is one of the major limiting factors for optimal function of CAR T cell therapy, further efforts must focus to overcome the microenvironment immunosuppressor effects. Combining CAR T cell therapy with other immunotherapy methods such as immune checkpoint inhibitors, cytotoxic agents, and hematopoietic stem cell transplant may lead to better clinical outcomes.

#### SP-08

##### Diagnostic and prognostic markers in ALL

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ALL can affect individuals of all ages, from newborns to the very elderly. In childhood, it is the most frequent type of cancer. It is relatively rare in young adults and older adults, while its prevalence increases in the elderly. Important advances have occurred over the years in the diagnostic work-up, prognostic stratification and treatment of adult and childhood ALL. A modern approach requires a rapid, broad and integrated biological work-up at presentation in order to enable an accurate diagnosis and to define the "profile/signature" of the neoplastic clone of each case. Optimally, this can be accomplished only through the joint effort of different laboratories dedicated to morphology/cytochemistry, immunophenotype, cytogenetics, molecular

biology, and sequencing. This integrated approach allows a correct differential diagnosis and permits to stratify patients into prognostic subgroups, optimizing treatment algorithms according to the prognostic categorization, implementation – when applicable – of targeted therapies and monitoring precisely the leukemic clone during the course of the disease. In virtually all patients with ALL minimal residual disease (MRD) can in fact be accurately monitored by flow cytometry and by PCR, and in most protocols treatment is diversified according to the MRD status after induction/consolidation therapy. Advancements in technologies are opening new avenues and indeed next generation sequencing (NGS) strategies are being widely applied to the study of acute leukemias. The integration of different sophisticated technologies is allowing to refine the genetic landscape and to identify further subgroups of ALL with a different prognostic likelihood which may in the future benefit from innovative/targeted therapeutic strategies. Within these, it is worth recalling the so-called Ph-like cases, initially identified by gene expression profiling (GEP), which carry several rearrangements that involve genes encoding tyrosine kinases, thus further confirming that these patients might benefit from TKI-based therapeutic programmes, if identified early. Another example is represented by the so-called early-T precursor ALL (ETP). First identified by flow cytometry or GEP in both children and in adults, these cases can display myeloid features and are often associated with a poor prognosis. An optimal management of ALL patients at all ages can only be accomplished through a close clinico-laboratoristic interaction at diagnosis, during the follow-up and at relapse.

#### SP-09

##### Ph-positive ALL: will we still need chemotherapy and stem cell transplantation?

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While in childhood ALL the cure rates are today in many centers/networks >80%, in adults the prognosis still remains unsatisfactory. Important advancements have nonetheless occurred in the management of adult patients based on the biology of the disease. Ph+ ALL is an illuminating example of how the understanding of a specific genetic abnormality has led over time to the use of targeted therapies. The results obtained with tyrosine kinase inhibitors (TKI) used front-line in adult Ph+ ALL have changed our approach to this condition in patients of all ages. It is thus mandatory that the abnormality is rapidly investigated at presentation. TKIs – alone or in combination with chemotherapy – have markedly improved the rates of response and overall prognosis of Ph+ ALL. The Italian cooperative group GIMEMA over the years has been using an induction strategy based on the use of a TKI (first, second, and third generation) plus steroids and CNS prophylaxis, with no systemic chemotherapy. This has led to a CR in 96–100% of patients (with no upper age limit) with no deaths in induction. A proportion of patients can obtain a complete molecular response (CMR). The percent of patients obtaining a CMR seems higher in patients treated with the 3<sup>rd</sup> generation TKI ponatinib. Some elderly patients treated only with TKIs are alive and well after many years from diagnosis. Other groups have used a combination between a TKI and de-intensified chemotherapy, in order to reduce the toxicities (and deaths) associated with conventional chemotherapy plus a TKI. With the advent of TKIs, the induction of Ph+ ALL patients – if identified promptly – is a virtually solved issue. Since patients who achieve a profound/complete molecular response fare significantly better, a CMR should be the primary endpoint of treatment. Allogeneic stem cell transplant (SCT) has always been considered the only curative strategy for Ph+ ALL patients. New strategies are however being investigated. The current GIMEMA front-line trial is using an induction-consolidation strategy based on the use of dasatinib followed by at least two cycles of the bispecific MoAb blinatumumab. The primary endpoint is the rate of CMRs. The MDACC is testing the combination of blinatumumab followed by ponatinib as front-line treatment.

If the combined use of TKI (plus steroids) and blinatumumab plus CNS prophylaxis will allow to obtain high rates of sustained marrow CMRs, the possibility that a proportion of Ph+ ALL patients may be cured/controlled without systemic chemotherapy and/or allogeneic stem cell transplant will

become a reality. This is of particular relevance as the incidence of Ph+ ALL increases with age, being approximately 50% in elderly/old patients.

#### SP-10

##### Future goals in CLL therapy

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Chemotherapy/chemoimmunotherapy have been the backbone of CLL treatment for decades. The scenario has changed in recent years following the development of mechanism-based drugs. The first have been agents capable of targeting pathways downstream of the B-cell receptor (BCR). Indeed, signaling activation via the BCR plays a primary role in driving CLL cell proliferation and survival via the cascade of involved and upregulated protein kinases. The first developed and approved drugs have been ibrutinib, a BTK (Bruton tyrosine kinase) inhibitor, and idelalisib, a PI3 kinase delta inhibitor. Ibrutinib and idelalisib (with rituximab) have been approved by EMA for the treatment of CLL patients who had received at least one line of therapy and, as first line treatment, for patients with 17p deletion/TP53 mutation. More recently, FDA and EMA have approved the use of ibrutinib front-line for all CLL patients. Great interest has been generated by the results obtained with the second generation Bcl-2 inhibitor venetoclax, which has a more profound debulking activity compared to the BCR antagonists. The results obtained have led to the approval of venetoclax for the treatment of patients with CLL with 17p deletion who have been treated with at least one prior therapy. Recently, FDA has extended the indication to all CLL patients with or without 17p deletion following at least 1 prior therapy. Venetoclax is also approved in combination with rituximab, based on the results of the Murano trial.

It is clear that the overall management of patients with CLL has changed dramatically in a short time period and is constantly evolving. This has opened challenging issues in terms of accessibility to technologies and drugs, as well as sustainability worldwide. To an extent that the management options are dramatically different according to countries/regions. In an ideal setting, patients at the time of treatment should be tested for 17p and 11q deletions, TP53 mutations and for the IGHV status. The biologic profile indeed guides treatment, when available. Patients with a 17p deletion and/or TP53 mutation should not be treated with chemoimmunotherapy, but rather with a BCR inhibitor. Since in many countries ibrutinib is approved front-line for all CLL patients, irrespective of the presence of a TP53 disruption, the challenge may be to identify patients who can be spared continuous long-term ibrutinib treatment. Indeed, evidence has been provided that short-term chemoimmunotherapy may be highly effective in patients with a favorable biologic profile. Many of them may reach a status of minimal residual disease (MRD) negativity. At the time of re-treatment, all patients should be tested/retested for 17p and 11q deletions, and for TP53 mutations. Again, this guides re-treatment decisions. Thus, all efforts should be made to enable patients to be tested at least for 17p deletion (and for TP53 mutations if 17p negative) and for the IGHV status. Recently, attention has focused also on the impact of the presence of a complex karyotype that could further refine the prognostic stratification of CLL patients.

Great interest is stemming from the possibility that through the combined use of new drugs a more profound debulking of the disease may be obtained. Indeed, preliminary data suggest that such combinations may be followed by a MRD-negative response in a high proportion of patients. If confirmed, and associated with a good safety profile, this may further change our strategy towards the management of CLL, entering a potential era of disease eradication and treatment discontinuation. This possibility, unthinkable until recently, could allow to potentially eradicate the disease over a definite time period. We are witnessing a very challenging time that may induce the hematologic community to rethink our overall approach to CLL. This clearly would make drug availability for the most frequent leukemia in the Western world a further major challenge.

#### SP-11

##### Recent advances in the management of thrombotic thrombocytopenic purpura (TTP) and their effect on the role of apheresis in its treatment

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The American Society for Apheresis (ASFA) publishes guidelines on the use of therapeutic apheresis every 3 years with the goal of providing the best available evidence for apheresis practice as well as clinical expertise. The 2016 (7th edition) ASFA Guidelines contains 87 diseases (up from 78 in the 6th ed.) and 179 indications. The presentation will discuss the principles of the ASFA guidelines and will highlight few hematological disorders represent in the ASFA therapeutic Apheresis guidelines such as Hereditary Hemochromatosis, Heparin Induced Thrombocytopenia, HELLP syndrome and red blood cell exchange to prevent alloimmunization after exposure to rhesus (D)-positive red blood cells.

#### SP-12

##### Medical decision making in apheresis medicine: when the guidelines do not cover your patient's condition

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The field of apheresis medicine continues to grow, and new technologies continue to emerge for the application of apheresis to an expanding number of disorders. Apheresis practitioners need tools that help to decide whether and how to apply apheresis to the treatment of an individual patient. The ASFA Guidelines (to be discussed by Professor Schwartz), with their fact sheets and Indication Categories, provide an excellent assessment of which disorders are indications for apheresis, where apheresis fits into the treatment scheme for these disorders, and the quality of the published evidence that underlies the recommendations. The McLeod Criteria ("plausible pathogenesis," "better blood," "perkier patients") provide a system for taking stock of the available data related to apheresis as treatment for a given disorder and of the plausibility of achieving a benefit with apheresis. The Corollary Considerations (potential reversibility with apheresis, ineffectiveness of first-line therapy, established goals for a therapeutic trial) provide a framework for incorporating clinical judgment into decision making when dealing with a disorder not reviewed in the Guidelines, and for formulating a specific, defined therapeutic trial. Equipped with these tools, we can take stock of how published evidence relates to our own knowledge, and temper them with an individualized judgment as to the correct course of action for our patient's needs and preferences, thereby reaching rational decisions in our practice of apheresis medicine.

#### SP-13

##### "Chronic myeloid leukemias" session: are the results that we can obtain with imatinib all the same in the world?

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Imatinib was the first tyrosine kinase inhibitor (TKI) used in chronic myeloid leukemia (CML) treatment and has dramatically changed the disease outcome. The ten years of follow-up report of the IRIS study, a randomized trial comparing interferon alfa and cytarabine with imatinib as initial therapy in patients with CML, showed that 83% of the patients in the imatinib group had a complete cytogenetic response and an estimated survival rate of 83%. A total of 260 patients (47.0%) were alive and still receiving study treatment at ten years (Hochaus et al., 2017). However, can we expect the same results in different populations around the world? Which are the factors that interfere with imatinib results?

For example, clinical outcomes of patients with (CML) treated in the community setting may be different from those treated in clinical trials. A study analyzed 222 patients treated in the community setting and reported that 40% of patients never had cytogenetic or molecular monitoring at any time (Di Bella et al. 2012). A study in China showed there was a significant difference in MMR rates between a group of patients with 3 or more PCR monitoring tests per year and the group of patients with 2 or fewer PCR tests per year (76.9% vs. 52.2%).

Other factors can affect imatinib efficacy, such as adherence, the price and the access to medication. A Brazilian study demonstrated that participation in clinical trials, a better quality of life and higher socioeconomic status were all related to better compliance. Patients with major molecular response (MMR) had a significantly better MPR than those who failed to achieve MMR (De Almeida et al., 2013). A retrospective study conducted in India showed that the 5-year EFS in adherent and nonadherent patients were 76.7% and 59.8% respectively ( $p=0.011$ ). Nonadherent patients were less likely to achieve complete cytogenetic responses (26% versus 44%) at any point, and it was a significant factor for EFS in a multivariate analysis (HR1.6;  $p=0.048$ ) (Ganesan et al., 2011).

Biological factors, as the type of BCR-ABL transcript, may contribute to outcome in CML. Patients with BCR-ABL e14a2 transcripts have higher rates of CCR at six months and higher rates of optimal molecular response at three months compared with e13a2 or with both transcripts, but no difference in 5-year overall, respectively (Pagnano et al., 2017; Pirfmann et al., 2017). Other studies showed a negative impact for the e13a2 transcript in OS, PFS and FFS (Castagnetti et al., 2017). E14a2 was an independent factor for the achievement of a stable deep molecular response (Breccia et al., 2018), which might impact in discontinuation trials.

Generic formulations have been used recently as a more cost-effective treatment, but few studies have prospectively evaluated the efficacy and safety of these drugs. Generic formulations of imatinib are used in India since the early 2000s (Parikh et al. 2002) in most countries since 2016. Monitoring of the short and long-term efficacy and safety is fundamental. Finally, alternatives to decrease differences and to standardize care in management across different countries includes establishing and following guidelines for CML treatment, such as ELN recommendations (Baccarani et al., 2013) or NCCN (NCCN Guidelines, 2018) and to provide access to treatment and monitoring.

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#### SP-14

##### Treatment discontinuation in chronic myeloid leukemia, when and how

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Chronic myeloid leukemia (CML) patients have reached a near-normal life expectancy thanks to tyrosine kinase inhibitors (TKI). These drugs, however, can be associated with several persistent low-grade side effects that affects quality of life, and possibly serious long-term toxicities. For a life-long lasting disease adherence may be an issue. Furthermore, growing old patients accumulate comorbidities and clinicians have to consider interactions of TKIs with concurrent treatments, whereas in youth there are other problems, for instance several studies have shown an increased incidence of spontaneous abortions and congenital malformations among women who become pregnant while taking a TKIs. Besides, as more and more patients are living with their disease, high treatment costs are becoming an important issue.

In the last years several reports have assessed the feasibility of treatment cessation in patients in persistent deep molecular response (DMR). At least 20 discontinuation studies have been reported, with more than 2000 patients involved in the analysis. Most studies included patients who discontinued imatinib but recently data have been presented on second generation TKI cessation, even though with a shorter follow up. Inclusion criteria usually required at least 3 years of TKI treatment and 2 years of deep molecular response (MR) before discontinuation. However, definitions of MR and criteria for treatment resumption varied widely among these studies: the older ones mostly required an undetectable minimal residual disease in order to stop TKI and a confirmed detectable transcript was used criteria for treatment resumption while the most recent ones included patients in Molecular Response 4 (MR4) or MR4.5, with major molecular response (MMR) as the most used criteria for treatment restart.

Consequently, treatment free remission (TFR) rate ranged between 30% to 70%, with the oldest reports mostly showing a success rate ~40% and the more recent ones, which employed less stringent criteria for treatment discontinuation and therapy resumption, ~60%. Treatment discontinuation was proven to be safe, since patients who restarted treatment regained a deep MR and no progression was observed in all the reports presented so far, with the exception of a patient in the A-STIM trial who molecularly relapsed, re-achieved a deep MR after restarting treatment and later suddenly progressed to lymphoid blast crisis.

These studies also tried to identify predictive factors of a successful TFR but the results have been inconsistent. However, treatment duration has been shown to be a significant factor in several reports, including both the STIM and the EUROSKI trials. Sokal score, MR duration and response to first line TKI treatment are also quite frequently reported as predictive factors, and it has been proposed to take them into account along with treatment duration when considering a patient for a TFR attempt. At present, although definitive recommendations for treatment discontinuation cannot be given, minimum requirement for stopping treatment have been proposed: achievement of

MR4 or lower response maintained for 2 years; follow-up in a center where standardized molecular biology is performed. Nowadays inclusion of patients in clinical trials is suggested whenever possible but many physicians have already started to introduce TKI discontinuation in the clinical practice.

### SP-15

#### A translational perspective on diffuse large B-cell lymphoma

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Diffuse large B-cell lymphoma (DLBCL) is the most common form of B cell non-Hodgkin lymphoma (B-NHL) and accounts for ~40% of all new diagnoses of B-NHL in adulthood. The neoplastic cells of DLBCL express B-cell markers, including CD20, and surface or cytoplasmic immunoglobulin is often demonstrated. CD10, BCL6, and IRF4/MUM1 are variably expressed, and the proliferation index as measured by Ki67 staining is typically high. Though the etiology of DLBCL is unknown in most cases, it can arise from transformation of an indolent lymphoma, such as follicular lymphoma and chronic lymphocytic leukaemia. More than half of DLBCL patients can be cured with standard R-CHOP regimens, however approximately 30 to 40% of patients will develop relapsed/refractory disease that remains a major cause of morbidity and mortality due to the limited therapeutic options [1–3].

The heterogeneous disease entities all included in the same diagnostic grouping is a major reason of different treatment response among patients. Therefore, researchers and clinicians have focused to investigate separate entities of DLBCL. Great strides have been made in classifying different subgroups of DLBCL along with identification of their corresponding pathogenic drivers, largely through the discovery of genomic techniques such as next generation sequencing (NGS) and gene expression profiling (GEP) [4]. GEP has identified subgroups of DLBCL (GCB (germinal center B-cell-like; originating from centroblasts in the dark zone), ABC (activated B-cell-like; derived from activated B cells that are in transition to becoming plasmablasts), and unclassified DLBCL) according to cell of origin that are associated with a differential response to chemotherapy and biological features. The ABC subtype, for example, is characterized by constitutive activation of nuclear factor kappa B (NF- $\kappa$ B) pathway and has a more aggressive clinical course and more unfavorable outcome than GCB-DLBCL [5].

NGS has been primarily used to identify potentially targetable somatic mutations in DLBCL to improve treatment. Consistent with their clinical and genetic (clonal) heterogeneity, on average, 30 to more than 100 genetics aberrations per case have been identified in DLBCL including aberrant somatic hypermutations, nonrandom chromosomal deletions, balanced reciprocal translocations deregulating the expression of proto-oncogene products such as BCL6, REL, BCL2, or c-MYC, and often associated with dysregulated apoptosis or defective DNA repair [6,7]. In a recent study, Reddy et al. screened 1001 newly diagnosed DLBCL patients and identified 150 putative driver genes. Furthermore, CRISPR based functional screening results indicated 35 genetic drivers as potentially targetable genes in DLBCL. NGS studies have also profiled specific alterations in GCB and ABC subtypes; *EZH2*, *SGK1*, *GNA13*, *SOCS1*, *STAT6*, and *TNFRSF14* have more frequently mutated in GCB-DLBCLs, while *ETV6*, *MYD88*, *PIM1*, and *TBL1XR1* have more frequently mutated in ABC DLBCLs [8]. In another study, Schmitz et al. performed multiplatform genomic analysis in 574 DLBCL biopsy samples to identify genetic subtypes with distinct responses to therapy. They identified four genetic subtypes in DLBCL, termed MCD (based on the co-occurrence of *MYD88*<sup>L265P</sup> and *CD79* mutations), BN2 (based on *BCL6* fusions and *NOTCH2* mutations), N1 (based on *NOTCH1* mutations), and EZB (based on *EZH2* mutations and *BCL2* translocations). BN2 and EZB subtypes have been associated with favorable survival in contrast; MCD and N1 subtypes have showed inferior outcomes [9]. Functional investigation of the mutant alleles and conceptual understanding of the complexity will enable the tailor therapy in DLBCL.

The availability of sophisticated molecular methods has not only increased our understanding of DLBCL subtypes and the molecular basis of chemotherapy resistance but also led to the development of new noninvasive monitoring tools. Deep sequencing of circulating tumour DNA (ctDNA) from liquid

biopsy (serum, plasma etc.) has recently emerged as a promising noninvasive approach for analyzing genetic diversity, clonal evolution and residual disease in DLBCL [10].

Continued improvements in the understanding of the molecular biology of DLBCL with clinical characteristics and noninvasive monitoring of the disease will provide new avenues for genomic research and may aid in clinical decisions.

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### SP-16

#### Marginal zone lymphoma

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Marginal zone lymphomas represent heterogeneous, indolent, chronic B-cell lymphomas. Three subtypes are recognized: the extranodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT lymphoma), the most common entity of MZL, the splenic marginal zone lymphoma (SMZL) and the nodal marginal zone lymphoma (NMZL). Two novel entities, non-chronic lymphocytic leukemia (non-CLL) monoclonal B-cell lymphocytosis (MBL), probably closely related to SMZL, and a broad category of less well-defined provisional entities primarily involving the spleen, termed splenic B-cell lymphoma/leukemia, unclassifiable (SLLU) have been included in the last WHO classification. The treatment modalities vary considerably based on subtype and site of involvement. Radiotherapy is the preferred choice for localized stages in EMZL not dependent to microbial pathogens and in patients who failed antibiotic therapy or present local recurrence. Rituximab alone or combined with chemotherapy can be considered in patients with relapsed/refractory localized disease or in disseminated cases. In SMZL, the currently used therapies for symptomatic patients, are rituximab alone with or without maintenance or splenectomy when massive splenomegaly. In NMZL, a similar strategy as that used for FL is proposed. Chemotherapy-free approaches have shown some activity but need further investigations. A better understanding of the pathogenesis of MALT lymphoma, identifying key molecules in the development or progression of MZLs, may provide the rationale for clinical trials. Identification of high-risk patients and “risk-adapted” strategies are strongly advisable.



**SP-17****Essential treatments of non-Hodgkin's lymphoma**

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In this report we will discuss the three most challenging types of non-Hodgkin's lymphomas: follicular (FL), mantle cell (MCL) and diffuse large B cell lymphomas (DLBCL). FL and MCL are described as low-grade NHL and DLBCL is the most frequent aggressive NHL.

Low-grade non-Hodgkin lymphomas (LG-NHL), also known as indolent lymphomas, include a peculiar group, generally characterized by incomplete response to therapy, poor perspective of cure and frequent relapses [1]. Histologically, these neoplasms display predominantly small lymphoid cells with condensed chromatin, small quantities of activated cells, a diffuse or nodular architectural pattern and low mitotic activity. The most prevalent subtypes of LG-NHL are B-cell lymphomas: follicular lymphoma (FL; comprising 29% of all NHL), lymphocytic lymphoma (12%), mucosa-associated lymphoid tissue (MALT) lymphoma (9%) and mantle cell lymphoma (MCL; 7%) [2].

Indolent clinical courses with prolonged survival are expected for all these entities, with the remarkable exception of MCL, which presents with a more aggressive clinical behavior [3]. Special attention should be brought to FL and MCL due to its more aggressive clinical features that often lead to treatment challenges. Currently, the main first-line therapeutic choices for LG-NHL include an anti-CD20 monoclonal antibody (rituximab) combined with chemotherapy. In spite of greatly improving survival, the inclusion of rituximab seemed not to change the paradigm of incurable disease for LG-NHL [4,5]. Complementarily, most LG-NHL cohorts did not reach a sufficiently long follow-up time to observe therapeutic impact on the risk of death, such as that observed for rituximab maintenance in FL [6,7].

An increasing number of studies have helped to elucidate both the biology of the neoplastic cells and the composition of the tumor microenvironment in LG-NHL, especially for FL [8–12] and, to a lesser extent, for MCL [13,14] and lymphocytic lymphoma [15,16]. As a result of these investigations, new therapeutic approaches beyond rituximab appeared for LG-NHL, such as lenalidomide (an immunomodulatory imide drug), and ibrutinib (Bcr tyrosine-kinase inhibitor) [17–19]. Novel therapies introduced a new era in LG-NHL research and treatment, marked by transduction pathway targeting. This scenario stresses the need for studies that address the natural history of these diseases so far, enabling future comparisons in new transitional contexts.

For DLBCL the first question is: "Is R-CHOP adequate for aged less than 60?" The answer is yes, for the majority of patients. In 1993, Fisher confirms first-generation chemotherapy (CT) CHOP as first-line therapy compared to second- and third-generation CT [20]. So, how to improve CHOP? More drugs? dose-intensification? myeloablative consolidation? addition of Rituximab or adding radiotherapy? The French group demonstrated that R-ACVBP was superior to R-CHOP [21]. Dose-dense therapy, with shorter intervals of CT, did not improve survival when Rituximab was added [22]. High dose CT, promised in phase II previous studies still in CHOP era, did not demonstrated advantages in Rituximab era [23]. Meta-analysis including 15 prospective and control studies with more than 2000 patients did not demonstrated advantage of HDCT as consolidation [24]. Important and permanent conclusion was that Rituximab added to CHOP CT improve survival, including high risk young patients [25]. However, Rituximab as maintenance did not demonstrated advantages in terms of EFS and OS. Radiotherapy demonstrated essential in patients presenting "bulky" disease and partial remission after R-CHOP CT [26]. Strategies of "precision medicine" as interim PET-driven treatment and Cell of origin-driven treatment are now included in clinical practices. Predictive value of interim PET in DLBCL was demonstrated. Gene expression profiling and immunohistochemistry help to selected patients for other therapeutic approaches in Germinal-Center B type or double/triple hit types [27]. In this perspective, introduction of Bortezomib, particularly in ABC DLBCL, Ara-C in clinical approach, could improve survival [28]. New drugs as ibrutinib could be used in relapsed ABC DLBCL type or in first-line associated with R-CHOP [29]. In conclusion, R-CHOP still remains the standard therapy

for most patients affected by DLBCL. However, it is unsatisfactory for high-risk and in some biological types of DLBCL.

For elderly patients presenting DLBCL what can we do better? Can we treat more patients with curative intent? How can we improve assessment of these patients? The ESMO guideline for patients over 60, includes three groups: health, >80 without cardiac dysfunction and Unfit or cardiac dysfunction. For the first group, curative intent using R-CHOP 21×8 or 21×6 (for low risk) could be adequate. For patients >80 without cardiac dysfunction, the use of attenuated regimen like mini R-CHOP×6 is suggested. For Unfit and/or presenting cardiac dysfunction, R-CEOP or R-GCVP (gemcitabine containing regimen) or palliative care may be proposed. A frequent problem in this group of patients is the early mortality particularly in the first cycle. The German group suggested a prophase with vincristine and prednisone with the rationale of improvement of performance status, prevention of lysis tumor syndrome and amelioration of the first-cycle effect. In elderly, increasing knowledge of (different) biology and increase recruitment to clinical trial are needed.

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## SP-18

### First-line treatment of Hodgkin lymphoma

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Thanks to the optimal use of available modern treatment modalities, Hodgkin lymphoma (HL) is now a success story of modern oncology, with 5-year survival rates exceeding 80–85% for most patients.

However, this success comes at considerable human cost, including treatment-related late effects, compromised health-related quality of life (HRQL); and potential loss of young lives.

In order to achieve an optimal therapeutic strategy with the highest cure rate and the least morbidity and mortality, the accurate staging of the disease and the search for presence of adverse prognostic factors still remain milestones in defining the more appropriate first line treatment. A risk-adapted treatment, based on well-established pretreatment prognostic factors has been widely

adopted since at least three decades. According to this, three risk categories were defined: limited, intermediate and advanced disease. More recently, the response-oriented approach has been demonstrated able in further improving the risk to benefit ratio.

The response to treatment is an important predictor of outcome, especially because the non-responders have worse prognosis and need to be rapidly identified to decrease failure rates. Different trials worldwide have shown [18F]-fluoro-2-deoxy-D-glucose-PET (FDG-PET) as a strong independent prognostic factor for monitoring HL patients after 2-3 cycles of chemotherapy. This method is already considered the gold standard for the assessment of response and plays an essential role through the identification of patients who might be eligible for less or more intensive approach. The 2018 Hodgkin lymphoma ESMO Clinical Practice Guidelines for diagnosis and treatment for the first time includes one approach not guided by interim PET and one PET-guided approach.

#### Treatment of limited-stage disease

Combined-modality treatment consisting of a brief ChT followed by RT was shown to result in superior disease control compared with RT alone.

Although two or three cycles of doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) followed by conventionally fractionated RT represent the standard of care for limited-stage HL, a PET oriented decision making has to be considered. In fact, as demonstrated by the RAPID and H10 Trials, patients with early negative PET and treated with ChT alone still have a good overall prognosis. Thus, this approach may be offered to individual patients when the late risk of delivering RT is thought to outweigh the short-term benefit of improved disease control.

On the other side, early treatment intensification appears to improve the prognosis of patients with a positive interim PET. The H10 study revealed a significantly reduced relapse rate in those patients with a positive interim PET after two cycles of ABVD who completed ChT with two cycles of bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose (BEACOPP-Esc) instead of additional cycles of ABVD before involved-node RT (INRT).

#### Intermediate-stage

HL is usually treated with combined modality approaches. Four cycles of ABVD followed by conventionally fractionated RT at 30Gy are widely considered the standard of care for intermediate stage HL. However, early treatment intensification with BEACOPP-Esc appears to improve the prognosis of patients with a positive interim PET.

#### Advanced-stage

For patients up to the age of 60, six to eight cycles of ABVD or six cycles of BEACOPP-Esc followed by involved site RT on residual initially bulky sites represent today a widely accepted initial approach for treating patients with advanced stage disease. BEACOPP-Esc is associated with a higher response rate, although some concern on long term toxicity still exists.

With the advent of FDG PET, a response adapted strategy has become a standard approach, offering the opportunity to better tailoring treatment intensity to the right patients, i.e. to de-escalate treatment in the best responders, and to limit a more aggressive treatment only to poor responders. Recently, brentuximab vedotin has been demonstrated one of the most effective single agent in patients with relapsed HL, and his role in front line also emerged, suggesting that a further improvement in curability of HL it is possible.

#### What is next?

In addition to i) a further fine tuning in timing of early FDG-PET response assessment (after two or even one course of ChT), and ii) waiting for the possible introduction in the first line armamentarium of new drugs like the anti PD1 family, efforts in improving clinical decision making for patients and providers may represent a new challenge. It is now evident that in addition to expanding treatment options, we need to establish modern, robust, and dynamic decision models for short-term disease outcomes and longer-term estimates for late effects risks and impacts on HRQL.

**SP-19****When do we prefer chemo-free regimens in mantle cell lymphoma?**

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Mantle cell lymphoma (MCL) is a rare form of lymphoma, constituting 5–7% of Non-Hodgkin Lymphomas (NHL). Historically, MCL was associated with a median survival of only 3–5 years [1,2]. During the past decades the outcome has improved especially for young patients, by an intensified front-line regimen including rituximab and ARA-C, followed by consolidation with high dose therapy and autologous stem cell transplantation (ASCT) [3,4]. However, only 24% of patients can undergo ASCT because of well documented toxicity of chemotherapy [2].

Discrepancy between trials and real-life data is remarkable. High risk MCL Prognostic Index (MIPI) patients constituted 43% of patient population in the Swedish and Danish lymphoma registry, which included a total of 1389 patients diagnosed with MCL between the years 2000 and 2011 [2]. On the contrary, Nordic MCL-2 trial [5] and European Mantle Cell Lymphoma Network MCL Younger trial [4] cohorts include only 23% and 14% high risk MIPI patients, respectively. In these trials clinical and biological diversity of MCL has been underestimated and, 85% of patients were classified as having a low or intermediate risk disease, resulting in superior survival rates. Large cohorts of patients were routinely treated uniformly aggressively, without regarding specific clinical or biological characteristics. This approach in the trials led to universally aggressive treatment strategy in MCL, causing an illusion that aggressive therapy delivers better outcome [6].

On the other hand, TP53 mutation identifies younger MCL patients who do not benefit from intensive chemo-immunotherapy. When they stratified 183 young MCL patients from MCL2 and MCL 3 trials, TP53 mutated cases constitutes 11% of all and they had a dismal outcome with a median survival of only 1.8 years, 50% of them relapsing at 1 year. TP53 mutation was significantly associated with high Ki67 index (Ki67 >30%), blastoid morphology, high MIPI score, inferior responses to both induction and high dose chemotherapy [7]. Several chemo-free regimens, such as Bortezomib [8], Tamsirolimus [9], Ibrutinib [10], Lenalidomide [11], Acalabrutinib [12] have recently been approved by FDA. Among these agents, Ibrutinib deserves further attention. Single agent ibrutinib resulted in an overall response rate (ORR) of 68%, complete remission (CR) rate of 21% and median progression free survival (PFS) of 13.9 months in a heavily pretreated MCL cohort, 86% of which had intermediate or high MIPI score [10]. Median duration of response was 4.5 years in patients achieving CR and patients who had single prior line of therapy had two times longer duration of response compared to patients with >1 prior line of therapy [13]. Although Ibrutinib is ineffective in blastoid histology, recently published PHILEMON trial showed that the combination of ibrutinib with lenalidomide and rituximab resulted in an ORR of 66% and CR rate of 64% in a cohort of 50 relapsed or refractory MCL patients. The most striking result was the ORR of 73% and CR of 64% among eleven TP53 mutated patients, which means that there was no significant difference compared to TP53 unmutated cases [14]. In the recently published AIM trial, Ibrutinib and Venetoclax combination was used in twenty-four MCL patients, 75% of them having high risk MIPI score. The CR rate was reported to be 62% and of 12 patients with TP53 aberrations, six (50%) achieved CR and, minimal residual disease was found negative in 10 of 13 assessable patients (77%) [15]. Ibrutinib for bridging to allogeneic hematopoietic stem cell transplantation in 22 patients with MCL resulted in non-relapse mortality rate of 5% and relapse incidence of 19%. The preliminary results showed PFS rate of 76% and overall survival rate of 86% at 1 year, showing that bridging to transplantation with Ibrutinib is feasible [16].

Two trials assessing first line treatment with chemo-free agents were published in the literature. Lenalidomide plus rituximab as initial treatment was evaluated in a cohort of thirty-eight MCL patients, 32% of them having high risk MIPI score. The results revealed ORR of 92%, with a CR rate of 64%, PFS being 85% and OS being 97% at 2 years [17]. In another study which was presented in ASH 2016, induction with Ibrutinib plus rituximab followed by shortened cycles of chemo-immunotherapy was performed in fifty young newly diagnosed MCL patients, resulting in an ORR rate of 100% and a CR

rate of 72% following only induction (before consolidation with chemo-immunotherapy). Preliminary data indicate that the chemo-free induction with ibrutinib plus rituximab in newly diagnosed MCL was efficacious and well tolerated [18]. Efficacy and safety may provide a window of opportunity for less chemotherapy need for consolidation.

To conclude, the backbone of the treatment in MCL is chemo-immunotherapy and, although outcome in MCL is improving, there is room for progress particularly for high risk and TP53 mutated MCL. Trials' cohorts do not exactly reflect real life patients. Introduction of Ibrutinib is a significant advance for MCL treatment. TP53 aberrations impact on outcome and it is not yet clear how to confront; however, early evidence supports administration of combined chemo-free regimens.

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### SP-20

#### From allogenic transplantation to precision immune therapy: the role of effector cells

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Allogenic transplantation (AlloT) was used in the early fifties, to replace bone marrow progenitor cells (BMPCs) after radiation injury, then developed to replace leukemic BMPCs by normal BMPCs. In addition, BMPCs include also immune cells, making AlloT as an immune therapy to control or to eradicate leukemic residual disease. AlloT was proposed to treat all the hematological malignancies in the situation of advanced disease or disease associated with very poor prognosis. Balance between efficacy and toxicity is associated to Graft Versus Tumor (or Leukemia) (GVT/L) and Graft Versus Host (GVH). Modern immune therapy began with Coley who stimulated immune system through inflammation. Paul Ehrlich developed the concept of an immune protection against cancer, and in early sixties, Burnet and others defined the “self” and “nonself”, leading to the concept of cancer immunosurveillance. However, AlloT failed to get major responses in solid cancers, questioning on the accessibility and the targeting of cancer cells by immune effector cells. In solid cancers, developments included the direct use of cytokines and immune effector cells, ex vivo activated and amplified, named lymphokine-activated killer cells (LAK) or tumor-infiltrating lymphocytes (TIL) considered as antigen-specific T-lymphocytes. However, these cell-drug therapies were heterogeneous mixtures between killer cells and also T regulators (Tregs) that reduce the anti-tumor effect. In addition, clinical comparison between autologous and allogenic transplantation, particularly in lymphoid malignancies, highlighted the balance between relapse-mortality and mortality due to the procedure. So, the differences between “self” and “nonself” were supported not only by cytotoxic T-cells (CTLs), but also by natural killer (NK) and NKT lymphocytes through killer-inhibitory receptor (KIR) molecule mismatch. After discovering circulating messengers, named cytokines or chemokines, immunologists focused on cell membrane receptors, signal transduction factors and more recently on membrane checkpoint molecules and their particular functional intrication. However, we have to keep in mind that these tools are acting on specific cells and, at the end, we need to get them at the right place, in sufficient number and with effective targeting. Finally, immune therapy has to become precision immune therapy, with the right choice for the right patient, a situation that could mix different tools. In addition, HLA-haplo-identical (HLA-HI) AlloT could be a platform for combining cellular therapy and immune checkpoint inhibitors, a basis for associating other immune modifiers or specific cell-drugs. Vaccination effect particularly using APAVAC® (Urodelia Inc., France) could prolong Chimeric-Antigen T-cells (CAR-T cells) or CAR-NK or be prolonged by amplifying specific CTL, NK, NKT or and  $\gamma\delta$  T-lymphocytes.

## Speaker Presentations – Oncology Program

### SP-21

#### Systemic therapy for potentially resectable metastatic rectal cancer

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The treatment of metastatic colorectal cancer (mCRC) patients relies on a different philosophy than other metastatic tumors because of the potential of cure. Patient-related, disease-related and treatment-related variables have an important impact disease prognosis. A multidisciplinary council should be incorporated to treatment decision all relevant active role players of therapeutic process. Colorectal cancer can present as synchronous or metachronous metastatic; main site of metastasis is liver and/or lung. Overall, mCRC patients can be classified (mainly for liver metastatic cases) as resectable, potentially resectable/convertible, and unresectable. Different criteria for these definitions have been offered yet a definitive guideline was not set. In general, the key consideration for this classification is probability of achieving complete resection with negative margins and maintaining adequate organ function. The term “conversion” has been proposed to designate to change the status of isolated, unresectable metastatic patients into resectable with perioperative neoadjuvant treatment. Systemic chemotherapy; its role, optimal timing and schedule are ongoing debates for potentially resectable mCRC. Perioperative chemotherapy may provide the advantages of possible micrometastatic disease treatment, testing of biologic behaviour and possible facilitation of impossible frontline resection. Oxaliplatin-, irinotecan-based treatment with or without VEGF or EGFR directed therapies could be offered to patients for 6 months as a perioperative approach. A progression free survival (PFS) benefit have been shown with fluorouracil-oxaliplatin based chemotherapy but this benefit did not reflect to overall survival. Previous chemotherapy exposure, the degree of benefit achieved with this agents and specific adverse events related to them are important while choosing the perioperative regimen. Besides, chemotherapeutics may be associated with adverse outcomes such as irinotecan-based steatohepatitis, oxaliplatin based sinusoidal liver injury and bevacizumab related perioperative bleeding and thrombosis. The optimal time interval between surgery and last chemotherapy cycle should be at least six to eight weeks if bevacizumab was applied in order to avoid adverse events. EGFR directed therapies have conflicting results for borderline resectable mCRC patient treatments. EPOC study which involves patients treated with FOLFOX-cetuximab showed detrimental results in experimental arm (14.1 versus 20.5 months; hazard ratio 1.48;  $p=0.03$ ). NCCN guidelines suggest FOLFOX, FOLFIRI (irinotecan-FU-Leucovorin) or CAPOX (capecitabine and oxaliplatin) with/out bevacizumab; FOLFIRI with/out cetuximab or panitumumab; or FOLFOX with or without panitumumab or cetuximab (if RAS wild type). FOLFOXIRI (Fluorouracil-Oxaliplatin-Irinotecan in modified doses) regimen with or without bevacizumab have been shown to be associated with higher resection rates in some trials however controversial results also exist. Metastatic rectal carcinoma patients may differ than colon cancer patients because of potential need for locoregional and symptomatic control. Neoadjuvant chemoradiation can be offered as a part of neoadjuvant therapy for these patients. Overall, the likelihood of achieving R0 resection in initially unresectable metastatic patients is 10–15%. Five-year survival rate for these patients can reach to 30–35% which is better than treatment with chemotherapy only (5-year survival rate 10–11%). A number of new agents (afibercept, regorafenib, and TAS-01) and immunotherapeutics in dMMR tumors have been offered for mCRC patients however their role in potentially resectable patients have yet to be defined.

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## SP-22

### Overcoming resistance in Her2-positive metastatic breast cancer

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In the last 30 years, one of the most remarkable benefit in survival has been observed in Her2-positive breast cancer subgroup, with a median overall survival surpassing 50 months in advanced setting.

Trastuzumab, pertuzumab, TDM1, lapatinib and neratinib are the standard approved antiHer2 targeted therapies.

In the metastatic setting, combination of trastuzumab, pertuzumab and taxane has been the standard first line therapy after the reported CLEOPATRA trial. In this trial, addition of pertuzumab to taxane and trastuzumab resulted, statistically significant, superior progression-free (PFS) and overall survival (OS) (18.7 and 56.5 months, respectively). However, only about 10% of the patients were pre-treated with trastuzumab and at least 12 months of drug-free period was required for the inclusion. Additionally, central nervous system metastasis was a disclusion criteria.

In the second line, TDM-1 monotherapy was superior than lapatinib and capecitabine combination in terms of overall survival (4 months benefit) in the EMILIA trial and superior than any chemotherapy choice of the physician (6.9 months benefit in OS) in TH3RESA trial. In both trials only about 11% of patients had CNS metastasis. In TH3RESA trial, all patients were pre-treated with antiHer2-targeted therapies, trastuzumab and lapatinib.

In the third-line and later, lapatinib and capecitabine, trastuzumab and vinorelbine (HERNATA), trastuzumab and lapatinib, trastuzumab and eribulin or gemcitabine combinations are the reasonable options.

There are still unanswered questions in standard therapy options. First, is TDM1 use effective after exposure to pertuzumab? In a series of 78 patients, overall response rate (ORR) of 17.9% and one third of the patients still on therapy over 6 months, was reported. Second question is the effectiveness of pertuzumab in trastuzumab pre-treated patients. In real-life data (PHEREXA trial) addition of pertuzumab to trastuzumab and capecitabine resulted a PFS and OS advantage of 1.1 and 8 months, respectively. Another question is to overcome resistance in hormon responsive subgroup of Her2 positive breast cancers. In the PERTAIN trial, addition of pertuzumab to trastuzumab and hormonal therapy yielded a PFS advantage of 4 months. In this trial, 57% of the patients were pretreated with chemotherapy.

Molecular biomarkers have still been investigated to find the optimal sequence, benefit from antiHer2 therapy and decrease resistance to antiHer2 treatment. In studies of CLEOPATRA and EMILIA about one-third of the patients had PiK3CA mutations and correlated with bad prognosis. Patients with PiK3CA mutations were reported to benefit more from dual antiHer2 therapy and TDM1, correspondingly. HER2 mRNA is another candidate predictive biomarker that correlates with antiHer2 therapy benefit. Tumor infiltrating T cells (TIL) were reported to correlate with good prognosis in CLEOPATRA trial. Studies on new mutations developing during antiHer2 therapy, liquid biopsy, circulating tumor cells methodology and functional imaging are ongoing and will give us a new horizon.

New antiHer2 agent are under development. Margetuximab, Fc optimized antiHer2 monoclonal antibody, have been investigated in a phase III SOPHIA trial, in patients pretreated with at least two lines of antiHer2 therapy, and the results are awaited, eagerly. Her3 targeted patritumumab in combination with trastuzumab is under evaluation in a phase II trial. There are also encouraging studies with bi-specific antibodies as ZW25 (HER2/HER2), MCLA-128 (HER2/HER3) and antibody-drug conjugates such as DS-8201, SYD-0985, XMT-1522, MEDI-4276 and MM-302..

Another strategy to overcome resistance is to combine antiHer2 therapy with PI3K-mTor pathway inhibitors as everolimus or taselelisib, alpelisip or buparlisip.

Immunotherapy is an emerging era in the treatment of Her2 positive breast carcinoma and new studies are on the way.

## SP-23

### Precision immune medicine for cancer

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Cancer cell growth is associated to an immune surveillance failure, making the restore to an immune control of cancer cells as a major therapeutic way. The extraordinary progress in biological knowledge makes possible to obtain efficient bio-clinical tools and to better define therapeutic strategies for Immune Precision Therapy. Monoclonal antibodies represented one of the most important clinical success stories, particularly for B-cell lymphoproliferative disorders with rituximab, and more recently, firstly by inhibiting immune checkpoints within the tumor microenvironment that limit immune suppression, secondly by enhancing some immune functions through other different targets. The aim is to control cancer cells, a situation that could be measured biologically by lowering/eliminating cancer residual cells, and clinically by improving the response duration with no or low toxicity. At the end, this effect is supported by enhancing the number, the functions and the activity of the immune effector cells, including natural killer (NK), NKT,  $\gamma\delta$ T, cytotoxic T-cells directly by suppressing the specific recognition through antigen presentation or indirectly through vaccines, and by lowering the functions of the immune suppressive cells. Beyond these new tools and their personalized usage, new considerations have to be taken in account, such as epigenetic regulation particularly from microbiota, to evaluate cellular metabolism, considering transversal cellular functions and regarding that biological targeting is evaluated at a tissue and body level. So, precision immune medicine is the new step and has to take into account the immune homeostasy balancing between Immunosenescence, immuno-exhaustion and immune activity, patient per patient. Genetic context, epigenetic control and the capacity of the organism to control latent infections represent the different aspects of this new approach of the Precision Immune Medicine.

## SP-24

### The bioinformatics of precision cancer medicine

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Precision medicine studies are for detection of best therapeutic protocol and to avoid any complications. Novel technologies enforce and accelerate rapid development in this area and big gene packages can be evaluated at the same time. Although this multiplex study seems like an advantage, in case of a wrongful evaluation of this big data, it is very misleading.

If we just focus on the cancer cells and their genetic variations only, we will miss the big picture. Both cancer cell variation studies, germline studies and clinical genetic evaluations must be harmonized in all cases. The main list of titles of genetic background of precision medicine are given below.

#### Variations in cancer cells

*Triggering mutations;* Somatic mutations necessary for the start-up of cancer. *Progression mutations;* Secondary mutations causing disease progression and drug resistance.

*Novel variations of drug metabolism genes; Mutations in drug metabolism genes which effects drug metabolism just in cancer cells.*

#### **Germline variations**

*Familial cancer gene variations; These germline mutations sometimes trigger cancer but sometimes their variations just enforcing cancer progression or causes secondary cancers in immune compromised cancer patient.*

*Drug metabolism variations; These genetic changes cause variations in drug metabolism rate and side effects due to metabolites.*

*Other genetic diseases – effect on metabolism; Frequency of genetic disorders is very frequent in population and nearly 10-20% or them rare disorders. Most of them have a multisystemic effect in patients and may change therapeutic steps and success rate.*

*Germline mutations in cancer causing genes (KRAS-NRAS-BRAF); Germline mutations in these genes also causes RASopathies, a common group of genetic disorders (1/1000). Mutations in high-risk codons of tyrosine kinase activation are also frequent germline mutation targets for RASopathies. It sometimes causes faulty evaluations.*

*In summary; bioinformatics and clinical genetic evaluation processes must run together for an effective personalized medicine study to avoid complications and higher success rates in cancer therapy.*

## **Speaker Presentations – Pediatric Hematology Program**

### **SP-25**

#### **A better understanding of sickle cell trait**

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Sickle cell trait is a condition in which persons are heterozygous for the sickle cell mutation in the beta-globin gene, where they have inherited normal adult Hemoglobin A from one parent, and sickle Hb (Hb S) from another and they are termed as having hemoglobin AS (HbAS). It's very common condition worldwide, particularly in Africa, Middle East and India. There is an estimated 9.0% of blacks, 0.7% of Hispanics, and 1.5% of babies born in the United States have sickle cell trait. However, it is found in much higher percentages in Africa in places such as Nigeria where >25% of population are SCT and eastern province of Saudi Arabia and tribal areas of India. SCT patients have positive sickling test, and confirmed by having Hb S level around 40% confirmed on HPLC or other confirmatory test. If patient has co-inherited alpha thalassemia, then Hb S level is usually lower than that. One of the reasons for this high prevalence of SCT is its protective effect against the most severe form of malaria (malaria Falciparum) and hence it is usually found in areas endemic for malaria. Usually SCT patients are asymptomatic and these patients are picked incidentally or in routine screening programs, however several complications have been increasingly linked to SCT, including splenic infarction particularly at high altitude or during infection, increasing risk of venous thromboembolism and renal damage. The most serious complication is its effect on the kidney, with an increased risk of renal medullary cell carcinoma, hematuria and nephropathy, and inability to concentrate urine (hyposthenuria). These patients have increased risk of end stage renal disease and increased risk of albuminuria. Recently there is an increasing report of sudden death during strenuous exercises and exposure to heat leading to rhabdomyolysis and death particularly among army personals (on training) and athletes leading to authorities to demand pre-testing athletes before participating in high-level sport activities.

The link between SCT and both maternal and fetal pregnancy-related complications require well-designed studies, although asymptomatic bacteriuria has shown the most consistent associations with SCT in the literature. There is a strong evidence supporting practicing prevention programs in areas of high incidence where candidates are tested for the gene pre-marriage or early as needed and appropriate counselling is given.

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### **SP-26**

#### **New therapies in sickle cell disease**

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Sickle Cell Disease (SCD) is the most common inherited blood disorder in the world. The polymerisation of HbS leads to a chronic haemolytic anemia and a wide range of acute and chronic complications related to vaso-occlusion, inflammation and tissue ischemia and injury. There is significant heterogeneity in the clinical course of the disease with a spectrum comprising of patients with variable severe acute and chronic complications to patients requiring no treatment. Hydroxyurea, initially approved for the treatment of SCD adult patients by FDA in 1998 and approved by EMA for adults and children in 2007, remains the cornerstone of treatment but it is not administered to all patients and a proportion of them do not respond. Chronic blood transfusion or exchange transfusion programmes, indicated for specific complications are the other main modality used for SCD patients but they also not free of complications. Allogeneic stem cell transplantation represents the only established curative treatment, but it is associated with high morbidity and is not available to the majority of patients.

Considering the global burden of the disease there are definitely unmet clinical needs, which, along with a better understanding of the disease pathophysiology, have led to an increasing interest in the development of new treatment strategies. Completion of multicentre randomized clinical trials is also considered an achievement, compared to low recruitment rates and other difficulties that existed in the past and has also contributed significantly. Pathophysiologic mechanisms targeted by new treatment strategies include HbF induction, HbS polymerisation/sickling, cell adhesion to the endothelium, inflammation, oxidative stress, rheology and vascular flow, coagulation and, ultimately, correction of the abnormal gene.

Induction of Hemoglobin F (HbF) production, which is well known to prevent HbS sickling within red cells, is the most important mechanism of action of hydroxyurea. Several HbF inducing agents are currently evaluated in clinical trials including hypomethylating agents and histone deacetylase (HDAC) inhibitors. Limited data are available with 5-azacytidine. The oral butyrate HQK1001 did not give positive results in several trials and trials with panobinostat are ongoing. Limited data are available with pomalidomide, currently investigated in a phase 1 trial.

Apart from HbF induction, other antisickling mechanisms include interference with HbS polymerisation by increasing oxygen affinity, modifying allosteric state, blocking intermolecular contact or altering red cell hydration status. Early phase safety and dosing studies have been conducted with 5HMF (Aes103). Voxelotor (previously known as GBT 440) is a promising oral anti-S polymerization agent that has entered phase 3 randomized trials and final results are anticipated. SCD101 is a natural product that has been administered in phase 1 dose-escalating trial. Nlprisan is another herbal antisickling agent that has been tested in phase 1 trials. Sanguinate, a bovine pegylated Hb product, has been granted orphan drug status and is now in a phase 2 randomized trial. Senicapoc, a Gardos channel inhibitor did not result in clinical benefit in a phase 3 trial.

Adhesion of platelets and blood cells to the endothelium is one of the most promising targeted pathophysiologic pathways. Crizanlizumab is a monoclonal antibody against P-selectin which is up-regulated in endothelial cells and platelets in SCD. Its administration has been evaluated in a double blind, randomized, placebo-controlled phase 2 trial and resulted in a significantly lower rate of painful crises, with a low incidence of adverse events. Additional trials are planned with this agent. Rivipansel is a small molecule pan-selectin inhibitor that has been evaluated in a randomised phase 2 trial and further trials are scheduled with this molecule as well. Poloxamer, a non-specific surfactant with anti-adhesion properties, has also been tested within clinical trials for its impact on SCD painful episodes. Intravenous g-globin (IVIg) is being tested as an agent inhibiting neutrophil adhesion and inflammation.



Propranolol has been used for blocking  $\beta_2$  adrenergic activation of adhesion. Limited phase 1 data are available and there are ongoing trials.

Inflammatory pathways are the target of another group of investigational products. Regadenoson, a selective adenosine receptor agonist has been recently evaluated in a phase 2 trial, but it did not reduce invariant NKT (iNKT) cell activation which is involved in ischemia/reperfusion related injury. However, NNKT120, a humanised monoclonal antibody against iNKT cells produced rapid and sustained depletion of iNKT cells in adults with SCD in a pilot phase 1 trial and will be further tested for its impact on painful episodes. Leukotriene inhibition with agents such as Montelukast and Zileuton is another approach under investigation in early phase clinical trials. The use of simvastatin, an established agent against endothelial inflammation, has also resulted in reduction of pain as well as improvement of laboratory parameters of inflammation in a pilot trial and will probably be further investigated in the future.

