

The background is a vibrant blue with a complex, layered design. It features several overlapping circular shapes in various shades of blue, from light cyan to deep navy. Each circle is filled with a pattern of fine, parallel diagonal lines, creating a textured, woven effect. The circles overlap in a way that creates a sense of depth and movement, with some appearing to be in front of others.

AHOS 2022

ABSTRACTS

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ORAL PRESENTATIONS

SESSION 1 (Orals 1-6)
Friday 16th of September 2022

01. COEXISTENCE OF ≥ 2 HIGH-RISK MOLECULAR ABNORMALITIES SUPERVENES THE PROGNOSTIC VALUE OF THE REVISED INTERNATIONAL STAGING SYSTEM FOR MYELOMA: REAL-WORLD DATA ANALYSIS FROM THE GREEK MYELOMA STUDY GROUP

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OBJECTIVE: Revised International Staging System (R-ISS) has improved the prognostic value of ISS in multiple myeloma (MM). Recently, the Mayo Additive Staging System incorporated +1 q21 to determine a 5-factor 3-tier system, providing an add-on value on R-ISS. The prognostic impact of the coexistence of ≥ 2 high-risk molecular abnormalities, including +1 q21, compared to R-ISS, has not been validated adequately. The aim of this study was to evaluate the prognostic impact on survival of the coexistence of ≥ 2 high-risk molecular abnormalities, defined as Ultra High Risk (UHR) MM, in comparison with R-ISS and other established prognostic markers, in the real-world setting. **METHODS:** We analyzed the data of 1352 consecutive newly diagnosed MM patients, treated between 2002-2021 and which had been tested for molecular abnormalities i. e. del17 p, t(14; 16), t(4; 14) and +1 q21 using fluorescence in situ hybridization. Patients with ≥ 2 high-risk features were classified as UHR. We compared the two groups for age, performance status, ISS, R-ISS, lactate dehydrogenase (LDH), albumin, hemoglobin (Hb), $\beta 2$ -microglobulin, estimated glomerular filtration rate (eGFR), 1st and 2nd line therapies and response rates. A Cox regression model was used to determine independent prognostic factors for overall survival (OS). Progression-free survival (PFS) and OS were plotted with Kaplan-Meier; a $p < 0.05$ was considered as statistically significant.

RESULTS: 116 (9%) were classified in the UHR group vs. 1236 (91%) in the non-UHR group; 106 patients had 2, and 10 patients had 3 molecular abnormalities. The most common combination of high-risk features was +1 q21 plus t(4; 14) (40%). Median age, sex, performance status, LDH and serum albumin, did not differ, whereas the UHR group had lower eGFR, higher β 2-microglobulin and lower Hb. Early stage (ISS1/R-ISS1) was more frequent in the non-UHR group; 1st line treatment, including autologous transplantation (ASCT), and second line treatment were well balanced between groups. Overall response rate after induction therapy was 86% and did not differ between groups. Complete response was lower in the UHR group (11% vs. 19%). After a median follow up of 49 months (95% CI: 44-54), 59% of patients were alive. Median PFS was significantly shorter for the UHR group (15.8 vs. 31.9 months; HR: 0.45, 95% CI: 0.36-0.58). Median OS was 28 months (95% CI: 18-38) for patients in the UHR group vs. 69 months (95% CI: 61-77) for others. In the univariate analysis, age, anemia, eGFR, upfront ASCT, R-ISS and UHR myeloma were independent predictors for OS. In the multivariate analysis UHR myeloma was the strongest independent predictor for OS (HR: 0.42), supervening the prognostic value of R-ISS (R-ISS1 vs. R-ISS2 HR=0.58, R-ISS2 vs. R-ISS3 HR: 0.75). Additionally, UHR status singled out a distinct group within R-ISS2 patients with significantly worse OS (38 months, 95% CI: 28-48 vs. 64 mo, 95% CI: 55-72).

CONCLUSION: According to our analysis of a large cohort of newly diagnosed MM patients UHR myeloma, was the strongest independent predictor for OS, supervening the prognostic value of R-ISS. Moreover, UHR status could serve as an additional prognostic marker for R-ISS2 patients, helping thus to optimize therapeutic approach of MM patients.

02. EFFICACY AND SAFETY OF DARATUMUMAB WITH IXAZOMIB AND DEXAMETHASONE IN LENALIDOMIDE-EXPOSED PATIENTS WITH ONE PRIOR LINE OF THERAPY: RESULTS OF THE PHASE 2 STUDY DARIA

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OBJECTIVE: The use of lenalidomide in frontline therapy for patients with newly diagnosed multiple myeloma (NDMM) has increased the number of patients who become refractory to lenalidomide at second line. In this context, we assessed the efficacy of daratumumab in combination with ixazomib and dexamethasone (Dara-Ixa-dex) as second-line therapy in patients with RRMM who have been previously treated with a lenalidomide-based regimen.

METHODS: DARIA is a prospective, open-label, multicenter, phase 2 study. Eligible adult patients with RRMM had measurable disease after one prior line with a lenalidomide-based regimen and a Karnofsky Performance Status (KPS) score of ≥ 70 . Treatment with Dara-Ixa-dex comprises an induction phase of nine 28-days cycles and a maintenance phase. In induction, patients received DARA 16 mg/kg (weekly for cycles 1-2, bi-weekly for cycles 3-6, and every 4 weeks thereafter) administered intravenously until November 2020 and subcutaneously at a fixed dose of 1800 mg thereafter; 4 mg oral ixazomib (days 1, 8, and 15 of each cycle); and 40 mg oral dexamethasone (weekly, each cycle). In maintenance, Dara-Ixa were administered every 4 weeks until disease progression or unacceptable toxicity, with dexamethasone being discontinued. The primary endpoint was overall response rate (ORR). Secondary endpoints included progression-free survival (PFS), the toxicity profile of Dara-Ixa-dex, and the effects of the combination on serum bone metabolism markers (C-terminal telopeptide of type 1 collagen [CTX], tartrate-resistant acid phosphatase isoform 5 b [TRACP-5 b], bone-specific alkaline phosphatase [bALP], and osteocalcin [OC]) from baseline until disease progression.

RESULTS: Overall, 50 patients have been enrolled (mean [range] age: 69.0 (50.0-89.0) years; female: 28 [56.0%]). At screening, 24 (48.0%) patients had a KPS score ≥ 90 , and most were at revised ISS stage I and II (47, 94.0%). Thirty-two (64.0%) patients were refractory to lenalidomide, and 15 (37.5%) had prior ASCT. ORR was 50.0% (25 patients); one (2.0%) patient had a complete response, 13 (26.0%) a very good partial response (VGPR), and 11 (22.0%) patients had a PR. The median (range) time from first Dara-Ixa-dex dose until first response (\geq PR) is 1.0 (0.9-3.7) month. The median PFS was 8.1 months (95% CI: 5.8-15.6). After a median (range) follow-up of 12.4 (0.9-28.4) months, 14 (28.0%) patients are still on treatment; reasons for treatment discontinuation were progressive disease (28 patients, 77.8%), physician's decision and fatal serious adverse event [SAE] (3 patients, 8.3% each), and adverse event [AE] (2 patients, 5.6%). Following 15 months of treatment, the median change from baseline for CTX, TRACP-5 b, bALP and OC were significant ($p < 0.05$). Overall, 20 (40.0%) patients have ≥ 1 grade 3/4 AE, the most common being

thrombocytopenia (10 patients, 20.0%), and 14 (28.0%) patients have ≥ 1 SAE, the most common being acute kidney injury and pneumonia (2 patients [4.0%] each condition). Four fatal SAEs were reported (pneumonia, infection, urinary tract infection, and lower respiratory tract infection).

CONCLUSION: In conclusion, second-line treatment with Dara-Ixa-dex in patients with RRMM who were pre-treated with a lenalidomide-based regimen resulted in rapid (<2 months) and satisfactory responses along with a favorable effect on bone metabolism.

03. EFFICACY AND SAFETY OF BELANTAMAB MAFODOTIN WITH LENALIDOMIDE AND DEXAMETHASONE IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA NOT ELIGIBLE FOR TRANSPLANT; PRELIMINARY RESULTS OF A PHASE 1/2 STUDY

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OBJECTIVE: Belantamab mafodotin (belamaf), a multi-modal antibody-drug conjugate targeting BCMA, has shown efficacy and tolerability in pretreated patients (pts) with relapsed/refractory multiple myeloma. Herein, we aimed to evaluate the safety and efficacy of belamaf plus lenalidomide and dexamethasone (Rd) in transplant-ineligible (TI) pts with newly diagnosed multiple myeloma (NDMM).

METHODS: The ongoing, prospective, open-label, 2-part, phase 1/2 BelaRd study (NCT04808037) aims to enroll 66 pts with TI NDMM from a Greek center. Eligible are adult pts with Eastern Cooperative Oncology Group status 0-2 and adequate organ function. Part 1 (dose selection) evaluates the safety/tolerability of 3 belamaf doses (2.5, 1.9, and 1.4 mg/kg on Day 1 of every other 28-day cycle) plus Rd (each dose regimen administered to a cohort of 6 pts) over ≥ 4 weeks of follow up; subsequently, an additional 6 pts are enrolled in each dose cohort to establish the recommended phase 2 dose (RP2 D). Part 2 (dose expansion) evaluates the safety and clinical activity of belamaf RP2 D plus Rd in 30 additional pts. This descriptive analysis presents the safety data for all Part 1 pts and the efficacy data for all Part 1 pts with ≥ 2 post-baseline efficacy assessments by the cut-off date (14/01/2022).

RESULTS: Of 36 pts included, 35 (97.2%) continued study treatment by the cut-off date, and 1 (2.8%) had died due to a belamaf unrelated adverse event (AE). The pt median age was 72.5 years (range 64.0-86.0). Of pts with available data (30 [83.3%]), pts at revised International Staging System stages I, II, and III were 6 [20.0%], 21 [70.0%], and 3 [10.0%], respectively, and 3 (10.0%) had high-risk cytogenetics (i. e., del17 p13, t(4; 14), t[14; 16]). Median duration of therapy was 4.2 months (range 0.5-11.9) and median number of cycles reached was 5.0 (range 1.0-11.0). Twenty-two (61.1%) pts experienced at least one grade (Gr) 3-4 AE. One (2.8%) pt experienced a Gr 5 AE (pneumonia), unrelated to belamaf. Most common ($\geq 10.0\%$ of pts) Gr 3-4 AE were fatigue (13 [36.1%] pts), visual acuity reduced (6 [16.7%] pts), and rash (5 [13.9%] pts). Gr 3-4 thrombocytopenias and infections were not reported, as were any infusion-related reactions (Table). Pts with Gr 1-2 ocular symptoms, visual acuity reduced, and keratopathy, were 27 (75.0%), 21 (58.3%), and 18 (50.0%), respectively. Pts with Gr 3-4 ocular symptoms, visual acuity reduced, and keratopathy were 0 (0.0%), 5 (13.9%) and 0 (0.0%), respectively. Of all pts, 28 (77.8%) were evaluable for efficacy. At a median follow up of 4.2 months (range 0.5-11.9), the overall response rate was 96.4% (27/28 pts; complete response [CR]: 14.3% [4/28 pts]; VGPR: 35.7% [10/28 pts]; partial response [PR]: 46.4% [13/28 pts]); no disease progression was reported. Among pts achieving VGPR, 6/10 (60.0%) had negative status serum/urine immunofixation electrophoresis. Median time to PR or better was 1.0 months (range 0.9-2.0).

CONCLUSION: In pts with TI NDMM, belamaf every 2 months plus Rd showed an improved safety profile, especially at lower doses. Rapid and deep hematological responses were recorded.

04. A NON-INTERVENTIONAL, PROSPECTIVE, OBSERVATIONAL STUDY OF RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS TREATED WITH IXAZOMIB IN REAL-WORLD SETTINGS IN GREECE; INTERIM RESULTS OF THE 'OL-ORAL' STUDY

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OBJECTIVE: Ixazomib combined with lenalidomide and dexamethasone (IRd) is approved for adults with multiple myeloma (MM) after ≥ 1 prior therapy. Real-world data on IRd use in Greece are limited. The objective of this study is to generate data on progression-free (PFS) and overall survival (OS) rates, as well as on medication adherence in IRd-treated MM patients.

METHODS: Relapsed/refractory MM patients prescribed IRd for the first time, after 1-3 prior therapies, per the approved label, were eligible to consent and consecutively enrolled. Patients refractory to bortezomib, pre-treated with ixazomib, and having received >1 IRd cycles, are excluded. Data were collected by routine assessments, patient self-report, and medical chart review. We present interim analysis results with cut-off at 24 months after first patient's enrollment.

RESULTS: Forty eligible patients [57.5% (23/40) males; median (interquartile range, IQR) age: 71.7 (64.8-77.3) years] were enrolled from Sep-2018 to Sep-2020 by 14 hospitals. Prior to IRd, 80.0% (32/40) of patients had received proteasome inhibitors [77.5% bortezomib; 7.5% carfilzomib], 65.0% (26/40) immunomodulatory drugs (57.5% lenalidomide; 10.0% thalidomide; 2.5% pomalidomide), and 30.0% (12/40) autologous stem cell transplantation. At IRd initiation, the median (IQR) time since MM diagnosis was 3.5 (1.7-5.5) years. Of the patients, 85.0% (34/40) had ECOG PS 0-1, while 55.0% (22/40) had relapsed, 37.5% (15/40) relapsed and refractory, and 7.5% (3/40) refractory MM; 42.5% (17/40) were refractory to lenalidomide, while none were refractory to proteasome inhibitors. IRd was initiated as 2nd, 3rd and 4th line in 67.5% (27/40), 22.5% (9/40) and 10.0% (4/40) of patients, respectively, at the recommended dose in 40.0% (16/40); ixazomib, lenalidomide and dexamethasone were started at a lower dose in 12.5%, 42.5%, and 50% of patients, respectively. Over a median (IQR) observation period of 6.9 (4.4-15.5) months, a median (IQR) of 7.5 (4.5-12.5) IRd cycles were received. Overall confirmed response rate [\geq partial response (PR)] in the response-evaluable patients was 56.7% (17/30) [61.1% in 2nd and 50% in \geq 3rd line]. Mean (SD) time to first documented response \geq PR was 58.1 (27.0) days. Kaplan-Meier estimated median PFS time was 16.8 (95% CI: 4.8-not reached) months, while 6- and 12-month PFS and OS rates were 62.8% (95% CI: 43.2-77.3) and 58.0% (95% CI: 37.8-73.7), respectively, and 12-month OS rate was 82.9% (95% CI: 65.6-92.0). Adherence to ixazomib was high (median ratio of capsules taken/prescribed: 1). IRd discontinuation rate was 59.0% (23/39), due to disease progression (12/23), adverse event (AE) (8/23), death (2/23; unrelated to ixazomib in both cases), and lack of efficacy (1/23). Ixazomib-related AE rate was 42.5% (17/40) [serious AE rate: 17.5% (7/40)].

CONCLUSION: These results provide preliminary insight on patient and disease characteristics and clinical outcomes in MM patients treated with IRd in 2nd to 4th line in Greek routine settings. The Final results are awaited to complement these findings in a larger patient cohort.

05. IMPROVED SURVIVAL OF PATIENTS WITH PRIMARY PLASMA CELL LEUKEMIA WITH VRD OR DARATUMUMAB-BASED QUADRUPLETS: A MULTICENTER STUDY BY THE GREEK MYELOMA STUDY GROUP

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Objective: Primary plasma cell leukemia (pPCL) is a rare plasma cell disorder with poor outcome. Recently, IMWG revised its definition proposing cPCS of $\geq 5\%$ as the new cut-off value. There is limited information regarding the impact of novel anti-myeloma combinations, i. e., bortezomib-lenalidomide triplet (VRd) or daratumumab-based quadruplets (DBQ) on pPCL outcome. Considering the lack of prospective trials, our aim was to compare retrospectively treatment approaches, and to evaluate prognostic factors of overall survival (OS) in an extended cohort of pPCL patients fulfilling the new criteria, in the real-world setting.

METHODS: We analyzed 110 pPCL patients out of 3324 myeloma patients (3%), diagnosed between 2001-2021; 51% of patients were ≤ 65 years; ECOG was ≥ 2 in 46%; 65% had advanced bone disease and 15% had bone/soft tissue plasmacytomas; 72% had Bence-Jones proteinuria, 45% abnormal LDH, 27% hypercalcemia, 72% hemoglobin < 10 g/dL and 24% had eGFR < 30 ml/min/1.73 m²; del17 p, t(4; 14), t(14; 16) and 1 q21+ tested by FISH were detected in 56%; 30% had t(11; 14). RISS was distributed as follows: RISS1: 4%, RISS2: 58%, RISS3: 38%. Median cPCs% was 11% (range: 5-71%). Immunophenotype of PCs was similar in bone marrow and peripheral blood in 92% of patients; CD56 (-), cPCs was found in 52%. 37% had cPCS 5-20%; Patients' characteristics did not correlate with cPCs%, except from platelets (PLT) that were significantly lower in patients with $> 20\%$ cPCs.

RESULTS: 89% of patients received novel therapies; DBQ: 21%, VRd: 16%, bortezomib standard combinations (BSC): 52%, conventional chemotherapy (CT): 11%; 35% underwent ASCT. Response was distributed as follows: \geq PR: 83%, vgPR: 24%, CR: 26%. Median time to response was one month (range 1-5). Treatment with VRd/DBQ or ASCT strongly correlated with higher CR rates (45% vs. 19%; $p=0.007$; 52% vs. 11%; $p<0.001$, respectively). After a median follow-up of 51 months (95% CI: 45-56), 67 patients died (progression: 42, infection: 20, other: 5). Early mortality (\leq 1 month) occurred in 4/67 deceased patients; 51/110 patients received 2 nd line therapy. Median number of treatment lines was 1 (range: 1-5). Progression-free survival was 16 months (95% CI: 12-19.8), significantly longer in patients treated with VRd/DBQ vs. BSC/CT (25 months 95% CI: 13.5-36.5, vs. 13 months 95% CI: 9-16.8; $p=0.03$). Median OS was 29 months (95% CI: 19.6-38.3), significantly longer in patients treated with VRd/DBQ vs. BSC/CT (not reached vs. 20 months, 95% CI: 14-26; 3-year OS: 70% vs. 32%, respectively; $p<0.001$; HR: 3.88). Median survival after pPCL progression was 8 months (95% CI: 3.5-13.5). In the univariate analysis, ECOG \geq 2, PLT $<100.000/\mu\text{L}$, cPCs ($>20\%$), del17 p(+), upfront treatment with VRd/DBQ, ASCT and CR were independent prognostic factors for OS; treatment with VRd/DBQ, del17 p(+) and PLT $<100.000/\mu\text{L}$, significantly predicted for OS in the multivariate analysis ($p<0.05$).

CONCLUSION: These real-world data, based on the largest reported national multicenter series of pPCL incorporating the new criteria, has shown that treatment with VRd or antiCD38-based quadruplets induces deep and durable responses and is one of the strongest prognostic factors for OS representing currently the best therapeutic approach for pPCL; ASCT maintained its therapeutic value.

06. EVOLUTION OF ASYMPTOMATIC TO SYMPTOMATIC WALDENSTROM'S MACROGLOBULINEMIA. ASSESSMENT OF PROGNOSTIC MODELS.

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OBJECTIVE: Waldenstrom's Macroglobulinemia (WM), is a rare and indolent B-cell lymphoma that belongs to the lymphoplasmacytic lymphoma subtype, with the hallmark of monoclonal IgM secretion. Smoldering WM (SWM) is an entity that fulfills the diagnostic criteria of WM, but has no need of treatment and may remain stable life-long. Prognostic systems have been developed to detect WM patients at risk to become symptomatic and warrant closer observation. We studied clinical and laboratory prognostic variables and attempted to generate a risk stratification system encompassing the values that substantially affected the progression of smoldering to symptomatic WM. **METHODS:** We retrospectively studied 86 asymptomatic patients out of 161 diagnosed with WM. Patients' medical records were retrieved after patients' informed consent was obtained and relevant findings were collected. Time from diagnosis to time requiring treatment was defined as TTT (time to treat). Statistical analysis was performed using SPSS v. 26 software.

RESULTS: Eighty-six patients were included in our study with a median age of 64 years (range: 33-88), 41% were women and 59% men. Median follow up was 82 months (6-354), median (TTT) was 17 months (6-222) Twenty-nine patients (34%) evolved into symptomatic disease, with 16 of them (55%) having progressed into the first two years. Univariate analysis was initially performed using parameters known to be significant for disease's burden evaluation. In univariate analysis statistical significant values were abnormal LDH {LDH \geq upper normal limit (UNL)} (HR 1.6, CI 0.9-2.6, $p=0.052$), free-light chain ratio (FLCR) ≥ 10 (HR 2.015, CI 1.1-3.6, $p=0.02$), Bone marrow (BM) lymphoplasmacytic infiltration $\geq 50\%$ (HR 2.17, CI 1.4-3.4, $p=0.001$), b2-microglobulin ($\beta 2$ MG) ≥ 4 mg/dL (HR 2.5, CI 1.5-4.2, $p=0.001$), monoclonal IgM protein ≥ 4500 mg/dL (HR 1.7, CI 1.04-2.7, $p=0.032$), hypo-gammaglobulinemia (HR 1.6, CI 1.01-2.7, $p=0.044$). Statistically significant factors were applied in multivariate analysis producing a risk stratification Cox proportional-hazard regression model for TTT including LDH \geq UNL, BM infiltration $\geq 50\%$, FLCR ≥ 10 and $\beta 2$ MG ≥ 4 mg/dL. 66 patients had all the available data required by this model. Three risk groups to predict the probability of smoldering WM to evolve into symptomatic were defined; 0 points for patients (41%) with none of the above risk factors (37% patients evolved), 1 point for patients (26%) with one risk factor (66% patents evolved) and 2 points for patients (36%) with two or more (87% patients evolved) (HR 2.06, CI 1.41 -3.03, $p<0.0001$). Moreover we also applied in our cohort a prognostic model recently proposed (Mark Bustoros, et al. Journal of Clinical Oncology 2019 37: 16, 1403-1411 10.1200/JCO.19.00394) encompassing IgM ≥ 4.500 / μ L, BM infiltration $\geq 70\%$, $\beta 2$ MG ≥ 4 mg/dl, alb ≤ 3.5 mg/dl which was also statistically significant ($p<0,0001$).

