AHOS 2021

WEB-EVENT

ABSTRACTS

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ORAL PRESENTATIONS

01. ANALYSIS OF PATIENTS WITH LARGE GRANULAR LYMPHOCYTE LEUKEMIA IN A SINGLE CENTER

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OBJECTIVE: Large granular lymphocyte (LGL) leukemia is a disease of T-cell and natural killer (NK) cell lineage due to clonal expansion of lymphocytes with a characteristic morphological large granular appearance. LGL leukemia accounts for 2-5% of chronic lymphoproliferative disorders and it is commonly seen in older ages (only 25% of patients <50 years old). Typical features of T-LGL leukemia include an increase in the number of peripheral blood large granular lymphocytes, cytopenia, and splenomegaly without lymphadenopathy. The aim of our retrospective study was to describe the main clinical characteristics, response to therapy and outcomes of LGL leukemia patients in our center.

METHODS: We included 8 patients diagnosed with LGLL in 2016-2020. We retrospectively reevaluated all the patients to ensure that the diagnosis was correct according to WHO 2016 classification. Baseline patient characteristics were retrospectively assessed. Blood smear examination, flow cytometry analysis, bone marrow biopsy (when available) and molecular studies were reviewed in all cases to confirm the diagnosis.

RESULTS: The median age at diagnosis was 67 years (range: 44-88 years) and 5 of 8 patients (62.5%) were male. Most of the patients were asymptomatic at the time of presentation. Splenomegaly was present in 2 patients. The median lymphocyte count and neutrophil count was 2.9 × 10^9/L (range: 0.2-11) and 1.5 × 10^9/L (range: 0.5-3.7). Median hb level was 10. 65 g/dL (range: 7.2 -16.2). At diagnosis, 37.5% of the patients had neutropenia (<1.5 × 10^9/L) and anemia (<10 g/dL). Half of the patients had thrombocytopenia (<100 x 10^9/L). However, severe cytopenia (neutropenia <0. 5 × 109/L, anemia <80 g/L and thrombocytopenia <50 × 10^9/L) were only observed in a minority of the patients; 1, 2 and 2 respectively. Only 2 patients required red blood cell transfusions. LGLL would be associated with multiple conditions and autoimmune diseases were observed in 2 patients (25%), solid tumors in 1 patient and lymphoma in 1 patient. One patient died from infection 3 weeks after the diagnosis and could not get an therapy. Of 7 patients, 4 received treatment; 3 patients treated with cyclosporine, one patient received CHOEP regimen as a first line therapy.

CONCLUSION: LGLL is a rare disease and we presented real life experience of our center. Only 2 patients died in our study period and both of them had thrombocytopenia at the time of diagnosis. However thrombocytopenia was defined as an independent risk factor for worse survival in a previous study, we need more clinical trials to describe the risk factors for LGLL patient. Concomitant diseases (such as monoclonal gammopathy, lymphoma and autoimmune diseases) should be researched carefully in these patients.

02. RESVERATROL TARGETS LEUKEMIA STEM CELLS BY REGULATING LNCRNA EXPRESSIONS

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OBJECTIVE: Long non-coding RNAs (lncRNAs) are non-protein-coding RNA molecules longer than 200 nucleotides. They can regulate both transcriptional and post-transcriptional mechanisms by interacting with DNA, RNA, and proteins. They have broad biological functions, from apoptosis to hematopoiesis, and their deregulated expression is associated with many diseases. Leukemia stem cells (LSCs) can be derived from normal hematopoietic stem cells (HSCs) as a result of the accumulation of genetic/epigenetic changes that contribute to uncontrolled survival and self-renewal. As conventional leukemia treatments fail to target primitive LSCs, resistance and relapse can be observed overtime. Therefore, in the treatment of leukemia, it is essential to target the LSC to achieve full recovery. Phytoalexin resveratrol (trans-3,5,4´-trihydroxy-stilbene) is a natural non-flavonoid polyphenolic compound synthesized by resveratrol synthase enzyme following infection and injury in plants such as grapes, strawberries, peanuts. The anti-leukemic activities (proliferation, apoptosis, autophagy) of resveratrol, a potential chemopreventive and chemotherapeutic agent, have been investigated in many studies. In our previous study, it was revealed that resveratrol exerts anti-leukemic effects and induces apoptosis in LSCs, but not in normal HSCs. In this study, we aimed to identify lncRNAs involved in the anti-proliferative and apoptotic processes of LSCs in response to resveratrol treatment. It was aimed to determine the effect of the same dose of resveratrol on lncRNA expressions of HSCs.

METHODS: In the experiments, "Human Leukemia Cancer Stem Cell Line, Celprogen" and "Human Embryonic Hematopoietic Stem Cell Line, Celprogen" were used. Total RNAs were isolated from LSC and HSC cells treated or untreated with 16.7 µM resveratrol. Expression levels of 90 lncRNAs were determined by qRT-PCR. The fold changes of gene expressions were calculated by the 2-ΔΔCT method. Expressions of lncRNA with fold changes of ≥±2-fold and $p<0.05$ were considered significant.

RESULTS: Among the lncRNAs with lower expression in LSCs compared to HSCs; LincRNA-SFMBT2, PTENP1, antiPeg11, NTT, anti-NOS2A, TMEVPG1, DHFR upstream transcripts, GAS5 were upregulated (2.1- 8.3-fold) after resveratrol treatment. Among the lncRNAs with higher expression in LSCs than in HSCs; L1PA16, HOTTIP, SNHG5, Alpha 280, MALAT1, DLG2AS, Alpha 250, Zfhx2as, HOTAIRM1, UCA1, HULC, HOTAIR, NEAT1, H19 were also upregulated (2.13- 12.7-fold) after resveratrol treatment. Especially, the 8.5-fold increase in the expression of the tumor suppressor PTENP1, which suppresses oncogenic PI3K/Akt/mTOR signaling, and the 4.62-fold increase in the expression of LincRNA-SFMBT2, which acts as a tumor suppressor in AML are significant. In particular, resveratrol down-regulated L1PA16 whose expression is correlated with Myc oncogene (12.7-fold), oncogenic HOTTIP which regulates the balance of self-renewal and differentiation of stem cells in AML (11.34-fold), SNHG5 which increases leukemic cell proliferation and causes imatinib-resistance (8.99-fold) and MALAT1 which contributes to AML, ALL, CML and CLL cell proliferation by sponging certain miRNAs (7.61-fold). Moreover, the same dose of resveratrol had less effect on normal HSCs compare to LSCs.

CONCLUSION: In this study, it is revealed that the natural compound resveratrol alters the expressions of many lncRNAs that contribute to LSC proliferation and survival. In conclusion, these results support that resveratrol in combination with conventional leukemia therapy may be an adequate treatment strategy that can eliminate LSCs.

03. RUXOLITINIB THERAPY IN PATIENTS WITH POLYCYTHEMIA VERA

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OBJECTIVE: Ruxolitinib, a Janus kinase (JAK) 1 and 2 inhibitor, was shown to have a clinical benefit in hydroxyurea or the other initial therapy-resistant or intolerant patients with polycythemia vera. In this study, we aimed to report the effectiveness of ruxolitinib.
METHODS: Seven patients who received ruxolitinib therapy with a diagnosis of PV between March 2018 and August 2021 were included in this study. Patients with advanced myelofibrosis were excluded. Hemogram parameters, spleen size, symptoms, previous treatments, treatment duration/dose, and side effects of the patients were evaluated.
RESULTS: The median age of patients was 72 (71-80). Two were male and 5 were female. JAK2617F mutation was positive in all patients. The median spleen size was 17 (12-31) cm at the initiation of ruxolitinib therapy. Previous treatments were evaluated, 5 patients received hydroxyurea, 1 of them received hydroxyurea plus interferon. Ruxolitinib was first-line therapy in one patient. The median time to ruxolitinib treatment after diagnosis was 36 (2-72) months. The median initiation dose was 20 (10-40) mg per day. The median duration of therapy was 29 (2-40) months. Ruxolitinib was discontinued in 1 patient because of intolerance, 6 patients are still on treatment. No hemorrhagic or thrombotic attacks were observed during the follow-up period and phlebotomy was not required in any patients.
CONCLUSION: Despite the limited number of cases, this report showed that ruxolitinib is an effective and well-tolerated treatment option for therapy hydroxyurea or the other initial therapy-resistant or intolerant patients with polycythemia vera.

04. REAL-WORLD EVIDENCE OF CARFILZOMIB USE IN GREECE AMONG MULTIPLE MYELOMA PATIENTS WHO HAVE RECEIVED AT LEAST ONE PRIOR THERAPY

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OBJECTIVE: To understand usage, safety and effectiveness of carfilzomib in combination with lenalidomide and dexamethasone (KRd) or with dexamethasone alone (Kd) in Greece.
METHODS: This prospective observational study enrolled patients with relapsed multiple myeloma, who received ≥1 K dose in routine clinical practice.
RESULTS: Of the 119 enrolled patients, an equal proportion (45%, n=54) received KRd and Kd. The remaining patients (n=11, 9%) received other K-based triplets (not described here). At K initiation, median age of KRd and Kd patients was 65 and 70, respectively. Based on 32% of patients with known ISS status at K initiation, about half (47% KRd; 53% Kd) had an ISS stage 3. Among patients with derived frailty score (84%), over one-third were calculated as frail (34% KRd, 43% Kd). KRd patients had received a median of 1 prior line of therapy whereas Kd patients had 3. Previous HSCT was described for 28% of KRd and 39% of Kd patients. The proportions of patients exposed to lenalidomide (Len) were 44% and 83% for KRd and Kd respectively, of whom 92% and 89% were Len-refractory. Few KRd patients (9%) and 39% of Kd patients had previously received a monoclonal antibody. Of patients with a response assessment reported, a high overall response rate (ORR) of 75% was seen in KRd patients, with 29% achieving a complete response (CR) or better and 27% a very good partial response (VGPR). The ORR in Kd patients was 57%, including 15% of patients achieving a CR or better. The mean K dose intensity received relative to EU label was 97% for KRd (20/27 mg/m^2 for K) and 71% for Kd patients (20/56 mg/m^2 for K). The Kaplan-Meier median estimate of treatment duration was 9.3 months (95% CI: 6.1, 13.2) for KRd and 7.2 months (95% CI: 4.3, 10.4) for Kd patients. Adverse events (AEs) of grade 3 or above (Gr3+) were reported in 61% and 39% of KRd and Kd patients, respectively, of whom 35% and 13% had experienced a treatment-related AE. The most common AEs Gr3+ were blood disorders (24% KRd, 9% Kd), infections (32% KRd, 9% Kd), and vascular disorders (2% KRd, 4% Kd). Serious AEs occurred in 54% of KRd and 32% of Kd patients, respectively. Fatal AEs occurred in 6 KRd patients (2 due to infections) and 5 Kd patients (3 due to cardiac disorders). Discontinuation of K was mainly due to disease progression/refractoriness (KRd 33%, Kd 44%) and AEs (KRd 19%, Kd 11%).
CONCLUSION: In this real-world setting in Greece, KRd was used per the label. Compared with KRd, Kd was preferably given to patients who were older, frailer, and were more heavily pre-treated. In both cohorts, most of the Len-exposed patients were also Len-refractory. This explains the shorter treatment duration of KRd patients in the Greek vs the EU populations (9 vs 15 months). Despite their poor prognosis, both KRd and Kd patients achieved high ORRs, reinforcing that KRd regimen particularly, is an efficient and safe treatment option to overcome treatment refractoriness.

05. DOES METFORMIN INCREASE THE EFFECTIVENESS OF LENALIDOMIDE IN MYELOMA TREATMENT?

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OBJECTIVE: Our aim was to investigate whether oral metformin has an effect on myeloma treatment or not.
METHODS: U266 myeloma cell line was used and cell viability was confirmed using Trypan blue. Plasma cells were seeded into 1×104 cells/well and incubated with different concentrations of lenalidomide, metformin and lenalidomide-metformin combination. Cells were evaluated by direct microscopic evaluation, cell viability by MTS/PMS and apoptosis by flow cytometer. Results were evaluated using SPSS 21 program; student-t test and one-way ANOVA were performed.
RESULTS: In the viability experiment performed at IC50 doses, cell viability decreased in all groups (metformin alone, lenalidomide alone and combined administration) compared to the control group. Viability was lower in wells treated with metformin alone and combined administration compared to lenalidomide alone ($p = 0.48$ and $p = 0.32$, respectively). Viability rate in wells treated with metformin alone and combined administration was found to be close to each other. With Annexin FITC, which shows apoptosis, no staining was observed in the control groups. Significant staining with Annexin FITC was observed in all three groups (lenalidomide, metformin, and lenalidomide + metformin) ($p < 0.001$). The combination of lenalidomide + metformin did not prove to be better than either lenalidomide or metformin alone ($p = 0.39$).
CONCLUSION: Metformin is a cheap, safe, and easily available drug, it can be a preferred agent in the treatment of patients with myeloma. The results obtained should be supported by clinical data.

06. UPDATED OUTCOMES ON LENALIDOMIDE (LEN) REFRACTORY MM PATIENTS

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OBJECTIVE: Lenalidomide refractoriness constitutes an adverse factor of survival in MM as Lenalidomide relapsing/resistant patients were reported to respond difficultly to next treatment line. Lenalidomide is widely administered in doublet, triplet, or quadruplet schemas as first line treatment or relapse and is the only approved drug for maintenance treatment in MM. Almost all MM patients will become at some time point Len refractory. Len resistance definitions and cautious evaluation is still lacking. To update a previous study from our group assessing Len-dex treated MM patients' outcomes according to elapsed time until relapse under treatment.
METHODS: 186 patients were studied. 158 Len-Dex treated at any line and 18 receiving maintenance after ASCT, after informed consent was obtained initially. They were separated into 5 groups, including patients (1) with no response within two months (defined as primary resistant MM - PRMM) in the first, (2) progressing under treatment within 6 months from Len initiation in the 2nd (referred as very resistant MM - VRMM), (3) presenting progression under treatment within 7-12 months (Resistant MM - ResMM), (4) initially sensitive (ISMMP), progressing under treatment after more than 12 months and less than 4 years and (5) long-lasting response presenting eventually relapse (RALR) after more than 4 years from Len initiation. Statistical analysis was performed by conventional methods with the SPSS 21 software.
RESULTS: Of the 158 len-dex-treated, 16 were PRMM, 23 VRMM, 25 ResMM, 70 ISMMP, 24 RALR. Median overall survival after Len (LenOS) was 3 months (as it was in the former analysis) for PRMM patients with 2,4,4, 3,1,2 being in 1st, 2nd, 3rd and >4th line treatment. Only 5 PRMM patients received next treatment line after len and managed a further time to next treatment of 9 months. VRMM shared a slight increase of one month in survival after Len, 7 months LenOS vs 6 months in the former analysis, while median LenOS in ISMMM was the same (39 months). RALR patients improved their median LenOS to 87 months compared to 64 observed in previous data. The difference observed may be interpreted by the new agents available for MM treatment. LenOS was significantly different between all groups ($p<0.0001$). Median time from lenalidomide maintenance treatment to relapse was 28 months. Three patients while on maintenance became resistant at 4 months (2 pts) and 6 months (1 pt) respectively.
CONCLUSION: We confirmed our results that outcomes are very poor for PRMM and VRMM that constitute a minority of patients that probably cannot be rescued at present. Therapeutic efforts and innovation are mandatory for ResMM and ISMMP. Improved outcomes observed in RALR patients are encouraging in the era of novel agents and monoclonal antibodies availability.

07. INVESTIGATION OF CYTOGENETIC ABNORMALITY FREQUENCY AND THEIR ASSOCIATION WITH DISEASE BURDEN IN MULTIPLE MYELOMA PATIENTS

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OBJECTIVE: Multiple myeloma (MM) is a clonal plasma cell disorder that has a heterogeneous clinical course and treatment responses. This diversity is to some extent related to cytogenetic abnormalities (CAs). Chromosome banding (CB), fluorescence in situ hybridization (FISH), and/or single nucleotide polymorphism microarray analyses (SNPMA) are usually utilized to detect these abnormalities. Here, we retrospectively investigated the frequency of CAs of MM patients, as well as the associations between these abnormalities and LDH, β2-microglobulin (β2M), bone marrow plasma cell ratio (BMPCR), and extramedullary involvement (EMI).

METHODS: A total of 310 symptomatic MM patients were included. CB (G-banding with trypsin and Giemsa) and interphase FISH investigations from bone marrow samples were performed at diagnosis. CB was performed in 216 (69.6%) patients. Deletion (Del) 17p, del13q, translocation (t) (11,14), t(4,14), t(14,16), 1q amplification, and t(14,20) analyses were investigated in 233 (75.1%), 196 (63.2%), 122 (39.3%), 111 (35.8%), 108 (34.8%), 13 (4.1%), and four (1.2%) patients, respectively. The thresholds for the abnormalities were set at 10%. SPSS 26.0 (NY, USA) software program was used for the analysis and a p-value <0.05 was considered significant.

RESULTS: The mean age (± Standard Deviation-SD) of the patients was 65 ± 10. Among 216 patients in whom CB was studied, the results of 80 (37%) patients were inconclusive due to the insufficient number of metaphase cells. One-hundred and two patients (47.2%) have normal karyotype. Thirty-two (14.8%) and four (1.8%) patients had hypodiploidy and hyperdiploidy, respectively. By CB analysis; inv 6, trisomy 5, trisomy 7, and del 20q were detected each for one (0.46%) patient whereas inv 9 and trisomy 17 were detected each for two (0.9%) patients. Y chromosome loss was detected in four (1.8%) patients. By the FISH technique, del 13q was detected in 16 patients (8.1%) whereas del17p was detected in 14 (6%) patients. Regarding translocations, t(11,14) and t(4,14) were each detected three patients (2.4% and 2.7%, respectively). T(14,16) and t(14,20) were not detected in any patient. 1q amplification was detected in two (15.3%) patients. Of the patients, there was not any significant correlation between LDH, EMI, and CAs. B2M elevation had a significant correlation with only hypodiploidy among CAs (p=0.006). Regarding BMPCR, when patients were divided into three groups (as 10-30%, 30-60%, and 60% <) CAs were more common in patients with a BMPCR>60%.

CONCLUSION: In this study, we have focused on the frequency of cytogenetic findings as well as their associations with parameters attributed to disease burden, such as LDH, β2M, EMI, and BMPCR. It is an expected finding that CAs are observed more frequently in the group with higher BMPCR. These aforementioned parameters reflect MM burden to some extent. Among these techniques, FISH is the most widely used to estimate prognosis and tailor treatment. Compared to FISH, CB has a lack of sensitivity, it is operator-dependent and laborious to perform due to low plasma cell proliferative activity. SNPMA to investigate copy number changes are not widely available. It is essential to use these techniques to perform risk stratification and guide anti-myeloma therapy accurately.

08. PATIENTS WITH MULTIPLE MYELOMA ON TREATMENT WITH ANTI-CD38 OR ANTI-BCMA AGENTS HAVE A SUBOPTIMAL HUMORAL RESPONSE FOLLOWING COVID-19 VACCINATION

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OBJECTIVE: Recent data suggest a suboptimal antibody response to COVID-19 vaccination in patients with hematological malignancies, especially under immunosuppressive therapy. Herein, we evaluated the development of neutralizing antibodies (NAbs) against SARS-CoV-2 in patients with plasma cell neoplasms after vaccination with either the mRNA BNT162b2 or viral vector AZD1222 vaccine.
METHODS: Serum of both patients and controls was collected on day 1 (D1; before the first BNT162b2 or AZD1222 dose), on day 22 (D22; before the second dose of the BNT162b2 or 3 weeks post the first AZD1222 dose) and on day 50 (D50; 4 weeks post second dose of the BNT162b2 or 7 weeks post the first AZD1222 dose). NAbs against SARS-CoV-2 were measured using FDA approved-ELISA methodology ((ELISA, cPass™ SARS-CoV-2 NAbs Detection Kit; GenScript, Piscataway, NJ, USA).
RESULTS: Patients with MM (n=213), SMM (n=38) and MGUS (n=25) and 226 healthy controls, of similar age and gender, were enrolled in the study (NCT04743388). Two hundred and fifteen patients (77.9%) were vaccinated with the BNT162b2 and 61 (22.1%) with the AZD1222 vaccine. Vaccination with either two doses of the BNT162b2 or one dose of the AZD1222 vaccine leads to lower production of NAbs against SARS-CoV-2 in patients compared with controls both on day 22 and on day 50 (P<0.001 for all comparisons). After the first dose of the vaccine, on D22, the median NAb inhibition titer was 27% (IQR: 15.3-42%) for patients versus 38.7% (IQR: 22-54.3%) for controls (P<0.001). On D50, the median NAb inhibition titer was 62.8% (IQR: 26-88.9%) for patients versus 90% (IQR: 58-96.4%) for controls (P<0.001). The respective number of patients and controls who developed NAb titers ≥50% (clinically relevant titers) was 158 (57.3%) and 183 (81%), respectively (P<0.001). Furthermore, MM patients showed an inferior NAb response compared with MGUS on day 22 (p=0.009) and on day 50 (p=0.003); MGUS patients' NAb development was similar to controls. Importantly, active treatment with either anti-CD38 monoclonal antibodies or belantamab mafodotin and lymphopenia at the time of vaccination were independent prognostic factors for suboptimal antibody response following vaccination (OR: 9.4, 95% CI: 1.7-51.1, p=0.009, OR 2.9, 95% CI: 1.2-7.1, p=0.002 and OR: 3.5, 95% CI: 1.8-6.7, p=0.019, respectively). Seventy-one (33%) and 68 patients (31.6%) reported mild reactions after the first and second dose of the BNT162b2 vaccine, respectively. Twenty (32.8%) patients vaccinated with the first dose of AZD1222 also presented with local reactions.
CONCLUSION: In conclusion, MM patients have lower humoral response following SARS-CoV-2 vaccination compared to gender- and age-matched controls. Treatment with anti-CD38 and belamaf-based regimens as well as lymphopenia at the time of vaccination independently predicted for poor NAb development. These data underline the need for timely vaccination, ideally during a treatment-free period, and for continuous vigilance on infection control measures. The use of a third vaccination dose or the use of monthly administration of IV monoclonal antibodies against SARS-CoV-2 are under investigation for myeloma patients who do not respond to two vaccination doses.

09. OUTCOME AND PROGNOSTIC FACTORS IN PATIENTS WITH ADVANCED HODGKIN LYMPHOMA WHO BECOME PET/CT NEGATIVE AFTER 2 CYCLES OF ABVD: THE SIGNIFICANCE OF THE HISTOLOGIC SUBTYPE

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OBJECTIVE: Most patients with advanced Hodgkin lymphoma (HL) will achieve a negative PET/CT after 2 cycles of ABVD (interim PET, iPET). However, 20% of these patients will eventually relapse and to date, there are no studies effectively defining this patient subgroup. The aim of the current study was to describe the outcome and potential prognostic factors in iPET-negative [iPET(–)] patients from 15 Hematology departments in Greece.

METHODS: This is a retrospective analysis of 282 patients with advanced HL according to GHSG (stages III/IV or IIB with bulky mediastinal and/or extranodal disease), who received 2 cycles of ABVD and underwent PET/CT. iPET was interpreted according to the Deauville 5-point scale score (D5PSS) and scores 1-3 (residual uptake < liver) were considered negative. All patients continued on ABVD or AVD, apart from 1 patient who received BEACOPP due to treating physician's choice.