Oxidative mechanisms are another main target of novel treatments. L-glutamine increases NADPH and reduces oxidative stress in the sickle cells. It was the first agent to receive FDA authorisation for adults and children older than five with SCD, almost 20 years after hydroxyurea authorisation. Final results of the trial which was the ground for approval have been very recently published. Patients on L-glutamine had significantly lower rate of painful episodes, acute chest syndromes and hospitalisations compared to placebo and the safety profile was very favourable. The high cost of this new treatment and the lack of markers to monitor efficacy and toxicity will play a significant role in the widespread application of the agent. It definitely represents an important progress for patients not responding to or not receiving hydroxyurea. Combination treatment with hydroxyurea is also a promising strategy.

Alterations of vascular flow is another approach that has been investigated. In SCD NO, a very potent vasodilator, is depleted due to hemolysis. Phase 2 trials with inhaled NO did not give positive results for painful crises, but arginine, the substrate for NO synthesis has significantly reduced the severity of crises and is now being evaluated in phase 3 trials.

In an attempt to target activation of coagulation mechanisms, there are ongoing clinical trials using low molecular weight heparins and derivatives such as sevuparin based on their anticoagulant and anti-adhesive properties. Non-vitamin K oral anticoagulants is another other class of drugs currently on clinical trials. Antiplatelet agents have not led to the anticipated results.

Allogeneic stem cell transplantation remains the only established treatment targeting the abnormal S gene. The best results are achieved in paediatric patients with an HLA-matched sibling donor. However, sibling donors and transplantation programmes are generally available to a minority of SCD patients. Numerous clinical programmes are active worldwide exploring the usage of alternative donors, including haploidentical donors. Despite encouraging results, the alternative donor approach is still considered experimental and is acceptable strictly within the context of clinical trials.

In 2017 there was the first published case report of an adolescent with a severe SCD phenotype treated with gene therapy using BB305 lentiviral vector product, which encodes a human hemoglobin  $\beta$  chain variant with anti-sickling properties ( $\beta^A_{187Q}$ ). The patient who was on regular transfusions remained free of painful episodes and transfusions for fifteen months of follow up. The safety profile of the procedure was consistent with the myeloablative treatment required for an autologous procedure without any safety issues regarding clonal insertion or dominance. Phase I/II trials with BB305 and other lentiviral vectors targeting  $\gamma$ -globin chain are ongoing in France and USA but only very preliminary data are available. Encouraging preclinical data exist with gene editing techniques, targeting mainly BCL11A gene, in order to up-regulate HbF expression.

It is obvious that significant progress has been made in the field of SCD therapeutics. The two approaches that seem closest to being incorporated in clinical practice are oral L-glutamine, already approved by FDA and crinzalimumab, with positive results in a randomized, placebo-controlled trial. There is increasing interest in the clinical application of gene therapy and gene editing techniques. The combination of new approaches with existing treatments, mainly hydroxyurea, is also a promising for patients with severe complications, who do not respond to standard treatment. Exciting

developments are expected in the future and, hopefully, treatment will be accessible to SCD patients in all areas of high prevalence.

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#### SP-27

#### Non-transfusion-dependent thalassemia: an update on complications and management

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Beta-thalassaemia is a monogenic disorder leading to reduced or absent synthesis of the beta-globin subunit of adult haemoglobin [1]. Although non-transfusion dependent thalassemia (NTDT) is a group of thalassaemic disorders including patients who do not require frequent blood transfusions for survival, patients with NTDT may still require occasional or more frequent red blood cell (RBC) transfusion therapy in certain circumstances including but not limited to significant infection, pregnancy, periods of rapid growth, or surgery [2].

It is characterized by ineffective erythropoiesis, chronic haemolytic anaemia, and subsequent clinical complications. The clinical picture of NTDT patients, is predominated by the long-term effects of chronic anemia and tissue hypoxia and their compensatory reactions, including bone marrow expansion, ineffective erythropoiesis, and increased intestinal iron absorption [3].

In the past decade, several therapeutic options have emerged for patients with beta-thalassaemia. These advances aim at improving iron dysregulation, globin-chain imbalance, and/or ineffective erythropoiesis.

Lifelong disease management is required; individuals with severe disease will not survive childhood without appropriate treatment [4]

Our understanding of the underlying pathophysiological mechanisms of beta-thalassaemia and its associated clinical morbidity has increased substantially in recent years [5,6]. This new knowledge and an increasing awareness of the limitations of current management strategies

are driving research into novel therapeutic options for this patient population.

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**SP-28****Pediatric AML in 2018: advances in clinical practice**

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Acute Myelogenous Leukemia (AML) in children is far less common than Acute Lymphoblastic Leukemia (ALL), with an incidence of 7 new cases/10<sup>6</sup> children/year [1]. Recent understanding of the genetic and epigenetic heterogeneity of AML has provided new insights in the pathogenesis and classification, as well as, it has delineated treatment based on prognostic groups [2]. Genetic driver events for AML development include: gene mutations, chromosomal aneuploidies, fusion genes and complex karyotypes. Persistence of leukemia stem cells (LSCs) which possess a number of stem cell properties, including quiescence, are also linked to therapy resistance. Patients with a high LSC 17 score have a poor outcome with current treatments, including stem cell transplantation [3].

Treatment Risk Group (RG) classification depends on white cell count at diagnosis, age, cytogenetics, response to treatment- including minimal residual disease assessment (MRD). Patient outcome is also related to the treatment given, remission induction, the type of post-remission consolidation (chemotherapy vs. stem cell transplantation (SCT)) and the use of targeted therapies. Cytogenetic findings like: monosomy-5 and -7, t(6;9), t(9;22) and abnormalities in chromosome 12p, are universally considered high risk features in pediatric AML, together with the detection of FLT3 mutations. To the contrary, t(8;21)(q22;q22), inv(16)(p13q22), biallelic CEBPA mutation/FLT3-ITD negative and NPM1 mutation/FLT3-ITD negative are considered favorable features, provided there is prompt remission induction to the chemotherapy. Although not all treatment protocols apply the same prognostic factors, there is an effort to unify them in common concepts. In general, the genetic aberrations that are usually found are classified as: 1) type 1 mutations that induce cell proliferation and promote survival, 2) type 2 mutations: that inhibit cell differentiation, and 3) epigenetic regulator mutations, involving DNA methylation/histone modification [4].

Overall, pediatric AML has better prognosis than its adult counterpart. Current survival rates are around 70% and the Standard Risk Group (SRG) comprises 30–40% of all cases, far larger portion than what is seen in the adult population [1]. Patients with Down Syndrome and AML are a biologically and clinically discrete subset of pediatric AML: they require less intensive treatment and they are more prone to toxicity [5].

Historically, definition of remission is defined as bone marrow (BM) blasts <5%, absence of blasts with Auer rods, absence of extramedullary disease, absolute neutrophil count >1.0×10<sup>9</sup>/l, platelet count >80×10<sup>9</sup>/l and independence of red cell transfusion [1]. It has been proven that BM morphology evaluation is not an ideal technique for remission evaluation, as even patients with >5% blasts can be found MRD negative [6]. The NOPHO AML02 Protocol proved that irrespective of BM morphological assessment, MRD measurements better predicts event free survival (EFS) [7]. That was further defined with serial MRD evaluations during the course of the induction treatment: in a recent AIEOP Protocol, MRD detection following hematological recovery post the first and second chemotherapy induction courses, with a cut-off point for positivity of >0.1%, was a significant and independent prognostic factor [8]. Evolution of techniques has allowed to evaluate MRD with flow cytometry, or PCR/ NGS, depending on the genetic marker, and there are newer protocols that allocate patients to treatment according to the combination of cytogenetics and MRD detection during induction, like the MyeChild01 Protocol. MRD measurements can also predict relapse during the course of treatment. For sure, AML heterogeneity may preclude adoption of a single MRD detection approach. The adoption of a flexible approach with available platforms to track MRD in any patient, might lead to a more personalized management, but this has not been proven as yet. For now, early detection of MRD has served as a tool for risk and therapy stratification in childhood AML [9].

Thus, it is important to promote a fast and deep remission status, and this is the role of induction treatment. Intensity of induction may improve outcome. Although high dose Ara-C is not superior to standard dose Ara-C during the

initial induction chemotherapy block, there have been efforts to augment the efficiency of induction treatment by intensifying the anthracycline dose or adding of third agent. Anthracycline intensification may be beneficial, but the addition of etoposide or 6-thioguanine during induction has no definitive beneficial effect. There is an effort to incorporate Gemtuzumab Ozogamicin during induction, but definitive results are pending. A Japanese study has provided better outcome by prolonging Ara-C administration during the initial induction course to 12 days. The specific anthracycline used (doxorubicin, liposomal doxorubicin, idarubicin or mitoxantrone), if used in high doses, produces similar results in survival, although idarubicin might get more patients into remission [1]. The total number of cycles delivered by different protocols vary from 4 to 8, but overall with similar results. The role of maintenance treatment following intensive blocks of chemotherapy is only supported by the BFM group and there is currently randomization to decrease its length to 8 weeks.

Gemtuzumab Ozogamicin (GO) is a humanized anti- CD33 monoclonal antibody conjugated to calicheamicin. It binds to CD33, is then internalized and releases calicheamicin intracellularly, leading to cell death. Approximately 80–90% of AML cells express CD33. At the dose of 3 mg/m<sup>2</sup> it saturates about 80% of CD33 on the cell surface, and there is rapid re-expression of CD33 molecules on the cell surface after their first exposure. Fractionated dosing delivers 9 mg/m<sup>2</sup> (MDT for single dose) while lowering the peak GO blood level and minimizing off-target toxicities, like veno-occlusive disease of the liver and thrombocytopenia. As studies do not provide uniform results, a recent meta-analysis of 11 randomized clinical trials proved that with the use of GO there is improved relapsed free survival but also early mortality, thus there was no improvement in complete remission rate. GO improved overall survival in patients with favorable cytogenetics.

The role of SCT in first remission is established for all secondary AML in the absence of favorable risk cytogenetics, in patients with refractory/ resistant disease and in patients with poor risk cytogenetics / molecular aberrations [10]. In this setting even an autologous SCT might be of value, in the absence of a suitable allogeneic donor [10].

The heterogeneity of AML also provides different opportunities for targeted therapies on top of the use of GO, like FLT3 and c-Kit inhibitors (sorafenib, dasatinib), RAS inhibitors (trametinib) and others. Novel investigational therapies also include epigenetic modifiers like azacytidine, decitabine, newer FLT3 inhibitors like midostaurine, BCL-2 antagonists (venetoclax). Recently developed immune-base therapies like PD1-PDL1 and CTLA-4 inhibitors, CAR T-cell immunotherapy and bi-specific antibodies infusions involving the CD33 and other molecules are in the pipeline of development for AML patients.

With all the above knowledge and developments there is a great hope to improve outcome and decrease immediate and long-term toxicity for children with the diagnosis of AML.

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### SP-29

#### MUD, cord blood or haplo-identical transplantation in the future

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Allogeneic hematopoietic stem cells transplantation (alloHSCT) is one of the best therapeutic options available for patients affected by various malignant diseases and other nonmalignant disorders involving the hematopoietic system.

Since the first alloHSCTs have been performed the prognosis of patients undergoing to this procedure has largely improved but in this field there are still several questions that currently represent an unmet medical need.

The gold standard for all the patients lacking an HLA identical sibling still remains the use of a matched unrelated donor but also in this setting there are some open questions about the procedure itself and upon all, about the indication and allocation of alloHSCT in light of the results of other therapies as monoclonal antibodies, target therapies and adoptive cell therapies.

Cord blood hematopoietic stem cell transplantation (CBHSCT) and haploidentical HSCT are the main alternative options for patients needing a transplantation but lacking both an HLA identical sibling or an HLA-matched unrelated donor.

Since the first UCBT was successfully performed in 1988 several studies have been carried out on this kind of HSCT in both pediatric and adult populations and no differences in the overall survival between patients given unrelated UCBT or bone marrow transplantation (BM) or peripheral blood hematopoietic stem cell transplantation (PBSC) were found both for malignant and for nonmalignant diseases. Even if the outcome of patients undergoing CBHSCT is similar to the outcome of patients undergoing BM or PBSC transplantation transplant related mortality (TRM) still remains higher in CBHSCT, mainly in relation to the delayed hematological and immune recovery, and the risk of early adverse transplant-related events is inversely correlated with both the number of cells infused per kilogram of recipient body weight and HLA mismatches in the donor-recipient pairs. As it can be estimated that only 20% of CBUs collected and stored in cord blood banks worldwide contain a sufficient number of cells for transplantation in an adult patient of standard weight, different strategies, such as double cord blood transplantation, cord blood hematopoietic stem cell ex vivo expansion and direct intra-bone CB injection, have been proposed to overcome this restriction but all these approaches are still considered experimental and larger studies are needed to evaluate their safety and efficacy.

The use of an haploidentical donor (Haplo) has been shown to be another promising option for patients needing an alloHSCT but lacking a donor with the great advantage that haploidentical donors are readily available for collection and also for subsequent transplants and/or donor lymphocyte infusion donations when needed.

Starting from the 90' some groups showed that was possible to achieve a sustained engraftment of donor hematopoiesis without the occurrence of GVHD using a "megadose" of CD34+ cells after ex vivo depletion of T-cells: however, this approach was associated with high risk of graft failure and high incidence of relapse. More recently other approaches, such as additional post-transplant cell therapies, new T cell depletion techniques (as TCRalpha-betaCD19 depletion) and the use of un-manipulated, non-ex vivo T-cell-depleted haploidentical grafts (Haplo) have been used with different platforms for GvHD prophylaxis giving encouraging results. Moreover, the addition to the Haplo HSCT of more sophisticated cell therapy post transplantation cell therapy protocols will probably overcome many of its limits in the next future.

The results of studies comparing CBHSCT with Haplo are still limited and up to date no big differences have been highlighted in terms of overall survival, so both strategies are feasible and valid for patients with an indication for alloHSCT but longer follow-up is needed to validate these data. The ultimate decision between Haplo and CBHSCT should be done based on Center's expertise, policy, costs of the procedures and the availability of clinical trials.

### SP-30

#### Haploidentical non-T-depleted HSCT in high-risk pediatric AL

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Relapsed/refractory acute leukemias continue to be a challenging problem of pediatric oncology. Haploidentical non-T-depleted HSCT is believed to give patients a good chance of rapid immunohaematological recovery after HSCT and long-term relapse-free survival considering graft-versus-leukemia effect. We present own results of haploidentical nonmanipulated HSCT in children with AML and ALL of poor prognosis.

Study group included 41 patients with advanced acute leukemias: 28 patients with AML and 13 with ALL. AML group included: slow responders/very poor genetic in CR = 1, 5 patients; CR >1, 11 patients; non-CR, 6 patients; secondary AML in CR, 6 patients. ALL group: CR >1, 5 patients; non-remission/MRD increase, 8 patients. The median patient age was 8 (1–18) years. The earlier group of patients received universal RIC consisted of Flu 180 mg/m<sup>2</sup> + hATG 40 mg/kg with Busulfan 8 mg/kg or Treosulfan 30–36 g/m<sup>2</sup>. Toxicity of this conditioning regimen was mild. Last year we started a new concept of personalized conditioning according to disease status and previous treatment response. All children received non-T-depleted related grafts after in-vitro incubation with vincristine and methylprednisolone. aGVHD prophylaxis consisted of CSA or tacrolimus and low-dose Mtx. Hematologic recovery WBC >1×10<sup>9</sup>/l, PLT >20×10<sup>9</sup>/l occurred in all but one patient at an average on d+11. One patient transplanted in leukemia progression and sepsis died of infection before WBC recovery, all others recovered with donor graft. Acute GVHD > II occurred in 12% patients and more frequently occurred in CSA group, compared to tacrolimus group. After d+100 about 40% of survivors had signs of GVHD, extensive in half the time. Extensive chGVHD in 75% was caused by intentional reduction of immunosuppression due to high risk of leukemia progression. At present 13/28 (46%) AML patients and 3/13 (23%) ALL patients are alive with a median follow-up 60 and 17 months, respectively. Causes of mortality: ALL group TRM, 3 (23%); relapse, 7 (54%); AML group TRM, 6 (21%); relapse, 8 (29%); first tumor (Ewing's Sarcoma) relapse, 1 (4%). The 5-year OS estimated by Kaplan-Meier for AML group is 54.3%. Only 1 patient with AML is alive with disease presence for 13.5 months after HSCT. For ALL group the results are much worse: 1-year OS is 41.7%, but 3-year OS is only 15.6%. All survivors with ALL received personalized intensified conditioning regimens. HSCT from haploidentical family donor gives good chance for long-term survival to children with very-poor risk AML due to "graft-versus-leukemia" effect. This method provides early BMT avoiding unnecessary chemo along with time and money expenses. For ALL individualization of conditioning may help to improve the HSCT results. chGVHD is still a problem, but nowadays it still has not been separated distinctly from the antileukemic effect of allogeneic graft.

**SP-31****Viral infections except cytomegalovirus in pediatric stem cell transplantations**

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Viral infections are one of most of important causes of morbidity and mortality after hematopoietic stem cell transplantation especially in patients who have received allogeneic transplants (allo-HSCT). Although most viral infections are clinically asymptomatic or presented with minimal clinical manifestations, some viral infections may result in fatal complications depending upon the degree of immunosuppression and exposures [1]. Reactivation of latent viruses such as Herpes Simplex virus (HSV), Varicella-Zoster Virus (VZV), Cytomegalovirus (CMV), Epstein Barr Virus (EBV) is seen frequently during allo-HSCT. Viruses acquired from community such as respiratory viruses (RSV, parainfluenza, influenza, adenovirus), gastrointestinal viruses, human herpes virus (HHV 6), hepatitis B, and hepatitis C are important pathogens. Children are especially high-risk population for community acquired respiratory viral infections [2]. Increasing usage of HLA-mismatch, unrelated donors as sources of HSC's, and antithymocyte globulin (ATG) as the standard prophylaxis of graft versus host disease (GVHD) in HLA-mismatch and unrelated donor transplantation cause an increasing risk for viral infections in recipients [1,3]. Nowadays molecular diagnostic methods like detection of antigen or utilization of polymerase chain reaction facilitated diagnosis of viral infections. Prophylactic strategies like using acyclovir prophylactically and giving preemptive therapy are very important for the reduction of viral infections and diseases. In the recipients of HSCT, immunotherapeutic strategies to restore virus-specific immunity, such as reducing immunosuppressants is advocated in cases of severe viral infections [2]. The antiviral treatment for some of viral infections are as follows: Acyclovir is recommended for severe mucocutaneous or visceral HSV and VZV disease [1]. The recommended drug for acyclovir-resistant HSV is foscarnet and cidofovir. Ganciclovir and foscarnet are effective against HHV-6 [4]. B-cell monoclonal antibody rituximab is recommended for severe EBV infections. Aerosolized ribavirin and RSV-specific immunoglobulin or intravenous immunoglobulin can be used to treat RSV pneumonia. Oral oseltamivir or inhalational is the most widely used therapeutic agent for influenza. Ribavirin and cidofovir may be effective against adenovirus. Cidofovir and foscarnet can be used to treat hemorrhagic cystitis due to BK virus infection. Reduction of immunosuppressants is sometimes not feasible in patients due to risk of GVHD, giving donor lymphocyte infusion and ex vivo generation of virus specific CTL for EBV, CMV, JC virus and adenovirus are now advocated in the treatment of these viral diseases [1,5–7]. The aim of this presentation is to review the current concepts of diagnosis, prophylaxis, preemptive treatment and definite treatment of viral diseases if possible in pediatric stem cell recipients.

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**SP-32****The approach and diagnosis of Coombs negative hemolytic anemias**

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Anemia affects 1.6 billion of people worldwide, about 10% of these individuals are affected by rare anemias of which 80% are hereditary [1]. Hereditary anemias (HA) embrace a highly heterogeneous group of disorders characterized by anemia of variable degree and by complex genotype-phenotype correlations. Differential diagnosis, classification, and patient stratification among HA are often very difficult.

To date, the major current application of next generation sequencing (NGS) in diagnostics is through disease-targeted tests for which multiple causal genes are known. Some studies have already demonstrated the utility of targeted-NGS (t-NGS) approach in the study of specific subtypes of HA patients. Here, we described the diagnostic workflow based on t-NGS that we developed for the diagnosis of patients affected by HA. Within this wide group of disorders, we included: (1) hyporegenerative anemias, as congenital dyserythropoietic anemias (CDA); (2) hemolytic anemias due to red cell membrane defects, as hereditary spherocytosis (HS) and stomatocytosis (HSt); hemolytic anemias due to enzymatic defects, as pyruvate kinase (PK) deficiency [2–5]. We generated two consecutive versions of the same custom gene panel: the first including 34 genes, the second 71 genes. The probe design was performed by SureDesign (Agilent Technologies, USA). Sample preparation was obtained by HaloPlex Target Enrichment kit for Illumina Sequencing (Agilent Technologies), and high-throughput sequencing was performed by Illumina NextSeq 500. For bioinformatic analyses we used Agilent SureCall software (v 3.0.3.1, Agilent Technologies). The pathogenicity of each variant was evaluated according to the guidelines of ACMG [6,7].

We investigated 74 probands with clinical suspicion of HA. Our approach revealed a diagnostic yield of 64.9% of analysed patients. Genetic data by t-NGS analysis confirmed the clinical suspicion in 54.2% of patients. Of note, most of these patients were originally suspected to suffer from red cell membrane disorders (HSt or HS).

Conversely, t-NGS analysis modified the original diagnosis in 45.8% of patients. Particularly, 81.8% of these patients were clinically suspected to suffer from CDA. Of note, among 22 patients originally classified as CDA, we identified 45.5% of cases with a conclusive genetic diagnosis of congenital hemolytic anemias due to enzymatic defects. Indeed, we diagnosed: (i) one case with biallelic mutations in *GPI*, the causative gene of hemolytic non-spherocytic anemia due to glucose phosphate isomerase deficiency; (ii) another case due to mutations in *AK1* gene, the causative locus of hemolytic anemia due to adenylate kinase deficiency; (iii) eight cases due to mutations in *PKLR*, the causative gene of pyruvate kinase (PK) deficiency [7].

Our observation about congenital hemolytic anemia patients misdiagnosed as CDAs is highly relevant: it underlines how t-NGS analysis is valuable not only for achieving a correct and conclusive diagnosis but also for guiding possible treatment of HA patients. This is mainly true for the treatment of PK deficient-patients, for whom it is now available an allosteric activator of PK enzyme that is able to increase the enzymatic activity in patient erythrocytes treated ex vivo [8].

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## Speaker Presentations – Nursing Program

### SP-33

#### CMV reactivation, treatment, and nursing role

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Cytomegalovirus (CMV) is a herpesvirus, which is similar to other viruses, after a primary, usually asymptomatic infection, remains in the host cells in latent form and reactivates during periods of deep T-cell immunodeficiency after transplantation.

CMV can manifest as infection or disease: in case of infection, the virus replication is detected in plasma or whole blood by pp65 antigenemia or DNA or messenger RNA PCR; in case of CMV disease, the patient reports symptoms and/or signs in an organ, which refer to CMV pneumonia, gastrointestinal disease, hepatitis, retinitis, or CNS disease.

CMV infection is a major infectious complication after hematopoietic stem cell transplantation (HSCT), mainly most common in allogeneic rather than

autologous HSCT. CMV can reactivate in up to 80% of CMV-seropositive patients. If the patient is seronegative, prevention starts with the selection of an appropriate donor: a CMV-seronegative donor is preferred for a CMV-seronegative recipient, if available. Further, the use of blood products from CMV-seronegative donors and leukocyte-depleted filtered blood products decrease the risk. Other risk factors for CMV recurrence after allogeneic HSCT depend on the type of conditioning before transplant, the transplant typology, the immunosuppressive treatment, the occurrence and treatment for acute and/or chronic GVHD and the immune recovery after HSCT.

In order to detect a CMV reactivation, patients should be monitored more frequent in the first 30 days after transplant and weekly within 100 days after HSCT. Treatment is divided in prophylaxis (antiviral medications are given to prevent a primary, reactivated or recurrent CMV infection) and pre-emptive therapy (antiviral agents are given for an asymptomatic CMV infection detected by a screening assay).

In case of CMV disease, the first line antiviral agent is ganciclovir given intravenous; valganciclovir is the prodrug to ganciclovir, can be used when oral therapy is appropriate and in absence of gastrointestinal Graft versus Host Disease. Foscarnet is an alternative drug for intolerance to ganciclovir, in case neutropenia has complicated the patient's course or if there is a patient's refractory infection.

If the viral load or antigenemia level increase after the first two weeks of treatment, drug resistance to the antiviral drug should be taken into concern. Further drugs for CMV treatment are cidofovir, which is nephrotoxic, and in the last period, newer agents as maribavir, letermovir and brincidofovir are under development and evaluation.

The management of CMV reactivation seems to be a physician's issue, but nurses play a key role in counselling, education of patients and caregivers, ensuring proper administration for medication, monitoring and inform patients about potential side effects and assessing patient adherence to the therapy.

## Oral Presentations

### Acute Lymphocytic Leukemias

#### OP-01

##### Personalized MRD monitoring in children ALL according to new immunophenotypic markers

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**Objective:** Improvement of diagnosis of minimal residual disease (MRD) in acute lymphoblastic leukemia (ALL) in children by flow cytometry.

**Case report:** The estimation of the MRD in ALL in children is an independent prognosis factor included in the risk-stratification of patients in most treatment programs. Despite the diversity of the flow-cytometric protocols of the MRD evaluation proposed by various international research groups, there is still no single approach.

**Methodology:** In the study was enrolled 155 patients with B-linear ALL. The diagnosis was established by the combination of morpho-cytochemical and immunophenotypic studies of bone marrow (BM). The number of MRD cells was analyzed in 341 samples of BM in patients with B-linear ALL at different stages of therapy (15th, 33rd and 78th days). Each BM sample in the MRD diagnosis was characterized morphologically and immunologically, the data were compared and analyzed with respect to morphological and immunological criteria for the allocation of patients to risk groups.

**Results:** B-linear ALL group consisted of 155 patients aged 1-18 years. In 93.8% of cases, pre-pre-B immunosubvariant was diagnosed, in 6.2% was pro-B. The frequency of the most widely used aberrant immunophenotype CD58++CD38- of B-lymphoblasts was identified only in 54.3% of cases. As additional criteria for the aberrant, it is advisable to use CD58++CD10++, CD38lowCD10++, CD123+CD81low, CD9++ CD81low, CD66c+ whose frequency during primary diagnosis is 72.7%, 55.0%, 85.7% 87.5% and 75.0% respectively. Taking into account the effect of remission induction therapy on BM, MRD cells on the 15th day of therapy are B-linear precursors. In the case of the pre-pre-B immunosubvariant, their amount can be assessed based on CD19+CD10+/CD34+ immunophenotype. In the case of CD10-negative (pro-B) immunosubvariant, MRD cells should be identified according to cyCD22+nuTdT+ immunophenotype. Starting from the 33rd day of treatment and further, MRD cells can be detected only on the basis of an aberrant immunophenotype, the criteria that are displayed at the stage of primary diagnosis. According to the evaluation of the MRD-status, the following clinical data were obtained: on the 15th day, 11.5% of patients with MRD-negative status were identified, for them it is possible to consider the issue of reducing anthracycline doses taking into account the clinical factors of the prognosis; on the 33rd day, 60.0% of the patients achieved MRD negativity; on the 78th day, a group of patients with a late response (50.0% of 14 traced in 3 points) was identified.

**Conclusion:** Immunological evaluation of MRD should be performed under morphological control. Criteria for aberrant leukaemic blasts should be established in each case on the basis of enhanced immunophenotyping at the primary diagnosis.

#### OP-02

##### Cytotoxic effect of three species of *Centaurea* genus on acute lymphoblastic leukemia cell line (NALM-6)

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**Objective:** Medicinal plants are considered as one of the ideal therapeutic sources for cancer due to their bioactive contents. *Centaurea* genus have shown potential anti-tumor activity on some cancer cell lines in previous studies. The aim of this study was to evaluate the cytotoxic effect of three species of *Centaurea* genus (*C. albonitens*, *C. pseudoscabiosa*, *C. salicifolia*) on Nalm-6 cell line that have not been investigated before.

**Methodology:** In this experimental study, to explore the effects of *Centaurea* extracts on Nalm-6 and MDBK cells, the cells were treated with increasing concentration of extracts (10-90 µg/ml), their cytotoxic and anti-proliferative effects were evaluated using trypan blue, MTT assay and DAPI staining. Moreover, we performed Annexin V/PI staining and cell cycle analysis to further investigate how *Centaurea* species exert their cytotoxic properties.

**Results:** The results of trypan blue, MTT assay and DAPI staining assays revealed that the methanolic extracts of the *Centaurea* species exhibit cytotoxic and anti-proliferative properties against Nalm-6 cells in a dose- and time-dependent manner ( $p \leq 0.001$ ). Interestingly, there was no considerable cytotoxicity in normal cells, MDBK. The flow cytometric analysis validated that *Centaurea* dose dependently induces apoptosis and G1 phase arrest in Nalm-6 cells ( $p \leq 0.01$ ).

**Conclusion:** Our study suggests that *Centaurea* extracts might provide insight into a drug discovery for acute lymphoblastic leukemia treatment, however further researches are necessary.

#### OP-03

##### A patient who was diagnosed with PH negative precursor B-ALL and developed neuropathy and died afterwards

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**Objective:** Cure rates in adults, especially patients who relapsed or with a primer refractory disease with Philadelphia chromosome-negative (PH2) B- precursor acute lymphoblastic leukemia (ALL) are very low. In the past remission rates in relapse/refractory (r/r) ALL changed between 40%-45% and median overall survival rate (OS) was up to 9 months. Blinatumomab, that has an engaged antibody structure with a bispecific T cell that directs CD31 T cells to lyse CD19 + B cells, is an indication for the treatment of the patients with r/r B- precursor ALL. In the randomize phase 3 TOWER study that compared blinatumomab to standard chemotherapy (SOC), it was shown that blinatumomab and median OS was significantly longer (median 7.7-4.0 months, risk rate, 0.71; 0.55-0.93; P 5.01). During the study, almost all the patients (99%) had an adverse event in both treatment arms (AE); Grade  $\geq 3$  AE rates were similar (87% to 92%), but serious AEs' rates were higher in the arm with blinatumomab (62% to 45%). Study of TOWER has shown that neurological incidents are similar in both arms (resp. 9.4% and 8.3%). Headache, insomnia, tremor, dizziness is detected at 1%, somnolence is at 3%, seizure is at 2%.

**Case report:** In this report, we wanted to present a patient who was diagnosed with Ph negative Precursor B-ALL and developed neuropathy and died afterwards. In March 2018, a 62-year-old female patient was diagnosed with Ph- Pre B-ALL. Patient was treated respectively with 2 cycle of HyperCVAD and FLAG-IDA. She showed resistance to all treatments. In response it was decided that the patient was to treated with Blinatumomab and after that allogeneic stem cell transplantation. Blinatumomab was started with the dose of 0.9 mcg/day. It was planned to go up to 28 µg/day from the 8th day on. At the start of the treatment she was detected to have 40% blast at her bone marrow biopsy and in her complete blood count (cbc) Wbc was 250/µL, hb g/dl was 7.5, plt was 12,000/µL. On the 8th day of the treatment cbc was wbc: 2460/µL, hb:9.5 g/dl, plt: 46,000/µL. After starting Blinatumomab, erythrocyte and platelet transfusion were no longer needed. Hematological response was succeeded. But after the third day of treatment grade 3 sensory neuropathy and grade 1 motor neuropathy were developed in the hands. Later motor neuropathy increased to grade 3. Patient developed flapping tremor in hands, somnolence, vertigo, and delirium. No hepatic impairment was detected. Neuroimaging couldn't be performed based on the general status of the patient but a neurologist was consulted. Neurological examination showed no evidence of side findings and cerebral hemorrhage was not considered. Treatment was interrupted on the 8th day but consciousness gradually clogged and coma developed. After starting the Blinatumomab treatment the patient died 15 days later.

**Conclusion:** In our case blinatumomab is effective hematologically. On the other hand, unidentified neurological AEs were found. In this article, we wanted to report new AEs such as sensory and motor neuropathy, flapping



tremor, delirium and coma. Therefore, patients should be watched closely when using this treatment.

#### OP-04

##### First use of plasmapheresis in the treatment of T cell engaging therapies related adverse effects

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**Introduction:** Despite advances in intensive chemotherapy regimens and supportive care only 30-40% of adult and 60-70% of AYA (adolescent and young adult) acute lymphoblastic leukemia (ALL) patients achieve long term disease-free survival, including those who undergo hematopoietic stem cell transplantation. Therefore, new treatment methods are needed in adult and AYA ALL. New immunotherapy options like bispecific T cell engaging (BITE) antibodies and CAR-T cells are among those. Blinatumomab belonging to a (BITE) antibodies.

Cytokine release syndrome (CRS) and neurotoxicity appear to be the most significant side effects in these studies. CAR-T therapy can also cause neurotoxicity, up to half of patients in studies.

**Case:** We report here a case with aphasia and grade 2 CRS, associated with blinatumomab treatment, treated with plasmapheresis after the discontinuation of the drug and the successful reintroduction.

At 2010, thirteen-year-old patient diagnosed with precursor B cell ALL (Philadelphia chromosome negative), treated with a pediatric regimen, long-term remission achieved. In October 2016, he was admitted to our hospital due to relapsed precursor B cell ALL. CVAD/MA regimen started. Due to refractory disease, FLAG-IDA regimen was given. Cerebrospinal fluid analysis and magnetic resonance imaging of brain were negative for CNS involvement. Bone marrow aspiration and biopsy showed relapsed disease after FLAG-IDA regimen. Allogeneic stem cell transplantation performed from HLA full matched, unrelated donor. At day 100 after transplantation, bone marrow biopsy/aspiration showed refractory disease with five to ten percent infiltration of bone marrow with malignant cells. Patient had recurrent fevers, grade 2 CRS considered, and steroid therapy started without stopping blinatumomab. Dose escalated to 28 micrograms at day nine. On the eleventh day of treatment, infusion was stopped because of a sudden onset of aphasia and disorientation. Pulse steroid was given. Because of no clinical improvement, plasmapheresis decision was taken. Patient underwent two cycles of daily plasma exchange with fresh frozen plasma. After session one, dramatic clinical improvement was seen. Steroid therapy was discontinued. Blinatumomab infusion started after second plasma exchange at 28 micrograms dosage at thirteenth day. The treatment completed to 28 days without additional problem

**Conclusion:** Plasmapheresis may be useful in treating both, T cell engaging therapies related, CRS and neurotoxicity by lowering cytokine levels.

#### OP-05

##### Association of PRKRAP1 pseudogene in HLA-DR53 haplotypes with acute lymphoblastic leukemia

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**Background:** It has been observed that the frequency of HLA-DR53 (HLA-DRB4) homozygosity is higher specifically in male patients with childhood

acute lymphoblastic leukemia (ALL). In our study, we aimed to compare the HLA-DR53 marker protein activator of interferon induced by protein kinase EIF2AK2 pseudogene 1 (PRKRAP1) positivity in male and female patients and healthy controls to show that the correlation between ALL disease and HLA-DR53 haplotypes. The relationship was associated with the recently identified PRKRAP1 pseudogenes in HLA-DR53 (HLA-DRB1\*04, \*07, \*09) haplotypes in patients and healthy controls.

**Materials and methods:** A total of 60 ALL patients and 100 healthy controls were studied. HLA alleles were analyzed by using sequence-specific primer-polymerase chain reaction (SSP).

**Results:** The associations of specific *DRB1* alleles with ALL were evaluated in a case-control study consisting of the 60 patients with ALL and 100 healthy controls. The patients with ALL were having significantly higher frequencies of the *DRB1\*04* allele ( $p=0.0001$ ) compared with healthy controls. Also, the patients with ALL appeared to have higher frequencies of *DRB1\*07* allele than healthy controls, this difference was statistically significant ( $p=0.007$ ). We observed that HLA-DR53 homozygosity were higher in ALL patients than healthy controls ( $p=0.0001$ ). We observed that HLA-DR53 homozygosity were higher in male patients than the female in all cases, but this difference was not statistically significant ( $p=0.301$ ). All patients with ALL were successfully genotyped for the PRKRAP1 gene. PRKRAP1 positivity was identified in 50 patients with ALL (31.3%). PRKRAP1 gene amplification were identified in 36 in male patients with ALL (81.8%) and 14 in female patients with ALL (87.5%) ( $p=0.715$ ). There were not significant association between HLA-DR53 homozygosity and PRKRAP1 positivity in gender groups ( $p=0.602$ ). PRKRAP1 gene amplification positivity was found to be 36.1% in male patients with HLA-DR53 homozygous patients and PRKRAP1 gene amplification positivity was found to be 50.0% in female patients with HLA-DR53 homozygous patients ( $p=0.368$ ).

We assumed that this change in the idea that pseudogenes are the oldest non-functional residues in recent years, so we can suggest that the association of ALL with HLA-DR53 homozygosity has been reported in HLA-DR53 haplotypes because of pseudogene.

#### Anemias

#### OP-06

##### Management of a patient with posterior reversible encephalopathy syndrome associated with HELLP syndrome

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**Objective:** HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets) syndrome can be observed in the postpartum period and is considered a variant of preeclampsia. The clinical appearance can vary from asymptomatic elevation in transaminases to fulminant liver failure. Posterior reversible encephalopathy syndrome (PRES) characterized by neuroimaging findings can be observed as a rare complication triggered by the HELLP syndrome. The aim of this manuscript is to present a case of PRES associated with HELLP syndrome along with a review of the literature.

**Case report:** A 21-year-old female patient was referred to our hematology clinic due to hemolytic anemia after a cesarean delivery that was performed due to macrosomia at 38 weeks of gestation. The patient complained of headache, blurred vision, nausea and vomiting, swelling in the legs, and abdominal pain. On physical examination, blood pressure was 114/57 mmHg, and pulse rate was 88 bpm. Abdominal tenderness was noted on superficial palpation, and the scar from the cesarean section was present in the suprapubic region. All other systemic examinations were normal. Serum biochemistry test results were as follows: ALT, 143 U/L; AST, 387 U/L; LDH, 2781 U/L; total bilirubin, 5.5 mg/dL; indirect bilirubin, 3.12; urea, 209 mg/dL; and creatine, 7.1 mg/dL. On complete blood count, platelet count was  $29 \times 10^3/\mu\text{L}$  and Hgb was 7.5 mg/dL, and the patient was considered to have HELLP syndrome. The patient experienced generalized tonic-clonic seizure lasting less than 3 min during admission. Cranial MRI showed hyperintense lesions located in the cortex and white matter in occipital and parietal areas along with cortical

lesions scattered in the left cerebellum and right frontoparietal region On T2-weighted images. With these findings, the patient was considered to have PRES due to HELLP syndrome. Phenytoin was administered to the patient at a dose of 10 mg/kg/day followed by a maintenance dose of 5 mg/kg/day. Blood pressure control was achieved with oral nifedipine (10 mg/day) and methyldopa (250 mg/day). A total of three hemodialysis sessions were performed during follow-up. All laboratory tests and imaging findings were normalized, and the patient became stable with no recurrent seizures. She was discharged from the hospital with medical treatment recommendations and she was advised to attend control visit at outpatient clinics.

**Conclusion:** Hematological, cardiopulmonary, neurological complications due to HELLP syndrome further increase maternal and perinatal mortality. Radiological findings together with clinical findings lead to the definitive diagnosis of PRES. Diffusion-weighted MRI is the preferred method because of its high sensitivity and specificity, although computed tomography of the brain might show intracranial hypodense areas. Permanent brain damage, severe neurological deficit, or death can occur in 5–12% of such patients. If elevated blood pressure is accompanied by neurological symptoms such as visual impairment and headache in the prenatal or postnatal period in preeclamptic women, particularly in those with HELLP syndrome, PRES should be considered in the differential diagnosis. It must be kept in mind that PRES can recover without sequelae with early diagnosis and treatment.

#### OP-07

##### Treatment with magnesium supplement of patients with beta-thalassemia

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**Objective:** It is known that the risk of thrombus formation is significantly increased in diseases with magnesium deficiency. There is an evidence that in patients with homozygous  $\beta$ -thalassemia with magnesium deficiency, observed latent hypercoagulable disorders of hemostasis. The aim of this work was to investigate the effect of magnesium on latent hypercoagulation in patients with  $\beta$ -thalassemia.

**Methodology:** Examined 60 homozygous  $\beta$ -thalassemia women, 50 with heterozygous  $\beta$ -thalassemia and 30 blood donors, between the age of 18-40. Patients with  $\beta$ -thalassemia did not have clinically significant thrombotic complications. Magnesium deficiency was established on the basis of a study of the magnesium level in the serum and a questionnaire for the diagnosis of the magnesium deficiency MDQ. Hemostasis was studied: platelet count, activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TV), INR, fibrinogen concentration in plasma, fibrinolytic activity in XII-*acallicrein*-dependent spontaneous euglobulin lysis (fibrinolysis), antithrombin III and protein C activity; markers of activation of intravascular coagulation (markers of thrombinemia) - the D-dimer and soluble fibrin levels in plasma, the so-called. soluble fibrin-monomer complexes (RFMC). Patients with magnesium deficiency in addition to standard therapy were prescribed MagneB6forte (magnesium citrate, Mg<sup>2+</sup>, 100 mg, pyridoxine hydrochloride 10 mg) at 300 mg/day for 30 days.

**Results:** Out of 60 women with homozygous  $\beta$ -thalassemia latent hypercoagulation was detected in the 21 patients (group 1). Hypercoagulation was expressed due to increase in fibrinogen levels, markers of thrombinemia - D-dimer and RFMC, lysis time of the euglobulin clot, a slight decrease in APTT and antithrombin III. Patients of the 1st group had a reduced level of magnesium in the blood serum ( $0.64 \pm 0.03$  mmol/l), which was statistically significant when compared with the 2nd group ( $0.83 \pm 0.04$  mmol/l) and with the control group ( $0.88 \pm 0.05$  mmol/l).

**Conclusion:** Thus, latent hypercoagulant activity was observed in patients with  $\beta$ -thalassemia with hypomagnesemia. The prescription of Magne B6 Forte improved the parameters of hemostasis in these patients. Apparently, MagneB6forte should be prescribed to patients with  $\beta$ -thalassemia who have magnesium deficiency and latent hypercoagulation to reduce the risk of thromboembolic complications.

#### OP-08

##### Incidence of paroxysmal nocturnal hemoglobinuria in the patients with idiopathic portal vein thrombosis

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**Objective:** Paroxysmal nocturnal hemoglobinuria (PNH) is a very rare clonal hematopoietic stem cell disease characterized by chronic hemolytic anemia and thrombosis. Clinically, PNH occurs in three different forms: classic (hemolytic); bone marrow deficiency syndrome (hypoplastic); and a subclinical form. Although the disease typically manifests with signs of bone marrow deficiency, chronic intravascular hemolytic anemia and thrombotic events, particularly those affecting the abdominal veins, are considered the most important complication during its course. Thrombotic events are most commonly seen in the hepatic, splenic, mesenteric, renal and portal veins. We report data from a study of the occurrence of PNH among patients with idiopathic portal vein thrombosis (PVT).

**Methodology:** A total of 112 patients (42 males and 70 females) who were being followed up due to idiopathic PVT were enrolled into this prospective observational cohort. Those with laboratory and/or imaging evidence of any local or systemic factor that could lead to PVT (including factor V Leiden mutation, prothrombin gene mutation, systemic lupus erythematosus, anti-phospholipid syndrome, celiac disease, hepatic cirrhosis, chronic myeloproliferative diseases, malignancies, abdominal trauma or previous surgery) were excluded. JAK2-V617F and other activating mutations were studied to exclude chronic myeloproliferative diseases. PNH clone was examined in all patients using established FLAER methodology. Fluorescent aerolysin (FLAER) assay is acknowledged as the most appropriate detection method for GPI antigens, and enables highly sensitive measurements for the detection of PNH clone sizes as low as 0.01%.

**Results:** PNH clone positivity was identified in 4 patients (3.6%). The clone size was up to 3-5% in the granulocytic series in those patients. The mean ages of PNH negative and PNH positive patients were  $37.7 \pm 7.2$  years and  $39.3 \pm 2.8$  years, respectively ( $p=0.373$ ). The mean hemoglobin concentration was  $12.7 \pm 1.0$  g/dL and  $10.1 \pm 0.8$  g/dL in the PNH negative and positive groups, respectively ( $p=0.007$ ). The mean thrombocyte and leukocyte counts were lower in the PNH positive group than PNH negative group ( $p=0.000$  and  $p=0.003$ , respectively). The mean serum LDH level was  $170.6 \pm 29.4$  U/L in the PNH negative patients and  $323.6 \pm 29.6$  U/L in the PNH positive patients ( $p=0.002$ ). The mean serum indirect bilirubin level was  $0.8 \pm 0.1$  mg/dL in the PNH negative patients and  $1.5 \pm 0.2$  mg/dL in the PNH positive patients ( $p=0.005$ ).

**Conclusion:** PNH should be considered during differential diagnosis among patients with idiopathic PVT, particularly if anemia is accompanied by elevated LDH activity.

#### OP-09

##### Single center experience: long-term treatment results in thrombotic thrombocytopenic purpura

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**Objective:** Thrombotic thrombocytopenic purpura (TTP) is a rare and fatal disease with microangiopathic hemolytic anemia, thrombocytopenia, fever, neurological findings and renal failure. Therapeutic plasma exchange (plasmapheresis) in TTP therapy is accepted as a standard treatment method. In this study, the effect of plasmapheresis on clinical and biochemical parameters and its results were evaluated.

**Materials and methods:** Patients diagnosed with TTP between 2009-2017 were enrolled in Çukurova University Faculty of Medicine internal medicine hematology department, internal medicine intensive care unit and other service and intensive care units. Before and after each plasmapheresis procedure; peripheral blood smear, whole blood count, BUN, creatinine, LDH,

AST, ALT levels were evaluated. Patients were evaluated retrospectively in terms of gender, age, diagnosis and treatment history, frequency and number of apheresis application, treatment response, complications during the procedure.

**Results:** A total of 47 patients were included in this study. The M/F ratio of the patients was 23/24 (48.9/51.1%) and the mean age was 39±14.5. The response status was defined as refracture in 14 patients (29.8%), relapse in 2 patients (4.3%), exacerbation in 12 patients (25.5%) and remission in 19 patients (40.4%). 14 patients has been died and the mortality rate was higher than the literature (10%). 4.3% of the patients were relapsed and were found to be lower than the literature. The patients' remission rate (40.4%) was lower than similar literature (80%). Steroid therapy showed positive results in response, whereas immunosuppressive treatment decreased relapsed responses and these results were similar to the literature.

**Conclusion:** Therapeutic apheresis is the standard treatment for TTP disease. The mortality rate in TTP patients has decreased with therapeutic plasmapheresis treatment. Successful results are obtained with steroid treatment and immunosuppressive treatment in cases resistant to therapeutic plasmapheresis treatment. The positive results obtained with the combination of therapeutic plasmapheresis, steroids and immunosuppressive therapy in this study are statistically significant.

### Bone Marrow Transplantation

#### OP-10

#### qRT-PCR and STR-PCR chimerism method using after allogeneic hematopoietic stem cell transplantation

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**Objective:** Recently molecular chimerism analysis after allogeneic hematopoietic stem cell transplantation (AH SCT) has become more important. The use of quantitative chimerism methods aims to assess the kinetics of engraftment to determine graft rejection and failure or relapse of the underlying disease after AH SCT. The aim of the study was evaluation of two chimerism methods: Short Tandem Repeat-Polymerase Chain Reaction (STR-PCR) and Quantitative-Real Time-PCR (q-RT-PCR) after AH SCT.

**Methodology:** For comparison of chimerism analysis based on multiplex STR-PCR and q-RT-PCR, peripheral blood samples were obtained from 29 adult patients with acute leukemia (15 AML, 14 ALL) at the day +28 after AH SCT.

**Results:** We compared the result of chimerism analyses with qRT-PCR to those obtained by the golden standard multiplex STR-PCR method in 29 allogeneic hematopoietic stem cell transplantation patients. Using 34 different SNP gene loci was able to discriminate patient from donor cells in all patients whereas 16 different STR gene loci with the STR-PCR analysis using PCR products on genetic analyzer resulted in accurate donor-patient discrimination. Of the 29 analyzed samples we found in 79.3% concordant results for both chimerism methods. In all 20.7% discordant cases the q-RT-PCR method showed mixed chimerism (MC), whereas STR-PCR chimerism method found complete chimerism (CC). As a consequence, the qRT-PCR chimerism analysis method detected MC prior to the occurrence of relapse earlier than the STR-PCR chimerism method. All 6 discordant cases turn to MC in and/or after 6 months post-AH SCT and the 3 of 6 patients were dead.

**Conclusion:** The present study provides information about advantages of using quantitative chimerism method for Turkish patients after AH SCT. We propose that long-term quantitative chimerism methods along with standard STR-PCR methods may be valuable for early detection of mixed chimerism status.

### Chronic Myeloid Leukemias

#### OP-11

#### Organization of therapy of chronic myeloid leukemia (CML) in Azerbaijan: analysis and prospects

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**Objective:** Over the past few years, the situation with the diagnosis and treatment of CML has changed dramatically. Emergence of the tyrosine kinase inhibitors, which destroy tumor cells at the molecular level, enabled to obtain a high response rate to treatment. In 2014, the Institute of Hematology and Transfusiology, with support of Novartis Pharma AG company, initiated the implementation of infrastructure program to provide quality care for patients with CML. The main purpose of the program was the establishment of National Registry of CML patients, organization of a system for cytogenetic and molecular diagnostics and monitoring of the disease, and provision of these patients with necessary medications. The aim of this study was to evaluate the results of the development program that provides quality therapy for CML patients in Azerbaijan.

**Methodology:** The data of CML patients (766 patients) in Azerbaijan between 2008-2017 was analyzed. Based on the data, the primary morbidity and prevalence of CML, the distribution of patients by economic-geographical zones of Azerbaijan, age groups, sex, survival and mortality, and laboratory parameters of patients were determined. The responses to therapy with tyrosine kinase inhibitors (TKI), and the rate of the transfer to the second-line therapy as a result of the detection of resistance to the first-line drug were also analyzed.

**Results:** Within the framework of the program providing quality care for CML patients, a laboratory for cytogenetic and molecular genetic diagnostics of leukemia was established, enabling the organization of modern diagnostic and monitoring system. The National Chronic Myeloid Leukemia Registry and Follow-up System has been established by the Turkish company "Hemosoft IT and Training Services Inc". As a result of the approval of the state program in oncohematology, CML patients were provided with ITC second line Nilotinib (ITC first line Imatinib is supplied in the required quantity through the GIPAP Fund since 2004). From total 766 examined patients, 411 were women, and 355 were men. The median age at the time of diagnosis was 49. An increase in primary morbidity was noted. 26 persons diagnosed with CML in 2008, while it was 95 in 2017. The study for the presence of molecular response was conducted in 249 patients. A major molecular response (MMO) was noted in 200 patients; MMOs were not reached in 49, and the therapy was switched to Nilotinib. In some TKI therapy resistant patients, T3151 mutation, deletion of the RB1, P53, ASS genes and hypo- or hyperdiploidy of chromosome 8 were revealed. A comparative study of the survival curves of patients for the period 2008-2014 (in this period, only the first-line drug was used) and 2015-2017 (in cases of resistance, the second-line drug was used) showed an improvement in survival in the second period.

**Conclusion:** Azerbaijan has created the necessary infrastructure that ensures the quality of CML treatment. In future, it is necessary to achieve 100% monitoring of CML therapy by molecular genetic methods.

#### OP-12

#### Register and epidemiological features of chronic myeloid leukemia (CML) in Kyrgyzstan

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**Objective:** With increase in duration and quality of life at the background of the introduction of medicines ITK (Tyrosine Kinase Inhibitors) the accounting system and introduction of the Register of patients with CML

**Aim:** Assessment of the main epidemiological characteristics and compilation of the Register of patients with chronic myelogenous leukemia (CML) in Kyrgyzstan.

**Methodology:** The study included patients with CML from 8 regions of Kyrgyzstan. At the time of the analysis on July 1, 2018 of 384 patients from 8



regions of Kyrgyzstan were entered into the CML patient Register. The annual increase in the number of primary patients with CML is 20-24 patients. At the time of the analysis 344 (89.7%) patients remained under observation, 14 patients (3.6%) died and 26 (6.7%) - withdrew from the observation. In the Register were 49% of men and 51% of women, the median age of patients was 49 years (range 4-84 years). The peak incidence of 46.3% accounted for the age of 35-60 years.