CONCLUSION: Detecting WM patients that experience more aggressive features remains challenging, considering the rarity of the disease and the long follow-up needed. Here, we suggest a new model utilizing four parameters (BM infiltration, FLCR, LDH, $\beta 2$ -MG) that are in the work-up of the newly diagnosed patients with WM, to predict the risk of smoldering disease to rapidly evolve and require treatment.

07. THE SIGNIFICANCE OF ADDITIONAL CHROMOSOMAL ABNORMALITIES IN PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA (APL) IN THE ERA OF ALL-TRANS RETINOIC ACID: A LONG-TERM FOLLOW-UP STUDY

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OBJECTIVE: Introduction: Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) characterized by the t(15; 17)(q22: q21)/ PML-RARA translocation and is associated with long-term disease-free survival (DFS) in patients treated with current treatment regimens that include all-trans retinoic acid (ATRA), with chemotherapy or arsenic trioxide (ATO). The prognostic significance of additional chromosomal abnormalities (ACAs) is still under debate. Aim: We retrospectively studied the frequency and type of ACAs as well as the clinical and laboratory characteristics and outcome of patients with and without ACAs treated with ATRA-based protocols.

METHODS: We investigated 47 APL patients from 570 patients diagnosed with AML from 2000-2020. Cytogenetic analysis was possible in 42 patients. Median age was 39.5 years (range: 12-84), 20 women and 22 men, and median follow-up was 81 months.

RESULTS: Fourteen out of 42 patients had ACAs beyond the t(15; 17) with a rate of 33.3%. The most common ACA was trisomy 8 found in 6 patients, while 2 patients had loss of chromosome Y (1 patient with concurrent trisomy 8), and 1 patient had monosomy 13. Structural abnormalities were present in 7 patients. Complex karyotype was found in 4. Four ACAs have not been reported before, del(2)(p16 p23), del(11)(q14), del(14)(q24), t(6; 7)(p12; q21). Among the 28 patients with a typical t(15; 17)(q22: 21) rearrangement, 6 were high risk (21.4%), 15 intermediate and 7 low. Median age was 37 (12-80) years and 10/28 patients (35.7%) presented with LDH>400 IU. Twenty-seven patients received ATRA-based regimens, 25/27 with anthracycline (14 also received Aracytin), and 2/27 arsenic trioxide. Twenty-five patients achieved complete remission (CR1) and 2 died early due to TRM. Two relapsed (2/25: 8%) at 13 and 110 months. Among the 14/42 patients demonstrating ACAs, 2 were classified as high risk (14.3%), 10 as intermediate and 2 as low. Median age was 39 years (14-84), 6/14 (42.8%) presented with LDH>400 IU. All patients received ATRA-based therapy, 13 with anthracycline (7 also received Aracytin) and 1/14 with arsenic. Eleven achieved CR1 and 3 died due to TRM. Two patients relapsed (2/11: 18%) at 24 and 37 months. There was no difference in clinical or laboratory characteristics between t(15; 17) patients with or without ACAs. Although there was a difference in the probability of overall survival (OS) of patients with or without ACAs 70.7% vs. 88.8% and in DFS 77.8% vs. 95.8% at 5 years, this was not statistically significant. Multivariate analysis for OS revealed age as the only significant factor (p=0.025). Multivariate analysis for DFS did not reveal any significant factor.

CONCLUSION: APL is found in 8.2% of AML cases. 33.3% of patients present ACAs along with t(15; 17), with trisomy 8 being the most common. Prognosis of APL remains more favorable compared to other cytogenetic subtypes, regardless of the presence of ACAs. Further studies are needed to comprehend the biology of the disease with or without ACAs as well as to identify specific additional abnormalities that potentially affect prognosis.

08. VENETOCLAX IN COMBINATION WITH HYPOMETHYLATING AGENT FOR THE TREATMENT OF NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA: REAL WORLD DATA

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OBJECTIVE: The introduction of novel agents in the treatment of Acute Myeloid Leukemia (AML) has led to the improvement of both the survival and the quality of life of patients, especially those with comorbidities and/or of older age. The application of such treatments is associated with unique toxicities that may affect the overall outcome. In this study real world data from 13 centers of Greece and Cyprus regarding efficacy and safety of the combination of hypomethylating agent and Venetoclax (HMA+VEN) in the treatment of newly diagnosed patients with AML are presented.

METHODS: Sixty-five patients of median age 72 years (range; 48-81) with newly diagnosed AML were included in this retrospective study. Sixteen patients (24.6%) had poor performance status (ECOG≥2) and 24/65 (37.0%) had comorbidity index HCT-CI≥3. Most of the patients (38/65, 58.5%) were diagnosed with de novo AML, 19/65 (29.2%) with secondary and 8 (12.3%) with therapy-related AML. High risk cytogenetics were found in 64%(32/50) of patients.

RESULTS: Ven Administration: The majority of patients (54/65) received VEN in combination with azacitidine and 11 with decitabine. Twenty-two patients (33.8%) initiated treatment with HMA and VEN was added later. Most patients (58/65, 89.2%) received VEN at a final dose of 400 mg, but gradual increase of dose for tumor lysis syndrome (TLS) prevention was done in only 69%(40/58). Cytoreduction (hydroxyurea) prior to the administration of the combination received 9/58 patients. Of note, 4/10 of patients with WBC≥25000/μL did not receive any cytoreduction prior to the treatment initiation. Ten patients were taking drugs that interact with Ven metabolism, but in only one case Ven dosage was reduced. With median treatment of 4 cycles (range; 1-28) azacitidine dosage reduction was required in 9 and VEN dosage reduction in 23 patients. Efficacy: Thirty-nine patients

(60.0%) achieved CR/CRi at a median 2 cycles (range; 1-7). Twenty patients (30.0%) did not respond to the treatment and the remaining 6 (10.3%) were evaluated as in MLFS. With a median follow-up of 8.5 months (range; 1-27), the median leukemia free survival of the responding patients was 26.0 months (95%CI: 7.52-44.47). The median OS in the complete cohort was 24.0 months (95%CI: 8.125-39.875). Toxicities-Deaths: Hematologic toxicity was the commonest adverse event in the entire cohort with grade \geq 3: neutropenia reported in 81.6%(52/65), thrombocytopenia in 63%(41/65) and anemia in 63%(41/65). Biochemical TLS was reported in 6/65 (9.2%) patients. Clinical TLS developed in 2 patients, one case with grade 2 and one with grade 4. Infections were observed in 56.9%(37/65) of patients with 32.3%(21/65) being grade \geq 3. Twenty-four deaths were documented with 19 of them being related to AML. There were 3 deaths in patients in CR/CRi (sepsis=2, hepatic encephalopathy=1), one death in a patient in MLFS due to DIC and one due to sepsis in a patient prior to disease response evaluation.

CONCLUSION: The combination of HMA+VEN appears to be effective treatment for patients with newly diagnosed AML ineligible for intensive chemotherapy. Efficacy data in the real-life setting are in accordance with those reported in the clinical trials. Nonetheless, the management of toxicities by close monitoring of the patient and evaluation of possible drug interactions with proper dosage adjustment is of major importance for improving the outcome.

09. MHC-BASED LARGE-SCALE SCREENING FOR ANTI-TUMOR T CELLS IN CHRONIC LYMPHOCYTIC LEUKEMIA REVEALS CD8+ T CELLS WITH SPECIFICITY AGAINST THE CLONOTYPIC B-CELL RECEPTOR IMMUNOGLOBULIN

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OBJECTIVE: T cells in CLL appear selected by restricted antigens, with recent evidence suggesting that the selecting epitopes may lie within the clonotypic B-cell receptor immunoglobulins (BcR IGs). We previously performed ad hoc prediction of putative T-cell class I neoepitopes contained within the clonotypic BcR IGs of CLL patients. Here, we performed major histocompatibility complex (MHC)-based large-scale screening to identify autologous CD8+ T cells recognizing the predicted neoepitopes.

METHODS: We evaluated 653 peptides derived from the clonotypic BcR IGs of 25 CLL patients (median 21 predicted neoepitopes/patient, across 13 MHC-I alleles). Considering the MHC-I typing of each patient, we constructed patient-specific peptide-MHC multimers labeled with a unique DNA barcode plus a fluorochrome (PE). We generated MHC-specific multimer libraries which we then mixed with respective autologous T-cell enriched PBMCs. Duplicate samples/patient were analyzed. In addition, known viral peptide-MHC multimers labeled with a different fluorochrome (APC) as well as three MHC-matched healthy donor PBMCs were used as controls. PE- and APC-positive multimer-binding CD8+ T cells were sorted for each cell sample; subsequently, we performed DNA barcode amplification and sequencing. Sequencing data were processed (Barracoda software) to obtain the number of clonally reduced barcode reads assigned to a given sample and peptide-MHC specificity. The number of clonally reduced reads for a given pMHC specificity was used to estimate the frequency of T cells specific for a given epitope, based on the average number of T cell receptor-MHC multimer interactions detected in the total MHC multimer-binding T cell pool in a given cell sample.

RESULTS: Overall, 3 peptide-MHC multimers were recognized by CD8+ T cells: (i) VTVADTAVYY (peptide A, pA) and (ii) INLNPSLKRR (pB), both within the context of the A03*01 allele, and (iii) YSFTSYWINW (pC) within the context of the A24*02 allele. Peptide A was derived from the IGHV4-34 FR3 region of a somatically hypermutated clonotypic BcR IG, containing a single A to V somatic hypermutation (SHM) at position 96. Peptide B was derived from the IGHV4-39 FR2-FR3 junction of a somatically hypermutated clonotypic BcR IG, containing 3 SHMs (T to I at position 65, Y to L at position 67 and S to R at position 74). Peptide C was derived from the IGHV5-10-1 CDR1-FR2 junction of a clonotypic BcR IG assigned to stereotyped subset #1, containing its sole SHM (S to N at position 40). The immunogenicity of these peptides was further corroborated by the fact that they were recognized not only by the autologous T cells of the patient from whom the peptide was derived, but also by T cells of other patients as well as a healthy donor sharing the respective MHC allele.

CONCLUSION: This study serves as proof of concept that the targeted SHM which shapes the CLL BcR IG repertoire may produce idiotypic targets for T cell-based therapy or for peptide vaccine design. Functional and molecular characterization of the epitope-binding T cells is currently underway by our group, aiming to provide further insight on how these cells could be recruited into effective anti-tumor responses.

10. RISK FACTORS, PREVALENCE, AND OUTCOMES OF INVASIVE FUNGAL DISEASE POST ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN THE ERA OF NOVEL ANTI-FUNGAL PROPHYLAXIS

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OBJECTIVE: Allogeneic hematopoietic cell transplantation (alloHCT) is the only curative option for numerous hematologic disorders. Despite improvements in transplant modalities, invasive fungal infections (IFI) remain an important cause of morbidity and mortality. Therefore, we investigated risk factors of IFI in the era of novel anti-fungal prophylaxis.

METHODS: We retrospectively enrolled consecutive adult patients that underwent alloHCT at our JACIE-accredited center according to standard operating procedures (2013-2022). We defined IFI according to current consensus (2020) and guidance on imaging (2021, EORTC). We analyzed the following factors: age, disease, donor, HLA matching, conditioning, graft, severe acute and moderate/severe chronic GVHD, antifungal prophylaxis, immunosuppressants, IFI type (according to current consensus), galactomannan/ β -D-glucan, cultures, imaging, bacterial/viral infections, IFI treatment, relapse, treatment-related mortality (TRM), overall survival (OS).

RESULTS: We studied 473 allogeneic HCT recipients. Possible IFI was documented in 31/473 at a median of 112 (range 7-1353) post-transplant day, probable in 11/473 (5: positive galactomannan, 6: positive cultures) at 154 (12-469), proven in 10/473 (3: positive galactomannan, 7: positive cultures) at 226 (25-1146) day. Concurrence of bacterial or viral infection was documented in 20/52 and 17/52 patients. Second IFI episode occurred only in 3 patients (1: probable, 2: proven IFI), that succumbed to TRM (1) and relapse (2). During the aplastic period, caspofungin had been administered as primary prophylaxis (41/52) and amphotericin as secondary prophylaxis (11/52), which were then changed to posaconazole and isavuconazole respectively for the immunosuppression period. Independent risk factors for IFI were type of donor (20% in alternative, 12% in unrelated, and 5% in sibling donors, $p=0.006$) and moderate/severe chronic GVHD (15% versus 8%, $p=0.029$). Five-year OS was significantly lower in patients with IFI (46% versus 24%, $p=0.022$). IFI remained a predictor of OS ($p=0.044$), independently of donor type and chronic GVHD.

CONCLUSION: Our large real-world cohort confirms poor outcomes in patients with IFI, despite novel antifungal prophylaxis. High-risk populations, such as alternative alloHCT recipients or chronic GVHD patients may benefit not only from wider application of sensitive mycological testing but also from additional antifungal treatment modalities.

11. EARLY PREDICTION OF COVID-19 OUTCOME USING ARTIFICIAL INTELLIGENCE TECHNIQUES AND ONLY FIVE LABORATORY INDICES

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OBJECTIVE: There is an unmet need of early prediction in COVID-19 outcomes using routine markers. We aimed to develop a risk prediction model for intensive care unit (ICU) hospitalization using artificial neural networks (ANN) and the minimum number of routine laboratory indices.

METHODS: 25 laboratory parameters at first presentation to the Emergency Department (admission) of from 248 consecutive adult patients with COVID-19 were used for database creation and subsequent training and development of the ANN models (200 in the derivation and 48 in the validation cohort). A new alpha-index has been developed the alpha-index to assess the association of each parameter with outcome (ICU hospitalization).

RESULTS: The 248 records from each patient were split in three parts i) 166 (66.94%) used for the training of the computational simulations (training dataset), ii) 41 (16.54%) for documentation of the computational simulations (validation dataset) and iii) 41 (16.54%) for the reliability check of the computational simulations (testing dataset). The first five laboratory indices ranked by importance according to the alpha-index were Neutrophil-to-lymphocyte ratio (NLR), Lactate Dehydrogenase (LDH), Fibrinogen (Fib), Albumin (Alb) and D-Dimers. The best ANN architecture model with only these five laboratory indices achieved accuracy 95.97%, precision 90.63%, sensitivity or recall 93.55% and F1-score 92.06% in prediction of ICU hospitalization, which were verified in the validation cohort. Furthermore, we also found significant and strong associations of these indices with 9 other laboratory indices.

CONCLUSION: Our study reveals for the first time an ANN that can be used in clinical practice to early and accurately predict ICU hospitalization in COVID-19 early in a patient's hospital course using only 5 routine and easily accessible laboratory indices. Given that vaccinations and viral mutations constantly change the landscape of COVID-19, a prediction tool based on such robust variables is of high importance not only to reduce cost of hospitalization, morbidity and mortality, but also to accurately predict patients at high-risk that would benefit from prophylactic or pre-emptive treatments. Lastly, this artificial intelligence approach paves the way for future applications of the novel methodology in other clinical entities.

12. FOURTH VACCINATION WITH THE BNT162 B2 RESTORES SARS-COV-2 HUMORAL RESPONSE IN PATIENTS WITH MULTIPLE MYELOMA EXCLUDING THOSE ON ANTI-BCMA TREATMENT

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OBJECTIVE: COVID19 vaccination leads to a less intense humoral response in patients with multiple myeloma (MM) compared with healthy individuals, whereas the SARS-CoV-2-specific immunity fades over time. Booster doses have been implemented to maintain an adequate antibody response. The purpose of this study was to explore the kinetics of SARS-CoV-2 neutralizing antibodies (NAbs) in patients with MM after vaccination with the BNT162 b2 mRNA vaccine (Pfizer-BioNTech), focusing on their response before and after the fourth vaccination.

METHODS: NAbs were measured at baseline (before the first vaccination), before the second dose, one (M1 P2 D), three and six months after the second dose, before the third dose, one (M1 P3 D) and three months (M3 P3 D) after the third dose, before the fourth dose (B4 D), and one month after the fourth vaccination (M1 P4 D). The second booster shot was provided at 6 months following the first booster vaccination. The Institutional Ethics Committee approved the study. NAbs measurements were performed with GenScript's cPass™ SARS-CoV-2 NAbs detection Kit (GenScript, Inc.; Piscataway, NJ, USA). Statistical analysis was performed with SPSS (v.26) and all comparisons were made at the 5% significance level.

RESULTS: Overall, 189 patients with a median age of 67 years were included, whereas 108 (57.1%) were men. Among them 43 (23%) patients were receiving anti-CD38-based treatment, 9 (5%) were under anti-BCMA-based therapy and 137 (72%) were receiving other combinations. At baseline, no difference in NAbs was found among the three treatment groups. 28 (15%) patients were found positive for SARS-CoV-2 after receiving the third dose and before the fourth vaccination. No significant differences were found in terms of NAbs titer, age, or gender between patients with a history of COVID19 and those without. Overall, the median level of NAbs titer at M3 P3 D were 93.77% (standard error ± 2.28) but declined to 80.0% (± 2.54) at B4 D. However, the median NAbs titer increased to 96.1% (± 2.48) at M1 P4 D. The differences in NAbs between the subsequent timepoints were statistically significant ($p < 0.001$). Interestingly, patients under anti-BCMA therapy had significantly lower NAbs compared to those under anti-CD38 or other treatment at all three timepoints (p -values < 0.001). Gender, age, ISS, and RISS were not found to exert a statistically significant effect on NAbs levels at M3 P3 D, B4 D, or M1 P4 D. Furthermore, the NAbs levels one month after the second, third, and fourth vaccination were also compared for the whole study population. Statistical analyses showed the NAbs titers at M1 P4 D (mean $76.4\% \pm 4.14$) did not differ significantly ($p = 0.062$) with those at M1 P3 D (mean 80.55 ± 3.61) but were significantly higher compared to those at M1 P2 D (mean $61.02\% \pm 3.52$).

CONCLUSION: Booster vaccination with the BNT162 b2 results in substantially improved humoral response against SARS-CoV-2 in patients with MM. Anti-BCMA treatment remains an adverse predictive factor for NAbs response. Controls of similar age and gender at all timepoints (NAbs $\geq 50\%$ seen only in 59.1% at 1 MP3 D) as humoral immune responses are poorer in patients with underlying B-cell hematological malignancies.

13. USE OF A FOAMY-VIRUS VECTOR SYSTEM TO PRODUCE AN 'OFF-THE-SHELF' Fcγ-CR-T CELL PRODUCT FOR THE TREATMENT OF HEMATOLOGICAL AND SOLID TUMOUR MALIGNANCIES

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OBJECTIVE: Novel approaches, such as the use of Fc gamma chimeric receptor (Fcγ-CR)-T cells have expanded the applicability of cell therapies in both solid and liquid tumours with the added benefit of tackling some of the hurdles associated with CAR-T therapies. Previous studies have generated Fcγ-CR-T cells from autologous cells, which carry several limitations (prolonged production time, costly, manufacturing failure), whereas the use of Lentiviral vectors (LV) is endowed with extra limitations (packaging limits and mutagenesis risk). Our group has developed an in-house Fcγ-CR-T cell product, using a safer to LV, foamy virus (FV) vector.

METHODS: We constructed FV vectors expressing the CD16 V158, which has higher Fc binding, and purchased 2nd generation LV vector backbones. T cells were isolated from healthy donors, activated by CD3/CD28 beads and transduced with CD16-CR, LV or FV vectors. Transduction efficiency was assayed by flow cytometry (FCM) on day 3. The human cell lines Raji, Panc01 and DLD-1 were used for functional assays, in the presence of the antibodies (Abs) Rituximab and Cetuximab, respectively. The CR's Ab-binding capacity was assessed, as well as the cell aggregation promoted by the binding of the Ab to the CR. Their cytotoxic effect was evaluated against the CFSE-labelled Raji or DLD-1 or Panc01 cells at different ratios (5: 1, 10: 1) for 18 hours, in the presence of Rituximab (0.1 µg/ml) or Cetuximab (0.1 µg/ml), respectively. The% of live cells was assessed by flow cytometry and calculated as: $[1 - \text{live targets (sample)} / \text{live targets (control)}] \times 100$.

RESULTS: Transduction efficiency ranged from 58.3-69.2% with FV vectors (MOI 3-5) and 85.2-85.9% with LV vectors (MOI 10-20). The median Ab-binding capacity of FV-CD16-CRs was determined to be 68.7% and 71.3%, (n=3) for Rituximab and Cetuximab, respectively, whereas that of LV-CD16-CRs was 72.1 and 76.5, (n=3), respectively. Cell aggregation of effector and target cells was: (i) 32%, 39% and 36% for FV-CD16-CRs and (ii) 26%, 31% and 29% for LV-CD16-CRs, coated with Rituximab and Cetuximab, respectively, and it was specific for the Raji, DLD-1 and Panc01 cells, respectively. Next, we assessed whether CD16-CR-T cells were able to kill target cells in the presence of specific antibodies. Results showed that the FV-CD16-CR-induced% cell lysis was: (i) 26.3% and 51.5%, (ii) 41.5% and 57.7% and (iii) 39.4% and 57.3% at 5: 1 and 10: 1 ratio, in the presence of Rituximab and Raji cells, Cetuximab and DLD1 cells and Cetuximab and Panc01 cells, respectively. For LV-CD16-CRs the respective% lysis was comparable. More importantly, this lysis was shown to be specific (no lysis noted with untransduced T cells) and significantly lower in the absence of the antibodies.