RESULTS: iPET was negative in 77% (n=217) of patients. The 5-year progression-free survival (PFS) was 81% in the whole population of iPET(–) patients and 53% in iPET(+) ($p<0.0001$). Of note, 60% of iPET(+) patients were treated with BEACOPP. Patients' median age was 32 years (range: 15-84), 60% were male, 36% had stage IV and 67% had B-symptoms. Regarding the histologic subtype, 78% had nodular sclerosing, 15% mixed cellularity and 5% unclassifiable HL. Median IPS was

2.5 (range: 0-6, ≥3 in 49%), 66% had anemia, 51% leukocytosis, 16% lymphocytopenia, 71% ESR ≥50 mm/h and 77% albumin <4 g/dL, while 52% of the patients had stage IV according to initial PET/CT staging. Among iPET(–) patients 34 relapses were recorded (12 within the first 6 months and 7 within 1 year from treatment initiation; 10 patients relapsed between 1-2 years, 4 within 5 years and 1 patient relapsed later). In univariate analysis the histologic subtype and some demographic patients' characteristics were of clear or marginal adverse prognostic significance [male sex (p=0.08), age ≥45 years (p=0.078), mixed cellularity, p=0.005)]. In multivariate analysis only the histologic subtype of mixed cellularity was independent adverse prognostic factor for the outcome (hazard ratio 2.826, 95% CI: 1.316-6.066, p=0.008). The 5-year PFS was significantly higher in patients with nodular sclerosis versus mixed cellularity subtype (83% vs 58% respectively). No other known prognostic factor, including IPS, could predict the outcome of iPET(–) patients.

CONCLUSION: This study confirms the high risk of relapse (20%) in patients achieving negative iPET after 2 cycles of ABVD. We highlighted the significance of the histologic subtype, as the risk of relapse in patients with mixed cellularity exceeded 40%. No other potential prognostic factor associated with disease extent or aggressiveness was significantly associated with the outcome of this specific subgroup of iPET(–) patients. This study points out the need to search for new prognostic factors, which might improve the negative prognostic value of iPET. The impact of histologic subtype is described for the first time in the setting if iPET(–) HL and our findings provide new insights into the importance of histology in HL and its potential implication on treatment strategies.

10. THE EFFECTIVENESS OF OBINUTUZUMAB IN SALVAGE THERAPY IN DLBCL

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OBJECTIVE: To evaluate the efficacy of obinutuzumab used in salvage therapy in patients with relapsed-refractory DLBCL.
METHODS: A retrospective case study
RESULTS: Twelve DLBCL patients in total were given obinutuzumab in the hematology clinic of Kocaeli University between 2019-2021. One-third of the patients were stage four at diagnosis. Two-thirds of patients had extranodal involvement. All of these twelve patients received rituximab as first-line therapy. These twelve DLBCL patients were given obinutuzumab on any step-up salvage therapy. Ten patients were unresponsive to first-line treatment, two were CR, and these patients with CR relapsed within the first six months after treatment. In the second-line treatment, which is considered to be the first salvage treatment, four patients were given obinutuzumab and concurrently with obinutuzumab, one patient was given bendamustine, one patient was given gemcitabine, one patient was given DHAP, and one patient was given ICE chemotherapy regimen. All these patients who were given obinutuzumab on the first salvage treatment had progressed. Seven patients were given obinutuzumab in the second salvage treatment. Only one of these seven patients had a partial response to treatment, and all other patients had progressed. The patient who had a partial response was combined with DHAP.
CONCLUSION: In the light of these findings, we assumed that the addition of obinutuzumab did not differ in response to treatment in primary refractory DLBCL patients and recurrence within six months of after rituximab-containing regimen in DLBCL patients.

11. OUTCOME AND PROGNOSTIC FACTORS IN PATIENTS WITH ADVANCED HODGKIN LYMPHOMA AND POSITIVE INTERIM PET/CT AFTER 2 CYCLES OF ABVD: 11-YEAR EXPERIENCE IN HELLENIC DEPARTMENTS- CONCLUSIONS AND LIMITATIONS

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OBJECTIVE: The outcome of patients with advanced Hodgkin lymphoma (HL) who remain PET/CT positive after 2 cycles of ABVD (interim PET, iPET) is significantly compromised. These patients could be successfully salvaged by treatment intensification to BEACOPP, but more trial-based and "real-life" data are needed in order to predict their outcome. The aim of this study was the evaluation of treatment strategies, patient outcome and potential prognostic factors in iPET-positive (iPET+) patients from 15 Hematology Departments in Greece.

METHODS: This is a retrospective analysis of 282 patients with advanced HL according to GHSG (stages III/IV or IIB with bulky mediastinal and/or extranodal disease), who received 2 cycles of ABVD and underwent PET/CT. iPET was interpreted according to the Deauville 5-point scale score (D5PSS) and scores 4 and 5 (residual uptake >liver) were considered positive. In case of iPET positivity, further treatment decision (escalation to BEACOPP or not) was at the treating physician's discretion, but consistent strategies were generally followed within the same Department. Radiotherapy was also at physician's discretion.

RESULTS: iPET was positive in 23% of patients; 62/65 iPET(+) patients were ≤60 years old and

consisted the study population, as they were eligible for treatment intensification. Among these patients, 37 received intensified treatment: 36 with BEACOPP (of whom 31 received BEACOPP-escalated, 2 BEACOPP-14 and 3 BEACOPP-baseline) and 1 with ESHAP. In contrast, 25 patients continued with ABVD due to individual Department's treatment strategy (n=18), or because of treating physician's decision (n=7) or due to misclassification as D5PSS-3 (n=1). The 5-year progression free survival (PFS) was 53% in the whole population of iPET(+) patients. It was 59% vs 41% for patients who received intensified treatment or continued with ABVD respectively (p=0.09). In Departments which did not follow the treatment escalation strategy, the 5-year PFS was 32% for patients who continued with ABVD. Patients who remained iPET(+) with D5PSS-4 had 5-year PFS 60% vs 37% for patients with D5PSS-5 (p=0.13). Apart from patient's age, no other potential prognostic factors associated with extensive or aggressive disease affected the outcome of iPET(+) patients. Unexpectedly, patients <45 years old had inferior outcome in univariate analysis. In multivariate analysis, D5PSS-5 (vs 4) was an independent adverse prognostic factor for PFS (HR: 2.789, 95% CI: 1.049-7.416, p=0.04), whereas continuation with ABVD vs treatment intensification was of borderline significance (HR: 2.434, 95% CI: 0.934-6.340, p=0.069).

CONCLUSION: This study confirms the adverse prognostic significance of positive iPET in the "real-life" setting, as well as the effectiveness of treatment intensification with BEACOPP-escalated. The 5-year PFS almost reached 60% despite the fact that the study included only patients with "strictly" advanced-stage disease, without including early stages with adverse characteristics. iPET analysis is an area of growing interest and conventional prognostic factors may be supplemented or replaced by quantitative metrics and different scores of iPET positivity interpretation. However, larger cooperative efforts are needed in order to produce robust results and draw safer conclusions, because the number of patients with a positive iPET is small even within the context of large international randomized trials.

12. THE PROGNOSTIC IMPACT OF PRETREATMENT GERIATRIC NUTRITIONAL RISK INDEX IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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OBJECTIVE: The association of cachexia with poor prognosis in cancer patients has been demonstrated in previous studies. The prognostic value of the geriatric nutritional risk index (GNRI) is not clear in patients with diffuse large B-cell lymphoma (DLBCL). This study was designed to analyze the GNRI in DLBCL patients and to investigate its prognostic value in DLBCL.
METHODS: The archive records of DLBCL patients between 2008 and 2020 at the Akdeniz University Hospital Hematology Department were retrospectively analyzed. A total of 206 DLBCL patients were enrolled based on the following inclusion criteria: age over 18 years old, newly diagnosed with DLBCL, treated with R-CHOP, and complete clinical data. Patients with transformed non-Hodgkin lymphomas or central nervous system lymphoma were excluded from the study. Patients were classified into two GNRI-based groups based on nutrition status. The GNRI was calculated as follows: 1.489 × serum albumin level (g/L) + 41.7 × [actual body weight (ABW)/ideal body weight (IBW) (kg)]. If the ABW was higher than the IBW, we regarded the ABW/IBW ratio as 1 in our calculations. Determination of the cutoff value of the GNRI: Using Receiver operating characteristic (ROC) analysis for mortality, the optimal cutoff value of the GNRI determined by the Youden index was ≤104.238 with an area under the curve (AUC) value of 0.603 (95% CI: 0.533-0.670, p = 0.010), sensitivity = 81.25%, specificity = 38.1%).
RESULTS: The mean age of the 206 patients included in the study was 58.57 ± 13.86 years, of whom 54.4% were men and 45.6% were women. A total of 69.4% (n = 143) of the patients were classified in the GNRI ≤104.238 group, and 30.6% (n = 63) were classified in the GNRI >104.238 group. The incidence of B symptoms and extranodal disease was higher in the GNRI ≤104.238 group (p <0.001). Hemoglobin, absolute lymphocyte count, and albumin values were lower in the patients in the GNRI ≤104.238 group (p <0.001), while the CRP (p <0.001), LDH (p <0.001) and B2 microglobulin (p = 0.001) values were higher. A weak statistically significant negative correlation was observed between the GNRI and R-IPI (r = -0.356, p <0.001). The 5-year PFS rates were 60.2% and 69.8% in the ≤104.238 and >104.238 groups, respectively. No significant difference was found in terms of PFS between the groups (p = 0.361). The 5-year OS rates were 51.2% and 78.5% in the ≤104.238 and >104.238 groups, respectively. The OS of patients with a GNRI ≤104.238 was significantly lower than that of patients with a GNRI >104.238 (log-rank, p = 0.001).
CONCLUSION: There are few studies in the literature from the Far East exploring whether the GNRI is a prognostic indicator in DLBCL patients. In this relatively large and single-center study, we investigated the prognostic role of the GNRI in DLBCL patients and found that a low GNRI was associated with poor prognostic indicator. The GNRI is inexpensive, noninvasive and easily accessible; therefore, it is clinically useful.

13. REAL WORLD EFFECTIVENESS AND SAFETY OF PIXANTRONE IN RELAPSED/ REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS: A SINGLE INSTITUTION EXPERIENCE

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OBJECTIVE: Treatment of relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) remains an unmet need in every day clinical practice. Pixantrone is an approved by European Medical Agency (EMA) last generation anthracenedione developed to reduce the risk of cardiotoxicity. Real-world data regarding efficacy and safety of this regimen are limited. Our aim was to validate the efficacy and safety of pixantrone used as a salvage therapy in R/R DLBCL patients.
METHODS: We retrospectively analyzed R/R DLBCL patients treated at our institution with pixantrone as monotherapy between November 2017 and May 2021. Pixantrone was administered at a dosage of 50 mg/m^2 on days 1,8,15 of a 28-day cycle, for up to 6 courses.
RESULTS: Eleven R/R DLBCL patients (6 female / 5 male) underwent therapy with pixantrone for a median of 3 cycles (range 1-6). Median age was 76 (range 67-87). Six patients displayed GCB and five non- GCB subtype of DLBCL. All patients were initially treated with rituximab, cyclophosphamide, doxorubicin vincristine and prednisone (R-CHOP) or R-mini-CHOP. Regarding response assessment after first line treatment, 3/11 patients were considered as primary refractory. Median number of previous lines were 4 (range 3-5). Nine patients had cardiovascular comorbidities. Regarding efficacy of pixantrone therapy overall response rate (ORR) was 45.4%; 3 patients displayed complete response (CR) after cycle 2, 4 and 6 respectively. Two of the patients who achieved CR were treated with pixantrone as third line therapy and one as fifth line therapy. All patients who achieved CR displayed sensitivity to anthracyclines during induction therapy and DLBCL was of GCB subtype; 2 of them had extranodal sites of involvement (skin and oropharynx respectively); 2 patients achieved partial response (PR) after cycle 2 and 4, respectively. Four patients had stable disease and two patients had progressive disease. Median duration of response was 5 months (range 2-17 months). Three out of five patients who responded are still alive. Regarding safety 3 patients developed in total 4 episodes of neutropenia grade 3, one patient developed two episodes of grade 3 thrombocytopenia and one patient experienced 2 episodes of grade 3 anemia requiring red blood cell transfusions. No neutropenic fever were recorded during pixantrone treatment. Cardiac toxicity was also not evident.
CONCLUSION: Our results indicate that pixantrone may be a useful therapeutic option for elderly relapsed DLBCL patients, who displayed sensitivity to anthracyclines in the first line setting. Of note, we observed a comparable CR rate (27.3%) with the CR rate (20%) recorded in the multicenter prospective PIX301 trial suggesting that in the real-world setting pixantrone could be a reasonable option for relapsed patients with DLBCL. Nevertheless, further large real-world studies are warranted to identify the biological features of R/R DLBCL patients who may benefit from therapy with pixantrone.

14. COMPARISON OF IPSS, IPSS-R AND WPSS RISK GROUPS ON DARBEPOETIN RESPONSE IN MYELODYSPLASTIC SYNDROME

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OBJECTIVE: Anemia is a major burden for myelodysplastic syndrome (MDS) patients. Erythropoiesis-stimulating agents have been used to treat anemic MDS patients in clinical practice. In this study, we aimed to investigate whether the International Prognostic Scoring System (IPSS), Revised IPSS (IPSS-R) and WHO Classification-based Prognostic Scoring System (WPSS) prognostic risk groups could predict on erythroid response rates in MDS patients underwent darbepoetin therapy.
METHODS: Patients who were diagnosed with MDS and treated with darbepoetin during the course of their disease were retrospectively evaluated. Erythroid response rates were assessed according to International Working Group (IWG) 2006 and IWG 2018 criteria, separately.
RESULTS: A total of twenty patients (13 male (65%) and 7 female (35%) were included in the study. The mean age of patients was 76.7 years (44-90). At the time of diagnosis; 16 patients had anemia (80%), 7 patients had neutropenia (35%) and 6 patients had thrombocytopenia (30%). 90% of patients (n=18) had good cytogenetics findings while 2 patients (10%) were in the intermediate cytogenetics subgroup. The median duration of time between MDS diagnosis and darbepoetin initiation was 18.2 months (0-67). As per calculations at the time of MDS diagnosis; 12 patients (60%) were in the low-risk group while 8 patients (40%) were in the intermediate-1 risk group in IPSS. IPSS-R risk groups of patients were calculated as; 4 patients (20%) very low risk, 11 patients (55%) low risk, 4 patients (20%) intermediate-risk, and one patient (5%) high risk. WPSS risk groups of patients were calculated as; 4 patients (20%) very low risk, 9 patients (45%) low risk, 5 patients (25%) intermediate-risk, and 2 patients (10%) high risk. At the time of darbepoetin initiation, 6 patients (30%) were transfusion-dependent (TD) and 14 patients (70%) were transfusion-independent according to IWG2006 classification; while 10 patients (50%) were non-transfused (NTD), 8 patients (40%) had low transfusion burden (LTB) and 2 patients (10%) had high transfusion burden (HTB) according to IWG2018 classification. 45% of patients (n=9) and 55% of patients (n=11) had an erythroid response with darbepoetin therapy according to IWG2006 and IWG2018 response criteria, respectively. There was no significant difference between the groups when the IWG2006 and IWG2018 erythroid response rates were compared separately according to the groups in which the patients were in the IPSS, IPSS-R and WPSS scoring. IPSS, IPSS-R and WPSS risk groups were found to have no effect on darbepoetin response also in logistic regression analysis.
CONCLUSION: This study demonstrates that IPSS, IPSS-R and WPSS scoring systems had no predictive value on erythroid response rates in darbepoetin therapy. The main limitations of this study are the small number of patients and retrospective design. Although darbepoetin is an effective method to treat anemia and transfusion burden in MDS patients, it is necessary to determine which patients will benefit from the treatment.

15. DETERMINATION OF DRUG-DRUG INTERACTIONS IN AUTOLOGOUS AND ALLOGENIC STEM CELL TRANSPLANTATION PATIENTS AND EVALUATION ACCORDING TO TRANSPLANTATION TYPE AND TRANSPLANTATION PROCESS

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OBJECTIVE: Drug-drug interactions are a major cause of adverse drug events. The preventable or manageable nature of drug-drug interactions puts them at the center of interventions. Since hematopoietic stem cell transplantation is a challenging and multi-drug-involving process, drug-drug interactions are frequently encountered.
METHODS: In our study, the drugs used in 50 patients who underwent allogeneic stem cell transplantation and 50 patients who underwent autologous stem cell transplantation before the transplantation, on the day of transplantation and during the post-transplantation period were examined retrospectively in terms of interaction. Two paid software and two free software were used to examine interactions. The obtained data were analyzed with Microsoft Excel program.
RESULTS: 1400 different interactions were detected in 100 patients. While 1017 different interactions were detected in patients with allogeneic transplants, this number was 725 in patients with autologous transplants. Of these interactions, 342 were seen in both transplant types. A total of 3805 interactions were seen in patients with allogeneic transplants, compared to 2906 interactions in patients with autologous transplants. It has been observed that drugs such as cyclosporine, fluconazole, dexamethasone and levofloxacin, which are included in the transplantation protocols, are the most interacting drugs. In the list of interactions seen in patients undergoing allogeneic stem cell transplantation, cyclosporine was included in 685 interactions, fluconazole in 500 interactions, and dexamethasone in 419 interactions. In the list of interactions seen in autologous stem cell transplant patients, dexamethasone was included in 367 interactions, fluconazole in 337 interactions, and levofloxacin in 275 interactions. Interactions varied according to the type of transplant and at the same time, the interactions differed according to the part of the transplant process. For example, the interaction of methotrexate and cyclosporine was seen only after allogeneic transplantation, while the interaction of acetazolamide and dexamethasone was only seen before transplantation.
CONCLUSION: Drug-drug interactions emerge as an important problem in patients undergoing hematopoietic stem cell transplantation, and it is important to contribute to the determination of their clinical significance as well as to detect interactions. Frequent and important interactions according to transplant type and transplant process were determined in our study. In this risky patient group, it is essential to determine the interactions of the protocol drugs and the drugs used by the patients due to their comorbidities at the beginning of the transplantation process and to carry out the process in cooperation with the doctor-clinical pharmacist. Key words: HSCT, transplantation, drug interactions

16. EVALUATION OF COMPATIBILITY BETWEEN MANUAL PLATELET COUNTS PERFORMED USING A HEMOGRAM DEVICE AND PERFORMED USING SIMULTANEOUSLY PERIPHERAL SMEAR METHOD IN PATIENTS WITH THROMBOCYTOPENIA

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OBJECTIVE: Thrombocytopenia is a finding that often causes referrals to the haematology outpatient clinic due to being a symptom of various diseases and for the evaluation of bleeding risk especially in the pre-operative period. In daily practice, platelet count is determined with a hemogram device, but the electronic count made in these devices sometimes do not reflect actual platelet levels. In patients with thrombocytopenia detected by hemogram, manual platelet count is performed with peripheral smear to determine real values. For platelet count performed with peripheral smear, there are data in the literature that the number of platelets counted in each area should be calculated by multiplying with 10,000 or 20,000 at high magnification (×100) in microscopic analysis. In this study, it was aimed to evaluate the compatibility between hemogram device-counted platelet value and manual platelet count data obtained by multiplying the platelet count in each area by 10,000 at high magnification (×100) in peripheral smear.

METHODS: The study included 148 patients referred to us with thrombocytopenia detected by hemogram device measurement in the Haematology laboratory of Istanbul Prof. Dr. Cemil Taşcıoğlu City Hospital, between August 2015 and May 2021, whose platelet counts were also calculated manually via peripheral smear. The test results of the patients were evaluated retrospectively. Individuals with pseudo-thrombocytopenia were excluded because they would not show compatibility. Patients with accompanying platelet dysfunction were also excluded because smear was performed on finger prick samples. The compatibility between the values obtained from the hemogram measurements and the values obtained as a result of calculating the number of platelets in each area at high magnification (×100) (with 10,000 multiplication) in peripheral smears from EDTA tube samples was statistically evaluated with Bland Altman Analysis.

RESULTS: The mean age of the study group was 54.48 ± 19.93 years and 64 (43.2%) patients were male. The median value of platelet measurements in peripheral smear was 65 (10-140) ×103, while the median value in platelet measurement with hemogram was 65 (2-149) ×103. According to the Bland Altman analysis, only eight out of 148 (5.4%) measurements were observed to be outside the acceptable range. The mean difference between hemogram measurements and peripheral smear measurements was found to be 3.43 units (95% confidence interval: -0.522 - 7.387, p=0.088). In addition, it was shown that the compatibility did not change as the platelet values increased (p=0.685).

CONCLUSION: In cases where confirmation of platelet count is needed, accurate determination of platelet count by peripheral smear has a very important place in the evaluation of bleeding risk, especially in pre-operative evaluations. In this study, it has been shown that the value obtained by multiplying the number of platelets counted in each area with a coefficient of 10,000 instead of 20,000 during manual platelet counts in peripheral smear provides highly compatible results with the electronic platelet counts performed with hemogram devices.

17. IMMUNOGLOBULIN V(D)J RECOMBINATION, PROTEIN UBIQUITINATION, CELL ADHESION AND SONIC HEDGEHOG GENE VARIANTS ARE DETECTED AMONG FAMILIAL MULTIPLE MYELOMA SUBJECTS FOLLOWING WHOLE EXOME SEQUENCING

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OBJECTIVE: Familial MM cases have been associated with some rare, germline variants, mostly among epigenetic modification genes and needs to be validated in other populations. The aim of this study is to investigate formerly reported rare genetic variants in our population and to search for additional ones.

METHODS: After ethical committee approval, hematology centers in Turkey were informed about collaboration in this familial MM genetic association study. Inclusion criteria was defined as having one or more first, second or third degree relative who has MM or plasma cell disease. After informed consent peripheral blood sample or rarely DNA from pathological samples were collected. Initially NGS analysis have been performed on 33 samples from 23 families targeting the 14 variants in 6 genes reported earlier to be associated with familial presentation (EP300, CDKN2A, USP45, ARID1A, KDM1A, DIS314) (Pertesi et al., Leukemia, 2020). To perform deeper analysis, whole exome sequencing (WES) within 3 families (6 patients) of first degree relationship was carried out. The features of the new variants was examined by NCBI dbSNP and MutationTaster in silico analysis.

RESULTS: 30 MM families (63 patients) were included in the study. The relation was first degree in 69% of the families, second degree in 4% and third degree in 27%. None of the rare variants reported in earlier familial cases were observed among our subjects in targeted NGS panel. However, a heterozygote variant (rs3731249) beside targeted region in CDKN2A was detected in 3 patients. WES detected new rare variants which is not observed earlier. Family 1: Missense variants in BRIP1 (role: DNA double strand break repair) (rs886053214, rs886053215) and ACD (role: maintain telomere length) (rs1306270247). In silico prediction: Polymorphism. Family 2: Missense variant in RAG2 (role: V(D)J recombination of Ig and T cell receptor) (rs765298019). Prediction: Disease causing. Family 3: Missense variant in RET (role: receptor tyrosine kinase) (rs1366681125). Prediction: Polymorphism. Missense variants in CBL (role: protein ubiquitination) (rs754194646), APC (role: cell adhesion) (rs760591046) and PTCH1 (role: sonic hedgehog) (rs772574714). Prediction: Disease causing. All variants in the families were detected as heterozygotes in both patients. The variant in RAG2 cause severe combined immunodeficiency and histiocytic medullary reticulosis if inherited as homozygote. The variant in PTCH1 causes nevoid basal cell carcinoma syndrome. Germline mutations of CBL are related to the juvenile myelomonocytic leukemia and familial AML. APC mutations are related to the familial adenomatous polyposis and colorectal cancer.

