ARCHIVES OF HELLENIC MEDICINE: ISSN 11-05-3992

ABSTRACTS

ARCHIVES OF HELLENIC MEDICINE 2015, 32(Suppl 1):17–49
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2015, 32(Συμπλ 1):17–49

ACUTE MYELOID LEUKEMIA

P01

EFFECT OF THE CALCIUM CHANNEL BLOCKER VERAPAMIL ON CELL CYCLE AND APOPTOSIS IN AML CANCER CELL LINES (HL-60)

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Objective: The drugs that are used in the chemotherapeutic treatment of cancer are quite toxic effects on target cells. To this end, giving specific doses of verapamil to the HL-60 AML cell line and apoptosis and cell cycle was evaluated.
Methods: HL-60 AML cell line was selected in this study. This cell line containing 10% FCS with 1% penicillin and streptomycin produced sub cultured in RPMI-1640. The effective dose (viability value) was determined by MTT method by 10, 30, 50, 80 μM of giving increasing doses verapamil to the HL-60 cell line 24 hours incubation. Determined the effective dose of verapamil, given to HL-60 cells, cycle and apoptosis were examined by flow cytometry. In Saline with HL-60 cells were used as control.
Results: Verapamil (50 μM) lead to increased programmed cell death ratio at the 24.hours compared to control and this result was statistically significant ($p < 0.05$). Diploid cell cycle verapamil untreated group in G1 phase decreased according to verapamil treated group and a significant increase in S phase formed a significant difference ($p < 0.05$), but formed no significant difference ($p > 0.05$) in G2 phase. When the ratio of aneuploid cells in the G1 phase of verapamil untreated group compared to the group administered with verapamil creates increased a significant difference ($p < 0.05$). Decrease in S phase does not constitute a significant difference ($p > 0.05$).
Conclusion: The first main control point is DNA damage censor in the transition of G1/S phase. In the early to mid-G1 phase of damaged cells in the G1 phase are hanged back, damaged cells in late G1 phase, will continue in the S phase. Thus, cell G1/S transition of the cell phase ratios we have achieved with verapamil is arrested synchronization, which is consistent with this information. Combining verapamil with other chemotherapeutic drugs may result in increasing effect in AML treatment.

P02

ACUTE MYELOID LEUKEMIA RELAPSING AS GRANULOCYTIC SARCOMA OF THE UTERINA CERVIX: A CASE REPORT

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Introduction: Granulocytic sarcoma (GS) is defined as a tumor mass composed of immature myeloid cells localized in any extramedullary site. GS can be isolated or encountered during the course of acute myeloid leukemia (AML), myelodysplastic syndrome or chronic myeloproliferative neoplasms. It may be detected coexistent with the initial diagnosis of these diseases or may be seen in the relapse or as the first sign of the disease relapse. We present the case of a patient whose disease relapsed as GS of the uterine cervix.
Case: A 63-year-old female AML diagnosed patient who was given radiotherapy for 2 days after the cervix uteri cancer prediagnosis, followed for 1,5 years in remission, applied to hematology department with complain of dysuria. In the blood count leukocyte 61400/uL, hemoglobin 10.2 g/dL, platelets 24000/Ul, in the biochemical analysis, urea 150 mg/dl, creatinine 2.5 mg/dL, LDH 1179 U/L, and in the peripheral blood smear, 60% myeloid and monostoid blasts were detected. In the all abdominal MRI, a rectum and bladder invasive mass which infiltrated the cervix uteri completely were detected. Endocervical curettage biopsy (MPO and CD117 positive, CD34, TDT, Ki67, HPV, p53 negative) was compatible with GS and in the bone marrow biopsy 95% blasts was detected and the patient was diagnosed with relapse AML accompanied by GS. Idarubicin+Ara-C induction chemotherapy was initiated and the patient died of sepsis on the 24th day of chemotherapy.
Conclusion: Clinically the incidence of GS in AML is 3–5%.The presence of GS is associated with a generally poor outcome and a shorter overall survival. GS can be found in almost any organ: the most common sites of involvement are bones, soft tissues, lymph nodes, skin, gastrointestinal tract. GS of the uterine cervix is very rare. MPO is the single most sensitive and specific antibody for detection of myeloid differentiation.

P03

A CASE REPORT: GRANULOCYTIC SARCOMA WHICH CAN BE CONFUSED WITH HISTIOCYTIC SARCOMA

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Introduction: Granulocytic sarcoma is a solid tumor formed by granulocyte precursors outside of bone marrow. Granulocytic sarcoma may manifest as a sign of acute myeloid leukemia (AML). In this case report, the patient we aimed to present was firstly diagnosed with histiocytic sarcoma after undergoing a biopsy, later he underwent a lymph node biopsy from the neck area to confirm this diagnosis, which resulted in granulocytic sarcoma.
Case: A 58-year-old male patient who was diagnosed of histiocytic sarcoma after tonsillectomy. The patient consulted us. Blood count results were as follows: leukocyte 7330/uL, hemoglobin 14.5 gr/dl, thrombocyte 314000/uL. Biochemical analysis resulted was normal. Peripheral blood smear test did not reveal any atypical cells, however during bone marrow biopsy 3-4% immature cells were detected. In the PET-CT, lymph node located in the left-cervical section was considered. After excision, positive staining with myeloperoxidase (MPO), CD68, CD34 and CD56 markers confirmed the diagnosis of granulocytic sarcoma. The patient was administered idarubicin + cytosine arabinoside protocol. Upon detecting a progression in the following thoracic CT scan the patient was administered high dose cytosine arabinoside + idarubicin protocol. The mass regressed. However, after this therapy the patient died from opportunistic fungal infection.
Conclusion: Granulocytic sarcoma may occur in relation with AML. It is involved with central nervous system, skin and lymph nodes. It is a sign of poor prognosis for 2-14% of patients suffering from AML. Very occasionally it does not accompany AML, in our case bone marrow biopsy resulted with a myeloblast ratio of 4% and thus AML was not present. In our case, during cervical LAM biopsy MPO, CD68, CD34 and CD56 markers were confirmed and thus the patient was diagnosed with granulocytic sarcoma.

P04

BILATERAL SIXTH NERVE PALSIES POSSIBLY ASSOCIATED WITH ARSENIC TRIOXIDE IN ACUTE PROMYELOCYTIC LEUKEMIA

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Introduction: Herein, we reported an 30-year-old patient with acute promyelocytic leukemia (APL) who was treated with low-dose all trans retinoic acide (ATRA) and arsenic trioxide (ATO) because of bilateral sixth nerve palsies possibly associated with arsenic trioxide achieving molecular complete remission.
Case: A 30-year-old female patient was admitted to our department in November 2014. Pancytopenia was identified in this patient. Bone marrow aspiration biopsy was reported as acute myeloid leukemia. RT-PCR showed the proportion of fusion gene PML-RARα was positive (53%). Diagnosis of APL was confirmed and treatment was started. She developed sudden blurred vision and diplopia. She developed an isolated bilateral 6th nerve palsies, more prominent on the left side, which were at onset suspected to be caused by isolated leukemic infiltration. The cerebrospinal fluid examination and brain MRI were performed in terms of nerve involvement and resulted normal. So 6th nerve palsies were considered to be caused by a drug reaction. ATRA and ATO treatment was stopped and she was followed. Her complaints improved. She was treated with ATRA at 40mg/day for 15 days and idarubicin at 5mg/m^2 for 4 days per week. Consolidation treatment with ATRA has been continued seamlessly therefore adverse ocular reaction was considered to be possibly associated with arsenic trioxide.
Conclusion: Treatment with ATO is alarming to patients and physicians alike due to the broad adverse effect profile. Unexplained strabismus and diplopia should be evaluated as a potential sign of CNS involvement and initially conventional imaging and cerebrospinal fluid examination should be performed. If CNS involvement of APL is not detected, abducens nerve palsy can be considered to be caused by a drug reaction. Herewith a thorough understanding of the safety and potential side effects of ATO as a therapeutic agent is necessary, in order to minimize its toxic complications.

P05

CLINICAL ANALYSIS OF 11 PATIENTS WITH MYELOID SARCOMA AS A SINGLE CENTER EXPRIENCE

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Objective: Myeloid sarcoma (MS) represents the proliferation and accumulation of myeloblasts at extramedullary sites. While extramedullary involvement in acute myeloblastic leukemia (AML) is uncommon in itself, MS without any bone marrow involvement are extremely rare and has a diagnostic and therapeutic challenge. Here, we presented the clinical features, diagnosis, treatment modality and results of MS patients as a single center experience.
Methods: This study included evaluation of 11 patients with MS from March 2010 to January 2014, retrospectively.
Results: Seven of 11 patients were male 4 were female. Median age was 41.0. The patients were presented with the involvement of L3-SI vertebra (1), conjunctiva (1), eye lid (1), lower cervical region (1), skin (1), testis (1), inguinal region (2), and pharynx (3). Chronic

myeloid leukemia was developed after MS was diagnosed and 2 months later accelerated to blastic phase in 1 of 11 patients. He was treated with combined chemotherapy regimens, after achieving complete remission HLA identical unrelated bone marrow transplantation (BMT) was performed. But He was died related to chronic graft versus host disease and pulmonary aspergillosis 6 months later after BMT. Among 11 patients 6 were treated with chemotherapy, 2 chemotherapy plus radiotherapy, 5 patients were treated without chemotherapy, but treated with surgical resection. Of 3 of 11 patients were follow out after diagnosis of MS. Chemotherapy regimen was combined with idarubicine and cytarabine similar to AML. The average survival time of MS patients treated with or without chemotherapy were 19 and 11 months respectively, suggesting prolonging of survival time of patients treated with chemotherapy. The average survival time of MS patients treated with chemotherapy plus radiotherapy was 23 months, better than chemotherapy alone and without chemotherapy. Moreover one patient who was treated using chemotherapy combined with BMT is not alive now, living times was 26 months.

Conclusion: We found that chemotherapy similar as treatment of AML can decrease the probability of disease progressing into bone marrow abnormality, and if chemotherapy combines with radiotherapy and bone marrow transplantation, the survival time of MS patients can be longer. More research is necessary to elucidate the molecular pathogenesis of MS, its prognostic impact, and optimal treatment modalities.

P06

EXPRESSION PROFILING OF A PANEL OF APOPTOSIS-ASSOSSIATED MICRORNAS IN ACUTE MYELOID LEUKEMIA IDENTIFIES DIFFERENTIALLY EXPRESSED MICRORNAS THAT TARGET EPIGENETIC MODIFIERS

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Objective: Identifying molecular aberrations in Acute Myeloid Leukemia (AML) is still an unmet research target. We evaluated the expression of a panel of apoptosis-associated microRNAs (miRNAs) in leukemic blasts isolated from AML patients and investigated their predicted targets.

Methods: We used bone marrow or peripheral blood that were donated by eight AML patients (5 male, 3 female) at diagnosis. Mononuclear cells were isolated by Ficoll-Histopaque (Sigma Aldrich) density gradient centrifugation and were cryopreserved in liquid nitrogen at the Cancer Biobank Center of the University of Ioannina. MicroBeads technology was used for magnetic cell sorting of CD34+ cells of patients' samples, while mononuclear blood cells from healthy individuals were used as controls. Small RNA (<200 b) was isolated using the NucleoSpin® miRNA kit (Macherey Nagel). Simultaneous quantification of 84 apoptosis- associated miRNAs was performed by using the miScript miRNA PCR Array Human Apoptosis (MIHS-114ZF, Qiagen) in a LightCycler® 480 instrument (Roche AG, Rotkreuz, Switzerland), and relative quantitation of expression was determined by the comparative CT method. For miRNA target prediction we used the RNA22 tool: http://cm.jefferson.edu/rna22v2 and http://cm.jefferson.edu/rna22v2.0.

Results: We found 51 downregulated and 12 upregulated miRNAs compared to control. Among the downregulated miRNAs was the miR-29 family and among the upregulated was the miR-181 family, both of which have been previously implicated in AML. The top 10 downregulated miRNAs were miR-31-5p, miR-451a, miR-144-3p, miR-29b-3p, miR-204-5p, miR-9-5p, miR-409-3p, miR- 542-3p, miR-29c-3p and miR-29a-3p, whereas the top 10 upregulated miRNAs were miR-186-3p, miR-149-3p, let-7c-5p, miR-222- 3p, miR-214-3p, miR-181c-5p, miR-181a-5p, miR-181b-5p, miR-34a-5p and miR-181d-5p. Deepest downregulation (over -50fold) was seen for miR-144-3p, miR-451a and miR-31-5p. We used RNA22 to identify genes that are predicted to be simultaneously targeted by all of the 10 top downregulated miRNAs and also the genes that are predicted to be simultaneously targeted by all of the 10 top upregulated miRNAs. The predicted targets for all top 10 downregulated miRNAs include NSD1, KAT6B and SACS. NSD1 is an histone methyltransferase, whereas KAT6B is an histone acetyltransferase. The predicted targets of all top 10 upregulated miRNAs include 36 genes among which are DICER1, ZNF507, ZNF704 and MLLT6.

Conclusion: A variety of microRNAs are dysregulated in patients with AML. We confirm that the miR-29 family and the miR-181 family have altered expression in AML. Among predicted targets of the downregulated miRNAs are genes involved in chromatin remodelling, suggesting that altered function of epigenetic modifiers in AML may be due to dysregulation of miRNAs.

MYELODYSPLASTIC SYNDROMES & PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

P07

RETROSPECTIVE EVALUATION OF DEMOGRAPHIC AND CLINICAL FEATURES OF PATIENTS WITH MDS: SINGLE CENTER EXPERIENCE

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Objective: Myelodysplastic syndromes are heterogenous disease and have complex clinical presentation. Clinical and demographic data of 158 patients with Myelodysplastic Syndrome (MDS) followed in Ege University School of Medicine Department of Hematology, were analyzed retrospectively.
Methods: Those patients who were followed-up with the diagnosis of MDS, were evaluated in terms of their ages, genders, complaints and laboratory values based on their files.
Results: The average age at the time of diagnosis was 66 years old. While 79 of them were male, 79 cases were female. 27.2% (43) of the patients were in low risk MDS group, 48.7% (77) were intermediate-1, 9.5% (15) were intermediate-2 and 4.4% (7) were patients with high risk MDS according to IPSS. 50% (79) of patients had RA, 13.3% (21) had RAEB-2, 3.2% (5) had RARS, 8.9% (14) had RAEB-1, 19,7% (31) RCMD, 3.8% (6) had RT and 5q syndrome and 9.5% of patients had secondary MDS. Twenty-nine of the 114 patients that were checked for cytogenetic analysis, had abnormal cytogenetic. For the cytogenetic analysis; 12 patients had 5q deletion, 9 patients had trisomy 8, 3 patients had 20 q deletion, 7 patients had 7 q deletion and 3 patients had RB1gen (13q14) mutations were observed. Median survival was calculated as 24 months. During the follow up period, 10 patients progressed to AML. Twelve percent (19) of the 158 patients died during the follow-up period. Disease progression and infections were the major causes of the death. 4 patients had progression AML and 15 patients died because of the co-morbidities.
Conclusion: Myelodysplastic syndromes are complicated and heterogeneous disorders which are not well understood yet. Individualized approach is essential for these patients. Clinical and demographic characteristics of each patient should be determined before therapy.

P08

HEREDITARY ICHTHYOSIS VULGARIS AND MYELODYSPLASTIC SYNDROME: A CASE REPORT

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Introduction: Hereditary ichthyosis (HI) vulgaris is an autosomal dominant disease first evident in early childhood. Unlike acquired ichthyosis HI is rarely associated with hematologic malignancies. In this case we present a girl with HI vulgaris with MDS-RAEB.
Case: G.A. is a twenty-one-year-old girl who has HI vulgaris. She has been consultated by her dermatologist because of her anemia. Otherwise she had no symptoms. She had hepatosplenomegaly and different types of scaling in different areas. There is moderate ectropion where the exposed conjunctiva was thickened and hyperaemic. The laboratory findings were: WBC:3.11 K/uL, HGB:11.2 g/dl, NE:1.54K u/L, MCV:814 fL, PLT:89 Ku/L, AST:70 U/L, ALT:60 U/L, LDH:199 U/L. In her peripheral blood smear there were anisocytosis, hyposegmentated and hypogranular neutrophils and low thrombocyte level. In her bone barrow aspiration there were hypolobulated neutrophils, eryhtroid serial dysplasia, dismegakaryopoesis and 6-8% elevated blasts. She is now using topical retinoids that her dermatologist suggested. She has been following by the haematology clinic for about seven months. Her family and she went for HLA matching testing for probable future allogeneic bone marrow transfusion. In her follow-ups there has been no need for blood transfusion and her neutrophil level has never been below 500 K/uL.
Conclusion: The myelodysplastic syndromes (MDS) compose a heterogenous group of clonal stem cell disorders characterized by ineffective hematopoiesis in one or more cell lineages and have a propensity to progress to AML. MDS patients are often asymptomatic and the diagnosis is made at the time of routine laboratory screening tests that reveal cytopenias in one or more lines or dysplasia on the blood smear. There are not many cases in literature that report an association between HI and hematologic malignancies. In the present case the patient with HI also has MDS-RAEB which has a potential to progress acute myeloid leukemia.