CONCLUSION: Our group has developed for the first time a FV vector for the generation of CD16-CR-T cells, 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 Fcγ-CR-T cells derived from a non-pathogenic viral backbone such as the FV, could be a safe, efficient and affordable alternative to LV-derived vectors for immunotherapy

14. EFFICACY AND RELIABILITY OF T CELL DEPLETED HAPLOIDENTICAL STEM CELL TRANSPLANTATION IN HEMATOLOGIC DISORDERS: A RETROSPECTIVE STUDY

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OBJECTIVE: A promising recent strategy for haploidentical transplantation is the depletion of T lymphocytes based on the selective elimination of T cells by manipulation, which enables a very low incidence of transplantation-related mortality, and graft-versus-host disease (GVHD). It is more expensive than the conventional unmanipulated methods, and further, requires dedicated transplant centers and sufficient stem cell processing facilities which, therefore, results in limited experience and comparison data from the research perspective. This retrospective study aimed to evaluate the relapse, survival, and clinical data of the patients and to analyze the outcomes of the technique.

METHODS: Medical files of patients who underwent haploidentical stem cell transplantation via alpha beta T cell depletion between January 2012 and December 2020 in Medstar Antalya Hospital, Antalya, Turkey were retrospectively evaluated. Inclusion criteria for haploidentical T cell depleted HSCT were i) at least 2 HLA incompatibility, and, ii) a maximum 50% mismatched HLA.

RESULTS: The study included 56 adult patients who underwent haploidentical stem cell transplantation via alpha beta T cell depletion. The median age of the patients at the time of HSCT was 41.5 years (range, 20-70 years); 22 (39.3%) patients were female. After the transplantation, half of the patients (50.0%) needed immunosuppressive drugs and 17.9% of the patients experienced a post-transplant relapse. The mortality rate was 55.4% where transfer-related mortality (TRM) and non-transfer-related mortality (NTRM) were 25.0% and 30.4%, respectively. The 100-day mortality rate was 19.6%. The median overall (OS) days was 1101 days (142-3813 days), whereas the median progression-free OS was 302.5 days (11-2479 days). Being older (age >40), having hypertension, having acute liver involvement, and having systemic fungal infection were found as risk factors that significantly increased mortality (with 3.5-, 2.8-, 3.7-, and 2.7-fold increases, respectively).

CONCLUSION: To conclude, T-cell depleted HSCT is an effective and reliable technique that has the potential to decrease morbidity and improve relapse-free survival for patients requiring unrelated donor transplantation for hematologic malignancy.

15. 19 YEARS' EXPERIENCES OF THERAPEUTIC APHERESIS CENTER OF EGE UNIVERSITY MEDICAL FACULTY

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OBJECTIVE: Therapeutic apheresis is the process of removing the disease-causing substances from the patient's blood.

METHODS: We retrospectively analyzed the therapeutic apheresis procedures performed in our center between January 2003 and April 2022.

RESULTS: In our center, 14077 sessions of therapeutic apheresis were performed on 3935 (1875 men and 2060 women) patients. The median age of these patients is 17.5 (2- 88). 7502 sessions of therapeutic plasma exchange in 1598 patients, 5060 sessions of stem cell apheresis in 2109 patients, 436 sessions of LDL apheresis in 48 patients, 134 sessions of Red blood cell (RBC) exchange transfusion in 46 patients, 670 sessions of photopheresis in 43 patients, 26 sessions of granulocyte apheresis for 12 patients, 160 sessions of leukapheresis in 84 patients, 64 sessions of thrombopheresis in 30 patients were performed. Donor lymphocytes were collected from 8 donors. Twenty-five sessions of double filtration and immune absorption were applied to 5 patients. Central venous catheters (2790 femoral, 159 jugular, 188 subclavian) were used in 3137 procedures, fistula in 242 procedures, and peripheral veins in 613 procedures as vascular access. Peripheral vascular access was used in only 4 patients in photopheresis procedures, and the remaining 39 patients had a catheter. Table 1 shows the number of therapeutic apheresis procedures performed by years.

CONCLUSION: While the number of therapeutic apheresis procedures has increased until recent years, the procedures have decreased with the COVID-19 pandemic. Both hematological and non-hematological indications are increasing. Considering these indications will increase the number of patients benefiting from these treatments.

16. TREATMENT FREE REMISSION (TFR) AFTER DISCONTINUATION OF TYROSINE KINASE INHIBITORS (TKIS) IN CHRONIC MYELOID LEUKEMIA (CML) PATIENTS

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OBJECTIVE: TKI fundamentally improved survival rates of CML patients. Decision of TKI discontinuation may be related to adverse effect, cost, impact on quality of life or even with the decision to conceive. However, this remains a challenge for healthcare professionals. So far, a number of studies have been conducted to demonstrate the possibility of TKI cessation in well responding patients.

METHODS: We retrospectively analyzed the data in 40 CML patients who discontinued TKIs at our institution.

RESULTS: TKI treatment was discontinued in 40 patients, 26 females and 14 males (22 Imatinib, 16 Nilotinib, 2 Dasatinib). Median age at diagnosis was 47 years (9-83). Twelve patients (30%) were receiving their 2nd or 3rd line treatment. All patients achieved complete cytogenetic remission (CCyR), whereas MR4.5 was obtained in 37 patients (93%). Thirty-four patients (85%) discontinued therapy electively due to sustained deep molecular response (DMR), 3 due to intolerance, 1 for financial reasons, 1 due to occurrence of multiple sclerosis and 1 after diagnosis of a secondary cancer. At the time of discontinuation, median MR4.5 duration was 48 months (range 5-163). After a median follow up of 18 months since discontinuation, 15 patients (38%) experienced loss of MMR at a median of 4 months (range 3-24; 4 after 6 months). Patients receiving imatinib, nilotinib and dasatinib lost their response at a rate of 36%, 44% and 0% respectively. Relapse rate for patients with stable MR4.5 for at least 2 years was 38% (12/31), while it was 50% (3/6) for those less than 2 years. All relapsing patients were retreated and 80% (12/15) achieved MMR at a median of 4 months.

CONCLUSION: Our data show that some patients with deep responses (62% from our cohort) can achieve TFR. As retreatment is usually successful after loss of MMR, discrimination of higher risk patients for resistant relapse needs to be elucidated.

17. RARE ASSOCIATION DETECTED IN THE LONG ROAD TO DIAGNOSIS: PRIMARY HYPERTROPHIC OSTEOARTHROPATHY AND MYELOFIBROSIS

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INTRODUCTION: Primary hypertrophic osteoarthropathy (PHO; pachydermoperiostosis) is a rare autosomal recessive disease that develops as a result of prostaglandin-degrading enzyme 15-hydroxy-prostaglandin dehydrogenase (HPGD) deficiency or mutations in the prostaglandin transporter SLC02 A1 gene, impairing prostaglandin metabolism and causing multisystemic involvement. The disease is mainly characterized by hypertrophic skin changes, clubbing, and gradually developing periostosis of the distal bones of the leg and forearm. It has been reported that myelofibrosis can be seen in the form that develops with mutations in the SLC02 A1 gene

CASE REPORT: 28-year-old male patient; He applied with the complaints of swelling in the knees, wrists and ankles, excessive sweating and thickening of the skin, droopy eyelids, weakness, and abdominal pain, which started to be noticed by the age of 22 and progressed over the years. The patient's parents were not related and they had no history of the disease. It was learned that the patient had been under investigation for intermittent anemia and spleen enlargement for about 10 years, and vitamin B12 and folate deficiency were detected, but the etiology could not be determined. On physical examination, the patient was pale, his facial skin was very thick and with acne, his facial features were coarse, and he had bilateral blepharoptosis with deep lines on the forehead, thickening and curving of the scalp (cutis verticis gyrata) (Figure 1). His knees, wrists, and ankles were enlarged, and clubbing was present in his fingers (Figure 1). Sign of arthritis wasn't detected. On abdominal examination, the liver was palpable 4 cm below the rib and the spleen extended into the left inguinal region (Figure 1). Peripheral smear revealed pancytopenia (wbc: $3,79 \times 10^9/L$, neu: $2960 \times 10^9/L$, hb: 7 g/dl hct: 22.4%, mcv: 87 plt: $64 \times 10^9/L$) in hemogram, and leukoerythroblastosis and diffuse tear cells in erythrocytes were observed. Bone marrow aspiration was dry-tap, increased imprint and dysplastic megakaryocytes were seen. Bone marrow biopsy was hypocellular and consistent with myelofibrosis. JAK2 V617 F and JAK2 exon 12 gene mutations weren't detected. Cortical thickening in the long bones was seen in bone X-ray (Figure 2). In the whole body bone scintigraphy, diffusely increased activity uptakes were observed in the periosteal region of both tibia and two femoral diaphysis, and the findings were found to be compatible with hypertrophic osteoarthropathy.

CONCLUSION: PHO is a rare autosomal recessive disease with multisystemic involvement. The exact incidence of the disease is unknown, and the disease is usually self-limited without affecting survival. It stabilizes and even resolves, on average, ten years after the first onset of symptoms. However, patients may encounter significant comorbidities such as bone marrow fibrosis and compressive neuropathy. Primary HOA is usually treated symptomatically with non-steroidal anti-inflammatory drugs (NSAIDs) and plastic surgery. Although theoretically increased PGE2 plays a role in the pathogenesis of PHO and NSAIDs are potent prostaglandin inhibitors; NSAIDs do not cause regression of skeletal findings in patients. Treatment is difficult in patients who develop myelofibrosis and there is no effective treatment method. It has been shown on a case-by-case basis that corticosteroids can reduce transfusion dependence in this patient group in which classical JAK stat inhibitors do not work.

18. A RARE NEPHROTIC SYNDROME ASSOCIATED WITH CHRONIC LYMPHOCYTIC LEUKEMIA: FOCAL SEGMENTAL GLOMERULOSCLEROSIS

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INTRODUCTION: Although autoimmune complications occur in approximately one quarter of chronic lymphocytic leukemia (CLL) cases, non-hematological autoimmunity is very rare. Glomerulonephritis, angioedema and paraneoplastic pemphigus are among the non-hematological autoimmunities most clearly associated with CLL. Focal segmental glomerulosclerosis (FSGS) associated with CLL has been addressed with limited case reports in the literature and is a condition with little experience.

CASE REPORT: An asymptomatic 61-year-old female patient was referred with the findings of lymphocytosis and lymphadenopathy detected during her routine controls. In his physical examination, no additional findings were found except for pathological lymphadenopathies in the neck and axillary region. Laboratory findings revealed leukocytes 18200/mm³, lymphocytes 12700/mm³. Platelets and hemoglobin levels and other biochemical tests were normal. Increased uniformity of mature lymphoid cells and basket cells were observed in the peripheral smear. At the flow cytometry of peripheral blood, CD5+/CD19+/CD23+ association was found to be 79% in the lymphoid population, and the patient was diagnosed with Rai stage 1/Binet stage B CLL with the present findings. Although the patient's lymphocyte level increased to 18000/mm³ in the 20-month follow-up, for whom a drug-free follow-up was decided, there was no additional laboratory change. However, newly developed pretibial edema was detected. Kidney biopsy was performed from the patient who was found to have 1.2 g/24 h proteinuria, mostly albumin, and serum albumin 3.6 g/dl in the examinations. Global sclerosis was present in 6 of the 11 glomeruli observed in the biopsy, and segmental sclerosis was present in the other glomeruli. In addition, mild chronic inflammation in the interstitial area, moderate fibrosis, prominent medial hyalinization of the vessels and atrophy of the tubules were present. In direct immunofluorescence, there was no accumulation of IgA, IgG, IgM, C3, C1 q, C4, Fibrinogen, Kappa and Lambda, and amyloid was negative. The patient's creatinine value was normal in the last 2 months during the technic period, but proteinuria increased to 3.4 g/24 hours. Although Rai stage 1/Binet stage B continued, 6 cycles of fludarabine, cyclophosphamide, rituximab (FCR) combination therapy was planned for the patient who was considered to have secondary FSGS due to underlying malignant disease. Proteinuria decreased to 1.1 g/24 hours after the first cycle and completely disappeared after the third cycle. In the 6 th year of his treatment, the patient continues to be followed-up, both with a complete response in terms of CLL and without any kidney problems, including proteinuria.

CONCLUSION: Glomerulonephritis are rare conditions in the course of hematological cancers. FSGS is the least reported glomerulonephritis among the renal lesions associated with hematological malignancies, and has been most frequently demonstrated in patients with Hodgkin lymphoma. Although membranoproliferative and membranous glomerulonephritis are more common with CLL, its association with FSGS has been reported in only 5 cases, as far as we can detect in the literature. It was thought that the FCR regimen containing agents that can be used in FSGS, which is still an effective treatment in young patients with IGHV mutated, without 17 p deletion or TP53 mutation, may be a good option for CLL-related FSGS.

19. GLOFITAMAB IN RELAPSED/REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA: REAL WORLD DATA

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OBJECTIVE: Glofitamab is a T-cell-engaging bispecific antibody connecting CD20 on B cells and CD3 on T cells. In Phase II expansion study, the ORR was 51.6% and CR rate was 39.4% in R/R DLBCL patients (Dickinson et al. JCO2022). In this retrospective study, we aimed to report the outcomes of patients who used glofitamab via compassionate use in Turkey.

METHODS: Glofitamab is available via compassionate use in Turkey for patients >18 years and with R/R DLBCL, transformed FL and PMBCL who had received 3 lines of treatment previously. Patients received 1000 mg obinutuzumab 7 days prior to first dose of glofitamab. Glofitamab was given intravenously at a fixed dose 2.5/10/30 mg on C1 D1G8, and then at the target dose from C2 D1 q3 w, for up to 12 cycles. Response rates are based on Lugano criteria (Cheson et al. JCO2014). Response evaluations were done by FDG PET/CT after the 2nd-4th cycles at the discretion of the treating physician.

RESULTS: As of July 1st, 2022, 46 patients used Glofitamab on compassionate use. The results of 42 pts who at least used glofitamab once are represented here. Median age was 54.5 (range: 20-81) years, 64.3% were male, and the median lines of prior therapies was 4 (range: 3-6). Except 2 patients who had tFL, the rest 40 patients had DLBCL (Table 1). The patients received median 4 cycles (1-12) of Glofitamab. Seven patients (16,7%) died before response assessment. In efficacy-evaluable patients, the ORR was 28.5%(12 pts) and the CR rate was 19%(8 pts). While, 3 patients (7.1%) had SD, 47.6% of patients (n=20) had PD. A total of 5 patients proceeded to SCT (3 AlloSCT, 2 ASCT). The most common toxicities were hematological; neutropenia was observed in 41.5% of patients and in 23% it was ≥grade 3, anemia was observed in 38.1% of patients and in 19% it was ≥grade3, thrombocytopenia was observed in 28.6% of patients and in 19% it was ≥19%. Cytokine Release Syndrome(CRS) was encountered in 12 patients (28.6%), in 4 patients it was ≤grade2 but in the rest 4 patients it was ≥grade3. Neurological toxicity was observed in only 3 patients(all≤grade2). We were in the COVID19 pandemic era and 9 patients (21.4%) had COVID19 infection during treatment. The median follow-up was 5,78 months (range: 0,30-14,19). The median OS was 7 months (95% CI: 4.02-10.03) (Figure 1). Seventeen patients were alive and 25 patients had died at the time of analysis (PD n=14, COVID-19 n=5, sepsis n=3, AlloSCT-related complications n=2, unknown n=1).

CONCLUSION: To our knowledge, this is the largest real world data on the effectiveness and toxicity of Glofitamab treatment in R/R DLBCL patients. The response rates are lower comparing to Phase I study, but our cases were more heavily pre-treated and more than half of the patients had received ASCT previously and were refractory to first-line therapy. Seven months median OS seems to be promising in this heavily pretreated group and moreover 5 patients (12%) who died due to COVID19 infection and 2 patients who died due to transplantation related complications after AlloSCT should also be considered.

20. CENTRAL NERVOUS SYSTEM RELAPSE IN PATIENTS WITH PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA: INCIDENCE AND RISK FACTORS IN THE RITUXIMAB ERA

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OBJECTIVE: Central nervous system relapses (CNSR) are uncommon in primary mediastinal large B-cell lymphoma (PMLBCL) with a reported incidence of 2.3-3.8% in the Rituximab era. Clinical risk factors for CNSR have been recognized in diffuse large B-cell lymphoma (DLBCL), but may not be applicable in PMLBCL, a pathobiologically distinct entity. To evaluate the incidence of first CNSR events without prior systemic progression and explore prognostic associations with baseline characteristics, CNS-IPI, and induction immunochemotherapy.

METHODS: This is a multinational, retrospective study of 596 PMLBCL patients treated with immunochemotherapy±radiotherapy (R-CHOP 59%, DA-EPOCH-R 41%) between 2000 and early 2022. The cumulative incidence of first CNSR (CI-CNSR) was estimated considering the competing risks of death from any cause or prior systemic disease relapse/progression.

RESULTS: Baseline characteristics were: Median age 32 (16-85), females 64%, stage III/IV 16%, ≥ 2 extranodal sites 11%, performance status (PS) ≥ 2 17%, elevated LDH 83%, IPI ≥ 2 29%, CNS-IPI 4-6 6%, any serositis 43%, kidney involvement 4.2%, adrenal involvement 2.4%, kidney and/or adrenal involvement 5.4%. Only 17 patients (2.9%) received CNS prophylaxis [high-dose methotrexate (HD-MTX) 9, intrathecal MTX \pm other 7, both 1]. Kidney and/or adrenal involvement was highly correlated with advanced stage, ≥ 2 extranodal sites and high CNS-IPI (4-6) ($p < 0.001$), with the vast majority of the latter also having kidney and/or adrenal involvement. With a 55-month median follow-up [interquartile range (IQR) 32-97 months], all 10 first CNSR events (9 isolated and 1 associated with systemic relapse) were recorded within 2 years of diagnosis [median time 7.5 months, IQR 6-8, range 5-13 months], for a 2-year CI-CNSR of 1.78% (95%CI 0.9-3.2%). Two of 10 CNSR cases had received CNS prophylaxis with HD-MTX. All CNSR were parenchymal and only 2/8 were successfully salvaged (2 still under treatment). Four patients with CNSR had kidney involvement (plus adrenal in 2/4). Two of seven patients with both kidney and adrenal involvement and 2/17 with kidney infiltration only relapsed in the CNS. Kidney [subhazard ratio (SHR) 15.4, $p < 0.001$], adrenal (SHR 13.6, $p = 0.001$), any kidney or adrenal involvement (SHR 12.5, $p < 0.001$), and high CNS-IPI (4-6, SHR 13.0, $p < 0.001$) were associated with CNSR in univariate analysis. All 4 patients with high CNS-IPI who experienced CNSR (out of 35), had also kidney and/or adrenal involvement. Looser but significant associations were observed with IPI ≥ 2 (SHR 6.3, $p = 0.009$), advanced stage (SHR 5.5, $p = 0.007$), PS ≥ 2 (SHR 6.6, $p = 0.005$), and ≥ 2 extranodal sites (SHR 5.4, $p = 0.009$) but not chemotherapy backbone (R-CHOP or DA-EPOCH-R), CNS prophylactic therapy, age, gender, B-symptoms, LDH elevations, serositis or PMLBCL-specific prognostic indices (stage IV/ extranodal plus bulky or high LDH ≥ 2 x).

CONCLUSION: In PMLBCL, CNSR is rare and appears to be primarily associated with kidney and/or adrenal involvement. CNS-IPI is also strongly prognostic but highly correlated with kidney and/or adrenal involvement. No late (> 2 years) occurrences were seen and 9/10 relapses were isolated in the CNS. No inferences regarding the value of primary CNS prophylaxis can be made. Even in this very large series multivariate is not reliable due to the small number of events. A larger multinational effort is warranted.

21. EVALUATION OF SAFETY PROFILE OF RITUXIMAB+LENALIDOMIDE PROTOCOL IN FRAIL ELDER RELAPSED/REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA PATIENTS

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OBJECTIVE: In our knowledge, there is no standardized treatment for frail elder relapsed or refractory (R/R) diffuse large B cell lymphoma (DLBCL) patients. Chemo-free regimens have promising results with acceptable toxicity profile. We aimed to evaluate safety profile and adverse reactions of rituximab+lenalidomide (R2) protocol in elder DLBCL patients.

METHODS: Five patients who had R/R DLBCL and were ineligible for autologous stem cell transplantation between December 2020- March 2022 included in our study. Age, sex, ECOG performance status (PS), Cumulative Illness Rating Scale-Geriatric (CIRS-G). R2 protocol was planned as rituximab 375 mg/m² D1+ lenalidomide 5-20 mg D1-21 for 6 cycles. Response assesment was performed by PET/CT according to Lugano criterias. Cytopenias, infectious complications, gastrointestinal or skin reactions of individuals were reported.

