Emerging Therapies in Myelofibrosis: Highlights From SOHO 2020

Lisa Nodzon, PhD, ARNP, AOCNP®, of Moffitt Cancer Center, highlights new therapies in development for myelofibrosis that were discussed by Srdan Verstovsek, MD, PhD, of The University of Texas MD Anderson Cancer Center, at the 2020 SOHO Annual Meeting.

Several clinical trials investigating novel agents and combinations in myelofibrosis (MF) are showing promise. Such data have implications for advanced practitioners (AP) managing disease-related symptoms associated with splenomegaly, constitutional symptoms, and symptomatic anemia.

At present, two Janus kinase inhibitors (JAKi) are U.S. Food & Drug Administration approved for frontline MF: ruxolitinib (Jakafi) and fedratinib (Inrebic). However, patients with MF who are red blood cell (RBC) transfusion dependent, either progress on or are resistant to or intolerant to ruxolitinib, have disease-related cytopenias such as anemia or thrombocytopenia, or have high-risk disease, continue to have unmet needs. An emerging focus is on exploring novel agents or ruxolitinib-based combinations that may augment disease responses by targeting alternative pathways to yield more favorable outcomes in subpopulations.

LUSPATERCEPT

Luspatercept (Reblozyl), an erythroid maturation agent that enhances late-stage erythropoiesis, showed a clinically significant response in a phase II trial for MF-associated anemia (Gerds et al., 2019). Interim analysis reported the median duration of RBC transfusion independence ≥ 12 weeks was 39 weeks and 32 weeks for patients receiving concomitant ruxolitinib vs. those not receiving ruxolitinib, respectively. Treatment-related adverse events (AE) included hypertension (11%), diarrhea (4%), and bone pain (8%). This promising activity led to the phase III double-blind INDEPENDENCE trial, which is actively enrolling high-risk or transfusion-dependent MF patients and comparing the efficacy and safety of luspatercept with concomitant JAKi therapy. Positive study results are encouraging as JAKi are a mainstay in MF management, and transfusion-dependent anemia is an area of unmet need.

Key Points

- There is an emerging focus on clinical trials with the two approved JAK inhibitors, ruxolitinib and fedratinib, as monotherapy or as ruxolitinib-based combinations.
- Advanced practitioners should be aware of the on- and off-target effects of novel therapies.

MOMELOTINIB

Emerging JAKi on the horizon in phase III studies with promise for improving disease-related anemia, splenomegaly, or thrombocytopenia in the second line include momelotinib and pacritinib. The MOMENTUM trial is comparing momelotinib to danazol for primary MF (PMF), post-polycythemia vera MF, or post-essential thrombocytopenia MF previously treated with a JAKi and in patients who are anemic (hemoglobin < 10 g/dL). Momelotinib has demonstrated improvement in RBC transfusion dependence in a phase I/II study of high- and intermediate-risk MF patients (Tef-

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feri et al., 2018). Grade 1/2 peripheral neuropathy was reported in 47% of patients. Peripheral neuropathy may not be reversible and therefore requires careful monitoring. A first-dose effect of dizziness, hypotension, nausea, flushing, and headache has been reported.

PACRITINIB

The ongoing PACIFICA trial explores pacritinib vs. physician's choice in front- and second-line patients with PMF or secondary MF with preexisting severe thrombocytopenia (platelets < 50,000/μl), which portends a poor prognosis (Harrison et al., 2019). Primary analysis will examine spleen volume reduction at 24 weeks and secondary analyses will explore ≥ 50% reduction in total symptom score. Nonhematologic AEs are mainly gastrointestinal (nausea and diarrhea). One advantage is that pacritinib is not as myelosuppressive as other JAKi.

IMETELSTAT

For intermediate-2 or high-risk MF patients, imetelstat, a telomerase inhibitor, is showing promise in a phase II trial with patients who are refractory to JAKi, with data suggesting a survival benefit of 29.9 months with 9.4 mg/kg compared with 19.9 months with 4.7 mg/kg (Mascarenhas et al., 2018). A phase III trial exploring overall survival as an endpoint with imetelstat at 9.4 mg/kg every 3 weeks compared with best available therapy for intermediate-2 or high-risk MF is anticipated to open in 2021. Notable AEs include grade 3/4 neutropenia, thrombocytopenia, and nausea.

The Advanced Practitioner Perspective

Evolving data from clinical trials exploring novel agents require APs to stay current in order to improve the quality of care for patients with MF. Diverse novel agents in the pipeline have unique mechanisms of action capable of producing AEs whether given as monotherapy or overlapping in combination. Advanced practitioners are in a pivotal position to provide disease education, the rationale behind the use of novel agents, and treatment-related toxicity management.

Disclosure

Dr. Nodzon has consulted for AbbVie, AstraZeneca, and Genentech.

References

Gerds, A., Vannucchi, A., Passamonti, F., Kremyanskaya, M., Gotlib, J., Palmer, J.,...Verstovsek, S. (2019). A phase 2 study of luspatercept in patients with myelofibrosis-associated anemia [Abstract 557]. *Blood (ASH Annual Meeting Abstracts), 134*(supplement_1). https://doi.org/10.1182/blood-2019-122546

Harrison, C. N., Gerds, A. T., Kiladjian, J.-J., Döhner, K., Buckley, S. A., Smith, J. A.,...Verstovsek, S. (2019). Pacifica: A randomized, controlled phase 3 study of pacritinib vs. physician's choice in patients with primary myelofibrosis, post polycythemia vera myelofibrosis, or post essential thrombocytopenia myelofibrosis with severe thrombocytopenia (platelet count <50,000/mL) [Abstract 4175]. *Blood (ASH Annual Meeting Abstracts), 134*(supplement_1). https://doi.org/10.1182/blood-2019-129245

Mascarenhas, J., Komrokji, R., Cavo, M., Martino, B., Niederwieser, D., Reiter, A.,...Kiladjian, J.-J. (2018). Imetelstat is effective treatment for patients with intermediate-2 or high-risk myelofibrosis who have relapsed on or are refractory to Janus kinase inhibitor therapy: Results of a phase 2 randomized study of two dose levels [Abstract 685]. *Blood (ASH Annual Meeting Abstracts), 132*(supplement 1). https://doi.org/10.1182/blood-2018-99-115163

Tefferi, A., Barraco, D., Lasho, T. L., Shah, S., Begna, K. H., Al-Kali, A.,...Pardanani, A. (2018). Momelotinib therapy for myelofibrosis: A 7-year follow-up. *Blood Cancer Journal, 8*(3), Article number: 29. https://doi.org/10.1038/s41408-018-0067-6