P09

THE AWARENESS OF PNH: A SINGLE CENTER EXPERIENCE FROM ANTALYA, TURKEY

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Objective: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, life-threatening but treatable disease characterized mainly by destruction of red blood cells by the complement system. The heterogeneity of the clinical manifestations and lack of awareness of PNH may cause delayed diagnosis. The fluorescein-labeled proaerolysin (FLAER) test by using flow cytometry is the gold standard methodology for screening of paroxysmal nocturnal hemoglobinuria.
Methods: We analyzed 388 cases screened for PNH with FLAER according to the main symptoms and laboratory findings from 2012 to 2015 in Akdeniz University Hospital, retrospectively.
Results: The median age was 47 years (range: 1-94 years) and the M/F ratio was 178/210. The commonest reason for screening for PNH at onset were PNH related symptoms (30.7%) (weakness, dyspnea, abdominal and chest pain, erectly dysfunction and dyspahegae), bone marrow failure syndromes (28.3%) and thrombosis (29.6%). Screening was performed in hematology and internal medicine department, respectively. Positive FLAER results were detected nearly 10 percent of patients (38/388, 9.8%).
Conclusion: PNH should be considered as a differential diagnosis in patients with unexplained abdominal pain, dyspnea, renal failure, thrombosis and non-immune hemolytic anemia. Awareness of the possibility in a potential case is crucial for early diagnosis of PNH.

CHRONIC LYMPHOCYTIC LEUKEMIA & HAIRY CELL LEUKEMIA

P10

ZAP-70 AND CD38 EXPRESSION AS A PROGNOSTIC MARKER FOR CHRONIC LYMPHOCYTIC LEUKEMIA

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Objective: Chronic Lymphocytic Leukemia (CLL) is one of the most common type of leukemias and lymphioid malignancies in adults. In The last decade several studies revelaed some new prognostic markers like IgVH mutational status, iFISH, ZAP-70, CD 38. IgVH gene analysis is time consuming, expensive and difficult. ZAP-70 and CD38 expression is associated with IgVH mutation. The co-expression of these two molecules in neoplastic B cells is associated with high risk disease.
Methods: We aimed to assess the prognostic significance of correlation between ZAP-70 and CD38 expression by the different cut-off values of CD38. A total of 124 CLL patients referred to our clinic were retrospectively analyzed.
Results: The immunophenotype of all patient was CD5+CD19+ CD20+CD23+Ig light chain κ/λ. The CD 38 were analysed in CD5+CD19+ cells. ZAP-70 was assessed in CD19+ B cells. The cut-off value of ZAP-70 were 20%. By CD38 there are two cut-off values, 7% and 20%. 124 patients, 85 male and 39 female ages between 31-87. By RAI staging; 50 patient stage 0 (40.3%), 21 stage I (16.9%), 11 stage II (8.9%), 24 stage III (19.4%), 18 stage IV (14.5%). Median follow up is 36 months (4-68 months). When the 20% cut-off applied for CD38, 62 patients were CD38(-)/ZAP70(-), 26 patients CD38(+)/ZAP70(+), 28 patients were in CD38/ZAP70 incompatible group. When the 7% cut-off value applied for CD38, 49 patients were CD38(-)/ZAP70(-), 48 patients CD38(+)/ZAP70(+) and 27 patients were in CD38/ZAP70 incompatible group. In the both cut off values for CD38, the double negative patients (CD38-/ZAP70-) have a higher remission time than double positive ones (CD38+/ZAP70+). 20% group: 58.8–3.3 months; 7% group: 66.4–5.8 months ($p < 0.001$). When the incompatible groups compared for both cut-off values the CD38-/ZAP70+ group had a higher remission time than CD38+/ZAP70+ ones (20% group: 16.4–2.5 months, 7% group: 47.3–33.4 months).
Conclusion: Detection of CD38 and ZAP70 expression by flow cytometry is easier and cheaper than IgVH mutation analysis. In CLL patients co-expression of CD38/ZAP70 is associated with poor prognosis and double negative group is related with a better prognosis. When the incompatible group analyzed the CD38-/ZAP70+ patients have a better prognos and higher treatment free survival.

P11

PROGNOSTIC SIGNIFICANCE OF SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 5 AND 5B EXPRESSION IN EPSTEIN-BARR VIRUS POSITIVE PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Objective: Signal Transducer and Activator of Transcription (STAT) proteins have been intensively studied in hematologic malignancies, and the efficacy of agents against STATs in lymphomas is already under research. The correlation of STATs with viral lymphomagenesis is being also actively studied. The objective of the present study was to investigate the expression of STAT5 and STAT5b in patients with Chronic Lymphocytic Leukemia (CLL) in correlation to the presence of Epstein-Barr virus (EBV) and its major oncoprotein (Latent Membrane Protein 1, LMP1).

Methods: We investigated the expression of total STAT5 and STAT5b (by Western-blotting) in peripheral blood samples of sixty three patients with CLL and fifteen healthy blood donors, in correlation to the presence of EBV (by RT-PCR for the BXLF1 gene) and LMP1 (by PCR and ELISA).

Results: STAT5b was only expressed in patients (but not in healthy blood donors) and total STAT5 but particularly STAT5b expression was correlated to the presence of the virus (77.3% versus 51.2%, p=0.006 for STAT5b) and to the expression of LMP1 (58.3% versus 21.6%, p=0.011 for STAT5b). Moreover, the expression of STAT5b and the presence of EBV and LMP1 were strongly negatively correlated to the overall survival of the patients (log rank test p=0.011, 0.015, 0.006 respectively).

Conclusion: This is, to our knowledge, the first report of a survival disadvantage of EBV-positive patients with CLL, and this is the first time that STAT5b expression is correlated to overall survival, a correlation that was found to be stronger than that of overall survival with the clinical stage of the disease in this group of patients. The correlation of STAT expression with EBV along with our survival correlations defines a subgroup of patients with CLL that may benefit from anti-STAT agents and paves the way for a more intensive study of the role of EBV in CLL.

P12

CLADRIBINE "RELATED" SEVERE AND FATAL BONE MARROW APLASIA IN A PATIENT WITH HAIRY CELL LEUKEMIA

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Introduction: Hairy-cell leukemia (HCL) is a B-cell lymphoproliferative disorder which is characterized by pancytopenia, splenomegaly, characteristic cytoplasmic hairy projections and a typical flow cytometric profile. The disease course is usually indolent and the current standard of care is treatment with purine analogs. Cladribine is preferred initial therapy because of its ease of administration and favorable toxicity profile.

Case: A73-year-old male patient was admitted with fever and cough to our emergency department. He was hospitalized because of community-acquired pneumonia and pancytopenia (hemoglobin: 10.4 g/dl, leukocyte: 850/μL, neutrophil: 580/μL, platelet: 125000/μL) and piperacillin tazobactam was started. Peripheral blood smear revealed cytoplasmic projections on medium size lymphocytes and CD19, CD20, CD25, CD11c and CD103 were positive with flow cytometric immunophenotyping. In the bone marrow biopsy, fat ratio was 70-80% and there was neoplastic infiltration of CD20, TRAP positive diffuse interstitial small lymphoid cells. Patient was diagnosed with hairy-cell leukemia. Single course of cladribine for 7 seven days with a dose of 0.1 mg/kg/day were started. After discharge he was readmitted to inpatient setting due to febrile neutropenia and he was unresponsive to granulocyte-colony stimulating factor (G-CSF) and he had prolonged severe cytopenias. Bone marrow aspiration and biopsy revealed aplastic bone marrow without any infiltration at second month of treatment. Other causes of acquired aplastic anaemia were excluded. He became totally dependent on erythrocyte and platelet transfusions, and due to prolonged severe neutropenia invasive pulmonary aspergillosis occurred. Unfortunately, he died due to sepsis with multiple organ failure 3 months after cladribine administration.

Conclusion: Treatment with purine analogues are well tolerated in the majority of patients with HCL. Common side effects of cladribine are immunosuppression and reversible myelosuppression. Recovery of peripheral blood counts may require weeks or even months. Cladribine associated irreversible bone marrow aplasia is extremely rare in the literature.

HODGKIN'S LYMPHOMA

P13

COMPARATIVE ASSESSMENT OF BONE MARROW INVOLVEMENT (BMI) BY BM BIOPSY (BMB) OR POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY (PET/CT) IN HODGKIN LYMPHOMA (HL)

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Objective: Recent data suggest that few HL patients have positive BMB in the absence of PET/CT evidence for BMI. The aim of this study was to correlate BMB with BM-PET/CT findings and to assess the impact of our published clinical prediction rule (Vassilakopoulos et al, Blood. 2005) on the frequency of BMI detected by either method.
Methods: PET/CT data were visually graded as follows: (1) no increased BM FDG uptake; (2) increased BM FDG uptake ≤liver; (3) increased BM FDG uptake >liver; (4) solitary osseous/BM focus without CT correlate; (5) multiple osseous/BM foci. Patients were classified according to our clinical prediction rule for BMI in low-, standard- and high-risk groups.
Results: PET/CT and BMB data were available for 179 patients. PET/CT was negative for BMI in 148 and positive in 31 patients: 4 had a single focus and 27 multiple foci. Only 14 patients had BMI by BMB (7.8%). None of the patients of PET/CT categories 1, 2, 3 or 4 had a positive BMB; 14/27 patients graded as "5" had positive BMB (52%). The frequency of BMI by BMB and by PET/CT was 0%, 1.5%, 21.1% and 0%, 6.2% and 39.6% in low-, standard- and high-risk group respectively. The outcome of patients with BMI by PET/CT was inferior (3-year PFS 56% vs 85%, p=0.001). Patients with diffuse FDG uptake >liver tended to have increased "inflammatory" activity (leukocytosis, anemia, elevated ESR and CRP, thrombocytosis).
Conclusion: PET/CT is more efficient than BMB in detecting BMI. There was no case of positive BMB in the absence of BMI by PET/CT. Increased diffuse BM FDG uptake is not associated with BMI. Our clinical prediction rule was adequately validated regarding the prediction of BMI by either BMB or PET/CT. These data suggest that BMB can be safely omitted in all patients with HL staged by PET/CT.

P14

PET/CT FOR THE EARLY INTERIM EVALUATION OF RESPONSE IN ADVANCED HODGKIN LYMPHOMA (HL) AFTER ABVDX2: EFFECTIVE SALVAGE WITH BEACOPP BUT LOW NEGATIVE PREDICTIVE VALUE FOR STAGE IV

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Objective: A positive PET/CT after ABVDx2 (PET-2) is a highly unfavorable prognostic factor in intermediate and advanced-stage HL. We report here our experience with PET-2 in patients with truly advanced HL and evaluate its prognostic accuracy.
Methods: 101 patients with advanced HL according to GHSG definition, who were treated with ABVD and underwent PET-2, were retrospectively evaluated. PET-2 was assessed according to Deauville criteria (scores 4-5 considered positive). Switch to BEACOPP-esc was at the discretion of the treating physician.
Results: The median age of patients was 31.5 years (100/101 <60 years), 57% were males, 84% had NS-cHL, 40% and 52% were classified as stage IV by conventional and PET-based staging respectively, and 67% had B-symptoms. The median IPS was 2; 46% had IPS 3-7. PET-2 was negative in 77 and positive in 24 patients (24%). Overall, 3-year PFS was 76%. The strong prognostic value of PET-2 was verified (3-year PFS 86% in PET-2(-) vs. 43% in PET-2(+) patients, p<0.0001), despite switch to BEACOPP-esc in 10/24 PET-2(+) patients (14 continued with ABVD). The 3-year PFS was 61% vs. 31% for PET-2(+) patients who received BEACOPP-esc and ABVD respectively (p=0.059). Based on conventional staging 3-year PFS did not differ between stage II-III and stage IV (89% vs. 82% respectively, p=0.36). When initial staging was based on PET/CT, the 3-year PFS was lower in stage IV compared to stage II-III patients (77% vs. 94%, p=0.057).

Conclusion: The results of our study confirm the strong prognostic value of PET-2, since the possibility of relapse was much higher in PET-2(+) patients, despite the more aggressive therapeutic approach adopted for 10/24 of them. Patients treated with BEACOPP-esc upon PET-2(+) tended to have superior outcomes. PET-2(-) patients with stage IV, as defined by baseline PET/CT, had inferior outcomes. This observation may have significant impact on treatment design.

NON-HODGKIN LYMPHOMAS

P15

COMPARISON OF IPI AND NCCN-IPI IN 324 DE-NOVO DLBCL PATIENTS: A MULTICENTER RETROSPECTIVE ANALYSIS

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Objective: Until recently, IPI was almost the only widely used prognostic indicator in diffuse large B-cell lymphoma (DLBCL). IPI, being developed in pre-rituximab era, fails to predict the prognosis in a considerable portion of patients with DLBCL. NCCN-IPI was recently claimed to better predict the DLBCL outcomes. We aimed to compare the prognostic significances of IPI and NCCN-IPI in DLBCL patients treated with R-CHOP.
Methods: All patients (n=324) diagnosed with DLBCL and treated with R-CHOP regimen and analysed retrospectively.
Results: Median follow-up was 3.7 years. Progressive free survival and overall survival (OS) were compared between risk categories. 5-year OS was 91% for both IPI and NCCN-IPI low risk groups whereas 44% for IPI and 29% for NCCN-IPI high risk group. NCCN-IPI and IPI have similar discriminations with concordance probability estimates (CPE) (0,67 vs 0,68 respectively). There is a good correlation with these two risk classification model determined with the weighted κ statistics (κW=0.6817, p<0.001).
Conclusion: The authors indicated that NCCN-IPI provided increased capacity to discriminate both high-risk and low-risk de-novo DLBCL patients. Huang et al justifying the better discrimination capacity of NCCN-IPI compared to IPI. Our report is based on the analysis of 324 de-novo DLBCL patients. Our patients were treated in various hospitals, which reflect the "real-life" characteristic of our cohort. In our study, NCCN-IPI couldn't better differentiate low risk group but it was able to discriminate OS more accurately in the high risk category compared to IPI. Recently published study showed that, even though gene-based predictors have good discriminating ability when used alone, IPI remains the most powerful predictor in DLBCL patients. DLBCL is a heterogeneous disease and we will probably explore more molecular, immunohistochemical and clinical (NCCN-IPI?) parameters in the future. These efforts will contribute to develop stronger risk classification process, maybe as a part of a never ending story.

P16

HIGH BONE TURNOVER AND LOW BONE MINERAL DENSITY IS PRESENT IN PATIENTS WITH NON-HODGKIN'S LYMPHOMA AFTER THE ADMINISTRATION OF FRONTLINE THERAPY

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Objective: The aim of the study was to evaluate the effects of chemotherapy on bone metabolism of patients with newly-diagnosed non-Hodgkin's lymphoma (NHL).
Methods: Bone mineral density (BMD) of the lumbar spine (L1-L4) and femoral neck (FN) of NHL patients was measured by DXA on day 1/cycle 1 (baseline) and on day 30 of the last chemotherapy cycle. The following bone metabolism markers were measured on the days of DXA: i) osteoclast stimulators [sRANKL and osteoprotegerin (OPG)], ii) osteoblast regulators [PTH, vitamin-D, and dickkopf-1 (Dkk-1)], iii) bone resorption markers [CTX and TRACP-5b], and iv) bone formation markers [bone alkaline phosphatase (bALP) and osteocalcin (OC)].
Results: Fifty-three patients have completed the study to-date: 36 (67.9%) had diffuse large B-cell lymphoma, 5 (9.4%) follicular (grade III), 4 (7.5%) mantle-cell, 6 (11.3%) marginal-zone and 2 (3.8%) T-cell NHL. Forty-seven patients (88.7%) received R-CHOP, 4 R-COP and 2 CHOP. At baseline, NHL patients had a median T-score of L1-L4 BMD of -0.63 (range: -4.27 to +3.68) and of FN BMD of -0.875 (-4.01 to +2.07). The administration of chemotherapy resulted in a dramatic reduction of BMD in L1-L4

(-1.12; -4.49 to +3.04; p<0.001) and in FN (-1.115; -3.68 to +1.12; p<0.001) compared to baseline. Patients who received 8 cycles of chemotherapy had a greater reduction of L1-L4 (p<0.001) and FN (p=0.001) BMD. Chemotherapy also resulted in elevations of CTX (p=0.017), TRACP-5b (p<0.001), bALP (p<0.001), OC (p<0.001) and Dkk-1 (p=0.022) compared to baseline values. All studied markers (except of sRANKL/OPG) were increased in NHL patients post-chemotherapy compared to 30 healthy controls (p<0.01). During study period, one male patient had a pathological fracture in his right FN.

Conclusion: Frontline treatment (chemotherapy and/or rituximab) results in high bone turnover, increased bone loss and reduced BMD in NHL patients. The prophylactic use of bisphosphonates or denosumab may be useful for preventing bone loss in these patients.

P17

PROGNOSTIC FACTORS IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMLBCL) UNDER STANDARD CHEMOTHERAPY WITH RITUXIMAB-CHOP (R-CHOP) WITH OR WITHOUT RADIOTHERAPY (RT)

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Objective: Prognostic factors (PFs) in PMLBCL have not been extensively studied. Prior to the Rituximab era, the International Prognostic Index (IPI) appeared to retain its prognostic significance. R-CHOP provides very good results, but the applicability of various PFs needs to be evaluated in order to define high risk patient subgroups, since more intensive chemotherapy might provide better results. Aim of the study was the identification of PFs in PMLBCL patients treated with RCHOP±RT.

Methods: 213 patients with PMLBCL were treated with RCHOP±RT. The following potential prognostic factors were evaluated: Age, gender, B-symptoms, stage III/IV, infradiaphragmatic disease, extranodal involvement, pleuritis, pericarditis, performance status (PS) ≥2, LDH levels, anemia, leukocytosis, ESR ≥30 mm/h, albumin <4 g/dL, bulky disease, age-adjusted IPI (aaIPI).

Results: The median follow-up was 50 months. Among 52 failures, 51 occurred within 17 months from diagnosis. The 3-year FFP was 75% and the 5-year OS 88%. The aaIPI (≥2) identified a minority of patients with a 5-year FFP of 64% vs. 79% for those with aaIPI 0-1 (p=0.04) and 5-year OS of 76% vs. 92% (p=0.003). Many of the examined variables had a significant or borderline association with both FFP and OS. In multivariate analysis of OS, extranodal involvement and bulky disease were independent PFs. OS at 5 years was effectively predicted, being 100%, 93% and 73% for patients with 0, 1 or 2 PFs respectively (p=0.0001). The corresponding 5-year FFP rates were 88%, 79% and 59% (p=0.002).

