malignancies. The development of anti-CD19 CAR T-cell therapy represents a major advance in the treatment of patients with chemorefractory B-cell malignancies.

https://doi.org/10.1016/j.htct.2022.09.1188

Sp04

HOW I TREAT DOUBLE-HIT LYMPHMOMA AND HGBL, NOS

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Introduction: The new world health organization (WHO) classification on lymphoid neoplasms, the WHO-HAEM5, renames the former group that double-hit lymphomas were in as "diffuse large B-cell lymphoma/high-grade B-cell lymphoma with MYC and BCL2 rearrangements (DLBCL/HGBL-MYC/BCL2)". This is mainly to highlight that the presence of MYC and BCL2 rearrangements form a unique phenotype, different than the MYC and BCL6 rearrangements (present in the former classification). Those lymphomas are composed of large or intermediate or blastoid cells, with aggressive clinical course and tendency to be resistant to standard chemotherapy. It's a group ideal for new therapies, such as the bispecifics and CAR T-cells, but lack data to support this since are underrepresented in clinical trials. Retrospective studies, with its inherit bias, consistently points to worst prognosis and poor outcomes with standard RCHOP treatment. How to best approach this hard-to-treat lymphoma is still a matter of debate. **Treatment considerations:** Roughly 65% of patients with DLBCL are cure with 6 cycles of RCHOP. When considering this regimen for HGBL, event-free survival (EFS) has been reported as low as 20% in 3 years. More intensive regimens, like R-DA-EPOCH and R-CODOX/M-IVAC, could increase this response, based on retrospective studies, with EFS 3y close to 80%. The role of autologous transplant as consolidation is controversial, and it's not routinely indicated. However, there are data that patients treated with RCHOP could increase progression-free survival (PFS) with this strategy, perhaps eliminating the difference between more intensive regimens. The lack of a direct comparison in a randomize phase 3 study between RCHOP or more intensive protocols precludes a firm conclusion. In the Alliance/CALGB 50303 study, that compared RCHOP with R-DAEPOCH in patients with DLBCL and PMBCL, there were no differences in 2y PFS between arms. But the number of patients with MYC rearrangement was too small to any conclusion regarding HGBL. Dunleavy et al conducted a phase 2 study with R-DA-EPOCH in 53 patients with MYC-rearranged DLBCL (24 were double-hit). EFS 4y was 71% and overall-survival (OS) 4y was 77%. Although this looks pretty good compared to the historic RCHOP, it's not a randomize study. New therapies have emerged as possible rescue in the relapsed/refractory DLBCL population, a group of patients with a dismal prognosis. The chimeric antigen receptor (CAR) T-cells have become a new standard of care for those patients, when available. Albeit with a small number of patients, the three main products (axi-cell, tisa-cell and lisocell), used for rescue of DLBCL patients, had shown activity against HGBL. That holds true in latter lines and as a first salvage treatment, as the recent trials comparing with autologous transplant. The zuma-12 is a phase 2 study with axi-cell as first-line of treatment with high-risk DLBCL patients, a population enriched with HGBL. Early reports are impressive, with nearly 80% of complete remissions. However, long term follow-up will be necessary to see with the responses are durable. Bispecifics are other very important players on that field, with the first reports of high activity in high-risk DLBCL, even after CAR T-cell failure. **Conclusions:** HGBL is an aggressive form of lymphoma, with tendency of a worst prognosis with conventional treatment. Intensive regimens seem to fare better than RCHOP, although with more toxicity and no randomize studies supporting this indication. New treatments, mainly CAR T-cells and bispecifics, are very promising and possibly will became standard of care for such patients but were in the therapy algorithm is still to be decide.

https://doi.org/10.1016/j.htct.2022.09.1189

Sp05

APPROPRIATE MANAGEMENT OF POLYCYTHEMIA VERA WITH CYTOREDUCTIVE DRUG THERAPY

EUROPEAN LEUKEMIANET 2021 RECOMMENDATIONS

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Classical Philadelphia-negative myeloproliferative neoplasms (Ph-neg MPNs) including polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF) are characterized by uncontrolled clonal proliferation of multipotent bone marrow progenitors, sustained by acquired mutations in JAK2, CALR and MPL genes. Expansion of the mutated clone triggers an inflammatory response that influences the development of associated vascular complications and disease progression into MF and acute leukemia. This presentation will focus on the recent recommendations by ELN in low-risk PV patients. According to ELN and NCCN patients with PV should be managed by the risk of thrombosis and cytoreductive drugs are recommended in high risk (over 60 y and/or prior thrombosis) while low-risk should be treated with low-dose aspirin and phlebotomy only. These guidelines have been reviewed by international recognized experts in the field of MPN. In January 2021, ELN promoted an international project specifically devoted to updating the clinical indications for using cytoreductive drugs in treating PV. The Expert Panel (EP), the chair and the methodologist were asked to grant the highest quality of the recommendations by adhering to standard methods for developing clinical practice guidelines, namely Grading of Recommendations Assessment,

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.

https://doi.org/10.1016/j.htct.2022.09.1190

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