**Results:** The incidence of chronic myelogenous leukemia in the Kyrgyz Republic by regions of the country was estimated at: 1.2 per 100,000 population 1 Osh region 0.3 2 Jalal-Abad oblast 0.2 3 Bishkek city 0.2 4 Talas oblast 0.2 5 Chuy oblast 0.1 6 Batken oblast 0.1 7 Issyk-Kul oblast 0.05 8 Naryn oblast 0.05 Total Kyrgyzstan 1.2 The largest number of patients was in Osh, Jalal-Abad oblasts and Bishkek city, due to the high population density in these regions. Given the incidence in the Talas region of 0.2, where there is no such population density, this fact requires further study of the causes of the disease. CML was diagnosed in the chronic phase, the phase of acceleration and blast crisis in 351 (91.4%) 26 (7%) and 7 (2%) patients. Imatinib received 378 (98.4%) Dasatinib 4 (1%) Nilotinib 32 (8.3%) Ponatinib 13 (4%). Primary or secondary resistance to Imatinib was in 49 (12.6%).

**Conclusion:** The majority of patients with CML in Kyrgyzstan have a high effectiveness of ITK therapy with the possibility of achieving a low level of minimal residual disease. The register of patients with CML allows you to integrate information into a single accounting system that characterizes the CML population in Kyrgyzstan.

### Chronic Myeloproliferative Disorders

#### OP-13

##### A rare case of FIP1L1-PDGFR-A-positive clonal hypereosinophilia

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**Objective:** A diagnosis of hypereosinophilia (HE) is made when the absolute number of eosinophils in two separate blood counts is equal to or exceeds  $1.5 \times 10^9/L$ . Its prevalence in the community ranges from 0.36 to 6.3 per 100,000. HE may develop due to non-hematologic (secondary or reactive) or hematologic (primary or clonal) disorders. We present a case of clonal hypereosinophilia associated with rare FIP1L1-PDGFR- $\alpha$  positivity, which was investigated for elevated eosinophil levels.

**Case report:** A 53-year-old male patient presented with complaints of fatigue and weight loss. In the previous three months, he had lost approximately 14 kg. The patient did not have any illness or medication use in his history. The test results were as follows: leukocyte count was  $42.9 \times 10^9/L$ , neutrophil count was  $31.3 \times 10^9/L$ , eosinophil count was  $0 \times 10^9/L$ , hemoglobin was 13 g/dl, and platelet count was  $79 \times 10^9/L$ . In the peripheral blood smear, showed the percentage of eosinophils was 60%, neutrophil percentage was 30%, and 10% was other cells. There were no precursor or blast cells. Physical examination indicated mild splenomegaly and no lymphadenopathy (LAP). No mass or LAP was found on the neck, thorax, and abdominal tomographies. In the tests for hypereosinophilia, no parasites were detected in the microscope or culture. Echocardiography EF was 60%, ECG showed a normal sinus rhythm, and troponin was found to be within the normal range. Thyroid function tests and immunoglobulins, normal viral hepatitis markers, ANA, anti-dsDNA, cANCA, pANCA, galactomannan, brucella and anti-HIV test results were all negative. On the bone marrow aspiration, elevated eosinophil levels (12-15%) and normal myeloid-erythroid maturation were observed, while atypical cells and elevated blast count were not observed. Myeloid series markers (CD13, CD33, CD15, CD45) were found to exceed 20% in the flow cytometry study sent from the bone marrow. Chromosome analysis results were negative for Jak-2 mutation and t(9;22). FIP1L1-PDGFR- $\alpha$  was positive while PDGFR- $\beta$  and FGFR-1 tested negative. The bone marrow biopsy was reported as Chronic Eosinophilic Leukemia (NOS). The patient began treatment with imatinib upon diagnosis of clonal hypereosinophilia.

**Conclusion:** HE is divided into two subgroups, familial and acquired. Familial HE is rare. Acquired HE is further divided into secondary (reactive), clonal HE, and idiopathic HE. Taking into account the biopsy results and genetic results for our case, clonal HE was considered. There is a significant body of data indicating that 100 mg/day of imatinib is sufficient for FIP1L1-PDGFR- $\alpha$ -positive clonal eosinophilia. Our patient was started on treatment with imatinib. HE is a heterogeneous group of diseases consisting of various causes, clinical findings, and prognoses. Subsequent to understanding the pathogenesis of the different varieties of HE, significant results have been achieved in the treatment of patients with the development of targeted therapies such as imatinib and anti-IL-5 antibody.

#### OP-14

##### Clinical and genetic analysis of the bcr-abl negative chronic myeloproliferative diseases in initial diagnosis: single central experience

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**Objective:** Chronic myeloproliferative diseases (CMPD), are clonal stem cell disorder characterized by the uncontrolled proliferation of myeloid lineage cells in the bone marrow. Polistemia vera (PV), essential thrombocytosis (ET), and primary myelofibrosis (PMF) are bcr-abl negative CMPD of this disease group, namely under the category of CMPD. After the identifying of the JAK2V617F mutation, the classification of CMPD have changed and the existence of this mutation has been included in the World Health Organization (WHO) diagnostic criteria. Thereafter, MPL and calreticulin mutations were defined in the 2016 WHO revision classification of CMPD, with the showing of them in the pathogenesis of CMPH.

**Methodology:** In this study, the demographic characteristics, subtype, risk status and mutation analysis of patients diagnosed with bcr-abl negative CMPD were investigated, between July 2017 and June 2018.

**Results:** Twenty-eight patients were diagnosed with CMPD. Twelve (42.9%) of them were PV, whereas sixteen (57.1%) were ET. Seventeen (60.7%) of the patients were female, eleven (39.3%) were male and the median age was 53 (38-82) years. Medians of hemoglobin (hb), Hematocrit (htc), leukocyte and platelets were 18 (14.2-20.4) g/dL, 56.5% (44.4-65.2),  $12,400/mm^3$  (5,300-18,900) and  $390,000/mm^3$  (151,000-609,000) in patients diagnosed with PV and 13.8 (12-16.8) g/dL, 42.2% (36-48.5),  $10,500/mm^3$  (6,500-21,800) and  $759,000/mm^3$  (451,000-1,189,000) in ET, respectively. Splenomegaly was noted in 11 (55%) [6 (55%) = PV, 5 (45%) = ET] of patients. JAK2V617F mutation was detected in sum of eighteen patients, nine of them (75%) diagnosed with PV and rest of them (N=9, 56.3%) diagnosed with ET. Calreticulin mutation was detected in four patients diagnosed with ET and JAK2V617F negative (57.1%). MPLW515K/L wasn't detected in any of patients. Neither of mutations was detected in three of the patients, so they were triple negatives. At the time of diagnosis, 15 (53.5%) patients were at high risk and cytoreductive treatment was started. Portal vein thrombosis was present in two patients with PV at the time of diagnosis and who were also JAK2V617F mutation positive. Five patients had a medical history remarkable for thromboembolic event (four patients with coronary artery disease and one patient with ischemic cerebrovascular event), all of which were JAKV617F mutation positive.

**Conclusion:** Pathogenesis, classification and risk groups of CMPDs have been well characterized with the identification of some genetic mutations in recent years. The first of these somatic mutations is JAK2617F, found to be approximately 95% positive in PV, approximately 50-60% in ET and PMF, whereas calreticulin and MPL mutations aren't detected in PV. According to literature, calreticulin mutation is positive approximately 25% and 17%, while the MPL mutation is approximately 6% and 10% in the ET and PMF, respectively. The positivity of calreticulin was found to be associated with a lower risk of thrombosis, it was associated with lower hb/htc and higher platelet levels. The effect of any mutation on leukemic transformation and

surveillance is unclear. JAK2V617F, CALR and MPL are the most frequently identified somatic mutations in the pathogenesis of CMPD, which are now important in the diagnosis, risk classification and follow-up of the disease and gain importance in the personalization of patients' treatments.

## Coagulation and Infections

### OP-15

#### Flow cytometry analysis of the acute EBV infection among patients with haematological disorders

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**Objective:** Flow cytometric immunophenotyping is used in the evaluation of leukemias and lymphomas, moreover, this test can be relevant for patients suspected for infectious mononucleosis. It is known that Epstein-Barr virus (EBV) can be associated with haematological disorders. In this study, we aimed to evaluate the immunophenotypic characteristics of lymphocyte populations and subpopulations in peripheral blood among EBV anti-viral capsid antigen (VCA) IgM seropositive patients with haematological disorders including Hodgkin (HL), non-Hodgkin lymphoma (non-NHL), acute myeloid leukemia (AML), Acute lymphoblastic leukemia (ALL) and multiple myeloma (MM).

**Methodology:** The study included 31 patients with haematological disorders (3 with HL, 9 with non-NHL, with 3 AML, 13 ALL and 3 MM) whose samples were anti-VCA IgM positive or anti-EBV nuclear antigen (EBNA) IgG positive with immunoblot assay. T-lymphocyte subsets were measured in peripheral blood by the flow cytometry. Surface antigens (CD3 and CD19) were used to identify T- and B-cells. CD3+ T-cells were analyzed for CD4 and CD8 cell expression. And also B-cells were analyzed for CD20, CD22 and CD23 antigens. Patient data were obtained from the hospital medical information registration system retrospectively.

**Results:** The mean age was 24.68±19.91 years. EBV VCA IgM seropositivity was seen in 11 patients and the remaining 20 patients were positive for anti-EBNA IgG. When compared with EBV VCA IgM negative cases, there were no statistically significant differences regard to CD4+, CD8+ T cells and CD20+, CD22+ and CD23+ B cells counts ( $p>0.05$ ). Additionally, the CD4+/CD8+ ratio was not found to be decreased significantly in anti-VCA IgM seropositive patients.

**Conclusion:** The findings of this study claim that the immunophenotypic features of acute EBV infection including a decrease in B-cells and the CD4+/CD8+ ratio are not sufficient to establish the diagnosis of acute infectious mononucleosis among patients with haematological disorders

### OP-16

#### An approach to superwarfarin poisoning due to Brodifacoum exposure

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**Objective:** Superwarfarins are long-acting, oil-soluble anticoagulants. They have a mean half-life of approximately 24 days, which is approximately 100 times stronger than warfarin. Here we aimed to present the case of a patient we followed who had superwarfarin poisoning after spraying with Brodifacoum as a rodenticide.

**Case report:** A 25-year-old female patient who was previously healthy was admitted for non-traumatic ecchymoses that lasted for 1.5 months and prolonged hemorrhage that lasted for 2 days following a tooth extraction. It was determined that the patient had been exposed to the rat poison Brodifacoum approximately 1 month ago. In the physical examination, arterial blood pressure was 120/70 mmHg, pulse was 76/min, and there were several ecchymoses of approximately 1×1.5 cm in size in the extremities. The results of examination of other systems were normal. Laboratory examination results were as follows: Hgb, 12.5 g/dL; MCV, 85.8 fL; leukocyte, 12,500/mm<sup>3</sup>;

platelets, 279,000/mm<sup>3</sup>; prothrombin time (PT), 147.1 s; INR, 11.44; partial thromboplastin time (aPTT), 70.7; bleeding time, 10 min 15 s; fibrinogen, 472 mg/dL; D-dimer, negative; Factor VII, 3%; Factor VIII, 100%; vWF, 122%; Factor IX, 23%; Factor V, 41%; and Factor X, 6%. Mixture test result was normal, and liver and kidney functions were normal. In the peripheral smear, platelets were aggregated, erythrocytes and normocytes were normochromic; and 70% PMNL, 23% lymphocytes, 6% monocytes, and 1% eosinophils were detected in the blood count. Superwarfarin poisoning due to Brodifacoum exposure was considered in the patient. After the patient was administered 20-mg intravenous vitamin K and fresh frozen plasma for active bleeding, INR result was 1.3. The patient was followed up with 3×20-mg oral vitamin K. During the 2-month follow-up period, vitamin K dose was gradually reduced and discontinued.

**Conclusion:** Rodenticides are toxic substances that are exposed most frequently due to their high availability and can be lethal even in a single dose in humans. Many of these are long acting anticoagulants, such as brodifacoum, bromodiolon, difenacoum, pidon, and valon, and are referred to as "second generation anticoagulants" or "superwarfarins." Because superwarfarins have long-term anticoagulant effects at low doses, in case of exposure to them, they show anticoagulant effects by inhibiting the synthesis of clotting factors through vitamin K. As a result of impairment in clotting mechanism, ecchymosis, gingival bleeding, subconjunctival hemorrhage, massive hematemesis, and intracranial bleeding can occur. In patients with superwarfarin poisoning, long term 50–200 mg daily oral vitamin K1 should be administered. In conclusion, patients with anticoagulant effects following exposure to superwarfarin require close monitoring and repeated vitamin K therapy for several weeks.

## Immune Thrombocytopenia

### OP-17

#### IL-1beta, IL-6 and TNF-alpha levels in women working in half- or whole-night shifts

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**Objective:** Aim of the current study was to determine the effects of perturbed sleep in women working in half- and whole-night shifts on plasma IL-1beta, IL-6 and TNF-alpha concentrations.

**Methodology:** Following ethical consent from Malatya Clinical Experiments Ethics Committee (No 2016/197), female nurses who have been working in Turgut Ozal Health Center at least for 5 years were volunteered in the study. Participants were matched for the menstrual phases as being follicular and luteal. Criteria for inclusion were being healthy, being at the ages of 18-40, not smoking, not using painkillers, not being in the stage of menstruation. Study compared the three groups of nurses under either normal daytime shifts (Group 1, n=20), or whole night shifts between 16:00-08:00 h (Group 2, n=20), or half-night shifts between 16:00-24:00 h (Group 3, n=20). Blood samples were taken at the beginning and at the end of the shifts to assess plasma IL-1beta, IL-6 and TNF-alpha levels. One-way ANOVA was used for the statistical comparisons and the data is presented as mean±SEM.

**Results:** IL-1beta levels were higher in the beginning of the shifts than the end of the shifts ( $p=0.000$ ). Additionally, IL-6 and TNF-alpha levels were higher in the nurses under whole-night shifts ( $p<0.05$ ).

**Conclusion:** Increased IL-1beta levels in the beginning of the shifts might be representing body's early response to an approaching challenge, namely the hard work required during the shifts. Moreover, higher cytokine levels in the nurses having whole-night shift suggests that this schedule activates the immune system and, therefore, a special attention needs to be paid to its long-term consequences. Supported by Scientific Research Projects Unit (BAP) of the Inonu University (2017/649).

**OP-18****Thrombocytapheresis decreases systolic blood pressure and increases sympatho-vagal balance**P. Çakan<sup>1</sup>, M. Özgül<sup>2</sup>, M. Erkurt<sup>2</sup>, E. Kaya<sup>2</sup>, S. Yıldız<sup>1</sup>, İ. Kuku<sup>2</sup><sup>1</sup>Departments of Physiology Faculty of Medicine, Inonu University, Malatya, Turkey; <sup>2</sup>Departments of Hematology, Faculty of Medicine, Inonu University, Malatya, Turkey

**Objective:** The autonomous nervous system tightly controls the blood pressures (BP) and heart rates (HR) through its sympathetic and parasympathetic (vagal) branches. During the process of blood withdrawal for transfusion, blood pressure decreases in the donor and this is eventually compensated by increased heart rate. However, the effect of selective removal of platelets on that system is not well known. Therefore, the current study aimed to investigate the effects of thrombocytapheresis on sympathovagal balance by means of heart rate variability (HRV) technique.

**Methodology:** Following ethical approval of the study by the Malatya Clinical Experiments Ethics Committee (No 2018/62), a total of 100 platelet donors were included in the study (age 29.0±0.9 years, weight 77.0±1.4 kg, BMI 25.8±0.7). Blood pressures were measured before and after the transfusion. HRV was assessed by 5-min continuous electrocardiographic recordings at four occasions, i.e. 5 min before (-5 min), at 10 min (10 min), at 45 min (45 min), and at end (last 5 min) of thrombocytapheresis. HRV parameters included time domain variables (SDNN-standard deviation of normal RR intervals, rMSSD- root mean square of the successive differences, pNN50-percentage of successive NN (R-R) intervals that differ by more than 50 ms) and frequency-domain variables (VLF-very low frequency, LF-low frequency, HF-high frequency and LF/HF ratio) together with HR. Normally distributed data were analyzed by paired t-test but the data with non-normal distribution were compared by Wilcoxon signed rank test. Significance was set at p≤0.05 and the results are shown as mean±SEM.

**Results:** Systolic BP decreased from 112.9±1.3 mmHg to 107.3±1.3 mmHg.

**Conclusion:** The results show that thrombocytapheresis decreases systolic blood pressure and increases heart rate. Additionally, thrombocytapheresis also decreased the HRV parameters which are frequently associated with better health status. Moreover, LF/HF, accepted as marker for sympathovagal balance, is increased dramatically towards 45 min of thrombocytapheresis suggesting that sympathetic system is markedly activated by this process.

**OP-19****Management of adult immune thrombocytopenia: single-center experience of 9 years**

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**Objective:** Immune thrombocytopenia (ITP) is a hemorrhagic disease with autoimmune destruction of thrombocytes. There is no established clinical or biochemical diagnostic criterion. The diagnosis of ITP is based on the exclusion of all causes of secondary thrombocytopenia. Recent studies have shown that in addition to antibody-mediated platelet destruction, Fc-independent platelet clearance, attenuation of the platelet-mediated hepatic thrombopoietin generation and decreased production of CD8 + T-suppressor constitute the pathogenesis of ITP. Most of the cases are asymptomatic. Symptomatic patients have thrombocytopenia related skin and mucous membrane bleeding, they can also experience fatigue and a reduced quality of life.

**Methodology:** 110 patients with ITP were retrospectively evaluated. 104 (94.5%) patients required treatment and all cases received steroid agents as first-line therapy. There was no indication for the treatment in 6 (5.5%) cases. Steroid-resistant or dependent patients have undergone splenectomy or received combined treatment as second line therapy.

**Results:** In our study, 110 patients with ITP were analysed for the clinical characteristics and response to treatments. The median age of the patients was 45 (20-90) years. Of the 110 patients, 27 were males (24.5%) and 83 were

females (75.5%). Median follow-up duration was 37 (1-190) months. Mean and median platelet counts were 16,000/µL and 8,000/µL at presentation, respectively. At the time of diagnosis, 19 (17.3%) cases were asymptomatic, 87 (79.1%) cases had minor bleeding and 4 (3.6%) had major bleeding. Of 110 ITP cases 6 (5.4%) were followed without any treatment; 95 (86.4%) received standard dose prednisolone (MP), 9 (8.2%) received high dose dexamethasone; remission rates were 80% (n=76) and 88.9% (n=8), respectively. There was no significant difference between MP and dexamethasone in respect of remission rates (p=1.00). Of 59 refractory and recurrent ITP cases 39 (66.1%) were treated with splenectomy (76.9% remission), 20 (33.9%) with rituximab or other immunosuppressives (75% remission). Complete remission was obtained in 77 (70%) patients and partial remission in 32 (29.1%) patients in the final evaluation of the patients.

**Conclusion:** Corticosteroids are still most effective treatment as a first line option in ITP patients. Dexamethasone have similar efficacy to MP with shorter treatment duration and fewer side effects. Splenectomy keeps its major role as a second-line treatment modality with high remission rates.

**Lymphomas****OP-20****Gene expression analysis of plasmablastic lymphoma identifies down regulation of B cell receptor signaling and NF-kappaB-related genes compared with diffuse large B-cell lymphoma: a single institute experience from Saudi Arabia**G. Elyamany<sup>1</sup>, M. Aljabry<sup>2</sup>, A. Alzahrani<sup>1</sup>, S. Asiri<sup>1</sup>, M. Al Shahrani<sup>1</sup>, O. Alsuhabani<sup>1</sup><sup>1</sup>Prince Sultan Military Medical City, Riyadh, Saudi Arabia; <sup>2</sup>King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia

**Objective:** Plasmablastic lymphoma (PBL) is an aggressive subtype of non-Hodgkin's lymphoma (NHL) which shares many morphologic and immunophenotypic features with multiple myeloma. There is no standard chemotherapy protocol for treatment of PBL. Pathogenesis of PBL is poorly understood in terms of molecular events and signaling pathways; thus limiting the utility of new-targeted therapies. Proteasome inhibitor (bortezomib) blocks NF-κB pathway, thereby sensitizing myeloma cells to cytotoxic chemotherapy, however, clinical efficacy of bortezomib in PBL remains unknown. Gene expression profiling (GEP) offers a unique opportunity to comprehensively analyze the phenotype of cell populations and provided insights and better understanding of the pathophysiology, molecular characteristics and biology of PBL. Our study could help in the development of novel agents or new treatment regimens for PBL.

**Methodology:** In this study, we assessed the GEP pattern of most important pathways related to lymphoma ontogeny in a series of small cohort of PBL compared with similar gene set in reactive lymphoid tissue (tonsils) and aggressive (relapsed) DLBCL. Diagnosis of PBL was based on morphology and immunoperoxidase staining criteria as established by World Health Organization (WHO) 2008 classification system. GEP (154 gene-set) was assessed by Nano string technology, in a cohort of PBL patients (PBL; n=8); utilizing mRNA from formalin fixed paraffin embedded diagnostic biopsy tissue. This data set was compared with similar gene set in reactive lymphoid tissue (tonsils; n=30) and aggressive (relapsed) DLBCL patients (DLBCL; n=60). Data was analyzed using nSolver software (Nanostring Technologies Seattle WA).

**Results:** Marked suppression of PAX5/BCR/MYD88 pathway as well as germinal center related genes confirmed the GEP signature of PBL in all pts. All NF-κB-related genes were down regulated in PBL pts.; while downstream genes related to proliferation (c-myc, Cyclin Ds) were up regulated (>1.5 fold change; p4.0 fold increase); compared to aggressive DLBCL and reactive tissue.

**Conclusion:** This data, signify the differential expression in genetic pathways in PBL from DLBCL and control group. Our findings could help in the development of novel agents or new treatment regimens for PBL. This study provides informative data to determine the clinical efficacy and therapeutic importance of proteasome inhibitors (Bortezomib) among PBL patients as genes related to NF-κB pathway were significantly suppressed in PBL.



**OP-21****Can Ki-67 expression determine prognosis better at double/triple expressor lymphoma?**

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**Background:** Diffuse large B cell lymphoma (DLBCL) is the most common type of non-hodgkin lymphoma. IPI scoring system and some biomarkers such as c-myc are in use to determine the prognosis of the patients. Recently it has been named as double hit lymphoma when bcl-2 (or bcl-6) positivity is detected in addition to c-myc positivity obtained by FISH technique, and all of these three are positive, it has been called triple hit lymphoma. If these markers are only detected with immunohistochemistry, then it's been named as double expressor (DE)/triple expressor lymphoma (c myc and bcl2 ± bcl6). **Methodology:** 55 patients (28 female, mean age:66±18) who were diagnosed DLBCL and have complete pathological results were enrolled to our study. Mean IPI score was 2±1. Mean Ki 67 rate was 37.6±25.6. There were 7 DE patients (2 of them alive) and 4 TE patients (2 of them alive). Our DE lymphoma rate was 11.8% and TE lymphoma rate was 6.7% among our DLBCL patients. No t(8,14) positivity obtained by FISH method was detected among blood samples. We did not search this marker at tissue samples. The median survey was 16.2±2.8 months for DE and 16±7 months for TE, and 28.7±3 months for others; although P value had no clinical significance. Average Ki-67 rate was 37.6±25.6%. All of the patients were separated due to Ki-67 below or above 40% and Kaplan-Meier analysis was performed (log rank p=0.02). The positivity rate based on c-myc value was 32±4 and the negativity rate was 18±5 (p=0.04)

**Results:** The prognosis of the DE and PE patients differs by considering Ki 67 evaluation although not statistically significant (p=0.59). Ki-67 value positive 6 patients had mean survey of 11.6±5.3 months in contrast to 5 negative patients as 21.6±8.2 months. If we evaluate non DE/TE patients as Ki-67 status (below or above 40) ; the mean survey among 17 patients was 22.7±4.7 months at Ki67 positive group and 34.7±4.2 among 27 patients at negative group (p=0.113).

**Conclusion:** The interpretation of our results is controversial because of lack of our patient number. It is important to consider c-myc at DLBCL prognosis evaluation. In addition, using Ki 67 index in clinical practice would be a useful guide for prognosis estimation among DE&TE and non-DE&TE patients. The standard treatment protocols must be reevaluated for these patients.

**OP-22****A first-time report on the co-occurrence of sarcoidosis and ALK(-) CD30(+) anaplastic large cell lymphoma that is highly responsive to brentuximab vedotin treatment**

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**Objective:** Sarcoidosis is known to be associated with higher incidence of solid tumors and hematological malignancies. ALK(-)CD30(+) anaplastic large cell lymphoma is a type of non-Hodgkin lymphoma showing poor prognosis, and seldom co-occurs with sarcoidosis. As this rare and highly mortal disease did not respond to classical chemotherapies and showed remission with brentuximab vedotin (BV) treatment, we are presenting our first case reported from Turkey hoping to contribute to the literature.

**Case report:** A 21-year-old male patient presented to the emergency department with complaints of fever, abdominal pain and distention. Abdominal USG examination revealed free fluid accumulations in perihepatic, perisplenic and pelvic regions, and numerous lymph nodes within the abdomen along midline at peripancreatic, paraaortic, paracaval areas. Thorax computed tomography (CT) showed minimal pericardial effusion, multiple lymphadenopathies, several lymph nodes at left axillary region and left-sided pleural effusion with 1 cm thickness. Additionally, abdominal CT revealed diffuse free fluid accumulation in the abdomen. According to his past medical history, the patient was diagnosed with sarcoidosis 8 years ago. Patient's left supraclavicular lymph node biopsy result, histomorphological

and immunohistochemical findings were primarily consistent with ALK(-) CD30(+) anaplastic large cell lymphoma. Patient's pleural fluid sample and bone marrow sample were also found to be affected, and therefore the patient was considered stage 4. CHOEP treatment was initiated. The patient's abdominal distention persisted, and he also developed difficulty in breathing. Totally 2000 cc/day drainage was recorded from thoracentesis and paracentesis catheters. The patient's fever persisted on the 15th day of CHOEP chemotherapy despite parenteral antibiotic administration, and his overall condition failed to improve; and EPOCH chemotherapy was initiated. However, his fever returned on the 15th day of EPOCH chemotherapy, with worsening overall condition and his WBC 52,200/µL. BV treatment was initiated. The patient achieved complete remission after 4 cycles of BV treatment, and received totally 8 cures of BV. The patient's sarcoidosis did not show exacerbation during this treatment. For consolidation, autologous stem cell transplantation was planned for the patient.

**Conclusion:** The risk of lymphoma development on top of sarcoidosis should be kept in mind, and patients should be carefully monitored in this regard. BV is a very effective agent in cases with CD30(+) ALCL. We hereby presented our case with the hope of contributing to the related literature as our case is the first reported case having sarcoidosis concurrent with ALK(-)CD30(+) ALCL, and showed excellent response to BV treatment.

**OP-23****Mitoxantrone-melphalan conditioning regimen for autologous stem cell transplantation in relapsed/refractory lymphoma**

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**Objective:** High dose chemotherapy followed by autologous stem cell transplantation (ASCT) has become the standard approach for patients with relapsed/refractory Hodgkin lymphoma (HL) or non-Hodgkin's lymphoma (NHL). In this study, we report the outcome of the mitoxantrone-melphalan conditioning regimen for lymphoma.

**Methodology:** 53 patients who were relapsed/refractory HL (n=14) and NHL (n=39) using mitoxantrone and melphalan regimen followed by ASCT have been included in the study. The transplant regimen consisted of mitoxantrone (60 mg/m<sup>2</sup>) and melphalan (180 mg/m<sup>2</sup>) followed by peripheral blood stem cell infusion (PBSC).

**Results:** Prior to high dose chemotherapy, 37.7% of the patients were in complete remission (CR) and 45.3% were in partial remission (PR), and 16.9% had stable or progressive disease. After high dose chemotherapy and PBSC, 44 out of 51 patients achieved CR (86.2%). CR was achieved in 24 out of 33 patients (72.7%) who were transplanted in active disease. At a median follow up of 25.4 months (1.8–131.3 months) after ASCT, 13 patients relapsed/progressed and eight patients died. The estimated two-year overall survival (OS) was 81.9%, event-free survival (EFS) was 59.3%, respectively. According to pre-transplant evaluations, OS was 80.6% in pre-transplant CR group, 91.3% in PR group and 56.3% in refractor group. However, the duration of the median OS was not reached in all groups. There was a statistically significant difference between the groups (p=0.053). There was no significant survival difference between patients with DLBCL, HL and others. The 5-year OS, EFS of patients with DLBCL were 75.6%, 39.2%, respectively, which were not significantly different from those of patients with HL (90.9%, 66.7%, respectively; p=0.59, p=0.91).

**Conclusion:** High dose chemotherapy followed by ASCT is an effective conditioning regimen in relapsed/refractory lymphoma patients who are undergoing ASCT.

**OP-24****Analysis of clinical and histopathological prognostic factors in gastrointestinal system lymphomas**

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**Objective:** The gastrointestinal tract is the most common site of extranodal lymphoma involvement (5-20%) and the most frequent type is non-hodgkin lymphoma. GI involvement is often secondary to widespread nodal disease, but primary lymphomas are also rarely seen. In this study, the relationship between clinical and histopathological features and prognosis in primary gastrointestinal lymphomas (PGIL) was investigated.

**Methodology:** 111 patients diagnosed as lymphoma from gastrointestinal system biopsy or surgical resection materials at our center from 2006 to 2018 were studied. The impact of histopathological findings and clinical parameters on prognosis was assessed by evaluating demographic data, primary/secondary involvement status, stage, serum lactate dehydrogenase (LDH) levels, International Prognostic Index (IPI) and performance scores, survival rates and treatment procedures.

**Results:** Ninety of the cases were diagnosed by endoscopic biopsy and 21 by surgical resection. 75 of the samples were from stomach, 20 small bowel, 14 colon-rectum and 2 pancreas. 54.1% (n=60) of the patients were male and 45.9% (n=51) were female. The median age at diagnosis was 66. Histopathologically, 106 (95.4%) were B-cell and 5 (4.6%) were T-cell lymphoma. The distribution of gastric lymphomas were as follows: 65 (86.6%) diffuse large B cell lymphoma (DLBCL), 6 (8%) MALT lymphoma, 1 (1.3%) Burkitt's lymphoma, 1 (1.3%) were T-cell lymphoma (unclassifiable). After the exclusion of the cases with secondary involvement or lost to follow-up there were sixty-nine primary GIS lymphoma cases. According to the Lugano staging system 39 (57%) of the cases were stage I, 17 (25%) were stage II (1), and 3 (4%) were stage II (2), 5 (7%) were stage IIE and 5 (7%) were stage IV. When the patients were evaluated according to the treatment modalities, 41 patients received only chemotherapy (CT), 8 patients had CT and radiotherapy (RT), 3 patients had surgery and CT, and 1 patient received only RT. There were no data-follow-ups of 16 patients. Of the 41 patients who received CT alone, 29 had CR, 4 had PR, and 4 had progressive disease. As 2 patients died during treatment and 2 patients were out of follow-up no response assessment was achieved. The overall survival rates of primary GIS lymphomas were 67%, 56% and 47% for 1 year, 3 years and 5 years respectively. When the cases were grouped as gastric (n=43) and intestinal (small bowel, colon) (n=19) lymphomas, statistically significant correlation was found between elevated serum LDH level and primary gastric lymphomas (p=0.033). Serum LDH elevation (p=0.029), poor performance score (>1) and surgical resection (p2) (p=0.009) and surgical resection (p=0.003) were associated with worse progression-free survival (PFS).

**Conclusion:** Gastrointestinal system lymphoma is a rare and heterogenous disease which may be affected by various clinical and demographic parameters. Thus, it is essential to evaluate the cases with multidisciplinary approach.

**OP-25****Clinical aspects of primary thyroid lymphoma**

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**Objective:** Primary thyroid lymphoma (PTL) is a rare malignant disease, which can be life threatening due to airway obstruction and rapidly growing mass. Women are more commonly affected than men. Patients typically present in the sixth or seventh decade of life, with men often presenting at a younger age than women. Most thyroid lymphomas are non-Hodgkin lymphomas of B-cell

origin. The only known risk factor is preexisting Hashimoto's thyroiditis. The most common type of PTL is diffuse large B-cell lymphoma, which behaves in a more aggressive manner than mucosa-associated lymphoid tissue lymphoma. Fine needle aspiration cytology (FNAC) is an important tool in early diagnosis of PTL. Patients with PTL were retrospectively evaluated and are hereby presented. The objective of the study is to summarize our experiences in the diagnosis and prognosis of different subtypes of PTL.

**Methodology:** The clinical data of 19 PTL patients who were treated in our hospital from January 2000 to December 2017 were retrospectively analyzed to determine the typical clinical and sonographic profiles of thyroid lymphomas.

**Results:** All the patients showed symptoms of rapidly developing neck swelling or mass sensation when they underwent diagnostic procedures. Among nineteen patients, women (n=16) were more commonly affected than men (n=3). Six patients (32%) were presented with large, painless thyroid mass accompanied by severe obstructive symptoms of the upper respiratory track. The mean age at diagnosis was 59 (16-87) years. More than half of the patients were (n=11) euthyroid and eight patients were hypothyroid. Those eight hypothyroid patients and one euthyroid patient had hashimoto thyroiditis. Ultrasound findings revealed that five patients (26%) showed diffuse heterogeneous hypoechoic parenchyma with intervening echogenic septa-like structures and fourteen (74%) showed markedly hypoechoic masses. Ten patients had nodular lesions with indistinct borders, three patients had macrocalcification and four patients had nodular microcalcification. Nine patients (47%) underwent total thyroidectomy. Histological analysis of the lymphomas using paraffin-embedded sections revealed that two lymphomas were Hodgkin lymphoma and seventeen lymphomas were non-Hodgkin lymphoma with a B cell origin. Extranodal marginal zone B cell lymphomas of the mucosa-associated lymphoid tissue lymphoma type in one (MALT, 5%), diffuse large B cell lymphoma in thirteen (68%), follicular lymphoma in two (10%) and Burkitt lymphoma in one (5%). Only one patient progressed with central nervous system involvement and died in following two months. The analysis showed complete remission in thirteen patients (68%) and progressive disease in six patients (31%). Thirteen patients (68%) were alive at the time of data analysis. The median OS could not be achieved due to early deaths.

**Conclusion:** Primary lymphoma of the thyroid is a rare but distinct entity from other thyroid neoplasias since its treatment differs. PTL should be suspected when a patient presents with an enlarging neck mass. Prompt and accurate detection and diagnosis in the early phase of PTL are crucial for the treatment of this disease. Biopsy should be performed rapidly. Surgery can be considered in the setting of compressive symptoms or airway compromise.

**Multiple Myelomas****OP-26****The outcome of autologous stem cell transplantation in multiple myeloma in Saudi Arabia: a single institution experience**

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**Objective:** Data from on clinical outcomes of autologous stem cell transplantation (ASCT) in multiple myeloma (MM) patients from developing countries is lacking. The purpose of this study is to evaluate the outcomes of ASCT in MM from a tertiary care institution's database.

**Methodology:** A retrospective review of electronic medical records of patients with the diagnosis of MM who underwent ASCT in a single institution (KFSHRC) during the period from January 1984 to April 2015.

**Results:** One hundred and seventy one patients with the diagnosis MM were recorded in the KFSHRC Tumor Registry during the period from 1984 to 2015. The median age on presentation was 51 years (range 23-69 years). There were 100 male and 71 female patients. Most common subtype was IgG/Kappa (48%). Most patients presented with advanced ISS stage III (43%). Disease status before ASCT: (38% CR, 37% PR, 11% VGPR, 12% sCR). High-dose melphalan 200 mg/m<sup>2</sup> was used for conditioning. 18% of patients received

maintenance therapy after ASCT while 82% did not. Five-year overall survival was 85% while 5-year disease free survival was 34%.

**Conclusion:** This is the first study that reports the outcome of ASCT in MM patients in Saudi Arabia. Mean age at presentation is lower than average in western countries. Data shows better median OS than what is reported in literature from the developed countries. This needs further investigation to delineate the differences in biology and characteristics of the disease between patients in Saudi Arabia and the developed countries.

#### OP-27

##### Case report: multiple myeloma transformation after allogeneic stem cell transplantation (ASCT) for AML

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**Objective:** This is a case presented with Multiple Myeloma diagnosis 1year after allogeneic stem cell transplantation for the therapy of AML subtype-M6.

**Case report:** In December 2014 a 61-year-old man attended to the hospital for weight loss, bone pain, loss of appetite and weakness. It is diagnosed as AML subtype M6 after the physical examination and regular tests. Induction therapy (3+7) was performed after this diagnosis. 3 cycles consolidation therapy was done as a complete response achieved after the induction therapy. ASCT was done from fully compatible siblings (from his brother with 10/10 HLA) in September 2016 as it's known a very high-risk subtype. In September 2017 bone marrow biopsy was repeated because of the bone pain and the weakness symptoms. It found 15-20% of plasma cell infiltration as the result of this biopsy. IgG kappa band was found as the result of the serum immunofixation. Genetic tests were negative. IgG was 2656 mg/dl, beta2 microglobulin 4.19 mg/dl and kappa total light chain 762 mg/dl. The patient was multiple myeloma Durie Salmon IA, ISS II, R-ISS II and on November 9th 2017 the VCD therapy was started. Bone marrow re-biopsy was determined remission after 4 cycles of VCD. Autologous stem cell transplantation was performed on 6th of April 2018 after Melphalan 200 mg/m<sup>2</sup> therapy. On April 19 2018 neutrophil was engrafted and also thrombocytes engrafted one day after. The remission was observed at 30 and 90 days follow-up.

We want to present this case because of according to our research there is no other case like this in the literature.

#### OP-28

##### Factors associated with renal failure and renal function recovery in multiple myeloma

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**Objective:** Renal failure is a common initial presentation of multiple myeloma (MM) and causes significant morbidity and mortality. This study aimed to investigate the factors associated with renal failure and renal recovery in MM.

**Methodology:** The clinical features and prognostic factors were retrospectively analyzed for 169 newly diagnosed MM patients at single center. Statistical analyzes were performed using chi-square test using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). A value of less than 0.05 was considered significant. The patients with renal failure (Cre  $\geq$ 2mg/dl) at diagnosis were compared with the cases with normal renal function (Cre <2 mg/dl). Patients with renal failure at diagnosis were further analyzed with regard to renal function recovery after 2 and 4 cycles of anti-myeloma treatment.

**Results:** The median age of the patient population was 64.8 (39-88) years with male/female 98/71. Forty (23.7%) patients presented with renal failure and 19 patients required hemodialysis. According to the International Scoring System, 43 (25.4%) patients had low (I), 46 (27.2%) patients had intermediate (II), and 80 (47.3%) patients had high (III) ISS score. There were no significant difference between the patients presenting with normal renal function (RN) and the patients presenting with renal failure (RF) in terms of age, gender, bone involvement, the ratio of first-line bortezomib containing regimen. Compared with the RN group significantly more patients in RF

group had light chain myeloma (p=0.028), high ISS (p=0.003), elevated serum lactate dehydrogenase value (p=0.001), initial hypercalcemia (p=0.001) and anemia (p=0.002). Response rates ( $\geq$  partial response (PR)) after 2 cycles of anti-myeloma treatment and referral to high dose therapy and autologous transplantation were similar in both groups. However, in the RN group, the ratio of patients achieving  $\geq$ PR after 4 cycles of treatment was higher than RF group (p=0.019). Sixteen (42%) of the forty patients with renal failure at the time of initial diagnosis fully recovered after first-line anti-myeloma treatment. Patients who are renal functions recovered (RFc) were compared with the patients whose renal functions did not recover (RFnc). There was no statistically significant difference between the RFc and RFnc groups in terms of age, gender, ISS, serum lactate dehydrogenase level, hypercalcemia, anemia, bone involvement and initial requirement for hemodialysis. Response ( $\geq$ PR) to 2 cycles of anti-myeloma treatment was similar in each group. On the other hand, having light chain myeloma (p=0.012) and lambda light chain (p=0.002) had negative impact on renal function recovery. Fourteen of the 27 patients (51.9%) who received bortezomib containing first-line treatment had renal function recovery. Renal function recovery was significantly associated with the use of bortezomib in firstline therapy (p=0.004).

**Conclusion:** Initial presentation with renal failure is a poor prognostic feature and has negative impact on response to anti-myeloma treatment. On the other hand, renal function recovery is not always parallel to myeloma response. Along with sufficient supportive therapy, having a non-light chain myeloma and prompt initiation of bortezomib based first-line treatment seem to be best indicators of renal function recovery.

#### Myelodysplastic Syndromes

##### OP-29

##### Determination of p53 genetic polymorphisms in myelodysplastic syndrome cases

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**Background:** Myelodysplastic syndrome (MDS) is a clonal disease with reduced hematopoiesis and elevated apoptosis and increased risk of acute myeloid leukemia (AML) conversion. The pathogenesis of MDS has not been fully elucidated. Approximately 50% of patients have a karyotype abnormality and this ratio is increased to 80% in the secondary MDS. P53 is a key regulator of stem cell homeostasis that impacts an array of cellular functions including genomic surveillance, cell-cycle regulation and apoptotic and inflammatory response. Since P53 is involved in the maintenance of genomic integrity, it is one of the most frequently genetically altered genes in various cancer types.

**Aim:** In our study, to investigate the effect of p53 single nucleotide polymorphisms (SNPs) on abnormal differentiation of MDS, we examined 4 common polymorphisms (rs35163653, rs35993958, rs1800371, rs1042522) of p53 gene in 100 patients diagnosed with MDS.

**Material and methods:** After DNA extraction from blood samples of MDS cases, PCR analysis was performed via melting curve analysis for each p53 polymorphism. The results were evaluated using LightCycler software and SPSS ver 25.0.

**Results and discussion:** Among the 4 polymorphisms studied, a significant change was found in the study group in rs1042522 C/G (R72P) conversion polymorphism. In our study, we found that non-ancestral allele is higher for rs1042522 polymorphism (C:0,295 G:0,705). rs1042522 polymorphism is associated with hematologic cancers in some studies; similar to previous findings, our data shows that this polymorphism is associated with MDS. Our allele frequency results are consistent with HapMap allele database for Caucasians population.

**Conclusion:** Genome-wide association studies have shown linkage SNPs that alter p53 function and select malignancies. One of the most well-studied nonsynonymous SNPs, rs1042522 (R72P), located within codon 72 has been implicated in susceptibility and predisposition to solid tumors. Thus, we investigated its effect upon hematological disorders and concluded that



people with the rs1042522 polymorphism are at increased risk of MDS. Our study is the first one in the literature showing the impact of rs1042522 polymorphism in the MDS patient group. We may suggest that rs1042522 polymorphism can be used as a marker to diagnose MDS in the future with clinical correlations.

### Stem Cell Transplantation

#### OP-30

##### Evaluation of B and T cell chimerism after allogeneic stem cell transplantation in hematologic malignancies

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**Objective:** The goal of chimerism monitoring after allogeneic haematopoietic stem cell transplantation is to reveal the conditions that may be curable in the early stages and have an effect on survival like disease relapse, graft rejection and GVHD, before the settlement of the clinical conditions. The aim of this study is to evaluate chimerism of B and T cell lineage comparing with total leukocyte chimerism results and to determine their relationship between disease relapse, graft rejection, GVHD and death.

**Methodology:** Patients with a hematologic malignancy, undergone allogeneic hematopoietic stem cell transplantation from a HLA matched sibling or unrelated donor followed between November 2014 and November 2016, in the Department of Hematology Intensive Chemotherapy and Transplantation Unit, were included in this study. In addition to the standard chimerism carried out on 28th and 90th days post-transplant, samples were taken simultaneously for B and T cell chimerism evaluation. The results of this evaluation were analyzed according to their success in predicting clinical conditions such as relapse, disease-free survival and GVHD. The relationship between the chimerism situation and death, relapse and chronic GVHD was investigated by Fisher's 2x2 tables verification analysis because of the number of cases. Kaplan-Meier analysis were used for survival evaluation.

**Results:** The average age of the 21 patients included in the study was 38.1±13.2 years (17-60). The frequency distribution of myeloproliferative neoplasms were AML (n=6), MDS (n=5), CLL (n=2), PMF (n=1). Lymphoproliferative neoplasms constituted 1/3 (33.3%) of transplantation indications and the distribution was Hodgkin lymphoma (n=3), ALL (n=2), CLL (n=1), ve follicular lymphoma (n=1). Only one patient (4.7%) had relapse. 11 (52.3%) patients developed the acute form of GVHD, while 10 (47.6%) developed chronic form. Chronic GVHD was as classic form in 5 patients, and as overlap (OL) syndrome in 5 patients. Disease-free survival was found to be 1-14 months, with an average of 7.25±3.8 months. The average overall survival was found to be 11.38±4.8 months (ranging between 4 and 20 months). No significant relationship was established between total leukocyte chimerism, B and T chimerism and relapse and event-free survival. The difference between the groups was not found to be statistically significant (p value respectively 0.584 and 0.380).

**Conclusion:** Chimerism analysis of hematologic malignancies may be not an effective method for short-term follow-up in the early stages. Analysis of leukocyte subsets in early stages also showed no significant difference with the total leukocyte chimerism. Due to the low number of patients in relapse, total leukocyte chimerism and leukocyte subset analyses were not found to be superior to each other. Dynamics of the relationship between leukocyte subset chimerism analyses and immune reconstitution was not informative because of the low patient number. In conclusion, although B and T cell analyses is an applicable method in clinical practice, especially for relapsed patients more trials with higher number of relapsed cases are needed for further assessment.

### Gastrointestinal Cancer - Colorectal/Noncolorectal

#### OP-31

##### The role of B-1 lymphocytes in antitumor immunity in patients with gastric cancer

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**Objective:** To study the B-cell humoral immunity in patients with gastric cancer.

**Methodology:** The study included 50 patients with gastric cancer. Group 1 - patients with gastrectomy and spleno-protective D2-lymphodissection. Group 2 - patients with gastrectomy, D2-lymphodissection and splenectomy. Subpopulations of B-cells were studied in a direct immunofluorescence reaction using a triple fluorescent label on a flow cytometers- Facs Can, Lysis II and FacsCanto II, Facs Diva program. The expression of membrane antigens was evaluated in the gate CD19+B-cells: CD20, CD21, CD23, CD38, HLA-DR, CD71, CD10, CD95, CD25, CD5, CD56 and IgG-λ and IgG-κ light chain immunoglobulins.

**Results:** In 33% of patients with gastric cancer at the preoperative period, a decrease in the relative number of B-cells (less than 5%) moreover in 38% decrease in the absolute number was revealed. After 3 months since the operation in 52% of cases the relative number of B cells as well in 31% of cases the absolute content of B cells was reduced. Before operation significant number of B-cells with a low level of CD21+ expression, a prominent proportion CD23+ number and clonal B-cells cases were detected. CD23+ B-cells had a weaker expression of the antigen of mature B-cells CD20. The number of CD19+CD5+B-cells on average was 17.7% and in 3 patients more than 40%. It was found that some of these cells demonstrates the CD38+ and CD25+ activation antigens. Such coexpression can be observed within the B-cell population of the marginal zone of the spleen. The resumption of this population occurs only in the spleen. In the group 1 reliable correlations (before and after the operation) between the relative and absolute number of CD19+B cells, as well as CD19+CD21+cells, were obtained. In the 2-nd group, the relative number of B-lymphocytes, CD5+B-cells, CD19+CD38+ cells was reliably correlated. After surgical treatment the percentage of cells with CD5+antigen expression significantly increased (t = -6.015).

**Conclusion:** Immunity disorders in patients after splenectomy primarily affect the B-cell immune response, including thymus-independent antigens of the second type, which is provided by the population of B1a-lymphocytes. The data obtained show a change in the composition of B-cell subpopulations. CD5+B-lymphocytes percentage increased significantly from 12.9 to 21.8% in the group of patients with standard D2-lymphodissection and splenectomy, while the total number of CD19 + lymphocytes and CD19+ CD21+ cells decreased. The antibodies produced by B1-lymphocytes are almost exclusively IgM. IgM plays an important role in the induction of apoptosis of tumor cells. Approximately half of serum IgM is secreted by B1-cells. Thus, in patients of the experimental group, there may be a decrease in antibody production, a weakening of both general and antitumor immunity.

### Hematology - General

#### OP-32

##### Hematological malignancies and outcomes in patients with Fanconi anemia: a single center experience

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**Objective:** The risk of malignancies is increased in patients with Fanconi anemia (FA) and of these malignancies hematological malignancies constitute



the largest group. Herein we evaluated the outcomes of our FA patients who developed hematological malignancies.

**Methodology:** Nine patients developed hematological malignancies in a cohort from a single center. Of these 8 developed AML and 1 developed MDS. The outcomes of these patients were summarized.

**Results:** The median age at diagnosis of FA was 12 years (1-15) and median age at diagnosis of hematological malignancy was 15 years (7-29). Two had t(1;9), 1 had del7, 1 had der(3)/der(8), 1 had 17p/11p anomaly at diagnosis of hematological malignancy. One of the patients deceased without receiving any treatment for AML, four of the patients received AML treatment protocol, 1 received low dose methotrexate, 1 patient received mini-FLAG and another patient received methylprednisolone only. The patient with MDS underwent HSCT directly without any chemotherapy prior to. Two patients underwent HSCT. All of the patients died except for the patient with MDS who underwent HSCT without chemotherapy prior to HSCT.

**Conclusion:** The patients with FA are not only prone to development of hematological malignancies but also have high chemotherapy and radiotherapy sensitivities related to sensitivity for cross-linking agents. In our cohort the mortality rates was very high after development of AML and the diagnosis of a preceding MDS, with regular bone marrow examinations, might be helpful to decrease the mortalities. Additional studies in larger cohorts might test the efficacy and safety of HSCT without chemotherapy among FA patients who developed leukemia.

### OP-33

#### Etiological classification of neutropenia detected in children between 3 months and 18 years of age: a cross-sectional study in a tertiary center

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**Objective:** Neutropenia is the decrease in absolute neutrophil count (ANC) to 2 standard deviations below the mean. Infections, drugs, malignancies, immunodeficiency and autoimmunity may cause neutropenia. This study aims to investigate the etiology of neutropenia as well as evaluating immune mechanisms related to infection and drug-induction by anti-neutrophil antibody (ANoA) testing.

**Methodology:** This study is a single center, cross-sectional study. Between November 2015 and February 2016, 13,000 blood counts were analyzed from the blood sample that sent to Istanbul University Istanbul Medical Faculty Pediatric Central Biochemistry Laboratory. In our study, 312 neutropenic patients aged 3 months to 18 years were evaluated and their etiology was investigated. 149 of the patients were female (47.8%) and 163 were male (52.2%). Of the control group (39), 27 (69.2%) were female and 12 were male (30.8%). Serum samples of 106 patients with infection or drug-related neutropenia (Group I-n), 39 healthy age-matched children (Group II), initial serum samples of 12 patients who had persistent neutropenia (Group I-np) and 94 patients that recovered from neutropenia (Group I-nr) were compared for antineutrophil anticor (ANoA) levels. The initial (S1) and final (S2) serum samples of 12 patients with persistent neutropenia (Group I-np) were also compared.

**Results:** Causes of neutropenia were found to be related to infections (50.3%), drugs (18.9%), malignancies (10.9%), metabolic disorders (9.6%), sequestration (8.3%), congenital/acquired bone marrow failure (7.4%), immunodeficiency (5.1%), congenital neutropenia (4.8%), chronic idiopathic neutropenia (2.6%), nutritional deficiency (1.3%) and secondary autoimmune neutropenia (0.6%). No statistically significant difference in ANoA levels were found between the serum samples of Group I-n and Group II; Group I-np and Group I-nr; and initial and final samples of Group I-np ( $p > 0.05$ ).

**Conclusion:** Since ANoA detection did not provide sufficient insight, we argue that it is not necessary for routine use and further research in the etiology of neutropenia is required.

### Leukemia/Lymphoma/Histiocyte Disorders

#### OP-34

#### Analysis of genetic abnormalities in newly diagnosed acute lymphoblastic leukemia patients at King Faisal Specialist Hospital and Research Centre

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**Objective:** Acute lymphoblastic leukemia (ALL) is a heterogeneous hematological neoplasm arising from B and T lymphocyte precursors with diverse genetic alterations. Identifying genetic abnormalities is essential for classification, risk stratification, minimal residual disease monitoring and targeted therapy administration. This extensive study provides details of ALL genetic aberrations in our community and compares these findings with international reference data.

**Methodology:** Analysis for bone marrow aspiration of 568 newly diagnosed ALL patients at King Faisal Specialist Hospital and Research Center (KFSH&RC) between 2012-2016 was carried out through karyotyping and a specific FISH panel. However, an adolescent age-group (15-19 years) is separated as individual entity. This lead results in a better understanding and concordance with different conflicted epidemiological studies in which a childhood ALL case might be considered with (0-14 years) or (0-19 years). Finally, the collected results were also paralleled to the reference data acquiring from the current World Health Organization (WHO) classification for hematological and lymphoid neoplasms, 2008, and its update 2016.