Conclusion: This is the largest series reported so far; RCHOP±RT provided satisfactory results in PMLBCL in terms of FFP and OS. The aaIPI was moderately predictive of the outcome. The combination of extranodal involvement and bulky disease defined a subgroup of patients with high risk of failure and death, who might be candidates for treatment intensification.

P18

PROGNOSTIC SIGNIFICANCE OF VON WILLEBRAND FACTOR ANTIGEN IN WALDENSTROM'S MACROGLOBULINEMIA

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Objective: Patients with Waldenstrom's Macroglobulinemia (WM) can manifest unique hemostatic disorders, including acquired von Willebrand syndrome (AVWS), paraprotein-induced platelet function defects, factor X deficiency, etc. Von Willebrand factor (vWF), a glycoprotein produced by the endothelial cells and megakaryocytes, plays a key role in primary hemostasis but is also a marker of endothelial "stimulation". The aim of this study was to evaluate vWF in WM and explore possible correlations with clinical data, including PFS and OS.

Methods: The analysis included 42 patients with symptomatic WM and 19 healthy controls of matched gender and age. According to IPSSWM, 22% had low, 43% intermediate and 35% high risk WM, respectively. The vWF antigen (vWF Ag) levels were measured in serum collected before initiation of therapy by means of a latex particle-enhanced immunoturbidimetric assay (HemosIL vWF antigen) with an automated coagulometer (ACL Top 3G, Instrumentation Laboratory, Lexington, MA, USA).

Results: Although the majority of WM patients had increased levels of vW antigen, 6/42 (14%) had vWF Ag levels <40 U/L;

which could be compatible with AVWS. There was an inverse correlation of platelet counts with levels of vWF Ag (R=-0.336, p=0.032) and vWF Ag ≥median was less frequent in patients with low (11%) vs. patients with intermediate (59%) or high (62%) risk IPSS (p=0.036). Median follow up of symptomatic patients was 4 years. Patients with vWF Ag levels within the upper quartile (i.e. vWF Ag ≥200 U/dL) had a median progression free survival of 12 months vs. 63 months of patients with vWF Ag < 200 U/L (p<0.001). The median survival for patients with vWF Ag ≥200 U/dL was 37 months (4-year survival 29%) vs. 4-year survival of 97% for patients with vWF Ag <200 U/L (p<0.001).

Conclusion: We conclude that serum vWF may become an important prognostic marker in WM and needs further investigation in larger cohort of patients.

P19

RETROSPECTIVE EVALUATION OF OUTCOMES OF DA-EPOCH-R REGIMEN IN PATIENTS WITH ADVANCED STAGE NON-HODGKIN LYMPHOMA AND WITH HIGH KI-67 EXPRESSION: SINGLE CENTER EXPERIENCE

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Objective: In most of CD 20(+) NHLs, rituximab-containing regimens mainly as R-CHOP have been defined as the standard therapy. Recently, molecular and biological features of the tumor including Ki-67 expression have been described that have potential impact on outcome and treatment decissions. The purpose of this study was to evaluate the efficiency and safety of the dose adjusted etoposide, prednisolone, vincristine, doxorubicin, and cyclophosphamide with rituximab (DA-EPOCH-R) regimen on patients with Non-Hodgkin Lymphoma (NHL) with advanced stage and high Ki-67 expression.

Methods: Ten patients (5 female and 5 male) with Non-Hodgkin Lymphoma were analyzed retrospectively who had received DA-EPOCH-R regimen. The characteristics of patients were illustrated in table 1. The median age of patients was 49,7(17-76) years old. All patients were stratified as in stage III/IV. Patients were treated with 3-6 cycles of DA-EPOCH-R.

Results: The results showed that the overall response rate of patients was 90%, including 9 patients (90%) in complete remission (CR) and 1 patient (10%) in stable disease (SD). At a median follow-up of 13,4 months. The major toxicity of DA-EPOCH-R regimen was hematologic toxicity. Other toxicities were mild, no treatment-related deaths occurred.

Conclusion: It is concluded that DA-EPOCH-R regimen is an effective and safe protocol for the patients with NHL with advanced stage and high Ki-67 expression. More and comparative studies are need to define the exact role of DA-EPOCH-R regimen in patients with poor molecular and biological features.

P20

A YOUNG MAN WITH A PALPABLE MASS IN THE LEFT AXILLA

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Introduction: Anaplastic large cell lymphomas (ALCLs) are a frequent subcategorie of Peripheral T-Lymphomas. A high fraction of ALCLs are associated with translocations involving ALK, the Anaplastic Lymphoma Kinase gene, located on chromosome 2p23. We will describe a case of ALK+ T-Lymphoma in a young adolescent.

Case: A 19-year-old adolescent was referred to our Department because of a painful enlargement in the right axilla. Patient's history as well as family history were unremarkable. Clinical examination revealed swelling in the left armpit (10 cm x 15 cm) accompanied with ulceration and cellulitis and palpable lymph nodes in the left cervical region. Laboratory examination revealed only an elevated ESR (85 mm) with no other abnormal findings. In PET scan there was abnormal 18-FDG uptake (SUV max: 18.5) in posterior cervical, left supraclavicular and subclavian Lymph nodes and a sizeable mass along the left lateral chest wall. Spleen also showed diffuse pathological uptake. Biopsy of the lymph nodes showed High grade Anaplastic large T-cell lymphoma ALK positive. According to cotswolds modification of Ann Arbor staging system, patient's stage was IISXBE with an IPI score II. (low intermediate) Patient received 6 cycles of CHOEP. After those 6 cycles, PET SCAN was negative and the patient received two more cycles of CHOP. After the completion of treatment, a left spontaneous pneumothorax was diagnosed, which required surgical intervention.

Conclusion: Our patient remains in complete response, three years after completion of treatment. Several studies have shown that ALCLs CD 30(+) ALK (+) represent a distinct clinicopathologic entity and have a distinctly better clinical outcome than ALK - systemic ALCLs. It is also known that normal serum LDH and an IPI score of ≤3 predicts a favorable clinical outcome.

P21

PRIMARY AND SECONDARY LYMPHOMA INVOLVEMENT OF THE BREAST; TWO CASES

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Introduction: Primary lymphoma of the breast is a rare form of NHL, representing approximately 0,5% of all breast malignan-

cies and 2,2% of all extranodal lymphomas. However, secondary involvement of the breast with lymphoma is not unusual. Diffuse Large B Cell Lymphoma (DLBCL) is the most common histopathological subtype. Here we report two cases of breast lymphoma one is primary and the other is secondary, who both achieved complete remission (CR) with standard chemotherapy.
Cases: Case 1: A 55-year-old woman presented with a painless left breast mass. Breast ultrasonography showed a non-homogeneous mass in the left breast and a pathological lymph node in left axilla. As the fine needle aspiration biopsy (FNAB) resulted negative, segmental mastectomy was performed. Histopathological diagnosis reported as DLBCL. In PET/CT; a few milimetric mild-metabolic jugulary and axillary LAPs were found. There wasn't bone marrow infiltration. 2 cycles of R-EPOCH were performed and CR achieved as control US showed no residual mass. It has planned to complete chemotherapy six cycles.
Case 2: A 36-year-old woman presented with servical mass and asymetrical tonsil hypertrophy; diagnosed as DLBCL by the biopsy of left palatine tonsil. PET/CT showed multiple servical and axillary LAPs and multiple hypermetabolic masses in right and left breasts. Since the defined lesions were bilateral and multifocal; lymphoma involvement was thought as the most probable diagnosis. FNAB was performed from her right breast but the results were non-diagnostic. There wasn't bone marrow infiltration. After two cycles of R-CHOP, control PET/CT showed anatomic and metabolic CR in breast lesions and LAPs. Chemotherapy was completed to eight cycles.
Conclusion: Lymphoma is the most common malignant disease metastatizing to the breast and rarely it presents as primary breast involvement. Considering lymphoma in the differential diagnosis of breast masses is important for developing an effective diagnostic and therapeutic approach.

P22

NODAL MARGINAL ZONE LYMPHOMA: OUR EXPERIENCE IN A PARTICULAR CASE

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Introduction: Nodal Marginal Zone Lymphoma (NMZL) is a primary nodal B-cell neoplasm that morphologically resembles lymph nodes involved by MZL of extranodal or splenic types, but without evidence of extranodal or splenic disease. It's rare, approximately 1% of NHL cases. Nodal MZL usually progresses to a higher grade histologic subtype, such as diffuse large B-cell lymphoma. We present an unusual case of NMZL with transformation to Acute Leukemia.
Case: A 49-year-old man presented with a 3 week history of fever, cough and dyspnea. His physical examination revealed swollen lymph nodes in all anatomical sides, his chest computer tomography (CT) showed mediastinal mass and pleural effusion and the bone marrow biopsy NMZL with bone marrow infiltration. He received four cycles of the combination of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP regiment), achieving partial response and then four more cycles. Soon after he relapsed. During his hospitalization lactate dehydrogenase (LDH) was elevated and he was diagnosed with bone marrow necrosis. He received salvage therapy with ESHAP regiment. Thirteen days later he presented with skin and eye damage. Skin biopsy revealed Hematodermic Lymphoma. After that he presented dyspnea and his chest computed tomography revealed excessive mediastinal enlargement. He was treated with radiotherapy but he quickly progressed to mixed phenotype acute leukemia and he died .
Conclusion: NMZL comprises a biologically and clinically heterogeneous spectrum of lymphoma cases. Transformation to a large B-lymphoma may occur. In our case the patient progressed to Hematodermic Lymphoma with mediastinal enlargement and then to acute leukemia which is extremely rare. Since there are not yet specific diagnostic hallmarks and treatment consensus guidelines for NMZL, we share our experience to this direction.

P23

PROGNOSTIC SIGNIFICANCE OF BODY MASS INDEX (BMI) IN PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA (DLBCL) TREATED WITH RITUXIMAB-CHOP (R-CHOP) OR SIMILAR COMBINATIONS

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Objective: Recent data suggested that increased BMI correlates with favorable outcome in white American males with DLBCL, while other studies provided controversial results. The aim of this study was the evaluation of the prognostic value of BMI in DLBCL.
Methods: 664 patients with DLBCL treated with R-CHOP or similar regimens were evaluated.
Results: The median BMI was 26.5 kg/m^2, 156 (23%) patients were obese (BMI ≥30) and 273 (40%) overweight (BMI 25-29.9).

Increased BMI correlated with increased age, while decreased BMI with PS ≥2, ≥2 E-sites and B-symptoms. 7-year PFS of patients with BMI ≥30, 25-29.9 and <25 was 76%, 72% and 68% respectively (p=0.085 for BMI ≥30 vs. <30). BMI had not prognostic impact in patients <60 years. On the contrary, males >60 years with BMI≥30 and females >60 years with BMI ≥25 had more favorable outcomes than those with lower BMI. Similarly, BMI ≥30 was a favorable prognostic factor only for patients without B-symptoms. In multivariate analysis BMI had no independent prognostic impact in the whole patient population, while BMI ≥30 was an independent prognostic factor in males >60 years (p=0.03) along with LDH and PS, and BMI ≥25 was an independent prognostic factor along with LDH and stage III/IV in females >60 years (p=0.055). In a preliminary analysis of 277 patients, DI of chemotherapy did not differ between patients with BMI ≥30 or <30, while DI of Rituximab was slightly (but statistically significantly) lower in obese patients (p=0.01).

Conclusion: The effect of BMI on prognosis appears to be restricted to elderly DLBCL patients with different, possibly, cutoff (30 vs 25 kg/m^2) for males and females. This could not be attributed either to the unfavorable prognosis of patients with weight loss, since the observation was restricted to patients without B-symptoms, or to differences in DI of immunochemotherapy according to BMI. A possible correlation with pharmacokinetic parameters needs verification.

P24

A CASE OF SPLENİC MARGİNAL ZONE LYMPHOMA WITH CRYOGLOBULINEMIA

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Introduction: Splenic marginal zone lymphoma (SMZL) is B-cell neoplasia, manifested by small cells and it targets white pulp follicles, bone marrow and peripheral blood cells. Cryoglobulinemia is presence of cryoglobulins in the blood,which are abnormal immunoglobulins precipitating reversibly in low body temperature (<37°C). Autoimmune reactions may accompany SMZL. In this report we aimed to present SMZL case with ımmunolojıc and coagulation disorder.

Case: A 66-years-old male patient was diagnosed with SMZL after splenectomy performed 6 years ago. He applied with asthenia and weight loss. Physical examination revealed bilateral sub-knee purpuric eruption. Blood count resulted with hemoglobin 7.7 g/dl, MCV 106 fl, WBC 24700 u/L, platelet 78000u/L, LDH 1286 u/L, haptoglobulin 32 mg/dl, reticulocyte 8.9%, also direct and indirect coombs were resulted positive.The prothrombin time was 34.6 seconds, INR 3.7, aPTT 51 seconds, and following values were found 1/1 dilution PT 22.3, INR 2.5, aPTT 51, the factor inhibitor test resulted positive. The patients factor II, VII, VIII, IX, and X levels were low. Autoimmune hemolytic anemia and hemophilia manifested in the patient and 48 mg/day metilprednizolon was administered. During 6th day of therapy, hemolysis and coagulation parameters of the patient were not recovered; his cryoglobulin level was 0.147 OD. The HCV, HBV, HIV antibodies were negative. CHOP chemotherapy regime was used. However, in first week, he developed respiratory hemorrhage and died.

Conclusion: Autoimmune hemolytic anemia, immune trombocytopenia, coagulation disorders, positive direct Coombs are confirmed 10-20% patients suffering from SMZL. There is a significant relation with SMZL and hepatitis-C virus. In our case, cryoglobulinemia was present even though HCV was negative. In SMZL patients with autoimmune hemolythic anemia and coagulation disorder, if steroid therapy does not benefit them,cryoglobulinemia should always come to mind. The real treatment of cryoglobulinemia is treatment of the underlying disease. For these patients chemotherapy must come to mind urgently.

MULTIPLE MYELOMA AND OTHER PLASMA CELL NEOPLASMS

P25

CIRCULATING LEVELS OF ADHESION MOLECULES IN 206 PATIENTS WITH MULTIPLE MYELOMA: A SINGLE CENTER PROSPECTIVE STUDY

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Objective: Interactions between plasma cells and cells in the bone marrow microenvironment, through adhesion molecules, play a key role in the biology of multiple myeloma (MM) and regulate tumor growth, survival and migration in the bone marrow. The aim of our study was to evaluate the levels of soluble adhesion molecules in patients with different plasma cell dyscrasias and explore the correlations with disease characteristics, reported outcomes and how they are affected after treatment with novel agents.

Methods: Levels of circulating adhesion molecules VCAM-1, ICAM-1, P-, L- and E-selectin were measured with ELISA in serum of 47 patients with MGUS, 61 with AMM and 145 with symptomatic MM. Same adhesion molecules were measured in serum of 87 patients with symptomatic disease at first relapse that received second line therapy with novel agents, 47 received RD and 40 VD. Measurements have been conducted before initiation of therapy for newly diagnosed patients, or before the administration of the

first RD or VD, and after 4 cycles of therapy.
Results: Patients with MM had increased levels of VCAM-1 and ICAM-1 compared with MGUS, AMM patients and controls, while the levels of selectins did not differ. Patients with ISS-1 had lower circulating levels of VCAM-1 and higher circulating levels of P-selectin. For MM patients, there was a positive correlation between VCAM-1 and ICAM-1, and a negative correlation between VCAM-1 and P-selectin. Serum VCAM-1 showed strong correlation with β2-microglobulin and creatinine. P- and L-selectin negatively correlated with β2-microglobulin and creatinine. For patients with symptomatic disease median follow-up was 31 months, and median OS was 53 months. Median PFS was 23 months. Patients with VCAM-1 >median had median PFS 19 months vs 32 months of the others, and they also had median OS of 45 months vs 75 months. Patients with low P-selectin
Conclusion: Our study provides evidence about the role of microenvironment in the biology of myeloma patients. VCAM-1 had an independent prognostic value for both PFS and OS in patients with newly-diagnosed symptomatic disease. Also levels of ICAM-1 and VCAM-1 predicted for time to progression in patients with asymptomatic disease. Reduction of VCAM-1 and ICAM-1 after treatment with novel agents reveals an effect of these drugs on the microenvironment, while Rd altered also the levels of all studied selectins suggesting an effect of Rd on the vascular niche and the endothelium.

P26

THE ANTI-MYELOMA EFFECT OF BORTEZOMIB IS INDEPENDENT OF THE BCL-2 STATUS

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Objective: The transcription nuclear factor-kappa B (NF-kappaB) offers a significant survival potential in multiple myeloma (MM) cells. Bortezomib inhibits the degradation of IkappaB and hence sequesters cellular NF-kappaB, blocking NF-kappaB transcriptional activity, and thus it leads to reduced levels of growth factors and cell adhesion molecules. Bortezomib also enhances apoptosis in MM cells by bypassing anti-apoptotic mechanisms. Bcl-2 is an anti-apoptotic protein that confers unregulated growth and resistance to conventional chemotherapy in MM cells. The aim of this study was to evaluate the effect of bortezomib on patients with relapsed/refractory MM regarding their bcl-2 status.
Methods: We evaluated the immunophenotypic findings of myeloma cells in the bone marrow biopsies of 24 patients (14M/10F; median age: 59 years, range: 35-71 years) who had received >4 lines of treatment previously, including autologous stem cell transplantation. Twelve patients had IgG MM, while 6 had IgA, one non-secretory and 5 light-chain MM. Bortezomib was given at the dose of 1.3mg/m^2, iv or sc, in 3-week cycles, on days 1, 4, 8, and 11 of each cycle along with standard dose of dexamethasone. The patients were assessed before treatment and after 4 cycles of treatment.
Results: Fourteen (58%) patients had achieved a partial response, while 2 (8%) patients had stable disease after 4 cycles of therapy. Cellularity was reduced in all patients after 4 cycles of treatment. Plasma cell infiltration was reduced in 19 (79%) patients. Bcl-2 was strongly positive in all pre-treatment biopsy specimens. This strong positivity persisted even after the 4 cycles of bortezomib administration. Other immunophenotypic characteristics, including epithelial membrane antigen (EMA), CD79-alpha, and cyclin D1, have not altered following bortezomib treatment.
Conclusion: Previous studies with MM cell lines have suggested that agents that reduce NF-kappaB also lower bcl-2 levels and promote apoptosis. These results suggest that the anti-myeloma effect of bortezomib is independent of bcl-2.

