Current clinical trials investigating novel agents and combination therapies for myelofibrosis (MF) were presented during the ninth annual Society of Hematologic Oncology meeting. These evolving data have implications for advanced practice, where the focus is on patient education and managing disease-related symptoms and treatment toxicities. Currently, ruxolitinib (Jakafi) and fedratinib (Inrebic) are two Janus kinase inhibitors (JAKi) approved for front-line MF therapy. Despite improved outcomes driven by JAKi, there exists unmet cardinal needs for subsets of MF patients who either progress on or are resistant to or intolerant of ruxolitinib, have disease-related cytopenias, have high-risk disease, or have disease-related symptoms affecting quality of life.

**Luspatercept**

Novel agents for red blood cell (RBC) transfusion-dependent MF patients are showing promise. Luspatercept (Reblozyl), an erythroid maturation agent that enhances late-stage erythropoiesis, showed meaningful responses in a phase II trial for MF-associated anemia (Gerds et al., 2019). Achievement of RBC transfusion independence (TI) of >12 weeks was reported for 36% and 19% of patients receiving concomitant ruxolitinib compared with those not, respectively. Treatment-related adverse events include hypertension (11%), diarrhea (4%), and bone pain (8%). Luspatercept vs. placebo in myeloproliferative neoplasm-associated MF patients with high-risk disease or transfusion dependence is under investigation in the phase III double-blind INDEPENDENCE trial with RBC TI as a primary endpoint (Mesa et al., 2021). These results are encouraging as transfusion-dependent anemia is a cardinal area of unmet need.

**COMBINATION THERAPY**

Combination therapy augments disease responses through synergism by targeting alternative signaling pathways. This treatment strategy is under investigation for MF patients with disease-related cytopenias such as thrombocytopenia and suboptimal responses to JAKi. The front-line phase II MANIFEST study for JAKi naive patients showed that CPI-0610, a bromodomain and extraterminal domain protein inhibitor that functions as an epigenetic modifier, combined with ruxolitinib produced a spleen volume reduction (SVR) in 63% and ≥50% total symptom score (TSS) reduction in 58% of patients at 24 weeks (Mascarenhas et al.,...
Most common adverse events of any grade were nausea (18%) and respiratory tract infections (18%). Grade 3 thrombocytopenia and anemia were 4.7% and 17%, respectively.

**Key Points**

- Novel therapies are demonstrating benefit for subsets of MF patients who progress on or are resistant to or intolerant of ruxolitinib, have disease-related cytopenias, have high-risk disease, or have disease-related symptoms.
- It is important for advanced practitioners to be cognizant of the unique mechanisms of action leading to adverse events.

The combination of navitoclax and ruxolitinib also showed efficacy in a phase II study of MF patients with high-molecular risk (HMR) mutations of ASXL1, SRSF2, EZH2, U2AF1, and IDH1/2 (Pemmaraju et al., 2020). Of the 34 patients enrolled, 58% harbored HMR mutations with 42% having ≥ 2 HMR mutations. At week 24, 27% achieved an SVR, 30% had ≥ 50% TSS and 21% showed grade 1 to 2 improvement in bone marrow fibrosis. Clinical responses were independent of the HMR mutations. Grade ≥ 3 adverse events occurred in 85% of patients with the most common being thrombocytopenia (53%) managed with dosing modifications, anemia (32%), and pneumonia (12%). Both agents are currently being investigated in combination with ruxolitinib in phase III clinical trials.

**MOMELOTINIB**

Momelotinib and pacritinib are JAKi in phase III trials with encouraging results for improving splenomegaly or cytopenias (Harrison et al., 2019; Tefferi et al., 2018). Enrollment has completed for the phase III MOMENTUM trial assessing momelotinib vs. danazol for primary MF, post-polycythemia vera MF, or post-essential thrombocytopoiesis MF patients previously treated with a JAKi and anemic (Hgb <10g/dL). Momelotinib is a novel JAK1/2 and ACVR1 inhibitor with potential for improving disease-related anemia and splenomegaly (Tefferi et al., 2018). Endpoints for this trial include TSS, TI, and SVR at 24 weeks. Momelotinib previously demonstrated improvement in RBC transfusion dependence in a phase I/II study of high/intermediate-risk MF patients (Tefferi et al., 2018). Grade 1/2 peripheral neuropathy was reported in 47% of patients and may be irreversible; therefore, it requires careful monitoring. Patients should be counseled and monitored for a first-dose effect of dizziness, hypotension, nausea, flushing, and headache (Tefferi et al., 2018).

**PACRITINIB**

The phase III trial PACIFICA is exploring pacritinib vs. physician’s choice in front- and second-line patients with primary MF or secondary MF with preexisting thrombocytopenia (platelets <50,000/µl) that portends a poor prognosis (Harrison et al., 2019). The primary endpoint is SVR with secondary endpoints of TSS and overall survival (OS) at 24 weeks. Pacritinib is not as myelosuppressive compared with other JAKi, with nonhematologic adverse events being primarily gastrointestinal.

**KRT-232**

Patients with primary resistance to or progression after ruxolitinib have poor OS. BOREAS is a phase III trial evaluating the disease-modifying effects of KRT-232, an MDM2 inhibitor restoring p53 function resulting in apoptosis in JAKi relapsed refractory MF patients with intermediate-1, -2 or high-risk disease (Verstovsek et al., 2021). KRT-232 demonstrated an SVR in 16% and ≥ 50% TSS in 30% of patients with 87% reduction in circulating CD34+ cells by week 24. These responses were superior in patients off ruxolitinib vs. those on at therapy baseline. The safety profile is tolerable; however, prophylaxis for nausea and emesis is advised.

**IMETELSTAT**

Branching out from JAKi to new therapies targeting alternative signaling pathways is an approach to expand the scope of response beyond that of SVR and TSS to OS and marrow fibrosis. Imetelstat, a telomerase inhibitor, demonstrated a dose-dependent OS benefit of 28 months (9.4 mg/kg) vs. 19 months (4.7 mg/kg) for intermediate-2 or high-risk MF patients who are refractory or resistant to JAKi (Mascarenhas et al., 2018). The 28 months OS benefit is encouraging compared with historical 14 months OS after ruxolitinib discontinuation. Grade 3/4 neutropenia (34% and 13%) and thrombocytopenia (42% and 29%) were more common with the 9.4 mg/kg dose than the 4.7 mg/kg dose, respectively, and reversible within 4
weeks. A phase III trial exploring OS as an end-point utilizing imetelstat 9.4 mg/kg every 3 weeks compared with best available therapy for intermediate-2 or high-risk MF is ongoing.

**The Advanced Practitioner Perspective**

The future is optimistic with novel agents in the pipeline yielding beneficial responses for unmet cardinal needs of MF patients. These agents may extend the goals of treatment beyond alleviating symptom burden, reducing splenomegaly, and improving cytopenias. These evolving data require advanced practitioners to stay current on these diverse novel agents while being cognizant of the unique mechanisms of action capable of producing adverse events whether given as monotherapy or in combination.

**Disclosure**

Dr. Nodzon has served on the speakers bureaus for AbbVie and Genentech and as a consultant for AbbVie, AstraZeneca, Genentech, Pharmacyclics, and Takeda.

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