Development and Evaluation (GRADE) (WHO Handbook for Guideline Development, 2011). These main questions will be presented and discussed. **Question 1** - What benefits should be expected from cytoreductive drugs over phlebotomy in "low-risk" PV patients? **Question 2** - Which "low-risk" PV patients might benefit from cytoreductive drugs? **Question 3** - Which cytoreductive drugs should be preferred in "low-risk" patients? **Question 4** - Which PV patients treated with HU should receive a different cytoreductive 223 drug? The results and recommendations were approved by Delphi consensus rounds and virtual meetings. The EP recommended that PV patients younger than 60 years old and/or free of prior thrombotic events start cytoreductive drug therapy if at least one of the criteria is fulfilled: 1) strictly-defined intolerance to phlebotomy, 2) symptomatic progressive splenomegaly, 3) persistent leukocytosis (> 20.000/mmc), 4) progressive leukocytosis 6) inadequate hematocrit control requiring phlebotomies, 7) persistently high cardiovascular risk, and 8) persistently high symptom burden. RopegIFN or pegylated IFN-alpha-2a was the recommended cytoreductive drug for the above patients. Finally, the EP suggested that either rIFNα or ruxolitinib should be considered for patients treated with hydroxyurea but requiring a therapy change. The purpose of cytoreductive therapy is to obtain hematological responses, since normalizing blood counts with phlebotomy and/or cytoreductive drugs is thought fundamental to reduce the incidence of both arterial and venous thrombosis. However, despite achieving similar hematological responses, it is likely that the various cytoreductive drugs administered both in the first and second line do not have equal antithrombotic activity. In fact, for each of the three cytoreductive drugs currently used in clinical practice (Hydroxyurea [HU], Interferon [IFN], Ruxolitinib [Ruxo]), additional antithrombotic properties are recognized. For instance, HU is thought to have minimal antiinflammatory properties [19], whereas there is evidence that IFN and Ruxo can normalize inflammatory markers, further mitigating thrombotic risk [20, 21]. Unfortunately, clinical trials comparing head-to-head the standard HU with IFN or Ruxo did not provide solid evidence of superiority of the latter in terms of thrombosis reduction. It should be noted, however, that the design of these studies envisaged hematological responses as primary end-points and the trials were not powered to directly evaluate a decrease in thrombosis risk. On the other hand, it is not yet demonstrated that hematological response is a valid surrogate of thrombosis [22-24]. Both the National Comprehensive Cancer Network (NCCN) and the European Leukemia Net (ELN) recommend a risk-stratified approach to the treatment of an individual patient and in ET and PV patients are [Treatment focuses primarily on mitigation of thrombosis risk and most patients with ET and PV should receive low-dose aspirin As the prognosis for ET and PV varies substantially between patients, both the National Comprehensive Cancer Network (NCCN) and the European Leukemia Net (ELN) recommend a risk-stratified approach to the treatment of an individual patient [4,8]. This is exemplified by two large retrospective studies evaluating prognostic factors and outcomes among patients with MPNs [9,10]. Conventionally, patients age ≥ 60 years or with prior thrombosis are classified as high-risk [4]. However, the association of a higher thrombosis risk with the presence of JAK2/MPL mutations in ET patients is increasingly recognized and included in the validated International Prognostic Score of Thrombosis in ET (IPSET) [5,11]. The impact of other factors such as leukocytosis in PV patients or the influence of co-mutations continues to evolve and is not part of the current guideline recommended approach to treatment selection [5,6,12–14]. Treatment focuses primarily on mitigation of thrombosis risk and most patients with ET and PV should receive low-dose aspirin [4,8,15]. prevention and treatment of major arterial and venous thrombosis in PV and ET with the aim to report: (i) quantitative estimates of major thrombosis incidence; (ii) rates of thrombosis under treatment with cytoreductive drugs; (iii) incidence of thrombosis under aspirin and oral anticoagulants.

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Sp06

VACCINATION AGAINST SARS-COV-2 FOR MYELOMA PATIENTS: DO WE NEED A BOOSTER DOSE AND HOW FREQUENT?

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Patients with multiple myeloma (MM) are at increased risk for severe COVID-19 disease, hospitalization and death. In this context, it is essential to maintain an adequate immune profile. A third (first booster) dose has been offered with priority to patients with MM due to their immunocompromised status and the suboptimal immune response to the initial vaccination schedule against COVID-19. Three important studies that investigate the immune profile following a booster vaccination with a mRNA-based vaccine have been recently published. The first study was published in Blood (2022;139 (9):1409-1412) by Terpos *et al* and included 167 consecutive patients with MM who were vaccinated with the booster BNT162b2. All patients had been fully vaccinated with the 2-dose BNT162b2. Median time between the second and the booster dose was less than 5 months. The booster dose significantly improved the median neutralizing antibody (NAb) response in patients with MM (27.1% before to 96.7% after the third dose $p<0.001$). Importantly, almost half of the patients with suboptimal NAb responses at one month after the second dose of BNT162b2 developed NAb titers of at least 50% at one month after the booster dose. Treatment with anti-BCMA agents emerged as a significant adverse predictive factor for NAb response to the booster shot. None of these patients achieved a NAb level above the positivity threshold. The second study was published in Cancer Cell (2022;40(5):441-443) by Aleman *et al* and included 261 patients with MM with available anti-SARS-CoV-2 spike (S) IgG measurements at least 1 week after the third vaccine shot. Anti-S IgG levels increased significantly after administration of the third dose both in patients with and without prior history of COVID-19 ($p<0.001$), although the depth of humoral response was inferior to healthy individuals. Importantly, 60 out of 68