P27

THE RAPID RESOLUTION OF PSEUDOHYPERPHOSPHATEMIA IN AN IGAκ MULTIPLE MYELOMA PATIENT AFTER THERAPY WITH A BORTEZOMIB-CONTAINING REGIMEN: A CASE REPORT

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Introduction: Hyperphosphatemia might be encountered in renal failure, tumour lysis syndrome, hypoparathyroidism, pseudohypoparathyroidism, lactic acidosis, and ingestion of exogenous phosphate-containing sources. Hyperphosphatemia in multiple myeloma (MM) is rare; and is expected when glomerular filtration rate (GFR) is <30 ml/min. We present a MM patient with pseudohyperphosphatemia.
Case: A 54-year-old male patient was admitted with weakness. The laboratory analyses revealed anemia, hypoalbumenia, hyperglobulnemia, hypercalcemia (10,1 mg/dl), hyperphosphotemia (20 mg/dl), GFR was 61 ml/min. Serum parathormone, vitamin D levels, the 24-hour calcium and phosphorus excretions were normal. There was a monoclonal spike in the β-region of serum protein electrophoresis. Serum IgA and kappa were, respectively, 6060 mg/dL and 5860 mg/dL. Serum immunoelectrophoresis showed monoclonal bands in IgA and κ regions. Bone marrow aspiration revealed 22% plasma cells. He was diagnosed as stage III IgAκ MM according to International Staging System. He was given calcium acetata 500 mg three times a day for two days with no significant change in phosphorus level. He was administered VCD (bortezomib, cyclophosphamide, dexamethasone) protocol.

On the fifth day of VCD, phosphorus became 3.2 mg/dL, total protein/albumin were 8.4/2.9 mg/dL.
Conclusion: Hyperphosphatemia in MM might be explained by the binding of paraprotein to phosphate or the interference of globulin fraction with colorimetric assays, resulting in falsely elevated phosphorus levels. Two ml of serum should be deproteinized with 200 μl of sulfosalicylic acid to remove the paraprotein. Our patient had no hypocalcemia, advanced renal failure or any sign of hyperphosphatemia; so, considering pseudohyperphosphatemia we discontinued calcium acetate, and instituted chemotherapy. He is the first reported MM patient whose phosphorus normalized shortly after a bortezomib-containing regimen. In case of suspicion of pseudohyperphosphatemia in MM; serum should be deproteinized and effective chemotherapy should be started to lower the paraprotein level. Bortezomib-containing VCD protocol was observed to correct pseudohyperphosphatemia rapidly.

P28

THE PROGNOSTIC VALUE OF C-TERMINAL CROSS-LINKING TELOPEPTIDE OF COLLAGEN TYPE-I (CTX) IN PATIENTS WITH MULTIPLE MYELOMA

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Objective: The aim of this study was to evaluate the impact of bone markers on the survival of multiple myeloma (MM) patients who are treated upfront with novel agents.
Methods: We studied 122 consecutive, unselected, newly diagnosed patients with symptomatic MM who received upfront treatment with novel agents: 75 with IMiDs-based and 47 with bortezomib-based regimens. The circulating levels of the following bone remodeling markers were evaluated at diagnosis: i) osteoclast regulators: sRANKL and osteoprotegerin (OPG); ii) osteoblast inhibitor dickkopf-1 (Dkk-1); iii) bone resorption markers: CTX and TRACP-5b; and iv) bone formation markers: bone-specific alkaline phosphatase (bALP) and osteocalcin.
Results: At diagnosis, MM patients had increased serum concentrations of sRANKL, OPG, CTX, TRACP-5b, Dkk-1 and sRANKL/OPG ratio and decreased levels of bALP compared to 30 controls ($p<0.01$), while their levels correlated with the extend of bone disease. The median survival of all patients was 59 months. In the univariate analysis, among the studied bone markers, only CTX, as a continuous variable, was predictive of survival (HR: 1.292, $p=0.024$). Patients with low CTX concentrations (<0.28 ng/ml; lower quartile; N=29) had superior survival compared to patients with higher CTX concentrations (not reached vs. 54 months respectively; $p=0.034$). This was more profound in patients treated with IMiDs-based regimens: the median survival of those with low CTX levels (<0.28 ng/ml) has not been reached yet vs. 39 months of all others ($p=0.02$). On the contrary, in patients who were treated with bortezomib-based therapies, high CTX could not define such a poor prognosis group.
Conclusion: Our study suggests that in the era of novel agents, only CTX, among 7 serum bone remodeling markers, correlated with survival and could distinguish a subset of patients who receive frontline IMiDs-based therapies and have poor prognosis. This was not observed with bortezomib-based therapies, possibly due to the beneficial effect of bortezomib on bone metabolism.

P29

BONE MARROW BIOPSY SHOULD BE CONSIDERED FOR THE INITIAL EVALUATION OF INDIVIDUALS WITH ASYMPTOMATIC MONOCLONAL GAMMOPATHY AND IMMUNOPARESIS OR MONOCLONAL COMPONENT ≥1G/DL

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Objective: The aim of the study was to identify factors that could aid in the evaluation of individuals presenting with asymptomatic monoclonal gammopathy.
Methods: We analyzed the database of patients who were referred to our department for evaluation of asymptomatic monoclonal gammopathy. A bone marrow (BM) trephine biopsy, serum and urine protein electrophoresis with immunofixation and quantitative immunoglobulins are routinely performed in all patients with monoclonal gammopathy.
Results: Our analysis included 162 patients: 53% had a monoclonal IgG, 15.5% IgA, and 24% IgM, while 4% had a biclonal paraprotein; 63% had a kappa light chain. The median serum M-protein was 0.95 g/dl (range 0.1-2.99 g/dl) and was higher in those with IgG or IgA vs. those with IgM ($p=0.009$). Immunoparesis of at least one of the uninvolved immunoglobulins was present in 38% and of both of the uninvolved immunoglobulins in 6% of patients. Median infiltration by monoclonal cells in BM biopsy was 7% for those with an IgM-gammopathy and 15% for those with monoclonal IgG or IgA ($p=0.047$). There was a significant correlation of the size of M-protein and of the BM infiltration ($R=0.592$, $p<0.001$). Among those with M-protein<0.5 g/dl, 11% had≥10% clonal cells in their BM biopsies while the respective rates were 88% for those with M-protein ≥1 g/dl and 97% for M-protein ≥2 g/dl. Immunoparesis

of at least one of the uninvolved immunoglobulins was associated with ≥10% BM clonal cells in 90% of patients. In regression analysis, immunoparesis of at least one of the uninvolved immunoglobulins (OR:6.45, 95%CI:2.32-18, p<0.001), an IgG or IgA monoclonal protein (OR:2.67, 95%CI:1.1-6.4, p=0.028) and an M-protein ≥1 g/dl (OR:5.4, 95%CI:2.23-13) were independently associated with ≥10% clonal infiltration in BM biopsy.

Conclusion: BM biopsy can reveal asymptomatic myeloma or Waldenstrom's Macroglobulinemia that may escape identification with standard criteria and should be included in the initial workup of individuals with asymptomatic monoclonal gammopathy.

P30

T-REGULATORY CELLS ARE SIGNIFICANTLY REDUCED AFTER TREATMENT WITH LENALIDOMIDE, BUT NOT WITH BORTEZOMIB, AND CORRELATE WITH THE ACHIEVEMENT OF AT LEAST VGPR IN PATIENTS WITH MULTIPLE MYELOMA

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Objective: Immune dysfunction is an important feature of multiple myeloma (MM) and has been associated with reduced survival. Studies have shown that regulatory T cells (Tregs) are implicated in the immune surveillance of different tumors, including MM. Data regarding alterations of Tregs during therapy with novel agents (NA), i.e. bortezomib and lenalidomide, are limited. Our aim was to explore the alterations of Tregs and T subpopulations (i.e. T4, T8, NK, NK-like), as well as changes in the levels of cytokines related to Tregs function and MM biology (IL-6, IL-2, IL-17, TGF-β), during treatment with NA and to explore possible correlations with disease characteristics and response parameters.

Methods: We evaluated 29 patients with symptomatic MM, at diagnosis or relapse (M/F: 15/14, median age: 61 years, range: 39-77 years). Eleven patients received bortezomib-dexamethasone (BD) (group A) and 18 patients received lenalidomide-dexamethasone (Rd) (group B). The median number of previous treatment lines was 1 (0-3).

Results: In group A, no significant alterations of Tregs %, T subpopulations or cytokines was observed. In group B, there was a significant reduction of Tregs % (p<0.001) and this was more profound in those who achieved ≥very good partial response (vgPR; p=0.04). No alterations regarding T subpopulations or cytokines was observed. Significant correlations between disease characteristics and Tregs were not observed in either group of patients. In the cox regression analysis, Tregs % did not correlate with progression-free survival (PFS).

Conclusion: We have demonstrated that Tregs % are significantly reduced after treatment with Rd especially in patients with ≥vgPR, suggesting a possible relation of immune surveillance with quality of response. However, PFS was not affected in the current study. Bortezomib-based treatment has no impact on Tregs number or function. No relation between Tregs % and relative cytokines was proved in the current study, indicating the unexplored immune mechanisms underlying MM.

P31

LACK OF SURVIVAL IMPROVEMENT WITH NOVEL ANTI-MYELOMA AGENTS FOR PATIENTS WITH MULTIPLE MYELOMA AND CENTRAL NERVOUS SYSTEM INVOLVEMENT: THE GREEK MYELOMA STUDY GROUP EXPERIENCE

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Objective: Multiple myeloma of the central nervous system (CNS-MM) is a rare extramedullary manifestation of MM. It occurs in less than 1% of MM cases and exhibits a dismal prognosis with overall survival (OS) of less than 6 months. The purpose of the current study was to describe the incidence, the clinical and laboratory characteristics, the response to treatment, the outcome and the possible prognostic factors of CNS-MM survival, in the era of novel agent-based combinations (NAC). To our knowledge this is one of the largest studies including CNS-MM patients treated in the vast majority with NAC and mostly with bortezomib-based combinations.

Methods: We retrospectively reviewed the medical records of

30 consecutive patients with CNS-MM, diagnosed and treated in 12 Centers of the Greek Myeloma Study Group.
Results: Between January 2000 and December 2013, 31 (0.9%) out of 3408 newly diagnosed symptomatic MM patients, consecutively diagnosed and treated during the same period developed CNS-MM (M/F: 15/16, median age: 59 years, range: 20-96 years; newly diagnosed/relapsed-refractory: 2/29; median time to CNS-MM diagnosis: 29 months). Twenty-six percent of patients had circulating plasma cells (PCs) or plasma cell leukemia (PCL) at the time of CNS-MM diagnosis and 39% had skull-derived plasmacytomas, suggesting hematological and contiguous spread. Treatment for CNS-MM was offered in 29/31 patients and 11/29 responded (NAC: 18/29, additional radiotherapy: 9/28, intrathecal chemotherapy: 13/29). The median post CNS-MM survival was 3 months (95% CI: 1.9-4.1) and did not differ between patients treated with NAC and/or radiotherapy vs. others. In the multivariate analysis, prior treatment of MM with NAC, extramedullary disease (EMD) during MM course (i.e. plasmacytomas, circulating PCs or documented PCL) and abnormally high LDH at MM diagnosis were independent prognostic factors, whereas treatment of CNS-MM with NAC did not predict for post CNS-MM survival.
Conclusion: Despite the relatively limited number of patients due to the rarity of CNS-MM, our results suggest that NAC do not seem to improve post CNS-MM survival. Patients with EMD display shortened post CNS-MM survival and should be followed thoroughly.

P32

PROGRESSION-FREE SURVIVAL 2 (PFS-2) IS THE MOST SIGNIFICANT PROGNOSTIC FACTOR OF LONG-TERM SURVIVAL IN THE ERA OF NOVEL AGENTS: A SINGLE MYELOMA CENTER EXPERIENCE

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Objective: Before the era of novel agents (NA), 3-4% of Multiple myeloma (MM) patients were considered as long-term survivors (LTS) (i.e. patients remaining alive for >10 years). Herein, we describe the incidence, characteristics and prognostic factors of LTS MM patients of a Greek hematology center.
Methods: We checked the database of our center for the presence of LTS. In addition to Progression Free Survival (PFS) and overall survival (OS), we evaluated PFS2, defined as the time from MM diagnosis to second objective disease progression, or death from any cause.
Results: We identified 50 LTS (7.7%; M/F: 23/27, median age: 65 years, range: 47-72 years) out of 648 consecutive MM patients who were diagnosed between 1989 and 2013. LTS were younger and most of them presented with ISS stage I/II compared to all others (p<0.001). LTS had higher hemoglobin, lower creatinine and lower beta2-microglobulin at diagnosis compared to controls (p <0.05). Bence-Jones proteinuria and immunoparesis at diagnosis presented less frequently in LTS; recovery of immunoparesis after 1st line treatment was more common in LTS (p <0.05). 72% of LTS received novel agents (NA) during the course of MM. The number of patients treated with NA and the response rate after 1st line therapy did not differ between LTS and the other patients; LTS received more frequently autologous transplantation at 1st line and NA at 2nd line treatment compared to all other patients (p <0.05). After a 12-year median follow-up (range: 2-180 months), 28/50 LTS vs. 84/598 of other MM patients were alive (p <0.001); 22 LTS patients died (due to MM: 13 patients, irrelevant causes: 9 patients); 12/28 alive LTS were in CR during evaluation. The median PFS and OS for LTS vs. other patients was 81 months (95% CI: 56-105) vs. 17 months (95% CI: 15-19) and 200 months (95% CI: 180-219) vs. 33 months (95% CI: 30-36), respectively (p<0.05). In the multivariate analysis, PFS-2 was the only positive predictor for long-term survival (p <0.001; HzR: 0.98. 95% CI: 0.96-0.99); 28% of patients with PFS2 ≥4 years were alive after 10 years compared to 0.4% of those with PFS2 <4 years.
Conclusion: In conclusion, the percentage of LTS has increased in the era of NA. LTS present with more favorable disease characteristics compared to other MM patients. PFS-2 was the most significant prognostic factor of long-term survival, suggesting that disease control during the initial phase of MM, where sensitive clones still prevail and when there is no drug resistance, should be the main goal of the treatment strategy. Finally, about 1/3 of patients who displayed disease control of ≥4 years after 2 treatment lines, enjoyed a long-term survival and most importantly, 1/3 of them remained in CR and could be considered as "cured" from MM, challenging the dogma of incurable disease.

P33

CHANGES IN CHROMATIN STRUCTURE AND KEY-MOLECULES OF THE DNA DAMAGE RESPONSE PATHWAYS AFFECT THE TRANSFORMATION PROCESS OF MYELOMAGENESIS AND THE OUTCOME OF ANTI-MYELOMA THERAPY

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Objective: Important anticancer drugs exert their antitumor effects through the production of DNA interstrand cross-links (ICLs). However, the precise mechanisms contributing to differ-

ential response of patients to chemotherapy with these drugs are poorly understood.

Methods: DNA damage response (DDR) signals, chromatin structure and transcriptional activity were examined following ex vivo melphalan treatment of peripheral blood mononuclear cells (PBMCs) from 25 healthy controls (HC) and 15 newly-diagnosed multiple myeloma (MM) patients, responders (≥PR, n=9) and non-responders

Results: The accumulation of monoadducts was inversely correlated with the first-phase repair capacity of PBMCs, being significantly higher in HC than in responders and lowest in non-responders (P<0.001). Also, although ICL "unhooking" rates were similar in all individuals, accumulation of ICLs was significantly higher in HC compared to responders (P<0.01), due to higher levels of monoadducts (precursors of ICLs) left unrepaired in PBMCs. Minimal amounts of ICLs were observed in non-responders. Moreover, DSBs burden was significantly higher in HC than in responders' PBMCs, due to higher accumulation of ICLs (precursors of DSBs) and lower rates of DSBs repair in these cells (P<0.01). Minimal amounts of DSBs were observed in non-responders. Interestingly, apoptosis rates were inversely correlated with the DSBs repair efficiency of PBMCs, being significantly higher in HC compared to responders and lowest in non-responders (P<0.05). An inverse correlation was found between the chromatin condensation and the repair capacity of PBMCs, with the looseness of the chromatin structure being significantly higher in non-responders compared to responders and lowest in HC (P<0.05). Finally, an altered expression of several DNA damage response-related genes was found between HC and MM patients as well as between responders and non-responders.

Conclusion: Changes in chromatin structure and key-molecules of the DDR pathways affect the repair capacity of MM patients, thus contributing to both myelomagenesis and the outcome of anti-myeloma therapy.