RESULTS: Median follow up after first relapse was 14 months (2-22 months). Response assessment could not be done as one patient could not complete 2 nd cycle an done patient could not be visited as he suffered from cardiopulmonary prolonged comorbidities. 3 patients were detected stage 4 B, 1 of stage 2 B and 1 of 1 B. 3 of 5 patients had also extranodal involvement. Median CIRS-G score of individuals was 15 points (10-17) and ECOG PS was 2. 4 patients were initiated asetilsalisilic acid prophylaxis and 1 patient was already under proplaxis of rivaroxaban due to venous thromboembolism history. Lenalidomide dose reduction required for 3 individuals due to grade 3 cytopenias. 3 patients had infectious complications (2 acquired community pneumonia 1 urinary tract infection) but all of them were managed as outpatient. 1 patient had gastrointestinal side effect. None of the patient had thromboembolic event. 2 of 5 patients was reported as partial response (PR) and 2 of them were refractory to R2 protocol. One patient was detected early relapse after PR. 2 patients died due to progressive disease.

CONCLUSION: R/R DLBCL management especially in elder patients is challenging due to clonal evolution or addition of new mutations that cause drug resistance. Thus, fraility of patients, polypharmacy and increased side effects are major causes of low response rates. In our study, R2 protocol was evaluated as well tolerated with well designed supporting treatments. In conclusion, R2 combination seems to be promising alternative protocol with manageable toxicity profile and acceptable response rates.

22. A CASE WITH CD30-POSITIVE DIFFUSE LARGE B CELL LYMPHOMA

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INTRODUCTION: Diffuse Large B-Cell Lymphoma (DLBCL) is the most common type of Non-Hodgkin Lymphoma in adults. Addition of Rituximab (anti CD20 monoclonal antibody) to the classical CHOP protocol resulted in a significant increase in survival. Although CD30 has been identified as a surface marker of Reed Stenberg cells, it can also be expressed by non-Hodgkin lymphoma subtypes such as DLBCL. Although the prognostic importance of CD30 positivity in DLBCL is not yet known, it paves the way for alternative treatment methods.

CASE REPORT: A 65-years-old female patient who had been followed up with the diagnosis of diabetes mellitus was examined for B symptoms and DLBCL was diagnosed by tru-cut biopsy taken from nodular lesion measured 6 cm in long axis in the lower lobe of the right lung. The patient, who was stage 4 B in Ann-Arbor Staging and was in high-risk group according to the International Prognostic Index (IPI), was given 6 courses of rituximab, cyclophosphamide, doxorubusin, vincristine (R-CHOP) regimen. Positron Emission Tomography / Computed Tomography (PET / CT) scan was performed at the end of the treatment, and it was evaluated as complete response. The patient, who was followed up at three-month intervals, presented with the complaint of 4 kg loss in 1 month in the 2 nd year follow-up. In the whole body computed tomography of the patient, lymph nodes with the largest 2.7 x1.6 cm in size were detected in the mediastinal, abdominal and left inguinal regions. The excisional biopsy from the inguinal region was reported as follicular lymphoma grade 3 b. The patient was evaluated as Ann Arbor Stage 4 B, FLIPI score of 5 in high-risk group with PET/CT scan and examinations. Autologous stem cell transplantation was planned after salvage therapy with ESHAP protocol. Ibrutinib 560 mg/day treatment was started due to the decrease in the performance of the patient who had H1 N1 infection while receiving salvage therapy. After six courses of ibrutinib treatment, progressed lymph nodes were detected in the control PET/CT imaging and the patient was diagnosed with CD30 + DLBCL with excisional biopsy from the inguinal lymph node. The patient was started on brentuximab 1.8 mg/kg and bendamustine 70 mg/m². Treatment and follow-up of the patient have been continued in our clinic.

CONCLUSION: CD30 expression can be detected in 30% of DLBCLs. While minor and focal CD30 expression is detected in the vast majority of cases, strong and diffuse expression is rarely observed. CD30 expression is expected more frequently in young patients with DLBCL who have a low IPI score and whose DLBCL originated from the non-germinal center. Although our case was advanced age and in advanced stage, CD30 positivity was detected and targeted therapy was administered.

23. THE PROGNOSTIC SIGNIFICANCE OF SERUM BETA-2 MICROGLOBULIN (SB2 M) LEVELS IN PATIENTS WITH HODGKIN LYMPHOMA (HL): FINAL ANALYSIS ON 915 PATIENTS TREATED WITH ABVD OR EQUIVALENT (ABVDEQ) CHEMOTHERAPY OR COMBINED MODALITY THERAPY (CT/CMT) FOCUSING TO THE DETERMINATION OF OPTIMAL CUT-OFFS

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OBJECTIVE: Serum beta2-microglobulin ($\beta 2$ m) is a well- established prognostic factor for several hematologic malignancies, but its role in HL is still controversial. We aimed to investigate the prognostic significance of $\beta 2$ m levels in a large series of homogeneously treated HL patients.

METHODS: We analyzed 915 patients with HL treated with ABVDeq (1990-2019) and selected solely based on the availability of pretreatment $\beta 2$ m levels. $\beta 2$ m levels (upper normal limit 2.4 mg/L) were analyzed in relation to other baseline features and the outcome. Freedom From Progression (FFP) was defined as time between treatment initiation and treatment failure (toxic death, primary refractoriness, PR with switch to alternative chemotherapy or relapse); deaths of unrelated causes were censored. Overall Survival (OS) and Disease-Specific Survival (DSS) were measured from treatment initiation to death of any cause or HL-related causes respectively. Sequential cut-offs (1.8-3.5 by 0.1 mg/L increments) were used to explore the potential impact of $\beta 2$ m on outcomes.

RESULTS: The median serum $\beta 2$ m levels were 2.20 mg/L (IQR 1.80-3.00, range 0.50-14.40) and 383/915 patients (42%) had elevated levels (>2.4 mg/L). $\beta 2$ m correlated strongly with all baseline features. Univariate Analysis: FFP was significantly inferior in patients with higher $\beta 2$ m at all tested cut-offs. At 2.4 mg/L ("normal versus high") the 10-year FFP was 80% vs 70% ($p=0.001$) after a median follow-up of 81.1 months. However, the best cut-off was 2.0 mg/L [10-year FFP 83% vs 70% ($p=0.001$)]. A dose-response relationship was seen across quartiles Q1-4 with 10-year FFP 84%, 78%, 73% and 68% ($p=0.001$). In early stages (IA/IIA), statistically significant results were obtained at cut-offs between 1.8 and 2.1 mg/L. The best cut-off was 1.9 mg/L [10-year FFP 88% vs 78% ($p=0.003$)]. In advanced stages, none of the cut-offs yielded statistically significant results (borderline at 2.0 mg/L; 10-year FFP 74% vs 64%, $p=0.09$). Multivariate Analysis: $\beta 2$ m levels remained significant for FFP after adjustment for IPS factors, ESR and B-symptoms at 2.0 mg/L [haz-

ard ratio (HR) 1.55, $p=0.01$) in the whole series of 915 patients; it was not significant at the "normal versus high" comparison at 2.4 mg/L. In early stages, s β 2 m was a significant predictor of FFP at both cut-offs of 2.0 mg/L and 2.4 mg/L (HR 1.65, $p=0.034$ and 1.67, $p=0.038$). In advanced stages, s β 2 m was an independent prognostic factor for FFP at 2.0 mg/L (HR 1.44, $p=0.098$ despite the lack of univariate significance), but not at 2.4 mg/L. The 10-year OS and DSS was lower in patients with elevated β 2 m levels (10-year rates 90% vs 77%, $p<0.001$ and 93% vs 86%, $p=0.002$). Similar results to FFP were obtained by multivariate analysis of DSS for all 915 and early-stage patients.

CONCLUSION: Higher s β 2 m was a significant independent predictor of FFP in HL but the optimal cut-off appears to lie within the normal limits, performing better than a "normal versus high" evaluation (cut-off 2.4 mg/L) and being 2.0 mg/L for the whole series and 1.9 mg/L for early-stage patients. The prognostic significance in advanced stages was weaker (best cut-off 2.0 mg/L). Serum β 2 m was also highly predictive of OS and DSS. An analysis of corrected serum β 2 m according to renal function is ongoing.

24. A RARE PARANEOPLASTIC CONDITION IN HODGKIN LYMPHOMA; EVANS SYNDROME

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INTRODUCTION: Evans syndrome (ES) is a spectrum of diseases in which the combination of autoimmune hemolytic anemia and immune thrombocytopenia or sometimes neutropenia. ES has been accepted usually as an idiopathic condition, but it may be secondary. The coexistence of autoimmune cytopenias and Hodgkin lymphoma (HL) is rarely observed and the rate of ES in HL patients is not clear.

CASE REPORT: A 56-year-old male patient presented with fatigue, lower back pain, loss of appetite, and eruption, particularly in the abdominal region. The patient, who experienced weight loss as a B symptom, had no history of recent infection. Upon physical examination, lymphadenopathies of approximately 2 cm were detected in the bilateral axillary and right inguinal regions, with diffuse petechiae and purpura throughout the body. According to laboratory tests, hemoglobin was 6.5 g/dL, platelets were $11 \times 10^3/\text{mm}^3$, reticulocytes were 9.9%, lactate dehydrogenase was 518 U/L (normal range <248), sedimentation was >140 mm/hour. Some increases in spherocytes and true thrombocytopenia were observed in peripheral smears. Immunoglobulin G +3 was detected by the direct anti-human globulin test and +2 positivity with AHG and +4 positivity with enzyme by the indirect anti-human globulin test. There was no monoclonal gammopathy based on immunofixation electrophoresis, and other autoimmune and viral tests were negative. A diagnosis of ES was made for the patient who had autoimmune hemolytic anemia and concomitant immune thrombocytopenia. In FDG-PET/CT involvement with high SUVmax values in the pathological size was observed in the mediastinal, axillary, intra-abdominal, and inguinal regions and in the form of diffuse lymph nodes and the spleen. The patient was diagnosed with stage 3 B classical-type nodular sclerosing HL by excisional lymph node biopsy of the right inguinal region. Methylprednisolone treatment was started 1 day later, as treatment response might be delayed in a patient for whom the ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) protocol was started. Following administration of 250 mg/day for the first 3 days, continuation of 1 mg/kg/day methylprednisolone treatment was planned. However, the patient had a platelet count of $3 \times 10^3/\text{mm}^3$ and mucosal bleeding, and intravenous immunoglobulin (IVIG) treatment at 1 g/kg/day for 2 days was given 5 days after ABVD. The platelet value increased to $67 \times 10^3/\text{mm}^3$ at 4 days after IVIG. Steroid treatment was discontinued for this patient, who was given 10 days of steroids, and ABVD treatment response was awaited. His hemoglobin level to 9.5 g/dL and his platelet level to $101 \times 10^3/\text{mm}^3$ before the first course on the 15 th day of ABVD treatment; his skin lesions resolved completely, and hemolysis parameters regressed during follow-up. Hemolysis status and thrombocytopenia did not recur after ABVD treatment.

CONCLUSION: The coexistence of autoimmune cytopenias and HL is rarely observed, and according to previous reports, it is encountered in approximately 0.5-4.2% of HL patients. In contrast, the rate of ES in HL patients is not clear; to our knowledge, 16 patients have been reported in the literature. Response rates to treatment are variable and response to treatment may be poor, particularly with underlying conditions. If detected, the underlying lymphoma should be treated.

ABSTRACTS
POSTER PRESENTATIONS

P1. UNRAVELLING IMMUNE CHECKPOINT INHIBITORS CARDIOTOXICITY. EARLY SIGNS OF ENDOTHELIAL ACTIVATION, INCREASED AUTOPHAGY AND INFLAMMATION

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OBJECTIVE: Immune checkpoint inhibitors (ICIs) are novel immunotherapeutics with profound anti-cancer efficacy and severe immune-related adverse effects (irAEs). Cardiotoxicity, is among the most life-threatening irAEs, often under-evaluated in ICI-treated patients and lacks of evidence-based clinical management. Therefore, the discovery of a prophylactic therapy against ICI-related cardiotoxicity remains an unmet clinical need. Herein, we investigated the cardiotoxic effects of ipilimumab (IPI, anti-CTLA-4), pembrolizumab (PEM, anti-PD-1) and avelumab (AVE, anti-PD-L1) in vitro and established an in vivo model of ICI-related cardiomyopathy

METHODS: Primary murine cardiomyocytes (mAVCs) and spleenocytes were isolated from C57 BL6/J male mice and were incubated with IPI, PEM and AVE at a concentration range of 0-100 µg/ml for 24 h. ICI-conditioned media from spleenocytes were transferred onto mAVCs for additional 24 h. Cell viability was assessed by MTT assay. Human (hu-PD-1) and Murine PD-1 (muPD-1) extracellular domains (ED) were biotechnologically produced and PEM binding was assessed by circular dichroism (CD) and in silico docking experiments. In order to generate a PEM-induced cardiomyopathy in vivo model, C57 BL6/J male mice were randomized into i. Control (IgG4, 2 mg/kg) and ii. PEM (2 mg/kg) (n=9/group) groups and treated for 5 weeks. IgG4 and PEM were administered once weekly intraperitoneally, while PEM dose was directly translated from human dose. Mice underwent weekly echocardiography analysis and blood sampling, while at the end of the experiments, mice were sacrificed for blood and myocardial sampling and histology, flow-cytometry and molecular analyses. Since we observed an early PEM-induced cardiotoxicity after 2 weeks, the in vivo experiment was repeated for 2 weeks (n=5/group) and mice underwent the same interventions

RESULTS: Only IPI led to cytotoxicity in primary spleenocytes, and was therefore excluded from the study. PEM and AVE did not induce any direct cytotoxicity on mAVCs, whereas incubation of mAVCs with PEM and AVE conditioned media, revealed that only PEM could induce Immune cell (IC)-dependent cytotoxicity at 50 and 100 µg/ml. PEM increased Tnfa, Inos, Rela, Ifng mRNA expression in spleenocytes and Tnfa, Tgfb, Inos, Rela, Ifng as well as autophagy markers Lc3 b, Lc3 a, Becn2, Atg5 and Endoplasmic Reticulum (ER) stress markers Canx and Ddit3 in the mAVCs. CD and in silico experiments revealed that PEM binds on the muPD-1 ED similarly to the huPD-1 ED

(positive control), which supports the translational value of the murine model. In vivo, PEM decreased Fractional Shortening% (FS%) after 2 weeks an effect exacerbated after 5 weeks of treatment. Intramyocardial IC infiltration, myocardial fibers' atrophy and a significant increase in Lys6 Clow monocytes in the heart and blood and in circulatory T-cells was observed in PEM group at 5 weeks. Molecular analysis revealed that PEM increases myocardial ICAM-1 and iNOS expression after 2 weeks showing early endothelial activation and increases E-selectin, ICAM-1 and autophagy (LC3 B, Beclin-1), ER stress (Bip) and inflammation markers (STAT3 phosphorylation, IL6 and IFN- γ) expression after 5 weeks of administration.

CONCLUSION: PEM induces IC-dependent cytotoxicity on primary mAVCs via induction of inflammation, autophagy and ER-stress, whereas it induces cardiotoxicity via FS% decrease, early signs of endothelial activation and subsequent establishment of inflammation and autophagy in the myocardium.

P2. SWEET SYNDROME IN A PATIENT WITH MYELODYSPLASTIC SYNDROME

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INTRODUCTION: Hematological Malignancies can be complicated by dermatological manifestations and clinicians should keep this in mind. A case of a patient with Myelodysplastic Syndrome complicated by Sweet Syndrome is presented.

CASE REPORT: A 61 year old women with a history of ovarian cancer diagnosed thirteen years ago and Myelodysplastic Syndrome diagnosed 9 months ago was admitted to the Hematology Department because of fever, skin lesions and pancytopenia. Erythematous Skin lesions mostly in lower extremities were present for the past ten days. The lesions were painful and ulcerated. New lesion in legs, arms and head developed during the next 24 h after her admission. The patient was treated with full spectrum antibiotics a dermatological and hematological evaluation followed. The skin biopsy was consistent with Sweet syndrome. The hematological evaluation confirmed the presence of high risk Myelodysplastic syndrome, with excess blast and complex karyotype (5, 7, 17) and loss of T53 gene. The MDS is considered secondary to alkylating agents for the ovarian cancer. Treatment included methylprednisolone 32 mg and azacytidine 75 mg/m² for 7 days. Transfusions of RBC and platelets were given accordingly. The following days the patient had thoracic pain and a CT scan findings were nodule infiltrations, ground glass and tree in bud pattern in both lungs Skin lesions gradually improved and fever stopped. An attempt to taper the methylprednisolone doze was complicated with fever and new skin lesions. A lung CT scan a week later was almost normal. The patient is continuing her treatment for MDS and receives also 20 mg of methylprednisolone.

CONCLUSION: Sweet syndrome (acute febrile neutrophilic dermatosis) is a rare disease. Most of the cases are idiopathic, but it has been associated with drugs and malignancies. It can cause systemic symptoms and rarely leads to organ failure. Diagnostic criteria have been set for the classic form (von de Driesch) as well as the drug induced (Walker and Cohen). It has been associated with infections, pregnancy, drugs, autoimmune diseases, solid tumors and hematological malignancies. Reports on pathogenesis of SS describe it as complex and multifactorial. In myeloid malignancies the disease itself creates the proper environment for neutrophil adhesion and inflammation. Genetic predisposition has been reported in a few cases. Acute myeloid leukemia and Myelodysplasia are the most common hematologic malignancies associated with SS. Skin lesion should be differentiated form other causes in these patients (eg leukemia cutis). Treatment used in those patients (eg GCSF, ATRA, FLT3 inhibitors) have been reported to induce SS as a paraneoplastic manifestation. Azacitidine has been reported as an inducer of SS as well as a therapeutic approach to MDS patient with SS because of its effect on regulatory T cells. Nevertheless SS should be included in differential diagnosis of skin lesions in these fragile patients and treated accordingly. Patients with no history of hematologic malignancy and SS should be in close monitoring as it can herald the diagnosis of a blood disorder.

P3. CD20 (+) ACUTE LYMPHOBLASTIC LEUKEMIA AND THE ROLE OF RITUXIMAB

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OBJECTIVE: Important progress has been made in the treatment of pediatric acute lymphoblastic leukemia (ALL) in the past years. However, this has not been achieved in the adult ALL setting, where long-term remission often remains an unreach goal. A percentage of B-ALL leukemic cells express the CD20 surface antigen which has been associated with a worse prognosis for these patients. Adding anti-CD20 monoclonal antibody to the standard chemotherapy regimens has been reported to improve the outcome both at diagnosis or the refractory/relapsed setting. The aim of this study was to examine the impact of anti-CD20 targeted therapy in a group of 224 ALL patients, retrospectively studied in our center

METHODS: There were 63 patients with T-ALL and 161 with B-ALL and 69 of them had a CD20 (+) phenotype at diagnosis. The median age was 28 (14 - 79) years, in thirty-seven the diagnosis was pre-B ALL whereas ten had mature ALL. Fifteen patients were Ph(+) and 18 presented with WBC>30000/UL

RESULTS: No statistical difference was found between CD20 (+) and CD20 (-) patients in terms of remission and survival rates: 5-year DFS was 40.3% and 41.9% (p=0.7) and 5-year OS was 50% and 47.9% (p=0.3), for CD20 (+) and CD20 (-) respectively. Twenty-four of 69 CD20 (+) patients received 4-8 doses of the anti-CD20 monoclonal antibody rituximab with their standard chemotherapy regimen. There was only one hypersensitivity reaction during rituximab infusion. Complete remission was achieved in all of the patients, with the majority (15/24, 62.5%) achieving an early remission. Relapse was seen in 17/43 (39.5%). The addition of rituximab did not offer any survival benefit in our patient group: 5-year DFS was 47% vs 42% (p=0.78) and 5-year OS 49% vs 60.4% (p=0.67) in patients receiving or not rituximab respectively. Multivariate analysis revealed as significant factors for OS younger age, LDH and early remission. In conclusion and in contrast with the literature, no survival disadvantage was found for our group of CD20 (+) patients. In addition, rituximab infusion failed to prove significant advantage in both remission induction and patients' survival

CONCLUSION: Treatment outcome remains suboptimal for adult ALL patients compared to children. The use of intensive, pediatric-inspired treatment protocols in combination with novel targeted agents are expected to improve survival in adults with ALL.

P4. AN ACUTE MYELOID LEUKEMIA CASE WITH MULTIPLE GENETIC FACTORS

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OBJECTIVE: Acute myeloid leukemia (AML) is a cancer of the myeloid line of blood cells, characterized by the rapid growth of abnormal cells that build up in the bone marrow and blood and interfere with normal blood cell production. Our patient is a 44 years old male patient with no known diagnosed illness before. In July 2021 he was diagnosed with AML due to acute leucosis, deep vein thrombosis and thrombophlebitis. He was treated with 7+3 then HiDAC chemotherapy regimens after then in October 2021 an allogeneic bone marrow transplant from his brother was performed. After 3 months of remission he went to hospital with fever and cough. We saw acute leucosis in hemogram. We performed a blood smear which was 44% blast cells reported. After then we diagnosed our patient with relapsed AML. In our patient's genetic tests FLT-3 negative IDA positive IDH positive and CEBPA was positive. Additionally in karyotype trisomy 8 is seen. With all this information we want to discuss genetic prognostic factors of acute myeloid leukemia.