CONCLUSION: MM development is multistep and familial MM probably involves different variants across families worldwide. RAG2, CBL, APC, PTCH1 may be added to the list reported earlier by other groups.

18. RETURNED SINGLE-CENTER EXAMINATION OF INVASIVE FUNGAL INFECTIONS IN PATIENTS WITH NEUTROPENIC FEVER REQUESTING CHEMOTHERAPY IN EGE UNIVERSITY HEMATOLOGY CLINIC BETWEEN JANUARY 2016 AND DECEMBER 2019

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OBJECTIVE: In this single-center study we aimed to determine the incidence of İFİ, risk factors, treatment approaches in patients with hematological malignancy who developed febrile neutropenia (FEN) after chemotherapy (CT) and/or autologous stem cell transplantation (OCD), to determine effect of different parameters on survival, to reveal the data of our clinic and to compare them with world data.

METHODS: In our study, approximately 1004 patients with hematological malignancies hospitalized in Ege University Hospital Hematology Clinic between January 2016 and December 2019 were analyzed retrospectively on the electron file. 149 patients with FEN receiving CT who comply with the European Organization for Research and Treatment of Cancer classification/Mycoses Study Group (EORTC/MSG), who are >18 years of age, who have not ASCT were included in the study. Patients age, gender, hematological diagnosis, disease stage, CT, treatment phase, comorbidities, neutrophil and C reactive protein level at hospitalization, primary AF prophylaxis, secondary AF prophylaxis, the day of neutropenia when systemic AF treatment was initiated, primary AF treatment which started, neutrophil, C reactive protein and Procalcitonin level when İFİ was detected, galactomannan (GM) antigen for Aspergillus, radiological findings supporting İFİ, detected fungal agents, fungal focus, response to AF treatment, patients who received secondary AF therapy, patients who get dual and triple AF treatment, using status of granulocyte-colony stimulating factor (G-CSF), duration of neutropenia, duration of hospitalization, duration of AF treatment, death from İFİ and death from other causes were recorded.

RESULTS: FEN was detected in 131 of 149 patients included in the study. According to the EORTC criteria, 100 patients were classified as possible İFİ, 29 patients as probable İFİ, and 20 patients as proven İFİ. Fungal foci were not detected in 120 patients and the causative agent was not observed. Different specimens of 29 patients were evaluated and Candida was detected in 22 specimens, Aspergillus in 5 specimens, and Mucor in 2 specimens. All 149 patients received different combinations of AF treatment and the average time to receive AF was 37.4 days. The mean hospitalization period of the patients was 83.1 days, and the time until the diagnosis of İFİ was 29.7 days. Exitus due to İFİ was detected in 37 patients, hospitalization of 108 patients was terminated with discharge, and hospitalization in 3 patients ended with death due to different reasons. It was determined that hematological diagnosis, age, and gender had a statistically significant effect on survival and the accompanying disease had a statistically significant effect on mortality ($p<0.05$). There was no statistically significant effect on survival of EORTC/MSG criteria, use of G-CSF, AF prophylaxis, duration of AF and concomitant disease.

CONCLUSION: Neutropenia is the most important risk factor for infection in patients with hematological malignancies. Fungal infections such as Mucormycosis, Coccidiomycosis, Cryptococcosis, Histoplasmosis, especially Candidiasis and Aspergillosis, are important in terms of morbidity and mortality in this patient population. Since most fungal infections have nonspecific symptoms, recognition of their findings makes the diagnostic process difficult for clinicians and often requires the initiation of empirical AF therapy. Early diagnosis and treatment are of great importance in patients.

19. OBINUTUZUMAB IN TREATMENT-NAIVE AND RELAPSED REFRACTORY CLL PATIENTS: MULTI-CENTER REAL LIFE TURKISH DATA

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OBJECTIVE: Chronic lymphocytic leukemia is characterized by abnormal proliferation of mature lymphocytes at lymph nodes, spleen and bone marrow. It is the most common leukemia in adults. Treatment is not indicated in asymptomatic patients and patients with early stage disease. In patients with treatment indication there are different options including chemotherapies and targeted therapies. Obinutuzmab, a new anti-CD 20 antibody, is a treatment option in CLL patients. In the literature, randomized studies reported that it was an effective and safe drug with manageable adverse effect profile. But there are limited real life data in the literature.

METHOD: 74 CLL patients who were treated with obinutuzumab in 12 centers in Turkey were included. The characteristics of the patients, treatment and follow up data were retrospectively analyzed from the archive of related hematology clinics.

RESULTS: 74 patients (37 [50%] female and 37 [50%] male) were enrolled. The median age at the time of initiation of treatment was 71 (range, 44-84). The median CIRS score was 7 with a range of 2-18. The indications of treatment were doubling time (14 patients, 19%), anemia and thrombocytopeni (37 patients, 50%), symptomatic and progressive lymph nodes and splenomegaly (23 patients, 31%). The median lymphocyte, LDH and creatinine clearance were 53000/microl (range, 4900-438000), 279 IU (range, 113-764), 57 ml/min (range, 34-140), respectively.

When we analysed the data of treatment, 29 patients (39%) were relapsed/refractory and 45 (61%) patients were treatment naive. The relapsed or refractory patients were treated with obinutuzumab after a median 1 (range, (1-7) line of therapy. The patients were treated with rituximab based chemotherapies (R-CHOP, R-CVP, R-Bendamustin, R- FC) ibrutinib or venetoclax before initiation of obinutuzumab.

16 (21.6%) patients were treated with Obinutuzumab as monotherapy and 58 (78.4%) patients were treated with combination therapy. In combination therapies, clorambucil (40 patients, 69%), bendamustin (2 patients, 3.4%), venetoclax (10 patients, 17.2%) and fludarabine and cyclophosphomide based chemotherapies (6 patients 10.4%) were used.

Efficacy data were analyzed in 41 eligible patients. Overall CR and PR rates were 43% and 48.7%. 2 (4.8%) patients had stable disease and 1 patient (2.6%) had progressive disease. When we performed a subgroup analysis in relapsed/refractory and treatment naive patients, in the relapsed refractory group CR and PR rates were 23% and 29%, respectively. In the treatment naive group CR

and PR rates were higher as expected, 68% and 25%, respectively. In 18 (24.3%) patients, another line therapy including venetoklax, ibrutinib and rituksimab based chemotherapies were used after obinutuzumab due to insufficient response, relapsed disease or progression.
Safety data, revealed that the most common adverse effect was neutropenia documented in 41.4% of the patients with a median grade 2 range, 1-4 reaction. In 5 patients with neutropenia febrile neutropenia was reported. In 2 (2.7%) patients, the treatment was stopped due to grade 4 neutropenia and recurrent febrile neutropenia attacks. The second most common adverse effect was infusion reaction and reported in 17 (23%) patients. The median grade was 2 with a range of 1-4. Other adverse effects were thrombocytopenia (grade 3-4 [7 hasta, 9.4%)], grade 1.2 [15 hasta, 20.2%]), tumor lizis syndrome (grade 1, 2 [5 hasta, 6.7%]), anemia (grade 1, 2 [16 hasta, 21.6%]). At the last visit, 16 patients (21.6%) died. Only 2 of the patients died due to progressive disease. Other reasons for death were COVID infection (1 patient, 6.25%), cardiac reasons (arrhythmia, MI, 4 patients 25%), stroke (2 patients, 12.5%) and in 3 (18.75%) patients the reason could not be documented.
CONCLUSION: In this real life data, we documented that obinutuzumab had a high overall response rate in both relapsed refractory and treatment naive group with a manageable adverse effect profile. As randomized controlled studies, this data from Turkey also revealed that obinutuzumab is an effective and safe drug in CLL patients.

20. IMPACT OF ≥2 CHROMOSOMAL ABERRATIONS IN KARYOTYPE ON IBRUTINIB EFFICACY IN RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (RR CLL) PATIENTS. PRELIMINARY RESULTS OF A SINGLE CENTER STUDY

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OBJECTIVE: Ibrutinib is a Bruton tyrosine kinase inhibitor approved for the treatment of relapsed refractory CLL. Because of its proven efficacy in genetically high-risk patients, it is also approved at induction in the presence of del (17p). Its therapeutic potency has been also tested in relation to numerous recurrent mutations such as NOTCH1, ATM or BIRC3. However, there is a lack of studies on the impact of complex cytogenetics on ibrutinib efficacy. Aims: To determine the impact of ≥2 chromosomal aberrations in metaphase karyotype on ibrutinib efficacy in a series of R/R CLL with a long follow-up time.

METHODS: Patients and Methods: Sixty-one R/R CLL patients were studied. Their files were retrieved after their informed consent was obtained. Thirty-six percent had unmutated IGHV mutational status, 22% showed del (17p) by interphase FISH analysis and 45% had complex karyotype (determined in half of the patients and defined as such when at least two distinct chromosomal aberrations, numerical±structural, were present). Ibrutinib monotherapy was prescribed in 2nd, 3rd, 4th, 5th and ≥6 th line in 28.6%, 30.6%, 18.4%, 8.2% and 14.2% respectively. Best response to Ibrutinib was complete (CR) in 12.8%, partial (PR) in 78.7%, minimal (MR) in 4.25% while resistance also occurred in 4.25% of patients. Median time from diagnosis to ibrutinib administration was 78 months and median treatment duration was 29.5 months. Treatment was discontinued because of side effects (13.6%), progression disease (27.8%) or death (11.7%). Ten percent of patients presented Richter syndrome while on therapy. Ibrutinib treatment is ongoing for 46.9% of patients. Median follow-up time from ibrutinib initiation to last follow-up or death is 34 months.

RESULTS: As expected, response rate was highly correlated with survival after Ibrutinib administration (p=0.004) and no correlation was observed with mutational status or del (p53). Interestingly, patients with karyotype with ≥2 chromosomal aberrations presented an inferior survival (p=0.05) compared to the others. In the few cases were Richter occurred and complex karyotype was present, a strong correlation was observed but numbers are too low to reach statistical conclusions.

CONCLUSION: Complex karyotype may represent an adverse prognostic factor of Ibrutinib efficacy. Further studies are needed.

21. DEVELOPMENT OF NEUTRALIZING ANTIBODIES AGAINST SARS-COV-2 IN HEALTHY SANITARY WORKERS AND OCTOGENARIANS POST-BNT162B2 MRNA COVID-19 VACCINE: FIRST RESULTS OF A PROSPECTIVE TRIAL IN 366 INDIVIDUALS

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OBJECTIVE: Efficacy of vaccines against SARS-CoV-2 virus is of great importance in order to mitigate COVID-19 pandemic. The BNT162b2 mRNA vaccine is the first approved by both FDA and EMA vaccine with confirmed clinical activity in phase 3 trials. However, the immune responses against SARS-CoV-2 after BNT162b2 vaccination have not been fully elucidated in several population subsets including octogenarians and patients with malignancies or autoimmune disorders. The aim of this prospective study (NCT04743388) is to evaluate the development of neutralizing (NAbs) and anti-spike RBD IgG antibodies against SARS-CoV-2, as well as the levels of cytokines and the induced B- and T-cells subpopulations following vaccination with BNT162b2 vaccine. Participating groups include healthy sanitary workers, elderly individuals and patients with hematological malignancies or solid tumors under different types of treatment. Herein we present preliminary results of the BNT162b2 vaccine effects in the development of anti-SARS-CoV-2 antibodies in healthy sanitary workers and octogenarians.

METHODS: Healthy sanitary (i.e., physicians and nurses) workers of Alexandra hospital, Athens, Greece and volunteered octogenarians were included in this study. The inclusion criteria included (a) age higher than 18 years and (b) the absence of any known auto-immune or malignant disease. NAbs against SARS-CoV-2 and anti-Spike-RBD IgG antibodies were measured using FDA approved methods, i.e., the cPass™ SARS-CoV-2 Neutralization Antibody Detection Kit (GenScript, Piscataway, NJ, USA) and the Elecsys Anti-SARS-CoV-2 S assay (Roche Diagnostics GmbH, Mannheim, Germany), respectively. Time-points for blood collection were day 1 (D1) (first BNT162b2 dose), D8, D22 (second dose), D36 and D50 for healthy sanitary workers and D1, D22 and D50 for octogenarians. The study includes also a follow-up of the antibodies levels every 3 months till month 18 post the delivery of the second dose (D22) of the vaccine.

RESULTS: The study population included 254 healthy sanitary workers (92 males/162 females; median age: 49 years, range: 25-70 years) (group 1) and 112 octogenarians (51 males/61 females; median age: 85 years, range: 80-95 years) (group 2). Twenty-one donors from group one and ten from group two had NAbs inhibition titers >30% (threshold for positivity) at D1; these titers significantly expanded at D8 indicating the presence of sustained rapid anti-SARS-CoV-2 antibody production in COVID-19 healers. NAbs titers (in negative at D1 donors) from group one, were found to increase significantly already at D22 (day of second vaccination), plateaued two weeks (D36) after the second dose of the vaccine (NAbs inhibition ≥90%) and remained at high levels at D50 (NAbs inhibition ≥90%). Notably, the NAbs titers (in negative at D1 donors) had lower increases in ages 50-70 vs. 25-49 at D22; this age-related effect of the vaccine efficacy was confirmed in octogenarians who at D22 developed significantly lower NAbs titers vs. all other age groups. Similar kinetics were found in donors of groups one and two for the anti-spike RBD IgG antibodies.

CONCLUSION: We conclude that the BNT162b2 mRNA vaccine is highly effective in producing high anti-SARS-CoV-2 antibody titers in healthy donors. Given however that this readout is age-dependent, we suggest that the second timely vaccination is needed, especially in the elderly population.

22. THE OUTCOME OF COVID-19 IN PATIENTS WITH HEMATOLOGICAL MALIGNANCY

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OBJECTIVE: Coronavirus disease-19 (COVID-19) was declared a global pandemic by the World Health Organization on 11 March 2020. Immunosuppression is an important risk factor for COVID-19 disease. Previous studies have shown the prevalence of cancer in COVID-19 patients to be 2%, 3.7% of patients with COVID-19 are immunodeficient, and the prognosis of COVID-19 in patients with hematological malignancies is worse than in patients without cancer and even patients with solid organ tumors. The aim of this study was to evaluate patients who were being followed up for malignant hematological diseases and developed COVID-19, to examine the effect of the COVID-19 infection on the malignancy-related clinical course and overall survival, and to determine the factors affecting mortality.

METHODS: This retrospective study included patients with a history of malignant hematological disease and COVID-19. Demographic and clinical information about both hematological disease and COVID-19 were recorded. Diagnosis, disease status, and treatment protocols were recorded for the hematological disease, the status of which was classified in 4 groups as initial diagnosis, remission, stable, or relapsed/refractory disease. For COVID-19, symptoms, severity of infection, hospitalization, need for mechanical ventilation or intensive care, COVID-related treatments, and mortality were recorded. COVID-19 severity was defined as mild (outpatient), moderate (hospitalization), or severe (ICU). Patients were subgrouped for analysis as hospitalized and non-hospitalized, and survivors and non-survivors. These groups were compared with each other, in respect of the characteristics related to the clinical course of COVID-19 and the data related to the hematological disease.

RESULTS: 77 patients included. COVID-19 was seen more frequently in patients in the MPN (22.1%), NHL (19.5%) and MM (15.6%) groups. Active treatment of chemotherapy, immunotherapy or immunosuppressive therapy was being received by 43 (55.8%) patients. Mortality rate due to COVID-19 was 20.8%. No statistically significant difference was determined between the survivor and non-survivor groups in respect of age and gender distribution or the presence of any comorbidity and also leukocyte, neutrophil, lymphocyte, and monocyte values. Platelet count and hemoglobin count were significantly lower in the group with mortality than in the group with recovery.

CONCLUSION: Most patients with blood cancer have a suppressed immune system because of the biology of the malignancy itself and cancer treatments. The aim of this study was to examine the course of COVID-19 in patients with hematological malignancies and to determine the factors affecting the severity of the infection. It should be kept in mind that low hemoglobin and platelet levels contribute to mortality. In addition, it is important to protect patients with hematological cancer from COVID-19 infection and undertake effective vaccination due to its more aggressive and mortal course than for patients without a malignancy. Further studies and long-term observations are required with a larger number of patients to determine predictive factors associated with the severity of the clinical course and mortality.

23. LINKING GENOTYPE TO PHENOTYPE IN COMPLEMENT DYSREGULATION OF SEVERE COVID-19

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OBJECTIVE: Coronavirus disease-19 (COVID-19) has led to unprecedented morbidity and mortality worldwide, emphasizing the unmet need for early prediction of severe COVID-19, especially in special populations that might benefit from targeted treatment. Although complement inhibitors have shown safety and efficacy in severe COVID-19, proper patient selection is needed. In this context, we aimed to validate whether complement-related variants previously identified to predict severe COVID-19 are associated with an impaired complement phenotype.

METHODS: We prospectively studied consecutive adult Caucasian patients hospitalized with COVID-19. Through targeted next-generation-sequencing we identified variants in complement factor H/CFH, CFH-related, CFI, CFB, CFD, C3, CD55, C5, CD46, thrombomodulin/THBD), and ADAMTS13 (A Disintegrin and Metalloproteinase with Thrombospondin motifs). Plasma was isolated from sodium citrate tubes collected at hospitalization for non-ICU (intensive care unit) patients or at ICU admission for ICU patients and stored immediately. Taking into account the difficulties of functional complement assessment in clinical laboratories, we studied markers that would be potentially accessible in everyday clinical practice or the setting of a clinical trial. Therefore, we measured thrombomodulin/THBD (R&D, Bio-techne, Minneapolis, MN USA), C3a (Invitrogen, ThermoFischer Scientific, Waltham, MA USA) and C5a (Affymetrix, Bender Medsystems, Vienna Austria) using commercially available ELISA assays.

RESULTS: We studied 133 COVID-19 patients, 80 with moderate disease hospitalized in COVID-19 general ward, and 53 with severe disease hospitalized in ICU. Among 381 complement-related variants identified, we documented rs1042580 (THBD) and rs800292 (CFH) that have been previously shown to predict severe COVID-19. THBD values were significantly increased in patients requiring ICU hospitalization compared to non-ICU patients (median 2.3, interquartile range [1.6] versus 1.4 [0.79] ng/ml, p=0.025), and patients harboring the rs1042580 (THBD) variant (p=0.032). Similarly, C3a values were significantly increased in patients requiring ICU hospitalization compared to non-ICU patients (410 [14.1] versus 312 [19.1] ng/ml, p=0.035). Despite increased levels of C5a in ICU patients, this difference did not reach statistical significance (72.1 [7.2] versus 43.4 [11.3] ng/ml, p=0.244).

CONCLUSION: We reveal for the first time that genetic dysregulation is associated with an impaired complement phenotype in severe COVID-19. Considering the clinical phenotype associated with genetic variants, these are also expected to significantly contribute to better selection of patients that would benefit from targeted complement inhibition.

24. USE OF A FOAMY-VIRUS VECTOR SYSTEM TO PRODUCE AN "OFF-THE-SHELF" ANTI-CD19 CAR T CELL PRODUCT

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OBJECTIVE: Anti-CD19 chimeric antigen receptor (CAR) T cells have transformed the field of cancer immunotherapy. Current CAR T cell trials use autologous cells, with several limitations (prolonged production time, costly, manufacturing failure), whereas the Lentiviral vectors (LV), used for commercial products, are endowed with extra limitations (packaging limits and mutagenesis risk). Our group has developed an in-house anti-CD19 CAR-T cell product, using a safer to LV, foamy virus vector (FV).

METHODS: We constructed FV vectors expressing the anti-CD19 CAR and eGFP from an EFP1 and IRES2 promoter, respectively. 2nd generation LV vector backbones were purchased from a commercial vendor. Peripheral blood from healthy individuals and cord blood (CB) were used as T cell sources. T cells were activated by antiCD3/CD28 beads and transduced with antiCD19 CAR-T, LV or FV vectors. Transduction efficiency was assayed by flow cytometry (FCM) using either an anti-protein L antibody or recombinant CD19 protein. FV and LV CAR-T cells were expanded with Rapid Expansion Protocol (REP) and their cytotoxic effect was evaluated against the CD19+ Raji and Daudi cell lines and against the CD19- cell line, HL60. Cytotoxicity was calculated as: [1-live targets (sample)/live targets (control)]×100. CAR-T cell activation was also assayed by INF-γ ELISA.

RESULTS: LV and FV vector titers were between 3-5×10^5 TU/ml and 2-4×10^5 TU/ml, respectively, regardless of the presence of the eGFP cassette. Transduction efficiency ranged from 40-80% at MOI 5-10 with FV vectors and was comparable to the transduction efficiency of LV vectors at a much higher MOI (10-30). Following REP, the vast majority of cells consisted of CAR T cells, regardless of the vector used or the T cell source and isolation method. For cytotoxicity assays, CAR T cells were incubated with CFSE-labelled Raji and/or Daudi cells at different ratios (5:1, 10:1) for 18 hours. At the end of the incubation period, the % cell lysis was 87.3 (SD 6.38) and 92.4 (SD 3.2) at 5:1 and 10:1 ratio, respectively (n=3). Similar results were obtained for LV vectors. When CD19- HL60 cells were used as targets, no lysis was noted, indicating a specific anti-CD19 cytolytic effect of CAR T cells. In two paired activation experiments, CB-derived FV-CAR-T cells secreted 560 and 437 pg/ml of IFN-γ; similarly, LV-CAR-Ts secrete 534 and 554 pg/ml IFN-γ. Untransduced control cells, produced 68 pg/ml and 12 pg/ml for FV-CAR-T and LV-CAR-T experimental arm respectively.

CONCLUSION: Our group has developed for the first time a FV vector for anti-CD19 CAR T cell production, with an efficient gene transfer to human T cells and with potent in vitro cytotoxic properties, similar to their LV-derived counterpart. Overall, we provide a proof of concept that allogeneic, in-house CAR T cells derived from a non-patented viral backbone such as the FV, could be a safe, efficient and affordable alternative to LV-derived vectors for immunotherapy.

STAT5 INHIBITOR PIMOZIDE INDICATES A THERAPEUTIC APPROACH FOR OVERCOMING PONATINIB RESISTANCE IN K562 LEUKEMIC CELLS

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OBJECTIVE: Signal Transducer and Activator of Transcription 5 (STAT5) is a transcription factor that plays a key role in neoplasia, triggered by the fusion oncogene BCR-ABL1; it is not only an essential protein for the pathogenesis of chronic myeloid leukemia (CML), but also its overexpression is associated with drug resistance developed toward various generations of Tyrosine Kinase Inhibitors (TKIs); these are still accepted as gold standard therapeutics for the cure of CML. In this study, we investigated whether suppression of STAT5 via a "STAT5 inhibitor" Pimozide resulted in any regain of chemosensitivity to third-generation TKI Ponatinib.

METHODS: This study was designed on both parental CML cell line K562WT and its 1nM Ponatinib resistant counterpart, indicated as K562-Pon1, for analysis of cytotoxicity (WST-1), apoptosis (Annexin V), cell cycle assays, qPCR, and Western Blot experiments.

RESULTS: It was observed that Pimozide was more effective in resistant cells compared to wild type cells for inducing apoptosis and block cell arrest; in addition, STAT5 was a significant protein for regaining chemosensitivity to Ponatinib when its expression was suppressed both at mRNA and protein level. We also obtained gratification results when Pimozide and Ponatinib were used as a combination therapy, especially on resistant cells by inducing apoptosis and G0/G1 arrest of leukemic cells.

CONCLUSION: we consider that STAT5 inhibitor Pimozide can be a good alternative or combination therapy with TKIs for patients suffering from chemotherapeutic drug resistance.