P34

EARLY DEVELOPMENT OF OSTEONECROSIS OF THE JAW IN PATIENTS WITH MULTIPLE MYELOMA WHO RECEIVE ZOLEDRONIC ACID THERAPY: THE ROLE OF GENETIC FACTORS

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Objective: One of the complications of bisphosphonates is osteonecrosis of the jaw (ONJ). The aim of this study was to investigate a possible association between SNPs in CYP2C8 and PPAR-γ and the risk of developing ONJ in a large number of multiple myeloma (MM) patients who received zoledronic acid (ZA) for their bone disease.

Methods: We screened 36 patients who developed ONJ and 104 patients who did not develop ONJ for the SNPs of interest in PPAR-γ (rs1152003) and CYP2C8 (rs193495) genes by direct sequencing of peripheral blood derived DNA.

Results: The median follow up of the patients was 72 months and the median time to ONJ development was 47 months (range: 7-182 months). Patients who developed ONJ had a median of 31 ZA infusions versus 25 infusions for the others. However, 31% of patients who developed ONJ had received <24 ZA infusions. An extraction preceded the development of ONJ in 60% of patients, it was unprovoked in 20% and it was associated with trauma/inflammation in 20% of patients. In patients with <24 infusions of ZA, the presence of SNPs in both PPAR-γ and CYP2C8 was associated with a significantly higher probability of ONJ development (55% versus 16%, p=0.011 and 29% versus 7%, p=0.07, respectively) and a shorter time to development of ONJ (19 versus 69 months, p<0.001 for PPAR-γ). Combining the genotype risk, those with high risk of SNPs in both genes had a 70% cumulative incidence of ONJ within 24 months from initiation of ZA versus 17% for those carrying one of the two SNPs and 0% for those without any high risk of SNPs (p<0.001).

Conclusion: We conclude that SNPs in the CYP2C8 and PPAR-γ genes are associated with a risk of early development of ONJ. However, increasing cumulative dose of ZA increases substantially the risk of ONJ in all patients, independently of genotype-defined risk.

P35

CENTRAL NERVOUS SYSTEM RELAPSE AFTER CHEMOTHERAPY IN A PATIENT WITH MULTIPL MYELOMA

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Introduction: We report a case of central nervous system relaps with intraparancimal,dural and leptomeningeal involvement after high dose chemotherapy.

Case: A 72-year-old man received two cycles of bortezomib and dexamethasone as an induction treatment for stage IIIA IgA kappa multipl myeloma. Partial response achieved after two cycles of bortezomib and dexamethazone and continued to treat. Biphosphonate treatment was given because of lytic bone lesions. Four months after bortezomib and dexamethasone terapy increased plasma cells in the bone marrow was observed. Patients were considered refractory multiple myeloma and began

therapy with lenalidomide and dexamethasone. Two months after lenalidomide -dexamethasone therapy the patient admitted with sudden trensient loss of vision,headache. Cranial computer tomography imaging revealed mass lesion occupying bilateral frontal lobes, was determined mega cisterna magna, both cerebral hemispheric cortical sulci were detected especially in the parietooccipital expanded to be more specific. Heterogenous dural and leptomeningeal infiltration was detected. After lenalidomide therapy symptoms related with central nervous system involvement and cytopenias related bone marrow infiltration got worse. The patient was lost from sepsis and renal failure.

Conclusion: Central nerveus system involvement of multipl myeloma is rare. It may manifest is dural myeloma or intraparenchymal infiltration or with diffuse leptomeningeal involvement. İn the literature there is no standart therapeutic approach regarding the central nervous system relapse after high dose therapy and median survival of patients with cns relapse is 2 to 3 months. There are no treatment guideline for central nerveus system myelomatosis in the literature. Systemic chemotherapy regimes, radiotherapy and intrathecal chemotherapy were tried, but thy have not prolonged survival. The central involvement of myeloma patient is presented for contributions to the literature.

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PATIENTS WITH CONCURRENT CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) AND MULTIPLE MYELOMA (MM)

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Objective: MM and B-cell CLL are two distinct lymphoproliferative disorders that arise at different stages of the B-cell maturation pathway. Their coexistence has sporadically been reported, with their clonal relationship being controversial.

Methods: We report a series of 5 patients with similtaneous CLL/MM.

Results: 5 patients (60% females) were diagnosed as symptomatic MM 7 years (4-10) after the initial diagnosis of CLL. Mean age at CLL and MM diagnosis was 68 (63-73) and 75 (67-79) years respectively. Adverse prognostic factors at the time of CLL diagnosis were unmutated CLL (60%), CD38+ (40%) and complex caryotype (20%). 60% of patients had received at least one CLL therapy-line, while all the patients were stable, with a long follow up period before developing MM . MM type was IgG (60%), LC (20%) and IgD (20%), while patients' DS stage was III (100%) and ISS stage was II (40%) and III (60%). Most common symptoms were: bone disease with multiple fractures (80%), anemia (60%), severe renal failure (60%) requiring hemodialysis (40%). 60% of patients had bone marrow infiltration >60%. Hypercalcemia, immunoparesis and thrombocytopenia presented more rarely (20%). Two patients presented the same clonality at CLL and at MM diagnosis. One patient had kappa-restricted CLL cells and lamda-restricted myeloma cells, while in the two last ones the CLL light chain restriction was unclear. At the time of MM diagnosis, bone marrow biopsy revealed 2 distinct populations (60%) or total infiltration by CLL (20%) or MM (20%) cells.

Conclusion: MM can occur late at the course of CLL, with severe manifestations. One case presented clearly 2 different clones, while for the others, IgH rearrangement studies need to be done in order to understand the biology of this coexistence.

P37

SKELETAL-RELATED EVENTS REMAIN A SIGNIFICANT COMPLICATION OF MULTIPLE MYELOMA EVEN IN THE ERA OF NOVEL AGENTS

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Objective: The aim of this study was to evaluate the SREs incidence in the era of novel agents.

Methods: We retrospectively evaluated 400 consecutive patients with symptomatic MM (207M/193F, median age: 63 years). All patients had a whole-body skeletal survey using conventional radiography at diagnosis and then at the time of relapse or whenever clinically indicated.

Results: At diagnosis, the skeletal survey detected osteolytic disease in 284 (71%) patients. SREs were observed in 167 (41.7%) patients at diagnosis: 104 (26%) patients presented with pathological fractures, while 22 (5.5%) patients required surgery to bone, 21 (5.2%) radiotherapy and 20 (5%) patients presented with SCC. The incidence of SREs was higher in patients with osteolytic lesions (49.5% vs. 24%, $p<0.001$). However, approximately 25% of patients without lytic lesions presented with a SRE at diagnosis. During first line treatment, 7 (1.75%) patients developed a SRE: 2 on bortezomib- and 5 on IMiD-based regimens. The median follow-up was 39 months. At the time of first relapse (n=176), 3 patients presented with fractures and 35 patients required local radiotherapy to bone (SRE incidence: 21.6%). Patients who had received only bortezomib-based regimens (VD or VCD, n=20) had lower SRE rate (2/20, 10%) vs. all others (36/156, 22%). In total, during the course of their disease, 52.8% of the patients presented with at least one SRE. Presentation with SREs at diagnosis did not predispose for SREs during the disease course, regardless of anti-myeloma treatment, possibly due to the low

number of fractures and the higher number of radiation needed after frontline therapy.
Conclusion: SREs remain a significant complication of MM. Despite high response rates after frontline therapy >20% of patients required radiotherapy at the time of relapse. The fracture rate was low during first line therapy and at first relapse probably due to the extensive use of BPs and bortezomib, which has bone anabolic effects.

P38

CIRCULATING TISSUE INHIBITOR OF METALLOPROTEINASE-1 CORRELATE WITH ADVANCED STAGE AND ABNORMAL BONE REMODELING IN MULTIPLE MYELOMA PATIENTS AT FIRST RELAPSE WHO RECEIVE THE COMBINATION OF LENALIDOMIDE AND DEXAMETHASONE

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Objective: Tissue inhibitors of metalloproteinases (TIMPs) are endogenous inhibitors of metalloproteinase activities and thus they modulate matrix metalloproteinase function and suppress extracellular matrix turnover. Pre-treatment serum TIMP-1 is associated with advanced myeloma but there is no information for the role of TIMP-1 at the time of relapse.
Methods: Circulating TIMP-1 levels were evaluated in 36 myeloma patients at first relapse who received the combination of lenalidomide plus dexamethasone (RD) at the standard dose, according to their renal function. Patients were also given zoledronic acid, 4 mg iv, monthly, both pre- and post-RD. Serum TIMP-1 was determined on day 1/cycle 1 and on day 28/cycle 3 of RD, using an ELISA methodology (Oncogene Science, Cambridge, MA, USA) along with serum markers of bone remodeling (CTX, TRACP-5b, bALP and osteocalcin) and osteoblast/osteoclast regulators (Dkk-1, sRANKL and OPG).
Results: The mean serum TIMP-1 level of all patients was 251.1 ng/ml (SD 95.4 ng/ml). Only two patients (1M/1F; 5%) had elevated values of TIMP-1 (UNL 459 ng/ml for males and 374 ng/ml for women). Patients had increased levels of Dkk-1, sRANKL, sRANKL/OPG ratio and bone resorption markers (CTX, and TRACP-5b) ($p<0.01$ compared with 25 healthy controls). Serum TIMP-1 correlated with OPG ($r=0.644$, $p<0.001$), creatinine ($r=0.572$, $p<0.001$), beta2-microglobulin ($r=0.481$, $p=0.003$), TRACP-5b ($r=0.449$, $p=0.006$) and Dkk-1 ($r=0.444$, $p=0.007$). Patients with ISS-3 disease at diagnosis continued to have higher levels of TIMP-1 at first relapse compared with those with ISS-1 or ISS-2. No significant alterations of TIMP-1 were observed after 3 cycles of RD. TIMP-1 did not predict for survival, both as continuous variable and as dichotomous variable, in this cohort of patients.
Conclusion: We conclude that serum TIMP-1 is not elevated in myeloma patients at first relapse although its levels correlate with abnormal bone remodeling and ISS. This may be due to the continuous use of zoledronic acid in our patients.

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VEGFR-1 CORRELATES WITH INCREASED MICROVESSEL DENSITY AND INFERIOR SURVIVAL IN NEWLY DIAGNOSED PATIENTS WITH MULTIPLE MYELOMA

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Objective: The aim of the study was to evaluate placental growth factor (PlGF) and vascular endothelial growth factor receptor-1 (VGFR-1) in symptomatic multiple myeloma (MM), compare the results with asymptomatic MM and MGUS and explore possible correlations with marrow angiogenesis (microvessel density, MVD) and survival.
Methods: Circulating levels of PlGF and VEGFR-1 were measured in 64 patients with newly diagnosed MM (16 with asymptomatic MM and 48 with symptomatic MM), 8 with MGUS and 20 healthy controls, using an electrochemiluminescence immunoassay. MVD was evaluated in trephine biopsies according to standard procedures.
Results: Symptomatic MM patients had elevated PlGF (median 19.5 pg/ml, range 6.7-91.3 pg/ml vs. 16.1 pg/ml, 10.9-25.0 pg/ml of control group; $p<0.01$) and elevated VEGFR-1 levels (88.6 pg/ml, 51.5-320 pg/ml vs. 73.3 pg/ml, 62.9-100.8 pg/ml; $p<0.001$). In MM patients there was a positive correlation between PlGF and VEGFR-1 ($r=0.62$, $p=0.009$ for asymptomatic and $r=0.36$, $p=0.01$ for symptomatic MM). Eighteen (37%) patients with symptomatic MM had low grade, while 20 (41%) had intermediate and 10 (20%) high grade angiogenesis. The median values and ranges of VEGFR-1 for low, intermediate and high grade angiogenesis were: 75.1 pg/ml (51.5-109.1 pg/ml), 94.2 pg/ml (61.2-143.8 pg/ml) and 151.8 pg/ml (103.7-320.0 pg/ml), respectively (p-ANOVA<0.0001). These patients received frontline therapy with novel agent-based regimens: 25 with lenalidomide-, 16 with thalidomide- and 7 with bortezomib-based regimens. The median follow-up period was 18.8 months and 8/47 patients have died. The probability of survival was 86% at 1 year and 78% at 2 years. In the univariate analysis the VEGFR-1 as a continuous variable correlated with higher risk of death (HR: 1.011, 95% CI: 1.004-1.018, $p=0.003$)
Conclusion: Our study suggests that myeloma patients have

increased circulating PlGF and VEGFR-1. High VEGFR-1 correlated with increased angiogenesis and inferior survival, supporting a significant role of VEGFR-1 in the biology of angiogenesis in MM.

P40

OSTEOPROTEGERIN IS A SIGNIFICANT PROGNOSTIC FACTOR FOR OVERALL SURVIVAL IN PATIENTS WITH PRIMARY SYSTEMIC AMYLOIDOSIS INDEPENDENT OF THE MAYO STAGING

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Objective: Deregulation of bone metabolism is common in plasma cell dyscrasias, including multiple myeloma (MM) and MGUS, but very little is known for bone remodeling in patients with primary systemic (AL) amyloidosis. The aim of our prospective study was to evaluate bone metabolism in newly diagnosed patients with AL amyloidosis, to compare the results with those of patients with other plasma cell neoplasms and explore possible correlations with disease characteristics, including survival.
Methods: We evaluated bone remodeling indices in 102 patients with newly diagnosed AL amyloidosis, 35 healthy controls, 35 newly diagnosed, symptomatic MM patients and 40 MGUS patients. An enzyme-linked immunosorbent assay (ELISA) was used for the detection of the following serum indices: i) osteoclast regulators: soluble RANKL and osteoprotegerin (OPG); ii) bone resorption markers: CTX, NTX and TRACP-5b and iii) bone formation markers: bone-alkaline phosphatase and osteocalcin.
Results: Bone resorption markers (CTX, NTX) and osteoclast regulators (sRANKL, OPG) were increased in AL patients compared to controls ($p<0.01$) but bone formation was unaffected. Myeloma patients had increased bone resorption and decreased bone formation compared to AL patients, while sRANKL/osteoprotegerin ratio was markedly decreased in AL, due to elevated osteoprotegerin in AL ($p<0.001$). Osteoprotegerin correlated with NT-proBNP ($p<0.001$) and was higher in patients with cardiac involvement ($p=0.028$) and advanced Mayo stage ($p=0.001$). OPG levels above the upper value of healthy controls was associated with shorter survival (34 vs. 91 months; $p=0.026$), while AL patients with OPG levels in the top quartile had very short survival (12 vs. 58 months; $p=0.024$). In Mayo stage-1 disease, OPG identified patients with poor survival (12 vs. >60 months; $p=0.012$).
Conclusion: We conclude that increased OPG in AL is not only a compensation to osteoclast activation, but may also reflect early cardiac damage and may identify patients at increased risk of death within those with earlier Mayo stage.

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DEVELOPMENT OF DOUBLE EXPRESSING DIFFUSE LARGE B-CELL LYMPHOMAS IN THE COURSE OF MULTIPLE MYELOMA, SUCCESSFULLY TREATED WITH RITUXIMAB AND LENALIDOMIDE

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Introduction: The coexistence of two distinct lymphoproliferative disorders is quite rare. We herein present a 63-year-old patient with multiple myeloma who developed diffuse large B-cell lymphoma (DLBCL) 16 years after the diagnosis of multiple myeloma (MM).
Case: In 1997 our patient presented with gradually worsening sciatica and a monoclonal serum spike. Further tests revealed multiple osteolytic lesions, a pelvic left plasmacytoma, 15% plasma cells infiltration in the bone marrow biopsy, an IgAκ paraprotein while the other tests were normal. He was diagnosed with IgAκ multiple myeloma, stage IIA according to Durie-Salmon and ISS 2; treatment was initiated with radiotherapy followed by chemotherapy. He relapsed 10 years after, with a tongue plasmacytoma and minimal bone marrow plasma cell infiltration (12%); he received bortezomib-dexamethazone, achieved complete remission and subsequently underwent autologous stem cells transplantation. Three years later, he complained of continuous and worsening epigastric pain and discomfort. Ultrasound followed by MRI revealed an abdominal mass and thickening of the terminal ileum, biopsy of which established the diagnosis of DLBCL of the "double expressing" (bcl-6, bcl-2) subtype. Staging examination tests revealed no other lesions, while the bone marrow had 65% plasma cell infiltration. R-EPOCH combination was started resulting in partial response. Because of coexisting myeloma, treatment continued with the combination of rituximab, lenalidomide and dexamethazone. After completion of 6 cycles of the above mentioned regimen, he achieved complete remission for both diseases and was submitted to a second autologous stem cell transplantation.
Conclusion: The interest of the present case lies on both the development of double expressing DLBCL in the course of MM and the very good response of this especially aggressive lymphoma to rituximab, lenalidomide and dexamethazone treatment.

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POEMS SYNDROME PRESENTING WITH INSIDIOUS DISTAL PARAPLEGIA

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Introduction: We describe a patient with POEMS on the purpose of emphasising the insidious symptoms of this rare syndrome. POEMS syndrome is a rare multisystemic disorder characterized by a combination of polyneuropathy, hemangioma, hyperpigmentation and hypertrichosis of the skin, variable endocrine disturbances, generalized edema, organomegaly and a plasma cell dyscrasia with an M-protein often associated with myeloma. Patients are often misdiagnosed with myeloma or monoclonal gammopathy of undetermined significance (MGUS).

Case: A 40-year-old woman presented to the clinic of neurology with numbness in her feet which has been occured for months. On detailed history she has no chronic illness and drug utilization. Peripheral neuropathy had been diagnosed with electromyography. Muscle power was grade three in bilateral legs. Lower limb reflexes were abnormal. No other finding was found with detailed physical examination. In a couple days, patient developed bilateral foot drop, paraesthesia of her feet. Thoracolomber MRI was performed due to her back pain. MRI showed a destructive sclerotic lesion on the level of T11. An enlarged spleen (17 cm) and hemangioma (8 mm) in the liver was also evident on abdominal ultrasonography. Primarily, metastatic lesions secondary to a solide tumour was considered. After detailed body scanning with radiologic and physical examination, no suspicious focus was found. Endocrinologic examination revealed hypothyroidism and three hypoechoic thyroid nodules. Urine was negative for Bence–Jones protein. Serum immunofixation was consistent with immunoglobulin Gλ monoclonal gammopathy. The lesion was biopsied under CT guidance and found to be a plasmacytoma, λ chain restricted. The presence of lytic lesions, splenomegaly, hypothyroidism, hemangioma and peripheral neuropathy the patient diagnosed with POEMS syndrome.