METHODS: a retrospective case record review study

RESULTS: Mutations in FLT3 (Fms-like Tyrosine Kinase 3) are the most common mutation in AML, nearly 33% of newly diagnosed patients have mutation on it. FLT3 internal tandem duplication mutations (FLT3-ITD) are associated with increased relapse and inferior overall survival. But our patient was negative for FLT3-ITD despite that he was relapsed disease. CEBPA (CCAAT Enhancer Binding Protein) is a transcription factor which is used in neutrophil differentiation. It is found in 10% of AML. Only isolated biallelic mutation (mean both N and terminus included) of CEBPA is associated with better prognosis. Monoallelic mutation doesn't show any difference for prognosis according to recent meta-analysis. Our patient was positive for CEBPA mutation but number of mutated alleles is not known. NPM1 (Nucleophosmin 1) encodes a phosphoprotein that normally shuttles between the nucleus and cytoplasm and plays a role in ribosome biogenesis, centrosome duplication during mitosis, and cell proliferation and apoptosis through p53 and p19 Arf [16]. Mutations in NPM1 occur in the C-terminus of the gene leading to loss of the nucleolar localization signal and gain of a nuclear export signal ultimately leading to cytoplasmic localization of this protein. NPM1 mutations are found in about 30% of all AML. The presence of an NPM1 mutation in AML with normal karyotype in the absence of a FLT3 ITD mutation portends a favorable prognosis. IDH1 mutation is found in 6-9% of adult AML. Its prognostic value isn't certain but it is associated with a worse prognosis. Additionally our patient had trisomy 8 which is associated with an intermediate prognosis like normal karyotype. Finally despite all with these prognostic factors was showing a better prognosis (except IDH1) our patient treated with FLAG-IDA regimens 2 times then we planned midostaurin for future. But after second FLAG IDA our patient suffered from acute cholecystitis. After surgery patient's general situation dramatically got worse due to septic shock and eventually lost his life.

CONCLUSION: Genetics play a role in AML for both diagnosis, treatment and prognosis but none of these factors are absolute. The importance of these factors is increasing but we need more data and studies especially meta-analysis and world wide large randomised controlled trials for treatments.

P5. ECTHYMA GANGRENOSUM AS THE PRIMARY MANIFESTATION OF ACUTE MYELOID LEUKEMIA

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INTRODUCTION: Ecthyma gangrenosum (EG) is a rare cutaneous infection that typically manifests in immunocompromised individuals and may be typically associated with *Pseudomonas aeruginosa*. EG may initially present as an erythematous macule and may evolve into a hemorrhagic vesicle that turns into a gangrenous ulcer with a necrotic scar. Besides immunocompromised patients, it can also appear in otherwise healthy immunocompetent individuals, with leukemia being one of the main predisposing conditions. Thus, EG presentation in a previously healthy individual may signal undiagnosed immunodeficiency and warrants further investigation. Acute monocytic and monoblastic leukemias account for less than 5% of AML cases, occurring most commonly in young and adult people, respectively.

CASE REPORT: We describe the case of a 50-year-old previously healthy woman presented at the emergency department due to rash deterioration with onset 14 days ago and fever with onset 4 days ago and normal laboratory work-up 6 months ago. Following the onset of fever episodes and the deterioration of rash, a workup was undertaken: laboratory results revealed normocytic normochromic anemia (Hb 9.0 g/dl, MCV 81 fL (80-99 fL), reticulocytes 0.23% (0.2-2%), and leukocytosis WBC 31.2 K/ μ L (neutrophils 19.4%, lymphocytes 13.1%, monocytes 67.50%-atypical cells, PLT 20 K/ μ L). Peripheral blood smear demonstrated 67% blast cells of the WBC count, and flow cytometry was indicative of acute monoblastic/monocytic leukemia (leukemic blasts revealed CD34+, CD33+, CD13+, CD64+, CD300 E+, CD4+. T1 T+, CD38+, CD11 a+, CD11 b+, CD11+/-, CD36+/-, CD16+/-, HLADR+/-, MPO+/-, CD14+/-). Bone marrow aspirate examination confirmed the diagnosis of acute myeloid leukemia, while molecular karyotype did not report any specific chromosome abnormality. A total body-CT revealed normal findings. A skin biopsy from the lesion was received, and the histopathological examination revealed vascular necrosis with several surrounding bacteria. Gram-stained sections showed gram-negative rods surrounding the necrotic vessels, indicative of *Pseudomonas aeruginosa* infection, while blood and lesion cultures also confirmed the diagnosis. Following the decreased levels of hemoglobin and the sharp increase of inflammatory markers [CRP: 41.8 mg/dL (0-0.8 mg/dL), PCT: 32.9 ng/ml (<0.2 ng/mL), ESR: 148 mm (0-20 mm), LDH: 888 U/L (135-214 U/L), β 2-microglobulin: 5.17 mg/L (1.42-3.21 mg/L)], transfusion with red blood cells and antibiotic therapy with meropenem, linezolid, vancomycin and isavuconazole was initiated. Despite the fever deterioration, chemotherapy was also induced on day 5 with the standard schedule (Idarubicin 12 mg/m² for 3 days and Aracytin 100 mg/m² for 7 days). Meanwhile, the lesions evolved into necrotic ulcers affecting the chest wall, the oral cavity, and the trunk. The patient developed sepsis and died within 2-3 weeks from hospitalization.

CONCLUSION: Although individuals with AML may present with bleeding disorders, cutaneous involvement is common. Reports of AML presenting with EG as the primary manifestation are scant: recognizing the underlying cause may be the key to a proper therapeutic approach.

P6. OCCURRENCE OF POOR RISK ACUTE MYELOID LEUKEMIA IN A HBS BETA+ THALASSEMIA TRAIT FEMALE ADULT AFTER LONG TERM TREATMENT WITH HYDROXYCARBAMIDE. A THERAPEUTIC CHALLENGE.

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INTRODUCTION: Sickle cell disease (SCD) is characterized with multiple severe clinical manifestations. Several therapeutic measures have been used with Hydroxycarbamide to be the standard of care for SCD since it was shown to improve the clinical course. The increased risk of malignancies including leukemias in SCD patients has not been correlated with the use of hydroxycarbamide. Although the safety of Hydroxycarbamide has been questioned, there is no clear evidence of mutagenic effect in SCD patients. A few cases of myeloid malignancies have been reported worldwide.

We present a 55-year old Greek woman with combined heterozygous sickle cell anemia and thalassemia b trait, who developed acute myeloid leukemia after 25 years of hydroxycarbamide therapy.

CASE REPORT: Our patient was diagnosed with combined heterozygous sickle cell anemia and beta thalassemia trait at the age of 3 years. Splenectomy was performed at the age of 20 due to spleen enlargement and increased transfusion needs. At age of 30 (in 1997) she started receiving hydroxycarbamide at dose of 1.5 mg/Kg in order to reduce the number of painful crisis and the need of red blood cell transfusions. The following years she experienced avascular necrosis of both femoral head treated with arthroplasty. She gradually developed severe pulmonary disease, dysrhythmia as well as mild left ventricular diastolic heart disease. While she was regularly transfused and de-ironed, she developed severe neutropenia, which was initially attributed to anti-inflammatory medication or the use of hydroxycarbamide, which was temporarily suspended. Thereafter the bone marrow evaluation confirmed the diagnosis of AML. Flow cytometry analysis showed a population 10.5% with granules SSc and phenotype CD34+CD117+CD33+CD11 b+CD64+CD19-CD3-CD10-CD4-(APL variant?). The RT-PCR for PML/RARa was negative. The karyotype was complex [60, XX, -X, -2, -4, -5, -6, -7, +8, +11, -12, -15, -16, -17, -18 (15)/46, XX(4)]. The trephine biopsy showed 30% blasts (MPO+, CD34+, CD117+, LAT-1-, Glycophorin-, CD20-, CD3- with dysplastic abnormalities of erythroid precursors and megakaryocytes). The bone marrow NGS analysis showed p53 mutation (NM_000546: exon 8: c. C832 T: p. P2785) (VAF 60.9%). The patient was not suitable for intensive chemotherapy due to severe comorbidities. So, she was treated with azacytidine (100 mg for 7 days). She received 2 cycles without response. Venetoclax at low dose was added in a third cycle. She was complicated with lung infection, cellulitis of the lower extremities and cardiac abnormalities. She passed away from multi-organ failure due to the toxicity and SCD complications, four months after AML diagnosis.

CONCLUSION: Hydroxycarbamide is still considered a rather safe and efficacious treatment for SCD patients, including children. A few cases of myeloid malignancies have been reported so far. Possible late effects including development of poor risk secondary leukemia after long term use of hydroxycarbamide should be discussed with the SCD patients. Keywords: sickle cell disease, multilineage dysplasia, acute myeloid leukemia, hydroxycarbamide.

P7. RETROSPECTIVE ANALYSIS OF CLONAL TRANSFORMATION IN CLL PATIENTS

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OBJECTIVE: Several studies show that in mature lymphoid malignancies, such as Chronic lymphocytic leukemia (CLL), the cellular propensity for clonal B cell development has been achieved at the hematopoietic stem cells (HSCs) level. It has also been reported that the genetic could also be traced back to the HSCs stage. These studies have suggested that even in relatively mature lymphoid malignancies, human HSCs could be a reservoir for genetic mutations, which constitutes a prime source for the initiation of leukemia/lymphoma development. The main objective of our study is to investigate the pre-clinical clonal evolution and any associated genetic lesions in lymphoid neoplasia, in order to shed light to the mechanisms of disease development and manifestation. This is achievable through our unique access to patient samples that were collected many years prior to the diagnosis with a hematological malignancy when registered as volunteer bone marrow donors at Karaiskakiou Foundation, access to follow up samples collected several years post diagnosis as well to the medical history of each patient during the course of the disease.

METHODS: Towards this goal, the aims of the project are (1) determination of clonal dynamics and identification of clonal populations that could evolve to disease progression, (2) evaluation of IGHV Somatic Hypermutation status (SHM) and stereotypy role in CLL development as both are used in clinical practice as prognostication markers, (3) explore the impact of LPD specific genes and chromosomal aberrations in disease progression and (4) identify the association of the expression of crucial prognostic markers (LcK and CD38) in patient progression status.

RESULTS: Clonal IGH VH-JH rearrangements have been identified in 94% (31/33) of our CLL patients [80.6% (25/31) are monoclonal and 19.3% (6/31) are bioclonal]. The diagnosis identified leukemic clone was detectable (MRD POSITIVE) in 51.6% (16/31) of patients paired pre-diagnosis samples. In 12.9% (4/31) patients the pre-diagnosis identified clone was at the same size with diagnosis sample. IGHV% analysis results show that 74% of our under study CLL patients have SHM status Mutated (good prognosis), 23% have SHM status Un-mutated (bad prognosis). 16% of patients are assigned to a subset stereotypy (prognosis depends on type of assigned subset). NGS sequencing on CLL patients diagnosis samples identified significant pathogenic gene mutations associated with LPDs, CLL and other hematological malignancies. Mutations were also found in clonal hematopoiesis driver genes in diagnosis and pre diagnosis samples. The analysis of post-diagnosis samples is under process.

CONCLUSION: The detection of tumour clones and their molecular progression from an early time point prior to diagnosis, in combination with the available medical history of the tested patients during the course of the disease, will provide invaluable insight in the evolution and pathogenesis of hematological malignancies. This information will be of immense importance for improving the monitoring and clinical outcome of patients

P8. CLINICAL RELEVANCE OF HYPOGAMMAGLOBULINEMIA AND SERUM TGF-BETA1 IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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OBJECTIVE: CLL is a frequent and usually indolent disease that may require only follow-up. Only 1/3 of patients are symptomatic and will need treatment at the time of diagnosis. Hypogammaglobulinemia is frequently observed but its clinical importance and biologic mechanisms has remained controversial. It could be assumed that Tgf-beta1, a cytokine implicated in the suppression of B-cell proliferation and Ig secretion, is probably involved in the development of hypogammaglobulinemia. Our aim is to study any eventual clinical impact of hypogammaglobulinemia as determined by conventional immunoglobulin (IgG, IgA, IgM) measurements and by HEVYLITE TM that allows the separate quantification of the kappa- and lambda-restricted Ig of a given class and of the resulting ratio HLCR. In addition, we also determined and studied Tgf-beta1 serum levels at patients' diagnosis.

METHODS: 100 CLL patients were studied; 65%, 22% and 13% in Binet stage A, B and C respectively. Fifty-four percent never required treatment while 46% required treatment either at the time of diagnosis or during their follow-up. Patients' median follow-up time was 78 months, Median time to first treatment (TFT) was 53 months. Ig quantification was made by both classical nephelometry and by the HevyliteTM technique that measures the Ig fractions bound to either κ or λ light chains; the ratio of Ig- κ/λ of each Ig class (IgG-, IgA-, IgM-HLCR) was calculated, Tgf-beta1 serum levels was determined by ELISA. Statistical analysis was performed conventionally with the SPSS software v26.

RESULTS: Immunoelectrophoresis-proven paraproteinemia was present in 3 patients. Abnormal HLCR was present in 14%, 7% and 34% of patients, concerning IgG-, IgA & IgM-HLCR respectively. HLCR abnormality in the same patient concerned all 3 Ig classes in 2%, 2 in 19% and 1 in 35% of the cohort. While hypogammaglobulinemia determined by conventional techniques did not correlate with prognosis, patients with abnormal HLCR had a shorter time to treatment (TTT, $p=0,05$) and overall survival (OS, $p= 0,019$) than the rest. Serum Tgf-beta1 at diagnosis also correlated with hypogammaglobulinemia and its increased levels correlated with a shorter TTT ($p=0,024$) and OS ($p=0,015$).

CONCLUSION: A shorter time to treatment and overall survival was observed in CLL patients with abnormal HLCR and increased serum Tgf-beta1 at diagnosis.

P9. IMMUNOGENICITY OF A THIRD DOSE OF THE BNT162 B2 COVID-19 VACCINE IN PATIENTS WITH CLL. EFFECTS ON TREATMENT SELECTION.

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OBJECTIVE: The coronavirus disease 2019 (COVID-19) pandemic has become the main healthcare issue worldwide since its appearance at the end of 2019, with the disease affecting millions of people globally. Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) demonstrated efficacy in most of the general population. Chronic lymphocytic leukemia (CLL) is a disease of the elderly, associated with varying degrees of immune deficiency due to the disease itself or to the treatment. Hence, patients with CLL are more susceptible to severe complications from COVID-19. Moreover, antibody response following SARS-CoV-2 vaccination is shown to be suboptimal in CLL; it has been shown though that a booster dose of the BNT162 b2 vaccine may lead to a significant increase in the seroconversion rates of immunocompromised patients. The aim of this prospective, non-interventional study was to investigate the immunogenicity and efficacy of a third dose of the BNT162 b2 vaccine, as well as the effect of treatment on the serological response to the vaccine in adult patients with CLL.

METHODS: This is an extension of a previous study on the immunogenicity and safety of two doses of the BNT162 b2 mRNA Covid-19 vaccine in patients with CLL. Thirty-nine patients with CLL were included in the study. Patients were vaccinated with the third 30 mcg dose of the BNT162 b2 mRNA Covid-19 vaccine. Data on the treatment of the patients were collected and analyzed. Sera were tested before the first, after the second, before and after the third dose of the vaccine for IgG antibodies against the SARS-CoV-2 receptor binding domain (RBD) of the S1 subunit of the spike protein IgG. with the Abbott SARS-CoV-2 IgG II Quant assay (Abbott Laboratories, Abbott Park, IL, USA), a two-step chemiluminescent microparticle immunoassay was used, on the Architect i system. The IBM SPSS statistics, version 26 (IBM Corporation, North Castle, NY, USA) was used for the statistical analysis of the results.

RESULTS: The seroconversion rate increased from 28.2% before the third dose to 64.1% after the third dose and was higher in treatment naïve patients (72.7% versus 47.1% in actively treated patients, $p=0.042$). All but one patient achieving a seroconversion after the second dose retained after the third, while eight patients not achieving seroconversion after the second dose (38.1%), did so after the third. The seroconversion rate was not correlated with any of the studied baseline characteristics of the patients (age, gender, Rai stage, hemoglobin and gamma-globulin level, lymphocyte and platelet count). Notably patients actively treated with venetoclax (N=8) had a higher seroconversion rate than those treated with ibrutinib (N=7) (87.5% versus 14.3%, $p=0.001$).

CONCLUSION: This study confirms the beneficial effect of a third dose of the BNT162 b2 vaccine on the seroconversion rate in patients with CLL and strongly suggests that the use of venetoclax is correlated with higher immunogenicity/seroconversion rates than that of ibrutinib, in accordance with the results of another recent study. A treatment strategy change during the pandemic favoring the use of venetoclax may be suggested based on our results.

P10. RUXOLITINIB AS A SALVAGE TREATMENT OF REFRACTORY RELAPSED SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

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INTRODUCTION: Hemophagocytic lymphohistiocytosis (HLH), is a rare life-threatening clinical syndrome caused by cytokine overproduction and hyperinflammation which is characterized by histiocyte proliferation and hemophagocytosis. HLH may be inherited (primary) or secondary. The diagnosis is established when five out of seven clinical and laboratory criteria are met (fever, splenomegaly, cytopenia, hypofibrinogenemia or hypertriglyceridemia, hyperferritinemia, hemophagocytosis, low or absent NK cell activity, elevated soluble IL2 receptors). Prognosis in refractory relapsed is dismal.

CASE REPORT: We present a rare case of refractory relapsed secondary HLH, in a 35-year-old female patient with medical history of refractory MS treated with alemtuzumab eight months prior to HLH symptom onset. She presented to the hospital with fever, pancytopenia, elevated liver enzymes, hyperferritinemia, hypertriglyceridemia and hepatosplenomegaly. Laboratory and imaging evaluation excluded infection, malignancy and autoimmune disorders. Bone marrow aspiration and biopsy didn't reveal hemophagocytosis, however due to high clinical suspicion of HLH (HS score 99% probability) she treated initially with methylprednisolone pulses (1 g/day for 5 days), ivig (1 g/kg) and cyclosporine A (CsA) (aiming at levels around 200 microg/L). After partial remission for one month she was vaccinated with the first dose SARS-Covid mRNA vaccine. Two weeks post vaccination progression of disease was observed. We decided to start treatment according to HLH 2004 protocol (etoposide, CsA, dexamethasone), with clinical and laboratory improvement. Four months after diagnosis while she was receiving outpatient treatment with etoposide every two weeks, she was admitted to the hospital with septic shock caused by klebsiella pneumoniae. Due to her clinical instability she was transferred to the ICU without requiring intubation. Her laboratory parameters were significantly deteriorated (ferritin >32000 ng/ml, triglycerides 565 mg/dl, CRP 19,1 mg/dl, PCT 58 mg/dl). Although supported with broad spectrum antibiotics, ivig 1 g/kg, dexamethasone, etoposide, CsA, according to protocol doses, she didn't respond and her clinical condition as also her laboratory results were deteriorating further. We decided to proceed with plasma exchange therapy (three cycles) while waiting for the approval of ruxolitinib, as salvage third-line treatment. According to limited international literature, ruxolitinib is used for refractory relapsed HLH with beneficial outcomes. She responded immediately to plasma exchange treatment as a bridge therapy. Ruxolitinib was given at 15 mg twice-a-day at the beginning and after a week as her laboratory markers were significantly improved the maintenance dosage was modified to 10 mg twice-a-day. Ruxolitinib was administered in addition to CsA, dexamethasone, while the latter was successfully tapered down to 2 mg every other day and CsA to 75 mg/day. Taking into consideration the underlying MS the continuance of the triple therapy was necessary. The patient has been in remission, for 10 months. She is being monitored outpatient, without any need for further hospitalization or infections. Ruxolitinib managed to keep her in remission while the previous two line treatments failed. We have proceeded with HLA typing of her (high resolution) and her family (she has an haploidentical sibling), in order to be prepared for a future relapse that can't be managed with the available immunosuppressant therapies.

CONCLUSION: Ruxolitinib seems to be a promising treatment in poor prognosis patients with refractory relapsed HLH.

P11. NIEMANN-PICK DISEASE: UNUSUAL CASE REPORT

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INTRODUCTION: Niemann-Pick disease (NPD) is a rare, inherited metabolic disorders, in which sphingomyelin accumulates in lysosomes in cells. Niemann-Pick disease is divided into four main types: A, B, C1 and C2. Type A usually presents hepatosplenomegaly and growth failure. People with NPD type B often have hepatosplenomegaly, thrombocytopenia and recurrent lung disease. The signs and symptoms of NPD types C1 and C2 are very similar. People with these types develop severe neurological symptoms, severe liver disease and interstitial lung disease. NPD caused by mutations in the SMPD1 gene, which provides producing acid sphingomyelinase. Mutations in either the NPC1 or NPC2 gene cause NPD type C. These conditions are inherited in an autosomal recessive pattern. Because the disease is seen very rarely in adult and can be confused with other hematological diseases in clinical practice, we wanted to share our case to increase sensitivity.

CASE REPORT: A 53-year-old male patient presented with complaints of abdominal fullness and swelling. There was no history of travel and B symptoms in the patient's anamnesis. In the physical examination of the patient, massive splenomegaly and hepatomegaly were detected. Complete blood count revealed normocytic anemia. No significant feature was observed in the peripheral smear. Thyroid function tests, renal and liver functions were normal. C-reactive protein and erythrocyte sedimentation tests were normal. Brucella and leishmania serology were negative. There was no result in favor of acute viral disease in hepatitis-HIV and EBV serology. Bone marrow biopsy was performed. Abundant 'sea blue' histiocytes and foamy cells were seen in the aspiration. In the biopsy material, cellularity was 88%, hypercellular, cells belonging to all series and maturation stages were observed. Some of the megakaryocytes were small hypolobulated morphology and histiocytic cells were seen as foamy cytoplasm forming groups in places. Lysosomal storage disease was considered in the patient and Sphingomyelinase and B-glucosidase enzyme levels were requested. Sphingomyelinase: 0.16 nmol/mL/hr (1.3-15), B-glucosidase: 2.5 nmol/mL/hr (Adult Dry Blood = 0.94 - 5.29, Neonatal Dry Blood = 0.92 - 4.27). The lysosomal storage diseases genetic panel was studied and a c.416 T>C (p. Leu139 Pro) homozygous mutation was found in the chr: 11: 6412711 genomic position of the SMPD1 NM_000543/4 gene, and the gene was associated with autosomal recessive Niemann-Pick disease in the OMIM database. The patient was diagnosed with Niemann-Pick storage disease.

