that has not been used previously could be recommended[8]. BV and PD1-blockers are incorporated into the pre-ASCT salvage regimens in clinical trials. In the phase II BRaVE study, BV added to DHAP provided a complete metabolic response rate of 81% before ASCT, with a 2-year PFS and OS rates of 74% and 95%, respectively[9]. Similarly, pembrolizumab in combination with GVD provided an overall response rate (ORR) of 100%[10]. BV and nivolumab combination resulted in an ORR of 85%. The 3-year PFS rate for ASCT group was 91%[11]. Regarding these data, the need for ASCT will be an important point of debate in the next years. In case of primary refractory disease, chemotherapy-based salvage regimens remain the standard. Combination treatment with BV and nivolumab resulted in a 21-month PFS of 65% in this group[11], which may be a satisfactory option in the future. Post-ASCT consolidation with BV is now standard of care in patients with risk factors defined by AETHERA trial[12], which is supported by real-world data including pre-treated with and responsive to BV patients[13]. Novel agents are not recommended in the front-line management of early-stage disease. ECHELON-1 study performed on treatment-naïve stage III/IV cHL patients reported 6-year PFS, and OS ratio were 82.3% and 93.9% for BV-AVD cohort versus 74.5% and 89.4% for ABVD cohort[14]. Beside advanced stage cases, BV-based therapies should be considered for elderly, unfit patients who cannot tolerate combination chemotherapies, as they are associated with longer duration of response compared to BV monotherapy[8]. Giving decision about novel therapies, major adverse events, such as neuropathy for BV and immune related events for PD1-blockers. Optimal timing of BV and PD1-blockers and treatment strategies in case of resistance to novel agents are critical questions for the future of cHL management, which hopefully will be answered by the results of clinical trials and real-world data.

https://doi.org/10.1016/j.htct.2022.09.1187

Sp03

TREATMENT OF MANTLE CELL LYMPHOMA IN TRANSPLANT NON-ELIGIBLE PATIENTS

Valeh Huseynov

National Hematology and Transfusion Center, Azerbaijan

MCL is a rare but usually aggressive non-Hodgkin lymphoma that most commonly affects the elder population. It is now recognized as a heterogeneous disease with variable biologic and clinical behavior. MCL is considered incurable with current therapies and has historically been associated with a poor prognosis. . Large gains were made in the first decade of the new century when clinical trials established the importance of high-dose therapy and autologous stem-cell rescue and high-dose cytarabine in younger patients and the benefits of maintenance rituximab and bendamustine in older patients. Patients with mantle cell lymphoma (MCL) usually respond to initial combination chemotherapy, but the disease inevitably relapses and often follows an aggressive course. Treatment paradigms have evolved along two lines. Younger, fit mantle cell lymphoma (MCL) patients are generally treated with intensive strategies and older less fit patients with non-intensive strategies. Management of patients with newly diagnosed mantle cell lymphoma (MCL) depends on the age and fitness of the patient. For younger patients, the commonly accepted standard of care is a high-dose cytarabine-based induction chemotherapy followed by autologous stem cell transplantation (ASCT). In newly diagnosed patients with MCL ineligible for intensive therapy and ASCT, the standard-of-care has generally been R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), followed by rituximab, maintenance. In recent years, bendamustine-based therapy has been increasingly adopted for older MCL patients and more recently, vincristine has been replaced by bortezomib in the R-CHOP combination as VR-CAP for previously untreated patients. Traditionally, the treatment of MCL has been determined by patients being deemed “transplant-eligible” or “transplant-ineligible”. In particular, greater depth of understanding of the molecular pathophysiology of MCL has resulted in an explosion of specifically targeted new efficacious agents. In particular, agents recently approved by the Food and Drug Administration include the proteasome inhibitor bortezomib, immunomodulator lenalidomide, and Bruton's tyrosine kinase inhibitor ibrutinib. Newer data suggest more tolerable front-line therapy, including regimens incorporating novel agents, may produce similar outcomes to intensive historical induction regimens. This may in turn preclude fewer patients from autologous stem cell transplant and produce better long-term outcomes in transplant-ineligible patients. In the relapsed/refractory setting, novel agents and combination regimens are improving outcomes and changing the landscape of treatment. New therapies with distinct mechanisms of action, including novel immunotherapeutics, antibody-drug conjugates, and non-covalent BTK inhibitors, have demonstrated great potential for improving outcomes post–BTK inhibitor failure in relapsed/refractory mantle cell lymphoma. Although cBTK inhibitor has transformed the treatment landscape in B-cell malignancies, the majority of patients will eventually experience disease progression or treatment intolerance. There are 2 oral BTK inhibitors approved for use in relapsed MCL: ibrutinib and acalabrutinib. Acalabrutinib, originally referred to as ACP-196, is a novel, irreversible BTK inhibitor that was designed to be more kinase-selective than ibrutinib. Orelabrutinib is an orally administered, potent, irreversible and highly selective BTK-inhibitor being developed the treatment of B cell malignancies and autoimmune diseases. Tirabrutinib irreversibly and covalently binds to BTK in B cells and inhibits aberrant B cell receptor signalling in B cell-related cancers and autoimmune diseases. Zanubrutinib received accelerated approval in the USA on 14 November 2019 for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, based on overall response rate (ORR) seen in phase II and I/II clinical trials. Palbociclib is a specific, potent, oral inhibitor of CDK4/6 capable of inducing a complete, prolonged G1 cell cycle arrest (pG1) in Rb+ MCL cells. Zilovertamab vedotin is an antibodydrug conjugate, which binds specifically to receptor tyrosine kinase-like orphan receptor-1 (ROR-1), an oncoprotein that is pathologically expressed in mantle cell lymphoma and other

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

Guilherme Duffles [a,b],
Carmino Antonio De Souza [a]

[a] *Hematology and Blood Transfusion Center, University of Campinas (UNICAMP), Campinas, SP, Brazil*
[b] *Hematology Service, Oncologia D'Or, Rede D'Or São Luiz, São Paulo, SP, Brazil*

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

Tiziano BARBUI

Foundation for Clinical research- Ospedale Papa Giovanni XXIII- Bergamo- Italy

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,