VIEWPOINTS

Hematologic Updates from ASH 2022

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Novel data on myeloid malignancies

In 2022, both the World Health Organization[1] (WHO) and the International Consensus Classification (ICC)[2] revised their guidelines for classifications of myeloid neoplasms. At last year's ASH Meeting, these novel classifications were validated in a retrospective analysis of patients with myelodysplastic syndrome (MDS), specifically the uniqueness of molecularly defined entities.[3] This study underlined the clinical utility of recognizing multi-hit *TP53* MDS as a separate entity due to its strong association with poor survival.

In low-risk del(5q) MDS, the final results from the European phase III Sintra-REV trial demonstrated that early lenalidomide treatment in patients with anemia without transfusion requirement compared with placebo significantly delayed transfusion dependency (median, not reached vs 11.6 months; p=0.003) and reduced the risk of transfusion dependency by 70% (HR: 0.302 [95% CI: 0.132–0.692]; p=0.005).[4] Furthermore, 94.1% of patients treated with lenalidomide achieved a cytogenetic response versus none of those treated with placebo (p<0.001), with a complete response (CR) rate of 87.5%. The study was flawed by using placebo instead of erythropoietin stimulating agents (ESA) as an inappropriate comparator, however, the high rate of cytogenetic responses suggests a relevant disease-modifying effect that cannot be achieved by ESA. Moreover, retrospective data suggest that patients with cytogenetic remissions can maintain treatment-free remission, a possibility that merits further investigations in follow-up studies.

Recent advances in leukemias and lymphomas

In acute myeloid leukemia (AML), controversial findings were presented from the phase III ASAP trial investigating the benefit of salvage chemotherapy before allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients with relapsed or refractory (R/R) disease.[5] Patients with poor responsive non-favorable risk AML after first induction therapy or first untreated disease relapse were randomized 1:1 to receive either high-dose cytarabine and mitoxantrone followed by conditioning regimen (remission-induction arm) or undergo watchful waiting and sequential conditioning, with permitted low-dose cytarabine or single doses of mitoxantrone when clinically needed (disease control arm). Intensive remission-induction

chemotherapy compared with sequential conditioning prior to allo-HSCT did not improve disease-free survival (DFS) or overall survival (OS). Watch & wait strategy followed by sequential conditioning and allo-HSCT achieved comparable overall CR rates and survival outcomes. These data are potentially practice-changing, but it is reasonable to wait for confirmatory studies.

Data from the phase III ALPINE study suggests zanubrutinib, a next-generation Bruton tyrosine kinase (BTK) inhibitor, as a potential new standard of care (SoC) in patients with R/R chronic lymphocytic leukemia (CLL).[6,7] Results presented during the Late-Breaking Abstract session showed that zanubrutinib compared with standard ibrutinib significantly improved both the overall response rate (ORR) (86% vs 76%; p=0.0007) and progression-free survival (PFS) (2-year rate, 79.5% vs 67.3%, HR: 0.65 [95% CI: 0.49–0.86]; p=0.0024), while being associated with less cardiotoxicity.

During the plenary session, potentially practice-changing data in mantle cell lymphoma (MCL) were presented from the TRIANGLE trial, which investigated ibrutinib use in the first-line setting and where also the Swiss Group for Clinical Cancer Research (SAKK) participated.[8] Patients were randomized 1:1:1 to receive rituximab (R) plus alternating courses of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) and dexamethasone, cytarabine, cisplatin (DHAP) with (arm A+I) or without ibrutinib (arm A, control) followed by autologous stem cell transplantation (ASCT) or ibrutinib with R-CHOP/R-DHAP without ASCT (arm I), with a 2-year ibrutinib maintenance in the experimental arms. The addition of ibrutinib to standard treatment prior to ASCT significantly improved failure-free survival (FFS) (A+I vs A, 3-year FFS: 88% vs 72%, HR: 0.52; p=0.0008), while standard treatment with ASCT was not superior to ibrutinib-containing therapy without ASCT (A vs I, 3-year FFS: 72% vs 86%, HR: 1.77; p= 0.9979), thus challenging the benefit of ASCT in the context of an ibrutinib-containing regimen. Notably, comparison between the ibrutinib arms is still ongoing.

Studies on paroxysmal nocturnal hemoglobinuria and immune thrombocytopenia

In non-malignant hematologic disorders, results from the phase III APPLY-PNH trial support the use of iptacopan, an oral factor B inhibitor, in paroxysmal nocturnal hemoglobinuria (PNH).[9] In this study, patients with refractory hemolytic anemia despite prior standard therapy with intravenous inhibitors targeting the late complement pathway component C5 received iptacopan or SoC. Treatment with iptacopan resulted in clinically meaningful and significant improvement in hematological responses compared with SoC, with 82% of patients experiencing a ≥2 g/dL increase in hemoglobin (Hb) from baseline and 69% reaching an Hb level of ≥12 g/dL.

In immune thrombocytopenia (ITP), data from the phase III ADVANCE trial were presented on the safety and efficacy of intravenous efgartigimod, a therapy inhibiting neonatal Fc receptor-mediated clearance of immunoglobulin G (IgG), including platelet autoantibodies.[10] Efgartigimod versus placebo was associated with higher rates of sustained platelet response (21.8% vs 5.0%; p=0.0316), with an early increase in platelet counts. The early and sustained reduction in total IgG levels with efgartigimod is beneficial in ITP and might be also advantageous in other autoimmune diseases.

Conflict of interest

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Author contributions

The author has created and approved the final manuscript.

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