ABSTRACTS
POSTER PRESENTATIONS

P01. GASTROINTESTINAL HEMORRHAGE FOLLOWING MIDOSTAURIN ADMINISTRATION: A CASE REPORT AND REVIEW OF THE LITERATURE

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OBJECTIVE: Objective: Midostaurin is a multi-targeted protein kinase inhibitor indicated for FMS-like tyrosine kinase 3 (FLT3)-mutated acute myeloid leukemia (AML) and systemic mastocytosis (SM). It has been characterized as generally well tolerated when administered as a single agent. In combination with cytarabine and an anthracycline, most common side effects include neutropenia, thrombocytopenia and anemia.
METHODS: Case presentation and methods: We present a patient with therapy-related FLT3 positive AML with repeated episodes of melaena during remission induction, first and second consolidation therapy associated with midostaurin administration. We also conducted a review of the literature for similar cases by searching PubMed with and without using MeSH database through June 24, 2021. MeSH terms used: Staurosporine, Midostaurin, Protein Kinase Inhibitors, Acute Myeloid Leukemia, Systemic Mastocytosis, Gastrointestinal hemorrhage, Adverse Drug Events, Cytarabine. The relevance of candidate articles was evaluated based on Title and Abstract.
RESULTS: Results: A 68-year-old male with a history of primary refractory Epstein Barr virus positive diffuse large B cell lymphoma, not otherwise specified, was salvaged with rituximab-etoposide, methylprednisolone, high dose cytarabine, cisplatin and autologous hematopoietic stem cell transplantation following a BEAM conditioning. After eighteen months in remission, the patient presented with leukocytosis and thrombocytopenia during a routine check-up. Diagnostic work up revealed a 50% infiltration of the bone marrow by myeloblasts with a karyotype of 47, XY, +8, with FLT3 internal tandem duplication (ITD) low ratio and wild type nucleophosmin 1. A diagnosis of therapy related FLT3 positive AML was made. He received remission induction treatment with a 2+5 regimen (anthracycline plus cytarabine) and on day 8 he was started on midostaurin 50 mg twice daily. On day 21, the patient had melaena and a diagnosis of hemorrhagic erosive gastritis was made via upper gastrointestinal (GI) endoscopy. Subsequent exposure to midostaurin during consolidation with intermediate dose cytarabine (cytarabine 1.5 g/m^2) resulted in reappearance of melaena on day 17 of first consolidation and day 12 of second consolidation. Remarkably, the decrease of midostaurin by 50% during the second consolidation did not inhibit the appearance of melaena. Midostaurin was discontinued on all three occasions and the patient was supported with intravenous fluids, proton pump inhibitors and red blood cell and platelet transfusions. Midostaurin was withheld from the third consolidation and melaena did not reoccur. Our literature review revealed that this is the second case of midostaurin related GI in AML. Shimony et al described another case of necrotizing hemorrhagic gastritis in a patient with AML, after induction with midostaurin. Moreover, GI hemorrhage was observed in up to 14% of patients in clinical trials of midostaurin for the treatment of SM. The recommended starting dose of midostaurin is higher in SM (100 mg twice daily) and gastrointestinal involvement in mastocytosis might lead to increased bleeding tendency.
CONCLUSION: Conclusion: As the use of targeted therapies in AML increases significantly, the profile of side effects is continuously changing. Based on current evidence from the literature, GI bleeding related to midostaurin in AML is a rare but serious adverse event that haematologists need to be aware of.

P02. ACUTE LEUKEMIA CASES IN A GREEK HOSPITAL DURING ONE YEAR

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OBJECTIVE: Report of acute leukemia cases diagnosed in our hospital from September 2018 until August 2019. Leukemia is a malignant blood disease characterized by excessive and uncontrolled proliferation of malignant cells produced by bone marrow. Leukemia can be myelogenous or lymphogenic and it is distinguished in acute and chronic. Acute leukemia (acute myeloblastic and acute lymphoblastic) is a clonic disorder of naive hematopoietic cells with hyperplasia of immature cells (blasts) and suppressed differentiation, has a rapid evolution with severe clinical manifestation and bad prognosis if not treated promptly.
METHODS: Acute leukemia cases in one year period were reported and evaluated according to gender, age, number of blasts, presence of anemia, thrombocytopenia, leukocytopenia, leukocytosis and type of leukemia. The analyzer used for the blood count test was Sysmex XN-1000 Roche company and the microscopic examination of blood smear was stained with May Grunwald-Giemsa.
RESULTS: Totally 15 acute leukemia cases examined in our laboratory were reported, of which 6 were about male and 9 female. Regarding the age, 4 patients were <40 years old, 5 patients 40-60 y.o and 6 patients were >60 y.o. It is worth mentioning that 2 cases were about children aged 3 and 15 years old. The percentage of blasts reported in peripheral blood was 5-20% in 6 patients, 20-50% in 5 patients and >50% in 4 patients while the characteristic Auer sticks were observed in 8/15 peripheral blood smears. Anemia was reported in the majority of cases (14/15 patients), thrombocytopenia in 12/15 patients, leukocytosis in 10/15 patients while leukocytopenia in 5/15 patients. In adults, in 13/13 cases acute myeloblastic leukemia was diagnosed while in children 1/2 cases was diagnosed with acute lymphoblastic leukemia.
CONCLUSION: The majority of patients diagnosed with acute leukemia were adults >40 years old and mainly acute myeloblastic leukemia was developed. The number of acute leukemia cases diagnosed in our hospital during the last year is worrying as there is an increase in comparison with previous years.

P03. A CASE OF PHILADELPHIA POSITIVE ACUTE MYELOID LEUKEMIA COMPLICATED WITH TUBERCULOSIS

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OBJECTIVE: Philadelphia chromosome positive acute myeloid leukemia (Ph+ AML) was defined as a provisional entity in 2016 classification of myeloid neoplasms of World Health Organization. However, it is hard to differentiate de novo Ph+ AML from blastic phase of chronic myeloid leukemia. In the current literature it is controversial that a Ph+ AML patient should be treated with a cytotoxic chemotherapy or with tyrosine kinase inhibitor. Here we give a Ph+ AML patient presented with hepatosplenomegaly and concurrently diagnosed with tuberculosis.

RESULTS: A 22-year-old African male presented to our department with fever, night sweat and weight loss. He had been treated for malaria in his country about a month ago. Left lung sounds were decreased from basal to the middle zone, left upper abdomen was tender, spleen was palpable 10 centimeters below the costal margin and traube was dull on percussion. His complete blood count showed leukocytosis (31×10^9/L), anemia (hemoglobin 7.8 g/d), thrombocytopenia (53×10^9/L) and 80% of nucleated cells were blast on peripheral blood smear. Chest X-ray revealed pleural effusion, in ultrasound exam spleen was 25 centimeters in diameter and parenchymal echo compatible with infarction was seen. Flow cytometric analysis (FCA) were consistent with acute myeloid leukemia (AML). Eighty percent of nucleated cells were blastic on the pleural fluid smear. Acid-fast bacillus was not detected and adenosine deaminase level was normal, fluid exam for polymerase chain reaction (PCR) test for mycobacteria was negative as twice and all blood tests were negative for malaria, leishmaniosis, brucellosis and syphilis. Bone marrow aspirate was dry tap, genetic tests for AML were sent from peripheral blood and 7+3 chemotherapy (cytarabine plus idarubicin) was started. Conventional cytogenetics revealed 46, XY karyotype with t(9;22) and BCR- ABL1 (p210) with PCR method was positive of 17.4%. Imatinib 600 mg/day was added to 7+3 chemotherapy. Persistent fever even after extended spectrum antibiotics and resistant pleural effusion due to which is supposed to be relevant with AML provoked us to examine the fluid again for tuberculosis PCR and on the 30th day of his hospital admission, a tuberculosis diagnosis was made. Isoniazide, rifampicine, ethambutol and pyrazinamide treatment was started. Bone marrow aspiration on the 45th day of chemotherapy was consistent with remission, FCA detected residual disease of 0.169% and pleural fluid was detected negative for residual disease. Pleural effusion was then resolved. The patient was intended to refer to a transplant center since he had a Ph+ AML in remission but for social and economic reasons allogeneic transplant could not be performed. Then we planned to proceed with high dose cytarabine consolidation for four courses along with imatinib 400 mg/day. After 3 consolidative chemotherapy he was still in remission, however BCR-ABL1 level was 0.74% from his bone marrow aspirate while we were writing this report.

CONCLUSION: BCR-ABL1 fusion gene is an unfavorable risk factor for AML according to the 2017 European Leukemia Net risk classification. We think our case had probably a chronic CML stage but it had missed while moving around the other possible diagnoses causing organomegaly and pleural effusion.

P04. BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM (BPDCN): A RARE OCCURRENCE IN A YOUNG PATIENT

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OBJECTIVE: To present a case of a very rare and aggressive hematological neoplasm in a young patient with a solitary cutaneous mass.
METHODS: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is considered an orphan tumor due to its rareness and clinical aggressiveness with poor response to conventional chemotherapy. It derives from precursor of plasmacytoid dendritic cells (pDCs). BPDCN more often occurs in men (male-to-female ratio = 3.3:1) in the seventh or eighth decade of life, although it can occur at any age, including childhood. Its incidence is roughly 0.000045%. The tumor is characterized by a high frequency of cutaneous lesions at diagnosis, accompanied by extracutaneous involvement of the bone marrow, peripheral blood, and lymph nodes.
RESULTS: In December 2019, a 25 year-old-female presented with a solitary reddish mass 7×4 cm on the left tibia. The mass was noticed five months ago with gradual increase. The MRI, in October 2019, showed subcutaneous mass of 4×3.3×0.9 cm. Biopsy revealed infiltration of medium sized blast cells positive in CD2 and CD56, suggesting an aggressive NK lymphoproliferative disease. Although CBC and biochemistry were normal, infiltration of lymphoid-like blastic population, with the presence of nucleoli and small vacuoles, was observed at bone marrow aspiration. Bone marrow biopsy revealed 85% infiltration of blasts positive in CD4, CD56, CD123, HLA-DR and TCL-1. CT-scan showed small lymph nodes in cervix and in abdomen. A diagnosis of BPDCN was established (WHO 2016). Due to the aggressive behavior of the neoplasm and the lack of a standard first line treatment, multi-agent chemotherapy was decided and she received the Hyper-CVAD regimen. After first cycle (1A+1B) complete remission was achieved and a second cycle was given as bridge to allogeneic stem cell transplantation (allo-HCT). Additionally, four intrathecal administrations of methotrexate/cytarabine were performed as central nervous system prophylaxis. The patient received peripheral blood stem cell transplant from a HLA match sibling donor in July 2020. She presented mild chronic graft versus host disease (GVHD) 11 months after allo-HCT, which was treated with corticosteroids. Thirteen months post transplant, the patient remains in complete remission.
CONCLUSION: BPDCN is a rare and very aggressive disease with median survival of 12 months. There is no consensus for a worldwide standard of care treatment and multi-agent regimens designed for AML or ALL are usually used in order to obtain a complete remission. Treatment responses are mostly transient and overall outcome is generally very poor, due to the high rate of recurrence, with a median overall survival of 12 months. Allo-HCT is the best option, especially if offered in first remission, and may result in long-term survival, although is not feasible mostly due to advanced age at presentation. Better understanding of pathobiology of the tumor has contributed to introduction of new modalities such as anti CD123 directed immunotherapies, hypomethylating agents and BCL-2 inhibitor with promising clinical action and effectiveness.

P05. INVESTIGATION OF THE EFFECTS OF SYNTHETIC CANNABINOIDS ON THE PATHOGENESIS OF LEUKEMIA AND STEM CELLS

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OBJECTIVE: The popularity of synthetic cannabinoids is increasing due to their easy accessibility and psychoactive effects. The effects of cannabinoids, which are known to affect the endocannabinoid system (ECS) receptors, on Cannabinoid Receptor 1 (CB1), which generally affects the central nervous system, were investigated. Cannabinoid Receptor 2 (CB2), which has less studies in its field, is found in the cells that are responsible for regulating the digestive system and lymphatic system. Studies on cannabinoids on leukemia stem cells and hematopoietic stem cells, which are the precursors of leukemia cells, are generally on the natural cannabinoid delta-9-tetrahydrocannabinol (THC). There are no epigenetic studies on leukemia and synthetic cannabinoids. In our study, it was aimed to determine the cytotoxic and apoptotic effects of the widely used psychoactive substance synthetic cannabis [JWH-018] on stem cells and leukemia cells, and to determine the expression changes at the mRNA level of some genes involved in various important cellular processes and genes involved in epigenetic regulation.
METHODS: In our study, in cell culture studies carried out under in vitro conditions, cells were incubated in a medium containing the necessary substances for their survival, growth and proliferation, at 37° C, in an oven with 95% humidity and 5% CO_2. The cytotoxicity value of JWH-018 on cells was determined. Following cytotoxicity and apoptosis experiments, we examined the effects of JWH-018 on hematopoietic stem cells and chronic myeloid leukemia (CML) model K562 cells. After cytotoxicity and apoptosis experiments, we determined the genetic and epigenetic changes by Real Time PCR (RT-PRC). Finally, we carried out our statistical analysis studies.
RESULTS: Significant apoptosis was observed in leukemia stem cells and chronic myeloid leukemia cell line K562 cells after JWH-018 treatment compared to control cell groups. Epigenetic profiling results also support apoptosis results. As a result of epigenetic profiling, changes in JAK/STAT pathway genes, which have an important role in leukemogenesis, were observed to prevent cancer compared to the control group.
CONCLUSION: In our study, by analyzing epigenetic profiling in the process of carcinogenesis; The possible roles of gene expression changes, cell cycle, apoptosis, tumor suppressor, oncogene and some elements of the JAK/STAT pathway on the pathogenesis of leukemia have been determined. According to our literature search, synthetic cannabinoids have higher activities than natural cannabinoids, resulting in greater therapeutic effects and lower doses. JWH-018 has the potential to be more selective and potent than its natural counterparts. Apoptotic analysis and epigenetic profiling analyzes performed as a result of the studies represent a promising therapeutic approach.

P06. INVESTIGATION OF THE THERAPEUTIC EFFECTS OF BROMODOMAIN INHIBITOR PLX51107 AND HDAC INHIBITOR SAHA EPIGENETIC AGENTS UPON AML CELL LINE

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OBJECTIVE: Using the newly discovered structurally different PLX51107 inhibitor, which binds to lysine recognition motifs acetylated in bromodomains of the BRD4 protein, preventing BRD4 from binding to acetylated lysines on histones, and HDAC inhibitor SAHA (vorinostat) alone/combined applications, to evaluate the apoptotic, cytotoxic effects on leukemic cells, and to determine the cellular responses such as determining the expression changes in the mRNA level of selected genes in the carcinogenetic process.

METHODS: Under appropriate conditions, the HL60 and non-leukemia control groups were replicated and proliferation and cytotoxicity analyzes were performed with XTT reagent, and the IC50 dose was determined for Plx51107 and vorinostat. Upon apoptotic effect on cells according to the determined IC50 dose of the active ingredients and the selected target gene expression levels were evaluated by RT-PCR. The Effects of Plx51107 and Vorinostat on Expression Amounts of BRD4 Protein were investigated by western blot analysis.

RESULTS: The resulting data showed that the cytotoxic effect of Plx51107 and Vorinostat on the HL60 cell line was determined, and the IC50 value was; 6.68uM for Plx51107 at 72h; The Vorinostat was calculated to be 4.3uM at 48h. For the control group cell line without leukemia (NCIBL2171), 1.24um at 72h for P1x51107; It was calculated as 2.01um at 48h hour for the Vorinostat. When the cytotoxicity was evaluated with the combined administration of two active ingredients, the combination of the two active ingredients in this cell line was not evaluated since an antagonistic effect was detected between the doses for the NCIBL2171 cell line. When the combination analysis for the HL60 cell line was evaluated, the synergistic effect was found to be 1.5 times the P1x51107 IC50 dose, keeping the vorinostat IC50 dose constant. The apoptotic effects of the active substances on the cells according to the determined IC50 doses were evaluated by Annexin V analysis. According to the results, the apoptotic effects of the active ingredients on the cells were found in the range of approximately 80% -97.4%. According to the results of RT-PCR analysis of selected target genes, 1.23 and 15.8 times decrease was observed in bcl-2 and casp3 genes, respectively. For CDKN2A, one of the cell cycle genes, P1x51107 was 4.85 times 1.5 times the IC50 dose; For combo1, it was determined that there was 3.97 times decrease. Western blot analysis was performed by examining the expression changes of the selected target BRD4 protein on cells, considering the expression changes of the genes. According to the results of the analysis, the decrease in the expression change is also confirmed by the western blot analysis. Finally, with cell cycle analysis, the cell cycle stage of the agents (G1/S/G2) was examined.

CONCLUSION: As a result, Plx51107, a bromodomain inhibitor, showed a cytotoxic effect in the HL60 cell line and caused an apoptotic effect, and the decrease in the expression levels of the selected target genes was as expected. Therefore, it is thought that Plx51107 can be an important treatment approach for other hematological malignancies as well and support the rapid transition to clinical trials.

P07. PHILADELPHIA NEGATIVE B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA PRESENTING WITH ACUTE APPENDICITIS AND APPENDICEAL INFILTRATION

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OBJECTIVE: B-cell acute lymphoblastic leukemia can sometimes present with extramedullary involvement. Herein, we present a young adult with acute lymphoblastic leukemia whose presentation was acute appendicitis.

RESULTS: A 19-year-old male patient was admitted to the emergency department with complaints of abdominal pain, weight loss, fever, and bloating. In abdominal computed tomography, hepatosplenomegaly and periportal diffuse edema were observed and the image suggested appendicitis. The patient underwent appendectomy on 7 July 2021. After discharge from the hospital, the patient's complaints did not regress. Upon readmission to the hospital, complete blood count revealed lymphocytosis (100000*109/L), the hemoglobin was 13 g/dL, and the platelets were 91000*109/L. Diffuse blastic cell infiltration was detected in the peripheral blood smear. TdT, CD19, CD10, CD34, cytoplasmic CD79a, CD38, CD58, CD9, CD81, and CD20 positive blasts were detected in the flow cytometric analysis of the patient's peripheral blood suggestive of B-cell acute lymphoblastic lymphoma/leukemia. Atypical lymphoid infiltration was detected in the appendectomy material and the atypical blastic cells were positive for PAX5, TdT and CD34; bcl-2 was weakly positive and the Ki-67 proliferation index was high. Morphological and immunohistochemical findings were reported to be consistent with leukemic infiltration. In the bone marrow aspiration and biopsy, hypercellularity was detected with diffuse blastic infiltration. Conventional karyotyping, FISH analysis and molecular tests were performed and the BCR/ABL fusion (P190) was detected as negative in the patient's RNA sample. After sperm cryopreservation and checking for infectious parameters and cardiac functions, induction chemotherapy regimen was started as augmented-Berlin-Frankfurt-Munster protocol.

CONCLUSION: Appendiceal involvement of B-acute lymphoblastic leukemia has been reported but is extremely rare. Our patient had normal leukocyte counts at admission to the hospital with appendicitis. Although the chemotherapy was started more than three weeks post-operatively, complications such as infection or delay in wound healing can be seen because of neutropenia and also chemotherapy side effects. We preferred augmented-Berlin-Frankfurt-Munster protocol which had superior event free survival and overall survival rates according to the CALGB therapy, besides the patient could be able to receive effective central nervous system prophylaxis with this protocol. Acute leukemia cases, which are rarely diagnosed with extramedullary involvement, have been reported more frequently in the pediatric age in the literature review. As the adult hematology department, we wanted to present this unusual case.

P08. A SUCCESSFUL TREATMENT OF RELAPSED REFRACTORY MDS PATIENT WHO IS FOLLOWED UNDER HEMODIALYSIS

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OBJECTIVE: Relapsed refractory (R/R) Myelodysplastic syndromes (MDS) have poor outcomes who are ineligible for allogeneic stem cell transplantation. Recently, BCL-2 inhibitor venetoclax in combination with hypomethylating agents (HMAs) has been showed promising results comparing to HMAs alone. However, a standardized therapy has not been defined for MDS patients who are under hemodialysis. We aimed to present a case report about a successful treatment of R/R MDS patient azacitidine combined with venetoclax.

METHODS: A 48 year old female patient was admitted to Ege University Department of Hematology Clinic in complaint with symptomatic anemia refractory to erythropoietin stimulating agents (ESAs). She complained exercise intolerance, however she denied any B symptoms, lymphadenopathy etc. Her vital signs and physical examination were non significant. Laboratory findings were found as normochromic normocytic anemia (hb: 5.6 g/dL, platelets: 114×10^6/mcl) and mild thrombocytopenia. Her erythropoietin, ferritin, B12 and folic acid levels were normal. The bone marrow biopsy was resulted as MDS with excess blast (EB-1) 6-7% of cells. Her karyotype and cytogenetic analysis were normal; on the other hand IPSS level was high.

RESULTS: After 6 cycles of standard dose azacitidine, bone marrow biopsy resulted MDS-EB-1 with 7-8% of blastic cells. 2nd line she planned to be treated by 4 cycles of decitabine, but her transfusion dependency worsened during treatment, so we needed to reduce dose by 20%. After 4th cycles of decitabine, bone marrow blastic involvement persisted on 6%. As third line therapy, we performed azacitidine 75 mg/m^2 in combination with venetoclax 200 mg/d D1-14 for 6 cycles. Since transfusion dependency persisted on in the first 2 cycles, venetoclax dose was reduced to 100 mg/d for 14 days. She did not need any red blood cell transfusion after 3rd cycle. During treatment, no tumor lysis syndrome (TLS) was detected. After 6th cycle of treatment, bone marrow biopsy was resulted with <1% blastic cells and reduction of dysplastic changes.

CONCLUSION: High risk MDS patients have poor outcomes unless Allogeneic SCT is performed. Oral Bcl-2 inhibitors have promising results in high risk MDS patients, on the other hand there is not any data on its use of maintenance hemodialysis patients. Our patient was ineligible for Allogeneic HSCT despite her young age and good performance status. we were able to achieve hematologic response while we did not detect any side effects of HMA and venetoclax combination including TLS

P09.