**Results:** The median diagnosis age was 8 years (range 0.08-89 years) with a male to female ratio 1.5:1 in 568 newly diagnosed ALL patients. There were 118 (21%) cases referred from outside hospital to be diagnosed or in the process of transferring the patient. Cytogenetic and FISH abnormalities were evident in 431 samples (76%) of all cases. B-ALL and T-ALL constituted 489 (86%) and 79 (14%) of all cases. The pediatric ALL cases, excluding the adolescent group, represented 402 (71%) of all cases, of which B-ALL being the clear majority by 360 cases (90%). Cases in age between 15 and 19 years of age were account for only 56 cases (10%) of all cases. The adult-group consisted of 110 patients (19%) of ALL cases with B and T-ALL representing 77% and 23%, respectively (table 1). In the B-ALL group, Philadelphia-positive t(9;21) ALL, KMT2A (MLL) rearrangement, t(12;21) ETV6/RUNX1 translocation, hyperdiploidy, hypodiploidy, t(1;19), intrachromosomal amplification (iamp) 21 and complex groups were detected by classical cytogenetic, FISH or both in 8% (3% in pediatric-ALL, 7% in adolescent-ALL and 31% in adult-ALL), 4% (5%, 2% and 2%), 11% (15%, 0% and 0%), 40% (49%, 19% and 13%), 3% (3%, 7% and 0%), 2% (1%, 9% and 5%), 4% (5%, 5% and 0%) and 4% (3%, 7% and 6%), respectively (table 2). Investigation of genetic abnormalities among newly diagnosed T-ALL revealed only 46 positive cases (58%) with two third of these cases (31 cases) harboring a deletion of chromosome 9 short arm.

**Conclusion:** These enormous data supported the value of applying different diagnostic methods to detect genetic alterations among newly diagnosed ALL patients. In addition, our ALL population show a different pattern of genetic abnormality rates which is evident by a higher rate of hyperdiploidy and lower high risk genetics frequencies. These could have an impact on the relapse and overall survival. Further regional collaborative study between multicenter and correlation with the clinical outcomes are demanded to strengthen these observations and might have a positive effect on our ALL patients.

## Red Cells

### OP-35

#### Implication of HMOX1 and CCR5 genotypes on clinical phenotype of Egyptian patients with sickle cell anemia

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**Objective:** Sickle cell disease (SCD) is a relatively common inherited hemolytic anemia among individuals of African descent. Genetic factors might clarify clinical diversity of the disease and variations in treatment response. Some researchers investigated heme oxygenase1 (HMOX1) or chemokine receptor 5 (CCR5Δ32) genotypes among SCD patients and their correlation with fetal hemoglobin (HbF) and disease severity. However, there is no such records among Arab nations.

**Aim:** We aimed to estimate the prevalence of the HMOX1-413 A>T (rs2071746) and CCR5Δ32 (rs333) polymorphisms, and to assess their effect on SCD phenotype and HbF level among Egyptian patients.

**Methodology:** Polymerase chain reaction assay was used to determine these polymorphisms among 100 SCD patients and 100 healthy controls.

**Results:** Though not statistically significant, the frequency of individual carrying HMOX-1 polymorphic; AT and TT genotypes in both patient and control groups were (92% and 85% respectively). Regarding CCR5Δ32 polymorphisms, all SCD patients harbored the wild genotype (100%), while the heteromutant genotype was encountered in 2% of our controls. Patients harboring mutant HMOX-1 had less frequent vasoocclusive crisis (VOC)/lifetime, less VOC in the last year, less incidence of stroke, less frequency of hospitalization, and responded more frequently to hydroxyurea with statistically significant differences ( $p=0.028, 0.007, 0.046, 0.007, \text{ and } 0.011$  respectively). No significant associations with HbF level or other hematologic parameters were encountered among our cohort.

**Conclusion:** Our study results suggest a protective effect of mutant HMOX-1 genotypes in ameliorating phenotypic severity of disease. HMOX1-413 A>T (rs2071746) polymorphisms might prove to be a prognostic marker among Egyptian SCD, but not CCR5Δ32 (rs333) polymorphisms.

## Thalassemia

### OP-36

#### The relationship between endogen antioxidants and total oxidant and antioxidant capacity in patients with beta-thalassemia

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**Objective:** The patients with  $\beta$ -thalassemia are usually under oxidative stress due to iron overload as a result of ineffective erythropoiesis and repeated transfusions. The evaluation of antioxidant defense system can be easily done by measuring serum total antioxidant capacity. The aim of this study is to investigate the total oxidant (TOC) and antioxidant capacity (TAC) of patients with transfusion dependent (TDT) and nondependent (NTDT)  $\beta$ -thalassemia.

**Methodology:** Forty five patients (median age 26 years; age range 12-59) with  $\beta$ -thalassemia (15 nontransfusion dependent, 30 transfusion dependent) who were followed-up by Istanbul Medical Faculty Thalassemia Center were enrolled in this study. The sex and age matched 20 healthy subjects were used as control group. The total oxidant and antioxidant capacity were measured by Rel Assay Diagnostics, Total Oxidant Status (TOS) kit and Total Antioxidant Status (TAS) kit. This study was approved by the Institutional Review Board (Istanbul University, Istanbul Medical Faculty Clinical Research Ethics Committee).

**Results:** The total oxidant capacity was found higher in patients than control group without significant differences (23.1 vs 16.7  $\mu\text{mol/l}$ ). Beside this, the total antioxidant capacity of patients was significantly increased (2.75 mmol/l

vs 2.10 mmol/l;  $p=0.01$ ). Within patients group, there were no significant differences in terms of TAC and TOC level although TAC level was high in TDT group and TOC level was increased in NTDT group. There was no significant relationship between TOC and sex, age, ferritin and splenectomy status, as the same for TAC. We found low level of hematocrit in TDT group ( $30.6\pm 4.6$  vs.  $26.3\pm 2.9$ ;  $p=0.002$ ). and this may affect the insufficient increase TAC level in TDT group. On the other hand, the endogenous antioxidant molecule, the bilirubin was found high in NTDT group ( $5.7\pm 3.3$  vs.  $1.9\pm 1.4$ ).

**Conclusion:** The measurement of TOC and TAC status stands a useful, rapid, and simple method to evaluate the complex oxidative mechanism of disease. The results of this study might guide us to use the antioxidants to decrease the oxidative stress. The controversial results indicate us that more prospective and experimental studies are needed to clarify the oxidant and anti-oxidant mechanism of patients with beta thalassemia. This study supported by Istanbul University Research Fund

### OP-37

#### Pediatric thrombosis: a single center experience

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**Aim:** Etiology of pediatric thrombosis is multifactorial. Numerous congenital and acquired risk factors have been defined with different risk for thrombosis in recent reviews and meta-analyses. Herein we report the children diagnosed and treated with thrombosis in Istanbul Medical Faculty, Pediatric Hematology and Oncology Department between 2012-2018.

**Study:** A total of 100 children diagnosed with thrombosis between January 2012- December 2017 were included into the study. Fifty-three of the cases were male and 47 of cases were female. Median age at diagnosis was 11 years (10 days to 17,5 years). Thrombosis was arterial in 33 cases and venous in 67 cases. Median duration of follow-up was 38 months (3-61 months). Localisation of thrombosis were deep venous structures of lower extremity in 22 cases (22%), cerebral arterial in 22 cases (22%), cerebral venous sinuses in 13 cases (13%), deep cervical veins in 11 cases (11%), portal vein in 7 cases (7%), inferior vena cava and deep iliac veins in 7 cases (7%), arterial structures of lower extremity in 7 cases (7%), intracardiac in 5 cases (5%), superficial veins of lower extremity in 2 cases (2%), abdominal arteries in 2 cases (2%), retinal artery in 1 case, retinal vein in 1 case. The most common cause of peripheral venous and arterial thrombosis was catheterisation (36/40 cases) and infection and dehydration for cerebral venous sinus thrombosis (8/13 cases). All cases with portal venous thrombosis had the history of umbilical catheterisation during the newborn period and all cases with cardiac thrombosis had congenital heart disease with surgical intervention in 3 cases. Certain etiology could not be defined for most of the cranial arterial thrombosis, except for sepsis in 2 cases, trauma in 3 cases, vascular anomaly in one case, Factor 12 deficiency in one case and Factor 5 Leiden mutation in one case. Two cases with thrombosis in abdominal arteries (SMA and Renal artery) had the diagnosis of vasculitis. Hereditary thrombophilia tests were performed in 97 cases with positive Factor V Leiden homozygous mutations in 2 cases, Prothrombin 20210 heterozygosity in 2 cases, and MTFHR gene homozygous mutation in 5 cases and heterozygous mutation in 22 cases. Laboratory thrombophilia tests revealed Protein C deficiency in one case, and Factor 12 deficiency in one case. All patients diagnosed with acute thrombosis were treated with low molecular weight heparin with a median duration of 4 months (1-24 months). Fifteen patients were given ASA prophylaxis and 3 patients were on warfarin treatment for long term.

**Results:** The etiology of pediatric thrombosis is not clear in every case. In our study thrombosis was mostly developed as secondary to surgical interventions or infections. The testing for thrombophilia and the importance of positive factors in development of future thrombosis are controversial. Case-based definition of risk status depending on family history, clinical and laboratory findings and treatment according to risk definition are important for thrombosis in children.

## Chronic Lymphocytic Leukemias

### OP-38

#### Interleukin-6 and interleukin-10 gene polymorphisms at chronic lymphoid leukemia patients

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**Objective:** Chronic lymphoid leukemia (CLL) is a leukemia characterized by an abnormal proliferation of mature small monoclonal B lymphocytes in peripheral blood, bone marrow, and lymphoid tissue. Cytokines are molecules that play an important role in regulation of the immune system and inflammatory events in the organism. A significant proportion of the cytokines secreted from the immune system are interleukins (IL) and their main task is to stimulate the immune system cells. Therefore, the genotypic effects of these interleukins; IL-6 and IL-10 in the immune system in CLL were investigated in this study.

**Aim:** For this purpose, 100 patients with the diagnosis of CLL and 70 healthy subjects were included in this study.

**Methodology:** DNA was isolated from the blood samples obtained from the CLL patients and control groups. Polymorphisms in the promoter regions of the IL10 (1082 A\G and 819 C\T) and IL6 (174 G\C) genes were studied by RT-PCR. Genotype and allele frequencies were calculated by directly. The statistical significance of genotypic distributions between CLL patients and control groups was evaluated by chi-square test.

**Results:** IL 10 1082 A\G region, 45 wild-type AA, 40 AG and 15 mutant-type GG genotypes were detected in 100 CLL patients. Genotypic distribution of 819 C\T regions of IL10 was detected in CC in 37 patients, CT in 50 patients and TT genotype in 13 patients. IL 6 174 G\C region was detected in GG in 62 patients, GC in 30 patients and CC genotypes in 8 patients. There was no statistically significant difference between CLL patients and control groups of IL10 1082 A\G and 819 C\T and IL 6 174 G/C regions ( $p>0.05$ ). As a result of calculation of allele frequency of IL 10 1082 region, for the patient group A (0,65), G (0,35), while for the control group these values (0,61) and G (0,31) were obtained. The frequencies of C (0,57) and T (0,33) were found in the patient group of 819 region as C (0,48) and T (0,32) in the control group. IL6 174 region was calculated as G (0,82) C (0,28) in the patient group and G (0,63), C (0,23) in the control group.

**Conclusion:** Within the limits of this study about number of patients, IL 10 and IL 6 genotype frequencies do not appear to be associated with CLL patients as statistically. Mutant alleles of all interleukin SNPs were detected in the patient group at a higher frequency than the control group. Therefore, by increasing the number of samples, a possible relationship between SNPs of these interleukins and CLL may be determined in future studies.

## Poster Presentations

### Acute Lymphocytic Leukemias

#### PP-01

##### Successes in the field of child leukosology in Azerbaijan

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**Objective:** Until recently, the diagnosis of acute leukemia in Azerbaijan was equated with a death sentence. However, in the last ten years something incredible has happened in this area and patients have gradually started to get rid of the fateful "verdict". This happened as a result of the program approach to the treatment of these patients, chaining to the international experience. To prove this, we want to present the results of our research in this area.

**Methodology:** The study was held in the field of pediatric hematology on the basis of the Institute of Hematology of Azerbaijan. The group included 100 randomly selected patients aged 0-15 years with a primary diagnosis of acute lymphoblastic leukemia. Of these, there were 58 boys and 42 girls. The treatment was conducted according to two versions of the Moscow-Berlin program: "ALL-MB 91 and 2002", which lasts 2 years. Patients were divided into 2 risk groups: standard risk - 57, intermediate - 43 patients. The period of observation lasted from 2006 to 2016. The results were evaluated according to these criteria: complete remission - when the induction of treatment in the bone marrow of undifferentiated blasts is less than 5%, the observation group - the patients after the completion of the program treatment are observed for the next 3 years, the recovery group - who completed the three year remission period- Relapse - the return of the disease in both - bone marrow alone or outside bone marrow, lost from observation - the patients disappeared during the treatment, for no reason.

**Results:** 74 patients from 100 entirely completed two-year programmed treatment. Of these, 39 patients are in the convalescence group, 26 are under observation. In 9 patients, a relapse occurred within the first 6 to 24 months. Of these, 5 died within a short time without resuming treatment, 1 patient received PCT, the second child underwent BMT, the results were ineffective and both patients died. In the remaining 2 patients, the BMT was positively effective (1- in Azerbaijan, the second in Turkey). The period passed after TCM is from 1.5 to 6 years. The number of patients who did not complete the treatment program was 26. 15 of them died during the period of consolidation and maintenance therapy. The cause of death was: in 4 children various infectious complications against a background of leuko-neutropenic state. 1 child died of chickenpox infection by the end of the supportive therapy. And 1 more child died of a complication of toxic pancreatitis. In 8 patients a relapse was noted: 7 - bone marrow, 1 - neuroleukemia. The attempts to restore remission were unsuccessful and all the patients died after time. In one case, the parents refused further treatment, the reason was lack of financial support. After a while the child died of a bone marrow relapse. 1 patient on a background of remission moved to overseas for permanent residence. 5 patients are lost from under the observation. Another 5 children for various reasons (financial reasons, physically and psychologically) could not complete the program, suspending it at different stages of polychemotherapy. But observation for the next 3 to 5 years and periodic analysis showed preservation of remission obtained after the initial course of induction. These children are currently in the recovery group.

**Conclusion:** Thus, in the last 10 years the number of children recovering from acute lymphoblastic leukemia is about 58%. This is a noticeable great success in the field of pediatric oncohematology in Azerbaijan. Although we understand that these indicators are still inferior to the data of the world's leading clinics, where the rates go over 75 to 80%. But our success today gives us hope for further achievements against the background of a significant improvement in the material and technical base, improvement of the laboratory service and application of the state program in the field of oncohematology in Azerbaijan.

#### PP-02

##### A rare type of mixed phenotype acute leukemia T/B-lymphoid/megakaryoblastic

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**Objective:** Mixed phenotype acute leukemias (MPAL) consist a diverse group of hematological diseases and represent a diagnostic problem for pathologists and clinical practice. This rare group of acute leukemias is characterized by the presence of blasts that express antigens of more than one lineage to such a degree that it is not possible to assign the leukaemia to any one lineage with certainty. WHO classification calls in question the existence of mixed B- or T-cell and megakaryocytic or mixed B- or T-cell and erythroid leukaemias. It has been postulated that erythroid and megakaryocytic lineages are the earliest to branch off from the pluripotent haematopoietic stem cell, leaving progenitor cells with T-cell, B-cell, and myeloid potential. So in our clinic we met a very rare variant of MPAL - trilineage T-lymphoid/B-lymphoid/megakaryoblastic.

**Case report:** A 34-year old woman was hospitalized to our center in a wheelchair with severe dyspnea, generalized lymphadenopathy, difficulty in swallowing. Abdominal examination revealed no organomegaly. Her blood parameters were WBC-8,950/ $\mu$ L; RBC-4,660,000/ $\mu$ L; Hemoglobin-10,1 g/dL; Platelets-20,000/ $\mu$ L. Blast cells of peripheral blood were 11%. Subsequently bone marrow aspiration and excision biopsy of cervical lymph node was done. Bone marrow aspirate showed a cellular marrow with 25% blasts which were large anaplastic cells with a polymorphic structure of nuclei, in some cells were small granules. Cytochemical tests - MPO, lipids, NSE were negative in blasts. Flow cytometry showed two populations of blasts. One of them was positive for CD19, cyCD79a, cyCD3 and was interpreted as mixed phenotype blasts B/T-lymphoid. The other population was positive for CD41a, CD61, cyCD41a, cyCD61, CD33, CD19 which corresponds megakaryocytic line of differentiation. MPO was negative in two populations. Immunophenotyping of the cervical lymph node biopsy was performed. Leukemic cells were positive for CD34, cyCD3, CD19 and CD22. These results confirmed mixed phenotype blasts T/B-lymphoid. Megakaryocytic panel wasn't performed on lymph node. Chromosomal analysis showed normal karyotype. FISH analysis didn't find MLL gene rearrangement. Molecular genetic research didn't detected expression of gene BCR-ABL transcripts p190 and p210. Our patient was treated with protocol by RALL Study Group. After two phase of induction the complete remission was not reached. We got cytoreduction without hematologic recovery. MRD was positive, and lymph nodes-partial response. Later the progression disease was recorded with increase of MRD and the size of lymph nodes including data of PET. Patient was given salvage regimen with high dose Ara-C and mitoxantrone and high dose dexamethasone. The first complete remission was reached: MRD-negative bone marrow and PET/CT-negative remission. Later again early progression was recorded. The patient has 4 haploidentical siblings, but has no HLA-identical related and unrelated donors. Haploidentical related allogeneic stem cell transplantation was done. But the effect of the treatment was insufficient. The patient was discussed with Prof. Holzer. The biopsy of lymph node with immunophenotyping was planned. But the patient refused. Later the advanced progression was confirmed. Now the patient is alive and gets salvage low-dose therapy.

**Conclusion:** So MPAL present great difficulties in the diagnosis. Existence of mixed phenotype B- or T-cell and megakaryocytic or erythroid lineage require further study. The optimal therapeutic approach to these cases has not been defined. The prognosis of this type of acute leukemia is very poor.

#### PP-03

##### The study of quality of life in various variants of acute leukemia patients

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**Objective:** The progressive development of medicine, the change in the structure of the disease, and the use of new medications and new protocols for the acute leukemia (AL) patients always require the study of quality of life (QOL) in these patients. According to the accepted postulate, QOL



indicators are one of the most important indicators of treatment efficiency. QOL indicator is a subjective indicator of mental, physical, emotional and functional activity of patients and is based on the patient's response. Study of QOL indicator in AL patients with different clinical and morphologic types provides valuable information about individual response to the disease and the therapy. The aim of the study is to investigate QOL markers based on the age of the patients and immunohistochemical variants of the disease.

**Methodology:** The results of 78 patients (46 men (59%), 32 women (41%)) with AL in 2012-2017 were analyzed. The average age was 43 years (61 patients under 60 years old (78,2%) and 17 over the age of 60 (21,8%). Acute lymphoblast leukemia – 28 (36%), B cell type 21 (27%), T cell type 7 (9%), acute promyelocytic leukemia (M3) – 13 (17%), acute myeloblast leukemia (AML) -37 (47%), including M4 – 6 (8%), M5 – 3 (4%), M6 – 1 (1.3%), M1 – 13 (16.7%) and M2 – 14 (18%) patients. Patients were treated with standard treatment protocols and LDAC. 21 patients in control group were taken from healthy individuals. The study of QOL indicator was based on MOS SF-16 questionnaires in the main and comparative group.

**Results:** Out of 78 AL patients receiving stationary and outpatient treatment in 2012-2017 mortality was in 11 (14.1%), chemotherapy resistance in 21 (26.9%), clinical hematology remission in 40 (51.3%) patients. All immunohistochemical variants of AML patients, esp. in M3, M5, M6 QOL indicators, were significantly lower before and during treatment compared with the control group. Extremely low scores are recorded in everyday activity (Role-Physical Functioning), physical activity (Physical Functioning) and emotional activity (Role-Emotional). Low indicators were also found in Bodily pain, Vitality, General health and Mental health. At the beginning of the disease these changes are probably due to tumor intoxication (97.4%), anemic syndrome (100%), hemorrhagic syndrome (66.6%) and pain syndrome (29.4%). At the treatment period low QOL indicators are due to cytotoxic depression (100%), endogenous intoxication (100%), bacterial infections (96.1%), fungal infections (65.3%), bacterial septic shock (39.7%) and enteropathy (35.8%). In remission period, in all immunocytochemical variants of AL patients QOL were significantly higher than the preceding treatment, and were lower in comparison with the control group. The improvement of QOL markers is largely due to the fact that patients have access to the clinic, reduced stress, and hope of remission for the majority of patients.

**Conclusion:** The study of QOL indicators in AL patients suggests that adequate chemical therapy is important not only for the results of laboratory and instrumental examinations, but also for QOL indicators.

## Acute Myeloid Leukemias

### PP-04

#### Heritable RUNX1 and GATA2 mutation with a very rare gene variant associated with AML-MDS: a case report and review of literature

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**Case report:** A 15-year-old Saudi boy not known to have any previous medical illness presented to the emergency department in local hospital with history of prolonged epistaxis for almost 40 minutes not preceded by any trauma and an on/off vomiting. He has history of epistaxis since childhood which was never be investigated. No bleeding from other sites, no fever or chills, no rash, asthma, weight loss or easy fatigability. On presentation he has also history of productive cough but no shortness of breath. She had a significant family history epistaxis of his grandmother only, not affecting his siblings or parents or any cousin. On examination Vital stable, looking well. No skin rash, pallor, no jaundice, no lymphadenopathy or hepatosplenomegaly. On investigation he has pancytopenia WBCs: 3500/ul, Hb: 93 g/l, Platelet: 60,000/ul, Neutrophil 4%, Monocyte 35%, atypical cells 10%. Bone marrow in local hospital revealed hypercellular marrow with trilineage dysplasia, prominent basophilia and Myeloblast 6%. Patient is referred to our hospital as tertiary care center with pancytopenia and peripheral blast was 6%. BM was repeated which revealed atypical monocytosis and significant trilineage dysplasia and blast was 22%. Flow cytometry immunophenotyping performed on the bone marrow aspirate revealed a myeloid blast population that was

partial CD34+, CD117+, HL-DR+, CD11b+ CD15 partial+, c-MPO+, CD13+ and CD33+. The flow cytometry results support the diagnosis of acute myeloid leukemia. Cytogenetic analysis performed on fresh bone marrow aspirate revealed 45, XY, -7[20]. FISH is positive for monosomy 7 in 30/100. Based on the morphologic and cytogenetic findings, the patient was diagnosed with acute myeloid leukemia with myelodysplasia related changes. Molecular tests for FLT3 ITD, NPM1, CEBPA and KIT genes were negative performed on DNA extracted from fresh bone marrow aspirates. BCR-ABL1 and JAK-2 was also negative. Chromosomal breakage analysis was also negative. The sample (whole blood) is sent for molecular analysis of MDS/AML Sequencing panel for Next Generation sequence (NGS) to Mayo clinic USA. The result revealed that patient is heterozygous in the RUNX1 gene for rare variant designated c.611G>A, which is predicted to result in the amino acid substitution p. Arg204Gln. This variant is likely to be primary cause of disease. This patient is also heterozygous in the GATA2 gene for a variant designated c.554\_628delins 16, which is predicted to result in frameshift and premature protein termination (p.Pro185Leufs\*77). To our knowledge this variant has not been reported previously in any patient with autosomal dominant GATA2-related disorder but expected to be pathogenic. The patient is considered high risk AML with MDS related changes with GATA2/RUNX1 variant with monosomy 7. The patient has been offered 3+7 (Idarubicin 12 mg/m<sup>2</sup> and Cytarabine 100 mg/m<sup>2</sup>). Day 14 BM is hypocellular and no residual blast. D+28 is hypercellular but with 6% blast in bone marrow but D+34 BM hypercellular and no blast. FISH is still positive for monosomy 7. The patient is considered morphological remission without cytogenetic or molecular remission. The patient is considered Allo-SCT but no matched sibling donor is available. Patient has local MUD available and offered IDAC (Intermediate dose Ara-C) to bridge for MUD Allo-SCT. Although it was recommended to confirm the germ line nature of the GATA2 mutation by submitting additional material such as a skin biopsy or a buccal swab for germline GATA2 testing, it was not performed due to the patient's poor condition from persistent chronic infection. Other family members declined testing for GATA2 mutations.

**Conclusion:** In addition to RUNX1 and CEBPA, GATA2 gene mutations have only been recently reported involved in familial AML-MDS. Here we reported heterozygous RUNX1 gene variant and very rare heterozygous GATA2 gene variant which is never be published previously in any patient with autosomal dominant GATA2 related disorder. Heritable gene mutations as a predisposition gene to AML-MDS are likely under recognized, but have significant implication in managing the patients and the affected families. It is important to recognize this rare entity, be familiar with the clinical features, and seek appropriate laboratory testing when there is a clinical concern. This rare entity recognizes that patient should be undergoing Allo-SCT as soon as possible.

### PP-05

#### Safety and efficacy of different Ara-C regimens during the clinical course of acute myeloid leukemia

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**Objective:** Cytosine arabinoside (Ara-C) is the key chemotherapeutic agent for the management of acute myeloid leukemia (AML). Ara-C in consolidation therapy played an important role for preventing relapses of AML patients that achieved complete remission. However, the optimum dose of Ara-C is still not certain. We retrospectively evaluated patients with AML who were treated in a single center to identify certain variables that could have affected the outcomes, including the role of two different doses of Ara-C administered during the consolidation phase of the treatment schema. To compare the modified dose cytosine arabinoside (mDAC; Ara-C at a dose of less than 1.5 g/m<sup>2</sup> every 12 hours on days 1, 3 and 5) versus high dose cytosine arabinoside (HDAC; Ara-C at a dose of 1.5 g/m<sup>2</sup> and higher every 12 hours on days 1, 3 and 5) in post-remission therapy for acute myeloid leukemia to confirm the post-remission antileukemic efficacy, reliability, tolerability and toxicity of mDAC.

**Methodology:** The five hundred and five patients who admitted to our Hematology clinic and were diagnosed as acute myeloid leukemia, between 1999 and 2018, were evaluated. Following the detailed interim analyses 66 patients were included in to this study. The patients who received 3 consolidation chemotherapy after induction were selected for further analyses. The Ara-c doses were similar for every 3 consolidation chemotherapy received for each of the patients. The patients who received different numbers and different doses of consolidation chemotherapy were excluded from the analyses. The 66 patients who received cytosine arabinoside consolidation were assigned to two groups based on their cytarabine dose protocol. HDAC group (n=30) received,  $\geq 1.5$  g/m<sup>2</sup> every 12 h on days 1, 3 and 5 and mDAC group (n=36) received  $<1.5$  g/m<sup>2</sup> every 12 h on days 1, 3 and 5.

**Results:** We analyzed survival outcomes HDAC group versus mDAC group among the 66 adult patients with AML. Median following for all patients was 12 months (range 1-76 months). The median duration of overall survival was 31 months (95% C.I. 12.6-50.8 months) with HDAC and 22 months (95% C.I. 22.5-35.4 months) with mDAC (p=0.24). The estimated median duration of PFS was 23 months (95% C.I. 13.1-34.5 months) with HDAC and 16 months (95% C.I. 5.8-26.0 months) with mDAC (p=0.05). There were no statistically significant differences between HDAC and mDAC group in the incidence of hematologic and non-hematologic toxicity (p>0.05).

**Conclusion:** The results of our present study suggests that mDAC may have an equivalent post-remission antileukemic efficacy in comparison to HDAC for the management of AML patients. Likewise, there were no significant differences between HDAC and mDAC group in the incidence of hematologic and non-hematologic toxicity. Thus, mDAC seems to be is appropriate with higher reliability for AML patients.

### Acute Lymphocytic Leukemias

#### PP-06

#### Role of allogeneic HCT as post remission therapy for adult lymphoblastic leukemia/lymphoma following front line hyperCVAD

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**Objective:** HyperCVAD is a commonly used regimen in adults with acute lymphoblastic leukemia/lymphoma (ALL/LBL). Adult patients fit for pediatric inspired protocols have an excellent outcome with chemotherapy alone. However, it is unclear whether patients receiving HyperCVAD should undergo allogeneic HCT as post remission therapy. Our aim is to examine the role of HCT at CR1 in adult ALL/LBL following HyperCVAD.

**Methodology:** After IRB approval, adult patients with newly diagnosed ALL/LBL receiving front-line HyperCVAD from 2008-2017 were identified and records retrospectively extracted. Risk factors were defined as age >35 years, elevated presenting WBC (>30 and 100 in B- and T-cell disease, respectively) or high risk cytogenetics. The choice of HCT at CR1 was at the discretion of the treating physician. Categorical and continuous variables were compared using Pearson's chi-squared and Wilcoxon/Kruskal-Wallis, respectively. OS and EFS were computed using Kaplan-Meier method. Cox regression was used for multivariable analysis adjusting for elevated WBC, cell of origin, cytogenetic risk and induction failure.

**Results:** A. Baseline characteristics: A total of 85 patients were identified and included for further analysis. The median age was 23 (14-68) and 56 (66%) were males. Disease was of B-cell origin in 60 (71%) and 77 (91%) had ALL. Median presenting WBC was  $9 \times 10^9/L$  (0.8-693) with elevated WBC in 21 (26%). A total of 24 (28%) had adverse cytogenetics and 48 (56%) had at least one risk factor. All patients received HyperCVAD as induction and induction failure was seen in 10 (11.7%) while the remaining achieved CR1. Among 75 patients in CR1, minimal residual disease (MRD) was evaluable in 48 (56%) and was positive at CR1 in 19 (40%) which all became negative at 3 months. A total of 38 patients completed a full course of hyperCVAD while the remaining 47 received HyperCVAD followed by HCT in CR1. 3-year OS and EFS for the entire cohort was 56.4% (44-67) and 49.1% (34-58), respectively. Median follow up of alive patients was 30.1 months (2.4-108). B. Outcome Stratified by

Therapy: The cohort was subsequently stratified based on therapy received. Patients on HyperCVAD had a significantly lower proportion of elevated WBC at presentation (11% vs. 39%, p=0.004), induction failure (3% vs. 19%, p=0.011) with a trend towards lower incidence of high risk cytogenetics (18% vs. 36%, p=0.08). At multivariable analysis for EFS, induction failure was the only significant factor with HR 4.3 (1.3-12.9; p=0.02) with a trend towards significance for HCT in CR1 with HR 0.47 (0.19-1.08; p=0.07). However, HCT in CR1 was the only prognostic factor for OS with 0.32 (0.11-0.88; p=0.026).

**Conclusion:** We observed that HCT at CR1 resulted in a favorable OS in ALL/LBL patients following HyperCVAD front line therapy. Given that HyperCVAD is a widely used protocol for adult patients, further examination of this observation is warranted.

#### PP-07

#### A rare presentation of recurrence in acute lymphoblastic leukemia: isolated optic nerve involvement

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**Objective:** Central nervous system infiltration of optic nerve is a rare entity in patients with acute lymphoblastic leukemia. Ocular involvement is associated with progressive disease. Ophthalmic manifestations of acute lymphoblastic leukemia (ALL) can appear most frequently in patients in hematological relapse. In the current case report, we presented a case of ALL at hematological remission who has developed optic nerve involvement.

**Case report:** 48-year-old male patient was treated with the Hyper CVAD (cyclophosphamide, vincristine, adriamycin and dexamethasone) chemotherapy protocol as a remission induction and complete remission 1 (CR1) was achieved. He had no HLA mismatched donor therefore he was included in unrelated donor screening programme. He missed the follow up and received no chemotherapy since he was admitted to our hospital with ileus and hematological relapse. FLAG-IDA (fludarabine, cytarabine, G-CSF and idarubicin) regimen was given as salvage chemotherapy and CR2 was achieved. Unrelated donor was found so that allogeneic stem cell transplantation (ASCT) was planned. During preparations, second hematological relapse occurred and he was given salvage FLAGIDA chemotherapy again. He achieved CR3 and preparations for ASCT started again. In the meantime, he was admitted to our department with the complaints of pain and sudden vision loss in right eye. There was no atypical cell on peripheral blood smear. Bone marrow biopsy was performed in terms of ALL relapse, and no infiltration of blastic cells was observed. There was no evidence of simultaneous hematological relapse. Ophthalmological examination revealed a visual acuity of light perception in the right eye. Grade 4 papillitis, papillary edema and numerous spot hemorrhages were detected on fundus examination. In the orbital MRI, slight contrast enhancement in the retroorbital fat planes at the right orbital level, as well as a thicker appearance compared to the optic nerve symmetry of the right side were observed. The cerebrospinal fluid (CSF) did not show no abnormality. In cranial MRI, the right optic nerve was slightly thicker than left side, and no pathology was observed in other cranial structures. In daily ophthalmic examination, vision loss in the right eye and optic disc swelling and hemorrhages in posterior pole was increased. According to these results, optic nerve involvement and pseudotumor orbita was considered as initial diagnosis. Intrathecal chemotherapy with methotrexate-cytarabine were given immediately followed by B arm of HCVD (high dose of methotrexate and cytarabine) regimen and also patient were received pulse steroid. Now, the patient has 1/6 visual acuity in the right eye and he is followed by daily eye examination. He is in hematological remission and being prepared for ASCT.

**Conclusion:** This report points that orbital structures may be involved in ALL so ophthalmological examination is important to early diagnosis and treatment for improved visual outcome and long-term survival rate.

## PP-08

**Mucormycosis in a patient with acute lymphoblastic leukemia: a case report**

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**Objective:** Mucormycosis is a rare fungal disorder with high mortality and morbidity occurring particularly in patients with suppressed immune systems. The risk factors leading to the disease include diabetes mellitus (especially together with ketoacidosis), treatment with glucocorticoids, hematologic malignancies, hematopoietic cell transplantation, solid organ transplantation, treatment with deferoxamine, elevated iron levels, HIV infection, injectable drug use, trauma/burns, and malnutrition. We present a case of mucormycosis in a patient with acute lymphoblastic leukemia.

**Case report:** A 23-year-old male patient was diagnosed with acute lymphoblastic leukemia in March 2018. The Graall-2003 chemotherapy protocol was initiated. Following the induction phase, remission occurred. During the fifth round of chemotherapy the patient developed febrile neutropenia, the protocol for which was then followed. Afterwards, the patient developed abdominal pain and diarrhea. Abdominal tomography revealed neutropenic enterocolitis. Oral intake was discontinued, and metronidazole was added to the treatment regimen. As the fever did not subside, on the fifth day of treatment with piperacillin/tazobactam, caspofungin was added. Under this regimen, the fever, diarrhea, and abdominal pain all persisted. Piperacillin/tazobactam was then discontinued, and the patient was started on meropenem and vancomycin. On the twentieth day of treatment, black necrotizing areas started to appear in and around the nose. A sinus tomography was performed, and mucosal thickening was observed. Suspecting mucormycosis, caspofungin was discontinued and treatment with liposomal amphotericin B was started. The general condition of the patient deteriorated, with no reduction in fever, and the gradual expansion of the necrotizing area around the nose. The area around the patient's nose and sinuses were completely debrided. Biopsies taken from these areas were assessed to be mucormycosis. Following surgery, the patient's fever subsided, his overall condition improved, and long-term use of amphotericin B was continued.

**Conclusion:** During treatment for mucormycosis, surgical debridement of tissues should be performed together with the use of antifungal agents. When mucormycosis is suspected, aggressive surgical debridement of the affected tissues is necessary. Not only necrotic tissues should be removed, but also infected healthy-looking tissues as well. Liposomal amphotericin B is the preferred medication for initial treatment. Posaconazole or isavuconazole can be used by patients who do not respond to or cannot tolerate amphotericin B. Even with early diagnosis and treatment, the prognosis for mucormycosis is still poor.

**Acute Myeloid Leukemias**

## PP-09

**A rare entity: Philadelphia-positive acute myeloblastic leukemia with P190 fusion protein**

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**Objective:** Philadelphia chromosome positive with de novo acute myeloblastic leukemia (Ph + AML) is a rare entity. We present a case of patient with Ph(+) AML with p 190.

**Case report:** A 78-year-old male presented with anorexia, shortness of breath and weakness lasting for one month. His medical history was atrial fibrillation, congestive heart failure, chronic obstructive lung disease. There

was no history of any hematological disorder. There was no organomegaly and lymphadenopathy. The hematologic parameters were as follows: hemoglobin level 8.4 g/dl, Hct: 26%, white blood cells (WBC): 3200 mm<sup>3</sup>/uL, neutrophil count: 1200 mm<sup>3</sup>/uL, lymphocyte count: 1200 mm<sup>3</sup>/uL, monocyte count: 600 mm<sup>3</sup>/uL, eosinophil count: 100mm<sup>3</sup>/uL, basophil count: 100 mm<sup>3</sup>/uL, platelets count 214×10<sup>3</sup>/uL, urea nitrogen (BUN): 33 mg/dl, creatinine: 0.82 mg/dl, LDH: 173 IU/L, active prothrombin time: 28.1 second, prothrombin time: 17.3 second, INR: 1.51. ECO signs: ejection fraction (EF): 50%, left atrium dilatation, mitral insufficiency, respiratory function test signs: obstructive pattern. The patient had a Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 3. Peripheral smear test was seen 60% blast cells. A bone marrow examination showed 55% of myeloblastic infiltration. In flow cytometric analysis was showed expression of CD7, CD117, CD33, CD34 and HLA-DR positive, but CD64 CD13 CD14 were negative. The patient was diagnosed with AML (FAB M1).Molecular cytogenetic analysis was examined by FISH method. In 45% of cells analyzed were observed signal of t(9,22) (q34;q11.2). The BCR/ABL fusion gene analysis with PCR, p190 fusion protein identified positive in 48%, but p210 gene protein was negative. CEBPA, t (15,17) PML-RAR, FLT3 ITD, NPM1 mutation PCR analyses were normal. The high dose chemotherapy was not appropriate for this patient due to co-morbid diseases after he was diagnosed with AML. Therefore, the patient was administered azacitidine 75 mg/m<sup>2</sup> for 7 days, repeated every 28 days. The patient received treatment with azacitidine and tyrosine kinase inhibitors (imatinib mesylate 400 mg/per day from day 35 of the beginning induction chemotherapy) , The imatinib mesylate dose was increased to 600 mg/day after three courses of dose azacitidine and imatinib mesylate (400 mg/day),because of his cytogenetic response is lacking. While he was treated with chemotherapy in 9 months, his condition got worsen. He could not tolerate chemotherapy and he died in 12 months after diagnosis.

**Results:** Depending on the break point of the ABL gene two fusion protein have different sizes which the most common p210 and the smallest p190 fusion proteins [1]. Although a p210 fusion protein is detected 95% in chronic myeloid leukemia, a p190 protein occurs in the majority of B-cell acute lymphoblastic leukemia ,but p190 BCR/ABL is also occurred rarely in AML cases [2]. Recently several studies are reported that de novoPh+ AML expresses p190 fusion protein [3]. These patients have poor prognosis. The treatment algorithm( especially second tyrosine kinase inhibitors) is not certain.

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**Anemias**

## PP-10

**Molecular profile of hemoglobinopathy mutations in King Khalid University Hospital: a single center experience**

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**Objective:** Hemoglobinopathies are group of hereditary blood disorders that are characterized by either reduction or complete absence of  $\alpha$  or  $\beta$ -globin chain synthesis as in  $\alpha$ -thalassemia and  $\beta$ -thalassemia due to mutations, affecting critical areas of the  $\alpha$ - globin gene on chromosome 16 or  $\beta$ -globin gene on the chromosome 11, or structural abnormalities caused by a point mutation in the  $\beta$ -globin gene resulting in the production of abnormal hemoglobin S. These diseases are inherited in an autosomal recessive



manner, with severity ranging from asymptomatic individuals to transfusion dependent anemia, according to the nature of the mutation. The prevalence of the  $\beta$ -globin gene mutations in various areas of Saudi Arabia, previously reported as 0.01 to 0.15% in general population. The prevalence of SCT varies between 2% to 27%, while SCD is 2.7%. While there are no large-scale reports regarding the prevalence of  $\alpha$ -thalassemia.

**Aim:** Trying to detect The prevalence of sickle thalassemia (SCT) which is found to vary between 2% to 27%, while sickle cell disease SCD is 2.7% in Riyadh While there are no large-scale reports regarding the prevalence of  $\alpha$ -thalassemia. This is a single center experience in King Khalid University Hospitals

**Methodology:** A cohort of 236 samples, which were submitted for  $\alpha$  and  $\beta$ -globin gene mutation analysis in the Molecular genetic pathology lab of King Khalid University Hospital, Riyadh, Saudi Arabia during 2015 to 2018, by strip assay for alpha gene and direct Sanger sequencing for the entire genomic region (3-Exons and 2-Introns) of the HBB gene.

**Results:** Out of the total population tested, 162 (65.8%) were normal, (51/66) who were tested for alpha gene mutations were positive, 25 (49%) with single gene deletion, 4 (7.8%) double gene deletion, 16

**Conclusion:** The results of this retrospective study confirms the prevalence of hemoglobinopathies in the Saudi population and empathizes on the urgency to implement protocols and guidelines for more effective screening program.

#### PP-11

##### Iron deficiency and its level in Iranian pregnant women

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**Objective:** Iron-deficiency anemia is associated with adverse neonatal health outcomes. Iron status and its determinants were assessed in a representative sample of Iranian pregnant women. Blood samples were collected and a questionnaire was completed face-to-face.

**Methodology:** Hemoglobin (Hb) and mean cell volume (MCV) were measured using a Sysmex XS-1000 Hematology Analyzer and serum ferritin (SF) and transferrin receptor (sTFR) concentrations by immunoassay.

**Results:** In total, 2 dietitian clinics and 248 pregnant women were included. Approximately 38% of third-trimester and 6% of first-trimester women had SF levels less than 20  $\mu$ g/L. Approximately 23% of third-trimester and 4% of first-trimester women had anemia (Hb 8.5 mg/L). The median body iron stores were 8.1 mg/kg among first-trimester women, but only 3.6 mg/kg among third-trimester women. SF levels were significantly positively associated with age and education level, and were higher among nulliparous women and lower among multiparous women. sTFR concentrations were significantly negatively associated with age and were lower among smokers, nulliparous women, and women who planned their pregnancy.

**Conclusion:** Despite the fact that two thirds of Iranian pregnant women took iron-containing supplements, iron deficiency and iron-deficiency anemia were frequent in third-trimester women. The World Health Organization regards this as a moderate public health problem. National iron supplementation guidelines are needed in Iranian to optimize iron status during pregnancy.

#### PP-12

##### Is hereditary stomatocytosis a rare erythrocyte membrane disorder or an overlooked item?

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**Objective:** Hereditary spherocytosis is known as the most common erythrocyte membrane abnormality. There is a defect in the vertical interactions of erythrocyte membrane proteins in hereditary spherocytosis. Patients

with hereditary spherocytosis seem to have benefit from splenectomy. In hereditary stomatocytosis which is known as a very rare disorder, the problem is due to horizontal interactions of erythrocyte membrane proteins causing membrane sodium-potassium pump dysfunction. Hemolytic anemia is seen in hereditary stomatocytosis but splenectomy brings a high thrombotic risk. Differential diagnosis of these 2 clinical entities is of vital importance.

**Methodology:** Retrospective data from a total of 110 cases with suspicion of hemolytic anemia were analyzed. Demographic data, splenectomy status, treatments were recorded.

**Results:** Osmotic fragility and Eosin-5'-Maleimide (EMA) tests of the 110 hemolytic anemia suspected cases were analyzed. Twenty-six cases were diagnosed as hereditary spherocytosis, 5 cases were diagnosed as hereditary elliptocytosis and 4 cases were diagnosed as hereditary stomatocytosis. All the diagnosed cases were splenectomized and with clinically ongoing hemolysis.

**Conclusion:** As hereditary stomatocytosis cases were misdiagnosed, splenectomy is a common procedure for them with increased morbidity. Eosin-5'-Maleimide (EMA) test should be in work-up of all non-immune hemolytic anemia cases. We suppose that Eosin-5'-Maleimide (EMA) test will give more reliable results when used as a screening test in these patients.

#### PP-13

##### Is L-glutamine really effective in reducing painful crisis and hospitalization for sickle cell anemia patients in real life?

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**Objective:** Increased oxidative stress plays important role in the pathophysiology of sickle cell anemia (SCA). Nicotinamide adenine dinucleotide (NAD) is an anti-oxidant and L-glutamine is a precursor for NAD. Sickle red blood cells have a decrease in NAD redox potential and previous studies showed that oral L-glutamine administration improves NAD redox potential in patients with SCA and therefore reduce the number of painful crisis and hospitalization for these patients. In this study, we aimed to evaluate the efficacy and safety of L-glutamine for SCA patients in real life setting.

**Methodology:** Nine patients (5 male, 4 female) were included in this retrospective study. Mean age was 30.4 years (ranged between 22- 41 years). 4 patients were sickle cell anemia and 5 patients were sickle beta thalassemia. Before L-glutamine therapy, mean number of vaso-occlusive crisis was 5/year (4-6/year) and mean number of hospitalization was 4/year (3-5/year) for these patients. Six patients were using hydroxyurea (2x500 mg/day) and all were using folic acid (5 mg/day). L-glutamine was given at 20 g/day in 4 cases who weighed between 30-60 kg and at 30 g/kg/day in 5 cases who weighed >65 kg.

**Results:** At 24th week (6 months) of L-glutamine therapy, only 1 VOC developed in just 3 patients. VOC developed at 11th, at 12th and at 15th week of the therapy. These 3 patients hospitalized for VOC during follow-up. Two of them hospitalized for only 2 days in whom VOC resolved quickly. However, 3rd patient hospitalized for 1 week in whom we stopped using L-glutamine for 2 weeks before VOC due to unexplained liver enzyme increase and acidosis with mild creatinine increase. No VOC occurred or hospitalization was made for the remaining 6 patients. In addition, hemoglobin level gradually increased in 4 patients without VOC (from 7.4 g/dL to 9.1 g/dL; from 8.8 g/dL to 11.8 g/dL; from 9.6 g/dL to 10.6 g/dL; from 10.5 g/dL to 10.9 g/dL in these 4 cases) and was stable in 2 patients without VOC. Hb level decreased during VOC in 3 cases in whom VOC developed; however, in 2 of them, Hb level again gradually increased after resolution of VOC. Only grade 1 nausea was seen in 1 patient that resolved in few days. All patients are still under therapy and they all conclude that they feel better after L-glutamine therapy.

**Conclusion:** In real life, at 6 months of therapy, L-glutamine treatment was prominently efficacious in reducing the frequency of VOC and hospitalization for patients with SCA with mild adverse events.



## PP-14

**Intermittent bevacizumab therapy experience in hereditary hemorrhagic telangiectasia**

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**Objective:** Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is a rare autosomal dominant disease characterized by visceral arteriovenous malformations and mucocutaneous telangiectasia. Epistaxis, gastrointestinal bleeding and iron deficiency anemia are the most common clinical manifestations. Increased plasma levels of vascular endothelial growth factor (VEGF) is a major underlying mechanism associated with bleeding complications in HHT patients. Recently it has been shown that bevacizumab, a humanized monoclonal VEGF inhibitor, is effective in the treatment of HHT. We present three cases of HHT requiring massive transfusions due to severe gastrointestinal (GI) bleeding and do not respond to conventional treatment.

**Case report:** Three HHT patients with symptomatic gastrointestinal bleeding and iron deficiency anemia prospectively underwent off-label systemic treatment with the VEGF-inhibitor bevacizumab at a dose of 5mg/kg infusion every 2 weeks in 6 cycles. Patients were followed up for 6 months after completing the first treatment of bevacizumab and received a maintenance treatment at a dose of 1mg/kg infusion every 3 weeks in 6 cycles. Parenteral iron therapies were administered while the patients were under treatment for bevacizumab. Clinical symptoms, CBC, iron and ferritin levels were assessed before and after therapy.

**Results:** Three patients with a known diagnosis of HHT underwent bevacizumab treatment due to their resistance to intravenous iron and RBC transfusion treatments. After completion of first treatment with bevacizumab, there was a marked decrease in RBC transfusion requirements and a significant increase in hemoglobin levels. However, symptoms and hemoglobin values returned back gradually to pre-therapeutic levels after 5 months in all of the patients. Re-initiation of low-dose bevacizumab after recurrence was effective again. Patients did not require transfusion for 2 months after completing the second treatment. No therapy-related adverse events were observed during treatment.

**Conclusion:** Optimal bevacizumab dose has not been reported in HHT patients. This case series has shown that low dose bevacizumab is as effective as the oncologic dose in HHT patients. Therefore, intermittent and low-dose bevacizumab therapy in transfusion-dependent HHT patients is a good treatment option.

## PP-15

**Complement-mediated hemolytic uremic syndrome: a case report**

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**Objective:** Hemolytic Uremic Syndrome (HUS) presents with findings of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. Approximately 90% of patients develop a secondary HUS resulting from infection, medication, or autoimmune diseases. The remaining 5-10% constitutes atypical HUS, what has been newly termed complement-mediated HUS (cHUS), caused by complementary gene mutations and antibodies reacting to complement Factor H (CFH).

**Case report:** A 19-year-old woman presented with complaints of fatigue, nausea, and vomiting. Physical examination of the patient, who was not taking any medication, revealed no known disease. Test results showed a total leukocyte count of 6,200/mm<sup>3</sup>, hemoglobin (Hgb) of 7.8 g/dl, thrombocyte count of 65,000/mm<sup>3</sup>, serum creatinine of 2.3 mg/dl, LDL level of 1289 U/L, total bilirubin of 10.78 mg/dL, indirect bilirubin of 9.55 mg/dL. The direct coombs test result was negative and haptoglobin was low. Schistocytes were widely observed in the peripheral blood smear. Upon a pre-diagnosis of thrombotic microangiopathy, a sample of plasma was taken to analyze ADAMTS-13 level and plasmapheresis was begun. Creatinine levels increased

to 5.15 mg/dl on the fifth day of plasmapheresis therapy. The patient underwent hemodialysis due to the appearance uremic symptoms. Following three cycles of hemodialysis, creatinine level decreased to 1.9 mg/dl, uremic symptoms subsided, and urine output increased, at which point hemodialysis was discontinued. The ADAMTS-13 activity was 96.96% (reference range: 40-130) and ADAMTS 13 SI result was 0.97 IU/mL (reference range: 0.4-1.3), both within normal range. Clinical and laboratory findings of microangiopathic hemolytic anemia persisted on the sixth day of plasmapheresis therapy, upon which a diagnosis of cHUS was made and treatment with eculizumab was initiated. Ciprofloxacin was started for meningococcal meningitis prophylaxis. The patient underwent vaccinations for pneumococcal, meningococcal, and Haemophilus influenzae. The heterozygous mutation in the CFHR5 and CFI gene was detected. The patient underwent a total of 11 cycles of plasmapheresis and four weeks of treatment with 900 mg of eculizumab per week during hospitalization. Following treatment, leukocyte count was 4,200/mm<sup>3</sup>, Hgb was 11.6 g/dl, platelet count was 252,000/mm<sup>3</sup>, creatinine was 0.8 mg/dl, indirect bilirubin was 0.9 mg/dl, and LDH was 227 U/L. No schistocytes were observed on the peripheral blood smear. The patient received follow-up treatment with eculizumab once every two weeks.

**Conclusion:** Disorders related to the regulation of the complement system are among the main causes of cHUS, with more than 50% of cases associated with mutations in the regulation of alternative pathways of the complement. In the alternative complement pathway, complement factor H, factor I, factor B, membrane cofactor protein, thrombomodulin, and C3 mutations were found to lead to cHUS, a rare but life-threatening disease. Plasmapheresis and eculizumab are effective treatments for these patients. Eculizumab has now become the first choice for treatment of patients with cHUS.

## PP-16

**Clinical features and responses to eculizumab of paroxysmal nocturnal hemoglobinuria patients: a single-center experience**

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**Objective:** Paroxysmal Nocturnal Hemoglobinuria (PNH) is an acquired clonal hematopoietic stem cell disease classically characterized by chronic intravascular hemolysis, bone marrow failure, and thrombosis. Eculizumab is an anti-C5 monoclonal antibody proven to reduce hemolysis and thrombotic attacks in the treatment of PNH. We aimed to present our data on PNH, a rare disease, and to share our experiences treating PNH with eculizumab.

**Methodology:** Demographic and clinical characteristics, hemogram values, reticulocyte count, LDH levels, history of thrombosis, anticoagulant use, eculizumab treatment and responses, PNH clone percentages, and overall survival (OS) ratios of the study PNH patients were retrospectively analyzed. Diagnosis of PNH was obtained by means of the fluorescence aerosol (FLAER) test using peripheral blood flow cytometry. In this test, a diagnosis of PNH was made by detecting the absence of GPI proteins in at least two of three different cell lines consisting of granulocytes, monocytes, or erythrocytes. Due to previous transfusions, in order to obtain more sensitive and reliable data, the FLAER results in granulocytes and monocytes were taken into account.