Conclusion: POEMS syndrome is a rare multisystem syndrome associated with plasma cell dyscrasia and can reliably be distinguished from other diseases if a thorough history is taken and examination performed.

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THE DNA REPAİR CAPACİTİES OF THE İNTERSTRAND CROSS-LİNKS AND DOUBLE-STRAND BREAKS İN THE OUTCOME OF ANTİ-MYELOMA THERAPY - THE SYNERGISTIC EFFECT OF DNA REPAİR İNHİBİTORS

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Objective: Many important anticancer agents exert their antitumor effect through the production of DNA interstrand cross-links (ICLs). Herein, using the ICL-inducing drug melphalan, we investigated the underlying mechanisms in processing and repair of drug-induced DNA damage and their contribution to response of Multiple Myeloma (MM) patients to anti-myeloma therapy.

Methods: We examined the melphalan-induced DNA damage formation/repair in MM cell lines [melphalan-sensitive (RPMI8226) and melphalan–resistant (LR5)] and CD138+ bone marrow plasma cells (BMPCs) from MM patients (8M/7F; median age 61 years), responders (n=9) or non-responders (n=6) to subsequent melphalan therapy.

Results: Following *ex vivo* melphalan treatment of BMPCs, higher accumulation of monoadducts was observed in responders, due to the slower first-phase repair capacity of these cells ($P<0.01$). Although the ICL repair efficiencies were similar in all patients, accumulation of ICLs was significantly higher in responders' BMPCs ($P<0.01$), due to higher levels of monoadducts (precursors of ICLs) left unrepaired in these cells. Moreover, double strand breaks (DSBs) burden was significantly higher in responders, due to higher accumulation of ICLs (precursors of DSBs) and lower rates of DSB repair in these cells ($P<0.05$). An inverse correlation was found between the apoptotic rate and the DSBs repair efficiency of BMPCs, with the apoptotic rate being significantly higher in responders compared to non-responders ($P<0.01$). In line with BMPCs data, significantly higher accumulation of monoadducts, ICLs and DSBs were found in RPMI8226 compared to LR5 cells ($P<0.001$). Interestingly, in all cell types analyzed, co-treatment with DSB repair inhibitors (NU7026, IR-1) significantly increased the accumulation of DSBs and the melphalan sensitivity of the cells ($P<0.01$).

Conclusion: BMPCs from responders to melphalan treatment are characterized by the simultaneous accumulation of the extremely cytotoxic ICL and DSBs lesions. Moreover, our results suggest that DSB repair inhibitors offer a strategy toward the improvement of existing regimens in MM.

MYELOPROLIFERATIVE NEOPLASMS

P44

A RAPID AND SENSITIVE METHOD TO DETECT COMBINATIONAL MUTATIONS IN EPIGENETIC MODIFIER GENES IN PATIENTS WITH MYELOFIBROSIS

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Objective: The mutational spectrum in myelofibrosis includes driver mutations in genes such as JAK2, CALR, and MPL with approximate frequencies 60%, 23%, and 5% respectively. Recurrent mutations in epigenetic modifiers such as ASXL1, IDH1/2 and DNMT3a have also been described. Recent studies indicate that the number and type of mutations have important clinical consequences. In this report we describe a rapid and sensitive HRM analysis PCR method using the LightCycler4800 for the detection of ASXL1, IDH1/2 and DNMT3a mutations.
Methods: 119 patients with myelofibrosis were studied. DNA was extracted from peripheral blood samples by standard procedures. JAK2V617F and MPLW515L/K mutations were detected using standard PCR assays (sensitivity>1%). CALR exon 9 mutations were detected using an HRMA-PCR assay (sensitivity>2.5%). Mutations in ASXL1, IDH1/2 and DNMT3a genes were detected using HRMA-PCR methods for the respective amplicons according to the COSMIC database. Results were confirmed by Sanger sequencing.
Results: 65 of the 119 patients carried the JAK2V617F mutation (54.62%), 6 presented MPL mutations (5.04%), and 24 CALR mutations (20.16%). ASXL1 mutations detected in 45 patients (37.81%). In 25 cases ASXL1 mutations coexisted with JAK2V617F, in 6 with CALR mutations, in 3 with MPL, while in 10 cases ASXL1 mutations was the only molecular lesion. IDH2 mutations detected in 2 cases; in one patient coexisted with JAK2V617F and ASXL1 mutation, while in the other only with ASXL1. The IDH1 mutation was observed in one patient along with CALR mutation. DNMT3a mutations detected in 5 cases; in three along with JAK2V617F, in one with CALR and one alone.
Conclusion: Our findings indicate that HRMA-PCR represent a rapid and sensitive method for the detection of mutations in epigenetic modifiers genes. Our results suggest that routine screening for these mutations may be useful to determine a patient's risk for thrombosis, leukaemic transformation, and survival according to the bibliography.

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HEMATOLOGICAL COMPLETE REMISSION BY PONATINIB IN A CHRONIC MYELOID LEUKEMIA PATIENT WITHOUT T315I MUTATION

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Introduction: Imatinib was the first TKI developed to target the bcr-abl protein for the treatment of chronic myeloid leukemia (CML), and it was followed subsequently by nilotinib, bosutinib, dasatinib, and most recently, ponatinib. Ponatinib is a third-generation TKI that is uniquely effective in inhibiting the gatekeeper T315I mutation that confers resistance to all other kinase inhibitors.
Case: A 53-year-old male presented to hematology outpatient clinic with complaints of leukocytosis, in August 2009. Cytogenetic and PCR analyses showed the presence of Philadelphia chromosome. Imatinib mesylate 400 mg/day was started. In June 2013, BCR/ABL level was found 22.55% IS. Imatinib mesylate was discontinued due to loss of molecular response. Treatment was continued with dasatinib. In April 2014, BCR/ABL level was found 304,598% IS. In this time Dasatinib was interrupted and Nilotinib was started. In November 2014, again on the fact that loss of hematologic response, patient was evaluated refractory against second-line tyrosine-kinase inhibitors. A molecular study did not reveal a T315I mutation of the BCR-ABL gene. It was decided to start and continue ponatinib 45mg daily until an unrelated donor was found for stem cell transplantation. In follow-up, ponatinib related toxicity was not observed except constipation. Four months later, he re-achieved hematologic response.
Conclusion: Conclusion Ponatinib is a potent TKI that can overcome several resistance mechanisms is previously treated patients with CML. Unlike other BCR-ABL TKIs, ponatinib was designed to overcome the T315I mutation. This case report showing the effectiveness of ponatinib therapy for refractory against first and second-line CML patients not bearing the T315I BCR-ABL mutation. Further studies are necessary to confirm the efficacy and applicability of ponatinib therapy.

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INCREASED PLATELET COUNTS AT DISEASE DIAGNOSIS ARE RELATED WITH EARLY INTRODUCTION OF CYTOREDUCTIVE TREATMENT AND REDUCED EVENT-FREE SURVIVAL IN YOUNG ADULT PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA; A FOLLOW UP STUDY OF 33 PATIENTS

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Objective: Essental thrombocythemia **(**ET) is not such an innocent disease in young adults. Most thrombotic events occur during diagnosis and almost half of the initially asymptomatic patients will have an event during the course of their disease.
Methods: Herein, we analyzed retrospectively the medical records of 33 ET patients diagnosed below the age of 45 years and followed in a single institution from 1992 to 2014. Management was left at the discretion of the treating physician but antithrombotic agents were used from disease diagnosis in all patients. Among 33 young adult patients, 11 were males and 22 females. Eighteen patients were followed for a median period of 94.5 (range 45-178) months and left untreated and they were included in group A. While cytoreductive treatment was introduced in 15 patients included in group B. Among 15 treated patients cytoreduction was introduced from disease diagnosis in seven patients and in eight during the course of their disease after a median period on observation of 36 months (range: 6-168).
Results: We separated our patients into two groups according to the need to start any cytoreductive treatment and try to discover patient's characteristics at diagnosis that can predict the early use of cytoreductive treatment. Splenomegaly of any grade was palpated in 3/18 (16.5%) patients in group A and in 2/15 (13%) in group B; p=0.796. Although hematocrit levels were equal between the two groups [42.7% (34.7-47.6) in group A and 40.7% (37.3-46) in group B; p=0.84] as were also and the leucocyte counts [7.85 (5.6-13,2) x 10^3 pcm in group A and 9.73 (4.7-11.7) x 10^3 in group B; p=0.6], the median values of platelet counts at diagnosis was significantly higher in group B compared to group A [805 (490-2300) x 10^9 pcm versus 604.5 (490-921) x 10^9 pcm; p=0.012]. Fibrosis (grade I) at the initially performed bone marrow biopsy was met at higher percentages in patients allocated in group B 40% (6/15) in group B and 11% (2/18) at group A; p=0.03. JAK2V617F was detected in 40% (6/15) in group B and 50% (9/18) in group A; p=1. According to the IPSET-thrombosis scoring system in group A most patients had low thrombotic risk 10/18, 7/18 had intermediate thrombotic risk and 1/18 had high thrombotic risk. In group B 7/15 had low thrombotic risk, 3/15 intermediate and 5/15 had high thrombotic risk. In the total cohort of 33 young ET patients platelet counts at disease diagnosis can predict reduced event free survival (EFS). As an event were considered thrombohemorhagic complications, development of myelofibrosis and the need to start cytoreductive treatment. 10-year EFS was for patients with platelet counts <600 x 10^9 pcm 89%, for platelet counts between 600-800 x 10^9 pcm 66% and for platelet counts >800 x 10^9 pcm was 22% (p=0.003, Kaplan-Mayer, LogRANK test). On the contrary the presence of grade-I fibrosis was not associated with reduced EFS.
Conclusion: In young ET patients increased platelet counts at disease diagnosis can predict an eventful disease journey with early need for the use of cytoreductive treatment and reduced EFS.

P47

MULTICENTER-RETROSPECTIVE ANALYSIS OF TURKISH PATIENTS WITH CHRONIC MYELOPROLIFERATIVE NEOPLASMS

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Objective: Chronic Myeloproliferative neoplasms (CMPN) that are Philadelphia-negative malignancies include Polycythemia Vera (PV), Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF), according to WHO classification. The aim of this report was to determine the demographic features, disease characteristics, JAK mutational status, treatment strategies, and survival rates of 708 patients with CMPN from 8 centers in Turkey.
Methods: Across all of Turkey, 8 centers were enrolled in the study. We retrospectively evaluated 708 patients' results with CMPN.
Results: The JAK2V617F mutation was found positive in 75.11% of patients with PV, in 51.5% of patients with ET and in 50.4% of patients with PMF. Thrombosis occurred in 20.65% of patients with PV, in 15.12% of patients with ET and in 9.6% of patients with PMF. Bleeding at diagnosis occurred in 7.5% of PV patients, in 9% of ET patients and in 10.4% of PMF patients. Six hundred and eight patients (85.9%) had a cytoreductive therapy. The most common used drug was hydroxyurea (75.1%). Cytoreductive therapy was changed in 198 (28% of all) patients. In the second-line treatment, the most common used drug was anagrelide (147 of 198 patients). Anti-platelet therapy was used in 553 (78.1%) patients. Splenectomy was performed in 10 (1.4%) patients.

Eight PMF patients (1.1% of all CMPN patients) were treated with allogeneic stem cell transplantation. Progression to acute leukemia and secondary myelofibrosis were observed in 0.6 % and 11.3% of all patients, respectively. The median follow- up was 38 months (0-322) and overall survival (OS) was 86.7% at 10 years in all patients.

Conclusion: Our patients results is compatible the literature except the frequency of JAK2V617F mutation in PV patients. Hydroxyurea was the most common used cytoreductive therapy in our patient cohort.

P48

A CASE OF COLON ADENOCARCINOMA IN A PATIENT WITH CHRONIC MYELOID LEUKEMIA TREATED WITH DASATINIB

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Introduction: Chronic myeloid leukemia (CML) is a chronic myeloproliferative disorder, caused by the unregulated proliferation of granulocytes at different stages of development and maturation. Solid tumors may occur in 3% of the patients with CML. Especially, in older ages, a second malignancy is much more common.

Case: We report the case of a 54-year-old woman carrier Ph+ CML who developed colon adenocarcinoma under the therapy of dasatinib that was started after five years of imatinib therapy that was discontinued due to loss of molecular response. During treatment with oxaliplatin-capecitabine and dasatinib, CML relapse and serious myelosuppression were not observed.

Conclusion: Our report suggests that the clinician should carefully check the CML patients, especially elder, in terms of secondary malignacy on routine follow-up and dasatinib is an important treatment option for colon adenocarcinoma cancer in patients with CML.

TRANSPLANTATION AND GENE THERAPY

P49

LOW CIRCULATING MANNAN-BINDING LEPTIN LEVELS CORRELATE WITH INCREASED NUMBER OF FEBRILE EPISODES IN MYELOMA PATIENTS WHO UNDERGO AUTOLOGOUS STEM CELL TRANSPLANTATION AND DO NOT RECEIVE ANTIBIOTIC PROPHYLAXIS

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Objective: Patients with multiple myeloma (MM) are at a higher risk of infections. The mannan binding leptin (MBL) pathway of the complement system is part of the innate immune system and seems to influence the risk of infections in cancer patients during treatment. The aim of this study was to evaluate the impact of MBL levels on the risk of infections and of febrile episodes in MM patients who undergo autologous transplantation (ASCT).

Methods: We studied 100 MM patients who underwent an ASCT between 1996-2011. Sixty-seven patients participated in a randomized study, where in the A arm patients received prophylactic antibiotics during ASCT, while in the arm B there was no antibiotic prophylaxis. MBL serum levels were measured in all patients on the day of mobilization, using an ELISA methodology (R&D Systems, Minneapolis, MN, USA).

Results: Seventeen patients had MBL levels <500 mg/L (the lower normal limit). Of those, 11 received antibiotics prophylaxis and 6 did not. In general, there was no statistical difference regarding the development of fever or neutropenic fever between patients with MBL serum levels of <500 mg/L or >500 mg/L. However, among 17 patients with MBL levels of <500 mg/L, 6/11 patients who received antibiotics prophylaxis developed a febrile episode compared to 6/6 patients who did not receive antibiotics prophylaxis and developed a febrile episode (p=0.049). Nevertheless, patients with MBL levels <500 mg/L attained a lower response rate to first line therapy with antibiotics, requiring administration of a second line regimen, compared to patients with MBL levels of >500 mg/L (66.7% versus 88.9%, respectively; p=0.05).

Conclusion: MM patients who undergo ASCT and have low MBL levels have a lower response rate in first line antibiotic regimens, requiring more often administration of a second, more advanced, line of antibiotics. The administration of prophylactic antibiotics to these patients seems to reduce the number of febrile episodes.

P50

EFFICACY AND SAFETY OF BORTEZOMIB AND LENALIDOMIDE CONSOLIDATION POST-AUTOLOGOUS STEM CELL TRANSPLANTATION IN PATIENTS WITH MULTIPLE MYELOMA: FINAL RESULTS OF A PROSPECTIVE STUDY

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Objective: The primary endpoint of the study was to explore the efficacy of VR (bortezomib and lenalidomide) consolidation, without dexamethasone, in newly-diagnosed patients with multiple myeloma (MM), who received bortezomib-based induction treatment and then underwent autologous transplantation (ASCT). Secondary endpoints included: safety, time to progression (TTP), time to next treatment (TtNT), overall survival (OS) and VR effects on bone metabolism in the absence of bisphosphonates administration.

Methods: Between January 2010 and November 2013, 59 patients (30M/29F, median age 54 year) who achieved at least stable disease post-ASCT were entered into this study. Consolidation consisted of 4 VR cycles, which started on day 100 post-ASCT. Bortezomib was given at a dose of 1.3 mg/m^2, on days 1, 4, 8 and 11 of a 21-day cycle, while lenalidomide was given at a dose of 25 mg, p.o., daily on days 1-14. Patients did not receive any bisphosphonate during the study. We measured the following bone remodeling molecules on the day of stem cell collection and then before and after VR consolidation: sRANKL, osteoprotegerin, dickkopf-1, sclerostin, CTX, TRACP-5b, bone-specific ALP and osteocalcin.

Results: Before HDM, one (1.7%) patient had achieved a sCR, one (1.7%) CR, 30 (50.8%) vgPR, 22 (37.3%) PR, while 5 (8.5%) patients had stable disease. After ASCT, 34 (57.6%) patients improved their status of response, while after VR consolidation, 23/59 (39%) patients further improved their response status. Overall, 30 (50.8%) patients achieved a sCR, one (1.7%) CR, 26 (44.1%) vgPR and two (3.4%) PR. The most important adverse events included neutropenia (68%, grade 3/4 23%), thrombocytopenia (59%, 7%), peripheral neuropathy (56%, 2%), anemia (50%, 4.5%), skin rash (34%, 9%), infections (34%, 0%), fatigue (20%, 0%), diarrhea (16%, 0%) and constipation (14%, 2%). No patient developed deep vein thrombosis. Post-VR consolidation there was a reduction of sRANKL/OPG ratio and of sclerostin ($p<0.001$), while no skeletal-related events (SREs) were observed during the study period. The median follow-up after the ASCT was 35 months (range: 7-60) and 24 patients have progressed. The median TTP after the ASCT was 42 months. There was a trend for longer TTP in patients achieving sCR compared to others (48 vs. 35 months, $p=0.145$).