P10. HEMORRHAGIC COLITIS IN A PATIENT WITH CHRONIC MYELOID LEUKEMIA ON DASATINIB AND QUESTIONABLE CMV INVOLVEMENT

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OBJECTIVE: Treatment of chronic myeloid leukemia (CML) with tyrosine kinase inhibitors (TKIs) has dramatically changed prognosis for these patients. Dasatinib, a second generation BCR-ABL inhibitor is indicated as first line therapy in CM and Philadelphia positive acute lymphoblastic leukemia. It inhibits BCR- ABL, SCR kinases, c-KIT, EPHA-2 and Platelet-derived growth factor receptor. Most side effects such as myelosuppression and diarrhea are manageable. We present a case of a patient on dasatinib and hemorrhagic colitis or CMV colitis that is indicative of the challenge that TKIs pose for optimal management and treatment decisions.
METHODS: A 54-year-old women was diagnosed with CML in chronic phase and was initiated on dasatinib 100 mg daily. She achieved MR 4.5 in the first three months but also at this time she complained of abdominal pain and had a coloscopy that reveled mild colitis. Symptoms improved with no specific treatment. One year after the diagnosis she developed abdominal pain with a few episodes of diarrhea and noticed blood and mucus in her stool. Colonoscopy had a few ulcerative lesions. The biopsy revealed sings of mild inflammation and immunostaining for cytomegalovirus (CMV) was positive in a few epithelial cells. The patient was receiving already broad-spectrum antibiotics and nilotinib was discontinued. A PCR for CMV was borderline positive, the second on a second 400 copies/ml while the third had no CMV copies. Serum CMV IgM antibodies were negative during this period. No treatment for CMV was given. At this point the patient had no symptoms and dasatinib was restarted. She remains in close monitoring.
RESULTS: Hemorrhagic colitis and CMV colitis associated with dasatinib are rare events. There are no specific guidelines for their management. Reports of cases reveal the problem they impose for the best management since they include patients with mild symptoms and self-limiting disease while those with severe symptoms and CMV colitis were treated with ganciclovir or foscarnet and dasatinib was stopped. It should be noted that most of the cases with severe complications are in patients with Ph+ ALL or after stem cell transplantation. In CML cases dasatinib was re- introduced either in full dose or at a lower dose. In our patient dasatinib was reintroduced with close monitoring. BCR-ABL inhibitors interfere with the immune system. Patients should be screened for HBV before starting treatment and should be vaccinated for pneumococcal infection and annually for influenza. Dasatinib has been so far associated with a greater risk for infections compared to other inhibitors. CMV infection- usually a reactivation should be diagnosed using PCR and immunostaining in biopsy samples. Treatment includes ganciclovir, valganciclovir, foscarnet and cidofovir.
CONCLUSION: For CML patients on dasatinib that develop abdominal pain and gastrointestinal hemorrhage the differential diagnosis includes infections, inflammatory bowel disease, ischaemic colitis, bleeding disorders, vascular malformation, and drug- induced hemorrhagic colitis. Gastroenterologists, pathologists, and hematologists should work together for reaching the correct diagnosis. A close monitor for patients on TKI inhibitors for infections is essential.

P11. TREATMENT OF APLASTIC ANEMIA WITH IMMUNOSUPPRESSION AND ELTROMBOPAG

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OBJECTIVE: Treatment of aplastic anemia includes the use of immunosuppression and allogeneic stem cell transplantation. Recently, the use of small-molecule Thrombopoietin-receptor agonist eltrombopag showed promising results in severe aplastic anemia (SAA), while the combination of eltrombopag with immunosuppression as first-line treatment improved response rates.
METHODS: Since 2017, 12 patients (7 males and 5 females) with aplastic anemia were treated in our center with the treatment combination proposed by Townsley D, et al. (N England J Med 2017 20; 376(16): 1540-1550).
RESULTS: The median age was 42 years (range 15-66). Six patients were diagnosed with SAA, 3 with very severe aplastic anemia (VSAA) and 3 with moderate disease. Ten patients were newly diagnosed and 2 had been previously treated with cyclosporine and anti-thymocyte globulin (ATG) 7 and 16 years ago respectively. All patients had received red blood cell transfusions. Four patients had a PNH clone in neutrophils <10% (4-9.5%) and 1 patient >50%. The dose of ATG (rabbit) was 3 mg/kg of body weight for 5 days. Cyclosporine and eltrombopag (150 mg daily) started at day 1 and continued for 6 months. In 2 patients eltrombopag was continued for 18 months, while 8 patients received cyclosporine in decreased doses for 24 months. Grade II-III infections were detected in 3 patients (2/3 bacteremias). One patient died due to Ps. Aeruginosa and Fusarium infection. Increased viral loads of CMV and EBV (quantitative PCR) were detected in 5 patients (CMV: 2, EBV: 5) and gradually decreased. Other toxicities rated as grade ≥II were: hepatotoxicity (7 patients), nephrotoxicity (3 patients), and polyneuropathy (1 patient). Nine patients (75%) became transfusion independent in a median period of 65 days (range 10-200), while the absolute neutrophil count reached >500 per cubic millimeter threshold in a median of 35 days (range 9-150). Complete response (CR) was achieved in 40% and partial response (PR) in 30% of patients with an overall response rate of 70% in 6 months while the overall response rate in 12 months was 88% (CR 50%). In a median time of 26 months (range 3-40), 2 patients with PR relapsed. One patient with refractory disease underwent allogeneic stem cell transplantation. The overall survival in 12 months was 91%.
CONCLUSION: In summary, the addition of eltrombopag in the treatment of aplastic anemia led to high response rates, with higher CR rates compared to those described with ATG alone in the literature. Late responses (up to 12 months) can be seen, while toxicity is manageable. The combination of eltrombopag with immunosuppression is an excellent choice for patients that are not eligible for allogeneic stem cell transplantation.

P12. A STUDY OF RIBONUCLEOTIDE REDUCTASE MRNA EXPRESSION AND ITS PROGNOSTIC ROLE IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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OBJECTIVE: Ribonucleotide Reductase (RNR) converts ribonucleotides to deoxyribonucleotides required for DNA replication and repair. RNR consists of two subunits, subunit 1 (RRM1) and 2 (RRM2). Imbalance in the regulation of RNR activity and dNTPs' pool leads to genomic instability. RNR expression is a prognostic factor in pancreatic, non-small-cell lung, breast, and biliary tract cancer. RNR expression and its possible prognostic role in chronic lymphocytic leukemia (CLL) have not been investigated yet. In this study we evaluate the possible prognostic role of RNR expression in CLL.

METHODS: Peripheral whole blood samples were collected from 84, 27, 15, and 9 CLL patients before treatment, after one, two, and three lines of treatment respectively. RNA extraction and reverse transcription were carried out using standard protocols. A TaqMan based real-time PCR was performed on a CFX96 RT-PCR system (Bio-Rad Laboratories, Hercules, CA, USA). For both housekeeping and target genes, a TaqMan primer/probe mix was used according to the manufacturer's instructions (Applied Biosystems, Foster City, CA, USA). RRM1 and RRM2 mRNA levels were expressed as an RRM1-2/GAPDH ratio. Western blot analysis using RRM1 #3388, β-actin #4967 and anti-rabbit IgG HRP-conjugated #7074 (Cell Signaling Technology, Danvers, MA, USA) antibodies and ECL western blotting reagents was performed to detect RRM1 protein in 41 random patients. Statistical analysis was conducted using SPSS statistical software (version 22.0).

RESULTS: Our study included 135 CLL patients, with 56.3% females. The median age at diagnosis was 64 years. Peripheral blood was collected in 84 treatment-naïve patients (62.2%). Median follow up was 6.66 years (3.47-11.13) and median time from diagnosis until 1st line treatment was 23.1 months (IQR: 5.8-56.5 months). Sixty nine patients (51.1%) received 1st line treatment and 35 patients (25.9%) 2nd line treatment with median time between the two treatment lines 26.5 months (IQR: 7.8-40.8 months). Of the patients, 48.5%, 33.8%, 12.3%, 3.1% and 2.3% had Rai score 0, I, II, III, IV respectively. The median mRNA expression of RRM1 was 0.04 (IQR: 0-0.09) and of RRM2 was 0.01 (IQR: 0-0.1). RRM1 mRNA expression was significantly higher in patients without anemia (p=0.025) and without lymphadenopathy (p=0.002). Higher ESR (r=-0.30; p=0.028), LDH (r=-0.20; p=0.026) and Rai score (r=-0.18; p=0.037) were associated with lower expression of RRM1 mRNA. TP53 gene deletion was associated with higher RRM1 mRNA expression (p=0.036). Significantly higher RRM2 mRNA expression was reported in patients without lymphadenopathy (p=0.021) and Rai score 0 (p=0.003). The expression of RRM2 mRNA was increased in cases with Trisomy 12 (p=0.050). Before treatment, increased RRM1 mRNA expression was statistically significantly associated with lower Rai score (r=-0.30; p=0.005) and longer time periods between the first two lines of treatment (r=0.95; p=0.050).

CONCLUSION: For the first time, mRNA expression of RRM1 and RRM2 is studied in CLL patients showing pathophysiological involvement of RNR. RRM1 and RRM2 mRNA higher expression found in 17p deletion and trisomy 12 cases indicates a methylation-depended mechanism as shown in previous studies. These results demonstrate RNR's potential role as a prognostic factor, and make it a probable therapeutic target.

P13. CHRONIC LYMPHOCYTIC LEUKEMIA ASSOCIATED PARANEOPLASTIC DYSPHAGIA: A RARE CASE REPORT

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OBJECTIVE: Chronic lymphocytic leukemia (CLL) is a frequent hematological malignancy, on the other hand, it can rarely cause neurological symptoms. CLL related neurological symptoms is often associated with meningeal or peripheral nerve infiltrations. İn this report we aimed to present CLL related paraneoplastic dysphagia.

RESULTS: A 74 years-old male patient diagnosed with CLL and type 2 diabetes mellitus. At the time of diagnosis he didn't require treatment according to guidelines of the international workshop on chronic lymphocytic leukemia (iwCLL) and decided to monitoring. After a month he presented with progressive dysphagia and finally he needed feeding by percutaneous endoscopic gastrostomy. Cranial imaging did not indicate any significantly ischemic, hemorrhagic, traumatic event, intracranial mas sor leptomeningeal involvement. Cerebrospinal fluid samples worked up biochemical, flow cytometry, cytopathological analysis were non diagnostic. Upper gastrointestinal endoscopy was performed and exclude other pathologies like mass, stricture, esophagitis. Treatment decision was taken with high probability of paraneoplastic dysphagia with R-bendamustine regimen (rituximab and bendamustine). After 4 cycle of R-bendamustine, his dysphagia and oral intake improved and he gained weight.

CONCLUSION: CLL rarerly cause neurological symptoms and if it cause, reason is usually meningeal or peripheral nerve infiltrations. Paraneoplastic syndromes should be suspected in the differential diagnosis of neurological symptoms especially in individuals with previous history of CLL.

P14. CLL-ASSOCIATED FSGS

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OBJECTIVE: Chronic lymphocytic leukemia (CLL) is a hematological disease characterized by proliferation of monoclonal B-lymphocytes. Although autoimmune complications such as Autoimmune Hemolytic Anemia and Immune Thrombocytopenia are common in CLL patients, non-hematological autoimmunity is very rare. Nonetheless, the most common pathologies among the renal complications of CLL are Membranoproliferative Glomerulonephritis and Minimal Change Disease. Focal Segmental Glomerulosclerosis (FSGS) is the least reported of the renal disease associated with malignancies. Focal Segmental Glomerulosclerosis is mostly associated with Hodgkin lymphoma among the hematological malignancies. CLL-associated FSGS is a condition with limited case reports in the literature and low clinical experience. In this report, we present a case of secondary FSGS, a very rare complication of CLL, in a 61-year-old female patient and our treatment approach.
METHODS: A 61-year-old female patient, who was diagnosed with CLL with lymphocytosis and lymphadenopathy, was identified as Rai 1, Binet B with the current findings. Due to the development of pedal edema and proteinuria, a kidney biopsy was performed and she was diagnosed with FSGS. Secondary FSGS was considered in the patient with normal kidney functions, since the picture was not aggressive and there was a malignant disease in the background. FCR (fludarabine, cyclophosphamide, rituximab) treatment was planned and the patient was observed during the treatment.
RESULTS: FCR (fludarabine, cyclophosphamide, rituximab) treatment was applied as 6 cycles. Proteinuria, which was 3.4 g/24h before the treatment, was found to be 1.1 g/24h after the first cycle. Proteinuria completely disappeared after the third cycle. In the 5th year of her treatment, the patient continues to be followed up with complete response in terms of CLL and without any kidney pathology including proteinuria.
CONCLUSION: Autoimmune hematologic complications are common in CLL. The development of secondary FSGS, which is very rare in hematological cancers, has been evaluated as a non hematological immune complication of CLL. Since FSGS is not an antibody-mediated disease, it may seem surprising that remission is achieved with the FCR regimen. However, B cells play an important role on immune cells by antigen processing and presentation, interaction with auto-reactive T cells and antigen presenting cells, and cytokine secretion. B cell loss under FCR treatment might be affecting T cell activation and down-regulating co-stimulation. It was thought that the regimen, which is also an effective treatment in CLL disease, may be effective in terms of both FSGS and CLL-related FSGS.

P15. POOR NEUTRALIZING ANTIBODY RESPONSES IN PATIENTS WITH CLL, NHL AND HL AFTER VACCINATION AGAINST SARS-COV-2; A PROSPECTIVE STUDY IN 132 PATIENTS

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OBJECTIVE: We evaluated the production of anti-SARS-CoV-2 antibodies in patients with Chronic Lymphocytic Leukemia (CLL), Non-Hodgkin's Lymphoma (NHL) and Hodgkin's Lymphoma (HL) after full vaccination with the BNT162b2 vaccine.

METHODS: All participants (patients and controls) have been enrolled in a large prospective study (NCT04743388) evaluating the kinetics of anti-SARS-CoV-2 antibodies after COVID-19 vaccination in healthy subjects and patients with hematological malignancies or solid tumors. After vein puncture, the serum of both patients and controls was collected on day 1 (D1; before the first BNT162b2 dose), on day 22 (D22; before the second dose of the BNT162b2) and on day 50 (D50; 3 weeks post second dose of the BNT162b2). NAbs against SARS-CoV-2 were measured using FDA approved methodology (ELISA, cPass™ SARS-CoV-2 NAbs Detection Kit; GenScript, Piscataway, NJ, USA).

RESULTS: The study population included 132 patients [66M/66F] and 214 controls [96M/118F]. At the time of vaccination, 45 (48.9%) out of 92 symptomatic patients were receiving therapy, 47 (51.1%) were in remission after prior treatment and did not receive any therapy at the time of vaccination, whereas 40 out of 132 (30%) patients had asymptomatic disease without current or prior treatment. On D1, no patients or controls had NAb titers of ≥30% (positivity cut-off) and none of them reported a prior history of known COVID-19. After the first dose of the vaccine, on D22, CLL/Ly patients had lower NAb titers compared with controls: the median NAb inhibition titer was 18% (IQR: 8.5-29%) for CLL/Ly patients versus 41.6% (IQR: 25.3-59%) for controls; P<0.001 (Figure 1). More specifically, only 22% (29/132) of the patients versus 71% (152/214) controls developed NAb titers ≥30% on D22 (p<0.001). The respective number of patients and controls who developed NAb titers ≥50% was 9% (12/132) and 28% (81/214), respectively (p<0.001). After the second dose of the vaccine, on D50, CLL/Ly patients had lower NAb titers compared with controls. The median NAb inhibition titer was 32.5% (IQR: 13.5-93%) for patients versus 94.7% (IQR: 89-97%) for controls; p<0.001. More specifically, only 50.8% (67/132) of the patients versus 98.1% (210/214) of the controls developed NAb titers ≥30% on D50 (p<0.001). The respective number of patients and controls who developed NAb titers ≥50% was 43.9% (58/132) and 95.3% (204/214) (p<0.001). Among CLL/NHL patients, the multivariable logistic regression adjusted for active treatment, administration of rituximab in the past 12 months and disease type, showed that active treatment was significantly associated with lower antibody responses at day 50 (<50%) (OR: 0.15,

95%CI: 0.05-0.42, p<0.001), whereas patients with HL were more likely to achieve higher humoral responses (>50% at day 50) compared with other disease types (OR: 4.9, 95%CI: 1.29-18.4, p=0.019). There was a trend towards lower antibody response among those treated with rituximab in the last 12 months (OR: 0.33, 95%CI: 0.1-1.1, p=0.07).
CONCLUSION: The antibody-mediated responses to SARS-CoV-2 vaccination in patients with CLL/Lymphoma is suboptimal and humoral immunity seems to be deregulated. A booster third dose of IV MAbs against SARS-CoV-2 may be needed for these patients.

P16. A UNIQUE CASE OF NODULAR SCLEROSING CLASSICAL HODGKIN LYMPHOMA DEVELOPING AFTER A 4- YEAR LATENCY PERIOD AFTER THE DIAGNOSIS OF MYASTHENIA GRAVIS

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OBJECTIVE: Myasthenia gravis (MG) has been described as a paraneoplastic manifestation of both thymic and extrathymic Hodgkin lymphoma (HL). Nine case reports of MG associated with HL (thymic=6, extrathymic=3) were found in the literature. In most of them, the diagnosis of HL was made concomitantly or soon after the appearance of neurologic manifestations. Five patients with thymic disease underwent thymectomy and 2 had additional chemo±radiotherapy. In one patient with thymic HL, treatment modality is not reported, while all patients with extrathymic disease received appropriate chemo±radiotherapy. Among thymectomised patients, additional thymic histologic abnormalities were described in three cases (thymic hyperplasia=2, involuted thymus=1). In nearly all cases, neurologic symptoms regressed after HL treatment. We report a case of thymic HL, diagnosed 4 years after generalised MG presentation.

METHODS: A 21-year-old female patient was diagnosed with generalised MG after a 2-month history of proximal upper limb weakness, diplopia and unilateral blepharoptosis. Routine motor and sensory nerve conduction studies and electromyography studies of the upper limps were normal, while repetitive nerve stimulation of the median nerve at 3Hz showed a decremental response (25% and 35% before and after exercise respectively) consistent with MG. Autoantibodies to AChR were positive at 198 nmoles/L (cutoff<=0.1). Anti-MuSK, anti-LRP4 and anti-titin autoantibodies were negative. Chest CT was normal with presence of a thymic residue at that time. The patient was put on acetylcholine esterase inhibitor treatment with subsequent partial clinical remission.

RESULTS: Four years after MG diagnosis, the patient developed thoracic symptoms, mostly in the form of dry cough. Chest radiography and subsequent chest MRI showed a bulky anterior mediastinal lesion of 11.5×7.6×13 cm with contiguous left upper lobe lung involvement. The patient underwent Video Assisted Extended Thymectomy with partial left upper lobe lobectomy with a working diagnosis of thymoma. Histological examination revealed thymic and pulmonary infiltration by classical HL of nodular sclerosing type with negative EBER in situ hybridisation. 18-FDG PET-CT and bone marrow biopsy were negative for distant localisations. A stage IIXEA was assigned, classified as intermediate stage or early unfavourable according to the GHSG and EORTC classifications respectively. ABVD chemotherapy was started and the patient is now in complete metabolic remission after 2 cycles, with a total of 6 cycles planned. Anti AChR autoantibody titers were at 633 nmoles/L before thymectomy and at 452 nmoles/L after thymectomy and before start of chemotherapy. A repeat measurement was ordered after 4 ABVD cycles but results are not yet available. The neurologic symptoms are globally stable under continuous anticholinesterase treatment.

CONCLUSION: The case presented here is unique due to the unusually long time interval between onset of MG (with a negative chest CT at that time) and development of HL. This could suggest a two-step pathogenesis, with benign thymic microenvironment alterations leading initially to autoimmunity and later to lymphoid tumorigenesis.

P17. BREAST CANCER AS SECOND CANCER AFTER PRIMARY HODGKIN DISEASE

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OBJECTIVE: To describe a rare case with Breast cancer as a second tumor in a patient with a history of Hodgkin Lymphoma treated with chemotherapy, without radiotherapy.
METHODS: Clinical examination and breast imaging in a 26-year-old female patient with a palpable breast mass.
RESULTS: A 26-year-old female patient with a history of Hodgkin disease, stage III, subtype nodular sclerosis was diagnosed at the age of 15 years old. The patient had received chemotherapy according to the SIOP protocol without radiotherapy. She had a good response to the treatment protocol and she had a normal life remaining in full remission of Hodgkin lymphoma. The patient was married and she had a pregnancy, ten years after the end of the SIOP protocol. Pregnancy was uncomplicated and the patient gave birth by natural delivery to a healthy male infant. The patient did not breastfeed because of an anatomical variant in breast nipple. Three months after the delivery, she observed a palpable mass on the right breast. Clinical examination revealed a 2-3 cm solid mass on the lower quadrant of the right breast distant 4 cm from the nipple. Mammography, Ultrasound and Breast MRI was performed and revealed a suspect mass Birads IVc. Imaging staging was normal and no suspect axillary lymph node was indicated. Core biopsy was performed in our Breast Unit and the histopathological findings revealed a triple negative (ER-, PR-, HER2-, neu -), Grade III, Breast cancer with ki-67: 75%, p53: 50%. The oncologic council classified the breast cancer as high risk because the young age of the patient and the histological findings. So, the patient received neoadjuvant preoperative chemotherapy, surgical excision of the tumor, and radiotherapy. Two years later, she is in complete remission
CONCLUSION: Women with Hodgkin disease, who received radiotherapy, have a risk for a breast cancer in the fifth decade of life. In this case, the patient did not received radiotherapy, and the breast cancer was diagnosed very early, in the second decade of life. Although, triple-negative breast cancer is more likely to be diagnosed in young women, spread beyond the breast, surprisingly in this case there is local disease, lymph node negative. Diagnosis during pregnancy or childbed remains a challenge.

P18. INCIDENTAL FINDING OF CENTRAL PONTINE MYELINOLYSIS IN HODGKIN LYMPHOMA DIAGNOSED DURING PREGNANCY

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OBJECTIVE: To report an incidental finding of Central Pontine Myelinolysis (CPM) in a patient diagnosed with Hodgkin Lymphoma (HL) during pregnancy. CPM is a rare demyelinating disease of the pons typically occurring after rapid correction of severe hyponatremia, alcoholism, malnutrition and immunosuppression. Cases linking CPM to hematological malignancies have been reported however, they are seldom and of unknown pathophysiology.

METHODS: A 28-year-old primiparous woman at 27 gestational weeks (GW) was addressed to our hospital for investigation of normocytic normochromic anemia (Hemoglobin=7.7 g/dL) associated to markedly raised inflammatory markers (erythrocyte sedimentation rate, C reactive protein and α2 globulins) and low ferritin levels (21 ng/dL). She had no systemic B symptoms but reported pruritus. Except for hypoalbuminemia, laboratory work up was otherwise normal. Clinical examination was unremarkable. Magnetic resonance imaging (MRI) revealed mediastinal and anterior cervical lymphadenopathy. Histological assessment of cervical lymph node showed nodular sclerosis classical HL. A suspected lesion of the pons was found in the cross sections of the upper thorax which prompted brain MRI.

RESULTS: Brain MRI showed a hyper-intense signal in the central pons on T2-weighted and FLAIR images without contrast enhancement. A differential diagnosis of HL central nervous system (CNS) involvement, low-grade glioma and CPM was entertained. Gadolinium-enhanced images did not suggest lymphomatous or malignant involvement. Thorough neurological examination was unremarkable. Overall, neuroimaging findings along with patient's clinical presentation were supportive of CPM. Based on the clinical assessment, radiological imaging and negative bone marrow biopsy, the patient had Ann Arbor/Cotswold Stage IIA disease. She was given in total six cycles of ABVD chemotherapy (Adriamycin, Bleomycin, Vinblastine, Dacarbazine), two of which during pregnancy. At 36 GW a healthy infant was born, and the patient continued chemotherapy after delivery. Interim positron emission tomography (PET) performed after 2 and 4 cycles as well as at the end of chemotherapy showed complete metabolic response. Brain MRI following treatment completion showed also complete remission of the pontine lesion. The pathophysiology of CPM is not fully understood. CPM results from the physiologic imbalance of osmoles within the brain in regions most susceptible to osmotic stress. However, it can occur despite normal sodium levels like the case presented herein. The manifestations of CPM range from asymptomatic to lethal. Our patient was considered asymptomatic as her clinical features could not be related to CPM.

CONCLUSION: CPM can be related to HL irrespectively of electrolyte imbalance. Disturbance of osmotic equilibrium within the brain could be related to the lymphoma per se through currently unknown mechanisms. Neurologic manifestations can be absent, therefore, its frequency may be underestimated. MRI is useful due to its sensitivity in detection of demyelination. Nevertheless, diagnosis may be a challenge, given that clinical symptoms and findings on neuroimaging lack specificity. The clinical significance of CPM complicating HL is unknown. However, CPM can resolve after HL treatment without affecting patient's prognosis.