**Results:** Five of the patients were female (55.5%) and 4 were male (44.5%), with a median age of 33.5±12.3 years. Seven of the patients were diagnosed with classical PNH (77.8%), while 2 (22.2%) had PNH accompanied by bone marrow failure (aplastic anemia) (PNH/AA). The mean granulocyte clone size was 72.5% (19.3–98.1), the mean monocyte clone size was 75.4% (18.4–99.3), and the mean erythrocyte clone size was 42.8 (6.8–90.6). Upon referral, the following symptoms and findings were reported for the 9 patients: 6 cases of fatigue, 2 cases of dyspnea, 3 cases of abdominal pain, 1 case of dysphagia, 1 case of recurrent low-level tumors, and 2 cases of erectile dysfunction. In addition, at the time of diagnosis, hemoglobinuria and iron deficiency were detected in 5 patients, thrombosis in 1 patient, renal failure in 1 patient, and cytopenia without anemia (leukopenia and/or thrombocytopenia) in 5 patients. The mean hemoglobin level was 8.2 g/dL (5.7–10.1 g/dL), mean leukocyte count was 5.80×10<sup>3</sup>/μL (1.72–8.30×10<sup>3</sup>/μL), mean platelet count was

96.6×10<sup>3</sup>/L (42–214×10<sup>3</sup>/μL), mean lactate dehydrogenase level was 1312 U/L (423–2690 U/L), and mean reticulocyte level was 3.76% (1.1–6.3%). All cases received eculizumab therapy, of which 8 exhibited full or partial responses, while one was unresponsive to treatment. At the end of the median follow-up period of 46 months, all patients were still living.

**Conclusion:** PNH a rare hematologic disease. Following determination of the pathogenesis of the disease, besides the classical treatment methods, eculizumab is a popular treatment option. In 8 of the 9 patients treated with eculizumab, hemolysis decreased following treatment and blood transfusion was not necessary. The quality of life experienced by all patients was improved.

#### PP-17

##### Evaluation of the effects of iron deficiency anemic treatment in blood lipid levels and body measurements in middle age and adolosan women

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**Objective:** Anemia is the most frequently observed symptoms worldwide. Anemia is defined as a hemoglobin value of ≤13 g/dL in men and ≤12 g/dL in non-pregnant women according to World Health Organization (WHO). Iron deficiency anemia is the most common type of anemia worldwide. Hyperlipidemia and being overweight resulted from changes in lifestyle due to technological developments and from bad eating habits have become increasing health problems worldwide. Cytokines secreted from adipose tissue with the increase in fat mass leads to chronic inflammation in the body. There are interactions among iron deficiency anemia, hyperlipidemia, inflammation, and weight gain, including complex mechanisms. Although there have been several studies conducted on this issue recently, contradictory results are obtained.

**Methodology:** The present study aimed to evaluate the effects of oral iron treatment on waist circumference, body weight, lipid profile and C-reactive protein (CRP) level in female patients with iron deficiency anemia. For this purpose, hematological parameters, waist circumferences, lipid profiles and CRP levels of 31 female patients with iron deficiency anemia were measured at the beginning of the treatment (month 0), at the 3rd and 6th months, and the results were compared.

**Results:** The hematological parameters were observed to be returned to normal levels at the 3rd month. While no significant difference was observed regarding the total cholesterol and triglyceride levels during the iron treatment, an increase in low-density lipoprotein (LDL) levels at the 3rd month and a decrease in high-density lipoprotein (HDL) levels after the 3rd month were determined. CRP levels and body weight increased at the 3rd month. An increase in the waist circumference was observed at the 3rd month, whereas a decrease was observed after the 3rd month. A positive significant relationship was determined between hemoglobin levels and total cholesterol levels at the beginning of the study, whereas there was a negative significant relationship between hemoglobin levels and HDL levels at the 3rd month; and between hemoglobin levels and triglyceride levels at the 6th month.

**Conclusion:** In conclusion, there are various levels of association among iron deficiency anemia, hyperlipidemia, inflammation, and weight gain, and the patients should be evaluated in a multidisciplinary manner and followed up.

#### PP-18

##### Human parvovirus B19 and blood product safety: current and further perspectives

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**Objective:** Human Parvovirus B19 is a member of Parvoviridae family which can be transmitted through blood components and trans placental routes. It is known to cause erythema infectiosum, hydrops fetalis, aplastic crises in chronic hemolytic anemia, hematopoietic suppression with pancytopenia and aplastic anemia in immunocompromized patients. It attacks red blood cells

through P antigen in the immature erythroid cells close to the CFU-E stage leading to erythroid hypoplasia. We know that no specific screening tools are currently available for this virus in most of blood bank and transfusion service centers although high-risk groups, e.g. patients with sickle cell anemia and thalassemia are the major blood products consumers at our population.

**Case report:** We had a reported case of sickle cell anemia patient with pancytopenia and also grade II reactive and reversible myelofibrosis with acute Parvovirus B19 infection. Such findings may raise another suggestive theory of pathogenesis of Parvovirus B19 effect in those patients with chronic hemolytic anemia.

**Methodology:** Literature review of Parvovirus B19-induced fibrosis shows that T-helper 2 inflammatory cytokines of early phase of parvovirus B19 infection is fibrinogenic and can induce marrow fibrosis. Further literature review for blood donor screening program of this virus shows that some European countries e.g.: Netherlands use double positive IgG tests to provide B19V-safe blood products for those patients at risk like patients with chronic hemolytic anemia.

**Results:** Our opinion is although only four clinical cases of B19 infection are documented in the literature to be transmitted through blood components, the extent of transfusion could be theoretically severe in particular patient categories (e.g. immunocompromised patients, pregnant ladies, patients with chronic hemolytic anemia). Those recipients might be a target of B19V-safe blood components if such screening program or protocol is applicable.

**Conclusion:** Providing different suggested pathogenesis of Parvovirus B19 infection in patients with chronic hemolytic anemia, consideration of Parvovirus B19 safe blood and blood products in those patients is deserved to be carried out in some countries.

#### PP-19

##### Evaluation of autoimmune hemolytic anemia patients after splenectomy: single centre experience

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**Objective:** Autoimmune hemolytic anemia (AIHA) is a relatively uncommon disorder caused by autoantibodies directed against self red blood cells. It can be idiopathic or secondary. The aim of this study was to analyze the treatment responses of our patients who underwent splenectomy after receiving treatment for autoimmune hemolytic anemia between 2006-2017.

**Results:** We included data for all consecutive 25 patients with a definite diagnosis of AIHA who underwent splenectomy between 2006 and 2017. There was male predominance (n=16, 64%). Thirteen of the patients (52%) were primer AIHA and the other 12 (48%) were secondary AIHA. The causes of secondary AIHA are autoimmune lymphoproliferative syndrome (OILPS)(n=1), hairy cell leukemia (HCL) (n=2), non-Hodgkin lymphoma (NHL) (n=1), KLL (n=3), Hodgkin lymphoma (n=2), B cell lymphoma (n=2), CML (n=1), splenic marginal zone lymphoma (SMZL) (n=1). All patients received corticosteroid therapy prior to splenectomy and received 4 (16%) immunosuppressive therapy in addition to corticosteroid therapy. Splenomegaly was present in 21 patients (84%). In 9 (36%) of the patients, complications developed after splenectomy. (Sepsis (n=4), pulmonary embolism (n=4), portal vein thrombosis (n=1)). During follow-up, twelve patients showed relapse, within 6 months after splenectomy. Most common therapeutic modality was methyl prednisolone (n=11) in relapse patients. Rituximab (n/CR=4/2), cyclosporin (n/CR=3/1) and mycophenolat mofetil (n/CR=1/1) was given together with methyl prednisolone.

**Conclusion:** The diagnosis of AIHA is suspected in a patient who presents with the sudden onset of anemia, with laboratory evidence for hemolysis (i.e., increased lactate dehydrogenase (LDH), increased indirect bilirubin, reduced to absent haptoglobin) and detection of antibody and/or complement components on the surface of the RBC (i.e., a positive direct antiglobulin [Coombs] test), or, less commonly, in the circulation (ie, a positive indirect antiglobulin [Coombs] test). AIHA may also be subdivided into primary (or idiopathic) and secondary. Most cases are idiopathic with no underlying disorder or direct cause that can be found. The management

of AIHA is still based on expert opinion and corticosteroids remain the cornerstone of therapy. The ratio of female to male is about 1.5-2 and it is more common between 40-50 years. Treatment options in case of relapse include splenectomy, rituximab, immunosuppressive drugs (azathioprine, cyclosporine, cyclophosphamide) and immunoglobulin. Splenectomy is the only curative treatment option. Despite splenectomy, relapses are seen in one third of the patients. There is no common treatment protocol for treatment after splenectomy. Approximately half of our patients developed recurrence after splenectomy. The high of this rate may be that 48% of our cases due to the secondary AIHA Splenectomy is an important treatment option in autoimmune hemolytic anemia relapse patients. However, new drugs are needed for treatment of relapses because of low curing rates.

#### PP-20

##### Spectrum of bone marrow changes in advance stage chronic kidney disease

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**Objective:** The purpose of the study is to analyze various hematological manifestations of advanced stage CKD in peripheral blood and bone marrow (BM) of the patients, referred to us from the nephrology unit of our tertiary care medical set up.

**Methodology:** Patients of both sexes and all age groups with CKD stage III, IV and V were included in this study. Patient's histories were recorded. Complete blood counts, bone marrow aspiration and trephine biopsy were done and evaluated microscopically. Mean blood counts of the patients in three groups of CKD were compared. Frequencies of various bone marrow (BM) findings in patients of CKD were calculated.

**Results:** Out of 57 patients, 41 (71.9%) were males while 16 (28%) were females. Mean age was 60 years. There was no statistically significant difference between the mean hemoglobin, mean white cell count and mean platelets count of the patients in three groups of CKD. Reactive changes due to underlying CKD and inflammation were the most frequent findings in the BM of the patients.

**Conclusion:** Anaemia of mild to moderate severity and reactive changes in the BM are the most frequent haematological findings encountered in patients suffering from advanced stage CKD. Since CKD is predominantly a disease of the elderly so it is not rare to find the co-morbidities including plasmacytosis, malignancies and their effects on the BM in patients of CKD.

#### PP-21

##### Late diagnosis in Syrian immigrant patient; thiamine-responsive megaloblastic anemia syndrome

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**Objective:** Thiamine-responsive megaloblastic anemia (TRMA) also known as Rogers syndrome was first described by Porter et al in 1969. It is characterized by diabetes mellitus, megaloblastic anemia and progressive sensorineural hearing loss. TRMA is a rare autosomal recessive disorder. This syndrome is seen especially in consanguineous marriages and isolated communities. It has been reported in fewer than 80 families worldwide. Diagnosis relies on uncovering genetic variations (alleles) in the SLC19A2 gene, encoding for a high affinity thiamine transporter. This transporter is essentially present in hematopoietic stem cells, pancreatic beta cells and inner ear cells, explaining the clinical manifestations of the disease. The disease is usually diagnosed in childhood period. We presented a 21-year-old patient who was diagnosed with TRMA with the findings of pancytopenia.

**Case report:** A 21-year-old male patient was referred to our center upon the symptoms of fatigue, hearing loss and pancytopenia. He was emigrated from Syria to Turkey for years ago because of the Syrian War. Mother and father are first-degree relatives. He has hearing loss and inarticulated since he was 1 year old. He was diagnosed as type 1 diabetes mellitus at 10 years old and

treated with insulin. Erythrocyte transfusion had been performed several times due to the anemia. In laboratory tests; Wbc: 2480×10<sup>3</sup>/μL, Hgb:4.3 g/dL Plt: 8000×10<sup>3</sup>/μL, MCV:81 fL, Glukoz: 345 mg/dL, Creatinin:0.7 mg/dL, Ldh:92 U/L, Ferritin:1140 μg/L, VitB12: 702 ng/L, Folat: 5.2 μg/L were found. There was hepatomegaly and splenomegaly in abdominal ultrasonography. Megaloblastic changes were seen in peripheral blood smear but, there was no atypical cells. Bone marrow biopsy and flow cytometric evaluation were normal. Audio logic evaluation showed bilateral severe sensorineural hearing. Considering the laboratory test and clinical findings, a diagnosis of TRMA was suspected and the patient was started on thiamine hydrochloride (100 mg orally daily). An increase in leukocyte and platelet counts was observed on the 5th day of thiamine treatment. On the 10th day of treatment, an increase in hemoglobin level was observed. His pancytopenia was completely resolved. WBC: 7000×10<sup>3</sup>/μL, Hgb: 15 g/dL Plt: 234000×10<sup>3</sup>/μL, mcv: 91 were detected after two months of treatment. At the same time genetic evaluation was initiated. Homozygous mutation in the SLC19A2 gene (c.242\_243insA (p.Y81\*) (p.Tyr81\*)) was detected as a result of genetic evaluation.

**Conclusion:** Literature showed that the cases of TRMA are mostly diagnosed during childhood period. Our case was diagnosed at the age of 21. He is different from the others with this respect. Pancytopenia has been described several times in Rogers's syndrome. There were serious cytopenia in our case at the time of diagnosis. Rapid improvement in cytopenia was seen after the treatment with thiamine. In conclusion TRMA is a rare autosomal recessive disorder which typically has a clinical triad: megaloblastic anemia, diabetes mellitus and sensorineural hearing loss. Thiamine treatment should be continued for lifelong. Family screening should be performed, and genetic counseling should be offered when diagnosed.

#### Bone Marrow Transplantation

#### PP-22

##### Autologous stem cell transplantation and CMV

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**Objective:** CMV is associated with asymptomatic infection or CMV disease in patients with stem cell transplant (SCT), which is an important cause of mortality and morbidity. The aim of this study is to evaluate the frequency and risk factors of CMV reactivation and disease development in patients with AuSCT and to show them if there are more frequent follow-ups of CMV in AuSCT patients.

**Methodology:** 352 patients who underwent autologous stem cell transplantation and follow-up at Erciyes University Stem Cell Transplantation and Treatment Center between 2007-2016 were retrospectively examined. Patients undergoing OKHN were asked to follow CMV-PCR or antigenemia twice a week during hospital admission. 222 OKHN periods of 193 patients were included in the study. CMV-PCR level of >100 IU/ml was considered positive. Chemotherapy protocols taken during the 222 OKHN period, risk situations at the diagnosis, disease activation status during transplantation, pre-transplant CMV serology and viral serology were investigated. The amount of erythrocyte and platelet transfusion in the post-transplant period, the light and filtration status of the transfused blood product and the status of CMV serology were examined.

**Results:** CMV-PCR positivity after OKHN was detected in 51 patients (23%), 47 (21.1%) patients developed only asymptomatic CMV reactivation and 4 (1.8%) patients developed CMV disease. Ten patients with CMV PCR positivity were treated with preemptive therapy and 4 patients with CMV disease (CMV pneumonia) treatment. There was no significant difference between MM, HL and NHL after the development of CMV PCR positivity after AuSCT (22.2%, 19.4%, 31.7% respectively, p>0.05). There was no significant relationship between patients' performance status, age, number of transplants, risk of illness at the time of diagnosis, pre-transplant radiotherapy status, and CMV reactivation. There was a significant correlation between the activation status of the disease during transplantation and CMV reactivation (23.1% in remission, 17.8% in partial remission, 66.7% in active disease, p<0.05). There was no significant correlation between HBV, HCV and HIV pre-AuSCT



seropositivity and CMV reactivation; but 4 patients with CMV disease were HBV seropositive. There was no difference in the risk of CMV reactivation with chemotherapies taken before transplantation in HL and NHL patients. Although no significant difference was found in the MM patients with or without VAD or bortezomib treatment, in patients receiving immunomodulatory drug treatment, CMV reactivation was found to be statistically significantly lower (12.2% in the IMiD+, 27.7% in the non-IMiD,  $p < 0.05$ ). In patients receiving  $\leq 2U$  ES (erythrocyte suspension, CMV reactivation was 21.7%, while reactivation in patients receiving  $\geq 3U$  ES was 44.4% ( $p < 0.05$ ). CMV reactivation was 11.9% in patients who had undergone  $\leq 3U$  TS (thrombocyte suspension) replacements, 32.3% in patients who had 4-5U TS replacements, and 37.5% in patients who had  $\geq 6U$  TS replacements ( $p < 0.05$ ). A statistically significant relationship was found between CMV reactivation as the number of blood product transfusions increased.

**Conclusion:** Pre-transplant disease status in OKHN patients is an important risk factor for CMV reactivation. The significant decline in CMV reactivation with IMiD-derived therapies may be important in regulating treatment. Increase in CMV reactivation as blood products transfusion increases in patients increases the prediction that this group will be closely monitored for CMV reactivation and disease in patients.

#### PP-23

##### Extramedullary relapse of the AML following allo-HSCT: a case report

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**Objective:** Acute myeloid/myelogenous leukemia (AML) is a cancer of the myeloid line of blood cells which is characterized by rapid growth and accumulation of leukocytes in the bone marrow and interference with the production of normal blood cells. AML is the most common type of acute leukemia affecting adults and its incidence generally increases with age. AML in older adults has its main characteristics as pancytopenia and myeloproliferative hyperplasia to hypoplasia.

**Case report:** A 52 years old female patient had complaints of fatigue, fever and headache in January of 2014. She admitted to emergency room with those complaints. Leukocytosis was spotted in the complete blood counting. At the same time gingival swelling and inflammation was present. She admitted to our polyclinic with all those complaints. With examination and blood surveys she was diagnosed as AML M4. Idarubicine and ARA-C chemotherapy was started at 12 March 2014. 3 courses of treatment of high dose ARA-C consolidation chemotherapy was given after the patient was at remission. At 26 August 2014 allogeneic hematopoietic stem cell transplantation was made. EMA chemotherapy was started to be given to the patient because of the pathology result of bone marrow biopsy which is done in October 2014 as AML relapse. High dose ARA-C chemotherapy was given after EMA therapy. At March of 2015 DLI (donor lymphocyte infusion) was given to the patient. She had no complaints till June 2017. At that time she had a nodule in left inguinal region. In the pelvic MRI, a vascular invasive soft tissue tumor of  $5 \times 3 \times 2$  cm was reported. AML, blastic cell infiltration was reported in the pathological examination of the biopsy material taken from the tumor. New bone marrow biopsy results was reported as 4-5% blastic cells. Chimerism was 98% donor matched. The patient was accepted to have an extramedullary relapse and Idarubicine and ARA-C chemotherapy was started. The left inguinal tumor got smaller and the patient was discharged with the plan of a control MRI.

**Methodology:** When leukemic cells develop as a solid tumor at extramedullary sites, they are called 'granulocytic sarcoma.' In 1853, these tumors were given the name of 'chloroma,' because of the greenish color imparted by the presence of MPO. Large retrospective studies note the incidence of granulocytic sarcoma in patients with AML to be approximately 3% and occasionally these tumors may be the initial presentation of AML. Allogeneic hematopoietic stem cell transplantation (HSCT) is increasingly used as a potentially curative treatment for acute myeloid leukemia (AML). However post-HSCT relapse remains an important cause of treatment failure with relapse rates ranging from 30% to 70%, depending on a number of factors such as disease status at the time of transplantation, donor source, conditioning

regimen, and T-cell content of the graft. The outcome for patients with relapsed acute myeloid leukemia (AML) post-allogeneic hematopoietic stem cell transplantation (HSCT) remains poor, irrespective of treatment strategy.

**Results:** In this case, lessening of the size of an extramedullary relapse mass lesion after allogeneic hematopoietic stem cell transplantation was observed after salvage chemotherapy administration.

#### PP-24

##### Evaluation of hemoglobin levels with clinical outcome in patients undergoing hematopoietic stem cell transplantation

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**Objective:** Hematopoietic Stem Cell Transplantation (HSCT) is an effective way for treatment of leukemia patients. The time for discharging a transplanted patient is different and depends on blood counts and immune system recovery of the patient. During the hospitalization, the risk of infection and bleeding are high and the physician should be confident of patient's general condition. The purpose of this article is to assess the post-transplant Hb level in hematopoietic stem cell transplanted patients.

**Methodology:** In this retrospective study, the data were collected from patients file between 2008-2015 in Taleghani hematopoietic stem cell transplantation center. The comparison of Hb and one-year survival of 392 patients with allogeneic (AML, ALL, MDS) and 100 patients with autologous (MM, PNET, Hodgkin's and non-Hodgkin's lymphoma) HSCT were done. Kaplan-Meier and Cox Regression tests were used to investigate the differences between variables.

**Results:** There was a significant difference between Hb and survival in allogeneic (AML, ALL, MDS) and autologous (MM, PNET, Hodgkin's and non-Hodgkin's lymphoma) patients with HSCT ( $p < 0.05$ ).

**Conclusion:** Our results confirm an association between Hb level and on-year survival and hospitalization in patients with autologous and allogeneic transplantation. Hb level as a survival factor after HSCT can be helpful to predict the discharging time of patients and management of disease to improve a better treatment for the patients.

#### PP-25

##### A case of aplastic anemia with graft failure and autologous recovery post allogeneic stem cell transplant

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**Case report:** 25 years old female, with no significant past history, presented in July 2014 with pancytopenia (WBC's  $1.36 \times 10^9/L$ , ANC  $0.27 \times 10^9/L$ , Retic count 0.22%, Plt  $8 \times 10^9/L$ ). Bone marrow assessment showed empty marrow, with normal karyotype. Chromosomal breakage study was Negative. Flow-cytometry showed a small PNH clone (10.3%) within the granulocyte, monocytes (12.9%), and RBC's (0.2%). Serology was negative. The patient underwent Allogeneic-SCT, from her fully matched, ABO mismatched (Donor A+, Recipient O+) 20 years-old brother, in September 2014, with FLU/CY conditioning and MTX/CSA for GVHD prophylaxis. Both donor and recipient are CMV positive. The total infused CD34 Stem cell dose was  $6.3 \times 10^6$ , and TNC dose was  $8.9 \times 10^8$ . The neutrophils engrafted at D+21, while platelets engrafted at D+12. However, through the first year post-transplant, her lab showed persistent mixed chimerism with poor lymphoid engraftment below 50%, so the patient was kept on CSA. In October 2015, the patient got pregnant, and elected to continue CSA despite the risks. She aborted at week 31 due to IUFD, with signs of CSA toxicity. During pregnancy and after miscarriage she continued to lose myeloid and lymphoid engraftment with stable counts. Following CSA discontinuation in August 2017, her chimerism showed no donor cells with autologous recovery. When we studied the effect of different risk factors on the incidence of graft failure, a total of 95 patients with severe aplastic anemia, who underwent Allogeneic-SCT at our institute from MRD were analyzed. By using logistic regression, our results showed that major



ABO mismatch was significantly associated with mixed chimerism ( $p=0.04$ ), while TNC  $<2 \times 10^6$  and recipient age  $>20$ , were significantly associated with graft failure ( $p=0.02$ ,  $0.04$  respectively). The patient had both risk features (major ABO mismatch, and age at transplant).

#### PP-26

##### An unexpected complication: transverse myelitis after autologous stem cell transplantation

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**Objective:** Transverse myelitis (TM) is a neurological disorder caused by inflammation of spinal cord which may be associated with autoimmune, inflammatory, and infectious etiologies. Herein we reported a patient with diffuse large B cell lymphoma (DLBCL) who develop TM after autologous HSCT. A few cases have been reported in the literature that presented transverse myelitis development after allogeneic HSCT. However, TM after autologous HSCT has not been reported yet. To the best of our knowledge; the current patient is the first case reported in literature.

**Case report:** A 49-year-old male patient was diagnosed with stage 3 DLBCL in February 2016 and received 8 cycles of RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy followed by RDHAP (rituximab, dexamethasone, cytarabine arabinoside (ARA-C) and cisplatin) salvage chemotherapy. After 3 cycles of RDHAP chemotherapy, complete response (CR) was obtained and then HSCT was planned. During preparations for transplantation, left optic nerve involvement detected and three cycles of R-IDARAM (rituximab, idarubicin, dexamethasone, ARA-C, methotrexate) and intrathecal methotrexate and ARA-C chemotherapy were given due to CNS recurrence. After chemotherapy, the patient achieved CR so that, autologous HSCT was performed following the conditioning regimen including rituximab, carmustine and thiopeta. On the 20th day after HSCT, numbness and sensory loss of bilateral lower extremity and difficulty in urinating had started. Electromyography (EMG) and urinary system ultrasound revealed no pathologic finding. During follow-up, the patient's symptoms progressed and increased to T4 level and walking difficulty had begun. Neurological examination revealed hypoesthesia, lack of deep tendon reflexes (DTR), and 3/5 motor muscle weakness in bilateral lower extremity. There was no pathology detected in the neurological examination and cranial magnetic resonance imaging (MRI). Milimetric hyperintensity was detected in C5-C6 and T2-T5 segments of spinal cord on vertebral MRI. There was no atypical cell infiltration in the cerebrospinal fluid (CSF) sample but CSF protein levels were high. All viral and autoimmune markers showed no abnormal findings. According to these findings, the patient was diagnosed as TM. Pulse steroid started immediately. There was no improvement and intravenous immunoglobulin treatment was given. Since the patient did not respond to previous therapies, plasmapheresis was performed. Cyclophosphamide with the dosage of 1500 mg was given and methylprednisolone (MP) with the dosage of 80 mg in a day as a maintenance therapy was started. Then the patient referred to rehabilitation department to receive rehabilitation programme. During the follow-up period, significant improvement was detected in neurological examination. MP was given about 6 months and stopped with dose reduction day by day. The patient was discharged on the 90th day of autologous HSCT and most of all the symptoms relieved.

**Conclusion:** The frequency of myelitis among these complications is very low even there is no case reported after autologous HSCT. To conclude, TM is a rare condition after HSCT that thought to be caused by many reasons especially serious immunosuppression due to transplantation. It should be kept in mind for clinicians that TM may develop after autologous HSCT.

#### PP-27

##### Allogeneic haematopoietic stem cell transplantation in adult aplastic anemia patients

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**Objective:** Aplastic anemia (AA) is a rare and serious hematologic disorder. Immunosuppression and allogeneic haematologic stem cell transplantation (ASCT) are two main treatment options. Related HLA full-matched ASCT is very promising especially in young patients. Our aim is to retrospectively evaluate clinical characteristics and outcome in AA patients who were undergone ASCT in Ege University Hematology Department Stem Cell Transplantation Unit.

**Methodology:** Patients who were undergone ASCT in our department between January 2012 and May 2018 retrospectively evaluated. Patients demographic data, age at diagnosis, time between diagnosis and ASCT, treatment until ASCT, source of stem cell and number of CD34+ stem cell infused, transplantation regimen, prophylaxis for graft-versus host disease (GVHD), time of neutrophil and thrombocyte engraftment, information about acute and chronic GVHD, overall survival and final status were analyzed. Overall survival was calculated as the time between ASCT and the last patient visit.

**Results:** In six years period, 11 AA patients were transplanted. 3 patients had severe, 6 of them had very severe, 1 patient had not severe but transfusion depended and unresponsive to immunosuppressive treatment AA. One of the patients was Fanconi AA. PNH clone detected in two patients follow-up, they received eculizumab until ASCT. Male/female ratio was 7/4. Mean age in ASCT was 28.7 years (19-38), mean time from diagnosis to transplantation was 50.7 months (2-192). The source of stem cells was peripheral blood in all donors. 4 donors were unrelated. Mean CD34 + stem cell was  $8.58 \times 10^6/\text{kg}$  (5-14,87). Standard GVHD prophylaxis regimen was methotrexate 15 mg/m<sup>2</sup> on day +1, 10 mg/m<sup>2</sup> on day +3, +6, +11. and cyclosporin 5 mg/kg starting on day +1. and titrated according to blood drug level. There was no acute GVHD but 4 patients had chronic GVHD. One patient had grade 3 skin GVHD in 6th month of transplantation and eye GVHD in 12th month. Another patient grade 2 skin GVHD in 4th month and eye GVHD in 5th month. Other two patients had grade 1 skin GVHDs in 15th and 7th months respectively. Mean survival was 18.63 months (10 days-72 months).

**Conclusion:** ASCT is the only curative treatment in AA. 2 of our patients died in early post-transplantation period because of the septic complications. Other patients are alive (81%) and didn't encountered serious /life threatening complications. In young patients with HLA matched donors, ASCT is very effective and safe treatment modality.

#### PP-28

##### The comparison of melphalan administration on day -3 with administration on day -1 on neutrophil and platelet engraftment in multiple myeloma patients undergoing autologous stem cell transplantation

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**Objective:** High dose chemotherapy followed by ASCT is the most important step of MM treatment. Melphalan, an alkylating agent, is the most preferable drug for conditioning regimens and dosage and timing is important with regards to side effects or engraftment timing. Engraftment time is determinative on infections and hospitalization duration.

**Methodology:** We compared the neutrophil and thrombocyte engraftments retrospectively in patients with multiple myeloma who received melphalan 200 mg/m<sup>2</sup> single dose on day -3 and day -1 as conditioning regimen. There were 29 patients receiving melphalan on day -1 and 42 patient on day -3.

**Results:** The mean neutrophil engraftment times for day -1 group and day -3 group were  $12.8 \pm 2.4$  days and  $10.4 \pm 1.3$  days, respectively ( $p < 0.001$ ). The mean thrombocyte engraftment times for day -1 group and day -3 group were  $13.48 \pm 3.7$  days and  $12.7 \pm 3.3$  days, respectively ( $p = 0.36$ ). In day -3 group,

there was no failure neither in neutrophil nor in thrombocyte engraftment but 1 patient could just get thrombocyte engraftment on day 33. In day -1 group, 2 patients could not get engraftment failure.

**Conclusion:** Administration of melphalan on day -3 is better than on day -1 in terms of neutrophil engraftment and hence in terms of hospitalization duration.

### Chronic Lymphocytic Leukemias

#### PP-29

#### CD81 expression in the differential diagnosis of chronic lymphocytic leukemia

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**Objective:** Immunophenotyping has a central role in CLL. However, CLL is a very heterogenous disease, both morphologically and immunophenotypically; thus, its diagnosis may prove a challenge. In 1994, a scoring system composed of 5 cellular markers (CD5, CD22, CD23, FMC7 and membrane immunoglobulin) was developed by Matutes et al in order to differentiate CLL from other LPDs by its immunophenotypic properties. According to the Matutes system, the patient group exhibiting atypical immunophenotypic properties are hardly differentiated from other LPDs, particularly MCL. CD81 is a widely expressed tetraspanin that associates in B cells with CD19 in the CD19-CD21-CD81 signaling complex. CD81 is necessary for normal CD19 expression; cd81<sup>-/-</sup> B cells express lower levels of CD19, especially cd81<sup>-/-</sup> small pre-BII cells, which are almost devoid of surface CD19. We investigated CD81 expression in the differential diagnosis of CLL and MCL.

**Methodology:** The present study retrospectively evaluated the medical records of 120 patients diagnosed with CLL (n=101) and MCL (n=19) according to the WHO criteria in the Hematology Clinic of Ankara Diskapi Yildirim Beyazit Training and Research Hospital from January 2015 through December 2017. We retrospectively examined CD81 expression with 8 color Multiparameter Flow cytometry devices in 101 CLL and 19 MCL cases.

**Results:** We found negative CD81 expression in CLL cases whereas it was positive in MCL cases.

**Conclusion:** CLL and MCL are B cell LPDs expressing CD5. Flow cytometric immunophenotyping is beneficial for CLL vs MCL differentiation and commonly utilized for this purpose. The Matutes diagnostic scoring commonly used in CLL has now lost its importance because CLL cases exhibiting atypical immunophenotypic features cannot be properly diagnosed with this scoring. We determined that CD81 was a quite useful marker for differential diagnosis of CLL. Our results suggest that CD81 may be a valuable marker for the differential diagnosis of CLL. We are of the opinion that it should be definitely included in the diagnostic algorithm for CLL.

#### PP-30

#### Association of initial prognostic parameters and requirement for treatment in chronic lymphocytic leukemia

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**Objective:** B-cell chronic lymphocytic leukemia (CLL) is the most common haematological malignancy in advanced age. The clinical course of the disease is highly variable, therefore there is a need to investigate the various prognostic factors. The CLL cell typically expresses CD5, CD19, CD23 and a monoclonal surface Ig (K or λ) while CD20 is moderately/weakly expressed. We aimed to analyze the clinical, genetic and immunophenotypic features which might have prognostic value in CLL.

**Methodology:** Between February 2010 and June 2018, 87 cases diagnosed with CLL were retrospectively analyzed. Patients who were followed without treatment (T0 group) and who required at least one line treatment (T) were

compared. Patients who required 1 line treatment (T1) were also further compared with patients who required >1 line treatment (T2). Statistical analyzes were performed using chi-square test using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). A value of less than 0.05 was considered significant.

**Results:** The mean age of our patient population was 65 (±SD 12.8) with Male/Female 56/31. At diagnosis, 68 (78.2%) patients were at early stage (0, I, II) and 19 (21.8%) were at advanced stage (III, IV). Del 17p, del 13q and trisomy 12 were evaluated in 49, 41 and 31 patients and 5, 13 and 4 patients were found out to be positive, respectively. Anemia and thrombocytopenia were present in 25 (28.7%) and 16 (18.4%) patients, respectively. Twenty-one (24.1%) patients had B symptoms. Splenomegaly, lymphadenopathy and hepatomegaly were present in 34 (39%), 67 (77%) and 21 (24.1%) patients, respectively. Four of the 15 patients who had direct coombs positivity also had clinical evidence of hemolytic anemia. Four patients had immune thrombocytopenia, 2 of them had concurrent direct coombs positivity and one also had hemolytic anemia. The median Hb, leukocyte and platelet counts were 13.2 g/dl (4.4-17.5 g/dl), 23.6×10<sup>9</sup>/L (1.7-527×10<sup>9</sup>/L) and 200×10<sup>9</sup>/L (10-345×10<sup>9</sup>/L), respectively. Follow up period was median 38 months (3-180 months). Twenty-five (28.7%) patients were treated at the time of diagnosis. Thirty-three (37.9%) patients had T1 and 6 (6.9%) patients required T2. The ratio of male patients in group T were significantly higher than female patients (p=0.038). All patients in group T2 were male. More patients in group T had CD38 expression than group T0 (p=0.04). There was no significant difference between the groups in terms of FMC7 and CD11c expressions. Of the 5 patients with del 17p, 2 patients required treatment at diagnosis, 2 patients required treatment after 13 and 48 months of follow up, respectively.

**Conclusion:** In our CLL patients, requirement for treatment was associated with CD38 expression, del 17p positivity at diagnosis and male gender.

### Chronic Myeloid Leukemias

#### PP-31

#### The role of new tyrosine kinase inhibitors in chronic myeloid leukemia in Kyrgyzstan

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**Objective:** Studying of new tyrosine kinase inhibitors (dasatinib, nilotinib and ponatinib) in chronic myeloid leukemia in Kyrgyzstan. The advent of newer TKIs' such as, nilotinib, dasatinib and ponatinib have provided multiple options for patients. These agents are more potent, have unique side effect profiles and are more likely to achieve relevant milestones such as, early molecular responses (3-6 months) and optimal molecular responses (12 months).

**Case report:** In Kyrgyzstan patients with CML from 2003 treated with Imatinib and with 2017 year receive Dasatinib, Nilotinib, Ponatinib) under the Max Foundation program.

**Methodology:** The analysis of results of treatment at 275 with CML patients by medicines of Imatinib, Dasatinib, Nilotinib and Ponatinib in National Center of Oncology and hematology. The diagnosis and results of therapy were on hematological, cytogenetic and molecular-genetic studies. The frequency and spectrum of mutations of the BCR-ABL gene were studied and the value of clones of leukemic cells with BCR-ABL mutations in the development of resistance to imatinib therapy, which determine the low sensitivity to ITK, were determined. 1) to Dasatinib - F317V/L/I/C, T315A, V299L, Q252H. 2) to Nilotinib - Y253H, E255K/V, F359V/C/I. 3) to Ponatinib -T3151

**Results:** Imatinib had a hematologic remission of 98%, a large cytogenetic response of 92%, a complete cytogenetic response of 87% and 10-year survival rate of 84%. The progression rate during the year was 4%, the development of the phases of acceleration and blast crisis 2%. Imatinib had a hematologic remission of 98%, a large cytogenetic response of 92%, a complete cytogenetic response of 87%, a 10-year survival rate of 84%. The progression rate during the year was 4%, t acceleration and blast crisis 2%. Primary and secondary resistance to Imatinib 17-20%. The reasons for the secondary resistance to Imatinib were, when patient did not receive the drug for 6-8 months at 3-5 years of treatment, pregnancy at 1 and 2 years of therapy, 0.5% in the presence

of tuberculosis. Dasatinib and Nilotinib, there was a large cytogenetic response to 1 year of the disease in the acceleration phase and in patients with primary resistance in the chronic phase. When Using Dasatinib and Nilotinib, there was a large cytogenetic response to 1 year of the disease in the acceleration phase and in patients with primary resistance in the chronic phase. Ponatinib gave rapid hematologic remission and a large cytogenetic response in the acceleration phase in the first year of treatment and in patients in the blast crisis phase. The use of Imatinib in Kyrgyzstan increased the 5% survival rate of patients with CML from 1% to 95%. The choice between these two 2GTKIs is governed mostly by their potential toxicity profiles as well as the comorbidities of the patients. Also, the presence of BCR-ABL1 kinase domain (KD) point mutations influence the choice of the second-line TKI treatment in patients with CML-CP who are resistant to prior TKI therapy. For 5 patients of Y253H, E255K/V, or F359V/C/I mutations, Dasatinib was more effective than Nilotinib.

**Conclusion:** The use of new generation of Tyrosine kinase inhibitors such as Dasatinib, Nilotinib, Ponatinib gives a high chance of improving the survival of patients with CML in the accelerating phase and gives hope to patients in the blast crisis

#### PP-32

##### A case of myasthenia gravis developing from chronic myeloid leukemia with imatinib use: a case report

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**Objective:** Imatinib, used in the treatment of chronic myeloid leukemia (CML), is known to have numerous side effects. The most common ones are nausea, vomiting, diarrhea, edema, muscle cramps, myalgia, and cytopenia. Although most side effects are mild, some are very serious, and may result in dosage reduction or even discontinuation of the drug. While rare, paraneoplastic syndromes have been observed in CML, and several cases have been reported in the literature. We present a case of Myasthenia Gravis (MG) that developed in a patient with CML using imatinib.

**Case report:** A 21-year-old woman was diagnosed with BCR-ABL positive CML and started on imatinib at a dosage of 400 mg/day. During the fourth week of treatment, the patient, who had complete hematologic response, was admitted to the clinic with complaints of ptosis of the right eyelid, double vision, shortness of breath, and difficulty swallowing. Imatinib was discontinued in consideration of the side effects, and brain and orbital MRIs were performed. Imaging did not reveal any pathology that would explain the neurological symptoms. Acetylcholine receptor antibody (12.10 nmol/L), used to diagnose MG, was detected. Upon diagnosis of MG based on clinical, laboratory, and imaging findings, treatment was initiated with intravenous immunoglobulin (IVIG), methylprednisolone, and pyridostigmine bromide. Following treatment, the patient's shortness of breath and difficulty swallowing ceased completely. Plasmapheresis was started to treat the ptosis and diplopia; both subsequently improved. Imatinib was then resumed at 300 mg. Pyridostigmine continued to be used at 300 mg/day and IVIG at 2 mg/week, while the dosage of methylprednisolone was reduced. No neurological findings were revealed in the follow-up examinations.

**Conclusion:** Myasthenia gravis is an autoimmune disease characterized by weakness and fatigue of the skeletal muscle resulting from dysfunction of the neuromuscular junction. A number of medicines affecting the neuromuscular junction can lead to the development of MG or its exacerbation. A case of MG developing following use of dasatinib in the treatment of CML has been reported in the literature. However, there are no reports in English of MG associated with imatinib use. Paraneoplastic MG occurring simultaneously with a diagnosis of CML has been reported. We were not able to distinguish whether the MG that developed in our case was a paraneoplastic syndrome, or resulted from imatinib use, or else emerged sporadically.

#### Chronic Myeloproliferative Disorders

#### PP-33

##### A case of idiopathic hypereosinophilic syndrome with hepatic involvement

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**Objective:** Hypereosinophilic syndrome (HES) is characterized by permanent eosinophilic overproduction. HES is a rare disease that usually occurs in 20- to 50-year-old individuals. It is categorized as primary due to neoplasm, secondary or idiopathic and reactive. HES can involve any organ like skin, lungs, gastrointestinal tract, heart and central nervous system. Herein, we present an interesting case of a patient with idiopathic HES who presented with B symptoms and hepatic involvement.

**Case report:** A 38-year-old female presented to our institution with fever, weight loss and progressively weakness. The complete blood count was as follows: WBC 26100/mm<sup>3</sup>, hemoglobin 11.6 g/dL, platelets 350,000/mm<sup>3</sup>, eosinophils 55%, absolute total eosinophils 14.600/mm<sup>3</sup>. The other laboratory studies were alanine transaminase 24 U/L (normal, <35 U/L), aspartate transaminase 28 U/L (normal, <35 U/L), serum alkaline phosphatase 135 U/L (normal, 30–150 U/L), total bilirubin 0.41 mg/dL (normal, 0.3–1.2 mg/dL). The patient had no evidence of allergic or hypersensitivity conditions or connective tissue diseases based on pulmonary function tests and serologic tests. On abdominal tomography, hepatomegaly and numerous limited hypodense lesions in the liver and portocaval lymphadenopathies. A bone marrow biopsy for neoplastic or primary bone marrow disorders showed marked eosinophilia, but no other abnormalities. The histopathologic analysis of the liver specimen revealed necrotizing granulomatous hepatitis with giant cells were present in portal areas and parenchyma, also eosinophil-rich necroinflammatory foci containing mixed inflammation in the parenchyma was evident. Eventually, the patient was diagnosed with idiopathic HES with hepatic involvement based on the persistent elevation in eosinophil count for more than six months and clinically. The patient was initiated on methylprednisolone 60 mg/day.

**Results:** Hepatic involvement in HES has been reported in up to one-third of patients and typically presents as mild abnormalities in liver chemistry studies or hepatomegaly. The Budd-Chiari syndrome from hepatic vein obstruction may manifest following hepatic involvement in HES. However, clinically liver disease is less common, but isolated cases have been reported with patients presenting with hepatocellular damage due to chronic active hepatitis. Hepatitis associated with HES has frequently been designated as chronic active hepatitis, eosinophilic hepatitis, and hepatitis associated with HES. Sometimes the patient had gastrointestinal involvement with no clinical evidence of the more commonly affected pulmonary, neurologic or other system dysfunction. Idiopathic HES should be considered differential diagnosis in cases of hepatic enzyme elevation in patients with hypereosinophilia.

#### PP-34

##### Langerhans cell histiocytosis in adults: clinic presentation, treatment options and prognosis

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**Objective:** Histiocytosis are rare disorders characterized by accumulation of cells thought to be derived from dendritic cells (DCs) or macrophages. Disorders related with histiocytosis had 5 main groups containing more than 100 disorders. These groups are: (1) Langerhans-related histiocytosis, (2) cutaneous and mucocutaneous histiocytosis, (3) malignant histiocytosis, (4) Rosai-Dorfman disease and (5) hemophagocytic lympho histiocytosis and macrophage activation syndrome. Langerhans (L) related histiocytosis



are most frequently seen group along with being related to MAPK pathway and BRAF mutation and also our knowledge about treatment are insufficient. We aimed to present our experience about patients diagnosed with LCH, who have been followed-up in Hematology and Medical Oncology clinics at Ankara Numune Education and Research Hospital (ANERH).

**Methodology:** Ten patients were included in this retrospective study. We examined the patients diagnosis, clinic presentation, imaging and treatment separately and we compared them to each other.

**Results:** Six of 10 patients were younger than 30 years old, 4 of 10 patients were older than 30 years old. Three patients had Central Nervous System (CNS) involvement, 6 patients had bone involvement, 2 patients had Diabetes Insipidus (DI) at the diagnosis. One of 10 patient followed up without any treatment, 2 of 10 patients had surgical treatment, 2 of 10 patients had vinblastine and prednisolone (VP) treatment, 1 of 10 patient had 6-mercaptopurine treatment, 1 of 10 patient had cladribine and radiotherapy (RT), 3 of 10 patients had cytosine arabinoside (ARA-C) treatment at the first step of treatment. One of 3 patient was received RT concomitantly with ARA-C treatment. Seven of 10 patients are still alive, however 2 of 3 patients passed away because of progressive disease, 1 of 3 patient passed away because of sepsis.

**Conclusion:** Langerhans cell histiocytosis is mostly seen in children and young adults and contains wide range of clinical symptoms. Diagnosis is made by histopathological analysis and radiological findings. Scanning with PET- CT for determination of multiorgan involvement and scanning with cranial MRI for determination of CNS involvement are suggested. No standard treatment is still present for LCH. Treatments options in case presentations in the literature are: surgery, methyl-prednisolone injection or radiotherapy for bone lesions; quitting smoking for lung lesions, topical corticosteroids for skin lesions; vinblastine, prednisolone for systemic treatment. Two-klorodeoxadenosine and ARA-C treatments are used in the first lines of LCH in recent years. Another new treatment options are hematopoietic stem cell transplantation, BRAF inhibitors and immunotherapy. We have not to forget that LCH in adult are more aggressive than childhood period and It can be fatal therefore we suggest to early and aggressive treatment in some of the cases.

#### PP-35

##### Retrospective and multicenter analysis of efficacy and safety of ruxolitinib in 176 Turkish patients with myelofibrosis: updated data

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**Objective:** Ruxolitinib has been approved for the treatment of patients with high- or intermediate-risk myelofibrosis with symptomatic splenomegaly. The aim of this study is to assess the efficacy and safety of ruxolitinib in patients with myelofibrosis.

**Methodology:** Across all of Turkey, 15 centers were enrolled in the study. We retrospectively evaluated 176 patients who treated with ruxolitinib.

**Results:** Among 176 patients, 94 (53.4%) of them were male. The median age of the ruxolitinib treatment was 62 (28-87). Twenty-nine (16.5%) of the patients were post- ET MF, 47 were (26.7%) post-PV MF and 100 (56.8%) were diagnosed as PMF. Hepatomegaly and constitutional symptoms were observed in 50.6% and 84.7% of the patients, respectively. Antiplatelet, androgen, steroid and erythrocyte stimulating agent treatments were present in 53.4%, 10.2%, 6.3% and 4% patients, respectively. Splenectomy was performed only in 6% of the patients. Only 1 patient was undergone hematopoietic stem cell transplantation. JAK2 mutation and MPL mutation was detected in 113 (64.2%) of 176 and 6 (7.5%) of 80 patients, respectively. The median white blood cell, platelet and hemoglobin ( $\times 10^3/\mu\text{l}$ ) counts were 11 (0.8-68.9), 348 (42-1920) and 10.7 (6.6-14.9), respectively. Cytoreductive treatment was used in 153 (86.9%) patients. The most common drug in the first line treatment was hydroxyurea (131 of 153 patients, 85.6%). Anagrelide (n=17) and interferon (n=15) were the most common second line treatment agents. Only 8 patients (4.5%) had third line treatment. The most common agent was interferon (n=5). The median dose of ruxolitinib was 30 (10-40) mg at the beginning of the therapy. Dose change was made in 69 (39.2%) patients. Adverse events data were available in 132 (75%) of all patients. Forty seven (35.6%) of 132 patients had hematological (n=32, anemia; n=25, thrombocytopenia; n=1, neutropenia) and 20 (15.2%) had non- hematological adverse events [AST-ALT elevation (4), fatigue (3), urinary tract infection (3), abdominal pain (2), pneumonia (2), zona zoster (2), dizziness (1), gingival bleeding (1), rash (1), palpitation (1), electrolyte imbalance (1), nausea (1)]. The mean spleen sizes before and after ruxolitinib treatment were 219.67 $\pm$ 46.79 mm versus 199.49 $\pm$ 40.95, respectively (p=0.000). Spleen response data was available in 151 (85.8%) of all patients. Among baseline features that were tested for correlation with subsequent spleen response, none was significantly associated with spleen response. Overall, 26 patients died because of leukemic transformation (n=3), cardiac diseases (n=4), pneumonia/sepsis (n=8), acute respiratory distress syndrome (n=1), cholangiocellular cancer (n=1), bleeding (n=3) and disease progression without acute evolution (n=6). Death occurred after a median ruxolitinib exposure of 9.4 months (1-45.1 months); in no case the death was directly attributed to therapy. Estimated OS at 1 year was 89.5% and the median follow up was 10 (1-55) months. We could not show any relationship between OS and reduction in spleen size (p=0.73).

**Conclusion:** We observed a reduction in spleen size after ruxolitinib treatment in Turkish patients with myelofibrosis and constitutional symptoms were improved. Ruxolitinib is both safe and efficacious in Turkish patients with myelofibrosis.

#### PP-36

##### Hemophagocytic lymphohistiocytosis associated with acute hepatitis A disease

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**Objective:** Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome that is caused by excessive immune activation. Although it frequently affects infants up to 18 months of age, the disease is also seen in children and adults of all ages. HLH may occur as a familial or sporadic disease and may be triggered by a variety of events that impair immune homeostasis. Infection, which can trigger the disease in those who are genetically predisposed, may also cause sporadic cases. We herein present a case of HLH due to acute hepatitis A.

**Case report:** A 51-year-old male patient presented with complaints of nausea, vomiting, fever, and weakness. Physical examination revealed a body temperature of 38.5°C. There were no pathological findings apart from fever. Pancytopenia was detected in the complete blood count. Hemoglobin was 10.4 g/dl, leukocyte count was 2.3 $\times 10^9$ /L, and platelet count was 14 $\times 10^9$ /L. Blast cells were not observed in the peripheral smear. Laboratory findings were as follows: creatinine was 0.54 mg/dl, AST was 2680 U/L, ALT was 702 U/L, GGT was 667 U/L, ALP was 321 U/l, LDH was 2,000 U/L, indirect bilirubin was 0.5 mg/dl, direct bilirubin was 1.2 mg/dl, CRP was 18 mg/l, ferritin was



1,500 ng/ml, triglyceride was 386 mg/dl, INR was 1.1, and fibrinogen was 267 mg/dl. Bone marrow aspiration was performed. Macrophages, which phagocytize erythrocytes and thrombocytes, were observed in the aspiration. In order to confirm a diagnosis of HLH and investigate its etiology, tests for viral markers, ANA, anti-dsDNA, blood urine culture, and thorax and abdominal tomographies were ordered. Hepatitis A IgM was positive and the results of the other tests were normal. The patient was treated with 45 grams of IVIG for two days and was started on dexamethasone (10 mg/m<sup>2</sup>). The patient's fever did not recur, AST-ALT values progressively decreased, and his thrombocytopenia and leukopenia improved. On day 14 of treatment the patient was discharged with 16mg of dexamethasone and the following laboratory results: leukocyte count was 4.9×10<sup>9</sup>/L, Hgb was 11.7 g/dl, platelet count was 202×10<sup>9</sup>/L, AST was 34 U/L, ALT was 140 U/L, and LDH was 233 U/L. The dosage of dexamethasone was reduced, and treatment was continued.

**Conclusion:** Infections, malignancies, rheumatic diseases, and immunodeficiencies can all lead to secondary HLH. Brucella, gram negative bacteria, bacteria such as tuberculosis, as well as parasites and fungi such as leishmaniasis and malaria, and more commonly, viral factors can also result in HLH. The Epstein-Barr virus, cytomegalovirus, parvovirus, herpes simplex virus, varicella zoster virus, measles virus, human herpesvirus 8, H1N1 influenza virus, parechovirus, and HIV are all viruses that frequently cause HLH. Among these viral agents, HLH due to Hepatitis A is rare; only a small number of cases have been reported in the literature. The presence of mainly elevated transaminase in HLH may be the reason that viral hepatitis was overlooked. We should also consider HLH among the differential diagnoses in patients with fever, cytopenia, or organomegaly.

#### PP-37

##### Clinical and laboratory parameters of JAK2V617F mutation in essential thrombocytosis patients

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**Objective:** Myeloproliferative diseases (MPH) are clonal diseases in which uncontrolled proliferation of bone marrow of one or more myeloerythroid cells, hemorrhage and thrombosis anomalies with increased number of peripheral stool mature and immature cells, and acute leukemia progression. To investigate the distribution of JAK2 V617F mutation in the diagnosis of myeloproliferative diseases in our patients with the diagnosis of essential thrombocytosis investigate the relationship laboratory parameters, clinical, treatment options, and to compare them with the literature.

**Methodology:** Patients were included in the study, who were referred to the hematology polyclinic and were able to access the file information by the statistical unit of the automation information management system, who was diagnosed with essential thrombocytosis over the age of 18 years. A total of 100 patients were included in the study, 48 patients with negative JAK2 mutation and 52 patients with positive JAK2 mutation. Demographic characteristics, clinical, laboratory parameters and treatment methods were studied in each group.