Conclusion: Four cycles of VR consolidation without dexamethasone is an effective regimen which improves the quality of response in approximately 40% of patients and produces long TTP. In the absence of bisphosphonates, VR consolidation has beneficial effects on bone metabolism and is related with no SREs.

P51

SUCCESSFUL MOBILIZATION WITH PLERIXAFOR, USED AS SALVAGE REGIMEN AFTER CHEMO-MOBILIZATION, FOR PATIENTS WITH MULTIPLE MYELOMA WHO RECEIVED RADIOTHERAPY PRIOR TO AUTOLOGOUS TRANSPLANTATION

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Objective: High dose melphalan (HDM) and autologous stem cell transplantation (ASCT) remains the treatment of choice for eligible patients with multiple myeloma (MM). Prior administration of radiotherapy before ASCT has been associated with poor stem cell mobilization. We report two MM patients who underwent extensive radiotherapy prior to ASCT and required plerixafor administration as salvage mobilization agent, after chemo-mobilization with cyclophosphamide and G-CSF.

Methods: The first patient (a 42-year-old male) received radiotherapy (30Gy) in right costal arch for plasmacytoma and additional radiotherapy (30Gy) in T6-T9 vertebrae for T8 plasmacytoma. Patient's therapeutic regimen also included 3 cycles of PAD. Due to residual disease he received 3 additional PAD cycles. The second patient (a 52-year-old man) received radiotherapy (30Gy) on thoracic vertebrae due to plasmacytoma evolving from T2 vertebra. He also received 4 cycles of anti-myeloma therapy with VCD.

Results: The first patient received chemo-mobilization with 2.5 g/m2 cyclophosphamide and G-CSF. Initial stem cell harvested 0.8x10^6 CD34+/kg. Salvage administration of plerixafor on the night of first collection date resulted in a subsequent harvest of 6.2x10^6 CD34/kg. The latter collection allowed HDM administration and stem cell re-infusion. The second patient received stem cell mobilization with 2.5 g/m2 cyclophosphamide and G-CSF. Initial harvest resulted in collection of 1.2x10^6 CD34+ cells/kg. Plerixafor was administered and led to a second collection of 8.6x10^6 CD34+/kg that allowed administration of HDM.

Conclusion: Plerixafor has been reported to increase 4-5 times the number of collected stem cells when it is used as initial mobiliza-

tion regimen with G-CSF or 2-3 times when it is used as salvage regimen after chemo-mobilization with cyclophosphamide and G-CSF. Our cases support that plerixafor facilitates stem cell mobilization (>7 fold compared to chemo-mobilization) in MM poor mobilizers after radiotherapy. Further data are needed to clarify this issue and to determine the best mobilization regimen for this subgroup of patients.

P52

THERAPEUTIC CANCER VACCINE: PRODUCING DENDRITIC CELL FROM ALLOGENEIC DONOR STEM CELLS

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Objective: Tumor immunotherapy is a treatment modality that has been long attempted to use as a supportive treatment along with standard therapies. Cellular therapy, a method of tumor immunotherapy, is introduced in cancer therapy as allogeneic and autologous stem cell transplantation. Donor leukocyte infusion is a salvage method to regain remission in patients with recurrent or minimal residual disease after stem cell transplantation. T lymphocytes and antigen-presenting cells (dendritic cells) are two cell lineages that play crucial role in the battle of organism against cancer. Close similarity between cancer cells and normal cell structure is the most important reason of escape from defense cells, namely T lymphocytes. Stimulation and enhancement of T lymphocytes against cancer cells comprise principal part of therapy. Tumor immunotherapy involves active immunotherapy, passive vaccination and immunomodulatory therapies. Active immunotherapy provides better recognition of tumor-related antigens by immune system of patient, enhanced immune system and elimination of malignant cells. This modality employs therapeutic potential of donor specific and tumor specific immune responses. Active immunotherapy targets immunosuppressive and tolerogenic mechanisms suppressed by tumor. Active immunotherapy has emerged in clinical practice since 1990 following years of experimental studies.
Methods: To generate allogeneic dendritic cells, leukemic stem cells were isolated from blood samples drawn from patients with acute leukemia. Lysate was prepared from leukemic stem cells identified by flow cytometry. For allogeneic stem cell transplantation, stem cells and mononuclear cells (1x10 >6/kg) obtained from sibling donors by apheresis were separated to produce tumor vaccine. For dendritic cell transformation, GM-CSF and IL-4 were added to media where leukemic stem cell lysate from patient and mononuclear cells from sibling donor were treated. Surface markers for dendritic cells including CD80, CD83 and CD86 were evaluated in samples obtained from cultured cell on the hours 48, 72 and 96 by using flow cytometry.
Results: Mononuclear cells were detected by 27% among allogeneic hematopoietic cell groups harvested by apheresis. After culture under GMP conditions, mononuclear cell rate was found to be 24% on hours 96 and 120. It was seen that 88% of mononuclear cells transformed to mature dendritic cells after 96-hours culture.
Conclusion: In cancer patients, tumor vaccine obtained from allogeneic sibling donor can be used in lieu of autologous tumor vaccine and it is thought to be more effective. In cancer patients, minimal residual disease can be eliminated by active tumor vaccine after reducing tumor burden by standard methods. Allogeneic dendritic cells produced at 37°C in CO_2 media under GMP conditions can be used in tumor immunotherapy. More effective method would have been used by employing dendritic cells against cancer stem cells rather than cancer cells itself.

P53

SAFETY AND EFFICACY OF CHEMO-MOBILIZATION AND LARGE VOLUME LEUKAPHERESIS IN HEMATOLOGY/ONCOLOGY PATIENTS: A SINGLE CENTER EXPERIENCE IN 327 PATIENTS

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Objective: Autologous stem cell transplantation (ASCT) is widely used for the management of lymphomas and myeloma. To improve stem cell (SC) collection efficiency, chemo-mobilization combined with large volume leukapheresis has been evaluated as a more efficient apheresis procedure. Here we report our experience regarding the safety and efficacy of large volume leukapheresis.
Methods: Between 1996-2010, 327 patients with hematological malignancies or solid tumors have been recruited in our study. The vast majority of patients received intravenous cyclophosphamide (4 mg/m2 or 2.5 mg/m^2) with G-CSF for mobilization of peripheral blood SC (PBSC). PBSC collection was performed with a COBE Spectra Blood Cell Separator (COBE Laboratories, Lakewood, CO). Large volume leukapheresis was defined either by processing a minimum of 15L of peripheral blood or by processing more than three times the total peripheral blood volume, as previously reported.
Results: 327 patients underwent a cumulative total of 407 SC collections. Large volume leukapheresis was generally well tolerated with hypocalcaemia, decrease in platelets counts (median decrease 46.7%) and hypokalemia being the most common side effects. 90% of patients managed to collect sufficient number of SC for transplantation (defined as >3×10^6 CD34/kg) whereas most of these patients (67%) managed to collect sufficient SC with one harvest and 46 (16%) patients yielded enough cells to

allow a second transplantation. The median product volume per collection was 350 ml (range 50-838 ml). The median total CD34+ cell yield/kg was 6.46×10^6 CD34+ cells/kg (0-64.7). Factors that negatively affected SC yield were >2 lines of chemotherapy or radiotherapy before HDT, while patients with >65kg needed more often at least two days for sufficient SC collection.

Conclusion: Large volume leukapheresis in combination with stem cell chemo-mobilization is a relatively safe and highly efficient procedure, leading in a successful collection in the vast majority of patients, minimizing the use of more advanced and more expensive mobilization regimens.

P54

EFFICIENCY OF PLERIXAFOR FOR AUTOLOGOUS STEM CELL MOBILIZATION; A SINGLE CENTER EXPERIENCE FROM TURKEY

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Objective: In this study, plerixafor stem cell mobilizing activity was assessed in patients with autologous stem cell transplantation and the adequate number of stem cell could not have been collected with chemotherapy and G-CSF (granulocyte colony stimulating factor) before.

Methods: This study was participated by 25 patients, from whom adequate stem cell numbers could not have been collected with chemotherapy and filgrastim (10 mcg/kg) at Erciyes University Department of Hematology Apheresis Unit between 27.01.11 and 06.09.14. In the second-line treatment for 15 patients, subcutaneous plerixafor 0.24 mg/kg was applied, and the remaining 10 patients a couple of weeks later. The collected CD34 + cell numbers and percentage ratios were analyzed.

Results: Donors of 8 (32%), Multiple Myeloma, donors of 4 (16%) Hodgkin's lymphoma, and donors of 8 (32%) Non-Hodgkin's lymphoma (follicular, B and T cell lymphomas) and donors of 5 of (20%) is the diagnosis of testicular tumors. Sixteen patients were male(64%) and 9 were female (36%). Mobilization process for 10 patients using peripheral and central venous catheter was used in 15 patients. The median age of donors 46 (min: 17, max: 71), the median weight of 67 kg (min: 50, max: 96kg). Mean dose of G-CSF was 10.5 ± 2.0 (min: 6 max: 13). Before the procedure, peripheral CD34 (+) cell count was median 21.85/microliter (min: 2.20, max: 103.80)and median collected CD34 (+) cell count was 4X106 / kg (min: 2.35, max: 13.58). Five of our patients could not be gathered enough stem cells. Autologous stem cell transplantation was performed to 17 of all patients that adequate number of stem cells has been collected. Average neutrophil engraftment period of these patients was 10.6 ± 0.89 (min: 10, max: 13) days, and mean platelet engraftment period was 13.2 ± 3.02 (min: 10, max: 23)days. Five of the patients are still waiting for transplantation.

Conclusion: Plerixafor addition to G-CSF is effective on mobilization as well as the collection of adequate number of stem cells with drug combination in cases who have been scheduled with autologous stem cell transplantation and from whom adequate number of stem cells could not have been collected with chemotherapy followed by G-CSF.

P55

EVALUATION OF PERIPHERAL BLOOD STEM CELL MOBILIZATION AND COLLECTION IN ELDERLY PATIENTS

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Objective: Adequate hematopoietic stem cell mobilization and collection is essential for patients who are candidate for autologous stem cell transplantation. In this study we compared mobilization success rates, amount of collected stem cells and the factors that could affect the procedure for patients younger and older than 60 years old.

Methods: For this study, 112 patients who admitted to Erciyes University BMT Center for autologous stem cell transplantation were enrolled. Thirty-three of them (36%) were under 60 years called young group and 76 of them (%64) over 60 years called elderly group. Among the participants, 73 of them were multiple myeloma, 23 of them Non-Hodgkin's lymphoma, 17 of them Hodgkin's lymphoma. Between the groups we compared the amount of pre-apheresis white blood cell (WBC), platelets, peripheral CD34+ cells, value of collected CD34+ cells and mononuclear cells, mobilization failure and success rates and number of apheresis sessions.

Results: The median values of pre-apheresis peripheral CD34+ cells were 8.72×10^6/kg and platelets were 86×10^9/L in young group; CD34+ cells were 8.95×10^6/kg and platelets were 86.5×10^9/L in elderly group (p=0.918 and p=0.899, resectively). The median values of collected CD34+ cells were 7.61×10^6/kg (range: 2.52-46.62) and 7.60×10^6/kg (2.87-25.50) in under and over 60 years, respectively (p=0.800). Also the median values of total collected mononuclear cells (MNC) were 1.41×10^7/kg and 1.4×10^7/kg in young and elderly group, respectively (p=0.607). It was found as 1.89 days in elderly group and 1.7 days in young group when we compared their apheresis sessions (p=0.786). There was no statistical significance between two groups; despite the mobilization failure rates were 18% and 6% in patients older and younger than 60 years (p=0.087). On the other hand, the number of multiple myeloma in the patients with applied autologous stem cell mobilization was higher in elderly patients

than young ones (p=0.004) and we also demonstrated that the failure of mobilization were lower in patients with multiple myeloma than lymphoma patients (p=0.003). There was no significant difference between the amounts of pre-apheresis WBC, platelets and peripheral CD34+ cells in mobilization failure group and success group.

Conclusion: We demonstrated that the amount of pre-apheresis peripheral or collected CD34+ cells and numbers of apheresis sessions are not significantly different in comparison of the young and elderly patients who are planned autologous stem cells transplantation. Mobilization failure rate was higher in lymphoma patients than myeloma patients. It was also found that mobilization failure rates were higher in elderly patients than young patients.

P56

MOBILIZATION OF AUTOLOGOUS PERIPHERAL BLOOD STEM CELLS WITH SPECTRA OPTIA V5.0: A SINGLE CENTER EXPERIENCE WITH AN AUTOMATIC INTERFACE-CONTROLLED APHERESIS SYSTEM

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Objective: Available manual apheresis systems generally produce stem cell yields of consistently high quality that can be safely used for autologous transplantation. However, manual apheresis needs continuous interface monitoring/adjustment, suffers from interface instability in poor mobilizers, high collection variability, high platelet loss and failure to electronically document parameters. A new advanced apheresis system, Spectra Optia v5.0, featuring optical sensors, which provide real time automatic interface and product line control, was designed to override these disadvantages.

Methods: In our study, we evaluated data of 10 stem cell leukapheresis performed in 8 patients with various malignancies using Spectra Optia after 2011 to test its feasibility and effectiveness. We compared our data with those obtained from 225 patients that had undergone a stem cell collection for autologous transplantation in our Department between 2004 and 2011, using the COBE Spectra machine.

Results: The use and function of automatic interface control of Spectra were satisfactory. Due to the application of lower inlet volumes/min, as compared to corresponding volumes with the COBE Spectra machine, our apheresis with Spectra Optia usually took a longer time (median 447 min versus 317 min, p<0.005). Regarding other collection parameters, such as the percentage of CD34+ cells in the final leukapheresis product, total yield of CD34+ cells, and product volume data were comparable for both devices (0.74% versus 0.97% CD34+, p=0.103; 6.85 versus 7.1 x 106 CD34+/kg, p=0.752; and 403.5 versus 353 ml graft volume, p=0.094, respectively). Time to engraftment was also comparable for both apheresis devices. More specifically, time interval to neutrophil counts >500/μl, neutrophil counts >1500/μl did not significantly differ (10 days versus 9 days, p= 0.386 and 11 days versus 10 days, p=0.229, respectively). However a delay in platelet recovery with Optia device need to be confirmed with additional data from apheresis procedures (median time to platelet counts >25000/μl was 12 days versus 11 days for COBE Spectra, respectively; p=0.037). Platelet loss with Optia was less than with COBE Spectra (1278 versus 2415×103/μl, p=0.014). No significant differences were observed for product hematocrit between Optia and COBE Spectra (5.7% versus 6.6%, p=0.392).

Conclusion: The automatic Spectra Optia aphereses were associated with similar and equally variable stem cell collections as aphereses with COBE Spectra. Further data are needed to clarify the potential benefit of lower platelet loss using Optia. We continue to use this procedure in our center and updated results will be presented in the meeting.

P57

TECAM (THIOTEPA, ETOPOSIDE, ARA-C, CYCLOPHOSPHAMIDE AND MELPHALAN) AS CONDITIONING REGIMEN FOR AUTOLOGOUS STEM CELL TRANSPLANTATION IN PATIENTS WITH NON-HODGKIN LYMPHOMA: RETROSPECTIVE SINGLE CENTER EXPERIENCE

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Objective: High-dose chemotherapy regimens for conditioning followed by autologous stem cell transplantation (ASCT) generally provide favorable results in non-Hodgkin lymphoma (NHL). We have evaluated the efficacy and tolerability of a high-dose conditioning regimen comprising TECAM [thiotepa (40 mg/m2 x four days), etoposide (200 mg/m2 x four days), cytosar (200 mg/m2 x four days), cyclophosphamide (60 mg/kg x one day), and melphalan (60 mg/m2 x two days)] in patients with NHL.

Methods: Seven patients (4 F, 3 M) with NHL at various stages who underwent ASCT were included in this retrospective study. The median age at transplantation was 59 (range, 47–68). The diagnoses were as follows: 2 diffuse large B-cell NHL, 1 angioimmunoblastic T-cell lymphoma, 1 marginal zone lymphoma, 1 follicular lymphoma, 1 T-cell lymphoblastic lymphoma and 1 mantle cell lymphoma.

Results: All patients completed the therapy protocol. The median of collected CD34+ cells was 7.95x10^6/kg (range from 3.6 to 13.8x10^6/kg). Engraftment for neutrophils and platelets was always achieved except one patient. The median time to recovery of absolute neutrophil (500/μL) and platelet (20,000/μL) counts independent of transfusion was from 10 to 19 days (median, 12 days) and 11–41 days (median, 25 days), respectively. The median stay in hospital was 45 days (range, 25–108). Infections were well controlled with antibiotics and resolved after engraftment. Non-infective complications resolved after neutrophil recovery. One patient died due to transplant-related complications, as septic shock with acute distress respiratory syndrome. The overall response rate was 71% (4 CR, 57%; 1 PR, 14%), whereas 1 patient (14%) was refractory to TECAM.
Conclusion: Treatment of primary progressive and refractory NHL remains particularly difficult. ASCT with variety of conditioning regimen has been stil the best option. TECAM treatment regimen provided favorable outcomes as CR in 4 out of 7 patients, with no significant increase in infective and noninfective complications and only 1 transplant-related deaths. Randomized trials on large numbers of patients may be useful to confirm the high anti-NHL activity and low toxicity of this treatment schedule in poor-prognosis NHL patients.