P19. VERY LATE RELAPSES AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION IN PATIENTS WITH HODGKIN LYMPHOMA: PRESENTATION OF 2 RARE CASES

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OBJECTIVE: High-dose chemotherapy followed by autologous stem cell transplantation (HDT-ASCT) is the standard of care for patients with relapsed or primary refractory Hodgkin lymphoma (HL). However, half of these patients will not achieve long-term disease control, with the majority of HL relapses occurring within the first 2 years following HD-ASCT. The aim of this study was to describe two extremely rare cases of classical HL (cHL) and very late relapses occurring 17 and 20 years after ASCT and ≥20 years since initial diagnosis.

METHODS: Case A: A 21-year-old male was diagnosed with nodular sclerosing, stage IVA cHL and an IPS of 3 in 1987. He had initially presented with cervical lymphadenopathy and lung involvement. The patient received MOPP/ABVD without radiotherapy, but relapsed 2 years later. Eventually, he was treated with HDT-ASCT and achieved a complete remission (CR). Case B: A 35-year-old male with bulky cervical lymphadenopathy was diagnosed with nodular sclerosing stage IA cHL (early unfavorable disease, IPS: 1) in 1999. He received 6 cycles of ABVD but developed with primary progressive disease by the end of chemotherapy. The patient did not respond to a salvage combination with liposomal daunorubicin, etoposide, bleomycin and vindesine, but was successfully salvaged with ESHAP and subsequently ASCT, achieving a CR.

RESULTS: Case A relapsed 17 years following ASCT and 20 years after the initial diagnosis. He presented with nodular sclerosing, stage IVA disease with lung involvement and pleural effusion. He was treated with the combination of gemcitabine, vinorelbine, and doxorubicin (GND) and achieved a CR. The patient remains disease free until now, 14 years after the second relapse. Case B relapsed 20 years following ASCT and 22 years after the initial diagnosis. He presented with cervical, mediastinal, hilar, iliac and inguinal lymphadenopathy and was staged as IIIA. Interestingly, the patient relapsed with a mixed cellularity subtype with positive EBER in situ hybridization for Epstein-Barr virus (EBV), i.e. a different histologic subtype compared to the initial diagnosis. Currently the patient is on chlorambucil, vinblastine, procarbazine and prednisolone (ChlVPP) and response assessment is pending.

CONCLUSION: Studies focusing on very late relapses after ASCT are completely lacking from the literature. To our knowledge, the most delayed relapse has been described 13 years post ASCT (Keller SF et al, 2012). The two cases presented here are unique examples of unusually late relapses, exceeding 16 years. Due to the rarity of these events, there are neither prognostic factors for their occurrence nor for the prediction of their outcome. Similarly there are no established treatment strategies. The occurrence of such cases has various implications regarding the underlying pathophysiology of these relapses; The extremely late timing of relapse and the possibility of histological subtype shift raise questions regarding the identity of clonality between initial and recurrent disease. More effort should be made to find the histological material of these patients in order to clarify their clonal relationship, which may reasonably affect treatment decisions.

P20. A CASE OF CD8+ T-CYTOTOXIC CELL A CASE OF CD8+ T-CYTOTOXIC CELL LYMPHOMA A CASE OF CD8+ T-CYTOTOXIC CELL LYMPHOMA A CASE OF CD8+ T-CYTOTOXIC CELL LYMPHOMA

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OBJECTIVE: T-cell lymphomas are relatively rare with extranodal involvement, especially isolated bone marrow infiltration among Non Hodgkin's Lymphomas (NHL). Excisional biopsy of lymph node, bone marrow (BM) aspiration and biopsy, flow cytometric and immunohistochemical analysis may be helpful though it may be challenging to diagnose T cell lymphomas accurately. Here we aimed to present a case report about T cytotoxic lymphoma infiltration of bone marrow between large granular lymphoma (LGL) and peripheral T cell lymphoma- not other specified (PTCL-NOS)
RESULTS: A 64 year old male patient with hypertension was admitted to Ege University Hospital Department of Hematology to further examination of with persistent anemia and elevated sedimentation since 2019. He denied any B symptoms, skin changes, loss of appetite or palpable lymph nodes.
ON THE PHYSICAL EXAMINATION, HE SEEMED PALE BUT OTHERWISE NORMAL. LABORATORY FINDINGS AT THE TIME OF CONSULT WERE WBC: 16.940/ml, Hb: 9.9 g/dL, Htc: 27.8 Plt: 261.000 and his biochemical analysis including ferritin, B12 and folic acid were normal. Peripheral blood smear showed lymphocytes with basophilic cytoplasm, some of which had atypical morphology, anisocytosis, poikilocytosis. Positron emission tomography was resulted with no pathological lymph node Thereupon, bone marrow aspiration/biopsy was performed. Bone marrow flow cytometric analysis were resulted T cell infiltration of bone marrow with positive CD2, CD3, CD5, CD7, CD8 and negative of CD4, CD16, CD56. Histopathological findings were CD2, CD3, CD5, CD7, CD8, TIA1 positive and CD30, CD56, PD1, CD4 negative. Perphorin, granzyme, were dim. Though LGL was highly considered; no organomegaly and presence of cytopenia were unexpected presentation. Thereupon, CHOEP chemotherapy regimen was planned for the patient who was evaluated as CD8 + T lymphoma.
CONCLUSION: Isolated cytotoxic T cell lymphoma infiltration without organomegaly ofB symptoms within 2 years is an unexpected presentation. Histopathological evaluation of bone marrow or lymph nodes including B and T cell phenotype is essential for diagnostic evaluation although characterization of T cytotoxic lymphomas and epigenetic changes have not been evaluated accurately. CD3 and CD56 positivity especially in LGL is associated with a more aggressive clinic due to Stat5b mutations. Further investigation of large case series might be helpful to diagnose these subtypes better.

P21. INTERIM PET-BASED OMISSION OF RADIOTHERAPY OR INTENSIFICATION OF CHEMOTHERAPY IN YOUNGER PATIENTS WITH LIMITED-STAGE CLASSICAL HODGKIN LYMPHOMA: PRELIMINARY EXPERIENCE FROM A SINGLE REFERRAL CENTER

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OBJECTIVE: Combined modality therapy including ABVD and radiotherapy (RT) has been traditionally the treatment of choice for limited-stage Hodgkin lymphoma (HL) (I/II). The long-term side effects of RT consist the main reason for the attempt to exclude it from the treatment algorithm in a group of patients that are young and, thus, vulnerable to late-onset neoplastic and cardiovascular complications. In 2017, the EORTC H10 study demonstrated that RT can be safely omitted in case of a strictly negative interim PET (iPET) [roughly corresponding to Deauville-5-point scale score (D5PSS) 1-2], with a statistically significant but numerically negligible loss in disease control (about 2-3%), especially in early unfavorable disease. On the contrary, in patients who remain iPET-positive, RT is preserved and chemotherapy is intensified with excellent results. The aim of this study was the initial evaluation of the results of the above strategy adopted in our Center in 2018, as most of the relapses occur within 2 years from diagnosis and therefore, a preliminary assessment of the safety of RT omission regarding disease control can be performed in real-life setting.
METHODS: 52 patients <50 years old with a median follow-up of 18 months were retrospectively evaluated. Since the beginning of 2018 we used the aforementioned strategy in patients with limited-stage disease with mediastinal involvement. RT was maintained in patients without mediastinal involvement, those with iPET D5PSS-3 as well as those with D5PSS-4/5, who received BEACOPP-escalated and RT, and in patients >50 years old, who are potentially less susceptible to long-term complications.
RESULTS: Patients <50 years with mediastinal involvement: Among 41 patients included, 31 had early unfavorable and 10 early favorable HL according to EORTC. Among 24 patients who achieved D5PSS-1/2 (59%) only 3 received RT. The 2-year Progression-Free Survival (PFS) was 96% with only one event of primary refractory disease upon restaging that could not have been avoided with RT. Among 11 patients (27%) who achieved D5PSS-3, 7 received RT without any relapses. iPET remained positive with D5PSS-4/5 in 6 patients (15%), 5 of whom were switched to BEACOPP-esc and RT. The 1-year PFS was 50%. Patients <50 years without mediastinal involvement: Among 11 patients included, 10 had early favorable and 1 early unfavorable HL. Among 9 patients (82%) who

achieved D5PSS-1/2/3, 8 received RT. No relapses were observed. iPET was positive with D5PSS-4/5 in 2 patients that were treated with BEACOPP-esc and RT without any relapse so far.
CONCLUSION: These initial results demonstrate that when RT is omitted following a strictly negative iPET, the short-term relapse rate remains low and absolutely acceptable. In fact, the only observed failure event could not have been avoided with RT. However, the question whether RT remains necessary for patients with D5PSS-3 still exists. No safe conclusions can be made so far regarding the intensification of therapy in the subgroup with clearly positive iPET. These results encourage the continuation of this H10-based strategy in order to eliminate the long-term side effects of radiotherapy. Further observation and recruitment of much more patients in this real-life setting is scheduled.

P22. COVID-19 RELATED BONE MARROW APLASIA IN A PATIENT SUFFERING FROM SEQUENTIAL LYMPHOMAS IN REMISSION

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OBJECTIVE: Our aim is to present an unusual effect of Covid-19 infection in a hematological patient.
METHODS: We performed several examinations to investigate the observed pancytopenia.
RESULTS: A patient born in 1965 was diagnosed in 2008 with Hodgkin lymphoma stage II and he received 6 cycles of ABVD reaching complete remission (CR). In 2014 he experienced relapse. Lymph node biopsy and PET-CT confirmed a diagnosis of a stage III Diffuse Large B Cell Lymphoma (DLBCL). Patient was treated with 6 cycles of R-CEOP reaching CR. In 2018 patient experienced relapse with DLCL stage IV. He was treated with DICE in order to undergo HSCT but stem cell mobilization was unsuccessful and finally he completed his therapy with 3 additional cycles of DICE reaching CR. He remained in follow up and in February 2021 he had normal clinical investigation and his laboratory examinations displayed: White Blood Cells 6490/μl (neutrophils 63.3%, lymphocytes 23%, monocytes 9.6%, eosinophils 2.8%), Hemoglobin 14.9 g/dL and Platelets 207000/μl. In April 2021 the patient developed mild "flu like" symptoms and he was examined by a General Physician. Patient had elevated temperature (37.5 C) and myalgia but he denied shortness of breath, cough, vomiting or diarrhea. After tested by RT-PCR patient was found positive for SARS-COV-2 RNA in a nasopharyngeal swab. A chest X-Ray was performed showing no infiltrations. Patient remained at home receiving azithromycin for 6 days without developing any other symptoms. Two negative RT-PCR tests for SARS-COV-2 RNA were obtained 14 and 21 days after the diagnosis of the infection respectively. Six weeks after the initial documentation of Covid-19 infection patient was admitted to our department for his regular follow-up examination. He complained for fatigue and anosmia. Physical examination revealed normal findings. Blood count showed: White Blood Cells 2720/μl (neutrophils 51%, lymphocytes 35%, monocytes 10%, eosinophils 2%), Hemoglobin 9.9 g/dL and Platelets 40.000/μl. Bone marrow aspirate analysis by flow cytometry showed no clonal expansion, conventional cytogenetic analysis had normal results. A bone marrow biopsy was performed indicating extreme hypocellularity at the level of 5% in contrast to the last biopsy of the patient performed 2 years earlier showing normal cellularity (70%). Flow cytometry for paroxysmal nocturnal hemoglobinuria testing was negative. All investigations by RT-PCR or serological methods for acute infection of Cytomegalovirus, Epstein-Barr virus, parvovirus B19, Hepatitis B and C were also negative. Pancytopenia was not related to any drugs or toxic exposure. Patient has still pancytopenia three months after being twice negative tested for SARS-COV-2 RNA.
CONCLUSION: Our case indicate that heavily pretreated hematological patients may demonstrate after Covid-19 infection more pronounced effects, including peripheral cytopenias. Bone marrow aplasia caused by Covid-19 infection may reflect marrow stress responses. Nevertheless our case confirms that we still don´t know all the underlying contributory mechanisms leading to Covid-19 atypical clinical manifestations in hematological patients.

P23. IS IT A REALLY BAD PROGNOSTIC COMPONENT? EXTRANODAL INVOLVEMENT OF HEAD AND NECK IN DIFFUSE LARGE B CELL LYMPHOMA

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OBJECTIVE: Frequently, lymphomas originate from lymphoid tissues but nearly 30% of them present with tissues other than the lymphoid tissues which is defined as primary extranodal involvement. Site of head and neck is the second most common anatomical region in extranodal DLBCL. We aimed to analyze and to compare the patients presenting with nodal and extranodal head and neck involvement DLBCL as clinicopathologic features and overall survival rates.
METHODS: This study was conducted between January 2015 and January 2020 at Trakya University Hospital Adult Hematology Clinic retrospectively. We included 52 adult patients who presented with primarily nodal or extranodal head and neck region CD 20 positive DLBCL except central nervous system involvement or other than head and neck extranodal involvements. Extranodal involvements were defined as nasal cavity, paranasal sinuses, nasopharynx, larynx, tonsil, oropharyngeal mucosa, thyroid gland and salivary glands. Patients' age, gender, date of diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, presence of B symptoms, level of lactate dehydrogenase (LDH), pathology reports, Ann- Arbor stage, treatment, response status were evaluated. International prognostic index, revised international prognostic index, and National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI) were calculated. Patients' follow up periods and overall survival duration were reviewed.
RESULTS: Twenty four patients of 52 patients were in extranodal group while 28 patients in nodal group. Regarding gender, age, Ki67 proliferation index, BCL-2 positivity, B symptoms, performance status, LDH, prognostic indexes, response to 1st line treatment there were not a difference between groups while the difference were statistically significant in terms of cell of origin, BCL-6 positivity, Ann-Arbor staging (p values are 0.010, 0.016, 0.001, respectively). The distribution of extranodal involvements were as 10 patients with tonsillery, 5 patients with thyroid, 2 patients with nasopharynx, 2 patients with maxillary sinus, 2 patients with parotid gland and the others with nasal, tongue and buccal mucosa. When mortality status was evaluated, 17 patients died in nodal group while 14 patients died in extranodal group. The median survival time was 37 months (95% CI; 30.205-43.795) in nodal group and was 43 months (95% CI; 21.224-64.776) in extranodal group. This difference was statistically significant (p value 0.022).
CONCLUSION: The site and the number of the extranodal involvement of DLBCL determines the prognosis of the disease. In the studies, extranodal regions such as central nervous system (CNS), bone/bone marrow, pleura, liver, gastrointestinal (GI) system are in the high risk group and have poor overall survival rates although head and neck and Waldeyer's ring regions have better prognosis. Extranodal involvement is a predictor marker in prognostic indexes but in NCCN IPI only involvements of bone marrow, liver/GI, CNS and lung can be omitted in the calculation. In our study, we conclude that being the cell of the origin toward to GCB like, earlier detection and treatment of extranodal involvement of this region due to symptoms and being visual than nodal involvement render better survival in the head and neck extranodal DLBCL. Hence extranodal involvements which are limited to head and neck except CNS can be approved of a better prognostic factor.

P24. MULTIPLE PECULIAR EXTRANODAL LOCALIZATIONS BY PET IMAGING IN A PATIENT WITH OTHERWISE PRIMARY TESTICULAR (PT) BLASTOID MANTLE CELL LYMPHOMA (MCL)

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OBJECTIVE: PT lymphoma is an uncommon form of extranodal non-Hodgkin lymphoma (NHL) with diffuse large B-cell lymphoma (DLBCL) accounting for <80% of cases. MCL is an incurable B-NHL with variable clinical behavior. The majority of patients have advanced stage disease; the blastoid and pleomorphic variants typically behave aggressively. PT-MCL is extremely rare with only 4 reported cases so far. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG- PET/CT) has improved the assessment of disease extent in malignant lymphomas, including "primary extranodal" lymphomas.
METHODS: We present a case of an otherwise PT-blastoid MCL, presenting peculiar other extranodal localizations on baseline 18F-FDG-PET/CT pointing out to multifocal, extranodal-only disease with extremely unusual tropism.
RESULTS: A 61-year-old male presented with an incidentally discovered, painless, hard, right testicular nodule. Scrotal ultrasound revealed a 3.5×2.4 cm lobulated, hypoechoic, solid mass with increased vascularity and a second, similar lesion <1 cm. Complete blood count and serum biochemistry were normal. The histologic examination after right radical orchiectomy revealed diffuse lymphomatous infiltration with some cells resembling lymphoblasts and a very high mitotic activity (Ki67 95%). The neoplastic cells were CD20+, PAX-5+, CD5+, cyclin D1+, CD10-, CD23-, CD30-, BCL6- with monoclonal IgD(κ) and diffuse SOX11 expression. Fluorescent in situ hybridization revealed the t(11;14) translocation. The diagnosis of MCL, blastoid variant (BV), was made. Bone marrow (BM) aspiration, flow-cytometry and trephine biopsy were negative. Physical examination and whole-body computed-tomography did not reveal lymphadenopathy, organomegaly or other extranodal lesions. Central nervous system involvement was assessed at baseline due to the blastoid morphology and the knowledge derived from PT-DLBCL and was excluded by brain magnetic resonance imaging (MRI) and cerebrospinal fluid examination. Thus, the conventional Ann-Arbor stage was IEA. Despite the apparently localized disease, the baseline whole-body 18F-FDG-PET/CT revealed highly increased uptake at the right atrium of the heart -specifically one lesion at the auricle (SUVmax15.8) and a second one at the interatrial septum (SUVmax6.1)- as well as at the right iliopsoas muscle (rIM), (SUVmax10.6). Based on 18F-FDG-PET/CT the disease was upstaged as IVA. In the context of these peculiar findings, MRI of the chest and pelvis were performed, showing only a slight increase of signal intensity at the muscle fascia of the rIM at the same region where increased metabolic activity was observed, albeit without any visible tumoral mass. The patient received the combination R-HyperCVAD/R-HDMTX-AraC plus intrathecal infusions of methotrexate/cytarabine/dexamethasone. After two cycles, an interim 18F-FDG-PET/CT revealed complete metabolic response. He received a total of 6 (3+3) cycles with a sustained complete remission (CR) on end-of-treatment 18F-FDG-PET/CT. Consolidation with autologous stem cell transplantation was performed and maintenance rituximab infusions every 56 days

were initiated 3 months later. The patient remains in CR under rituximab maintenance 22 months after the initial diagnosis.

CONCLUSION: We describe the imaging findings and clinical course of a unique case of apparently PT-MCL, which proved to have extremely unusual extranodal-only localizations on staging 18F-FDG-PET/CT, without any nodal or BM involvement. The resolution of these clinically occult extranodal sites at the interim and final 18 F-FDG-PET/CT is an indirect proof of their true involvement in the disease process in the absence of histologic verification.

P25. SYMPTOMATIC OVARIAN INVOLVEMENT AS THE INITIAL PRESENTATION OF PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

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OBJECTIVE: Primary mediastinal large B- cell lymphoma (PMLBCL) is a mature aggressive B-cell lymphoma affecting mainly young and middle-aged individuals, predominantly women. The majority of patients present with bulky mediastinal lymphadenopathy, which frequently invades the adjacent structures. Extrathoracic distal extranodal involvement is rare at disease presentation, being more common at progression or relapse of PMLBCL.

METHODS: We present the case of a young female patient with a clinically silent bulky mediastinal mass presenting with symptomatic, bulky ovarian involvement at diagnosis of PMLBCL.

RESULTS: A 23-year old female presented at the Emergency Department of Kalamata General Hospital with abdominal pain of sudden onset. She reported night sweats without fever accompanied with weight loss during the last semester (9.4% of body weight). On physical examination she had right lower quadrant tenderness on abdominal palpation but also signs of the superior vena cava syndrome albeit without relevant symptoms. The complete blood count and serum biochemistry was within normal range, except for a highly elevated LDH level (2.82-fold above the upper normal limit). The chest X-ray film revealed a large mediastinal mass which was confirmed on CT scan measuring 15 cm at the maximal diameter. No Contrast Enhanced CT of the abdomen revealed a large (11×8.3 cm), solid shaped pelvic mass. Due to the progressively development of signs of acute abdomen, she was urgently transferred to the operation room where surgical resection of the right ovary and the adjacent mass was performed. The histological examination of the resected material revealed proliferation of large lymphoid cells with polymorphic nuclei and a wide rim of cytoplasm while focalized there were sustained ovarian follicles. This finding further supports the ovarian origin of the resected mass. The immunophenotype of the neoplastic cells was CD20+, CD79a+, PAX-5+, LCA+, BCL2+, MUM1/IRF4+, p63+ and BCL6+ in the vast majority of the cells. Immunophenotypic analysis for PDL-1 expression was positive in 100% of the neoplastic cells further supporting the diagnosis of PMLBCL. Complete staging with PET/CT scan demonstrated increased 18FDG uptake in lymphatic mass of the posterior and middle mediastinal as well as the right peribronchial nodules (SUVmax: 19.36). The patient received six cycles of the R-da-EPOCH chemotherapy protocol with rapid response based on radiological findings. Final disease assessment with PET/CT scan was consistent with complete metabolic remission.

CONCLUSION: In conclusion, ovarian involvement is very uncommon in PMLBCL and can be seen in different clinical settings; more frequently at disease relapse or progression and extremely rarely at presentation. CT staging may provide useful information regarding the actual incidence of subclinical ovarian involvement in this entity, since all the reported cases have been clinically silent; however, it is not clear whether PET/CT may actually increase the rate of the detection of ovarian involvement. This case represents the first report in the scientific literature describing symptomatic ovarian mass as the initial mode of presentation of PMLBCL.

P26. A MOLECULAR SIGNATURE OF CIRCULATING MICRORNA CAN PREDICT OSTEOLYTIC BONE DISEASE IN MULTIPLE MYELOMA

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OBJECTIVE: Multiple myeloma bone disease (MMBD) affects approximately 80% of newly diagnosed multiple myeloma (MM) patients and is associated with poor quality of life and possibly with worse survival. The pathophysiology of MMBD is intriguingly complex and results from the deregulation of bone remodeling. MicroRNAs (miRNAs) are single-stranded endogenous RNA molecules, approximately 22 nucleotides long, that regulate gene expression of protein-coding genes at transcriptional and/or post-transcriptional levels by interacting with 3′ untranslated region (3′ UTR) of target miRNAs. As result, miRNAs are implicated in the regulation of key cellular processes, including bone remodeling. However, there is almost no information for the role of miRNAs in the biology of myeloma-related bone disease. The purpose of the current study was the evaluation of an established panel of 19 microRNAs, that are associated with bone disease in osteoporosis of different etiology, in MMBD.
METHODS: Small RNAs were isolated from blood plasma samples of 62 newly diagnosed MM patients (35 with lytic bone disease and 27 without lytic lesions, using WBLDCT) and 10 healthy individuals who served as controls. Small RNAs were polyadenylated, and subsequently reversely transcribed into cDNA using a poly-T-adapter as a primer. The quantification of the 19 miRNAs, associated with bone disease, was performed with ready-to-use quantitative real-time PCR (qPCR) plates based on the SYBR Green chemistry. The normalization of the expression levels of each miRNA was implemented using the geometric mean expression of the endogenous miR-23a-3p and the synthetic cel-miR-39-3p, which served as an exogenous spike-in control. Finally, biostatistical analysis of the results using the IBM SPSS Statistics 20 software was performed.
RESULTS: The analysis of the obtained data unveiled five circulating miRNAs, namely, let-7b-5p (p=0.034), miR-143-3p (p=0.021), miR-17-5p (p=0.025), miR-214-3p (p=0.004), and miR-335-5p (p=0.022), that were significantly higher in the plasma samples of MMBD patients than in the plasma samples of non-MMBD patients and those of normal controls. Receiver operating characteristic curve and logistic regression analyses showed that these miRNAs could accurately predict MMBD. The best discriminatory ability was observed for miR-214-3p, followed by miR-143-3p, miR-335-5p, miR-17-5p, and let-7b-5p. The estimated median OS was 24 months (range: 6.0-32.0), while the median PFS was 20 months (range: 3.0-31.0). In univariate Cox regression analysis, lower plasma levels of let-7b-5p and miR-335-5p revealed a significantly increased risk for disease progression. Moreover, lower plasma levels of let-7b-5p and miR-335-5p retained their adverse prognostic significance independently of the established clinicopathological parameters such as patients' age, R-ISS stage, beta2M, and LDH.
CONCLUSION: In summary, our study indicates that increased levels of circulating let-7b-5p, miR-143-3p, miR-17-5p, miR-35-5p, and miR-214-3p can effectively predict (standalone and/or combined) the occurrence of MMBD in MM patients. Moreover, we provided sufficient evidence regarding the prognostic role of some of those miRNAs as potential non-invasive tumor markers in MM. To the best of our knowledge, this study provides, for the first time, evidence supporting the potential role of specific miRNAs in MMBD, setting the basis for more research in this topic able to elucidate the mechanisms and the clinical utility of those biomarkers in MMBD and MM prognosis.