**Results:** Mutation-positive cases have higher age of diagnosis and longer disease duration and thrombosis and splenomegaly were significantly higher in mutation-positive cases. Hemoglobin, neutrophil, eosinophil, RBC values were higher in mutation positive cases, but lymphocyte level was lower. In mutation-negative cases, the symptoms of erythromelalgia were significantly higher. The use of hydroxyurea and acetylsalicylic acid combination was higher in both groups.

**Conclusion:** We found that the risk of thrombosis was increased in the JAK2 mutation-positive group with ET. However, it is necessary to consider the advanced age, which is a risk factor for thrombosis in this group. These individuals need to focus on the accompanying and controllable thrombotic risk factors (smoking, hyperlipidemia, HT, DM) to prevent the risk of thrombosis. Appropriate treatment regimens should be given to patients and patients should be adequately informed about this.

#### PP-38

##### Acquired von Willebrand disease in chronic myeloproliferative disorders

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**Objective:** Chronic myeloproliferative disorders (MPD) are frequently encountered in the practice of hematology. Acquired von Willebrand Disease (aVWD) is a bleeding diathesis associated with von Willebrand Factor (vWF) deficiency or functional failure as a result of underlying disease. Chronic myeloproliferative disorders such as polycythemia vera (PV), essential thrombocytosis (ET), and chronic myeloid leukemia (CML) may co-occur with aVWD, although such cases are rare. The rate of acquired von Willebrand disease among MPD patients is substantial enough to merit serious consideration, as it is thought to play a role in hemorrhage. In this study we aimed to investigate the presence of aVWD in patients diagnosed with MPD.

**Methodology:** The present study was conducted prospectively on 70 patients admitted to Yüzüncü Yıl University Faculty of Medicine Department of Hematology (Turkey). Complete blood count, PT, aPTT, vWF:Ag level, vWF:RCof test, and Factor VIII levels were analyzed for all patients. A finding of vWF:RCof/Ag <0.7 was accepted as predisposition to aVWD.

**Results:** Of the patients, 33 (47.1%) were male, 37 (52.8%) were female, and the mean age was 50±16.25. Sixteen (22.8%) of the patients had a diagnosis of ET, 43 (61.4%) had CML, and 11 (15.8%) had PV. No significant difference in age with respect to the type of diagnosis was found (p=0.82). We detected aVWD in 19 (vWF:RCof/Ag test <0.7) (28%) of the 70 patients in the study group. Predisposition to aVWF was present in 7 (43.7%) of the 16 patients in the ET group, in 4 of the 11 PV patients (36%), and in 8 of the 43 CML patients (18.6%). There was no statistically significant difference in the presence of aVWD between the three disease groups (p=0.079).

**Conclusion:** It should be kept in mind that aVWD may play a role in etiopathogenesis in people with chronic myeloproliferative disease, especially in cases of hemorrhage occurring in ET and PV patients. In light of our data, we concluded that the presence of aVWD in chronic myeloid leukemia (CML) may be associated with other chronic myeloproliferative disorders similar mechanism. However, we did not find any study in the literature in which the relationship between CML and aVWD was examined and a similar relationship proposed. For this reason, further studies are needed to elucidate this relationship as well as other possible causes.

#### PP-39

##### Thiol– disulphide homeostasis in essential thrombocytosis patients

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**Objective:** This study aimed to show the status of thiol disulphide hemostasis in essential thrombocytosis patients, which is known to play a role in platelet function.

**Methodology:** 27 ET patients and 36 healthy control groups were included in the study. Serum total (–SH+–S–S–) and native (–SH) thiol levels were measured in all subjects with automatic method.

**Results:** Age and gender distribution were similar in both groups. Compared with the control group, in ET group there was increased native thiol and total thiol levels (p=0.001, p=0.046). There was no correlation between tiyol, total tiyol and disulphid levels with Jak2 mutation, hemorrhage and thrombosis. But thrombosis and thiol disulphate hemostasis has a positive correlation (p=0.058).

**Conclusion:** Our study showed that thiol-disulphate hemostasis slided to proliferative side in ET which is a proliferative disease. It is also known that platelets are more active in ET cases and thiol disulphate balance is important in platelet function. This result suggests that thrombotic complications may be reduced, if the formation of mechanisms (oxidation mechanisms) that will trigger the increase of disulfide groups must be achieved. However, more extensive study is needed on this subject.

**PP-40****Descriptive analysis of myeloproliferative diseases and its complications**

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**Objective:** Bleeding and thrombosis complications are often seen in myeloproliferative neoplasms (MPN) of essential thrombocytosis (ET), polycythemia vera (PV), primary myelofibrosis (PMF). Bleeding and thrombosis are major complications that increase mortality and morbidity rates. This study was conducted in order to determine the frequency of bleeding and thrombosis events in MPN patients diagnosed and followed up at our center and to investigate the risk factors mentioned in the literature.

**Methodology:** Patients who were diagnosed at our institution retrospectively are included in the study. Follow-up data were obtained from Nucleus and Core databases. Categorical and continuous data were compared with Chi-square and independent sample T-test. The statistical significance threshold was accepted as  $p < 0.05$ . Statistical packages for the Social Sciences v20.0 (SPSS Inc., Chicago, IL) software were used for statistical analysis.

**Results:** A total of 181 patients were evaluated. 89 of the patients had PV, 50 had ET, and 42 had PMF. At the time of diagnosis, the median age was 54 years. There were 50 patients who had thrombosis at the time of diagnosis and 22 patients who developed thrombosis at follow-up. Venous thrombosis is more frequent than arterial thrombosis. Portal vein thrombosis and Budd-Chiari syndrome were the most frequent cases of venous thrombosis. It was found that smoking was statistically higher in patients diagnosed with or without thrombosis ( $p = 0.006$ ). No association with other cardiovascular risk factors was found. The number of patients with bleeding complications at the time of diagnosis or follow-up was found to be less. There were 5 patients who were diagnosed with MPN with bleeding complication. There were 21 patients with hemorrhage complications at follow-up. The most frequent complication was gastrointestinal bleeding. Platelet levels of patients with complications during the course of MPH were found to be lower than those without complications ( $183 \times 10^3$  ( $131-490 \times 10^3$ ) vs  $563 \times 10^3$  ( $11-2282 \times 10^3$ );  $p < 0.001$ ). In terms of bleeding complication, there was no difference according to cardiovascular risk factors, JAK-2 positivity, MPN type, white blood cell counts.

**Conclusion:** The major complications in MPN patients, thrombosis and bleeding were found to be similar in the literature (39% thrombosis, 13% bleeding). According to the risk factors, only cigarette use is significant in the thrombosis arm, and the other risk factors (advanced age, male sex, MPN type, JAK-2 positivity) are not significant. The relatively low number of platelets at the time of diagnosis can be a sign of complication development during the course of the disease. In the literature high platelet count and being older are among the reasons for bleeding. However in our study platelet count and age are not different among bleeding and non-bleeding patients. The low number of participants in our study may be the reason for this result. Since the etiology-mechanism is not fully found in these complications, there is a need for national multicenter studies to identify risk factors or identify additional risk factors.

**Coagulation and Infections****PP-41****HIV infection related haematologic neoplastic diseases**

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**Objective:** HIV infection constitutes a risk factor for coming out of aggressive B-cell related haematologic neoplastic diseases by both disrupting B-cell proliferation regulations and creating additional predisposition for HHV-8 and EBV infections. Among these malignancies most common seen ones

are Kaposi Sarcoma and HIV related Non-Hodgkin Lymphoma. In this retrospective study, examination of clinical findings and the prognosis of the patients followed with HIV/AIDS related haematologic malignancies in our clinic was aimed.

**Case report:** 53 years old male patient had admitted to general surgery polyclinic of another medical center with abdominal pain. In his examinations HIV positivity and lymphadenopathies were observed. The patient has been directed to Hacettepe University and was diagnosed as Mantle Cell Lymphoma in our center. Alternating R-CHOP and R-DHAP chemotherapy. After the chemotherapy was completed, the patient underwent autologous stem cell transplantation. 22 years old male patient has been diagnosed as HIV positive 2 years ago. Antiretroviral therapy has been started then. In the follow-up of the patient he had complaints of weight loss, fever and night sweating. He admitted to university hospital after suffering a convulsion. A mass lesion of 39x22 mm was spotted in brain MRI. Mass biopsy was reported as Diffuse Large B Cell Lymphoma. After 6 courses of chemotherapy, the patient underwent autologous stem cell transplantation. 27 years old male patient had been diagnosed as HIV and HBsAg positive in Augustus 2015. Antiretroviral has been started. Totally 3 doses of HYPERCVAD, 3 doses of methotrexate and ARA-C chemotherapy was applied alternately to the patient who was diagnosed as ALL in March 2016. Relapse occurred one month later in December. BFM1A chemotherapy was started to the patient. Allogenic bone marrow transplantation was applied to the patient in March 2017. He was externed to come to his control examinations after taking immunosuppressive therapy. 65 years old male patient had admitted to infectious diseases polyclinic because of nausea, vomiting, fatigue and fever in November 2016. HIV positivity had been spotted. Endoscopy was applied to the patient because of nausea and vomiting. The pathology result of the biopsy taken from the ulcer covering the pylor and prepyloric antrum was reported as Diffuse Large B Cell lymphoma. After 2 doses of R-EPOCH chemotherapy, the patient was transferred to the Intensive Care Unit because a septic shock was occurred. The patient deceased because of MODS in his follow-up. 30 years old male patient being followed with HIV positivity was diagnosed as 4th stage Burkitt Lymphoma. After 4 doses of chemotherapy, his general condition worsened.

**Results:** HIV assays are necessary to be done to all haematological malignancy patients for diagnosis, also scanning for underlying haematological malignancy should be done to all HIV infected patients especially in the positivity of clinic and laboratory markers.

**PP-42****Pregnancy outcomes in a case of protein S deficiency carriers couple**

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**Objective:** Congenital protein S deficiency is an autosomal dominant disease, and the heterozygous state occurs in approximately 2% of unselected patients with venous thromboembolism. Protein S deficiency is a rare inherited thrombophilia often associated with fetal losses in pregnancy. Homozygous Protein S deficiency in neonates manifests as a catastrophic and fatal thrombotic complication termed Purpura Fulminans.

**Case report:** We present you a 34-year-old patient with history of four pregnancy since 2012. She had one extrauterine pregnancy in 2012. Then in 2013 she had one spontaneous abortion in first trimester, after in vitro fertilization procedure. Her third pregnancy ended at December 2014 with natural delivery, in adequate term, estimated Apgar score of neonate was 9. But, 8 days after delivery because of neurological symptomatology of neonate magnetic resonance imaging pointed thrombosis of cerebral vein sinuses, with infarct zones and elements of haemorrhage. Thrombophilia screening pointed low level (<10%) in neonate, also decreased level of protein S in mother (49%) and father (52%). Despite dramatic clinical presentation, neonate survive but with serious consequences if form of quadriplegia and episodes of epileptic seizures. The couple was counseled about the autosomal dominant nature of Protein S deficiency. The patient was advised early antenatal registration with thromboprophylaxis in next pregnancy, also in all

thrombosis provocative situations. Our patient during last pregnancy in 2017 start LMWH prophylaxis but proposed procedure of genetic examination she started in last trimester of pregnancy. Taking in consideration period of pregnancy, antenatal screening of fetus had not been performed. Genetic examination pointed that now 5 years old daughter is homozygous carrier of PROS 1 mutation, also gravida and her husband heterozygous for PROS 1 mutation. She delivered a male baby at November 2017 with Cesarean section. Course of delivery and puerperium were without thrombotic complications for patient and her neonate. In addition, genetic examination confirmed that neonate is heterozygous of PROS 1 mutation.

**Conclusion:** Pregnant women with Protein S deficiency are typically heterozygous. Partners of women with these defects should be offered screening to identify neonates who may be homozygous or carry combined defects, in whom prenatal diagnosis can be considered. Women with genetic of protein S thrombophilia are at very high risk of antenatal and postpartum venous thromboembolism and should receive thromboprophylaxis during pregnancy and puerperium.

#### PP-43

##### **A rare cause of pancytopenia: transfusion-associated graft versus host disease**

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**Objective:** While the transfusion of blood and blood products can extend human life, fatal complications may also result. One of these is transfusion-associated graft versus host disease (TA-GVHD), fatal in over 90% of cases. TA-GVHD may develop 4-30 days following blood transfusion and usually occurs in patients with weakened or suppressed immune systems. Diagnosis is usually delayed because non-specific symptoms are attributed to the underlying disease. In TA-GVHD, donor lymphocytes attack the recipient's antigen-presenting tissues. This immunological attack is clinically manifested by the dysfunction of the skin, liver, gastrointestinal tract, and bone marrow. We herein present a case of TA-GVHD that developed following transfusion

**Case report:** A 67-year-old male patient was admitted with complaints of rash, fever, and jaundice. A physical examination determined the presence of scleral icterus, deep ulcers and mucositis in the mouth, and widespread maculopapular rashes on the body. Respiratory sounds were decreased on the right and the heart sounds could be intensely heard. The patient's history revealed that he had undergone coronary by-pass surgery a month earlier, and that during the perioperative period a transfusion was performed using 5 units of erythrocyte suspension. The patient used metoprolol, aspirin (acetylsalicylic acid – ASA), and valsartan. On the peripheral smear no atypical cells consistent with leukopenia or thrombocytopenia were observed. The patient's laboratory results were as follows: hemoglobin: 9.2 g/dl, leukocyte count:  $0.23 \times 10^9/L$ , neutrophil count:  $0.01 \times 10^9/L$ , platelet count:  $95 \times 10^9/L$ , CRP: 127 mg/L, INR: 1.59, PT: 19 sec, aPTT: 36 sec, fibrinogen level: 428 mg/dl, D-dimer: 2.97 µg/ml, creatinine: 1.4 mg/dl, AST: 218 U/L, ALT: 324 U/L, GGT: 1138 U/L, ALP: 1400 U/L, LDH: 333 U/L, direct bilirubin: 4.83 mg/dl, and indirect bilirubin: 2.3 mg/dl. Direct and indirect Coombs tests were negative. The patient, who had a body temperature of 38.9°C, was started on a course of broad-spectrum antibiotic treatment. Bone marrow and skin biopsies were performed. The bone marrow aspirate smear was severely hypocellular. The skin biopsy was evaluated as grade 2, consistent with acute GVHD, leading to a diagnosis of TA-GVHD. Methylprednisolone, cyclosporine IVIG, and plasmapheresis were administered as treatment. The patient expired following multiple organ failure.

**Conclusion:** A history of transfusion in the previous month, sudden fever, maculopapular rash, diarrhea, icterus, nausea/vomiting, pancytopenia and/or abnormalities in liver function tests should warrant a preliminary diagnosis of TA-GVHD. There is no effective treatment for TA-GVHD, which has a mortality of 90-95%. For this reason, preventing TA-GVHD is of key importance. Blood and blood components must be irradiated by ionizing rays prior to transfusion. The risk of developing TA-GVHD is especially high in those with congenital or acquired immune deficiency or undergoing severe immunosuppressive

treatment, patients who have undergone hematopoietic cell transplantation or transfusions between relatives, and in cases of intrauterine or neonatal transfusions. In these patient populations, it is absolutely imperative that blood and blood products be irradiated.

#### PP-44

##### **Refractory thrombotic thrombocytopenic purpura in a patient with Kaposi sarcoma**

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**Objective:** Kaposi's sarcoma (KS) is a multifocal angioproliferative disorder of the vascular endothelium. Approximately 95% of KS lesions are positive for HHV 8. Iatrogenic KS is an autoimmune disease and is seen in immunosuppressive patients and transplant recipients. Rituximab is a chimeric monoclonal antibody that binds CD20 surface antigen in B cells and selectively provides B cell depletion. Recently published studies have reported that rituximab can be used in the treatment of relapsed refractory TTP cases.

**Case report:** A 70-year-old male patient with dark purple lesions on both legs applied to our hospital. He hospitalized, on the second day, his neurological findings improved. TTP was diagnosed in patient with anemia, thrombocytopenia, low ADAMTS13 value (0.54%), ADAMTS13 inhibitor presence (>90%) and schistocytes in peripheral blood smear. In patient who had not responded to steroid, plasma exchange (PEX) and vincristine treatments were given rituximab at weekly dose of 375 mg/m<sup>2</sup> for 4 weeks. After completing rituximab treatment, the platelet count increased to over 100,000/µL and clinical improvement was observed. The rash on the legs continued during the discharge and biopsy of the lesion was performed in the outpatient clinic. The biopsy showed that Kaposi's sarcoma with HHV8 positivity. The patient was serologically negative for HIV. Thrombocytopenia developed in outpatient clinic follow-up, and the patient was re-admitted due to TTP recurrence. Bortezomib was started as a rescue treatment for TTP. The patient who did not respond to bortezomib treatment started therapy with off-label eculizumab. Despite all treatments, resistant TTP patient died 4 days after the first dose of eculizumab.

**Results:** In this case, we present the coexistence of KS and TTP resistant to traditional and novel treatments. The Kaposi lesions of the patient were present during the diagnosis, intensified when treated with rituximab for TTP, and not fully remedied after the treatment. So far, a few cases of rituximab in the literature have been reported as a case of KS developing after treatment. It is emphasized that TTP and KS coexist similar to ours in one HIV + case. In a case, a hemolytic anemic patient was reported to have endemic KS prior to rituximab administration, and an exacerbation after rituximab treatment. Another case reported a case of iatrogenic KS after rituximab treatment in a patient with TTP. From here we can see that in our case, KS has been present from the beginning and is exacerbated by immunosuppressive treatment. At this point, it appears that rituximab is the cause of the exacerbation of KS. In addition, patients with refractory TTP are currently treated with corticosteroids, twice daily PEX and rituximab. It has been reported that bortezomib and eculizumab may also be used for refractory TTP. The patient treated with both medications, but there was no improvement in the patient's clinic.

**Conclusion:** Iatrogenic KS is a rare side effect of rituximab used for the treatment of TTP. We aimed to emphasize that iatrogenic KS can develop in patients receiving immunosuppressive therapy. In addition, refractory TTP is still an important problem despite novel therapy regimens.

## PP-45

**Decreased bone mineral density and related parameters in severe hemophilia A patients: a case-control study**

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**Objective:** Hemophilia A is a rare X-linked recessive inherited bleeding disorder characterized by a deficiency of Factor VIII. Osteoporosis is a systemic bone disease characterized by low bone mineral density (BMD) and the deterioration of bone tissue, resulting in increased bone fragility and risk of fracture. The low BMD levels of hemophilia patients have been linked to such predisposing factors as physical inactivity due to hemophilic arthropathy, smoking, vitamin D deficiency, oral glucocorticoid use, and elevated hepatitis C virus (HCV)/human immunodeficiency virus (HIV) seropositivity. The primary objective of this single-center study is to compare the BMD levels of patients with severe adult hemophilia A with those of a healthy control group. The secondary objective is to evaluate joint health and musculoskeletal function in the study group with respect to potential risk factors affecting BMD.

**Methodology:** This case-control study included 30 patients between the ages of 20–58 diagnosed with severe hemophilia A, who received care at the Adult Hemophilia Center, and 24 healthy volunteers of similar age range who live in the same area. Severe hemophilia A is defined as a Factor VIII level of less than 1%, corresponding to <0.01 IU/mL. For each participant, age, HCV/HIV seropositivity, body mass index (BMI), alcohol consumption, smoking status, oral glucocorticoid usage, and calcium/vitamin D usage were recorded. Dual-energy X-ray absorptiometry (DXA) was used to measure BMD, which was described according to the World Health Organization (WHO) classification system. The Functional Independence Score in Hemophilia (FISH) was used to make a performance-based functional assessment.

**Results:** The mean age of the study group was 29.65±10.2 (mean ± standard deviation), mean BMI was 22.89±4.04, and there were no significant differences between the study and control groups (p=0.144 and p=0.780, respectively). The patient group did not exhibit a significant level of alcohol consumption. Sixteen (40%) of the patients smoked, of whom 12 (30%) were considered heavy smokers. There was no significant difference in smoking status between the study and control groups (p=0.26), nor was any significant association between smoking and BMD found for the study group. DXA results are given as g/cm<sup>2</sup> and as T- and Z-scores. Comparisons of the study and control groups yielded the following results. The differences between the femoral neck BMD (in g/cm<sup>2</sup>) and T- and Z-scores for the two groups were significant (p<0.01 for all three). The differences between the lumbar total T- and Z-scores were also significant (p<0.01 for both), as were the hip total BMD (g/cm<sup>2</sup>) and T- and Z-scores (p<0.01 for all three). In the study group, the mean 25 OH vitamin D level was 11.475±4.386 ng/mL, which was significantly different from that of the control group (p<0.01). The mean FISH score was 25.725 (range: 13–32), and a low FISH score was associated with decreased BMD.

**Conclusion:** This study found that BMD values in patients with severe hemophilia A were significantly lower than those of a healthy control group with a similar age range. It also showed that those with lower activity levels due to their more severely affected musculoskeletal structures had lower BMD. These results emphasize the importance of early detection of comorbidities that decrease bone mass in patients with severe hemophilia A.

**Immune Thrombocytopenia**

## PP-46

**IL-1beta, IL-6 and TNF-alpha levels in women working under long-term (32–36 hour) shifts**

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**Objective:** This study was designed to study the effects of long-term (32-36) shifts on plasma IL-1beta, IL-6 and TNF-alpha levels in women working in health care system.

**Methodology:** Following ethical consent from Malatya Clinical Experiments Ethics Committee (No 2016/197), female nurses and female doctors who have been working in Turgut Ozal Health Center were volunteered in the study. Participants were matched for the menstrual phases as being follicular and luteal. Criteria for inclusion were being healthy, being at the ages of 18–40, not smoking, not using painkillers, not being in the stage of menstruation. In the study, health care providers who have been working in normal day-time working hours (Group 1, n=10) were compared with doctors who have been doing their pediatric residency (Group 2, n=10) with 32-36 h continuous shifts. For that purpose, blood samples were taken at the end of the shifts. One-way ANOVA was used for the statistical comparisons.

**Results:** Plasma IL-6, IL-1beta and TNF-alfa concentrations were higher in women working under long-term (32-36 h) shifts compared to women working in normal day-time hours (p<0.05).

**Conclusion:** According to the data obtained in the current study, it seems that long-term continuous shifts activate immune system as revealed by increased IL-6, IL-1beta and TNF-alfa concentrations. Thus, the data suggest that necessary measures need to be taken to prevent deterioration of health in resident assistants working in long-term shifts. Supported by the Scientific Research Projects Unit (BAP) of the Inonu University (2017/649).

**Lymphomas**

## PP-47

**Vitamin D insufficiency in non-Hodgkin lymphoma and its relation to adverse prognostic factors: a single center analysis**

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**Objective:** The purpose of this study is to find out the relation of hypovitaminosis D in 2 groups of lymphoproliferative disorders (CLL and DLBCL) to adverse prognostic factors in both diseases as disease stage, CD38 expression, serum LDH level and extra-nodal involvement. The study also compares between the severity of hypovitaminosis in both disorders.

**Background:** Higher levels of recreational sun exposure were associated with lower levels of NHL. The effect of 1,25 (OH)<sub>2</sub> D in lymphoma cells was observed in promotion of differentiation and anti-proliferative effects in vitro. We assessed the level of vitamin D insufficiency in 2 groups of newly diagnosed chronic lymphocytic leukemia (CLL) and diffuse large B-cell lymphoma (DLBCL) patients representing indolent and aggressive lymphomas and evaluated the relation of hypo-vitaminosis D and adverse prognostic parameters in both diseases as well as the effect of its insufficiency on the grade of lymphoma.

**Methodology:** 74 patients were enrolled in this cross-sectional study between 2013-2015. Patients were divided into 2 groups, newly diagnosed CLL and DLBCL (37 patients in each group). Vitamin D levels were assessed in both groups.

**Results:** All 37 patients with CLL had vitamin D insufficiency mean ± SD (4.80±3.25) and it was correlated with advanced Rai and Binet stage, while 91.8% of DLBCL patients had vitamin D insufficiency and that was correlated with bad ECOG performance, advanced Ann-Arbor staging, high LDH and extranodal involvement. Vitamin D levels in the CLL group were significantly lowered compared to DLBCL group.



**Conclusion:** Vitamin D level was significantly decreased in patients with CLL compared to DLBCL. However, we could not detect an impact of the severity of deficiency and the grade of lymphoma developed.

#### PP-48

##### The safety and efficacy of the biosimilar anti-CD20 antibody, Truxima, in haematological malignancy

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**Objective:** Truxima is the first biosimilar anti-CD 20 monoclonal antibody licensed by the European Commission for the treatment of cancer and launched in United Kingdom (UK) in April 2017. There are increasing centers introducing the Truxima in replacement to its originator (MabThera) in their clinical practice. However, there is currently limited real-life data on the efficacy and tolerability of Truxima. This is a multi-centre study to evaluate the safety and overall response rate of Truxima in combination with chemotherapy in patient with an underlying haematological malignancy.

**Methodology:** This study was conducted in London North West Hospital from 1st of October 2017 to 1st of April 2018 on patients who received Truxima with or without chemotherapy for B cell malignancy.

**Results:** There were 42 patients who received Truxima and 57% (24 out of 42) had a diagnosis of Diffuse Large B Cell Lymphoma (DLBCL). Truxima were generally well tolerated and 90% (38 out of 42) complication the infusion without any complications. There were three patients (7%) who experienced mild infusion related reactions (IRR) which were all grade 2 or less. Amongst the patients who were diagnosed with Diffuse Large B Cell Lymphoma 33% (7 out of 21) achieved complete remission.

**Conclusion:** There are no specific concerns with Truxima as it has shown clinical similarity to MabThera in terms efficacy and safety. Truxima is 10% cheaper per 100 mg in comparison to Mabthera (GBP314.33 Vs GBP349.25), therefore it has the advantage of significant budget savings. In the current economic crisis, these savings can have a significant impact on health gains at both patient and societal levels.

#### PP-49

##### Causes of thrombosis in Hodgkin lymphoma: single center experience

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**Objective:** Thrombotic risk is increased in lymphoma patients and could complicate clinical course of Hodgkin lymphoma (HL) lesser than non-Hodgkin lymphomas. Data is scarce in literature for the thrombotic risk factors due to the limited number of clinical events. In this study, we aimed to revise the underlying causes of the thrombosis in HL patients in our center.

**Methodology:** Retrospective data from a total of 133 HL patients were analyzed who were diagnosed between 01.01.2001 and 30.12.2017. Demographic data, disease status, treatments, possible risk factors for thrombosis were recorded. Univariate analyses were done by Chi-square test for categorical and by t-test for numerical variables, respectively. Multivariate analyses were done by Cox regression analysis.

**Results:** A total of 8 (6%) patients with thrombosis detected. Median age of patients was 30 (13-51), 3 of them were male. 71% of patients were stage 3-4 at diagnosis. During thrombosis disease status was active in 63%. Eighty-eight percent had at least one clinical risk factor for thrombosis. Only one patient had unprovoked thrombosis.

**Conclusion:** The results of our recent study revealed that thrombosis in patients with Hodgkin lymphoma were associated with complicated acquired clinical thrombotic risk factors including catheter utilization, immobilization, surgical spleen removal and tumor mass compression. Hodgkin lymphoma solely was not the main cause of thrombosis in our HL patient cohort.

#### PP-50

##### Brentuximab vedotin in CD30+ lymphomas: single center experience

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**Objective:** Brentuximab vedotin (BV) is an anti-CD30 antibody-drug conjugate, which has been shown to be effective in relapsed and refractory Hodgkin Lymphoma (HL) and CD30+ T cell lymphomas. In this study, we aimed to share our experience regarding the clinical response and toxicities of BV in our center.

**Methodology:** Retrospective data from a total of 133 HL and 13 CD30+ T cell lymphoma patients were analyzed who were diagnosed between 01.01.2001 and 30.12.2017. Demographic data, response to BV and side effects were recorded. Multivariate analyses were done by Cox regression analysis.

**Results:** There were 11 patients who received BV. Median age of diagnosis was 25 (17-65). 5 of them were male. Eight patients had Hodgkin lymphoma, 2 patients had T cell lymphoma and 1 had unclassifiable B cell lymphoma. 90% had stage 3-4 disease. Fifty-five percent of the patients had relapsed/refractory disease before BV. Median cycles of BV received were 4. All of the patients underwent autologous transplantation, 55% prior to BV, 45% post-BV. Forty percent of the patients had at least partial response to BV. Toxicities more than grade 2 were mostly hematologic (27%).

**Conclusion:** In our present study, we have shown 40% overall response in CD30+ lymphoproliferative disorders without serious hematologic and non-hematologic adverse effects. Only one patient of BV responders had a relapse following the use of BV. All of the cases were alive at last follow-up. BV is a safe and effective drug in CD30+ T cell lymphomas and HL.

#### PP-51

##### A mycosis fungoides case: two month later after Hodgkin lymphoma treatment

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**Objective:** Hodgkin lymphoma (HL), emerges from post-germinal center or germinal center B cells. HL accounts for approximately 10 percent of lymphomas worldwide and approximately 0.6 percent of all cancers. Mycosis Fungoides (MF) is a mature T cell non-Hodgkin lymphoma (HNL) with presentation in the skin but with potential involvement of the nodes, blood and viscera. The relationship between MF and HL was first reported in 1963. MF lesions usually appear before those of HL but the reverse has been also documented.

**Case report:** A 38-year-old male presented swelling on the neck, high fevers, sweating and weight loss. Physical examination revealed no findings other than left cervical and supraclavicular lymphadenopathy. Pathologic examination of the left cervical lymph node revealed classic HL- nodular sclerosis type. According to the results of PET/CT, patient diagnosed with stage 4B HL. He was initiated on chemotherapy with ABVD regimen. The response to chemotherapy was favourable and he completed 6 cycles of chemotherapy. PET/CT after second cycle and post-treatment investigations showed evidence of complete response. He did well for the next 2 months but then developed cutaneous lesions like multiple mild erythematous and dandruff patches on the trunk. The patient was referred to the dermatology department and biopsied the lesions in the skin. Eventually mycosis fungoides diagnosed after biopsy.

**Conclusion:** The synchronous or metachronous occurrence of HL and T-cell NHL in the same patient has been reported repeatedly. The most commonly described association is that of MF and HL. MF usually appears before HL, but the reverse has been also documented. Lipa et al. reported two patients developed mycosis fungoides many years after treatment for HL. Among peripheral T-NHL, MF is the neoplasm most commonly associated with HL. But the majority of these patients have been followed for a long time by MF whom subsequently developing HL. The relatively high frequency of this association has led some authors to speculate that MF and HL are derived

from the same clone. On review of the literatures, there are some hypotheses on the development of secondary malignant neoplasm. Some authors suggest that a genetic predisposition, an underlying viral infection, or possible mutagenic effects of cytostatic drugs as potential causes for developing concurrent B- and T-cell cancers. Maybe cancers may have a cancerogenic effect causing an increased risk of secondary malignancies, in particular lymphomas. Combined-modality treatment for HL had a significantly increased risk to develop a secondary malignant neoplasms when compared with chemotherapy alone. An association between the use of alkylating agents and topoisomerase II inhibitors and the development of t-AML/MDS has been demonstrated. Both drug classes are included in first-line chemotherapy protocols such as ABVD, BEACOPP and Stanford V. The time interval between HL treatment and the occurrence of secondary hematological malignancies is usually ranging between four and ten years in most cases. Interestingly in our case MF was diagnosed 2 months after HL treatment. When we did a case scan, we could not find the MF that developed so early after the HL.

#### PP-52

##### Clinical and pathological characteristics of non-Hodgkin lymphoma patients in eastern Turkey: a single-center study

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**Objective:** Non-Hodgkin lymphomas (NHL) are malignancies originating in various cells that compose the immune system. They present different morphological, immunological, and clinical characteristics according to differentiation stage. The prevalence of NHL varies with age, geographical region, exposure to infectious agents, and ethnicity. In this study we aimed to investigate the epidemiological, demographic and clinical characteristics, treatment outcomes, overall survival rates, and prognostic factors of NHL patients.

**Methodology:** Patients diagnosed with NHL at the Department of Hematology were included in the study. Epidemiological, demographic and clinical characteristics, overall survival rates, and prognostic factors were evaluated by reviewing patient records retrospectively. Age, gender, complaint(s) at diagnosis, type of diagnosis, diagnostic history, histopathological subtype, presence of B symptoms, nodal and extranodal status, disease stage, IPI score, imaging results, biochemical tests, treatment protocols, treatment responses, and overall survival outcomes for each patient were assessed. Patients were grouped according to age as either under or over 60 years old. Patient performance status was categorized as either 0, 1 (<2) or 2, 3, 4 (≥2) based on the Eastern Cooperative Oncology Group (ECOG) scale. Prognostic findings were evaluated using the IPI scoring system.

**Results:** A total of 386 patients diagnosed with NHL were included in the study. Of these, 242 (62.7%) were male and 144 (37.3%) were female. The average age of all patients was 57.25±16.22 (age range 18-94). The average age of female patients was 58,09 and the average age of male patients was 56,41. The most common NHL subtype was diffuse large B-cell lymphoma (DLBCL) (46.9%), consistent with the literature. The rate of primary extranodal lymphoma was similar to those reported worldwide and for Turkey. Advanced stage (III-IV), high-intermediate to high risk based on IPI score, bone marrow involvement, Hemoglobin levels below 10 g/dL, LDH levels above normal, primary nodal involvement, the presence of B symptoms, the exigency of autologous bone marrow transplant, and not receiving rituximab-based chemotherapy regimens as the primary treatment were all associated with shorter overall survival (p<0.05).

**Conclusion:** The prevalence, clinical characteristics, histopathological subtypes, treatment responses, and overall survival rates of NHL may vary according to geographical area. Variability may occur even in different regions of the same country. Treatment should be individualized according to disease subtype distribution.

#### PP-53

##### A rare presentation: lung adenocarcinoma following bone marrow transplantation for mantle cell lymphoma

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**Objective:** We present a case of lung adenocarcinoma developing 2 years after a high-dose chemotherapy preparative regimen and stem cell transplantation. To our best knowledge all mantle cell lymphoma and lung adenocarcinoma were reported as concurrent events. This is the first case of lung adenocarcinoma presented after ASCT due to relaps of mantle cell lymphoma.

**Case report:** A 55-year-old lady with a history of hypertension was investigated with lymphocytosis, thrombocytopenia and anemia. On physical examination, the spleen and the liver were palpable with adenopathy in the left inguinal regions. A computed tomography (CT) scan of the abdomen and pelvis revealed splenomegaly and conglomeration of lymph nodes involving left inguinal lymph nodes. CT scan of the chest showed three nodular mass lesions measuring up to 10 mm. Clonal B lymphoid cell increasing was revealed with CD5(+), CD19(+) CD20(+) CD22(+), CD23(+) CD79b(+) CD10(-) CD25(-) CD11c(-) CD200(-) by flow cytometry from peripheral blood. She had been diagnosed with stage IV mantle cell lymphoma by bone marrow biopsy. She had been diagnosed with stage IV mantle cell lymphoma by bone marrow biopsy and denied fever, chills or night sweats. The mantle cell lymphoma international prognostic index (MIPI) score was assessed high risk with the score of 6 points. Three cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) and R-DHAP alternately for her lymphoma treatment. After two consecutive treatment, examinations revealed that her lymphoma persisted in bone marrow and two cycles of R-GEMOX was administered. Due to progressive disease under treatment she was treated with two cycles of BORID. Pet-ct and bone marrow biopsy confirmed complete remission. Following that, stem cells collected with Endoxan and GCSF as a mobilisation protocol and infused successfully. Despite her disease was in remission transplantation, a nodular mass persisted with in constant size on CT scan of chest. At the end of 2 years of follow-up, a 50% progress was recorded in nodular mass. A biopsy of mass revealed lung adenocarcinoma with thoracotomy and the patient was referred to oncology department for adenocarcinoma treatment.

**Conclusion:** Procedures are necessary to understand the pathologies of the new formation during follow up a hematological malignancy. Treatment-associated secondary malignancies are encountered in hematological malignancies. Increased number of routine scanning procedure due to the disease control can be trigger of new solid malignancies. Lung adenocarcinoma after autologous stem cell transplantation is a rare presentation. Physician should be careful in terms of newly emerging secondary malignancies during hematological disease follow-up.

#### PP-54

##### An atypical presentation: follicular lymphoma with peripheral blood involvement

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**Objective:** Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma (NHL) subtype and has an indolent clinical course. At the time of diagnosis, widespread lymphadenopathies, splenomegaly and considerable bone marrow involvement is present but it is mostly asymptomatic despite advanced disease. Cytopenia is frequently observed in the presence of bone marrow involvement whereas the presence of lymphocytes is rarely seen in the peripheral blood at the time of diagnosis. The incidence of FL with PB involvement at initial diagnosis is reported as 7-11%. Although its rarity, a

patient with lymphocytosis who was diagnosed with follicular lymphoma is presented in this report.

**Case report:** A 67-year-old male, who had a medical history of mine work and chronic obstructive pulmonary disease, had a mass in the lower lobe of the left lung 2 years ago. The biopsy result of the mass had been reported as mesenchymal tumor. The patient had been treated with chemotherapy. Cure had been obtained after treatment and had been followed up. The patient was referred to hematology due to leukocytosis/lymphocytosis were detected in his follow-up. Bilateral cervical, axillary, inguinal multiple lymph nodes and splenomegaly (3 cm below the costal) were detected in physical examination. The patient did not have any of B symptoms. In laboratory examination was remarkable for; leukocyte:  $52 \times 10^9/L$ , lymphocyte:  $38.1 \times 10^9/L$ , Hb: 12.3 g/dL, platelet:  $173 \times 10^9/L$ , and biochemical tests including LDH and sedimentation were normal. Atypical small- to medium-sized lymphocytes (some with notched or cleft nuclei) were observed in the peripheral spread and thereafter bone marrow aspiration and biopsy were performed. The bone marrow biopsy was diagnosed as low-grade b cell lymphoma. CD19-20-23 was positive and CD5 was negative in flow cytometry. An excisional cervical LAP biopsy was performed and was resulted as the follicular lymphoma in grade 2. PET/CT was stained for staging. Bilateral cervical, axillary, mediastinal and bilateral inguinal lymph nodes with slightly increased FDG uptake and multiple lymph nodes that were smaller than 3 cm in size and slightly FDG uptake in the spleen and bone marrow and heterogeneous density with minimal FDG uptake in the left lower lobe of the lung lesion (residual malignancy?) was detected in PET/CT. A biopsy was planned for the lesion in the lung and the treatment will be planned according to the result of lung biopsy.

**Conclusion:** FL with PB involvement at the time of initial diagnosis is rarely observed and usually associated with nodal and/or extranodal involvement whereas pure leukemic form has been reported very rarely. Peripheral involvement is usually associated with a moderate and high Follicular Lymphoma International Prognostic Index (FLIPI) score. The presence of peripheral blood involvement in the follicular lymphoma is associated with poor overall survival and progression-free survival. However, according to literature, the presence of a pure leukemic form without nodal or extranodal involvement is more indolent than with nodal and extranodal involvement.

#### PP-55

##### Lymphomatoid papulosis after autologous stem cell transplantation in a patient with diffuse large B cell lymphoma

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**Objective:** Autologous stem cell transplantation (ASCT) is a treatment modality for relapse refractory diffuse large B cell lymphoma (DLBCL). It is known that lymphoproliferative disease can develop after stem cell transplantation. Post-transplant lymphoproliferative disease (PTLD) is less common after ASCT compared with that seen after allogeneic transplant. Herein we discuss a case of recurrence of cutaneous T cell lymphoma (CTCL) after ASCT in a patient with DLBCL in complete remission (CR).

**Case report:** A 64-year-old male with history of CTCL admitted to our department with the result of cervical lymph node biopsy as DLBCL in 2015. The patient who have stage 3SB disease at the time of diagnosis was treated with 6 cycles of RCHOP chemotherapy. PET imaging after treatment revealed CR1. Gastric extranodal recurrence occurred after 7 months of treatment. He was given salvage therapy after relapse and at CR2, he underwent ablative preparative regimen followed by ASCT. Post-transplant PET scan showed stable CR2. However, 6 months after transplantation, similar skin lesions occurred as he had 10 years ago. The skin biopsy resulted as CTCL. He was given symptomatic topical treatments and follow-up is still going on in the dermatology department. He was still in CR2 for DLBCL in this period.

**Results:** Post-transplant cutaneous lymphomas are rare entities that mostly observed after allogeneic HSCT, whereas a few cases of CTCL after ASCT was reported. CTCL constitute 30% of post-transplant lymphomas including lymphomatoid papulosis (LyP) and cutaneous anaplastic large cell lymphoma (cALCL). Our patient was diagnosed with LyP according to evaluations of the

dermatology and hematology departments. This case suggests a significant immunosuppression after autologous transplantation, as in previous cases. To the best of our knowledge; this case was the first report showing CTCL recurrence in a DLBCL in CR after ASCT.

**Conclusion:** It is important to distinguish LyP from cALCL because it has a lower risk of extracutaneous involvement and therefore differs in terms of prognosis and follow-up. There is no consensus on treatment of LyP. None of the current treatment modalities alter the natural course of LyP. Unless compulsory, therapies with high-risk side effects should be avoided. However, due to the risk of developing a life-long malignant lymphoma, LyP patients require long-term follow-up.

#### PP-56

##### A rare case report of primary bone lymphoma

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**Objective:** Primary non-Hodgkin lymphoma of bone (PBL) is a rare extranodal presentation of non-Hodgkin's lymphoma. Diffuse large-B-cell lymphoma (DLBCL) accounts for the majority of cases of PBL. It can be defined as a lymphoma that occurs in the bone, consisting of a single bone lesion with or without regional lymphadenopathies. Owing to its rarity, only a few retrospective studies have been published addressing the prognosis and treatment of primary bone lymphoma. In this paper, we report our experience with a case of PBL treated with chemotherapy.

**Case report:** A 39-year-old male presented with pain in left iliac bone since one year. The patient had no significant medical history. At the time of initial presentation, he had left-sided iliac pain without fever, weight loss, or fatigue. He had undergone X-ray screening of the pelvis result showed a bone destruction area in the left-iliac bone. The localized bone cortex was completely or partially discontinuous. Magnetic Resonance Imaging demonstrated that  $66 \times 29 \times 43$ mm size a mass lesion in the left side iliac medullary bone which destructed lateral cortex and prolapse to the gluteal area. PET-CT results neck, thorax, and abdomen were normal. PET CT revealed osteolytic sclerotic lesions involving left iliac bone and showed abnormal FDG uptakes involving the left iliac area. (SUV max: 9.6). The bone marrow aspiration smear did not show neoplastic involvement. A bone biopsy of the lesion and the pathological examinations suggested a diagnosis of primary bone DLBCL. Immunohistochemical results showed CD20(+), MUM-1(-), MYC(-), CD10slight(+), Bcl-2(-), Bcl-6(+), kappa(-)lambda(-) and Ki67+ (70-80%), which demonstrated DLBCL, germinal center B-cell-like (GCB). The patient first received 6 cycles of concurrent chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Patient is now on regular follow up and is disease free since last three months after treatment.

**Conclusion:** PLB is an uncommon disease and constitutes <5% of malignant bone tumors, 4–5% of extranodal lymphoma, and <1% of all non-Hodgkin's lymphoma. Most cases of PLB are of diffuse large B-cell lymphoma (DLBCL) subtype. We report a case of PLB (DLBCL subtype) of the left iliac bone, which is a rare presentation, in whom local control was achieved with chemotherapy alone without any need of surgical interference and RT. As a result of the rarity of this disease, randomized trials addressing treatment alternatives for PLB are not available. Currently multiagent chemotherapy with or without radiation therapy is the preferred treatment of adults with PLB. The role of consolidation RT has also been the subject of much debate over the past decades as more trials have emerged that can address the role of RT in the rituximab era. Radiation to areas, such as the pelvis, which contain significant marrow production, should be considered carefully.



**PP-57****How can we treat Hodgkin lymphoma developed after hematopoietic stem cell transplantation due to IL10R deficiency, Crohn disease and EBV infection?**

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**Case report:** A 8-years-old girl was referred for left cervical lymphadenopathy and persistent fever. Crohn's disease was diagnosed when he was examined for anal abscess at 1.5 months. Her past medical history was loaded with frequent and severe infections. She was born at term with 2800 g of birthweight, to first-degree consanguineous healthy parents. Her aunts were lost at early infancy of age due to unknown reasons. Very early-onset Crohn's disease suggested probability of inherited deficiencies of IL-10 or IL-10 receptor. A mutation at position c.G477A in exon of the IL10RB gene, resulting in a stop codon at position p.W159X of the corresponding protein product. She underwent hematopoietic stem cell transplantation with 10/10 HLA (high resolution) matched related mother at 6 years of age. Counts of CD34+ cells were  $22 \times 10^6/\text{kg}$ . Neutrophil engraftment occurred at day +13. She was discharged at day +28. She was discharged at day +28. After 2 years of bone marrow transplantation, EBV DNA titer was increased inspite of two cycles of rituximab therapy. Hodgkin Lymphoma mixt cellular subtype stage II was diagnosed after cervical lymphadenopathy excision. After 4 cycles of ABVD chemotherapy regimen and radiotherapy (19 Gy, bilateral cervical, mediastinum, hilus) full anatomic and metabolic response were achieved. She was following with remission, after 9 months sestion of therapy.

**Results:** Chronic intestinal inflammation is a known risk factor for the development of malignancies. Infection with Epstein-Barr virus (EBV) and long-term administration of immunosuppressive medication are also associated with a slight increase in the risk of lymphoma in young children with colitis and in adults with IBD. A Mendelian predisposition to B-cell lymphoma has been observed in some primary immunodeficiencies related to DNA repair (such as ataxia-telangiectasia) and dominant-negative STAT3 mutations but not previously in the monogenic form of IBD. Here, we report on the occurrence and recurrence of diffuse large B-cell lymphomas (DLBCLs) in 5 children with IL-10R1 (n=1) or IL-10R2 deficiencies (n=4). None of the DLBCLs was related to EBV infection. Our data strongly suggest the existence of a direct relationship between IL-10R deficiency and the development of B-cell lymphomas. Inflammatory bowel disease (IBD) encompasses a heterogeneous group of diseases that are characterized by chronic intestinal inflammation with a complex etiology. Very-early-onset IBDs (VEO-IBDs) are particularly severe, treatment-resistant conditions. Loss-of-function mutations in one or another of the interleukin-10 (IL-10) receptors two chains (IL-10R1 and IL-10R2) or in IL-10 itself are detected in about 20% of VEO-IBD patients. Studies of IL-10/IL-10R knockout mice have shown that this cytokine is a key checkpoint for maintaining immune homeostasis toward intestinal microbiota.

**PP-58****Angioimmunoblastic T-cell lymphoma associated Raynaud phenomenon and digital necrosis**

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**Objective:** Raynaud's phenomenon (RP) is episodic vasospasm of the peripheral vessels. It presents as episodic colour changes of the digits (sometimes accompanied by pain and paraesthesia) and the classic change is white (ischemia), then blue (de-oxygenation), then red (reperfusion). Raynaud's phenomenon can be primary (idiopathic) or rarely secondary to several different conditions. When secondary, it can progress to ulceration and necrosis of the fingers or less commonly, critical digital ischemia. Connective tissue disorders like systemic sclerosis, are most common causes of secondary RP (85-90%) and malignant disease are very rare. We could

not find a lymphoma associated RP, although a few different paraneoplastic vascular acrosyndromes are reported, our case is the first angioimmunoblastic T-cell lymphoma (AITL) associated RP resulting with digital necrosis.

**Case report:** A 60 years old patient who presented with complaints of weight loss and swelling in his neck was found to have a painless mobile lymph node of 3 cm in diameter on the left cervical regions. Tomographs showed multiple oval nodules with thickened cortices with multiple hilus echogenes in the neck, axillary, gastrointestinal, and inguinal regions. In the excisional biopsy. The tumor which was with extensive endothelial venule proliferation, was found to be composed of small- to medium-sized CD3 and CD4 positive atypical lymphoid cells and found to be compatible with AITL. The patient described finger pain and paresthesia at the time of admission at first and fourth fingers in the right hand and second and fifth at left, but there was no evidence on physical examination. While the diagnostic procedures were ongoing, pain increased in these fingers, paleness and coldness improved, and these fingers were examined cold and cyanotic when the patient came emergency service for unbearable pain at fingers. Upper limb pulses were palpable, doppler examinations had no arterial occlusion, but proximal venous occlusions were detected. He was given prostaglandin analogue iloprost (infusion mode at 3.3 µg/h), metilprednisolone (1 mg/kg), cardiac selective calcium channel blocker diltiazem 2×60 mg, cilostazol 1×100 mg, pentoxifylline 2×600 mg to provide arterial vasodilatation along with low molecular weight heparin. However, symptomatic relief was not achieved. With confirmation of the diagnosis, received CHOP followed by CHOEP (total 2 cycles) and vasodilatation was seen on the fingers to ascertain the temperature increase, but significant necrosis areas remained at the fingertips.

**Conclusion:** Secondary RP is mostly associated with immunological disorders and malignancy is very rare with predominance of carcinoma. On the other hand, AITL which counts for 1.2% of all non-Hodgkin lymphomas and 18% of peripheral T cell lymphomas, has autoimmune manifestations (such as autoimmune haemolytic anemia, cold agglutinin disease, rheumatoid factor positivity) and frequently associated findings. Lymphoma-associated digital ischemic syndromes (including Raynaud's phenomenon, acrocyanosis, acrocrosis) are very rare and 19 cases were reported. Our case is the first AITL associated RP, resistant to vasodilator treatment and resulting with digital necrosis.

**PP-59****Hodgkin lymphoma presented with massive pleural effusion**

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**Objective:** Pleural effusion can be seen at the hematological malignancies either at the time of diagnosis or during the course. In Hodgkin (HL) and non-Hodgkin's lymphomas (NHL), effusion is seen at a frequency of 20%-30%, especially if mediastinal involvement is present. In NHL, these effusions are often associated with malignant infiltration, whereas in HL, reactive inflammatory effusions are more frequent. The effusion is usually a secondary finding, which is detected during the staging investigations of HL patients who present with B symptoms or enlargement of lymph nodes. Herein, we present a case of nodular sclerosing type Hodgkin's lymphoma (NSHL) admitted and diagnosed due to severe pleural effusion.

**Case report:** An 18-year-old male patient was referred to our hospital with complaints of dyspnea and itching. We were consulted after thorsentesis of unilateral massive pleural effusion. He had complaints of weight loss (20 kg in the last 2 months), night sweat and itching during last month in the system question. There was no fever. On physical examination, cervical and axillary lymph nodes (LN, maximal 3 cm in diameter) was detected. The investigations of pleural effusion which is exudate, revealed Inflammatory cells in the effusion, no malign infiltration or specific microbial etiology was detected. Thoracic computerized tomography (CT) revealed massive effusion on one side and multiple mediastinal lymphadenopathies. Mycobacteria cultures obtained by bronchoscopy and thoracentesis were all negative. Excisional biopsy was performed from right axillary LN. Pathology was reported as NSHL and pleural biopsy was performed. It was also evaluated as NSHL involvement. The ABVD Protocol (doxorubicin, bleomycin, vinblastine, dacarbazine) was



started and remission was achieved with 6 cycles, mediastinal radiotherapy was obtained but early recurrence developed. The patient died because of infective complications during second treatment with DHAP.

**Conclusion:** In Hodgkin and non-Hodgkin's lymphomas, effusion is more common, whereas acute and chronic leukemia, and myelodysplastic syndromes are rarely accompanied by pleural involvement. In addition, 10-30% of patients receiving bone marrow transplantation develop pleural effusion. In the case of pleural effusions in hematological diseases, drug toxicity, underlying infectious, secondary malignant or rarely autoimmune causes should be sought carefully. HL usually has a reactive pleural effusion but in our case, it has been shown that, although malignant cells were not detected in effusion samples, pleural biopsy revealed primary HL involvement. In most cases, either reactive or associated with primary infiltration, pleural fluid responds to the systemic chemotherapy but pleurodesis may be necessary in resistant or recurrent cases.

## Multiple Myelomas

### PP-60

#### Case report: cardiac amyloidosis

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**Objective:** Systemic amyloidosis is a relatively rare multisystem disorder caused by extracellular deposits of insoluble fibril proteins in various tissues and organs. Amyloidosis patients may present to any specialty and the diagnosis is frequently delayed. Cardiac amyloidosis refers to the involvement of the heart by amyloid deposition whether as a part of systemic amyloidosis (as is most commonly the case) or as a localized phenomenon.