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EVALUATION OF FEBRILE NEUTROPENIC EPISODES IN AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMAS

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Objective: The most important cause of mortality in febrile neutropenic episodes (FNEs) that mature after autologous hematopoietic stem cell transplantations (aHSCT) is infections. Broad-spectrum empric antibiotherapy must be started immediately as a standard approach in FNEs. Identification of infectious agents in Non-Hodgkin Lymphoma (NHL) group was aimed.
Methods: One hundred and eight aHSCT data from 108 relapsed/refractory NHL patients who was underwent transplantation at the Hospital of Ege University, Adult Hematology Department, Transplant Center between 2008 and 2014 were analyzed retrospectively.
Results: Sixty-six patients were male and 42 female. The mean age was 53.1 years (19-76). Central venous catheter was used in 88 (81.5%) HSCTs. FNEs was detected in 106 (98.1%) HSCT. All the patients received antiviral and antifungal prophylaxis and antibacterial prophylaxis was used in 53 (49.1%) HSCT. In FNEs, 14.8% efficient pathogen microorganism was isolated from blood cultures. 72.8% of pathogens were gram-positive, 27.2% were gram-negative bacterias. 3.7% efficient pathogen microorganism was isolated from urine cultures, all of them were gram-negative bacterias. 19.4% efficient pathogen microorganism was isolated from catheter cultures. 57.1% of pathogens were gram-positive, 42.9% were gram-negative bacterias. 1.8% efficient pathogen microorganism was isolated from sputum, all of them were gram-negative bacterias. A pathogen was isolated in 8.3% of stem cell products. Serum galactomannan antigen (SGA) was detected positive in 12 (11.1%) episodes and false positivity of SGA was 8.8% in all HSCTs. CMV-DNA was positive in 10.2% episodes. Fifty-nine HRCT was performed in FNEs. Pneumonia was detected 15.7% in all episodes. 29.4% of pneumonia that detected in HRCTs was fungal and no viral pneumonia was detected.
Conclusion: It can supply useful additive for a better FEN management process if the medical centers follow their infection agents closely, perform CMV and SGA assays and modify their empiric antibiotic treatment policies in especially HSCT groups.

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AUTOLOGOUS HEMAPOIETIC STEM CELL MOBILIZATION AND HARVEST BY AGE GROUPS IN NON HODGKIN LYMPHOMA: A SINGLE CENTER EXPERIENCE

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Objective: Autologous hemopoetic stem cell transplantation (aHSCT) can offer potential long-term remission or cure in patients with relapsed or refractory non-Hodgkin lymphoma (NHL).The mobilization of HSCs can be a limiting factor for transplantation. HSCs mobilization, harvest and engraftment periods were evaluated by age groups.
Methods: Fifty-four relapsed/refractory NHL cases treated with aHSCT in Ege University between 2008-2014 were evaluated retrospectively. Patients were divided into 3 groups according to age range;first group was 18-59 years, second group 60-64 years and third group was >65 years old.
Results: Group 1 was consisted of 18 patients, group 2 of 17 and group 3 of 19 patients. All the patients were mobilised after a salvage chemotherapy regimen (ICE or ESHAP) combined with 10μg/kg/day dose of filgrastim. Mean collection day after filgrastim administration was 6.2 days for group 1, 5.2 for group 2 and 6.8 days for group 3. Mean apheresis cycle was 2.4 for group 1, 2.7 for group 2 and 2.9 for group 3. Mean total CD34+ HSCs number was 8.5x10^6 for group 1, 5.9x10^6 for group 2 and 7.4x10^6 for group 3. There was no statistically significnt difference between groups in terms of HSCs collection day and total apheresis cycle, but CD34+ HSCs number was statistically higher in group 1 compared to group 2, but interestingly there was no statistical difference between groups 1 and 3. OS after aHSCT

was 22.7 months in group 1, 20.4 in group 2 and 19.6 months in group 3. Transplantation related mortality (TRM) was 8% in group 1, 11.7% in group 2 and 20.1% in group 3 ($p<0.05$).

Conclusion: High-dose chemotherapy, followed by aHSCT, is an effective treatment option for patients with relapsed/refractory NHL, but TRM is significantly higher in >65 years old patients. Therefore, patients must be carefully selected. There is no reason to explain the HSC quantity difference between the groups,because there is no statistically difference between group 1 and 3 but HSC quantity is lower in group 2. Larger study groups and different parameters are needed to demonstrate this difference.

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AUTOLOGOUS HEMAPOIETIC STEM CELL MOBILIZATION AND HARVEST IN HODGKIN LYMPHOMA: A SINGLE CENTER EXPERIENCE

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Objective: Hodgkin lymphoma (HL) is one of the most common malignancies in young adults and has become curable for the majority of patients with autologous hematopoetic stem cell transplantation (aHSCT), even in advanced stage. The mobilization of hematopoietic stem cells (HSCs)can be a limiting factor for transplantation.HSCs mobilization, harvest and engraftment periods were evaluated.

Methods: Patients who was underwent aHSCT at the Hospital of Ege University, Adult Hematology Department, Transplant Center between 2008 and 2014 were analyzed retrospectively. Fify-six relapsed/refractory HL patients who was underwent aHSCT were included to study.

Results: The median age of the patients was 43 years (27-75 years), and of 36 (64.2%) males and 20 (35.8%) females.Thirty-five (61.4%) of the patients were nodular sclerosis HL,14 were (24.6%) mixed cellular HL,4 (7.0%) were lymphocyte predominant HL,and 3 (5.3%) were lymphocyte-rich HL. All the patients were mobilised after a salvage chemotherapy regimen (ICE or ESHAP) combined with 10µg/kg/day dose of filgrastim. Mean collection day after filgrastim administration was 5.6 days for female and 6.1 for male. Mean apheresis cycle was 2.5 for female and 2.4 for male. Mean total CD34+ HSCs number was $8.7x10^6$ for female and $7.5x10^6$ for male. Poor mobilization was not observed in any patient. There was no statistically difference between sex, mobilisation regimen and type of Hodgkin lymphoma in terms of HSCs collection day, total apheresis cycle and total CD34+ HSCs number. Mean neutrophil and platelet engraftment time was 12.4 and 14.4 days, respectively. There was no statistically difference in neutrophil and platelet engraftment time in terms of sex, type of HL and radiotherapy history.Transplantation related mortality was 1.7%, complete and partial remission after aHSCT was obtained in 37 (67%) and 9 (16%) of patients, respectively. Overall survival was significantly better in patients with complete remission ($p<0.05$).

Conclusion: High-dose chemotherapy, followed by aHSCT,is an effective treatment option for patients with relapsed/refractory Hodgkin lyphoma, allowing further consolidation of response.

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COMPARISON OF AUTOLOGOUS HEMATOPOETIC STEM CELL MOBILIZATION AND HARVEST DATA IN HL AND NHL PATIENTS

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Objective: Autologous Hematopoietic Stem Cell Transplantation (aHSCT) provides cure option for relapsed/refractory lypmhoma patients. Poor mobilization of hematopoietic stem cells (HSCs) can be a limiting factor for aHSCT. Non Hodgkin Lyphoma (NHL) and Hodgkin Lypmhoma (HL) was compared in terms of HSCs mobilization, harvest and engraftment periods.

Methods: Sex and age matched 55 relapsed/refractory NHL and 55 relapsed/refractory HL cases treated with aHSCT in Ege University Hospital between 2008-2014 were evaluated retrospectively.

Results: All the patients were mobilised after a salvage chemotherapy regimen (ICE or ESHAP) combined with 10µg/kg/day dose of filgrastim. Poor mobilization was not observed. Mean collection day after filgrastim administration was 6.1 days for NHL group and 5.9 for HL group. Mean apheresis cycle was 2.3 for NHL group, 2.4 for HL group. Mean total CD34+ HSCs number was $8.4x10^6$ for NHL group and $7.9 x10^6$ for HL group. There was no statistically difference between groups in terms of HSCs collection day, total apheresis cycle, and CD34+ HSCs number between groups. Mean neutrophil and platelet engraftment time was 11.7 and 15.7 days in NHL group, and 12.4 and 14.4 in HL group, respectively. There was no statistically significant difference between the groups.

Conclusion: Lymphoma type is not a predictor factor for HSC mobilization, harvest and engraftment. Larger study groups and different parameters are needed to demonstrate predictor factors for mobilization and engraftment.

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"REAL WORLD DATA" ON CLINICAL FEATURES, PROGNOSIS AND OVERALL SURVIVAL POST AUTOLOGOUS STEM CELL TRASPLANTATION IN MULTIPLE MYELOMA IN THE ERA OF NOVEL AGENTS: A REPORT OF THE GREEK SOCIETY OF HEMATOLOGY IN 489 PATIENTS

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Objective: Autologous stem cell transplantation (ASCT) and novel agent-based therapies have improved multiple myeloma (MM) outcome. In the era of novel agents, prognostic factors for post-ASCT survival are not clearly defined and data regarding the role of post-ASCT consolidation/maintenance (C/M) therapy are inconclusive. Our aim was to describe "real world data" on clinical features, prognosis and post-ASCT survival of MM patients treated with ASCT in Greece, in the era of novel agents.
Methods: We reviewed the medical files of 489 consecutive MM patients (M/F: 278/211, median age: 56 years, range: 31-79 years; ISS-1: 189, ISS-2: 141, ISS-3: 90, missing data: 69) treated with ASCT between 2000 and 2013 in seven Greek Hematology Centers.
Results: High risk cytogenetics, i.e. del17p and/or t(4;14), were found in 24/104 (23%) patients with available data; 220 (45%) patients received conventional treatment and 269 (55%) received novel agent-based therapies. The median number of induction cycles was 4 (range: 1-9). The median number of pre-ASCT treatment lines was 1 (range: 1-3); 470 patients underwent single and 19 tandem ASCT; 378 patients were mobilized with cyclophosphamide + G-CSF, 79 patients with G-CSF alone and 32 patients with multi-agent chemotherapy. The median number of CD34+ cells infused was 5.9x106/kg (range: 2.6-7.43x106/kg); 176 patients had ≥very good partial response (vgPR) pre-ASCT and 203 had ≥vgPR post-ASCT. Post-ASCT, 266 patients received consolidation and/or maintenance therapy (consolidation: 80, maintenance: 186); consolidation and maintenance treatment included interferon A or dexamethasone (36 patients), thalidomide (99 patients), bortezomib ± dexamethasone (26 patients), lenalidomide (78 patients) and bortezomib + immunomodulator (thalidomide or lenalidomide) + dexamethasone (27 patients). During evaluation, 337 patients were alive (68.9%) and 149 patients (30.5%) died (due to MM progression: 88%, ASCT-related: 2%, secondary malignancy: 2%); 3 patients did not have survival data. After a median post-ASCT follow-up of 56 months (95% CI: 51.2-60.7), the median post-ASCT time to progression and post-ASCT survival were 46 months (95% CI: 38-54) and 101 months (95% CI: 79-122), respectively. In the multivariate analysis, pre-ASCT treatment with novel agents and post-ASCT consolidation and/or maintenance therapy predicted for longer survival, whereas the presence of del17p and/or t(4;14) predicted for shorter post-ASCT survival ($p<0.05$).
Conclusion: In the era of novel agents, patients treated with ASCT enjoy prolonged survival outcomes. Pre-ASCT treatment with novel agents and any type of consolidation or maintenance therapy predict positively for post-ASCT survival, indicating the importance of continuous treatment in MM. High risk features remain a strong negative predictor for post-ASCT survival.

OTHER HEMATOLOGICAL MALIGNANCIES AND TREATMENT COMPLICATIONS

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HEMATOLOGIC MALIGNANCIES IN AN AEGEAN ISLAND POPULATION: THE CASE OF CHIOS

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Objective: This study aims at recording the frequency of the various sub-types of Hematologic Malignancies (HMs) in an island population so as to draw a first round of comparisons regarding their occurrence. The case of reference is the North Aegean island of Chios, the fifth largest Greek island in terms of size and the sixth in terms of population (51,390 habitants, year 2011). The study is designed so as to offer the basis for researches that may relate the prevalence of different HMs to special genetic, social and environmental conditions (e.g. poor quality of water). It is also expected that the study will inform health-related policies regarding, for example, the allocation of resources between central and remote (e.g. island) public health care facilities.
Methods: Prevalence of HMs patients between 1-1-2011 and 30-6-2015. Sources: Chios state hospital archives, all private practice archives by hematologists (total of 2). Classification: WHO 2008.
Results: Total HMs: 308. Lymphoid Malignancies (LMs): 171 (55%). Myeloid Malignancies (MMs): 138 (45%). LMs: 52 CLL/SLL,

37 PCN (27 MM, 10 MGUS), 15 HL, 13 FL (1 grade 3B), 12MZL, 10 DLBCL-NOS, 10 T-LGL, 8LL/ALL, 4 LPL-MW, 3 MALT, 3 HCL, 1MF, 1 Angioimmunoblastic T-cell, 1HDCN, MMs: 53 MDS (23 RA, 2 RAS, 5 RN, 14 RCMD, 9 RAEB2), MPN=72 (46 ET, 17 PV, 6 CML, 3 PM), 13 AML.

Conclusion: The 4.5 year period prevalence seems to be too high in comparison to all available international standards and therefore further study is needed.

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INVESTIGATION OF SEASONAL FREQUENCY AND PATHOGENS IN FEBRILE NEUTROPENIA

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Objective: Febrile neutropenia is the most frequent complication in patients with hematological malignancies. The most common cause of mortality of patients with febrile neutropenia is infections. Fever during neutropenia may be the only sign of a severe underlying infection. Infections can rapidly progress, leading to life - threatening complication. Therefore fever in neutropenic patients must be accepted as an infection and empiric wide – spectrum antibiotherapy must be iniated in order to avoid progression and possibly death. The aim of this study was to examine demographical and clinical characteristics of patients, difference in frequencies of episodes between months and seasons, distribution and frequency variance of isolated pathogens.

Methods: In this study 194 febrile neutropenic episodes of 105 patients with hematological malignancies who have been hospitalized between 1 June 2013 and 31 May 2014 in Akdeniz University Faculty of Medicine, Hematology Department were evaluated retrospectively.

Results: There was no difference in frequency of febrile neutropenic episodes between months ($p = 0.564$) and seasons ($p = 0.345$). There was no pathogen microorganism isolated in 54.6% of febrile neutropenic episodes. In 45.4% of 194 febrile neutropenic episodes pathogens were observed. 50.4% of all agents was gram negative bacteria, 29.2% was gram positive, 13.3% was viral agents, 5.3% was fungi and 1.8% was parasites. The most frequent gram negative bacteria was E. Coli and the most frequent gram positive bacteria was KNS.

Conclusion: This is the first study that examines FEN episodes according to months and seasons as far as we know.

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WHAT IS YOUR TREATMENT? DISSEMINATED HISTIOCYTIC SARCOMA

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Introduction: Histiocytic sarcoma (HS) is a rare, but aggressive and resistant hematopeietic malignancy. HS reflects the morphological and immunophenotypic characteristics of mature tissue histiocytes. Average presentation age is 44-55. Clinical presentation often involves gastrointestinal tract, skin and soft tissue, but has also wide range of extranodal areas such as bone, lymph nodes, liver, spleen, lungs and CNS.

Case: A 73-year-old female patient was admitted to our clinic with complaint of swelling in the left axilla. The physical examination revealed left axillary lymphadenopathie. In the blood count leukocyte 71300/uL, hemoglobin 10.1 g/dL, platelets 216000/uL, in the biochemical analysis, LDH 279 U/L were detected. PET/CT revealed increased FDG uptake in lymphadenopathies in the neck, left ear, nodular lesions on right hemithorax, the lower and upper limb bone, and bone marrow of left tibia (SUVmax between 0.5 and 4.9). It was determined CD23 positive, LCA weak positive, CD68 strong positive, Ki67 70-80%, CD1a and CD21 negative in the lymph node biopsy. According to present findings the patient was diagnosed as Histiocytic Sarcoma (WHO-2008). It was initially started CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regime.After second course of CHOP was observed progression in lesions. Additionally 4 courses of ICE (ifosfamide, carboplatin, etoposide) regime were applied. First 15 days of ICE regime a significant regression was observed in skin lesions, however reprogression was observed after 15 days. A month after the forth course of ICE the patient died because of febrile neutropenia and pneumonia.

Conclusion: There is no standart treatment protocol for HS, because it is rarely seen. CHOP and ICE are the most preferred treatment regimens. It was demonstrated progression to CHOP and ICE regime in the our case. HS is very rare subtype of NHL and should be detailed pathological examination, and further studies with case series are required to determine effective treatment protocols.

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MILIARY TUBERCULOSIS MIMICKING LYMPHOMA: A CASE REPORT

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Introduction: Miliary tuberculosis (MT) still remains a perplexing disease that continues to elude the most experienced clinicians and is a diagnostic and therapeutic challenge. We present two cases of miliary tuberculosis that mimic lymphoma. Mortality from this disease has remained high despite effective therapy being available.

Cases: The first case is a 27-year-old male who presented with fever with evening rise of temperature of several weeks of duration, anorexia, weight loss and weakness. He was a farmer. The second case is a 42-year-old female who presented with night sweats, coughing but no heamoptysis. She was a tailor. They both had no history of immunosuppressive agent intake or HIV. They both had sputum smear negativity and normal chest radiography. They both had elevated transaminases and C-reactive protein. They both had anemia but the LDH levels were in normal limits. The first case had massive splenomegaly and the second case had bilateral cervical, supraclavicular lymph nodes greater than 2 cm. In PET CT there were multiple lesions in the spleens and thoracal regions of both patients with increased FDG intensity. While splenectomy was performed to the first case, cervical lymphadenectomy was done to the second case. Both biopsy results were caseificated granulomatous inflammation. Anti-tuberculosis treatment was administered for six months to both patients. They have been still following up at hematology clinic and there are regressions in the lesions.

Conclusion: MT is a disease that may mimic malignancies and is not uncommon in developing countries. It should be considered in the differential diagnosis in patients with night sweats, anorexia, weight loss and fever even in the patients with a positive PET scan. Biopsy is the method of diagnosis.