P27. ABERRANT PLASMA CELL CONTAMINATION OF PERIPHERAL BLOOD STEM CELL AUTOGRAFTS, ASSESSED BY NEXT-GENERATION FLOW CYTOMETRY, IS A NEGATIVE PREDICTOR FOR DEEP RESPONSE POST AUTOLOGOUS TRANSPLANTATION IN MULTIPLE MYELOMA; A PROSPECTIVE STUDY IN 199 PATIENTS

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OBJECTIVE: High-dose chemotherapy with autologous stem cell support (ASCT) is the standard of care for eligible newly diagnosed Multiple Myeloma (MM) patients. Stem cell graft contamination by aberrant plasma cells (APCs) has been considered a possible predictive marker of subsequent clinical outcome, but the limited reports to date present unclear conclusions. We prospectively estimated the frequency of graft contamination using highly sensitive next-generation flow cytometry and evaluated its clinical impact in myeloma patients who underwent an ASCT.
METHODS: The study included the prospective analysis of all eligible MM patients who were diagnosed, treated and received an ASCT in our center, between April 2016 and March 2021. All patients underwent high-dose melphalan (HDM)/ASCT post induction treatment and were evaluated for the presence of APCs in their autologous stem cell apheresis collections. The presence of APCs in stem cell grafts was examined with next-generation flow cytometry (NGF) following the EuroFlow guidelines for the detection of MRD in MM. The apheresis products obtained were processed with the bulk lysis protocol and acquired cells were stained with the two established 8-color NGF panels, both containing the combinations CD19-PECy7, CD27-BV510, CD38-FITC, CD45-PerCPCy5.5, CD56-PE and CD138-BV421, with CD117-APC and CD81-APCH7 included in the surface tube and cytoplasmic kappa-APC and lambda-APCH7 in the intracellular-stained tube. Ten million cells were stained per tube and a minimum of five million events were recorded for further analysis. The BM niche profiling was examined for each patient who achieved CR on day 100 post ASCT using the NGF panels. A total of 17 BM subsets were characterized for each patient, which, beyond plasma cells, included B cells and their relative compartments (naïve, memory and B cell precursors), T cells and their CD27+ compartment, NK/NKT cells and their CD27+ compartment, erythroblasts, erythroid and myeloid progenitors, neutrophils, basophils, monocytes/tumor associated-macrophages, eosinophils and mast cells.
RESULTS: One hundred and ninety-nine myeloma patients were enrolled in this study. Patients received different induction regimens, according to our institutional pol-icy, with almost half of them receiving VRD. None of these patients received consolidation treatment, while all of them received lenalidomide maintenance (plus bortezomib every two weeks for those with high-risk cytogenetics only). Aberrant clonal plasma cells were present in 79/199 (39.7%) stem cell grafts evaluated within a median reached LOD of 3.6×10(-6) (range 2-4.8×10(-6). The median value of APCs in contaminated (con+) samples was 2.2×10(–5) of total nucleated cells; on a logarithmic scale, the distribution of the detection levels of APCs among con+ cases were 10% for levels higher than 10(-3), 26.6% for detection at levels 10(-3)-10(-4), 27.8% for levels 10(-4)-10(-5) and 35.4% for lev-

els lower than 10(-5). Importantly, con+ grafts conferred 2-fold and 2.8-fold higher patient-risk of not achieving or delaying reaching CR (4 vs. 11 months) and MRD negativity (5 vs. 18 months) post ASCT, respectively.

CONCLUSION: The evaluation of stem cell graft contamination with sensitive approaches may serve as a predictive factor post ASCT, which may clearly stratify patients into distinct risk categories according to their potential to progress. In this context, tailored therapeutic decisions would be made.

P28. CD56 EXPRESSION IN MULTIPLE MYELOMA: CORRELATION WITH POOR PROGNOSTIC MARKERS BUT NO EFFECT ON OUTCOME

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OBJECTIVE: CD56 or neural cell adhesion molecule (NCAM) is a membrane glycoprotein expressed on neural cells, muscle tissues and myeloma cells. Expression of CD56 has been studied in patients with multiple myeloma (MM) with controversial results. The scope of this study was to examine the expression of CD56 in MM patients at diagnosis and investigate its association with clinicopathologic parameters.

METHODS: We retrospectively collected and analyzed data from 109 patients with MM diagnosed over the last decade (January 2010 to June 2020). Expression of CD56 was assessed by immunohistochemistry in bone marrow biopsies. For the statistical analysis x2 test and Mann-Whitney U test were used to compare categorical and continuous variables in CD56+ and CD56– patients, respectively. The Kaplan-Meier method was used to calculate overall survival (OS) and survival curves were compared by the log-rank test to detect prognostic factors in univariate analysis. Parameters with p-values <0.10 along with CD56 expression were evaluated in multivariate analysis using a Cox's proportional hazard model. P values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS 21.0 for Windows (SPSS, Chicago, IL).

RESULTS: A total of 109 patients with MM were included, of whom 54 were males and 55 females. Sixty-eight patients were CD56+ and 41 patients were CD56–. In our study, absence of CD56 expression was significantly associated with several poor prognostic factors. Specifically, 51% of CD56– patients had increased lactate dehydrogenase (LDH) levels at diagnosis, whereas in CD56+ patients the percentage was 24% (p=0.006). Moreover, β2-microglobulin (β2M) levels were elevated (>5.5 mg/L) in 38% of CD56– patients compared to only 14% of CD56+ patients (p=0.013). Additionally, 35% of CD56– patients were stratified as having ISS stage III disease in contrast to 16% of CD56+ patients (p=0.046). Regarding the pathological characteristics, absence of CD56 expression was significantly associated with clonal bone marrow plasma cell infiltration ≥60% (66% of CD56– patients versus 38% of CD56+ patients; p=0.009). On the other hand, CD56 expression was significantly associated with a mature degree of plasma cell differentiation (p=0.044). Ninety out of 109 patients with MM were included in survival analysis. The median OS of CD56– patients was 79 months, while median OS of CD56+ patients was not reached (p=0.37). Univariate analysis revealed that only low serum albumin levels correlated with inferior OS rates. CD56 expression had no effect on OS in univariate analysis. In a multivariate model evaluating CD56 expression, male gender, serum LDH and albumin, only LDH (p=0.038) and albumin (p=0.022) had an independent effect on OS, while CD56 had no impact on outcome (p=0.40).

CONCLUSION: Our study confirmed that lack of CD56 expression is a possible marker of poor prognosis in patients with MM. The detection of CD56 expression by either immunohistochemistry or flow cytometry is simple and cheap, and it could be incorporated in future prognostic or predictive scores. Prospective studies are needed in order to evaluate the role of expression of CD56 as a predictive biomarker in the era of novel regimens.

P29. CIRCULATING SOLUBLE UROKINASE-TYPE PLASMINOGEN ACTIVATOR RECEPTOR LEVELS REFLECT RENAL FUNCTION IN NEWLY DIAGNOSED PATIENTS WITH MULTIPLE MYELOMA TREATED WITH BORTEZOMIB-BASED INDUCTION

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OBJECTIVE: Soluble urokinase-type plasminogen activator receptor (suPAR) has been implicated in the pathogenesis of kidney disease in different disease settings. The aim of this study was to investigate a possible link between suPAR circulating levels and renal impairment (RI) in newly diagnosed patients with symptomatic multiple Myeloma (NDMM) before and after frontline therapy with bortezomib-based regimens.

METHODS: suPAR was measured in the serum samples of consecutive patients with NDMM treated with bortezomib-based upfront regimens in a our institution. Each patient had two measurements: one at baseline before the administration of any kind of therapy, including dexamethasone, and one after best-response to first-line treatment. suPAR levels were also evaluated in apparently healthy individuals of similar age, gender and body mass index, who had donated their blood in the institutional blood bank (controls). Measurements of suPAR and other analytes were performed by means of immune-enzymatic techniques as follows: suPAR (ViroGates A/S, Birkerod, Denmark), Neutrophil Gelatinase-Associated Lipocalin (NGAL) (R&D Systems, Minneapolis, MN, USA); whereas Cystatin-C was measured with an immunoturbidimetric assay using the Roche Cobas 6000 Clinical Chemistry System. Apart from markers of renal function (Cystatin-C) and renal injury (NGAL), biomarkers of inflammation (hs-CRP and IL-6) and cardiac function (hs-Troponin-T and NT-proBNP) were also evaluated. eGFR values were calculated based on the Chronic Kidney Disease Epidemiology Collaboration Cystatin-C (CKD-EPI-CysC) equation.

RESULTS: Forty-seven patients with NDMM were included in the study. All patients received bortezomib-based frontline therapy as follows: VCD (n=32, 68%); VTD (n=7, 15%); VMP (n=7, 15%); and VD (n=1, 2%). Twenty-seven (58%) patients had baseline eGFR at diagnosis <60 mL/min/1.73 m^2, 23 (49%) had baseline eGFR <50 mL/min/1.73 m^2 and 10 (21%) had baseline eGFR <30 mL/min/1.73 m^2; whereas no patient was on dialysis. In the study were also included 24 healthy individuals of similar age, gender and body index who served as controls. suPAR levels were elevated in NDMM patients at diagnosis compared to healthy individuals ([mean, standard deviation (SD) (range): 4.1±2.2 pg/mL (1.4-13.0 pg/mL) versus 1.8±0.3 pg/mL (1.1-2.6 pg/mL), p <0.001] and they strongly correlated with disease stage (p-ANOVA<0.001). Interestingly, suPAR levels strongly correlated with eGFR values both at diagnosis ($r=-0.700$, $p<0.001$) and at best response ($r=-0.890$, $p<0.001$) and they were also associated with NGAL values both at diagnosis ($r=0.657$, $p<0.001$) and at best response ($r=0.586$, $p<0.001$). Furthermore, suPAR levels at diagnosis and at best response correlated positively with the (log) values of inflammatory biomarkers IL-6 and hs-CRP ($p<0.001$ for all correlations), as well as with the markers of cardiac function hs-Troponin-T and NT-proBNP ($p<0.001$ for all correlations).

CONCLUSION: In conclusion, circulating suPAR levels were associated with renal function in pa-

tients with NDMM both at diagnosis and at best response to bortezomib-based frontline therapy. Importantly, responders to anti-myeloma therapy continued to have elevated circulating suPAR, possibly reflecting underlying permanent kidney damage or persistent production from residual myeloma clones and associated myeloid immune cells. SuPAR has emerged as a useful biomarker of renal function in MM, whereas larger clinical studies may further determine the potential value of its integration in the clinical practice.

P30. COEXISTENCE OF MULTIPLE MYELOMA AND LEISHMANIASIS

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OBJECTIVE: Multiple myeloma, a clonal plasma cell disorder, commonly affects adults above 50 years age and accounts for about 10% of all hematological malignancies. Anemia, bone pains, renal failure are the most common symptoms at presentation. Though extra-medullary extra-osseous disease such as hepatosplenomegaly is well known in the course of the disease, clinician must be aware of conditions such as opportunistic infections under immunosuppressive period. In our case 68 years old man admitted to Ege University department of haematology with anemia, hepatosplenomegaly, increased globulin (7 g/dL) His past medical history includes hypertension and coronary artery disease. Patient then underwent diagnosis of suspected myeloma.

METHODS: 12.06.2019 Leu: 3190 Hb: 9.2 Htc: 28.6 Vit B12: 353 SGOT: 55 SGPT: 34 Albumin: 26 Globulin: 70 Creatinine: 0.98 Sedimentation Rate: 140 Uric acid: 7.6 Serum free light chain assay: Kappa free light: 152 Lambda free light: 152 Ratio: 1 Kappa/Lambda Total: 1.51 Immunoglobulins: IgA: 349 mg/dL IgM: 718 mg/dL IgG: 5100 mg/dL BMA/BMB: Plasma cell dyscrasia / 80% cellularity, 15% atypic plasma cells, IgG kappa-lambda myeloma FISH: Negative myeloma panel CRAB: Normocalcemia, renal dysfunction (–), Anemia and Bone lytic lesions were present Peripheral Smear: Platelet: Normal Leucocyte: Neu: 48% Lymp: 42% Monocyte: 10% Erythrocyte: Target cells, Rouleaux formation, hypochromia, normochromic normocytic anemia Viral Serology: HbsAg (–) AntiHbc IgG (+), AntiHbS Normal range, Anti HCV negative, Anti HIV negative.

RESULTS: When patient diagnosed with multiple myeloma he was started to given first VCD chemotherapy for multiple myeloma that consists of Bortezomib: 1.3 mg/m^2 d1-4-8-11 Cyclophosphamide: 500 mg D1-D8 and Dexamethasone: 40 mg d1-4-8-11 with prophylactic 400 mg asiviral and 50 mg allopurinol on 28.09.2019. After first VCD was given; second VCD regimen was successfully given to patient. But ongoing third regimen, patient suffered from abdominal pain and distension. Lab findings were: WBC/Neu: 2960/1840 Hb: 8.4 Plt: 135000 AST/ALT: Normal range ALP/GGT: 214/148 Creatinine: Normal Electrolytes: Normal CRP: 24.8 ESR: 54. Physical examination: Hepatomegaly. Abdominal ultrasonography was done. And on 31.10.2019 dated forth VCD regimen was started; patient was suffering from continuous abdominal distension. Abdominal ultrasonography showed hepatomegaly 194 cm with normal parenchyma, splenomegaly 211 cm, right renal cyst. Clinicians suspected about the situation whether amyloidosis consisted or not. Then liver biopsy was done on following days 05.12.2019. Patient was diagnosed with "Leishmaniasis" with liver biopsy. Then Infection Diseases Department admitted patient for leishmaniasis treatment with IV amphotericin b. After a successful treatment; patient was started to given fifth and sixth VCD regimens and assessed for the Autologous stem-cell transplantation.

CONCLUSION: Multiple myeloma (MM) patients are considered severely immune-compromised and at high risk of opportunistic infections, independently of the therapeutic approach and the response status. Leishmaniasis seems to behave as such an opportunistic infection, so including patients with HIV-acquired immunodeficiency patients who underwent an organ or hematopoietic stem cell transplantation and patients with lymphoproliferative disorders should be assessed for those opportunistic infections.

P31. INVOLVED SERUM IMMUNOGLOBULIN (Ig) IN MM PATIENTS EARLY AFTER LENALIDOMIDE TREATMENT PREDICTS SURVIVAL

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INTRODUCTION: MM is characterized by neoplastic plasma cells infiltrating the bone marrow and producing monoclonal immunoglobulin (Ig) in the serum and urine. Due to monoclonality, free light chains (FLCs) of Ig are also increased. The detected Ig and FLCs are currently in the diagnostic criteria and they are used widely for monitoring MM patients. However, response to treatment is assessed after 4-5 cycles of therapy and data in clinical practice are lost regarding the fluctuation of these variables during the course of the disease or their correlation with specific treatments. Recently, it was proposed that at least partial response after 1st cycle of lenalidomide treatment is necessary for long-term response (Gasiot, et al 2019).
OBJECTIVE: To investigate the possible prognostic value of serum Ig and FLC levels after 1 month of treatment with Lenalidomide-Dexamethasone (RD).
RESULTS: We studied 156 MM patients from diagnosis to last follow-up or death; their files were reviewed after patients' informed consent was obtained. Clinical and laboratory characteristics were collected. Ig and FLCs levels were measured at RD initiation and after one month of treatment. 10.2%, 38.2%, 26%, 14.6% and 11% were at 1st, 2nd, 3rd, 4th, >5th line treatment, respectively. Statistical Analysis was performed by SPSS software, v.25.
Patients' median age was 67 years, 53% were males. 33%, 23% 44% were ISS1, ISS2, ISS3 respectively. Ig type was 62% IgG, 25% IgA, 12% Light-Chain and 1% other types. Median overall survival (OS) of the whole series was 69.5 months, median OS after lenalidomide (LenOS) was 31.5 months while time to next treatment (TNT) was 17.5 months. Median serum levels of involved Ig at RD initiation were 25.1 g/L while after one month of RD were 14.05 g/L ($p < 0.001$). The median serum levels of involved FLCs levels at RD initiation were 232 mg/L while after one month was 64 mg/L ($p < 0.000$). Ig reduction of 50% was related to significantly improved OS ($p=0.026$) and LenOS ($p=0.035$) but not TNT ($p=0.347$). Similar analysis for FLCs showed that 50% decrease after 1 month of treatment was not related to survival (OS $p=0.262$, LeOS $p=0.905$, TNT $p=0.215$).
CONCLUSION: To conclude, 50% reduction of Ig after 1 month of lenalidomide therapy is related to survival. Thus, we confirm the results of previous study showing that Ig levels early after lenalidomide therapy are important.

P32. LONG-TERM COMPLETE CLINICAL AND HEMATOLOGICAL RESPONSE TO TREATMENT WITH SUBCUTANEOUS BORTEZOMIB: THE FIRST CASE OF TEM(P)I SYNDROME REPORTED IN TURKEY

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OBJECTIVE: TEMPI syndrome (telangiectasia, erythrocytosis with a high erythropoietin level, monoclonal gammopathy, perinephric fluid collection, and intrapulmonary shunt) was first described in 2011 as a syndrome based on a case series of 6 patients. A limited number of patients with TEMPI syndrome have been reported in the English literature to date. Here, we present the case of a patient with TEMPI syndrome, characterized by diffuse telangiectasia, who responded dramatically to bortezomib.

METHODS: Case report.

RESULTS: A 58-year-old nonsmoking female patient had a 10-year history of erythrocytosis, thought to be related to "polycythemia vera", and had been treated with intermittent phlebotomy in a hematology clinic. It was remarkable that the patient was simultaneously followed up for a diagnosis of "monoclonal gammopathy of undetermined significance". Additionally, she was diagnosed with "generalized essential telangiectasia" at a dermatology clinic approximately 5 years prior to presentation at our clinic and was followed up regularly with local therapies. Her oxygen saturation was 98% at room air and her physical examination was notable for telangiectasias on her face, chest, back, and upper limbs. Her laboratory workup showed a complete blood count significant for an elevated hemoglobin level of 18.1 g/dL and a hematocrit of 58.9%. Her blood chemistry results were unremarkable, and the erythropoietin level was very high (180 U/mL, normal range: 4.3-29 U/mL). Serum protein electrophoresis and immunofixation studies revealed an IgG-kappa monoclonal protein. The kappa/lambda light chain ratio was 5.1 (normal reference: 0.26-1.65). Bone marrow biopsy revealed 10% kappa-positive clonal plasma cells. The JAK2 V617F mutation test result was negative. A positron emission tomography scan was negative for any bony lesion or plasmacytoma. The patient was suspected to have TEMPI syndrome. The abdominal CT scan did not reveal perinephric fluid collections. The right-to-left circulatory shunt index was 7% (normal <5%) as determined by lung perfusion scintigraphy using technetium 99m macroaggregated albumin. With the diagnosis of TEMPI syndrome, she was started on a weekly regimen of bortezomib 1.3 mg/m^2 subcutaneously and dexamethasone 40 mg orally. There was a rapid resolution of the telangiectasias, normalization of the serum erythropoietin level and hematocrit, and finally disappearance of monoclonal gammopathy. The patient, who has been in our follow-up for 30 months, received bortezomib treatment and achieved a complete response. She has been followed up without medication for the last six months.

CONCLUSION: To the best of our knowledge, a total of 22 TEMPI syndrome patients have been reported in the English literature (as of June 2021), many of whom have been described in individual case reports. Sykes and his colleagues established TEMPI syndrome major (telangiectasias, elevated erythropoietin levels and erythrocytosis, monoclonal gammopathy) and minor (perinephric fluid collection, intrapulmonary shunt, venous thrombosis) diagnostic criteria. TEMPI syndrome is best classified as plasma cell dyscrasia with accompanying paraneoplastic manifestations, similar to POEMS and Schnitzler syndromes. We excluded these syndromes, and multiple myeloma with clinical, laboratory and imaging techniques. Finally, following the diagnosis of TEMPI syndrome, the complete clinical and hematological response to bortezomib was observed in follow-up.

P33. MULTIPLE MYELOMA IN A PATIENT WITH A DIAGNOSIS OF PROSTATE CA, BILATERAL HYDRONEPHROSIS AND STAGHORN CALCULI

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OBJECTIVE: Multiple myeloma (MM) is a malignant disease of plasma cells, with a median age of 65 years at diagnosis. 37% of myeloma patients are over the age of 75.
METHODS: An 85-year-old male patient with a history of receiving oxygen support at home for 12 hours after hospitalization and discharge 4 months ago due to COVID pneumonia and diagnosed with COPD, prostate cancer, coronary artery disease and diabetes was admitted to the emergency service with a decrease in oral intake and urine output for 3 days. The patient who was followed up with a urinary catheter at home who had no urine output on arrival, had a urine output of up to 300 cc after the catheter was changed. The patient's entrance laboratory examinations; Hgb: 7.4, WBC: 18300, PLT: 428000, procalc: 1.45, cre: 4.9, urea: 274, uric acid: 11.2, P: 7.4, CRP: 372.7. TIT: leuk:+3, eryt:+3, protein+2. E. coli was detected in the urine culture. In the patient who used monoket, coversyl, plavix, apidra, lantus, casodex; Coversyl was stopped, ceftriaxone and oxapar were started due to immobilization. The oral mucosa of the patient was dry. SpO_2: 99(4/lt/min O_2), HR: 97, BP: 160/83 were detected. The patient was hospitalized with a preliminary diagnosis of urinary infection, pre-renal ARF secondary to poor oral intake. Ultrasonography showed Grade 2-3 ectasia in the pelvicalyceal system of both kidneys and a hyperechoic appearance consistent with a 3 cm staghorn calculi giving acoustic shadow that caused focal ectasia in the upper pole of the left kidney. In abdominal CT, both renal collecting systems were Grade II ectatic, paraaortic paracaval, multiple pathological lymph nodes were observed in both parailiac and pelvis, mesenteric fatty tissues were heterogeneous. Bone marrow aspiration and biopsy were performed due to albumin/globulin reversal (proteinuria: 2469 mg/day, albumin: 2.6, globulin: 3.8, sedim: 103 mm/h) renal failure of unknown etiology. In the bone marrow biopsy, 30-40% plasma cell infiltration was observed, some of which were binuclear atypical. When evaluated together with the Kappa/lambda Light chain ratio (1320/161), it was found to be compatible with multiple myeloma and VD was started due to age and performance. Bilateral nephrostomy catheter was inserted in the patient by interventional radiology. Due to *E. coli* in urine culture, ceftriaxone was discontinued; meropenem and fosfomycin were started. Intravenous hydration was started in the patient who developed hypernatremia. Bortezomib and dexamethasone treatment was planned. Consulted with cardiology, It was reported that no pathology was observed that prevented chemotherapy.
RESULTS: Thoracic CT was requested with the suspicion of possible aspiration or COVID pneumonia. In the thorax CT, appearances consistent with pneumonic infiltration - subsegmental atelectasis were observed in the lower lobes of both lungs and on the right, with air bronchograms in them that were prominent in them. The patient, whose current treatment was continued, died as a result of cardiac and respiratory arrest.
CONCLUSION: Urinary tract obstruction is rare in patients with MM and usually occurs secondary to uric acid calculi or renal stones in hypercalcemia. In MM, renal problems due to accumulation of uric acid and light chains in the tubules rather than such obvious obstructive uropathy can be seen. Prevention of dehydration, hypercalcaemia and infections that can precipitate acute renal failure has paramount importance in MM. This report highlights the need to consider the diagnosis of MM in elderly patients presenting with staghorn stones and albumin/globulin reversal, renal insufficiency of unknown etiology.