seronegative patients before the third dose seroconverted with the booster shot. Neutralizing titers against the Omicron variant after the booster dose were detectable in only 54% of MM patients who responded to two doses of the vaccine (they had adequate protection against Wuhan variant) and in none of those who did not respond in the initial vaccine doses. The third vaccine shot significantly increased spike-specific CD4+ T cell-mediated cytokine responses, as well. The third study was published in Cancer Cell again (2022;40(6):587-589) by Enssle *et al* and included 71 patients with MM and 23 healthy controls. The authors observed a 4-fold increase in anti-S IgG levels from a median of 193.2 BAU/ml before to 776.0 BAU/ml after the booster dose in the MM cohort. However, a poor neutralization capacity against the Omicron variant was observed. Regarding cellular immunity, MM patients showed a significant T-cell response against the wild-type virus, the Delta variant and the Omicron variant, although the response was attenuated in the latter case. Overall, the abovementioned studies advocate for prioritizing patients with MM, especially those on anti-BCMA treatments, for additional booster shots, ideally with variant-adapted vaccines, or with the prophylactic administration of monoclonal antibodies against SARS-CoV-2. The standard vaccine seems not to prevent the infection with omicron variant(s) and thus general preventive measures including mask wearing and avoiding crowds remain important for these vulnerable patients.

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Sp07

REDUCED INTENSITY CONDITIONING FOR ALLOGENEIC STEM CELL TRANSPLANTATION (HSCT) IN ACUTE MYELOID LEUKEMIA

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Allogeneic transplantation (HSCT) is an effective curative therapy for high risk acute myeloid leukemia (AML) which account for 38% of the transplants in Europe (1). Prior to HSCT, a conditioning or preparative regimen is administered. The conditioning regimen has 2 components; one target the myeloid system aiming in eradication of the leukemic clones, while the other target the immune/lymphoid system to ensure engraftment and to prevent rejection. Some of the compounds used in the conditioning are more myeloablative in nature for example busulfan or melphalan) 2-4) while others are more lymphodepliting like fludarabine or Cytoxan (5). Traditionally, the pre HSCT conditioning was myeloablative (MAC) and includes total body irradiation (TBI) in combination with cyclophosphamide (CY) (2-3). High-dose busulfan (Bu) is the most commonly used TBI-free-based myeloablative conditioning (2-3). In HSCT from unrelated or mismatched donors the pre transplantation conditioning typically includes serotherapy with anti-thymocyte globulin (ATG) or the CAMPATH monoclonal antibody in order to avoid rejection and ensure engraftment while preventing graft versus host disease (GVHD) (5). However, the MAC is typically associated with significant morbidity and mortality due to the toxicity of the preparative regimen, GVHD, and the immune-deficient state that accompanies the procedure (2,5-6). This is especially true in patients above the age 55-60 years old and in patients with comorbidities which are the majority of AML patients. Extensive research, including pharmacokinetic and pharmacodynamics studies has been directed therefore towards the development of safer and less toxic conditioning regimens for HSCT, optimizing the conditioning allowing its applications to elderly patients and patients with comorbidities (2,5-6). These modern conditioning regimens which are based in part on the immune-mediated graft versus leukemia (GVL) effect are in principle low-dose, less toxic and tolerable conditioning regimens termed reduced intensity (RIC) with different immunosuppressive and myelosuppressive properties (5-7). These regimens combine immunosuppressive agents (such as fludarabine with or without serotherapy or targeted therapy with agents with moderate myelosuppressive effects or novel agents. However, they typically result in higher relapse rate especially in patients undergoing HSCT while not in remission and in patients with high risk leukemia including patients with adverse cytogenetics, high risk mutations and patients with positive measurable residual disease (MRD) at time of transplants. The optimal regimen is thus the one with intensive anti-leukemic activity, but with limited toxicity-the so called reduced toxicity regiments (RTC). These novel regimens are mostly fludarabine based and incorporate drugs like melphalan; thiotepa; treosulfan and clofarabine (8-11). Other protocols are the so called TBF protocol that include two alkylating agents like busulfan and thiotepa(9,11) and the FLAMSA protocol that includes fludarabine, cytarabine, and amsacrine (11).The RIC and RTC regimens enable HSCT in elderly patients and those with comorbidities reducing drastically transplant related mortality and organ toxicities in combination with improved anti leukemic effect. Efficient safe pre transplant conditioning protocols are continuing to be developed. Future protocols will most probably incorporate specific anti leukemic targeted novel compounds as well as monoclonal and radiolabeled antibodies.

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Sp08

LESSONS FROM THE EUROPEAN AND ISRAEL NATIONAL MDS REGISTRY

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On behalf of the Israeli MDS working group and EUMDS Registry/ XIII Eurasian Hematology Oncology Congress (EHOC) 2022. The myelodysplastic syndromes (MDS) are a group of clonal stem cell diseases with cytopenias and a tendency to transform to leukemia. Despite the progress, there is still lack of real world data about the disease. In 2008, top European experts