**Case report:** A 68-year-old male with a history of hypertension, atrial fibrillation and chronic kidney failure presented with worsening dyspnea on exertion, orthopnea, and lower-extremity edema that had persisted for the past 3 months. He denied any history of smoking or alcohol/drug abuse. Physical examination revealed a 3/6 holosystolic murmur in the mitral area and 2+ lower-extremity edema bilaterally. Initial laboratory data revealed anemia Hb 9.8 g/dl. Cardiac troponin (>100 ng/l) and NT pro BNP (>5000 pg/ml) were elevated. Skiagram of the chest revealed cardiomegaly (cardiothoracic ratio of 0.65). Electrocardiogram revealed AF, low QRS voltage and thickening of the left ventricular wall. A transthoracic echocardiogram revealed pericardial effusion, moderate concentric left ventricular hypertrophy, and ejection fraction 50%. CMR was pursued, which depicted delayed post-gadolinium enhancement of myocardium in a heterogeneous pattern that suggested amyloid deposition in the myocardium. A supportive treatment of heart failure therapy is started. A patient finally underwent an endomyocardial biopsy, which confirmed the presence of amyloid deposits. In the Congo red tint evidence of birefringent amyloid. An amyloid light chain (AL) was diagnosed. A complete work-up for systemic amyloidosis including serum protein electrophoresis, 24-hour urine protein electrophoresis, free light chain ratio was positive. A bone marrow suggested abnormal plasma cells of type lambda and co-expression of cyclin D1 (Translocation t (11:14)), further evidence of amyloid in the periosteal vascular wall (pelvic crest). In addition, we continued to see a known grade III chronic renal insufficiency with a current GFR of 49 ml/min. As previously described, a moderate albuminuria is detectable. Renal involvement is likely, but currently not therapeutically relevant. To demonstrate a systemic manifestation, a fatty tissue biopsy was performed. That was negative for amyloid deposits. The Chemotherapy after CyBorD (Cyclophosphamide p.o, Bortezomib s.c, Dexamethasone p.o) Protocol weekly administration was started. We intend to re-evaluate high-dose chemotherapy with autologous stem cell transplantation in response to the response to therapy.

**Conclusion:** Based on the type of amyloid protein, cardiac involvement in amyloidosis can be seen in the following five types: (1) amyloid light chain (AL) or primary amyloidosis, (2) transthyretin (TTR) or familial/hereditary amyloidosis, (3) systemic senile amyloidosis, (4) isolated atrial amyloidosis,

and (5) serum amyloid A (AA) or secondary amyloidosis. Endomyocardial biopsy has been considered to be a gold standard for demonstrating cardiac amyloid deposition. Measurements of NT Pro BNP troponins can be extremely useful in diagnosis and assessment of prognosis of AL amyloidosis. BNP/NT Pro BNP, in general, reflects high filling pressures, but amyloid deposits may have a local effect. Increase troponins are a marker of poor prognosis but the mechanism remains unclear.

### PP-61

#### Increase of CD33 expression in multiple myeloma estimates short survival

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**Objective:** CD 33 is being used in multiple myeloma extensively and has a role of sialic acid dependent adhesion molecule. The literature about the relation of bad prognosis of CD33 expression whether during the diagnosis or relapse has increased recently. In our study we aimed to evaluate the effect of CD 33 level of new diagnosed multiple myeloma patients to their survey.

**Methodology:** We included 22 multiple myeloma patients (14 female, 8 male, mean age:61±7) to the study. 16 of them were Ig G type, 4 of them were Ig A type and 2 of them were kappa light chain disease respectively. With ficoll hypaque technique; CD33APC, CD19 ECD, CD20PB, CD27PC27, CD28ECD, CD38A750, CD44FITC, CD45KRO, CD56PE, CD81PE, CD117PC7, CD138APC, ckappaFITC, clambda PE were studied from bone marrow materials of the patients (with Beckman Coulter Navios 3L10C). CD 33 positivity with the rates of 10, 20, 30, 40, 50, 60, 70, 80, and 90% by Kaplan-Meier analysis were performed.

**Results:** The mean follow-up time was 29.6±5.5 months. With CD33 10% positivity (19 patients positive, 3 of them negative), it showed statistically significant affect at the life curve (p=0.01) while 90% positivity of CD 33 expression (3 patients positive, 19 of them negative) showed statistically significant negative affect.(p=0.01) As much as CD33 expression increases(from 10 to 90%) , it has been detected that there was a negative impact on survival. (Intermediate values as 20, 30, 40, 50, 60, 70, 80 was statically insignificant)

**Conclusion:** CD 33 expression increase influences survey negatively. The accurate cut-off level of expression level can be determined when the patient count of the studies is enhanced.CD 33 can be a new target molecule for prognosis and also treatment in the future.

### PP-62

#### Lenalidomide provide better progression free survival than thalidomide and bortezomib in the first relapse of multiple myeloma patients after autologous transplantation

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**Objective:** In the literature there are many studies which evaluated the efficacy of lenalidomide, thalidomide and bortezomib based regimens. However, a few studies had aimed to compare these agents in MM. In this study we aimed to compare the efficacy of lenalidomide, thalidomide and bortezomib in the first relapse of MM patients after autologous stem cell transplantation (ASCT).

**Methodology:** Multiple myeloma patients who were undergone ASCT between the years 2004-2015 and then given lenalidomide, thalidomide or bortezomib in the first relapse were evaluated retrospectively. A total of 59 patients were included in this study. Overall survival (OS) and progression free survival (PFS) are taken as end-points of this study.

**Results:** In univariate analysis, the platelet engraftment duration ( $<10/\geq 10$  days) ( $p=0.071$ ) and treatment choice (lenalidomide, thalidomide and bortezomib) ( $p=0.001$ ) were found to effect PFS. After multivariate analysis, only the treatment choice after the first relapse after ASCT was found to be related with PFS. Lenalidomide group has a significantly higher PFS than thalidomide and bortezomib groups ( $p=0.004$ ). PFS durations were  $1585\pm 199$ ,  $642\pm 221$  and  $438\pm 102$  days in lenalidomide, thalidomide and bortezomib patient groups, respectively ( $p=0.001$ ). OS durations were  $1849\pm 147$ ,  $1881\pm 189$  and  $917\pm 135$  days in lenalidomide, thalidomide and bortezomib patient groups, respectively ( $p=0.312$ ). There is no difference of OS between the lenalidomide, thalidomide and bortezomib groups.

**Conclusion:** In this study we have found that in the setting of first relapse after ASCT the treatment choices between the lenalidomide, thalidomide and bortezomib particularly related with the PFS and not OS. We have shown that the lenalidomide based regimens provide a much better PFS than thalidomide and bortezomib based regimens. Class switching strategy between the myeloma treatment agents could provide better outcome and may help to overcome resistance against previous agents and clonal evolution of the disease.

#### PP-63

##### Clinical features and outcomes of solitary plasmacytomas: single-center experience from Turkey

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**Objective:** SP is a plasma cell dyscrasia that presents as a mass lesion consists of plasma cells that produces monoclonal immunoglobulins without any systemic involvement. SP accounts for approximately 5% of all plasma cell dyscrasias and mostly occurs in osseous tissue, however one third of patients have extramedullary plasmacytoma. In this paper, we analyzed our patients and aimed to reveal patients' characteristics and outcomes.

**Methodology:** Total of 52 patients who were referred to our clinics of hematology and radiation oncology with the diagnosis of SP from January 2006 to March 2017, were evaluated retrospectively. Age, sex, treatment procedures, radiotherapy doses, involved tissue data, relapse and response status, death times were recorded from hospital registries.

**Results:** Patients without MM at the diagnosis ( $n=35$ ) were irradiated., 8 of those were treated with chemotherapy adjacent to radiotherapy. SBP was the most common diagnosis as 69.2% ( $n=36$ ), one patient was diagnosed with SBP and extramedullary plasmacytoma (EMP) at the same time. Local recurrence was detected in 9 patients (17.3%), all relapsing patients (67.3%,  $n=35$ ) were received mean  $38.2\pm 9.0$  Gy dose of irradiation. Partial and complete responses were achieved in 92.3% of patients ( $n=48$ ). During follow-up MM developed in 7 of all 35 patients. Median OS was not reached, PFS was median 26 months. There were no significant PFS and OS differences between SBP and EMP groups ( $p=0.8$ ,  $p=0.7$ , respectively).

**Conclusion:** This registry-based study represents our experience on SP and provides the data showing that radiotherapy as a single regimen results in good outcomes. Due to limited number of patients, it is difficult to hypothesize that radiotherapy is the golden standard, but radiotherapy alone to involved area seems to be adequate and safe treatment option. Our findings is consistent with literature, however there is no prospective or large patient group of retrospective analysis in the literature.

#### PP-64

##### Investigation of B-lymphocyte F-actin cell skeleton in multiple myeloma patients

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**Objective:** Multiple myeloma (MM) is a type of cancer that originates from bone marrow and is characterized by abnormalities and uncontrolled proliferation of plasma cells, an important part of the immune system. It has been shown that there may be a relationship between the changes in F-actin

in cells obtained from different cancers, including MM cells, and the ability to migrate and spread to tissues. However, it is noteworthy that studies related to the subject are very limited and there are no studies investigating its clinical significance. The aim of our study in this direction is to assess possible changes in the actin cell skeleton in B lymphocytes of MM patients.

**Methodology:** Blood samples from 21 MM patients and 15 healthy controls, newly diagnosed and not yet started, were used in the study. The F-actin content of the cell skeleton was monitored by immunofluorescence imaging in the isolated B lymphocytes, and the F-actin level was determined from the cell lysates by western emulsion method.

**Results:** Immunofluorescence microscopy results in study showed that 71.4% of MM cases had increased F-actin content in B lymphocytes. Western emittance also showed increased density in the F-actin band at 75% of cases. When the results of both parameters were compared with healthy controls, a statistically significant increase was found (Yates chi-square test,  $p<0.05$ ).

**Conclusion:** These results suggest that there is a relationship between increased F-actin content and disease spread. We believe that increasing the number of cases and conducting studies that are used together in other advanced techniques will allow the F-actin changes in B lymphocytes to be used as a marker to determine MM malignant cell migration and spread.

#### Myelodysplastic Syndromes

#### PP-65

##### The engraftment determinants at autologous stem cell transplantation in patients with myeloma

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**Objective:** In this study we aimed the evaluation of engraftment determinants in patients with multiple myeloma which undergo autologous stem cell transplantation as retrospectively.

**Methodology:** Relationship between engraftment with days, age, sex, number of stem cells, number of erythrocyte suspensions, number of thrombocyte suspensions, myeloma type, pre-transplantation hemoglobin level, leukocyte count, thrombocyte count, pretransplant bortezomib or thalidomide use were investigated.

**Results:** A total of 40 patients were evaluated. Male/female was 22/18. Twenty-five of the patients were IgG, 8 were IgA, 6 were light chain and 1 was IgE myeloma. Mean stem cell count is  $6.23\times 10^6/\text{kg}$  ( $2.13-17.76\times 10^6/\text{kg}$ ) Spearman's analysis was used between engraftment with parameters for correlation. We found only a correlation between engraftment day with number of stem cells. We did not find a correlation between engraftment day with age, sex, number of transfused erythrocyte or thrombocyte suspensions, myeloma type, pre-transplantation hemoglobin level, leukocyte count, thrombocyte count, pretransplant bortezomib or thalidomide use.

**Conclusion:** The effect of other parameters such as sex, number of stem cells, number of erythrocyte suspensions, number of thrombocyte suspensions, myeloma type, pre-transplantation hemoglobin level, leukocyte count, thrombocyte count, pretransplant treatment type on engraftment is not clear. This retrospective study showed that infused stem cell number is only engraftment determinant at autologous stem cell transplantation in patients with myeloma.

#### PP-66

##### Successful treatment of patients with AML and MDS by decitabine; single centre experience

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**Objective:** Decitabine inhibits the function of DNA methyltransferases by incorporation into the DNA and prevent the methylation of cytosine during cell division, resulting in genome-wide demethylation. This drug is widely accepted as the treatment option for myelodysplastic syndrome (MDS) and elderly patients with acute myeloid leukemia (AML). The goal of this study was

to identify the safety and efficacy of decitabine in MDS and AML patients in our center.

**Methodology:** Decitabine administered 20 mg/m<sup>2</sup> by intravenous infusion daily for 5 consecutive days every 4 weeks. The primary end point was the overall response rate (ORR). Response assessed by 2006 International Working Group criteria for MDS. In addition survival, overall improvement rate (OIR), hematologic improvement (HI) and drug toxicity were analyzed.

**Results:** Results for MDS and AML were assessed separately. 25 MDS patients were enrolled. Median age was 67 years (range 23–82). All patients had International Prognostic Scoring System score of  $\geq 0.5$ . Median overall survival (OS) and progression free survival (PFS) were 21 months and 14 months respectively. At 1, 2 and 5 years OS were 62.9%, 47.1% and 17.7% respectively. At 1, 2 and 5 years PFS were 54.9%, 45.8% and 30.5% respectively. The ORR was 48% (11 marrow complete remissions [mCRs] plus 1 partial response [PR]) and the overall improvement rate (OIR) was 64%, which included 48% HI. OIR was 62.5% for intermediate-1 patients and 75% for intermediate-2 and high-risk patients. 88% of patients experienced stable disease (SD) or better. HIs were detected by the end of median two cycles. The OS and PFS outcomes of patients whom achieved response were observed statistically significantly better than the others ( $p < 0.013$  and  $p < 0.005$ , respectively). 13 AML patients were enrolled. Median age was 75 years (range 18–85) and 6 of 13 AML patients experienced CR (n=4) or PR (n=2) (ORR: 46.2%). Median OS and PFS were not reached due to 76% of patients (n=10) are still alive and 38% of patients (n=5) have been still receiving treatment. At 1 year OS and PFS were 61.4% and 77.8% respectively. Adverse events were evaluated for all 38 patients. Grade 3 or higher neutropenia, thrombocytopenia and febrile neutropenia, occurred at rates of 36.8%, 13.2%, 33% respectively. 7 of 25 MDS patients and 1 of 13 AML patients underwent ASCT.

**Conclusion:** The response to decitabine treatment was found to be associated with survival benefit in MDS patients. Our study shows that approximately half of AML patients achieved response. There is no serious adverse event observed except grade 3–4 hematological toxicity. As a result, decitabine is effective and safe with acceptable toxicity in intermediate or high risk MDS patients and elderly patients with AML.

#### PP-67

##### Granulocytic sarcoma with unusual localizations (breast and stomach) without bone marrow involvement after allogeneic transplantation

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**Objective:** Granulocytic sarcoma (GS) is a rare extramedullary solid tumor composed of immature myeloid cells associated with acute myeloid leukemia or myelodysplastic syndrome. Especially, involvement of breasts as a pattern of relapse after allogeneic stem cell transplantation (alloSCT) is extremely rare. We report case of high risk myelodysplastic syndrome (MDS) with relapse 18 months after alloSCT as a granulocytic sarcoma in the right breast without bone marrow involvement. We will also discuss clinicopathologic features of granulocytic sarcoma of breast and stomach after alloSCT.

**Case report:** A 56-year-old woman applied to our center due to cytopenia, and diagnosed with high risk myelodysplastic syndrome (MDS) in January 2016. At the time of diagnosis hemoglobin level was 8,5 mg/dl, white blood cell count was  $6 \times 10^9/l$  and platelet count was  $93 \times 10^9/l$  in peripheral blood count. Biochemical tests were normal. Blasts in the bone marrow aspirate were 12%. There were positive test results for cluster of differentiation (CD)34 (12%), for CD117 (20%) and for P53 (30–40%). Cytogenetic analysis showed normal karyotype. She received 4 cycles of decitabine 20 mg/kg/day intravenously (iv) on days 1–5. The patient underwent alloSCT (donor was her human leukocyte antigen [HLA]-matched brother) in June 2016. In December 2017 she was admitted with a palpable mass in her right breast that had been increasing in size for the past 3 months. Firm mass was palpated on the right breast with a size of 3.0×3.0 cm. There were no signs of retraction or skin abnormalities. Mammography planned for the patient because of

examined palpable mass. Mammography showed a single, irregular, poorly defined mass that was 2.5×3.5×4 cm in diameter, without calcification. Also a right axillary lymph node which was 1.5 cm in diameter with thickened cortex is detected. After a tru-cut biopsy diagnosis of granulocytic sarcoma of breast was made. Immunohistochemistry results were positive for CD34, lysozyme, and myeloperoxidase (MPO), CD117, CD33 and were negative for CD3, CD20, CD30 and PAX5. Her bone marrow aspiration and biopsy revealed no blast. Endoscopy has been planned due to abdominal pain and vomiting persisting for 1 month at time of diagnosis. Endoscopy revealed a mass in the fundus area, 3,5 cm in diameter, from which a biopsy sample was taken. The gastroscopic biopsy showed diffuse neoplastic infiltration that the cluster of tumor cells expressed CD43, CD117, CD33, CD34 and MPO. GS was diagnosed in the stomach also. Later, she was treated with idarubicin at 12mg/m<sup>2</sup>/day iv on days 1–3 and cytarabine (ara-C) at 100 mg/m<sup>2</sup>/day iv on days 1–7. DLI was planned following chemotherapy.

**Conclusion:** GS of breast is a rare extramedullary involvement of hematologic diseases. There is no specific radiological feature for presentation of GS of the breast. Our case also showed that careful histopathological review along with all panel of immunohistochemistry is extremely important for diagnose.

#### Stem Cell Transplantation

##### PP-68

##### Cerebral toxoplasmosis after allogeneic hematopoietic stem cell transplantation

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**Objective:** Toxoplasmosis is an uncommon but frequently life-threatening complication of allo-HCT and is caused by the protozoan parasite *Toxoplasma gondii*. It is the most common CNS opportunistic infection, with a high mortality rate. Toxoplasmosis usually (90%) develops within the first 6 months after HCT.

**Case report:** The patient was a 47-year-old male diagnosed with secondary acute myeloid leukemia (AML M4) from MDS. He received “7+3” induction therapy and achieved a complete remission. He then underwent consolidation allo-HCT from 10/10 HLA-matched unrelated donor after undergoing a fludarabine, mAMSAs, and HS-AraC pre-transplant conditioning regimen. The pre-transplant *Toxoplasma gondii* serostatus of the recipient was unknown, the donor was toxo-seronegative, pre-transplant cytomegalovirus (CMV) serostatus of the donor and recipient were positive. Engraftments of leucocytes, as well as granulocytes, were noted on day 12 post-transplant. Complete donor chimerism with PCR method was found on day 10 and maintained until now. Acute graft versus host disease was not observed. The patient was discharged from hospital on day 28 post-transplant. The early post-transplant period proceeded without complications. At day 37 post-transplant he presented with progressive fatigue and high fever CMV-reactivation. He received ganciclovir therapy. He also had hypo-regenerative anemia in major and (minor) incompatible SCT. On the day 151 post-transplant, he had a strong headache. The patient can no longer walk, has a falling tendency to the left and a weakness in the left body part. An MRI of the brain showed disseminated ring-enhancing lesions supra-/infratentorial. The neurology team was consulted and MRI spectroscopy showed atypical appearance for possible neoplasm or infarction. Lumbar puncture was remarkable for a high protein level of 132 mg/dl (normal 14–45), with negative infectious disease workup on the CSF, including PCR for herpes simplex virus, varicella-zoster virus, CMV, JC virus, *T. gondii* IgG antibody test, and bacterial and fungal isolate cultures. Serological tests of viral infections, including CMV, EBV, adenovirus, and human herpesvirus 6 as well as blood cultures, were negative. Here, cytological, the high-grade suspicion of meningitis was observed, so we started intrathecal-Triple therapy with dexamethasone, cytarabine, and MTX. In parallel, the patient received high-dose dexamethasone orally. After neurosurgical consultation, a brain biopsy was considered. The patient underwent an image-guided biopsy of the right



frontal lesion. The frozen section of the brain biopsy showed necrotic brain tissue with scattered, CNS tissue with vascular and parenchymatous, T-cell dominated inflammatory cell infiltration. PCR analysis for *T. gondii* DNA was positive. He was started on pyrimethamine and sulfadiazine with leucovorin therapy after infectious disease consultation. The left hemiplegia gradually improved and he was able to go home and walk with assistance.

**Conclusion:** Cerebral toxoplasmosis may be encountered up to 2 years following allo-HCT, with atypical features on imaging studies and negative CSF antibody testing. Pre-transplant serologic screening for *T. gondii* antibodies in allogeneic transplant candidates is warranted. Brain biopsy continues to be an important and informative diagnostic tool in patients with atypical brain lesions after allogeneic HCT. Blood serological testing may obviate the need for brain

#### PP-69

##### Relation of basal vitamin D and parathyroid hormone levels to CD34+ cell counts in multiple myeloma and lymphoma patients with stem cell mobilization

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**Objective:** In this study, we investigated the relationship between parathyroid hormone and vitamin D levels and the number of stem cells collected in multiple myeloma and lymphoma patients mobilized for autologous hematopoietic stem cell transplantation.

**Methodology:** This study was performed in patients with lymphoma and multiple myeloma who underwent autologous bone marrow transplantation at Inonu University Department of Hematology. Peripheral blood samples were taken from the patients before the mobilization chemotherapy and sent to the laboratory by the light protected test tubes and the levels of vitamin D and parathyroid hormone was studied by Roche e411 immunoassay device. In our study, G-CSF plus cyclophosphamide regimen was used for stem cell mobilization. After the mobilization regimen, the patients were monitored for the CD34+ cell counts in the peripheral blood, and the CD34+ cells were collected by Spectra Optia device and the number of CD34+ cells per kilogram was calculated.

**Results:** A total of 77 patients with 28 lymphoma and 49 multiple myeloma were included in the study. The mean age of the patients was 55±11 and 55 of them were male and 22 were female. Of the lymphoma patients, 25 are males and 3 are females; mean age 49±13. The parathormone level was 68.8±43.6 pg/mL, the vitamin D level was 7.68±5.85 ng/mL and the CD34+ counts were 9.08×10<sup>6</sup>/kg. The relationship between the levels of PTH and vitamin D and CD34+ cell numbers in lymphoma patients was not statistically significant. Of the multiple myeloma patients, 30 were male and 19 were female, mean age was 99±8.6. Parathormone level was 88.36±76.3 pg/mL, vitamin D level was 16.82. 68±14.15 ng/mL and CD34+ cell counts were found to be 10.28×10<sup>6</sup>/kg. The relationship between PTH and D levels and CD34 stem cell numbers in multiple myeloma patients was not statistically significant.

**Conclusion:** G-CSF and cyclophosphamide are widely used for stem cell mobilization. Similar to G-CSF, the use of PTH has shown that bone marrow progenitor cells are significantly mobilized to peripheral blood. Contrary to the use of G-CSF alone, the use of PTH in combination with G-CSF does not result in the depletion of bone marrow Lin/Sca-1, C-kit and CD34+ stem cells. Vitamin D receptor Knock-out (VDR KO) Rats treated with active vitamin D lead to monocyte/macrophage differentiation and an increase in the number of mature cells in both normal hematopoietic stem cell lines and leukemic cell lines. There was a negative correlation between the levels of PTH and D vitamins and CD34+ cell levels and this association was not statistically significant. As a result of our study parathyroid hormone and vitamin D levels are negatively correlated with CD34+ cell numbers, although there is evidence in the literature that PTH may have positive effects on stem cell mobilization.

#### PP-70

##### Relationship between peripheral blood and tissue chimerisms in patients with allogeneic peripheral stem cell transplantation: preliminary results

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**Objective:** Chimerism means the presence of donor-derived lympho-haematopoietic cells in recipient's organism following allogeneic stem cell transplantation (ASCT). There are studies revealing the relationship between graft versus host disease (GVHD) and tissue chimerism in the literature. In our study, we aimed to predict the probability of GVHD through evaluating the peripheral blood and tissue chimerisms on D+28.

**Methodology:** The results of ten patients who underwent ASCT in Istanbul Medical Faculty Stem Cell Transplantation Unit were interpreted. On D+28, patients' bone marrow biopsies and skin punch biopsies from anterior thigh were performed, and peripheral blood chimerisms were analyzed. In order to assess peripheral blood and tissue chimerisms, PCR amplification method which relies on fluorescent based short sequence repeat was used.

**Results:** The outcomes of ten patients (F:M=3:7) were evaluated. The median age was 27.5 years (range: 19–60 years). Four, 2, 2, and 1 patient were diagnosed with AML, HL, ALL (1 with b-ALL, other one with t-ALL), and AA, respectively. Five, 2, and 3 patients were treated with unrelated full-match, unrelated mismatch (9/10), related full-match peripheral blood stem cell transplantation, respectively. Seven patients were in complete remission, however, two patients, both of whom were diagnosed with HL, were in partial remission, and one AA patient had active disease before ASCT. All patients received IV cyclosporine and IV methotrexate for GVHD prophylaxis, however cyclosporine was replaced with IV tacrolimus due to allergic reaction in one patient (P7). Median follow-up time was 121 days (range: 60-198). None of the patients had GVHD on D+28. Nevertheless, during follow-up, GVHD developed in four patients (1 liver GVHD, 1 acute grade 3 skin, 1 acute grade 1 gastrointestinal, 1 acute grade 1 skin). All were started on 0.8 mg/kg methylprednisolone and additionally mycomofetil phenolate for the patient with liver GVHD (P4). Two of them have recovered, though it is very early to assess the other two patients' response to treatment. All patients had full chimerism in peripheral blood on D+28. P7 with AML, who had her own DNA in tissue chimerism and was full-chimeric on D+28, has been found to lost blood chimerism. Meanwhile her disease relapsed. Three patients had mixed, 6 patients had recipients' DNA in tissue chimerism evaluation. DNA could not be isolated from the tissue of P9 who had GIS GVHD. Two patients (P4 and 10) with GVHD had mixed tissue chimerism and, 1 patient with GVHD had her own DNA in tissue (P8). P3 had mixed tissue chimerism. She is on D+151, besides no signs of GVHD.

**Conclusion:** In the literature, the relationship between post-transplant chimerism and GVHD was investigated. Auffermann-Gretsinger et al. proved that having donor derived dendritic cells in tissue is associated with the development of GVHD in mice (Transplantation, 2006). Murata et al. showed donor derived endothelial cells in tissues of patients with GVHD (Blood, 2007). Thus et al. demonstrated that the risk of developing GVHD was significantly increased in patients who had more than 99% T-cell chimerism in peripheral blood (Chimerism, 2014). Short follow-up period and low number of patients are limitations of our preliminary study. We continue following patients and plan to have new ones in our on-going study.



## PP-71

**Chimerism by lineage-specific analysis in the course of clinical outcome**Y. Ogret<sup>1</sup>, F. Oguz<sup>1</sup>, M. Aktan<sup>2</sup>, İ. Hindilerden<sup>2</sup>, M. Nalcacı<sup>2</sup>, S. Besiik<sup>2</sup><sup>1</sup>Istanbul Medical School Department of Medical Biology; <sup>2</sup>Istanbul Medical School Department of Internal Medicine, Division of Hematology

**Objective:** Analysis of chimerism after allogeneic hematopoietic cell transplantation is important for assessing engraftment and the early detection of graft failure. In addition, in patients transplanted for treatment of malignant hematologic disorders monitoring of minimal residual disease with chimerism can provide early detection of imminent relapse and early therapeutic intervention by reduction of immunosuppression or infusion of donor lymphocytes.

**Methodology:** At present, the most commonly used technical approach to the investigation of chimerism is microsatellite analysis by PCR. The investigation of chimerism within specific leukocyte subsets isolated from peripheral blood or bone marrow samples by flow-sorting or magnetic beads-based techniques provides more specific information on processes underlying the dynamics of donor/recipient chimerism. We aimed to evaluate the impact of T-/B-cell chimerism status on the incidence and clinical course of acute graft-versus-host disease (aGVHD) in allogeneic transplant. We used peripheral blood and sorted leucocyte subsets by magnetic beads-based techniques.

**Results:** The subset was defined by clinician. Chimerism analysis was performed by STR. Of 9 patients 6 became myeloablative conditioning with BU/CY and 3 fludarabine based non-myeloablative (NMA) conditioning. The transplant indication were ALL (n=3), NHL (n=2), AML (n=2), and hemaphagocytic syndrome (n=1), CLL (n=1). Two patients received matched unrelated transplant. The remaining were transplanted from matched sibling. All of the patients achieved complete donor chimerism (DC) except one. The latter patient had CLL and showed until 7th month recipient's T cell hematopoiesis which turned at second year to DC with development chronic GVHD: 4 of 9 patients did not developed GVHD and 2 of them eventually relapsed with losing DC. One patient with aggressive peripheral T cell NHL showed DC with losing T cell subset DC which was proved to be recipient origin. The latter T-cell subset chimerism status documented also the tumor cell origin. The patient with hemaphagocytic syndrome became gradually mixed DC associated with mixed T cell subset DC.

**Conclusion:** The latter case had not developed GVHD when she has complete DC and had continued than her mixed chimeric status without graft rejection. Our study was targeted to document hematopoietic origin which could be deceptive without leucocyte subset analysis. During the last 30 years, several studies analyzing chimerism after hematopoietic cell transplantation have been published and showed that MC is an important predictive factor for graft rejection and relapse. To assess the leucocyte subset DC on clinical outcome we believe chimerism should be performed as monitoring.

**Central Nervous System Tumors**

## PP-72

**Effects of high ellagic acid concentration raspberry (Rubus idaeus) extract on apoptotic miRNA expressions in neuroblastoma cell lines (SH-SY5Y)**A. Demirci<sup>1</sup>, S. Yıldırım<sup>2</sup>, G. Aktemur<sup>2</sup>, N. Durcanoglu<sup>2</sup>, E. Aslan<sup>2</sup>, S. Aşkın<sup>1</sup>, M. Durmuş<sup>3</sup>, I. Akalın<sup>4</sup><sup>1</sup>Kartal Anatolian Imam Hatip High School, Istanbul, Turkey; <sup>2</sup>Istanbul Medeniyet University Faculty of Medicine, Istanbul, Turkey; <sup>3</sup>Gebze Technical University, Department of Chemistry, Istanbul, Turkey; <sup>4</sup>Istanbul Medeniyet University, Faculty of Medicine, Department of Medical Genetics, Istanbul, Turkey

**Objective:** In our body every cell has some specific tasks and correct perform of the latter is essential for hemostasis. Uncontrolled proliferation of the cells in anywhere of the body result in to cancer as one of the most common diseases either in Turkey or the world. Neuroblastoma is one of them and as a malignant tumor it usually develops in the sympathetic nervous system in early childhood. In the last decade, miRNAs were emerged as the kind of

non-coding RNAs and composed of 20-22 nucleotides that were responsible for regulation of gene expression in diverse pathways including apoptosis.

**Case report:** In this study, we aimed to investigate the underlying mechanisms of raspberry (Rubus idaeus) (known as one of the antioxidant and anti-carcinogenic plant) extract containing high ellagic acid concentration whether or not it induces apoptosis on neuroblastoma cell lines (SH-SY5Y) through apoptosis regulating miRNAs.

**Methodology:** High ellagic acid concentration (approx. 40%) containing extract has been obtained from 171,29 g raspberry and 104 µg/mL extract was suspended in DMSO. Then, the extract was applied to SH-SY5Y neuroblastoma cells (3×10<sup>5</sup> cells/well) in increased doses of 0,5, 1, 2, 10, 20, 50, 100, 200 and 400 µL of 104 µg/mL. Apoptosis was obtained at 4th dosage at first (or 10 µL) and therapeutic dosage was set as 5th dosage (or 20 µL) and repeated doses were administered daily. Same amount of DMSO and DMSO free cells were used as control. Then, total RNA was isolated from repeated cell culture samples using miRNeasy Kit (Qiagen) according to manufacturer's instructions. After complementary DNAs were randomly primed using miScript II Reverse Transcription (Rt) Kit (Qiagen), miRNA expressions were analyzed by real time PCR (RotorGene Q, Qiagen). Results were evaluated online at www.qiagen.com. Moreover, DAPI staining was done to demonstrate apoptosis.

**Results:** The expressions of miR-21 and miR-146a was decreased at therapeutic dosage (20 µL) and apoptosis were obtained at 24th and 48th hours after administration.

**Conclusion:** Our results for the first time represented that, high ellagic acid concentrated raspberry extract might have anti-cancer activity on neuroblastoma cell lines by inducing apoptosis through miRNA regulations. More studies are needed to verify the data and might be tested in vivo. Note: This project has been supported by Kartal IHL Okul Aile Birliği, Istanbul Medeniyet University on behalf of Agreement of Istanbul Medeniyet University and Istanbul Branch of Ministry of National Education. This project has been awarded as 3rd rank at 49th TUBITAK Undergraduate Project Competition District Final.

**Genitourinary Cancer – Prostate/Nonprostate**

## PP-73

**A metastatic RCC case report undergoing multiple treatment options**M. Buyuksimsek<sup>1</sup>, O. Kara<sup>1</sup>, E. Yetisir<sup>1</sup>, C. Mirili<sup>1</sup>, A. Oğul<sup>1</sup>, M. Tohumcuoglu<sup>1</sup>, H. Sumbul<sup>2</sup><sup>1</sup>Cukurova University, Adana, Turkey; <sup>2</sup>Adana State Hospital, Adana, Turkey

**Objective:** Defined as a typical internist's cancer, renal cell carcinoma (RCC) has many different clinical presentations. As there are currently several treatment options available for RCC, the treatment cascade is very important.

**Case report:** A patient diagnosed with RCC in 2009 was treated with interferon, sorafenib, everolimus, nivolumab and axitinib for 7 years. We wanted to present this case whom we followed up for 4 more years after the detection of hepatic metastasis.

**Results:** Renal cancers are defined as typical internist's cancers and a vast majority of such cancers (90%) are renal cell carcinoma. They are characterized by anemia, malaise and weight loss. The most common symptoms are abdominal pain, macroscopic hematuria and palpable abdominal mass; however, today only 10% of the patients present with this classic triad of symptoms. Only 2% of the cases also have hereditary syndromes. Smoking, obesity, hypertension and polycystic kidney disease are the most common etiological causes. Several treatment options have been developed for metastatic RCC in recent years; therefore, the cascade of these treatment options is main focal point. We wanted to present our case who was followed up for 7 years with metastatic RCC and treated with multi-step treatment cascade since it was a rare entity.

**Conclusion:** This patient who received cytokine treatment, tyrosine kinase inhibitor and immunotherapy was our first patient at our center who was treated with immunotherapy and axitinib consecutively.

## Tumor Biology /Immuno-Oncology

### PP-74

#### 18F-FDG PET/CT for bone marrow metastases detection

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**Objective:** Demonstration of FDG-PET possibilities for bone marrow involvement detection in patients with solid tumors.

**Case report:** Bone metastases are frequent complication of cancer and detected in up to 70% of patients with advanced breast and prostate cancer, bone marrow metastases are rather rare clinical phenomenon. On the other hand we know that in 20-40% of patients we can detect bone marrow involvement by applying sensitive immunocytochemical and molecular assays. Detection of bone marrow metastases in cancer patients might change the treatment plan of the patient (especially without any symptoms and signs of bone marrow infiltration) and associated with a poor prognosis.

**Methodology:** We would like to present our experience in diagnostic bone marrow involvement by introduction of two clinical observations of patients with B-cell lymphoma and breast cancer.

**Results:** FDG-PET/CT directly evaluate abnormal metabolism and can help us to detect bone marrow metastases earlier than other diagnostic tools. FDG-PET/CT is described by high accuracy, sensitivity and specificity in detection bone marrow metastases.

**Conclusion:** Nowadays FDG-PET/CT has emerged as a powerful modality for evaluation bone marrow and bone metastases and revolutionized the diagnosis and staging of patients with solid tumors especially when other diagnostic modalities are equivocal. We need further investigations to define the additional places of PET/CT when survival or treatment plan might be changed as a result of early diagnosis of bone marrow involvement.

## Hematology – General

### PP-75

#### Determination of oxidant and antioxidant levels in children with thrombocytosis

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**Objective:** In this study, it was aimed to determine the levels of oxidant and antioxidant molecules in children who were diagnosed with thrombocytosis in the Department of Pediatric Haematology of Kirikkale University Hospital.

**Methodology:** The complete blood count, C-reactive protein (CRP), malondialdehyde as oxidant (MDA), total oxidant level (TOL), superoxide dismutase (SOD) as antioxidant, paraoxonase 1(PON1), arylesterase (ARES), glutathione peroxidase (GPx) and total antioxidant capacity (TAC) levels of the children who were diagnosed with thrombocytosis and control group in the Department of Pediatric Haematology of Kirikkale University Hospital between the dates of January 2016 and May 2016 were measured. The oxidative stress index (OSI) was calculated.

**Results:** A total of 85 cases, 42 in the thrombocytosis group and 43 in the control group, were included in the study. In our study, 51.2% of the thrombocytosis group was composed of females and 48.8% of males and 59.5% of the control group was composed of females and 40.5% of males. The mean values of oxidant MDA and antioxidant SOD levels in the thrombocytosis groups was higher compared to the control group ( $p > 0.05$ ), while the mean values of oxidant TOS ( $p > 0.05$ ) and antioxidant TAK ( $p > 0.05$ ), SOD ( $p > 0.05$ ), PON 1 ( $p < 0.05$ ).

**Conclusion:** In our study, TOS, which shows total oxidant status, was higher in the thrombocytosis group, while TAK, which shows total antioxidant level, was found to be lower compared to the control group ( $p < 0.05$ ). This suggests that oxidant and antioxidant system balance in the thrombocytosis group is impaired and oxidant load is higher. Oxidant-antioxidant balance is thought to play a role in the pathogenesis and pathological results of thrombocytosis. It is considered that the antioxidant molecules were consumed to destroy oxidant

molecules through the stabilizing mechanisms that occur in the organism because of the excessive oxidative stress, and the level of antioxidants is decreased accordingly. Wu et al. Described a mutation in BLVRBS111L as a novel cause of thrombocytosis. This mutation; it affects the reaction that biliverdin IX $\beta$  reductase enzyme binds to NADPH, causing degradation of the heme tract, increase of reactive oxygen species and thrombocytosis. This study shows oxygen radicals as the cause of thrombocytosis. We have known since 1977 that platelets are capable of producing endogenous reactive oxygen products. We think that increased oxygen radicals in thrombocytosis cases stimulate membrane lipid peroxidation and increase MDA and TOS levels. We think that thrombocytosis is both a cause and a consequence of oxidant stress. In our study, we found that the level of antioxidant parameters increased in the level of oxidant parameters in the thrombocytosis group. Oxidant molecules activate thrombocyte cells and cause thrombus formation. We think that the use of antioxidants may reduce the morbidity and mortality caused by thrombocytosis.

### PP-76

#### The presentational complaint/finding of Fanconi anemia patients that urged the diagnosis

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**Objective:** Fanconi anemia (FA) is rare, inherited disease characterized by congenital physical abnormalities, including short stature, in addition to chromosomal instability, progressive bone marrow failure and cancer susceptibility. On the other hand, almost 20% of the patients do not have dysmorphic features of the disease and some others never develop bone marrow failure or cancer. We aimed to increase the awareness on FA among pediatricians, surgeons and hematologist via stressing the presentational findings in a retrospective cohort.

**Methodology:** Herein, we present the initial complaint or finding of 75 patients with FA who were diagnosed in a single center during the last 10 years. (January 2008-June 2018).

**Results:** Of these 75 patients (n=38 (51%) were females), the median age at evaluation was 11,69 years (1-30) and FA diagnosis was confirmed with chromosomal breakage assay in all of the patients. On admission mean Hb, WBC, platelet and MCV values were found as 11.72 g/dl (6-16.2),  $5.1 \times 10^9/L$  (2-11.4),  $161 \times 10^9/L$  (6-487) and 93.1 fL (75-115.7). The reason for admission to the hospital was heterogenous as following: 10 out of the 75 patients (13%) admitted related to family history of FA, 12 (16%) was diagnosed during evaluations for short stature, 16 (21%) was diagnosed during evaluations for congenital malformations, 3 (4%) was diagnosed during evaluations for café au lait spots, 10 (13%) presented with bleeding/petechia, 15 (20%) was easy fatigue/weakness, 5 (6%) was pre-operatively found incidental low hemoglobin levels, 4 (5%) was malignancy. The rate of consanguinity is relatively high in our study with a rate of 73.0% (of these 56% were first degree cousin marriage).

**Conclusion:** The diagnosis of FA might be difficult in those who present with subtle dysmorphic findings. Short stature is a common finding in FA patients and must prompt a diagnosis of FA among those with other features of the disease or in those who have no other explanation for short stature. The siblings of FA patients should be screened for FA, as well. Additionally, 5% of our cohort presented directly with malignancy and all AML patients should be screened for underlying FA during childhood.

## PP-77

**A rare cause of iron deficiency anemia: "IRIDA" due to a novel nonsense homozygous TMPRSS6 mutation**

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**Case report:** Iron-refractory iron deficiency anemia (IRIDA) is an autosomal recessive disorder due to loss-of-function mutations in TMPRSS6 gene resulting in inappropriately elevated hepcidin levels. The key features of the disease are very low mean corpuscular volume (MCV), low transferrin saturation, higher ferritin levels than expected in classical iron deficiency anemia (IDA), abnormal iron absorption and defective iron utilization (as evidenced by sluggish and incomplete response to parenteral iron). We present here a child who was followed up for unexplained microcytic anemia since early childhood. Eventually, the case was diagnosed as IRIDA due to a novel homozygous nonsense TMPRSS6 mutation. The 6-year-old Syrian male patient born to first-degree cousin marriage was admitted due to microcytic anemia known since one year of age. The patient had history of inadequate response to oral iron therapy, and was transfused twice before. Examinations including bone marrow aspiration studies did not identify the underlying cause. Among the family members, the 10-year-old brother also had microcytic anemia, and the mother had history of iron deficiency anemia during pregnancy. Laboratory data of the patient were as follows: hemoglobin 7.2 g/dL, MCV 49.8 fL, mean corpuscular hemoglobin concentration (MCHC) 27.6 g/dL, transferrin saturation level 6.7%, serum ferritin level 37 ng/mL and C-reactive protein negative. In the presence of microcytic anemia unresponsive to iron therapy, low transferrin saturation level accompanied by normal serum ferritin level and absence of an infection or an inflammatory condition, IRIDA was thought as the possible diagnosis. Identification of a novel pathogenic nonsense mutation [c.234C>G (p.Y78\*) (p.Tyr78\*)] in TMPRSS6 gene in homozygous state in the proband and his similarly affected sibling confirmed the diagnosis. The parents and sister were found as heterozygous for the same mutation. The patient received intravenous iron therapy which resulted in slow and partial increase in hemoglobin level. In his last examination which was carried out five months after parenteral iron administration, his hemoglobin and MCV levels were found as 10.0 g/dL and 53 fL, respectively.

**Conclusion:** Although it has been reported quite rarely until now, IRIDA is probably the most common reason of "atypical" microcytic anemias. Through the timely genetic diagnosis of this disorder with a quite favorable prognosis, unnecessary (invasive) examinations can be avoided.

**Hemostasis, Thrombosis, and Vascular Biology**

## PP-78

**Influence of ABO blood group on von Willebrand factor tests in healthy Saudi blood donors**

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**Objective:** Von Willebrand disease is a common bleeding disorder. The wide variation in VWF levels between and within normal individuals highlights the clinical challenge of defining its cutoff value. Although studies on the influence of ethnicity on ABO phenotypes and the levels of VWF have been carried out on different ethnicities, there is a lack of such data among Arab population. We aimed to evaluate the correlation of ABO phenotypes with all the parameters of the minimal test panel of VWF including (VWF:Ag,

VWF:RCo, VWF:CB and FVIII:C), tested in a normal Arab population, and to estimate ABO specific normal reference range.

**Methodology:** Samples from 87 healthy male blood donors, aged from 18 to 65 years old, were submitted to the blood bank. All donors' hemoglobin level had been checked with the eligibility acceptance for donation. Blood samples of 5 ml of EDTA and 10 ml of citrated blood were collected from each donor after the consent form was signed. The sample of EDTA was used for blood grouping. There were two tube citrated samples. The first tube was centrifuged at 3000 rpm for 15 min and platelet poor plasma was separated within 4 h of collection, frozen at -80 [ORDM]C and used later to test for factor VIII:C, VWF:Ag and VWF:RCo. The second tube was used for testing VWF:CB. Factor VIII:C and VWF:Ag that were measured by coagulation analyzer. Factor VIII was estimated by commercial factor VIII-deficient plasma. Immuno-turbidimetric assay was used to measure VWF:Ag. VWF:CB was assayed by ELISA commercial kit using human collagen type III. VWF:RCo was determined by latex enhanced immunoturbidimetric assay. Reference plasma commercial calibrator of each test was assigned for preparing calibration curve to calculate each analyte according to the manufacture's instruction. All statistical analyses were performed by using the SPSS

**Results:** Out of the 87 donor samples initially collected, four were excluded because of their significant evidence of bleeding disorders from level of VWF less than 30%. From the total of the sample population, there were 45.8% (n=38) group O, 27.7% (n=23) group A, 20.5% (n=17) group B and 6% (n=5) group AB. The level of factor VIII and VWF panel between the various ABO blood group phenotypes was estimated and analyzed. The highest mean values of factor VIII :C (128±21) range (86–170), VWF: Ag (125±27) range (71–197), VWF:RCo (109±19) range (71–147) and VWF:CB (91.4±8) range (75–107) were observed with type AB and the lowest mean values of factor VIII :C (81±23) range (35–128), VWF: Ag (85±28) range (30–141), VWF:RCo (73±26) range (22–124) and VWF:CB (70±20) range (30–110) corresponded to type O.

**Conclusion:** ABO phenotypes significantly influence plasma levels of VWF parameters in Arab nations as seen with other ethnicity. Hence, ABO specific normal ranges of the minimal test panel of VWF and factor VIII:C are essential for the appropriate prediction of mild von Willebrand disease. Further study including a larger categorized sample size is required to generalize the test panel on the Arab population.

## PP-79

**Severe factor XII deficiency with unusual presentation during pregnancy: a case report**

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**Case report:** Factor XII deficiency has been reported to be associated with recurrent miscarriages, however published studies seem contradictory and need to be elucidated. Here, we report a rare case of severe FXII deficiency with unusual presentation and unexpected outcomes during pregnancy. A 26-year-old multiparous female with prolonged APTT that was discovered during her routine gestational checkup. Coagulation profile showed extremely low FXII activity (2%). PC, PS, ATIII, LAC and aCL antibodies were unremarkable. She had three full term normal pregnancies without complications with normal vaginal delivery of normal healthy infants with no history of any previous pregnancy loss. Although she opted to take oral contraceptive pills with her Ob-Gyn, no thromboembolic episode or any other complications have been reported. In conclusion, the possibility of normal pregnancy with FXII deficiency merits to be documented so a case series can be generated. We affirm that the possible association of pregnancy loss with FXII deficiency merits reevaluation.



## PP-80

**Recurrent gastrointestinal bleeding in a patient with von Willebrand disease: successful treatment with propranolol**

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**Objective:** Patients with von Willebrand disease (VWD) have an increased frequency of angiodysplasia and vessel abnormalities. Especially in their gastrointestinal tract bleeding caused by angiodysplasia, can be severe and life-threatening. Currently, the lack of optimal treatment is difficulty for physicians. We presented a patient with type 3 vWD referred to the hospital with recurrent gastrointestinal bleeding. He was receiving regularly tranexamic acid and factor concentrate 3× times every week. We successfully treated with beta-blocker in addition to conventional treatment

**Case report:** A 10-year-old male patient was admitted to the emergency room with complaints of pallor and fatigue. He was diagnosed with type 3 von Willebrand factor deficiency (Factor VIII level: 2%, vWF Ag level: 2%, vWF Ricof: 2, and inhibitor negative) at the age of 2 years due to recurrent nose bleeding and bruises. At the age of 3, total gastrectomy, jejunojunal anastomosis, and esophagegjunostomy were performed despite intensive factor therapy and thrombocyte suspension. At that time, he had uncontrolled gastrointestinal bleeding because of the arteriovenous malformation on endoscopy. For this reason he received prophylactic factor therapy twice a week. Despite regular treatment for the last 2 years, it has been recurrent intermittent hematemesis and melena. There was anemia in blood count (Hb:6.6 g/dl, Hct: 21%). Meckel diverticulum wasn't detected on scintigraphy. Bleeding site was not detected in the repeated endoscopy. Rectosigmoid region had a focus on the old hemorrhage on colonoscopy. During active bleeding periods, factor therapy twice daily and tranexamic acid were applied. Erythrocyte-marked scintigraphy and capsule endoscopy showed activity at the ileum level and was evaluated as a bleeding center. It was thought that the angiodysplasia and vascular anomalies were caused bleeding. Propranolol therapy has been added to factor therapy. Because of increasing bleeding frequency, factor therapy was increased to 50 U/kg/day for 3 days. The patient is good now and he follows up by our hematology-oncology department without bleeding for 8 months.

**Conclusion:** Patients with vWD have an increased frequency of vessel abnormalities, telangiectasias and angiodysplasia especially in GI tract. VWF therapy is successful in case with acute management of GI bleeding but giving prophylactic factor therapy is less effective for preventing recurrent GI bleeding. Embolization, surgical resection can be used managed bleeding. But it can be limited in cases with multiple, diffuse lesions. New antiangiogenic agents may effect by suppression of vascular endothelial growth factor.

**Leukemia/Lymphoma/Histiocyte Disorders**

## PP-81

**Gene expression profiling of pediatric acute myelogenous leukemia identifies ASXL1 expression as an important prognostic marker independent of conventional risk parameters: single institute experience from Saudi Arabia**

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**Objective:** Mutational analysis (FLT3/NPM1/CEBPA) has improved risk stratification but the response to conventional therapy is variable with frequent relapses. FLT3 targeted therapies are showing variable therapeutic responses. Hence, improved insight into the biology of AML, especially is warranted to explore new therapeutic targets. ASXL1 is now established to play a key role in

the prognosis of several hematological malignancies, however, its role in AML remains controversial. In this pilot study, we correlated ASXL1 expression and associated pathway expression patterns with hematological data and overall survival (OS) among pediatric AML patients.

**Methodology:** We analyzed 60 cases of confirmed childhood AML (2007–2017). All patients had received standard AML chemotherapy with risk stratification. Chromosomal banding analysis and fluorescence in situ hybridization were used to detect genetic aberrations. Bone marrow or blood samples were screened for FLT3 mutations using polymerase chain reactions. Among 60 cases of pediatric AML, RNA from diagnostic BM biopsies (n=46) was subjected to expression analysis employing nCounter Pan-Cancer pathway panel by Nanostring technologies. Laboratory and clinical data were correlated with ASXL1 Expression and associated molecules.

**Results:** The most common chromosomal abnormality (9.6%) was t(8; 21). Mutational analysis of FLT (ITD/TKD) was performed in 65% of patients. These were positive in 18% of patients while 82% harbored the wild type FLT3. ASXL1 expression among the 46 AML patients were dichotomized into low ASXL1 Expression (13/46) and high ASXL1 Expression (33/46) groups based on ROC curve analysis (72% AUC; 93% sensitivity /55% specificity). Age, gender, hematological data or molecular risk factors (FLT3/NPM1 mutation) exposed no significant differences across these two distinct ASXL1 expression groups (p<0.483). High ASXL1 Expression show significant differential across two groups (p=0.1492); suggesting a non-canonical pathway of ASXL1 activation in this pilot study. High ASXL1 Expression was associated with high mortality (13/23 (57%) vs. 1/13; (8%) p<0.0048). Low ASXL1 expression expressers showed better OS.

**Conclusion:** Our pilot study identified high ASXL1 expression through non-canonical pathway as an important poor prognostic marker among AML patients. ASXL1 expression is highly significant, irrespective of chromosome or FLT3 mutation. ASXL1 expression is independent of conventional risk parameters and can be a potential therapeutic target. Our data correlates to previously published data confirming a high frequency of cytogenetic abnormalities which have prognostic significance in Childhood Acute Myeloid Leukemia. In addition, FLT3 mutations are not common in the Saudi Arabian population and have no clinical impact in pediatric AML.