P34. OUTCOME AND NUMBER OF TREATMENT LINES ADMINISTERED TO MULTIPLE MYELOMA PATIENTS' TREATED SINCE THE INTRODUCTION OF NEW DRUGS. A SINGLE-CENTER EXPERIENCE

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OBJECTIVE: Few years ago, two important studies (refs) showed that MM patients' treatment opportunity is disappointing from 3rd line with less than 50% of patients being treated either because of death or because of abandon of follow-up. The introduction of a new therapeutic armamentarium, with Thalidomide being the first biology-based new agent, eventually changed this disappointing state. To record the number of treatment lines and the course of MM patients treated in a single institution with any novel agent(s), to seek whether the availability of new options increased treatment opportunity

METHODS: We retrospectively reviewed 300 files from patients with symptomatic MM after their informed consent was obtained. The collected data were processed with the statistical analysis program SPSS, v.25.0.

RESULTS: Thirty hundred patients' files were reviewed, 173 (58%) were men and 127 (42%) women, with a median age of 67 years (range: 29-89). At diagnosis, 26%, 23%, 51% of patients were in ISS 1, ISS 2 and ISS 3 respectively. Ig Type was IgG in 61% of patients, IgA in 24%, Light Chain in 14% and other types in 2%. 204 (68%) succumbed while 96 (32%) are currently being followed with disease under therapy. Of the 204 deceased patients, all (100%) received 1st line treatment, while 178 (87.3%), 128 (62.8%), 84 (41.2%), 57 (28%), 33 (16.2%), 22 (10.8%), 16 (7.9%), 12 (5.9%), 9 (4.41%) received 2nd, 3rd, 4th, 5th, 6th, 7th, 8th and >9th treatment line respectively. Of the 97 patients that are currently alive, 28 (29.2%) are in 1st line treatment free of relapse, 27 (28.1%) are in 2nd line, 24 (25%) in 3rd line, 6 (6.3%) in 4th line, 8 (8.3%) in 5th line, 2 (2.1%) in 6th line and 1 (1%) in 7th line of therapy. Ninety patients underwent ASCT and 3 of them twice. Median OS of the whole cohort was 56 months (range: 0-376). The median OS of deceased patients was 50 months (0-376) while for patients currently under follow-up, median OS is 69.5 months (1-285). Patients' median time to next treatment (TNT) at 1st line was 10 months, at 2nd was 12 months, at 3rd line 7 months, at 4th line 8 months, at 5th line 5.5 months and >6th line 5 months. The treatment regimens used were 62% VD, 58% RD, 20% MP, 16% VCD, 12% MPT 13% PAD, 7% PD, 7% Daratumumab and 6% Ixazomib containing regimens, 6% VRD, 5% KD, 3% Bendamustine. Of course, re-administration of IMiDs in patients already treated with PI and IMiDs, was related to better TNT (p=0.01) compared to PI but not OS (p=0.229), due to continuous treatment. Depth of

response decreased with each additional line with 35% of patients reaching a response ≥VgPR at 1st line treatment while only 22% at 5th line treatment.
CONCLUSION: After new agents' introduction, therapeutic opportunities increased as well as treatment lines administered for the benefit of quality of life and longevity. Abbreviations MP: Melphalan-Prednisolone/Prednisone, VAD: Vincristine-Doxorubicin-Dexamethasone, PAD: Bortezomib-Dexamethasone-Doxorubicin: Velcade-Dexamethasone, TD: Thalidomide Dexamethasone, RD: Lenalidomide Dexamethasone, VRD: Velcade-Lenalidomide-Dexamethasone, PD: Pomalidomide-Dexamethasone.

P35. SMALL LYMPHOCYTE-LIKE PLASMA CELL MYELOMA: A CASE REPORT AND REVIEW OF THE LITERATURE OF A POTENTIAL DIAGNOSTIC PITFALL

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OBJECTIVE: Multiple myeloma is characterized by >10% monotypic plasma cell infiltration of the bone marrow and the production of a monoclonal protein in the serum and/or urine. Plasma cells have a characteristic appearance on light microscopy with basophilic cytoplasm and an eccentric nucleus. In a small subset, though, the neoplastic cell population has a lymphoid appearance. In those cases, immunophenotypic studies such as flow cytometry and immunohistochemistry are required to differentiate between multiple myeloma and an indolent B-cell neoplasm.
METHODS: A 75-year-old woman was admitted to the hospital with severe back pain. She had normochromic normocytic anemia (Hb 86 g/L, MCV 95 fl). Serum creatinine and calcium were within the normal range. Magnetic Resonance Imaging showed fractures in the second and third lumbar vertebrae. Multiple osteolyses in the skull and long bones were also present.
RESULTS: A bone marrow aspirate was performed as part of a diagnostic work up for her anemia and revealed a heavy infiltration of small lymphocyte-like cells. However, flow cytometry showed that this population had bright CD38 and CD138, and dim CD45 expression, highly indicative of multiple myeloma. Bone marrow biopsy revealed interstitial infiltration by lymphocyte-like plasma cells (65% of the nucleated cells), lambda monotypic, with cyclin D1 expression and partial CD20 expression. Bone marrow karyotype was 46,XX and there were neither t(4;14), t(14;16) translocations nor del(17p). Bone marrow infiltration by monotypic plasma cells, combined with anemia and bone disease, set the diagnosis of symptomatic multiple myeloma leading to treatment initiation. Quantitative serum immunoglobulin tests revealed hypogammaglobulinemia (IgG 373 mg/dL, IgM 23 mg/dL, IgA 48 mg/dL). Serum protein electrophoresis showed a small monoclonal component (0.019 g/dL) of lambda free light chains as shown on immunofixation. Lambda free light chains were markedly elevated with a serum free light chain ratio of involved to uninvolved 527.4/1 (free kappa: 7.11 mg/L, free lambda: 3750 mg/L). Severe proteinuria was also noted with a monoclonal band of lambda free light chains on urine protein electrophoresis and immunofixation. Lymphoid appearing plasma cells are present in less than 5% of multiple myeloma cases. The pattern of bone marrow infiltration is mostly interstitial in small lymphocyte-like myeloma cases as described in the literature. Bone disease and bright expression of CD38 and CD138 are universal findings in this subset of patients. Cyclin D1 is strongly associated with small lymphocyte-like myeloma, as this variant accounts for 40-50% of myeloma cases with t(11;14) translocation. Presence of CD20 and cyclin D1 expression could erroneously guide differential diagnosis to a cyclin D1-positive mature B-cell neoplasm, like mantle cell lymphoma and hairy cell leukemia.
CONCLUSION: Typical plasma cells are straightforwardly recognizable in bone marrow samples since they have a characteristic morphology of an eccentric nucleus and abundant cytoplasm. However, morphology can be misleading as many morphological varieties have been described. Rarely, the neoplastic plasma cells have features in common with mature small lymphocytes and are CD20 and cyclin D1-positive. This morphological variant is a potential mimicker of a mature B-cell lymphoma. In those rare cases, the clinicophenotypic correlation leads to the correct diagnosis.

P36. THE EFFECT OF BISPHOSPHONATE USE ON TREATMENT RESPONSE AND OVERALL SURVIVAL IN MULTIPLE MYELOMA PATIENTS

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OBJECTIVE: Multiple myeloma (MM) is a neoplastic plasma cell disorder characterized by clonal proliferation of malignant plasma cells in the bone marrow, presence of monoclonal protein in serum or urine, and end-organ damage associated with this monoclonal protein. Bisphosphonates are pyrophosphate analogs with a high affinity for calcium crystals. Due to the affinity of bisphosphonates for calcium, they bind rapidly to calcium-containing hydroxyapatite crystals, especially in the resorption zone. In this way, they prevent bone resorption. In this study, we aimed to investigate the effect of bisphosphonate use on treatment response and overall survival in patients with MM.

METHODS: All patients with MM who followed by the Hematology department of Fırat University Hospital in the last 10 years were included in this retrospective observational study. Age, gender, end-organ involvement, ISS staging, LDH level, IG subtype in diagnosis, bisphosphonate use (duration and dose), treatments, response status, and survival were investigated.

RESULTS: Ninety-one patients, of whom 53 were male and 38 females, were included in this study. The median age was 63.3 years in males and 63.7 in females. The most common immunoglobulin subtype was IgG kappa, while the least common subtypes were non-secretory and IgM kappa. According to the ISS staging system at the time of diagnosis, there were 40 patients in stage I, 17 patients in stage II, and 34 patients in stage III. There was a significant difference in mean survival times between ISS staging ($p=0.004$). At the time of diagnosis, 14 patients with high calcium, 77 patients had normal calcium., 38 patients had renal failure, while 53 patients had normal renal functions, 72 of the patients had anemia and 19 had normal hemoglobin levels, bone involvement was detected in 60 of the patients. LDH level was detected high in 20 patients. There was a significant difference between the creatinine categories in terms of mean survival times ($p=0.049$). The survival time of those with normal LDH levels was found to be significantly higher than those with high LDH levels ($p=0.007$). There was no significant difference in survival between bisphosphonate intake status and IG subtypes ($p>0.05$). The progression-free survival time of patients with normal LDH levels was found to be significantly higher than the progression-free survival time of patients with high LDH levels ($p=0.01$). There was no significant difference in progression-free survival between the ISS category, bisphosphonate intake status, creatinine category, and IG subtypes ($p>0.05$).

CONCLUSION: In this study, OS and PFS in MM patients were not affected by bisphosphonate use. however, LDH level influenced both OS and PFS, the increase in LDH level negatively affected the survival.

P37. TUMOR LYSIS SYNDROME AFTER FIRST DOSE OF VENETOCLAX-BORTEZOMIB-DEXAMETHASONE THERAPY IN A PATIENT WITH RELAPSED REFRACTORY Ig-D LAMBDA MULTIPLE MYELOMA

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OBJECTIVE: Venetoclax was shown as an effective treatment in multiple myeloma (MM) that particularly harboring t(11;14) (1.2). Venetoclax can cause tumor lysis syndrome (TLS) in acute myeloid leukemia, chronic lymphocytic leukemia, and mantle cell lymphoma (3). Herein, we present a case with TLS occurred after venetoclax treatment in MM.

RESULTS: A fifty-eight-year old male patient admitted to our clinic with symptoms of lumbar pain and high blood pressure. There was no other significant abnormality other than high blood pressure in the physical examination. First laboratory results showed anemia (Hb: 8 g/dL), increased creatinine (4.4 mg/dL) and hypercalcemia (12.8 mg/dL). M-spike was seen on serum protein electrophoresis. Immunoglobulin levels were normal for IgA, IgM and IgG. Lambda monoclonal band was detected in the immunofixation electrophoresis. Bone marrow aspiration and biopsy was consistent with MM that showed infiltration of atypical plasma cells with 60%. We could not test for IgD levels in our local laboratory but IgD staining performed in tissue samples and diffuse positivity was detected. The patient was diagnosed with ISS Stage III Ig-D Lambda MM in November 2019. t(11;14) and 1q amplification were detected on the FISH analysis. The disease was progressive after four cycles of Bortezomib-Cyclophosphamide-Dexamethasone regimen and 3 cycles of VRD (Bortezomib-Lenalidomide-Dexamethasone). After 3 cycles of VRD, acute renal insufficiency and hypercalcemia occurred. We had a plan for autologous hematopoietic stem cell transplantation (ASCT) and one cycle of Carfilzomib-Lenalidomide-Dexamethasone and 2 cycles of Carfilzomib- Lenalidomide-Dexamethasone were given. After this therapy serum free lambda light chain levels showed progression and anthracycline and platin based infusional chemotherapies and Daratumumab-Bortezomib-Dexamethasone were given afterwards. All of the bone marrow biopsies showed diffuse plasma infiltration after these therapies. Serum M-protein levels increased after 2 cycles of Daratumumab-Bortezomib-Dexamethasone and we planned to give Venetoclax-Bortezomib-Dexamethasone treatment regimen. On the 1st day of treatment 1.3 mg/m^2 dose of bortezomib, 20 mg of dexamethasone, and 400 mg of venetoclax were given. Venetoclax was given as 400 mg with allopurinol 300 mg because of high tumor load. After the first dose laboratory results were compatible with TLS. Hypocalcemia (7 mg/dL), hyperphosphatemia (8.0 mg/dL), hyperuricemia (14.8 mg/dL), and acute renal failure (creatinine: 1.5 mg/dL), LDH: 4510 U/L. One session of emergent hemodialysis was performed for laboratory TLS. After four days treatment regimen was re-started as lower doses of venetoclax. Slow ramp-up of venetoclax was ordered as starting with 100 mg up to 800 mg of maximum dose. We have performed ASCT after 3 cycles of this regimen.

CONCLUSION: We did not encounter any case in the literature that reported tumor lysis syndrome attributed to venetoclax treatment in MM. In the phase I trial a ramp-up regimen was applied (1). There was no tumor lysis adverse event in the phase III trial of venetoclax and the recommended starting dose was 800 mg/day. Tumor lysis syndrome prophylaxis was applied according investigator choice (3). Although we started with a lower dose with tumor lysis prophylaxis, the syndrome was seen. Ramp-up can be essential in selected cases with MM.

P38. TWO CLINICAL CASE REPORTS OF PATIENTS WITH SYNCHRONOUS NEWLY DIAGNOSED MULTIPLE MYELOMA AND SOLID MALIGNANCY

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OBJECTIVE: The occurrence of two or more malignancies in the same patient is a rare clinical entity. The association of two solid tumors or two onco-hematological disorders is more usual; however, the association between a solid malignancy with a hematological neoplasm is even rarer. Coexisting of multiple myeloma (MM) and primary malignant tumor at the diagnosis are rarely observed in clinical practice. We will describe two patients, one patient with MM with Amyloidosis and Breast cancer and a second patient with MM and Mesothelioma.
METHODS: Case report 1: A 74 year old women presented with weakness, back pain and abdominal discomfort. On physical examination the patient had a poor performance status, abdominal distention and paleness. Her laboratory tests showed anemia, paraproteinemia, proteinuria and high level of tumor marker Ca15-3. The CT-scan showed ascites, multiple osteolytic and osteosclerotic lesions in the spinal and pelvic bone. The ascites fluid examination showed plasma cell infiltration and a lot of syncytia of other malignant cells. The bone marrow examination showed 15% clonal plasma cell and syncytia of malignant cells (GATA 3+). Because of proteinuria the patient underwent fat biopsy that was positive for Amyloidosis and also showed very high levels for NT-proBNP. The mammography showed in the right breast a tumor, the biopsy relieved lobular carcinoma. The patient received one cycle chemotherapy with paclitaxel alternately with bortezomib and corticosteroids. Case report 2: A 65 year old women was admitted to the Internal Medicine Department with dyspnea, weakness and B-symptoms. The diagnosis of Mesothelioma was confirmed by biopsy-immunohistochemistry examination from pleural effusion and pleural mass. During diagnosis the laboratory tests showed anemia, hyperglobulinemia and paraproteinemia, a bone marrow examination developed a second malignancy multiple myeloma. The patient received first therapy for the mesothelioma (Carboplatin and Pemetrexed) in combination with high dose dexamethasone.
RESULTS: Case report 1: Unfortunately the patient developed during the first chemotherapy pulmonary infection, renal insufficiency without recovering and she died. Case report 2: Because of synchronous multiple myeloma and is planned to receive alternately antimyeloma treatment.
CONCLUSION: The cases described represents rare clinical conditions, through the synchronous occurrence of multiple myeloma with breast cancer or mesothelioma. The lack of studies on this synchronous association, as well as the few reported cases in the literature, inhibits a greater clarification of the involved pathogenesis. However, successful management of patient and increased life expectancy can be achieved by multidisciplinary management and patient oriented approach in multiple primary malignant synchronous tumors.

P39. DIAGNOSING A PATIENT WITH ERDHEIM - CHESTER DISEASE DURING THE COVID-19 PANDEMIC

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OBJECTIVE: Erdheim-Chester disease (ECD) is a rare clonal histiocytic disorder characterized by an insidious course with cumulative tissue infiltration by foamy CD68+CD1a- histiocytes and a progressive character that may be fatal if it remains untreated with an average time to diagnosis of 2.7 years. The COVID-19 has put an enormous strain on healthcare systems worldwide both directly, and indirectly resulting in the disruption of healthcare services to prevent, diagnose and manage the non-COVID-19 diseases.
METHODS: We describe the case of a 58 yrs male diagnosed with Erdheim-Chester disease with onset two years before current presentation with episodes of sporadic self-resolving mild fever and anemia of chronic disease during the COVID-19.
RESULTS: The clinical examination was normal, while the laboratory results revealed a mild anemia (Hb 11.8 g/dL, MCV 79 fL). Iron parameters were compatible with anemia of chronic disease (ferritin 135 ng/mL). Infectious and autoimmune diseases were excluded, while gastrointestinal endoscopy was not contributive. On abdominal CT, perirenal fat and fascia infiltration were noted. An 18F-FDG PET/CT scan demonstrated moderately increased radiotracer uptake of perirenal tissue. A CT-guided perirenal tissue biopsy revealed inflammatory reaction and fibrosis without features of a specific disease. Our diagnostic hypothesis of lymphoma was not corroborated by the perirenal tissue and bone marrow biopsy. During the follow-up, PET-CT was repeated without new findings. Additionally, the laboratory results revealed an elevated serum IgG4. To exclude Immunoglobulin G4 related disease (IgG4-RD), perirenal tissue biopsy was repeated, and the morphologic findings were compatible with IgG4-RD, but immunohistochemically, there was no increase in the number of IgG4+ plasma cells or an abnormal IgG4+/IgG+ ratio. The case was reviewed, and the diagnosis of ECD was evoked. Considering that ECD diagnosis may be established after consecutive biopsies, there was a clinical suspicion of a non-representative biopsy, and a new biopsy was scheduled. At admission, which coincided with the plateau of the second wave of COVID-19, patient was found febrile, and a molecular SARS-CoV-2 test confirmed the infection. He received supportive therapy and was then discharged in stable condition. A biopsy was performed two months later under ultrasound guidance and demonstrated histiocytes with abundant foamy (xanthomatous) cytoplasm and small nuclei, either single or in small clusters, into a fibrotic stroma. Multinucleated histiocytes were rarely identified. These cells were CD68, fascin, and cyclin D1 positive and S100, CD1a, ALK, and tryptase negative. The findings confirmed ECD diagnosis correlating with clinical and radiological features (hairy kidney appearance). Targeted next-generation sequencing demonstrated the presence of mutation V600E of BRAF on gene exon 15. We intend on treating him with the standard dose of interferon-alfa with a risk of disease relapse at discontinuation or as an alternative option with cladribine.

CONCLUSION: High suspicion and multidisciplinary team collaboration is paramount to achieve diagnosis in rare conditions such as ECD. Due to variable prognosis of ECD, after initiation of treatment a close follow-up will be scheduled. Additionally, disruptions in healthcare services in the pandemic milieu may disproportionately affect rare diseases and further study is required to better meet their needs in the pandemic setting.

P41. A RARE CASE REPORT: HAX1 MUTATION IN A ADULT WITH CYCLIC NEUTROPENIA

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OBJECTIVE: Background: Cyclic neutropenia is a rare genetic and hematologic is characterized by periodic neutropenia and recurrent infections. Although cyclic neutropenia is usually seen in children, there are rare cases that can be diagnosed in adults as well. ELANE mutation is the most common cause of severe congenital neutropenia as well as sporadic and autosomal-dominant cyclic neutropenia. Homozygous and heterozygous mutations in the HAX1 gene have been reported in autosomal recessive cases. In this study, we wanted to present a case diagnosed with cyclic neutropenia in adulthood and with HAX1 mutation.

RESULTS: Case Report: A 52-year-old male patient had been followed for 10 years due to neutropenia and recurrent infections. He has a history of recurrent neutropenic fever, oral ulcers and peritonitis. He had hypertension and chronic hepatitis b infection at his past medical history. The cause of the patient's neutropenia could not be clarified yet when he admitted to our center. On physical examination, there was no significant finding other than oral ulcers. In laboratory examinations; leukocyte: 4200/mm^3, neutrophil: 160/mm^3, hemoglobin 13 g/dL, hematocrit 38.3 6%, platelets: 289000/mm^3; liver, kidney, thyroid and bleeding function tests were normal. However, on the previous laboratory tests, neutrophil count was within the normal range in certain periods. When the patient was examined for immune deficiency, no significant finding was found. Bone marrow biopsy was applied to the patient, dysplasia findings and 4% blast cells were observed. The patient was searched for well known cytogenetic mutations (like as 5q, 20q) for myelodisplastic syndrome but no mutation was detected in bone marrow aspiration samples. Additionally, genetic mutations were screened for congenital neutropenia. No mutations were detected in ELA2, G6PC3, JAGN1, SBDS genes but homozygous c.130_131insA (pW44X) mutation was detected in HAX1 gene. The patient was started on granulocyte colony-stimulating factor (G-CSF) administration during episodes of severe neutropenia.

CONCLUSION: Cyclic neutropenia is a rare genetic and hematologic is characterized by periodic neutropenia and recurrent infections. The average periodicity is 21 days and usually consistent for an individual; however, cycle length can range from 14 to 35 days in different patients. Serious life-threatening complications such as necrotizing enterocolitis and peritonitis are seen less frequently than severe congenital neutropenia. Transformation into malignant diseases in cyclic neutropenia is a rare condition. ELANE mutations are the most common causes of severe congenital neutropenia as well as sporadic and autosomal-dominant cyclic neutropenia. Homozygous and heterozygous mutations in the HAX1 gene have been reported in autosomal recessive cases. When the literature is reviewed, there are studies showing that the most common cause of congenital neutropenia in Turkey is the homozygous c.130_131insA (pW44X) mutation. It has been shown that when G-CSF is started in patients diagnosed with cyclic neutropenia, the duration of neutropenia is shortened and infectious complications are reduced. In this study, we would like to emphasize that when neutropenia is detected in adult patients, the causes of congenital neutropenia should not be forgotten and rarer mutations such as HAX1 gene mutation should be screened.