CONCLUSION: Although Niemann-Pick disease is fatal and often untreatable, the sooner it is recognized, the better is the chance to slow down its progression and limit the complications. Patient education is crucial, and social worker involvement, including a geneticist, is essential. In some parts of the world, preventive strategies include prenatal screening, restrictions on issuing marriage licenses to two people with the same disease. Bone marrow transplantation, stem cell transplantation, and enzyme replacement are under investigation as potential treatment options.

P12. PREGNANCY ASSOCIATED ACQUIRED HEMOPHILIA A (AHA) TREATED SUCCESSFULLY WITH THE BISPECIFIC THERAPEUTIC ANTIBODY EMICIZUMAB

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INTRODUCTION: Acquired Hemophilia A (AHA) is a rare disorder resulting in spontaneous bleeding in individuals with no prior similar history. It is caused by spontaneous inhibition of clotting factor VIII by autoantibodies associated with drugs, autoimmune disorders, malignancies, infections and pregnancy, usually in the postpartum period. Emicizumab (Hemlibra[®]), a bispecific FVIII-mimetic therapeutic monoclonal antibody is already approved in congenital hemophilias with and without inhibitors. We report here, a case of newly diagnosed pregnancy associated AHA treated successfully with Emicizumab.

CASE REPORT: A 46 years old female, was admitted to our clinic due to persistent vaginal bleeding, extensive ecchymosis of her left thigh and coexisting fever. Previous medical history: Hashimoto's disease, fibromyectomy, in vitro fertilization (IVF) with donor ovules, which gave birth to twins, 11 months later. The patient referred appearance of multiple recurrent ecchymoses and episodes of menorrhagia during the last months, starting from the postpartum period. Laboratory examination revealed a significant drop in Hb (6.5 g/dl) and Ht (20%), normal platelets (PLT) and PT, prolonged aPTT (94.5 sec), fibrinogen: 549 mg/dl and D-dimers: 1955 ng/ml. Mixing tests confirmed the diagnosis of AHA. The initial FVIII activity was <0.25%. Immunology testing including ANA, AMA, anti-ENA, anti-dsDNA ACA, anti- β 2-GPI, lupus anticoagulant and immunoglobulins revealed ANAs positivity. Virology testing and cancer biomarkers were negative. Left lower extremity ultrasound depicted left thigh hematoma without pressure phenomena or signs of compartmentalization syndrome. Abdomen CT depicted bilateral hemorrhagic ovarian cysts. Thyroid function testing revealed hyperthyroidism. Initially, she was given bypassing hemostatic therapy with rhFVIIa Novoseven[®] and intensive immunosuppressive therapy with steroids, rituximab, and cyclophosphamide for six weeks according to the current International Recommendations. She was also given antibiotic prophylaxis, propylthiouracil and hormone therapy with chlormadinone and ethinylestradiol to stop menstruation. Despite heavy immunosuppression, FVIII activity levels remained very low (2%). The patient experienced a new episode of vaginal bleeding and a new hematoma on her left thigh's posterior surface. Additionally, she had an episode of febrile neutropenia treated with antibiotics and required continuous blood transfusions. She was started on subcutaneous Emicizumab, according to the proposed schedule. In two days, aPTT was normalized and all her bleeding manifestations were rapidly recovered. One month later, FVIII activity was measured by a chromogenic method to detect the patient's own FVIII for probable dose modifications. However, FVIII activity remained very low <2%. Immunosuppression was continued with mycophenolate mofetil (MMF). Nowadays, the patient is given Emicizumab every 4 weeks and lives a normal life. However, her own FVIII activity remains very low.

CONCLUSION: Emicizumab is an effective hemostatic therapy for AHA, even in females, with many advantages such as reduction of immunosuppression, subcutaneous administration and early discharge.

P13. UNUSUAL HEMATOLOGIC MANIFESTATIONS OF CELIAC DISEASE: A CASE SERIES

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OBJECTIVE: We highlight anemia as the presenting feature of celiac diseases (CD) which was undiagnosed for several years.

METHODS: We studied consecutive patients diagnosed with CD in our center over the last six years. We systematically recorded data at diagnosis and follow-up.

RESULTS: We identified five patients with chronic persistent anemia in whom the subsequent thorough examination revealed CD. Following CD diagnosis, patients were advised to follow a gluten-free diet, with recovery of their hematologic abnormalities. First patient A 40-year-old male patient was referred to our Outpatient clinic for remarkable thrombocytosis. Patient's medical history revealed IDA since childhood, smoking, mild essential hypertension controlled with dietary modifications, acute coronary syndrome (four years before) and a recent acute ischemic stroke while on clopidogrel. Abdominal CT scan was performed, which revealed the presence of mild mesenteric panniculitis. Then, screening for CD yielded positive results. A new gastroduodenoscopy was performed, during which examination of the duodenal mucosa revealed edema, scalloped duodenal folds, flattened villi and a duodenal biopsy revealed typical histologic signs of CD (modified Marsh Type 3, Table 2). Second patient A 17-year-old female patient was referred due to large atraumatic ecchymoses and bruising which had developed over the previous weeks, following treatment with a herbal slimming remedy. Patient's medical history revealed polymenorrhea and obesity. Gastroduodenoscopy was recommended due to B12 deficiency. It revealed macroscopic atrophy of the gastric mucosa. Duodenal biopsies detected flattening of folds with an increase of duodenal intraepithelial CD3 (+) lymphocytes (modified Marsh Type 3). Screening for CD yielded positive results. Third patient A 20-year-old female patient was referred due to anemia. Her medical history revealed IDA since childhood, periodically treated with oral iron supplements. Due to IDA chronicity, we thought to conduct screening for CD, which yielded positive results. Duodenal biopsies revealed modified Marsh type 3 findings. Fourth patient A 36-year-old female patient was referred for thrombophilia screening due to family history. The patient's medical history revealed recurrent hemoperitoneum (fourteen times), with ovarian cyst rupture of undetermined cause in some cases. Screening for CD was requested, with positive results. Endoscopy was performed and showed antral gastropathy. Biopsies revealed findings of chronic gastritis and modified Marsh type 3 a/b findings in duodenum biopsies. Fifth patient A 36-year-old female patient presented with mild anemia. Patient's medical history included Wolff-Parkinson-White syndrome and a recent history of

B12 supplementation due to a mild deficiency of B12 vitamin. In parallel, the patient suffered from an episode of superficial venous thrombosis. Based on these two facts, we screened for CD. Anti-Gliadin antibodies IgA were slightly elevated (16.1 AU/ml), AGA IgA, anti-tTG IgA and anti-EMA antibodies were negative. Endoscopic and histopathological findings were typical for CD (modified Marsh Type 3 a).

CONCLUSION: The clinical profile of CD patients is expanding, including various extra-intestinal conditions. Most CD manifestations are preventable or treatable with a gluten-free diet and iron supplementation. Early diagnosis and proper treatment are therefore vital for prevention of serious and potentially lethal complications.

P14. ADMINISTRATION OF THE ANTI-VON WILLEBRAND FACTOR NANOBODY CAPLACIZUMAB, IN A SEVERE CASE OF ACQUIRED THROMBOTIC THROMBOPENIC PURPURA WITH NEUROLOGIC MANIFESTATIONS

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INTRODUCTION: Acquired Thrombotic Thrombopenic Purpura (aTTP) is an immune-mediated deficiency of ADAMTS-13 with microvascular thrombosis due to von Willebrand factor-platelet aggregates, leading to ischemia and multiorgan dysfunction. Current treatment consists of daily plasma Exchange (PEX) and immunosuppressive therapy. Unfortunately, during the last 20 years, no progress in this direction is made, with the exception of the off-label use of Rituximab. Caplacizumab, a novel anti-von Willebrand factor nanobody, provides a new treatment paradigm. We report here Caplacizumab (Cablivi®) administration in a severe case of aTTP with neurologic manifestations.

CASE REPORT: A 31-year-old male was admitted to our clinic due to fatigue, petechiae, rash, lower limbs' numbness and disturbed consciousness level. Laboratory testing revealed anemia (Hb: 5.5 g/dl), thrombocytopenia (PLTs: 14 x10³/μl), LDH: 849 U/L, reticulocytes: 8.13%, TBil: 2.2 mg/dl, dBil: 0.2 mg/dl, direct-Coombs: negative, normal coagulation tests, D-Dimers: 3450 ng/ml. Peripheral blood smear: 8% schistocytes, microspherocytes; all consistent with MAHA. Liver and renal function were normal. Tumor markers, immune and virology testing were negative. Brain, thorax and abdomen CTs were normal. Blood samples taken by vein-puncture, upon admission, were sent for ADAMTS-13 determination, as TTP was suspected. Calculated French score: 2 and Plasmic score: 7 predicted the likelihood of severe ADAMTS-13 deficiency. He was urgently treated with corticosteroids and PEX. After the first PEX, he experienced epileptic seizures, which advanced to Status Epilepticus. With a Glasgow Coma Scale: 4/15, he was intubated and transferred to the ICU, for 6 days, undergoing daily PEX, immunosuppression with steroids, Rituximab and antiepileptic therapy. He was transfused with a total of 6 RBC units. Four days after admission, ADAMTS-13 levels were available and activity was <1%. A novel brain CT depicted a left intracapsule ischemic infarct and a left frontal region hematoma, due to fall during the seizures, without signs of intracranial hemorrhage. Brain MRI depicted three lesions of gliosis, without clinical significance. EEG showed generalized epileptiform abnormalities. Brain SPECT/CT-scan detected an asymmetric radiotracer distribution in the cerebral cortex. After ICU discharge, the patient was febrile, due to *Acinetobacter baumannii* central venous catheter infection, treated with iv Colistin and Tigecycline for 14 days. ADAMTS-13 activity 15 days, 1 month and one year after Caplacizumab administration were 13%, 80% and 72%, respectively. He resolved quickly and completely in clinical and laboratory levels as well. Recently, Caplacizumab received its first approval from EMA for the treatment of acute episode of aTTP, in addition to PEX and immunosuppression. So, Caplacizumab administration was decided, according to the suggested protocol, as our patient had serious cerebral vascular events. Nowadays, our patient is asymptomatic, lives a normal life and his lab exams, performed every three months are normal.

CONCLUSION: Caplacizumab prevents von Willebrand factor-platelet interaction and transformation. Treatment with Caplacizumab in our patient was safe and effective. He did not show any bleeding or thromboembolic events. He completely recovered from the first episode of TTP, with no complications or relapses. In the future, Caplacizumab is likely to change the way we treat aTTP, either combined with standard treatment options or with novel combinations with or even without PEX. However, more real-world data, with longer follow-up, are needed to establish the exact role of Caplacizumab in the algorithm of aTTP targeted therapies.

P15. EXTRAMEDULLARY HEMATOPOIESIS AS A COMPLICATION OF SYSTEMIC HEMATOPOIESIS

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INTRODUCTION: Mastocytosis is a clonal disorder of Hematopoietic Stem Cells that manifests as an uncontrolled expansion of mast cells (MCs); the latter reside in areas of the body that serve as a line of defense in invading pathogens such as the skin and the GI tract. Mastocytosis at the clinical level can be confined to the skin (Cutaneous Mastocytosis, CM) or affect other organs (Systemic Mastocytosis, SM) such as the bone marrow, the liver and the lungs. The molecular lesion in c-Kit that characterizes the abnormal MCs has helped in disclosing the clonal nature of the disease. MCs can release a plethora of enzymes and inflammation mediators that affect the function of many organs, including the bone marrow (BM). However, the alterations in the BM niche that these cells can propagate, could explain the often-observed anemia in patients with CM or SM with low levels of mastocyte infiltration in the BM.

CASE REPORT: In this context, we present a case of a 64 yo patient with CM who was referred to our unit from the Department of Dermatology for evaluation of the anemia (10.3 g/dL). The BM had minimal MDS-related changes in the erythroid compartment and a low level of MC infiltration (around 10%). The patient was placed on H-2 antagonists and sodium cromoglicate to alleviate GI symptoms. The patient's anemia deteriorated over the ensuing years despite the use of MC-directed cytotoxic therapies such as steroids, IFNg and midostaurin. The latter was continued for another 3 years since it alleviated disease symptomatology but had no effect in improving the anemia. A re-evaluation of the BM showed extensive fibrosis with a MC infiltration of no more than 15%. The patient also complained of back pain that was attributed to a mass growing in the upper part of his right kidney that was initially assumed to be a mast cell tumor. However, the biopsy showed that the tumor was a massive site of extramedullary hematopoiesis presumably developed as a physiological response to BM fibrosis.

CONCLUSION: To our knowledge, this is a rare case of extramedullary hematopoiesis in a SM patient who survived for a protracted period of time (16.5 years); the possibility that extensive fibrosis can be linked to midostaurin is not supported in the literature. It thus remains as a distinct scenario that the expanded life expectancy that midostaurin can offer in SM, gives ambient time for a full-blown BM fibrosis to develop, in effect facilitating the extramedullary hematopoiesis.

P16. THERAPEUTIC PLASMA EXCHANGE EXPERIENCE IN THYROTOXICOSIS

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OBJECTIVE: Therapeutic plasmapheresis in thyrotoxicosis is considered as category III according to the indications of the American Apheresis Association. In this study, we evaluated therapeutic plasmapheresis performed in our center for thyrotoxicosis within 17 years.

METHODS: Data of 305 plasmapheresis procedures performed on 65 patients in Ege University Medical Faculty Adult Apheresis unit between 2005 and 2022 were collected retrospectively.

RESULTS: Of the 65 patients, 44 were female and the median age was 38 (19-76). Four of the patients had toxic multinodular goiter, 55 had Graves' thyrotoxicosis, 4 had amiodorone-induced thyrotoxicosis, and 2 had iodine-induced thyrotoxicosis. The median plasmapheresis procedures were 3 (1- 22). Plasmapheresis was performed because of the ineffectiveness of antithyroid drugs in 31 patients, side effects of antithyroid drugs in 20 patients, the need for rapid response in 8 patients, and the need for both rapid response and side effects in 6 patients. Fifty-one patients were treated with fresh frozen plasma, 10 patients were treated with albumin, and 4 patients were treated with both albumin and plasma. The median fT3 value before the procedure is 4.36 pg/mL (2.46 -27), the median of the fT4 value is 4.88 ng/dL (1.23-12), the median fT3 after the procedure is 2.43 pg/mL (0.59 - 8.47)) and fT4 median of 2.31 ng/dL (0.68-3.84). The difference between fT3 and fT4 values before and after the procedure was significant. No side effects were observed in 58 patients, while infection developed in 2 patients, deep vein thrombosis in 2 patients, and hypocalcemia and itching developed in 3 patients.

CONCLUSION: Therapeutic plasmapheresis is an alternative method that can be used in preparation for ablative treatment in patients with thyrotoxicosis. It has been shown to be an effective and safe treatment when applied in centers experienced in this field.

P17. PATIENTS WITH HEMATOLOGIC MALIGNANCIES SHOW IMPAIRED HUMORAL RESPONSES AGAINST SARS-COV-2 FOLLOWING COVID-19 VACCINATION; A SYSTEMATIC REVIEW AND META-ANALYSIS

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OBJECTIVE: Patients diagnosed with hematologic malignancies constitute a particularly vulnerable population that has been severely affected by the corona-virus disease 2019 (COVID-19) pandemic. Formal trials of SARS-COV-2 vaccines excluded these patients whereas prospective observational studies suggest inferior responses to vaccination. The aim of this systematic review and meta-analysis is to evaluate the efficacy of the vaccination against SARS-COV-2 in patients with hematological malignancies.

METHODS: A systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. Scientific literature databases (Pubmed, Embase, and Scopus) were systematically searched until January 30, 2022. Random-effects (DerSimonian-Laird) models were used to estimate pooled Effect Size (ES) and Relative Risk (RR) of vaccinated patients and healthy controls that seroconverted. The cut-off values of each individual study were used to define a positive humoral response to vaccination against SARS-COV-2.

RESULTS: Sixty studies were included with a total number of 11916 patients. Among patients with hematological malignancies, 41% [95% (CI): 0.33-0.50] developed antibodies against SARS-COV-2 after the first dose of the vaccine and 62% [95% (CI): 0.57-0.67] after two doses of the vaccine. Respectively, 90% [95% (CI): 0.82- 0.96] of the healthy participants produced a sufficient amount of antibodies against SARS-COV-2 after the first dose of the vaccine and 99% [95% (CI): 0.97-1.00] following full vaccination. The Relative Risk (RR) for immunoconversion was calculated; RR: 0.48 [95% (CI): 0.97-1.00] and 0.59 [95% (CI): 0.53- 0.66] for first and second vaccine dose, respectively. The factors that may affect this reduced immune response, such as type of hematological malignancy, type and time intervals of treatment and the administered vaccine type were analyzed as independent risk factors for impaired immunoconversion. Subgroup analysis showed that factors with a statistically significant impact on seroconversion include the type of malignancy: multiple myeloma: (RR: 0.41 [95%CI: 0.25-0.67] and RR: 0.81 [95%CI: 0.74-0.88]) after first and second dose of vaccine respectively, non-Hodgkin lymphoma (RR: 0.62 [95%CI: 0.46-0.82]), chronic lymphocytic leukemia (RR: 0.54 [95%CI: 0.44-0.66]), active treatment at the time of vaccination (RR: 0.49 [95%CI: 0.40-0.59]), treatment with monoclonal antibodies (RR: 0.58 [95%CI: 0.41-0.81]), treatment with immunomodulators (RR: 0.85 [95%CI: 0.74- 0.97]), treatment with anti CD20 monoclonal antibodies (RR: 0.16 [95%CI: 0.09- 0.28]), autologous stem cell transplant (RR: 0.87 [95%CI: 0.82- 0.94]), treatment with Bruton Tyrosine Kinase inhibitors (RR: 0.22 [95%CI: 0.13- 0.37]), CAR-T cell therapy (RR: 0.44 [95%CI: 0.22-0.88]) and chemotherapy (RR: 0.75 [95%CI: 0.60- 0.94]). Differences in seroconversion rates were also found among different vaccine types: AZD1222 (ES: 0.47 [95%CI: 0.24- 0.71]), BNT162 B2 (ES: 0.63 [95%CI: 0.56- 0.69]), mRNA-1273 (ES: 0.72 [95%CI: 0.57- 0.85]).

CONCLUSION: Results of the meta-analysis show that patients with hematological malignancies develop antibodies against SARS-COV-2 at lower rates compared to healthy population. The factors that were shown to affect immune response could be further used to implement a personalized vaccination schedule according to each patients' hematological disorder and therapy scheme.

P18. THE FIRST BOOSTER DOSE OF THE BNT162 B2 VACCINE INDUCES SUSTAINED HIGH LEVELS OF NEUTRALIZING ANTIBODIES AGAINST SARS-COV-2 AT 6 MONTHS FOLLOWING VACCINATION IN HEALTHY INDIVIDUALS

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OBJECTIVE: The optimal time interval between the booster COVID-19 vaccination doses remains under question. The purpose of this study was to examine the kinetics of SARS-CoV-2 neutralizing antibodies (NAbs) after vaccination with the BNT162 b2 mRNA vaccine for a period up to six months after the third vaccination (booster dose). The potential impact of gender, age, and body mass index (BMI) on NAbs level was also investigated.

METHODS: This study enrolled healthy participants who were vaccinated with three doses of the BNT162 b2 mRNA vaccine. NAbs were measured using FDA-approved techniques on the first day (immediately before the first vaccination), one week later (day 8), on the day of the second vaccination (i. e., day 22), two weeks (day 36), one month, three months, six months, and nine months after the second dose, and at one month, three months, and six months after the third dose of vaccine. None of the participants was tested positive for COVID-19, therefore NAbs values reflect immunization dynamics.

RESULTS: Overall, 100 healthy participants were included in the study. The median age was 51 years, the median BMI was 26.0 kg/m², and the male-to-female ratio was 1: 1. NAbs levels increase and then decrease after each vaccination dose. However, after the third dose, the increase in NAbs is very rapid, whereas the decrease is much slower compared with the results after the second dose. The median NAbs titers six months after the third dose (M6 P3 D) were 95.5%, which was lower than the median values for M3 P3 D (97.2%) and M1 P3 D (97.8%). These two differences (M6 P3 D vs. M3 P3 D, M6 P3 D vs. M1 P3 D) were found to be statistically significant (p -values < 0.001). It is noteworthy that the inhibitory titers on M6 P3 D remained very high (95.5%) compared to the M6 median values (57.3%) (p < 0.001). It is worth noting that NAbs values six months after the third vaccination were comparable only to those two weeks (median 96.5%) and one month (96.3%) after the second vaccination. The higher NAbs titers after the third dose compared with those after the second vaccination were also reflected in the higher proportions of participants with moderate, high, or very high protection. Specifically, six months after the third dose, 96% of subjects had inhibition levels above 50% and 75%, estimating that they were moderately or highly protected. One and three months after the third vaccination, the corresponding percentages were 100% in both cases. Interestingly, six months after the second dose, 60% of the subjects had NAbs greater than 50% and only 20% of the participants managed to enter the high protection range. No statistically significant differences were found with respect to gender, age and BMI in the development of NAbs against SARS-CoV-2 in all time points.