## PP-82

**Hemophagocytic lymphohistiocytosis secondary to Leishmania infection in a child with multiple splenic nodules**

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**Case report:** Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder with a significant mortality rate associated with widespread inflammation due to massive amounts of cytokines released from activated macrophages, and is characterized by fever, hepatosplenomegaly and cytopenias. The disorder may be inherited (primary HLH) or may develop secondary to some events such as infections, malignant diseases, rheumatologic/metabolic disorders or use of certain drugs. A12-month-old girl was referred due to fever reaching 39°C for 15 days in spite of the use of antimicrobial agents and pancytopenia. Parenteral antibiotic therapy was started after taking samples for routine examinations including cultures. In the physical examination, paleness and hepatosplenomegaly were noted. Laboratory examinations revealed anemia (hemoglobin, 7 g/dL), neutropenia (absolute neutrophil count, 0.7×10<sup>9</sup>/L) and thrombocytopenia (platelet count, 67×10<sup>9</sup>/L), elevated levels of serum lactate dehydrogenase (986 IU/L), ferritin (889 ng/mL) and triglyceride (237 mg/dL), and low levels of fibrinogen (132 mg/dL) and albumin (2.91 mg/dL). In the abdominal ultrasonography, hepatosplenomegaly and multiple splenic hypochoic nodules the biggest of which reached 1.5 cm in diameter were observed. The patient received intravenous immunoglobulin (IVIG). Following IVIG therapy, fever of the case resolved dramatically. Bone marrow aspiration smears revealed hemophagocytosis in the hypercellular marrow. No parasites were observed. As the patient's findings met HLH diagnostic criteria, steroid



treatment (dexamethasone, 10 mg/m<sup>2</sup>/day) was initiated. In the follow-up, increase in leukocyte and thrombocyte counts was observed. In the 8th day of steroid therapy, Leishmania Elisa IgM and IgG were documented as positive. Therefore, steroid therapy was stopped and amphotericin B was started. In the follow-up, clinical and laboratory findings of the patient resolved, and she was discharged on the 18th day of her hospitalization. Discussion: Infections caused by Leishmania donovani may themselves be associated with findings mimicking HLH (such as fever, splenomegaly and cytopenia). However, leishmaniasis may also trigger the development of HLH (secondary HLH). If the distinction between primary and secondary HLH can not be made clearly, HLH treatment protocol is generally applied for 8 weeks, and if remission is obtained, the treatment will be stopped. However, amphotericin B treatment alone is adequate in HLH cases secondary to leishmaniasis. In a case with HLH, the possibility of leishmaniasis as the triggering cause should be kept in mind even if no amastigotes are observed in the bone marrow smears. Through the demonstration of leishmaniasis as the underlying cause of HLH, unnecessary use of immunosuppressive agents may be avoided.

#### PP-83

##### **Hemophagocytic lymphohistiocytosis (HLH) in a case with meningoencephalitis: can meningoencephalitis be the first sign of HLH?**

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**Case report:** Cases with hemophagocytic lymphohistiocytosis (HLH) may have signs of central nervous system involvement or meningoencephalitis. On the other hand, there are few cases with final HLH diagnosis in the literature whose initial manifestations were associated with neurologic disorders such as encephalitis or meningoencephalitis in the absence of other classical systemic findings of HLH. We present here a case who developed HLH while being followed up with the diagnosis of meningoencephalitis. A 13-year-old boy was referred with the complaints of fever, headache, vomiting and seizures. He had history of a neurologic disorder at the age of 1.5 years that was suggestive of herpes encephalitis clinically and use of multiple antiepileptic drugs thereafter. Physical examination revealed lethargy, difficulty in speaking and neck stiffness. Cerebrospinal fluid (CSF) examination results were as follows: leukocytes 27×10/mm<sup>3</sup>, elevated CSF protein (291 mg/dL), CSF glucose of 62 mg/dL (simultaneous blood sugar 136 mg/dL). Herpes PCR in CSF was found as negative. Encephalitis was thought, and acyclovir, vancomycin and dexamethasone were added to the ceftriaxone treatment begun previously in another hospital, and antiepileptic drugs were stopped. However, phenytoin was started again due to occurrence of a seizure. On the 4th hospitalization day, respiratory arrest developed. Cranial magnetic resonance imaging showed diffuse involvement consistent with meningoencephalitis, particularly suggestive of herpes encephalitis, midline shift and compression in the brain stem. In his follow-up, the boy received mannitol, steroids, intravenous immunoglobulins, propranolol (due to hypertension), and blood products including erythrocyte, thrombocyte and fresh frozen plasma transfusions. Development of acute renal failure was noted. Inotropic agents were given due to hypotension. Imaging studies displayed hepatosplenomegaly and diffuse abdominal ascites. On the 25th hospitalization day, bone marrow aspiration performed due to intractable thrombocytopenia and leukopenia displayed hemophagocytosis. Serum ferritin level was 2820 ng/mL, and triglyceride level was 320 mg/dL. Epstein-Barr virus serology was consistent with a past infection. As the patient met HLH diagnostic criteria, HLH-2004 treatment protocol was initiated, however, the boy was lost on the 29th hospitalization day after cardiopulmonary arrest. Discussion: In our case, HLH may have developed secondary to an infection or use of certain drugs. On the other hand, it has been rarely reported in the literature that cerebrospinal involvement may develop before the typical HLH-associated diagnostic systemic signs (such as bicytopenia and organomegaly) and be therefore the first presentation of HLH. Recurrence

of encephalitis picture in our patient may point to an underlying inherited genetic defect.

**Conclusion:** Not only HLH may develop secondary to an infectious disorder such as encephalitis/meningoencephalitis, but also encephalitis/meningoencephalitis may be the first sign of HLH. These cases should also be examined for a possible underlying genetic defect like other HLH cases.

#### PP-84

##### **First report of an SH2D1A mutation associated with X-linked lymphoproliferative disease in Turkey**

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**Case report:** X-linked lymphoproliferative disease (XLP) is a rare disorder which is characterized by an extreme vulnerability to Epstein-Barr virus (EBV) infection, frequently resulting in hemophagocytic lymphohistiocytosis (HLH). XLP-1, its more common subtype, is caused by defects in the SH2D1A gene that encodes the signaling lymphocyte activation molecule-associated protein (SAP), which regulates the activation of T lymphocytes. We present here an XLP-1 patient with a family history of multiple male children's death, who presented with EBV-triggered fatal HLH. To our knowledge, this is the first report of an SH2D1A mutation from Turkey. The 19-month-old male patient was admitted with the complaints of fever and abdominal distention. In the physical examination, paleness, elevated body temperature (39.5°C), dyspnea, tachycardia, abdominal distention and hepatosplenomegaly were noted. Laboratory findings revealed anemia, leukocytosis, elevated levels of serum lactate dehydrogenase, bilirubin, liver enzymes (aspartate and alanine aminotransferases), triglyceride, ferritin (841 ng/mL at the time of admission which rose to 28,321 ng/mL on the 5th hospitalization day) and decreased levels of serum albumin, sodium and plasma fibrinogen levels. In the family history, the death of a 2-year-old male sibling with the clinical diagnosis of HLH and of five young male children of unknown etiology among maternal relatives was noted. The patient received intravenous immunoglobulin. However, in the follow-up, fever recurred and his general condition worsened. Bone marrow aspiration revealed hemophagocytosis. Therefore, the patient fulfilled HLH diagnostic criteria. Plasma exchange was performed. Blood products, antimicrobials, and supportive therapeutic agents were used as indicated. The results of EBV serologic testing and polymerase chain reaction were both reported as positive, EBV viral load being 526,736 copies/mL. On the 6th hospitalization day, the HLH-2004 protocol treatment was initiated, and rituximab therapy was planned. Continuous veno-venous hemodialysis was performed. However, the vital signs of the patient deteriorated further and active gastrointestinal bleeding occurred. The patient was lost on the 10th day of hospitalization. In the cytotoxic lymphocyte activity analysis, low SAP expression in addition to signs of severe immunoinactivation was detected. In the genetic analysis, the c.163C>T (p.Arg55Ter) mutation in the SH2D1A gene, described previously as pathologic was identified. Genetic counseling was provided to the family.

**Discussion:** We report here an XLP-1 case who presented with EBV-associated HLH. In XLP cases, the most common clinical manifestation is fulminant infectious mononucleosis. Death is generally attributable to liver failure with hepatic encephalopathy or bone marrow failure with fatal hemorrhages in various organs. The only curative treatment of XLP is hematopoietic stem cell transplantation. Rituximab therapy has been reported to successfully induce

remission in some cases of XLP. Unfortunately, our patient was lost before we could start rituximab therapy.

**Conclusion:** In boys presenting with EBV-associated HLH, the underlying defect may be XLP. The diagnosis may be confirmed by genetic analysis in suspected cases which will enable valuable genetic counselling to the families.

#### PP-85

##### Comprehensive analysis of transcriptomic portrait of T-cell acute lymphoblastic leukemia by RNA sequencing

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**Objective:** T cell-acute lymphoblastic leukemia (T-ALL) is one of the most aggressive treatment-resistant types of leukemia, which has no specific prognostic marker for disease follow up. **Objective:** The aim of this study is to demonstrate the altered genes in T-ALL, WNT-specific analysis of exhibit abnormal activity in the T-ALL and identify the tissue-specific expressions of alternative splicing products by transcriptome sequencing.

**Methodology:** In this study, we have sequenced RNAs LiCl treated T-ALL cell lines (Jurkat and Molt4) and control samples by Illumina HiSeq 2500. To compare our results RNA-Seq data was retrieved from seven T-ALL patients and healthy thymocytes via the Gene Expression Omnibus (GEO) database (GSE49601). Gene expression data analysis was performed in the R environment with EBSeg. Gene expression related pathway information and enrichment retrieved from DAVID Bioinformatics Resources 6.8.

**Results:** WNT activated T-ALL cell lines were compared with controls and 426 genes were identified differentially expressed out of 26228. According to the pathway analysis, the most significant increase for these genes was found to be the "spliceosome" pathway ( $p=4.91E+11$ ) from the gene list we have obtained. 15 genes were (TRA2B, SNRPD3, EFTUD2, SNRPD2, SF3A3, CTNBL1, PRPF19, HNRNPK, DDX23, U2AF1, SNRPA, ACN1, SNRNP70, HNRNPC, PRPF38B) involved with this pathway. According to our gene expression analysis that specific for the WNT pathway, 8 genes out of 166 were dysregulated. In this set of genes, the expression of PLCB2, DVL2, DVL3, CTBP1, CSNK1E, RAC2 and CACYBP was increased, while the expression of GSK3B was decreased. When we visualize these genes on the WNT pathway, it seems that the signaling is canonically induced, but in fact, there is no signal going through the key protein  $\beta$ -catenin for this pathway; the signal was transferred to the non-canonical cell polarity pathway via CSNK1E and DVL and increased activation of the RAC2 gene. In addition to gene expression analysis, the expression levels of alternative splicing products for LEF1 and  $\beta$ -catenin, which are critical for the WNT pathway, were determined in T-ALL cell lines and patients. The expression levels of different splicing products of  $\beta$ -catenin in different tissues (thymus, bone marrow and peripheral blood) have changed. It has been shown that the oncogenic variant of two differently functioning variants of LEF1 is increased in patients and WNT activated cell lines, while the tumor suppressor variant has been increased in healthy controls whose expression is reduced in patients and on stimulated cell lines.

**Conclusion:** As a result of this study, we have found that a large number of genes/pathways (e.g., spliceosomes, amino acid biosynthesis, leukocyte transendothelial migration pathways) that are not previously described in the literature, display abnormal expression and RNA sequencing is an informative approach in the light of tissue-specific gene expression. In order to elucidate the pathogenesis of T-ALL and to define new molecular markers, it has great importance to validate whole transcriptome findings with different approaches and a wider group of patients. This study was supported by Istanbul University Research Fund with a project number 20440.

#### PP-86

##### Long term side effects of childhood acute lymphoblastic leukemia therapy on bone mineral metabolism

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**Objective:** Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy and reduction in bone mineral density is one of the most common long-term side effects of therapy. The aim of this study is to compare bone mineral density of survivors of ALL with healthy controls and to evaluate bone mineral metabolism of this survivors.

**Methodology:** In this study we formed a study group of 39 ALL survivors (aged 6-24 years) who completed their treatment 2 years at least and a control group of 25 healthy children (aged 5-21 years). Patients who underwent bone marrow transplantation, patients with Down Syndrome, familial osteoporosis or secondary tumors and patients older than 25 years of age were excluded. For each participant, physical examination findings, history of daily calcium and vitamin D intake, sunlight exposure, physical activity, family history of osteoporosis, presence of bone pain and myalgia, history of fractures were recorded. For the study group, medical records were evaluated and the treatment protocol used, risk groups, translocations, immunophenotype, presence of relapse, CNS complications and use of radiotherapy were noted. Early morning fasting venous blood samples were taken from all the participants to test for biochemical parameters (Ca, P, ALP, Mg, K, Na, Cl, AST, ALT, albumin, glucose, cholesterol, triglyceride, urea, creatinine), hormone levels (FSH, LH, vitamin D, fT4, TSH, PTH, E2, cortisol, insulin, testosterone) and markers of bone mineral metabolism such as Cross Linked C-telopeptide of Type 1 Collagen (CTX), Cross Linked N-telopeptide of Type 1 Collagen (NTX), Soluble Receptor Activator of Nuclear factor- $\kappa$ B Ligand (s-RANKL), osteoprotegerin (OPG) and plasma leptin levels. Second void urine samples were tested for urinary Ca, creatinine, Ca/Creat ratio and NTX. Bone mineral density (BMD) was determined with DEXA of lumbar spine and femoral neck and sex and age specific Z scores were calculated using computer software. Study and control groups were compared with respect to these parameters. The study group was further divided into subgroups as high risk group (HRG), medium risk group (MRG) and standard risk group (SRG); due to their risk groups and radiotherapy received [(RT(+)) and RT nonreceived [RT(-)] according to use of radiotherapy. These subgroups were then compared.

**Results:** When we compare the patient and the control groups, there was no significant difference between groups in Z score BMD and markers of bone mineral metabolism (CTX, NTX, s-RANKL, OPG). Leptin levels were higher in the study group. There was no significant difference in bone mineral density, markers of bone mineral metabolism and leptin between patients who underwent RT and those who did not. There was no significant difference in NTX, OPG levels, BMD and z scores between risk groups but s-RANKL and CTX were significantly higher in the MRG compared to SRG

**Conclusion:** Although childhood ALL patients are at risk of reduction in bone mineral density, they can reach normal BMD with time. They must be followed until they reach their peak bone mass for fractures and appropriate treatment should be initiated if necessary.

## Lymphomas

### PP-87

#### Nivolumab experience in a patient with refractory Hodgkin lymphoma

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**Objective:** Hodgkin's lymphoma (HL) is a malign disorder with characterized by enlargement of the lymph nodes. It is curable in over 90% of patients in childhood using chemotherapy and radiotherapy. The prognosis of patients with relapsed/refractory HL is poor and median overall survival (OS) is just over 2 years. Nivolumab, is a programmed death-1 checkpoint inhibitor. Clinical studies demonstrated that Nivolumab is effective in the majority of relapsed/refractory HL. Here we present the case with refractory Hodgkin Lymphoma, who did not respond to conventional treatments and used Nivolumab.

**Case report:** Half of 12-year-old female patient was referred to our hospital with fever, fatigue, bone pain and weight loss. Her complaints started 3 months before admission to the hospital. Physical examination was revealed conglomerate lymphadenopathies of the right anterior and posterior cervical area, Hepatosplenomegaly was not detected. Bilateral supraclavicular, mediastinal right axillar, paracardiac, coeliac and mesenteric lymph nodes, right lung middle lobe and right 2nd costa were involvement in PET imaging. Excisional biopsy of cervical node revealed classic type of nodular sclerosis Hodgkin's lymphoma (HL). She was diagnosed stage IV-B HL and we started to therapy with COPP-ABV protocol. After 4 cures of treatment, cervical excisional lymph node biopsy was done and found neoplastic lymphoid infiltration compatible with Hodgkin's lymphoma. The progression of disease was observed under the treatment. We started ICE protocol and planned to minimize the progression of disease before autologous transplantation. After 3 cure of ICE therapy, PET was revealed relapse/refractory disease. Radiotherapy applied to the bilateral neck, mediastinum and abdomen. Brentuximab therapy has been added to ICE therapy because of progressive disease. After the first dose of brentuximab, encephalopathy was observed. Refractory disease cannot be controlled by conventional treatments. And we decided to give Nivolumab therapy.

**Methodology:** It was given 3 mg/kg/dose every 2 weeks. After two cures of the therapy, the disease stopped progressing and the patient's pain reduced. We did not observe serious side effects with nivolumab.

**Results:** We could give Nivolumab only 4 cures and she died because of pneumonia and progressive disease.

**Conclusion:** Although there are not enough data in children, successful results have recently been reported with nivolumab in refractory HL adults in clinical trials. In 12-year-old girl with refractory HL, we used nivolumab and did not observe a serious side effect during the treatment. We observed a decrease of patient's pain and reduced of the progression. We need more data for Nivolumab therapy in children with refractory HL.

## Red Cells

### PP-88

#### Severe hemolytic disease of the newborn due to incompatibility of the Rhc subgroup

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**Case report:** Following the introduction and widespread use of Rh-D immunoglobulin, the rate of fetal death associated with hemolytic disease of the newborn (HDN) diminished considerably which led to a relative increase in the non-RhD isoimmunisation as a cause of HDN. The 18-day-old female newborn infant born at term was referred due to anemia and

indirect hyperbilirubinemia. In her history, she received phototherapy due to indirect hyperbilirubinemia for about two weeks which was started within her second postnatal day. Additionally, she used phenobarbital due to hyperbilirubinemia. In her laboratory examinations at the time of admission, hemoglobin and serum total bilirubin levels were 6.0 g/dL and 11.4 mg/dL, respectively. Blood groups of the baby and mother were both O RhD positive, however, direct Coombs testing of the baby was 4+ and indirect Coombs testing of the mother was also positive. Further testing revealed the presence of anti-c antibodies in the maternal blood sample. Notably, the mother had history of erythrocyte transfusions many years ago. The patient was given intravenous immunoglobulin and erythrocyte concentrate (O RhD positive and Rhc negative). In her follow-up examinations, findings associated with hemolysis including direct Coombs positivity resolved completely.

**Conclusion:** Isoimmunization due to Rhc is very similar to that of RhD. Appropriate protocols to screen pregnant women for irregular blood subgroup antibodies may be advised to decrease perinatal morbidity and mortality due to such incompatibilities. In addition, matching erythrocyte concentrates not only for ABO and RhD, but also for certain Rh subgroups like Rhc routinely before RBC transfusions in premenopausal females may avoid the development of non-RhD antibodies.

### PP-89

#### Diffuse large B cell lymphoma of the scalp

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**Introduction:** Several systemic aggressive lymphomas may have cutaneous manifestations but they rarely arise from scalp as primary location. Herein, we present the case of a patient who had a diffuse swelling in the left side scalp since 4 months of duration and progressively enlarging in size.

**Case report:** A 59-year-old female patient presented to the department of dermatology at the University Hospital in Düzce in December 2017 with lesion 4x5 cm located in the temporal area of the head. The lesion was excised by plastic surgery, pathology was reported as fibroma. After 2 months, she re-admitted complaining of subcutaneous dispersed mass lesions with a maximal 8x7 cm diameters appeared at scalp. In her dermatological examination; there were nodular fixed lesions, firm in palpation with dimensions of 8x2 cm in the left temporal region and 4x3 cm, 7x6 cm in the frontal region. The patient was directed to the hematology department due to the result of biopsies taken from the lesions in the temporal region and frontal region with 5 mm punch. The immunohistochemical staining was compatible with non-Hodgkin's lymphoma, diffuse large B-cell. There were no B symptoms in system query or hepato-splenomegaly or palpable lymph nodes on physical examination. Routine blood investigations were normal. There was no disease that causes immunosuppression. PET/CT was performed and showed dispersed extracranial soft tissue masses but did not reveal any other evidence of systemic lymphoma. Chemotherapy was planned for 6 cycles of R-CHOP (rituximab, cyclophosphamide, adriamycin and methylprednisolone) due to the diagnosis of primary scalp lymphoma. Control PET CT after 4th cycle showed that the lesions completely disappeared.

**Discussion:** Diffuse large B cell lymphoma (DLBCL) is the most common form of non-Hodgkin's lymphoma accounting for more than one-third of all lymphomas. Although it usually manifests with nodal disease, it can arise in other tissues such as intestine, bone, breast, liver, lung, skin, and central nervous system. Primary cutaneous lymphomas are described as lymphomas restricted with dermal or epidermal areas. Scalp is not a common area of manifestation even for primary cutaneous lymphomas and only 9 cases of scalp lymphomas were reported in English literature. We presented a rare case of DLBCL arisen from subcutaneous tissue of scalp as rapidly growing mass lesions and disappeared after 4 cycles of systemic chemotherapy.



**PP-90****Diffuse large B cell lymphoma limited to spine**O. Yalici<sup>1</sup>, H. Tuğba Yel<sup>1</sup>, K. Öneç<sup>1</sup>, A. Önmez<sup>1</sup>, B. Öneç<sup>2</sup><sup>1</sup>Department of Internal Medicine, Duzce University Faculty of Medicine, Duzce, Turkey; <sup>2</sup>Department of Hematology, Duzce University Faculty of Medicine, Duzce, Turkey

**Introduction:** Diffuse large B cell lymphoma (DLBCL), which is the most common type of non-Hodgkin lymphoma (NHL), is usually presented with nodal disease and diagnosed with excision of lymph nodes. Non-Hodgkin lymphomas limited to bones are counts for less than 1% of all NHLs. Herein we present a case of DLBCL who admitted with a mass lesion at spine and there was no other nodal or extra-nodal involvement was described.

**Case report:** A 58-year-old man, with a history of coroner arterial disease admitted with complaints of back pain weakness in both distal extremities, which were worsening in last 2 months. Physical examination revealed that muscle strength was 2/5 at lower left extremity and 4/5 at lower right extremity but there was no other abnormal finding. Computed tomography revealed a lesion in L5 vertebra, causing compression fracture. The pathological examination of biopsy from vertebral lesion was consisted with DLBCL. Positron emission tomography (PET) showed loss of height at L5 with high involvement (Suvmax 7.3) and showed no other pathological findings. The stage was determined as 1E, and he was treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) with intrathecal prophylaxis. After the second cycle, his pain and lower limb weakness was completely resolved. He had no neurological symptoms but after fourth cycle, a new mediastinal lymphadenopathy developed and a second line therapy would be planned after confirmation.

**Discussion:** Primary bone involvement counts for less than 5% of extranodal lymphomas. On the other hand, lymphomas are counts for only 7% of all bone tumors. Spine is a rare region for lymphoma infiltration but it should be kept in mind that lymphoma is a curable disease and patient could be cured without remaining neurological defects.

**PP-91****Case report: concomitant myelodysplasia in a patient with syphilis**H.D. Dincyurek<sup>1</sup>, S. Cor<sup>1</sup>, N. Gözçü<sup>1</sup>, B. Güvenç<sup>2</sup><sup>1</sup>Department of Internal Medicine, Cukurova University, Adana, Turkey;<sup>2</sup>Department of Hematology, Cukurova University, Adana, Turkey

**Objective:** Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disease with the stepwise acquisition of oncogenic driver mutations in malignant clone. These mutations can be acquired de novo or arise after mutagenic therapy (e.g. Radiotherapy or chemotherapy). Nutritional deficiencies, some medications, zinc excess and HIV infection can induce dysplasia and/or cytopenias, therefore MDS should be distinguished from these entities. Here we report, diagnosis and treatment of latent syphilis in a patient with MDS.

**Case report:** A 54-year-old man was admitted to our hospital with complaints of bruising, rash, fever and joint pain. The biopsy taken from the skin was reported as compatible with the leukocytoclastic vasculitis. Autoimmune disease markers were negative. Due to ongoing bicytopenia (anemia and leukopenia) bone marrow aspiration and biopsy were performed. Dysplasia without blast increase was detected in the evaluation. Bone marrow cellularity was normal. TPHA and VDRL tests were sent and found to be positive. The TPHA test titer was 1/640-1/1280 with dilution. The patient was diagnosed with secondary syphilis and penicillin therapy was started. Treatment was continued with ceftriaxone, whose skin rash resolved but the complaint of fever persisted. Cerebral imaging and cerebrospinal fluid analysis found to be negative for neurosyphilis. Due to suspicion of latent infection immunosuppressive treatment could not be given despite myelodysplasia. Dysplasia continued in bone marrow aspiration performed six months after treatment. The patient was followed with erythrocyte transfusion dependence. Iron chelating therapy was applied.

**Conclusion:** The organism that cause syphilis may be related to the onset of dysplasia in bone marrow in our patient. Probably, because of the

development of latent infection, the findings dysplasia could not be reversed despite of antibacterial treatment.

**PP-92****The value of magnesium levels in the haemostasis of patients with beta-thalassaemia**N. Alieva<sup>1</sup>, A. Kerimov<sup>2</sup>, T. Mammadova<sup>2</sup><sup>1</sup>Republican Thalassaemia Centre, Baku, Azerbaijan; <sup>2</sup>Institute of Haematology and Transfusiology, Baku, Azerbaijan

**Background:** Studies showing that thalassaemia patients have a tendency for thrombosis have been published. This study was aimed to investigate the relationship between magnesium levels and hypercoagulation disorders of haemostasis in patients with different forms of  $\beta$ -thalassaemia.

**Methods:** The study involved 110 women aged 18-40 years with different clinical forms of  $\beta$ -thalassaemia (32 major, 28 intermedia and 50 minor). The diagnosis of  $\beta$ -thalassaemia was verified by haemoglobin electrophoresis and characteristic clinical manifestation. Serum levels of magnesium and thrombinemia markers D-dimer and soluble fibrin monomer complex (SFMC) have been identified. All of the patients had no clinical symptoms of hypercoagulation. The control group consisted of 30 healthy women of comparable age group. Statistical analysis was done by variation statistics via standard software packages.

**Results:**  $\beta$ -thalassaemia major ( $\beta$ -TM) and intermedia ( $\beta$ -TI) patients exhibited decreased levels of magnesium, respectively,  $0.73 \pm 0.04$  mmol/L ( $p < 0.001$ ) and  $0.74 \pm 0.07$  mmol/L ( $p < 0.001$ ), ranging between 0.21 to 1.53 mmol/L. Magnesium levels of individuals with  $\beta$ -thalassaemia trait ( $\beta$ -TT) were normal -  $0.84 \pm 0.02$  mmol/L, ranging from 0.80 to 1.1 mmol/L. Thrombinemia markers of  $\beta$ -TM and  $\beta$ -TI patients were increased: D-dimer -  $481.0 \pm 5.1$  ng/mL ( $p < 0.001$ ) and  $492.5 \pm 4.0$  ng/mL ( $p < 0.001$ ); SFMC -  $5.83 \pm 0.2\%$  ( $p < 0.001$ ) and  $6.0 \pm 0.3\%$  ( $p < 0.001$ ), respectively. Twelve  $\beta$ -TM and 9  $\beta$ -TI patients had hypercoagulation findings. Patients with latent hypercoagulation exhibited more expressed changes: mean magnesium levels of  $\beta$ -TM were  $0.65 \pm 0.03$  mmol/L ( $p < 0.001$ ), D-dimer -  $652.0 \pm 4.2$  ng/mL ( $p < 0.001$ ), SFMC -  $6.81 \pm 0.18\%$  ( $p < 0.001$ ); mean magnesium levels of  $\beta$ -TI were  $0.63 \pm 0.05$  mmol/L ( $p < 0.001$ ), D-dimer -  $680.0 \pm 7.1$  ng/mL ( $p < 0.001$ ), SFMC -  $6.9 \pm 0.4\%$  ( $p < 0.001$ ). No signs of latent hypercoagulation were detected in  $\beta$ -TT (no statistically significant difference with control values).

**Conclusion:** The plasma magnesium levels of  $\beta$ -TM patients was 1.6 times, and  $\beta$ -TI was 2.1 times less than control values. One-third of patients with  $\beta$ -TM and  $\beta$ -TI had latent hypercoagulation and lower magnesium levels. Based on our data, it can be concluded that, the low serum magnesium level of  $\beta$ -thalassaemia patients is associated with an increased thrombosis risk.

**PP-93****Clinical and hemostasis factors of the latent hypercoagulation in patients with iron deficiency anemia**N. Alieva<sup>1</sup>, A. Kerimov<sup>2</sup>, P. Safarova<sup>2</sup>, E. Asgerova<sup>2</sup><sup>1</sup>Republican Thalassaemia Centre, Baku, Azerbaijan; <sup>2</sup>Institute of Haematology and Transfusiology, Baku, Azerbaijan

It is known that thrombotic complications are most often diagnosed with the development of the first episode of thrombosis. Recently, appeared data on the association of a detectable low level of serum iron with an increased tendency to thrombosis in patients with various chronic diseases. Latent hypercoagulation was found in patients with iron deficiency anemia (IDA). Detection of clinical and anamnestic symptoms and signs characterizing latent hypercoagulation in patients on time- an urgent problem.

**Objective:** To investigate clinical, anamnestic and haemostasiological signs of development of latent hypercoagulability in patients with IDA.

**Material and methods:** 128 women with newly diagnosed IDA, aged 18-40 years (mean age  $29.1 \pm 7.6$  years) were examined. The control group consisted of 30 age-comparable practically healthy women of blood donors. The diagnosis of IDA was established in accordance with the recommendations of WHO. In patients, hemostasis parameters were determined: APTT, fibrinogen, XII-a callicrein-depended fibrinolysis, antithrombin III and protein C activity;



markers of thrombinemia-level of D-dimer, soluble products of fibrin and fibrinogen degradation, soluble fibrin-monomer complexes (SFMC). Patients, after obtaining informed consent, were examined by means of our questionnaire "Addiction to increased thrombogenesis" (AIT). The AIT questionnaire consists of 39 questions, reflecting clinical symptoms and anamnestic signs - risk factors for the development of latent hypercoagulation. According to the results of the response, the sum of the scores >30 was accepted for the propensity of the patient for hypercoagulation. The patients with IDA who were examined did not have clinically expressed thrombotic complications. Controls were comparable to the age of 30 healthy women of blood donors. The results of the study were analyzed by parametric methods of statistical analysis.

**Results:** As a result of the conducted studies, it was established that of the 128 patients with IDA in 40 (31.2%), the markers of activated intravascular coagulation were revealed. According to the detected thrombinemia markers, patients with IDA were divided into two groups: the 1st group - 40 patients with hypercoagulation (ie with positive D-dimer and SFMC tests); The second group of 84 (68.8%) patients without hypercoagulation (ie having test parameters of hemostasiograms not differing from normal ones).

when comparing these two groups, in 1st group patients comparing with 2nd, changes in some indices of hemostasis were detected. Thus, a decrease in APTT was observed  $30.1 \pm 1.9$  versus  $34.0 \pm 2.4$  sec ( $p < 0.05$ ), fibrinogen  $306.7 \pm 1.8 \pm 267.0 \pm 11.2$  mg/dL ( $p < 0.01$ ), RFMC  $6.32 \pm 0.4$  -  $4.80 \pm 0.5\%$  ( $p < 0.01$ ), D-dimer  $610.0 \pm 23.8$  -  $340.1 \pm 28$ , 2ng/ml ( $p < 0.01$ ), the fibrinolysis time (lysis time of the euglobulin clot) was prolonged  $8.4 \pm 0.2$ - $5.9 \pm 0.4$  ( $p < 0.01$ ).

The parameters of prothrombin time, thrombin time, INR in the 1st and 2nd groups did not differ. When analyzing the anticoagulant link of hemostasis, it was found that the activity of antithrombin III was lower in the 1st group of patients  $99.05 \pm 1.9$  versus  $108.0 \pm 4.2$  ( $p > 0.05$ ), while the activity of protein C, not differed and was identical to the control group. When comparing platelet levels of patients with hypercoagulation and without hypercoagulation, there were no statistically significant differences  $235.5 \pm 34.4$  compared to  $228.5 \pm 35.3$  ( $p > 0.05$ ).

**Conclusion:** Thus, as a result of our studies of female patients with IDA who did not have clinical thrombotic complications, hypercoagulable abnormalities in hemostasis were revealed. About one third of the examined women with IDA had a tendency to increased thrombogenesis - latent hypercoagulation. According to WHO, iron deficiency in the human body is one of the most wide-spread nutrient deficiencies in the human body in the world. In our opinion, information on the presence of thrombophilia in iron deficiency should be taken into account when determining the tactics of therapy for IDA patients.

#### PP-94

##### Hodgkin lymphoma developed after hematopoietic stem cell transplantation due to IL10R deficiency and Crohn disease

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**Introduction:** IL-10 inhibits the release of several key cytokines and thereby has a significant anti-inflammatory effect in the gastrointestinal tract. Mutations of the genes encoding IL-10 and/or IL-10R have been detected in very early onset-inflammatory bowel disease patients. These patients are usually unresponsive to immunosuppressive therapies. Allogeneic HSCT is the current curative therapy. IL-10R deficiency also predisposes to the development of lymphoma. Here, we report on the occurrence of Hodgkin lymphoma in child with IL-10R deficiency after bone marrow transplantation. **Case report:** A 8-years-old girl was referred for left cervical lymphadenopathy and persistent fever. Crohn's disease was diagnosed when he was examined for anal abscess at 1.5 months. Her past medical history was loaded with

frequent and severe infections. She was born at term with 2800 gr of birthweight, to first-degree consanguineous healthy parents. Her aunts were lost at early infancy of age due to unknown reasons. Very early-onset Crohn's disease suggested probability of inherited deficiencies of IL-10 or IL-10 receptor. A mutation at position c.G477A in exon of the IL10RB gene, resulting in a stop codon at position p.W159X of the corresponding protein product. Colostomy had to be done at first year. She underwent hematopoietic stem cell transplantation with 10/10 HLA (high resolution) matched related mother at 6 years of age. Counts of CD34+ cells were  $22 \times 10^6$ /kg. Neutrophil engraftment occurred at day +13. She was discharged at day +28. Chimerism was 100% in post-transplantation +17, +91, +180th days and +13th months. +19th months active chronic inflammatory mucosa with crypt abscess in the colon was detected. After 2 years of bone marrow transplantation, EBV DNA titer was increased in spite of two cycles of rituximab therapy. Hodgkin Lymphoma mixt cellular subtype (EBV LMP focal positive) stage IIB was diagnosed after cervical lymphadenopathy excision. After 4 cycles of ABVD chemotherapy and radiotherapy (19 Gy, bilateral cervical, mediastinum, hilus) full anatomic and metabolic response were achieved. The number of EBV DNA copies decreased 34786 to 62. She was following with remission, after 9 months cessation of therapy for Hodgkin Lymphoma.

**Discussion:** IL-10R deficiency predisposes to the development of a subtype of diffuse large B-cell lymphomas (DLBCLs) with germinal center origin characterized by original constitutive activation of the NF- $\kappa$ B pathway and a defective local T-cell immune response. Chronic intestinal inflammation is a known risk factor for the development of malignancies. Infection with Epstein-Barr virus (EBV) and long-term administration of immunosuppressive medication are also associated with a slight increase in the risk of lymphoma in young children with colitis and in adults with IBD.

In our case, despite the HSCT at 6 years of age, she was diagnosed as Hodgkin Lymphoma at 8 years. In the literature, data support early HSCT in patients with an impaired IL-10 pathway; this procedure is able to cure inflammatory bowel disease and may well prevent the occurrence or recurrence of lymphoma.

**Conclusion:** Further work will be needed to fully elucidate the IL-10R pathway's protective effect, relationship between IL-10R deficiency and the development of lymphomas; and treatment results.

#### PP-95

##### Concurrent myelomatous pleural effusion and extramedullary mediastinal involvement as relapse manifestation of multiple myeloma

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**Introduction:** Pleural effusion directly attributable to multiple myeloma (MM) is exceedingly rare (1–2% of cases). Myelomatous pleural effusions may arise from either; extension of plasmacytomas of the chest wall, invasion from adjacent skeletal lesions, direct pleural involvement by myeloma (pleural plasmacytoma) or following lymphatic obstruction secondary to lymph node infiltration. We present a case of pleural effusion arising rapidly in a patient with serologic responsive MM and found to be a myelomatous effusion with mediastinal mass lesion.

**Case report:** A 85-year old woman with longstanding IgG kappa MM presented with new developing gradually increasing dyspnoea. Physical examination revealed pallor, tachypnea and respiratory sound weakening. She was on 7<sup>th</sup> cycle of bortezomib based treatment protocol and seemed to be serologically in very good partial response. Chest radiography showed a large right sided pleural effusion. Blood investigations revealed the following values: hemoglobin, 7.4 g/dL, total protein, 10.78 g/dL; albumin, 2.72 g/dL; M protein: 0.1 g/dL, creatinine: 1.3 mg/dl. The serum free light chain ratio: 7.6. Computed tomography of the thorax showed right sided pleural effusion (6 cm) and a mass lesion in the anterior mediastinum sized 7x4cm with a SUDmax 12.0 on PET-CT. Pathology and immunohistochemistry of the pleural

biopsy showed plasma cells with immunohistochemical staining including CD138 and kappa positivity. A chest tube is inserted through the chest wall into the pleural space and evacuation of fluid resulted improvement of dyspnoea. While the patient is serologically significant responsive management plan was made to extramedullary involvement. Radiotherapy to mediastinal mass lesion and intrapleural anti-MM treatment was decided. Bortezomib was given in the usual dose as 1.3 mg/m<sup>2</sup> through the chest tube. The patient is stable and continued to complete radiotherapy. Maintenance with an anti MM drug is planned.

**Conclusion:** Congestive heart failure secondary to amyloidosis, chronic renal failure, nephritic syndrome secondary to renal tubular infiltration with paraprotein and development of glomerular damage, direct infiltration of pleural fluid from adjacent tissues, hypoalbuminemia, pulmonary embolism, infection, secondary neoplasm, lymphatic drainage obstruction by plasma cell infiltration and pleural may etiologic factors in myelomatous pleural effusions. The outcome with new drugs is still obscure due to its rarity. For our patient, it seems to emerge from a refractory clone to the used treatment protocol.

#### PP-96

##### The role of HLA-DR supertypes in childhood acute lymphoblastic leukemia

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**Background:** The association between HLA class II alleles and childhood leukemia have been reported in a number of studies. This could be due to the role of HLA allele-restricted peptide binding and T cell activation, or linkage disequilibrium to an MHC-linked “leukemia gene” in the pathogenesis of childhood leukemia. HLA-associated susceptibility to childhood acute lymphoblastic leukemia (ALL) may provide clues to leukemogenesis in general and to the role of other risk factors.

**Aim:** Our study aimed to determine the association between the HLA-DRB1, HLA-DRB3, DRB4, DRB5 supertypes and susceptibility to ALL in children.

**Materials and methods:** This study included 86 high risk pediatric ALL patients who were consecutively admitted to the Pediatric Hematology Unit of Istanbul Medical Faculty and Yeni Yüzyıl Medical Faculty 100 healthy volunteers as a control group. Molecular HLA-DRB typing for patients and controls using the sequence-based typing (SBT-Invitrogen-SeCore Kit) was performed. The age range of patients was 2-17 years. A total of 86 patients were recruited (62 males and 24 females; sex ratio=2.58). In the control groups, the age range of was 20-35 years. The healthy control group was from the same geographical area. In brief, the 86 patients were diagnosed as childhood (≤17 years) ALL and the age mean of healthy controls was 25.28 years.

**Results:** The HLA-DRB1\*04, DRB1\*07 alleles were significantly more common in patients with ALL disease (34.3%, 16.9%) than the healthy control group (18.0%, 9.5%) (p<0.0001, p=0.035 respectively). The HLA-DRB1\*11 (21.5%) allele was significantly more common in healthy control group than the patient group (11.0%) (p=0.007). Homozygosity rates for supertypes were also compared between patients and controls. The genotypic homozygosity rates for DR53 (DRB1\*04, DRB1\*07, DRB1\*09) in patients and healthy control group were 24.4% and 4.0% respectively (p<0.0001). 21 out of 86 and 4 cases in control group were having DRB3 homozygote. In patient group, 13 out of 62 male patients were DRB3 homozygote, 8 out of 24 female patients were DRB3 homozygote (p=0.002). In control groups, there were no DRB3 homozygote in 36 male and 4 out of 64 females were DRB3 homozygosity.

**Conclusion,** The HLA-DRB1\*04 and \*07 alleles as DRB4 supertypes appear to be a susceptibility factor for the acquisition of childhood ALL and it may affect

the age of onset of ALL. However, further larger studies are needed to support the conclusions drawn from this study.

#### PP-97

##### Multiple red blood cell alloantibodies after blood transfusions in a nonhematologic patient

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**Introduction:** Factors implicated in red cell alloimmunization include recipient sex and age, history of pregnancy, number and timing of blood transfusions, recipient clinical diagnosis and treatment, genetic factors related to the antigenic response, and racial differences between donors and recipients. The prevalence for alloimmunization in patients, who receive incidental transfusions, and/or pregnant women is rare as between <1-3%. Patients with unexpected blood antibodies may be at increased risk for delayed transfusion. We herein report a case in which a patient who had shown a negative response in the first preoperative unexpected antibody screening test was given a blood transfusion for intraoperative bleeding and who later developed allo antibody.

**Case report:** A 73-year-old female patient presented to our hospital with chronic hip wound infection following a total hip arthroplasty. She experienced two surgical intervention and required transfusion 10 years apart. That time she underwent superficial irrigation and debridement for drainage. She received cross matched compatible 7 units packed red cells. At 6<sup>th</sup> day she developed subicter and fever. Her hemoglobin level was decreased (Hgb 10.2 to 6.2 g/dl), serum LDH and indirect bilirubin was increased (1270U/L and 2,1mg/dL respectively). Forward laboratory investigation revealed hemolytic anemia consistent with immune hemolytic anemia. The patient was placed on folic acid and methylprednisolone. Alloantibody screening showed multiple allo antibodies (Anti-Le<sup>a</sup>, Anti-E, Anti-C, Anti-S, Anti-Jk<sup>b</sup>). Her condition was interpreted as an ongoing delayed immune haemolysis. Supportive treatment and to devoid any new transfusion was recommended.

**Conclusion:** Other than ABO antibodies most other clinically significant red cell antibodies are immunoglobulin G (IgG) type and produced in response to immunization by antigen-positive red cells. Either donor red cells following transfusion or cells of fetal origin, following fetomaternal hemorrhage during pregnancy or at parturition. The antigens most frequently involved in alloimmunization belong to the Rh, Kell, Kidd, Duffy, Lewis and MNS blood group systems. Our patient had developed antibodies against multiple blood system antigens (Lewis, Rh, MNS, Kidd) which is unpredictable and rare. Because red cell antibody tests after transfusion are not routinely performed, many antibodies may (not) be detected at the time of a new transfusion event, posing the transfusion recipient at risk for transfusion delay or a (delayed) hemolytic transfusion reaction. Routine antibody screening at set time intervals after transfusion would reduce these risks.

#### PP-98

##### Cancer-associated thrombotic microangiopathies for refractory thrombotic thrombocytopenic purpura differential diagnosis

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Thrombotic microangiopathies (TMA) are a group of disorders characterized by disseminated occlusive microvascular thrombosis, thrombocytopenia, and ischemic end-organ damage, most commonly in kidneys and brain. Thrombotic thrombocytopenic purpura (TTP) is one of the TMAs related to a severe deficiency of ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13 activity; ≤10%). TTP patients are in general young, and female. Pathophysiologically, 75% of them have anti-

ADAMTS13 IgG, and 3% have inherited disease (Upshaw-Schulman syndrome) with mutations of the ADAMTS13 gene. In 22% of TTP patients the cause could not be documented. We report a male patient presenting with backpain and TMA who was not responsive to prompt plasmapheresis.

**Case report:** A 49-year-old man presented with back pain and fatigue for which he could not depict a duration time. He was pale and exhausted. A few echymoses were remarkable. No hepatosplenomegaly was palpated. Neurological examination was normal. Laboratory investigations revealed significant thrombocytopenia (10,000/ $\mu$ L) and severe microcytic anemia (6.4g/dL) with mild neutrophilic leukocytosis (11,200/ $\mu$ L). Serum creatinine, liver function tests, PT, aPTT and serum fibrinogen level were within normal levels. Serum LDH, indirect bilirubin and alkaline phosphatase levels were increased. Polychromasia and schistocytes were found on peripheral blood smear. Work up for hemolysis was positive, direct Coombs test was negative. With suspicion of TTP, methylprednisolone 1 mg/kg/day was given intravenously initially, and plasma exchange was started with 1.5 plasma volume exchanges and using fresh frozen plasma. Packed red blood cells were transfused and folate was supplemented. Severe thrombocytopenia and elevated LDH level persisted despite consecutive seven daily plasma exchange. Second line treatment was planned with Refractory TTP diagnosis. Serologic screening for HIV, hepatitis B and hepatitis C was proved to be negative. That time ADAMTS13 activity test result excluded TTP which were within normal. He had no drug history related with TMA and no clinical picture indicating systemic lupus erythematosus or antiphospholipid syndrome. Plasma exchange was ceased. Malignancy-associated TMA was suspected. CT scan showed gastric wall thickening with intraluminal prominence. Endoscopic biopsy revealed gastric cancer with signet-ring cell carcinoma histology.

**Conclusion:** Refractory TTP diagnosis should be made carefully before deciding second line treatment modality. Occasionally, TMA is the first manifestation of an occult cancer, and in large series approximately 3% of patients who were originally diagnosed with TTP, were in fact harboring an occult malignancy. TMA occurs in association with a variety of malignancies, especially adenocarcinomas. Presentation may be either at an early stage of cancer or associated with disseminated disease. ADAMTS13 activity is not significantly reduced in these patients.

#### PP-99

##### **Pseudo tumor cerebri associated with cyclosporine: a use for graft versus host diseases prophylaxis**

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**Introduction:** Direct association between Cyclosporine -A (CsA) use and Pseudo Tumor Cerebri (PTC) is rarely reported. We report a patient who underwent allogeneic BMT for high risk acute myeloid leukemia (AML) and developed PTC after CsA use for GVHD prophylaxis.

**Case report:** The patient is a 42-year-old female who underwent allogeneic 2nd BMT for relapsed AML from her sibling in May 2017. She was immunosuppressed with CsA. The patient was admitted to our service in July 2017 complaining of intense pulsing headache for a week, associated with vomiting, intense retroocular pain, diplopia, and photophobia. On ophthalmic examination, bilateral papilledema was observed. In view of the possibility of an expanding intracranial process, cranial magnetic resonance imaging was performed and evidenced no structural alteration Lumbar puncture was not performed because of the patient refusal. The presence of papilledema with a normal imaging exam, suggested PTC secondary to the use of CsA. The suspicion of PTC led to discontinuation of CsA and introduction of therapy with acetazolamide at 250 mg b.i.d. dose. The patient was discharged from the hospital after two weeks with a significant improvement of his visual complaints. After three months, complete resolution of the papilledema was observed.

**Discussion:** PTC is a syndrome characterized by the presence of intracranial hypertension with normal CSF findings and normal brain imaging. CSF aspiration should be performed after intracranial masses have been excluded

with MRI and is crucial of the diagnosis of PTC. The pathogenesis of PTC is still unknown, but it seems to be related to CSF hypersecretion or poor absorption, cerebral edema, and elevation in the cerebral venous pressure. The clinical manifestations of PTC are headache, nausea, vomiting, decrease in visual acuity, fatigue, diplopia, transient visual obscuration, strabismus and photophobia, and pulsatile tinnitus. Papilla edema occurs in 50% to 100% of the cases, can be asymmetric, and can result in visual loss. Many factors such as hematologic disorders, obesity, female sex, endocrine disorders, respiratory infections, viral, bacterial, systemic diseases and medications have been proposed as causes of PTC. Medication related PTC is generally associated tetracyclines, ciprofloxacin, nitrofurantoin, cytarabine, levothyroxine, amiodaron, lithium. CsA can be associated with serious side effects including paralysis, confusion, lethargy, depression, anxiety, insomnia, hallucinations, convulsions, aphasia and headache. The mechanism of CsA related PTC is unknown. CsA seems to cause neuro and microvasculopathy with optic nerve damage and papilledema. There is no established relation between serum CsA levels and PTC. Treatment consists incessation of CsA or drug replacement, with consequent improvement in visual acuity and decrease in intracranial pressure after some months. In rare cases with progressive symptoms decompressive lumbar puncture and diuretics, corticosteroids may be needed. Prognosis is usually good, but a small group of patients may have severe visual loss. In summary, cyclosporine must be added to the list of medications with a known association with pseudo tumor cerebri.

#### PP-100

##### **Case report of dasatinib related pleural effusion responding colchicine**

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**Introduction:** Dasatinib is a second-generation tyrosine kinase inhibitor (TKI) used in the treatment of imatinib-resistant CML. Pleural effusion (PE) seen in 14-39% of cases and the most common side effect causing dasatinib to be withdrawn or replaced. While there is no algorithmic guideline recommendation for PE management, the use of different TKI, dose reduction, steroid and diuretic use is recommended in PE treatment. Colchicine is a microtubule stabilizer agent used in the treatment of FMF, especially with serositis. Here, we report a case in which the patient was transferred to dasatinib due to imatinib resistance and grade 2-3 PE was developed in the first 3 months of treatment and PE was totally treated with the addition of colchicine.

**Case report:** A 37-year-old female patient was admitted to our clinic due to response loss under imatinib therapy. Imatinib treatment was discontinued and 1×100 mg/day dasatinib treatment was started. Routine controls performed at the 1st month of dasatinib treatment showed bilateral grade 3 pleural effusion and erythema nodosum-like rashes. Diuretic therapy was added to treatment for 1 week. After resolution of PE, same dosage re-administered. After 15 days grade 2 pleural effusion re-occurred. Colchicine which is very effective in treatment of FMF serositis, 0.5 mg 3 times/day added to treatment. The patient followed up closely. Although diuretics and steroids were not given there was a rapid improvement in the patient's complaints and a complete recovery in the control radiographs. Dasatinib was administered 1×100 mg and colchicine 0.5 mg/day, and no significant side-effect observed after 3 weeks.

**Conclusion:** The presence of PE which is due to immunomodulatory effect of dasatinib, considered as good prognostic factor for CML disease control. There is no literature for using colchicine in PE management but the fact that colchicine is effective in autoimmune FMF serositis, suggested that it may also be effective in the treatment of PE which occurred similar mechanism. As in our case, addition of colchicine to dasatinib first 1.5 mg/day and after effusion resolution 0.5 mg/day without reducing dasatinib dosage, was quite effective in managing PE. Combination of colchicine with dasatinib appears simple, achievable solution for the most common side effect that caused dasatinib withdrawal. The effect of colchicine on lymphocytes and the possibility of causing a loss of response in CML is an important issue. The results of a wider series of cases are needed in this regard.

**PP-101****Thalassemia prevention in Azerbaijan: what have we achieved so far?**

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**Objective:** Azerbaijan has long been known for high prevalence of thalassemia. The high incidence rate and poor quality of life necessitated a state intervention for prevention of the disease and for provision of quality care to the patients with thalassemia. These processes have been regulated by the “Law on State Care of Patients with Hereditary Blood Disorders”, adopted in 2005. Since then, substantial work have been done to ameliorate the care of these patients. Subsequent step was the approval of the “State Program for Thalassemia Prevention” stipulating the initiation of the compulsory countrywide premarital screening followed by genetic counselling and prenatal diagnosis of identified carrier couples. In this report, we present 3-year results and achievements of the prevention program in Azerbaijan.

**Methodology:** Since June 2015, according to new regulations, all couples applying for civil marriage record were required to be screened for thalassemia. Samples with MCV and MCH values below 80 fL and 27 pg, respectively, were further evaluated by capillary electrophoresis. Identification of variant hemoglobins were confirmed by high performance liquid chromatography. Couples, in which both partners were identified as carriers of clinically significant hemoglobinopathies, were referred to genetic counselling and prenatal diagnosis. Molecular testing of HBB and HBA gene mutations were performed by reverse dot blot hybridization and sequencing techniques.

**Results:** From a total of 430,668 individuals (population of Azerbaijan – 9,911,646) screened during the 3-year period (June 2015 to June 2018), 15,997 were identified as carriers of  $\beta$ -thalassemia (3.71%). 7.0% and 7.4% of screened couples did not apply for civil marriage record in 2016 and 2017, respectively. Both partners were identified as carriers in 159 at-risk couples. 32.2% of at-risk couples were in consanguineous marriages. Prenatal diagnosis was carried out on 76 fetuses; 14 of them were healthy, 43 were heterozygous, and 19 were identified as homozygous/compound-heterozygous. All affected pregnancies were terminated. Codon 8 [-AA] – 38.4%, IVS-II-1 [G>A] – 14.7%, IVS-I-110 [G>A] – 9.8%, Codon 8/9 [+G] – 7.1%, and Codon 44 [-C] – 5.8%, were the most prevalent HBB gene mutations among the couples referred to prenatal diagnosis. The incidence rate of  $\beta$ -thalassemia major/intermedia was 1.76 per 100,000 persons in 2014, while it was 1.11 in 2017, and it is projected to be 0.89 by the end of 2018. Overall, the incidence rate of  $\beta$ -thalassemia has been significantly decreased since the program was started

**Conclusion:** The initiation of prevention program raised public awareness of thalassemia in the country. Together with media coverage, screening of more than 4% of the population, randomized across the country, had a substantial influence on public awareness. The gap between the numbers of couples applying for the screening and the ones applying for civil marriage record could be explained by possible relinquishment of intention to marry, following revelation of the risks. Unfortunately, substantial proportion of at-risk couples were in consanguineous marriages, which is considered as one of the very strong contributors to high incidence of thalassemia in the region. Nevertheless, the prevention program achieved a significant decrease in incidence rate of  $\beta$ -thalassemia in the last 3 years.



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CLINICAL AND LABORATORY STUDIES

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