CONCLUSION: In conclusion, these results indicate the sustained humoral response against SARS-CoV-2 in healthy individuals even at 6 months following the first booster dose of BNT162 b2. Our data advocate for an extended time between the first and the second booster dose. A shorter interval can be considered for immunocompromised patients and the elderly, depending on the epidemic dynamics.

P19. SARS-COV-2 HUMORAL RESPONSES FOLLOWING BOOSTER BNT162 B2 VACCINATION IN PATIENTS WITH B-CELL MALIGNANCIES

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OBJECTIVE: Patients with B-cell malignancies have suboptimal immune responses to SARS-CoV-2 vaccination and are a high-risk population for severe COVID19 disease. Recent data in patients with chronic lymphocytic leukemia (CLL), Non-Hodgkin's lymphoma (NHL) and Waldenström macroglobulinemia (WM) report less effective humoral responses following vaccination against SARS-CoV-2, as reflected by low titers of neutralizing antibodies (NAbs).

METHODS: We evaluated the effect of a third booster BNT162 b2 vaccine on the kinetics of anti-SARS-CoV-2 neutralizing antibody (NAbs) titres in patients with B-cell malignancies. Patients with NHL (n=54) Waldenström's macroglobulinemia (n=90) and chronic lymphocytic leukemia (n=49) enrolled in the ongoing NCT04743388 study and compared against matched healthy controls. The blood collection schedule for this clinical investigation was as follows: on day 1 (D1) before the first vaccination, at three weeks (i. e., day 22 prior to the second dose), one month (D50) and three months (3 M) post second dose, and one month post the third vaccination (1 MP3 D).

RESULTS: A total of 193 patients who received three doses of BNT162 b2 mRNA vaccine were included in the study; patients with non-Hodgkin lymphoma (N=54), chronic lymphocytic leukemia (N=49), and Waldenström macroglobulinemia (N=90).. The median age of the entire patient cohort was 73 years, and almost equal numbers of men (47.2%) and women (52.8%) participated in the study. All patient groups had significantly lower NAbs compared to controls at all time points. One month post the third dose (M1 P3 D) NAbs increased significantly compared to previous time points (median NAbs 77.9%, $p < 0.05$ for all comparisons) in all patients. NAbs $\geq 50\%$ were seen in 59.1% of patients, 34.5% of patients with suboptimal responses post-second dose, elicited a protective NAb titre $\geq 50\%$. The increase in median NAb titer from before the third dose to one month post the third dose was significant in the CLL (34.06% vs 76.17% $p=0.001$) and WM (25.31% vs 82.22%, $p < 0.001$) subgroups, but not the NHL subgroup (18.5% vs 31.56%, $p=0.062$). Active treatment, rituximab and BTKi treatment were the most important prognostic factors for a poor NAb response at 1 MP3 D; only 25.8% of patients on active treatment had NAbs $\geq 50\%$. No significant between group differences were observed.

CONCLUSION: In conclusion, our study demonstrates that a third BNT162 b2 booster dose in patients with CLL, WM and less so NHL, improves the humoral response against SARS-CoV-2, as reflected by an increase in NAbs 1 month following the booster dose (median NAb 77.9% 1 MP3 D). Across all patient groups, approximately 34.5% of patients with a suboptimal response 1 month after the second dose, had a protective NAb titer of $\geq 50\%$ 1 month following the booster dose. As expected, antibody titers were lower compared with controls of similar age and gender at all time-points (NAbs $\geq 50\%$ seen only in 59.1% at 1 MP3 D) as humoral immune responses are poorer in patients with underlying B-cell hematological malignancies.

P20. ORAL ANTIVIRALS AGAINST SARS-COV-2 ARE HIGHLY EFFECTIVE IN PATIENTS WITH MULTIPLE MYELOMA AND SYMPTOMATIC COVID-19; RESULTS FROM A SINGLE-CENTER, PROSPECTIVE STUDY

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OBJECTIVE: Patients with multiple myeloma (MM) and COVID-19 have often severe clinical course and high mortality rates (~25%), due to the concomitant disease and treatment-related immunosuppression. Beyond supportive care, antiviral drugs, including molnupiravir and the ritonavir-boosted nirmatrelvir, have been licensed for the treatment of high-risk COVID-19. Although available evidence supports the use of antivirals in patients with SARS-CoV-2 to prevent severe disease, relevant data on MM patients is scarce. This prospective study investigates the effect of the aforementioned antiviral agents on COVID-19 severity and mortality in patients with MM.

METHODS: Consecutive patients with MM and COVID-19 were prospectively enrolled in the study, which started in February 2022. All patients had a positive PCR test for SARS-CoV-2. The patients received either ritonavir-nirmatrelvir or molnupiravir, according to the national guidelines. Treatment with antivirals was initiated during the first five days from COVID-19 symptom onset in patients without need for supplemental oxygen. All patients were at high risk for severe COVID-19 disease due to the underlying MM. Baseline demographic and clinical characteristics, as well as levels of neutralizing antibodies (NAbs) were collected and compared. The effect of different treatments on COVID-19 severity and mortality were examined.

RESULTS: A total of 64 MM patients infected with SARS-CoV-2 were included; 34 (53%) received ritonavir-nirmatrelvir and 30 (47%) molnupiravir. There was no difference in median age (65 ± 10 vs 62 ± 10 years, $p=0.387$), gender (44% vs 50% females, $p=0.638$), body weight (79 ± 14 vs 75 ± 16 kg, $p=0.255$), or any other baseline medical condition ($p>0.05$ for all comparisons), between the ritonavir-nirmatrelvir and the molnupiravir group, respectively. All patients were fully vaccinated (three doses of mRNA vaccines) against COVID-19. Moreover, NAbs titers before the infection were similar [median (IQR) 82% (28.5-95.5) vs 78.5% (20.5-95.25), respectively, $p=0.544$]. Regarding COVID-19 severity, the two groups did not differ significantly in terms of patients with severe symptoms requiring hospitalization [2.9% vs 6.7%, for ritonavir-nirmatrelvir vs molnupiravir, respectively, relative risk (RR) 0.44, 95%CI 0.04-4.63], need for tocilizumab (2.9% vs 6.7%, respectively, $p=0.48$) or corticosteroids (2.9% vs 6.7%, respectively, $p=0.48$). The outcome was also similar when comparing patients with severe/moderate COVID-19 between the two groups (11.8% vs 10.0%, RR 1.18, 95%CI 0.29-4.84, respectively). Finally, mortality was similar for the two groups, reaching 2.9% for patients on ritonavir-nirmatrelvir and 3.3% for those on molnupiravir (RR 0.88, 95%CI 0.06-13.50).

CONCLUSION: In conclusion, ritonavir-nirmatrelvir and molnupiravir are highly effective in preventing severe disease in MM patients with COVID-19 and we suggest that all myeloma patients who are affected by SARS-CoV-2 should start antiviral treatment within five days of diagnosis.

P21. COVID-19 SECONDARY COLD AGGLUTININ SYNDROME

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INTRODUCTION: COVID-19 is a global pandemic triggered by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). The autoimmune hemolytic anemia (AIHA), including cold agglutinin disease (CAD), is greatly affected by COVID-19. Infection, such as the Epstein-Barr virus (EBV) or Mycoplasma pneumonia, and Cytomegalovirus (CMV) can all contribute to the development of CAD (1-4). Herein, we report a patient with CAD associated with COVID-19 in whom anemia improved after intravenous immunoglobulin (IVIG) therapy.

CASE REPORT: A 50-year-old male patient with refractory acute lymphoblastic leukemia without comorbidity was admitted to the hospital to receive remission induction therapy. Laboratory results on day 46 of consolidative FLAG- IDA regimen revealed anemia with disproportionately low hematocrit and elevated mean corpuscular hemoglobin concentration. An analysis of a blood sample that had been pre-warmed to 37 °C produced hematocrit and mean corpuscular hemoglobin concentrations that were proportionate to the measured hemoglobin. Laboratory data were notable for hemoglobin 6.3 g/dL, hematocrit 7.7%, indirect bilirubin 0.23 mg/dL, lactate dehydrogenase 269 U/L, haptoglobin 235 mg/dl. The white blood cell count was $7.05 \times 10^3/\mu\text{L}$ (neutrophils 88.2%, lymphocytes 1%) and the platelet count was $27 \times 10^3/\mu\text{L}$. Other data were ferritin 5315 µg/L, D-dimer 3040 µg/L FEU, and C reactive protein 115 mg/L. Further evaluations revealed a 4+ (high titer) cold agglutinin antibody, and a 3+ direct antiglobulin test. We investigated the underlying cause of CAD and the patient's Covid-19 test was positive. The patient received 400 mg/kg of IVIG therapy for 5 days and his hemoglobin level improved gradually.

CONCLUSION: Due to molecular similarities, SARS-CoV-2 infection can cause autoimmunity and break immunological tolerance. It is possible that the production of pre-existing cold agglutinins and autoantibodies against RBCs is enhanced by COVID-19 (1-4). COVID-19 can cause AIHA, including CAS. Further prospective studies with larger numbers of patients are needed to assess the beneficial effect of IVIG therapy (1-4).

REFERENCES: 1. Cabo J, Brochier A, Saussoy P, van Dievoet MA, Capirchio L, Delire B, et al. Positive direct antiglobulin test in COVID-19 patients: Decision-making process. *Transfus Clin Biol* [Internet]. 2021; 28 (4): 414-9. Available from: <https://doi.org/10.1016/j.traccli.2021.05.010>. 2. Tsukamoto Y, Umeda M, Muto Y, Sugimoto T, Yamauchi M, Ando K, et al. Severe Anemia Due to Cold Agglutinin Syndrome in a COVID-19 Patient with IgM Monoclonal Gammopathy of Undetermined Significance Successfully Treated with Corticosteroids. *Intern Med*. 2022; 61 (11): 1789-93. 3. Al HM, Gareeb I Al, Kaushik A, Kujawska M, El G, Batiha S. Hemolytic anemia in COVID - 19. *Ann Hematol* [Internet]. 2022;(0123456789). Available from: <https://doi.org/10.1007/s00277-022-04907-7>. 4. Lazarian G, Quinquenel A, Bellal M, Siavellis J, Jacquy C, Re D, et al. Autoimmune hemolytic anemia associated with COVID-19 infection. *Br J Haematol*. 2020; 190 (1): 29-31.

P22. SERUM PROCALCITONIN LEVELS IN NEWLY DIAGNOSED HODGKIN LYMPHOMA: CORRELATION WITH OTHER INFLAMMATORY BIOMARKERS

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OBJECTIVE: In the recent years procalcitonin (PCT) has emerged as a useful biomarker for the diagnosis of sepsis and bacterial infection. Inflammatory markers such as C- reactive protein (CRP) and ferritin are elevated in the majority of patients with Hodgkin Lymphoma (HL), a finding that may cause diagnostic problems and unnecessary delay in treatment initiation. However, an ongoing infection very rarely coexists with HL at the time of diagnosis. PCT levels might be helpful in differentiating bacterial infection from non-bacterial inflammation. So far there are no other published studies evaluating serum PCT in previously untreated patients with HL.

METHODS: In order to assess whether and to what extent the underlying chronic inflammatory condition in HL is associated with elevated PCT levels, we recorded serum PCT levels as well as other routine inflammation markers in newly diagnosed HL patients. Values ≤ 0.50 ng/mL were considered as normal. Values between 0.10 and 0.50 were considered as normal but detectable, while values < 0.10 were considered as clearly normal and undetectable. Serum PCT levels were considered elevated if exceeded the cut-off value of 0.50 ng/L.

RESULTS: Among 137 patients diagnosed with HL and treated in our unit between April 2010 and August 2015, 55 had B-symptoms (40%), ESR was ≥ 50 mm/h in 77/130 (59%) and 116 patients (85%) had elevated CRP; the median CRP was 38.1 mg/L (range; 2.97-328.0). The median serum ferritin was 154.1 ng/ml (range; 7-6709) and leukocytosis (WBC $\geq 15 \times 10^9/L$) was recorded in 20 (15%) patients. Serum PCT levels were normal in the vast majority of the patients [clearly normal/undetectable 94/137 (68.5%) and normal/ detectable 41/137 (30%)] with median value < 0.10 ng/ml (< 0.10 -15.90). Only two patients had elevated PCT levels (1.5%). Patients who had serum PCT < 0.10 ng/ml had lower median CRP [25.75; range (2.97-203.0)] compared to patients with PCT ≥ 0.10 ng/ml who had median CRP of 92.50 mg/L (range; 3.34-328.0; $p < 0.001$). Almost all patients (40/41, 97.6%) with detectable PCT levels had also elevated CRP. Compared to patients with normal/undetectable levels, those with PCT ≥ 0.10 ng/ml had more frequently advanced disease stage (83%), B symptoms (73%), ESR ≥ 50 mm/h (82%), anemia (81%), hypoalbuminemia (90%), leukocytosis (27%) and higher serum ferritin, haptoglobin and $\alpha 2$ -globulin levels.

CONCLUSION: This is the first study showing that the inflammatory condition characterizing HL is not associated with meaningful serum PCT elevations, although CRP levels were elevated in 85% of the cases. Only extremely active disease may cause mild PCT elevations, but the frequency of this phenomenon does not exceed 1%. Consequently, normal serum PCT levels may rule out the diagnostic possibility of occult infection in HL patients, thus preventing extensive infection work-up, which may further delay treatment initiation.

P23. A CASE REPORT ALONG WITH LITERATURE REVIEW ON PROLONGED SPONTANEOUS REMISSION OF DIFFUSE LARGE B-CELL LYMPHOMA UPON WITHDRAWAL OF INFLIXIMAB IN A PATIENT WITH PSORIASIS: TREATMENT WITH APREMILAST AND LATE RELAPSE AFTER 3 YEARS

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INTRODUCTION: Diffuse large B-cell lymphoma (DLBCL) is a highly aggressive type of non-Hodgkin lymphoma with heterogeneous molecular signature and lethal outcome if left untreated. On the other side, the potential risk of tumor necrosis factor- α inhibitors (anti-TNF α)-associated lymphoproliferative diseases (LPDs) has been extensively studied in rheumatoid arthritis and Crohn's disease. As a result, a heterogeneous spectrum of iatrogenic lymphoplasmacytic proliferations evolving to lymphomas that may be developed after immunosuppression for autoimmune disorders is described in the WHO classification. However, the association of psoriasis with lymphoma development, especially in the era of novel biologic agents (NBA) has not been clearly elucidated.

CASE REPORT: Herein, we describe a rare case of psoriasis patient having been treated with infliximab and cyclosporine that developed DLBCL with multiple dismal prognostic characteristics and presented to our department for a second opinion, having been already programmed for immunochemotherapy. Interestingly in this case, the "rather accidentally" withdrawal of immunosuppression as the patient was seeking for a second opinion led gradually to spontaneous remission of this unfavorable and aggressive disease. However, while close follow-up had been decided over systemic therapy for this patient, lymphoma relapsed with the same features 3 years later, following treatment with apremilast and leflunomide due to clinical exacerbation of psoriasis. Then, standard immunochemotherapy for DLBCL was administered leading to disease remission along with complete metabolic response until now, having been maintained for 2 years.

CONCLUSION: Only ten such cases of LPD following NBA treatment have been described in the scientific literature so far. Notably in our case, the fact that the patient remained 3 years disease-free avoiding the toxicity of chemotherapy as well as the complete and sustained metabolic response having been achieved after standard chemotherapy for DLBCL, both strongly support that NBA withdrawal under very close monitoring could be a logical therapeutic approach even in patients with aggressive LPD with unfavorable prognostic features.

P24. LEUKEMIC FORM OF HIGH-GRADE B-CELL LYMPHOMA (HGBL) IN A VERY ELDERLY PATIENT WITH MULTIPLE COMORBIDITIES: EFFECTIVE TREATMENT WITH A MINI-R-DA-EPOCH VERSION

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INTRODUCTION: In the 2016 WHO classification of lymphoid neoplasms HGBL was defined as a separate entity, classified into double/triple-hit lymphomas and HGBL not otherwise specified (HGBL-NOS), which do not carry combined c-myc and bcl-2 and/or bcl-6 rearrangements and usually have the morphology of HGBL-DLBCL/BL. HGBL frequently presents with extranodal and bone marrow involvement, but rarely with frank leukemic picture. We report a case falling to the very uncommon category of frankly leukemic HGBL-NOS.

CASE REPORT: In May 2019 an 81-year old male presented with left-sided hearing impairment due to a 4.3 x4.0 cm nasopharyngeal mass. Biopsy indicated a B-cell neoplasm, CD20+, PAX5+, bcl-2+, bcl-6+, MUM-1+, c-myc+(95%), Ki67 60%. Laboratory testing revealed lymphocytosis, elevated LDH and β 2-microglobulin levels and chronic renal disease (creatinine 2.1 mg/dl). Peripheral blood smear showed 50% atypical blastoid cells with basophilic cytoplasm, fine chromatin and nucleoli. Bone marrow biopsy demonstrated 90% infiltration by a blastoid B-cell population (non-GCB phenotype, c-myc 90%) with myc but not bcl2 rearrangement by FISH. CT/MRI staging was negative and the diagnosis of stage IVA HGBL-NOS was established. Medical history included diabetes mellitus type 2, coronary heart disease/ bypass graft, heart failure and chronic kidney disease. Prephase with prednisone and cyclophosphamide was initially administered. Afterwards, we adopted an unpublished "mini" R-da-EPOCH version at 50% of initial doses, based on the R-mini-CHOP experience and the escalation rules of the original R-da-EPOCH. Six cycles were administered with a 25% dose increase at the 3rd and 30% at the 4th cycle, followed by two additional rituximab infusions and intrathecal CNS prophylaxis. End-of-treatment restaging demonstrated complete remission which lasted for almost 12 months, when metastatic lung cancer was diagnosed and the patient passed away soon later.

CONCLUSION: This report aims to present an exceptionally rare case of HGBL-NOS with leukemic involvement and c-myc rearrangements, in the context of t(8; 14) without BL morphology and a non-GCB phenotype. Given the localized nasopharyngeal presentation and the normal haemoglobin/platelet levels, the frank leukemic picture was totally unexpected and the morphology was impressive, mimicking acute leukemia. HGBL prognosis is poor and intensified immunochemotherapy is mandatory. Given the advanced age and serious comorbidities, effective anti-lymphoma treatment was a challenge. The oldest patients in R-da-EPOCH trials were 86-88 years old, however, disturbed renal function was always an exclusion criterion. In addition, full-dose R-da-EPOCH administration appears risky in very elderly, at the same time that R-mini-CHOP is a standard of care for very elderly DLBCL. Moreover, starting from R-mini-CHOP, very elderly patients might tolerate carefully escalated R-CHOP doses. Thus, in this patient, we started with 50% of dose level 1 and adopted an individualized dose escalation process. Despite age and serious comorbidities he tolerated some extent of dose escalation and unexpectedly achieved a complete remission, which was sustained for at least one year and might correspond to cure for this aggressive disease. Further to the exceptional leukemic presentation and morphology associated with this rare histology, this case illustrates the potential for cure in leukemic HGBL-NOS, which justifies individualized moderately intensive chemoimmunotherapy even in very elderly patients with severe comorbidities, given that there is no viable alternative.

P25. A RARE CASE REPORT: PRIMARY INTRAVASCULAR LARGE B CELL LYMPHOMA OF THE CENTRAL NERVOUS SYSTEM

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INTRODUCTION: Intravascular Large B-Cell Lymphoma (IVLBCL) is a very rare subtype of lymphoma and is characterized by obliteration in the lumen of small and medium sized blood vessels. Its annual incidence has been reported as less than 0.5/1,000,000. Central Nervous System (CNS) and skin involvement is more common, but infiltration can be detected in all extranodal organs and tissues. We aimed to present our case who was diagnosed as Primary Central IVLBCL while investigating the etiology of cerebrovascular event

CASE REPORT: A 48-year-old female patient with no known systemic disease other than hypertension was admitted to the neurology department with the complaints of balance disorder, weakness on the left side, and speech disorder. It was learned that the patient had been examined with similar complaints 1 month ago, the etiology of cerebrovascular event could not be determined, and she was followed up with the initiation of antiaggregant treatment. Simultaneous hemorrhagic and ischemic areas in different localizations were detected in cranial imaging. Considering the preliminary diagnosis of vasculitis and gliomatosis cerebri, a brain biopsy was performed from the right temporal region. Short-term pulse steroid was administered while waiting for the biopsy result. While CD20, bcl-2, Bcl-6, c-MYC, KI-67: 95% was found positive, Cyclin D1 was found negative in the patient's brain biopsy material. A diagnosis of IVLBCL was confirmed with the biopsy result. The patient was transferred to the hematology inpatient unit. Lymphadenopathy and hepatosplenomegaly were not detected in the patient who was somnolent and had left hemiplegia on physical examination. Cerebrospinal fluid (CSF) involvement was not observed in the CSF cytology of the patient. No disease infiltration was observed in bone marrow aspiration and biopsy. The patient treated with 2 courses of rituximab, idarubicin, ARA-C, methotrexate (R-IDARAM protocol) and intrathecal methotrexate, ARA-C were administered. Autologous stem cell transplantation was planned, stem cell mobilization was performed at the end of the 2 nd course of treatment and 4.93 million stem cells were collected. 41 Gy cranial radiotherapy (CRT) was applied to the patient whose CNS involvement continued after chemotherapy. After discharge, no residual lesion was observed in the cranial magnetic resonance imaging. Regression of the previously detected vasogenic edema and ischemic areas were also observed. The patient is still being followed in remission and autologous stem cell transplantation planned.

CONCLUSION: IVLBCL is a very rare lymphoma subtype. The mean age at diagnosis is 60, and the ratio of male to female is similar. Although the survival time is limited to months, it has been reported that 3-year survival is high in those who have received autologous stem cell transplantation. Since it is very rare, there is no common opinion on the treatment procedure. Methotrexate-containing regimens are used in patients with central nervous system involvement. Our patient was diagnosed at the age of 48 and was evaluated as a classical variant. Clinical and radiological complete response was obtained after 2 courses of R-IDARAM protocol and CRT.

P26. BELANTAMAB MAFODOTIN INDUCES IMMUNOGENIC CELL DEATH IN MYELOMA CELLS OF PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

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OBJECTIVE: Recently, FDA issued regulatory approval for the innovative monoclonal antibody-cytotoxin conjugate Belantamab Mafodotin (Belamaf), which targets the B-cell maturation antigen (BCMA) and is indicated for relapsed and treatment-refractory multiple myeloma (RRMM) patients. In vitro evidence supports that Belamaf contributes to the depletion of aberrant plasma cells through a multimodal mode of action; this includes the rapid intracellular release of Belamaf's cytotoxic component, monomethyl auristatin F (MMAF), resulting in direct cell killing or the induction of immunogenic cell death (ICD). In this study we analyzed the mechanism of action of Belamaf in vivo. For this, we determined the levels of three ICD markers, high-mobility group box 1 protein (HMGB1), calreticulin (CRT) and the immunopotent fragment of prothymosin a [proTa(100-109)], in the peripheral blood of newly diagnosed MM (NDMM) patients treated with Belamaf.

METHODS: Fifteen transplant ineligible NDMM patients were administered Belamaf as part of the induction scheme, which also included lenalidomide and dexamethasone. Peripheral blood samples were collected before and 24 h post Belamaf infusion. The concentration of HMGB1 was determined in patients' serum with a commercially available highly-sensitive ELISA (Cloud-Clone Corp.) and the levels of ProTa(100-109) were estimated in patients' plasma with an in-house developed competitive ELISA. The expression of CRT was evaluated on circulating plasma cells (CTCs) with flow cytometry, by adding an APC-conjugated rabbit anti-human CRT antibody (EPR3924, Abcam) and its relevant isotypic control, to a multiparametric panel containing fluorochrome-conjugated antibodies against human CD38 (FITC; Cytognos), CD45 (PerCPCy5.5; Becton-Dickinson, BD), CD56 (PE; Cytognos), CD138 (BV421; BD) and CD19 (PeCy7; Beckman Coulter). In total, 2 x10⁶ peripheral blood cells/sample were analyzed.

RESULTS: The concentration of HMGB1 in patients' serum showed a 3-fold increase 24 h after Belamaf administration (mean value prior and post Belamaf 63 ng/ml and 172 ng/ml, respectively; P<0.0001). The levels of ProTa had a clear tendency of increase (mean values 2.6 ng/ml prior vs. 3.2 ng/ml post Belamaf), though the differences did not attain statistical significance, probably due to the limited number of cases analyzed. In all but one patient, Belamaf treatment resulted in the significant decrease of CTCs by approximately one logarithmic unit, within 24 h following administration. In the vast majority of patients, the ratio of the mean fluorescent intensity (MFI) of CRT to the relevant MFI of its isotypic control on CTCs was 1.5-2-fold higher after Belamaf administration, showing that the remaining CTCs expressed higher levels of CRT on their cell surface. Interestingly, patients with a better 3-month response to induction therapy (very good partial response or better) had more profound evidence of ICD than those with partial response, and could be sufficiently clustered together in a PCA model including HMGB1 and ProTa ratios (concentrations post/pre Belamaf administration).

CONCLUSION: Belamaf is an effective drug against BCMA-expressing cells with promising potential for use at various lines of MM treatment. Our study provides clear evidence that Belamaf rapidly (at 24 h) promotes in vivo the ICD of myeloma cells and supports an association between the intensity of ICD induction with the subsequent response-to-treatment.

P27. PROGNOSTIC EVALUATION OF CIRCULATING PLASMA CELLS DETECTED WITH NEXT GENERATION FLOW (NGF) CYTOMETRY IN NEWLY DIAGNOSED MULTIPLE MYELOMA

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OBJECTIVE: The apparent heterogeneity of multiple myeloma (MM) necessitates the identification of novel biomarkers with a strong prognostic value. The presence of circulating tumor cells (CTCs) in newly-diagnosed MM (NDMM) patients has been proposed as a valuable prognostic biomarker. Nevertheless, current methodologies reported to date, yielded heterogeneous results due to variations in their detection efficacy. The purpose of this study was to evaluate the characteristics and prognostic value of CPCs utilizing highly-sensitive next-generation flow (NGF) cytometry, capable to detect aberrant plasma cells (APCs) at the level of 2×10^{-6} .

METHODS: Peripheral blood (PB) and matched bone marrow (BM) samples from 525 NDMM patients were prospectively evaluated with NGF for the presence of aberrant plasma cells (APCs) according to the Euroflow guidelines. The median limit of detection (LOD) for all samples analyzed was 2.2×10^{-6} . The levels of CPCs were correlated with various baseline clinical prognostic parameters, including the cytogenetic status and the ISS stage. The prognostic impact of CTCs on subsequent disease progression was estimated with log-rank test. Multivariate analysis was performed with Cox-proportional hazard model. The median follow-up period since the time of CTC evaluation was 42 months (range: 3-66 months).

RESULTS: CTCs were detected in 468/525 (89.1%) samples [range 0.0002% - 63.8% of peripheral blood nucleated cells (PBNCs)]. The majority of patients with detectable CTCs (402/468; 86%) showed a matched phenotypic profile of aberrant plasma cells in PB and BM. However, 66/468 patients (14%) had phenotypic discrepancies and had significantly higher levels of CTCs than those with a phenotypic agreement at the two sites (0.03% vs. 0.01%; $P=0.008$). Higher CTC numbers ($>0.1\%$ of PBNCs) correlated with increased BM infiltration, ISS-III stage and high-risk cytogenetics ($P<0.0001$). Inversely, the lower presence of CTCs ($\leq 0.001\%$ of PBNCs) correlated with decreased serum $\beta 2$ -microglobulin, higher hemoglobin levels and an elevated BM normal plasma cell compartment ($R^2=0.84$; $P<0.0001$). No association was detected between CTC numbers and the therapeutic response to induction treatment. However, patients with CTCs $\geq 0.02\%$ had a 2.2-fold higher risk of subsequent progression which was independent from ISS stage, induction regimen and baseline cytogenetics (HR: 2.4, 95% CI: 1.65-3.57; $P<0.001$).

Conclusion: NGF enables the detection of rare CTCs in NDMM, many of which would have been falsely missed with a lower sensitivity approach. The increased levels of CTCs have a negative prognostic impact on subsequent relapse, which stands independent from other established prognostic factors. Therefore, it is highly recommended that the evaluation of CTCs is included for the establishment of improved risk-stratification models.

P28. INFILTRATION PERCENTAGE OF BONE MARROW IN MULTIPLE MYELOMA: PROGNOSTIC SIGNIFICANCE AND BONE MARROW ASPIRATE VERSUS BONE MARROW BIOPSY EVALUATION

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OBJECTIVE: Plasma cell infiltration percentage of the bone marrow constitutes a diagnostic criterion of multiple myeloma (MM), nonetheless its prognostic value remains indeterminate and probably insignificant in the era of novel prognostic factors and therapies. However, the bone marrow plasma cell (BMPC) percentage before and after autologous transplant has been recognized as a prognostic factor for disease progression and survival. Moreover, BMPC percentage > 60% represents a marker for high-risk smoldering MM and a criterion for treatment initiation.

METHODS: We evaluated the prognostic significance of BMPC percentage in 345 newly diagnosed patients with MM, 154 female and 191 male, with a median age of 65 (29-88) years. Monoclonal paraprotein was of IgG class in 216 (62.6%), IgA in 70 (20%), IgD in 1 (0.35), light-chain MM in 35 (10%), and non-secretory MM in 23 (7%) patients. Sixty one patients (18%) had renal failure (creatinine > 2 mg/dl). All patients had a bone marrow aspirate result, whereas 228 (66%) had an additional bone marrow biopsy result (BMB). There was a profound correlation between the BMPC percentage of aspiration and BMB ($p=0.01$). In 28 cases the infiltration percentage was underestimated with aspiration over biopsy, whilst the opposite occurred only in 4 cases

RESULTS: The 5-year overall survival (OS) was 55% and median survival was 65 months (95%CI 56-73.7). Patients with less than 50% marrow infiltration demonstrated advanced survival rates compared to patients with BMPC $\geq 50\%$ (median OS 85 vs 48 months respectively, $p < 0.001$). The prognostic value of the BMPC percentage was more obvious in patients with minimal marrow infiltration rate: patients with BMPC <25% showed a survival advantage against those with 25-70% and >70% rates (median OS not reached vs 60 vs 53 months respectively, $p=0.004$). In a multivariate analysis, the BMPC percentage at diagnosis was not an independent prognostic factor for progression free (PFS) and overall survival (OS). The latter was significantly influenced solely by lactate dehydrogenase (LDH), age, disease stage, and renal failure. The BMPC percentage was significantly related to albumin levels, hemoglobin, LDH, disease stage ($p < 0.001$ for all) and renal failure ($p < 0.005$).

CONCLUSION: In conclusion, the BMPC percentage, even though it does not constitute an independent prognostic factor in MM, it provides useful information about its diagnosis and prognosis.

P29. MEASURABLE RESIDUAL DISEASE (MRD) - BASED RESPONSE ONE MONTH (+1 MO) POST AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN MULTIPLE MYELOMA (MM) PATIENTS - A SINGLE CENTRE EXPERIENCE

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OBJECTIVE: MRD study +1 mo post ASCT in MM patients.

METHODS: MRD available data of consecutive MM patients who underwent ASCT during 2020-2022 in our centre were analysed. Undetectable MRD was defined as presence of less than $<1 \times 10^{-5}$ cells with next-generation flow cytometry (NGF). Analysis was performed according to EUROFLOW protocol

RESULTS: We studied 15 male and 13 female MM patients, median age 53 (31-66) years-old, diagnosed with MM type IgG, IgA and light-chain (16, 6 and 6 patients, respectively). ISS and R-ISS at diagnosis was I, II, III in 7, 10, 6 and 9, 9, 3 patients respectively. ISS was not available in 8 patients. Extramedullary plasmacytoma was present in 6/28 patients at diagnosis. Cytogenetic data was available in 26/28 patients. Normal karyotype was detected in 21 patients. The rest 6 patients had complex karyotype, 2 of them hypodiploidy and 4 hyperdiploidy. Regarding FISH assessments 4/24 patients had del17 p, 3/19 had del1 p/add1 q and 4/17 had t(4; 14). No one had t(14; 16) or t(14; 20). 17 p aberration was combined with additional high-risk abnormalities in 4 patients. More specifically, complex karyotype was detected in 2/4 patients, t(4; 14) in 2/4, 1 p/1 q in 2/4. One patient had hypodiploidy concomitantly with 17 p, 1 p and t(4; 14) and presence of extramedullary plasmacytoma. High-risk cytogenetics were detected in 9/27 patients. Induction regimen with VCD was administered in 12 patients, VTD on 11, VRD in 2 and Dara-VTD in 2 patients. In 2/11 VTD and 1/2 VRD patients were switched to VCD due to intolerance. Four out of 12 VCD patients did not achieve VGPR. Thus, two patients were switched to VRD, one to KRd and one to DaraRd. A total of 9 (5-16) treatment cycles were administered. Patients received 3.92×10^6 (2.00-9.33)/kg BW CD34+ autologous stem cells infusions. Neutrophil and platelet engraftment occurred within 11 and 12 days respectively. Disease status pre-transplant was CR/VGPR/PR in 7/15/6 patients. Three patients relapsed during a median follow-up of 10 (1-33) months. More specifically, a male patient with multiple high-risk features relapsed in 4 months post ASCT, one more female also with high-risk features in 17 months and a male standard-risk patient in 30 months. MRD assessment was available one month (+1 mo) post ASCT in 26/28 patients, +6 mo in 8 patients, +12 mo in 4 patients and +18 mo in 5 patients. Pre-ASCT MRD was available in 11/28 patients; only 2 were MRD-undetectable. One-logarithm level MRD decrease was achieved in 4 patients and two-logarithm decrease in 2 patients post-ASCT. 4/9 patients with high-risk cytogenetics were in CR pre-ASCT. Remarkably, 8/9 patients of this group had undetectable MRD +1 mo post-ASCT; the ninth patient was lost to follow-up. Three out of the rest 18 standard-risk patients were in CR pre-ASCT and 7/17 achieved MRD-undetectable disease +1 mo post-ASCT.

CONCLUSION: Despite the limited patient number of the cohort, it is confirmed that ASCT deepens disease response in MM patients. Undetectable MRD is feasible even in high-risk patients. Further follow up is required to extract safer conclusions regarding the sustainability of undetectable MRD in these high-risk patients.

P30. SUSTAINED MRD AND PET/CT NEGATIVITY MAY GUIDE THE DISCONTINUATION OF LENALIDOMIDE MAINTENANCE AFTER ASCT IN MYELOMA PATIENTS

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OBJECTIVE: Patients with newly diagnosed multiple myeloma (MM), who are eligible for autologous stem cell transplantation (ASCT), are usually treated with induction therapy followed by ASCT and lenalidomide maintenance until disease progression or unacceptable toxicity. Both bone marrow and imaging sustained minimal residual disease (MRD) negativity are significant prognostic factors for both PFS and OS, but yet, they are not used for treatment decisions. A notable proportion of patients on lenalidomide maintenance will remain progression-free in the long-term. In this context, it is important to define the optimal duration and the criteria to discontinue maintenance safely.

METHODS: In this prospective cohort study, we included patients with newly diagnosed MM from January 1 st, 2016 to December 31 st, 2019, who received induction treatment and subsequently underwent ASCT followed by lenalidomide maintenance. MRD status was evaluated in patients who had achieved stringent complete remission (sCR) at 6, 12, 24, and 36 months after the initiation of maintenance. MRD samples were evaluated by next generation flow according to the EuroFlow guidelines. Patients who had at least 3 consecutive MRD negative results and had completed 36 months of maintenance, underwent a PET/CT scan. Those with negative PET/CT discontinued lenalidomide maintenance and MRD was performed every 6 months thereafter. In case of MRD conversion from negative to positive and/or relapse from sCR the patient restarted lenalidomide maintenance.

RESULTS: Overall, 151 patients received induction with proteasome-inhibitor-based regimens (VCD or VRD) and underwent ASCT. During a median follow-up of 60.5 months (range 47-74 months), 44 (29.1%) patients had disease progression and 20 (13.2%) patients died. Out of 107 patients who did not progress or die, 34 (31.7%) patients achieved sustained bone marrow MRD negativity and imaging MRD negativity at 3 years and thus they discontinued lenalidomide maintenance, according to study schedule. Their median age at MM diagnosis was 56.5 years (range 43-64). Twenty (59%) patients were males, whereas 19 (56%) had IgG, 9 (26%) had IgA and 6 (18%) had light-chain MM. Six months after discontinuation of lenalidomide maintenance, all evaluable patients (n=21) were found to be MRD negative, while 12 and 18 months post-lenalidomide discontinuation 82% of patients continued to be MRD negative. Two patients restarted treatment with lenalidomide monotherapy after converting from MRD negative to MRD positive at 12 months following the initial completion of maintenance. Both patients remain MRD positive and have no evidence of disease progression at 8 months after lenalidomide restart.

CONCLUSION: We conclude that sustained MRD negativity at 3 years post-ASCT and lenalidomide maintenance might help in the decision to stop maintenance treatment, although this has to be proven in prospective randomized clinical trials. Close follow-up with consecutive MRD testing can trace an early myeloma relapse.

P31. PRESENCE OF SKELETAL-RELATED EVENTS AND ABNORMAL MRI PATTERN AT MULTIPLE MYELOMA DIAGNOSIS INDICATE POOR PATIENT OUTCOMES

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OBJECTIVE: Data on the frequency of skeletal-related events (SREs) in patients with newly diagnosed multiple myeloma (NDMM) at a population-based level in the era of novel agents are rather scarce. In this context, we evaluated the incidence of SREs among NDMM at the time of diagnosis and at the time of first relapse and their impact on survival outcomes. Furthermore, we investigated the correlations among SREs, imaging pattern according to baseline magnetic resonance imaging (MRI), patient, disease and treatment characteristics, and their impact on patient prognosis.

METHODS: This is a prospective, observational study conducted at a single center from 2012 to 2020. The inclusion criteria included: (i) adult patients with NDMM; (ii) patients receiving first- and second-line therapy with novel agents including proteasome inhibitors, immunomodulatory drugs and anti-CD38 monoclonal antibodies; (iii) patients with available MRI examination at baseline. The primary end point of the study was the evaluation of the incidence of SREs at diagnosis, and their impact on survival. Secondary end points included: (i) distribution of different types of SREs at diagnosis and during first or second relapse; (ii) possible correlations between the incidence of SREs with disease and patients' characteristics.

RESULTS: Overall, a total of 370 patients with available baseline MRI were included. Among them, 200 (54%) were males and 99% were Caucasian. The median age at diagnosis was 65 (range 31-92). One third were categorized as ISS stage 1 (34%), one third as ISS stage 2 (35%), and another third as ISS stage 3 (31%). A total of 214 patients (58%) had IgG myeloma subtype, 90 patients had IgA (24%), and 62 patients had light-chain myeloma (17%). The majority of participants (n = 220, 60%) had ECOG performance status (PS) 0 or 1 at diagnosis. One hundred and twenty patients (n = 120, 32%) were classified as capable of only limited self-care or were completely disabled (ECOG PS: 3-4). Interestingly, this was mainly attributed to myeloma bone disease complications (105/120 patients). Overall, 294 (80%) of the patients presented with at least one lytic lesion according to the imaging assessment at baseline with either whole body X-rays or whole body low dose computed tomography at diagnosis. Among them, 208 (56%) presented with at least one SRE at diagnosis. Fractures were the most common reported SRE (48%). The incidence of SREs at diagnosis was higher in patients with osteolytic lesions, abnormal MRI pattern, hypercalcemia, and at least 60% bone marrow infiltration by plasma cells. Importantly, the patients with normal MRI pattern, who did not present with SREs at diagnosis, had statistically significant improved median OS in comparison with the patients who had abnormal MRI pattern and/or presence of SREs at diagnosis (9.3 versus 6.6 years, p = 0.048).

CONCLUSION: In conclusion, our study showed that SREs are frequent at the time of MM diagnosis and may have a prognostic value in combination with baseline MRI findings. Early detection of myeloma bone disease and tailored patient management are essential to optimize patient outcomes.

P32. EXTRAMEDULLARY PLASMABLASTIC PLASMACYTOMA OF THE GALLBLADDER. CASE REPORT AND REVIEW OF THE LITERATURE

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OBJECTIVE: Multiple myeloma (MM) is the most common primary bone-originating tumor, whereas extramedullary plasmacytoma (EMP) is a plasma cell tumor that arises outside the bone and is most commonly found in the head and neck area. Gastrointestinal and particularly gallbladder involvement is exceedingly rare and symptoms, if any, are usually similar to those seen with cholelithiasis. EMPs are cytomorphologically divided from mature to atypical, plasmablastic, or anaplastic neoplastic cells and treatment options usually include surgical resection and/or systemic therapy.

METHODS: In this report, we present a rare case of plasmablastic EMP that was incidentally found on computed tomography (CT) in an asymptomatic patient with only mild right upper quadrant and epigastric tenderness on physical examination. A cholecystectomy was performed with histopathology showing infiltration of the gallbladder by a lambda-chain monoclonal population of CD138+, CD79+, CD56+, CyclinD1+ and IgA+ plasma cells, with a significantly elevated Ki67 index of 98%. An additional fluorodeoxyglucose-positron emission tomography (FDG PET)-CT that was performed due to the onset of left thigh pain also demonstrated a bone plasmacytoma. Further bone marrow (BM) workup did not show evidence of MM. The patient was started on daratumumab, bortezomib, lenalidomide and dexamethasone (DVRD regimen), while also being scheduled for autologous stem cell transplantation. After his fourth treatment cycle a repeat PET-CT showed partial remission of the femoral lesion and no signs of BM involvement or recurrence in the gallbladder. This rare case prompted us to conduct an extensive search of the existing literature concerning extramedullary plasmacytomas of the gallbladder. A total of 14 cases were identified, which were analyzed, in order to present the diagnostic, therapeutic, and prognostic features of the disease.

RESULTS: The majority of patients were male (64.2%), with a median age of 66 years and common presenting symptoms included abdominal pain in 64.2%, jaundice and/or nausea in 21.4%, while 7.1% (1) was completely asymptomatic, similarly to our case. Half of all patients had concurrent MM, but only one had a plasmacytoma with plasmablastic cytomorphology, like our patient with a Ki67 index of 50%. Concerning treatment, 57.1% were treated with cholecystectomy, 14.2% with chemotherapy following cholecystectomy, 21.4% solely with chemotherapy and 7.1% solely with radiation therapy. Death occurred in 14.2% and tumor remission in 85.7% of cases (at the time of case presentation).

CONCLUSION: Lastly, we point out the distinct features of the extremely rare plasmablastic cases, compared to more mature EMP subtypes. Most notably, plasmablastic EMP may be challenging to differentiate from gallbladder lymphoma, has a higher proliferative index and worse prognosis compared to mature EMPs, thus demanding a more aggressive treatment approach.

