

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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JAK2 Inhibitors in Myelofibrosis

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H&O What is myelofibrosis (MF)?

AP MF is a BCR-ABL1-negative, chronic myeloproliferative neoplasm (MPN). It is characterized by bone marrow fibrosis and mobilization of myeloid progenitor cells into the peripheral blood, with extramedullary hematopoiesis leading to complications such as splenomegaly, hepatomegaly, and portal or pulmonary hypertension. MF is also characterized by a systemic inflammatory state that underpins constitutional symptoms such as fatigue, night sweats, bone pain, and pruritus. The disease may arise de novo (primary MF), or following fibrotic transformation of pre-existing polycythemia vera or essential thrombocythemia. The median age at the time of diagnosis is 65 years. Consequently, few patients are eligible for allogeneic stem cell transplant, which is the only treatment that is capable of inducing complete hematologic, cytogenetic, and molecular remissions.

H&O How is MF currently treated?

AP Current treatments are directed towards palliation of anemia, symptomatic splenomegaly, constitutional symptoms, or disease complications from extramedullary hematopoiesis. Patients with symptomatic anemia can be treated with androgens (eg, oral fluoxymesterone), prednisone, danazol, thalidomide (Thalomid, Celgene), or lenalidomide (Revlimid, Celgene). Response rates are approximately 20%, and response durations average 1–2 years. The use of erythropoiesis-stimulating agents is limited by their relative ineffectiveness in transfusion-dependent patients and their propensity to exacerbate splenomegaly. Hydroxyurea is the most common first-line treatment for

symptomatic splenomegaly; however, its efficacy in the presence of massive splenomegaly appears to be modest, and may aggravate pre-existing cytopenias. The use of splenectomy and splenic or hepatic radiation in the setting of hydroxyurea-refractory organomegaly is limited by postoperative thrombosis or infection, and the occurrence of severe cytopenias, respectively. Standard treatments for MF are generally ineffective for alleviating disease-associated constitutional symptoms.

H&O How did the recent discovery of the Janus kinase 2 (JAK2) gene (*JAK2 V617F*) mutation challenge prior diagnostic and treatment approaches in MF?

AP The key relevance of *JAK2 V617F* is in the insights it provided into the pathogenesis of MPN. Approximately 50–60% of MF patients harbor the *JAK2 V617F* mutation, and 8% harbor mutations in the myeloproliferative leukemia (MPL) gene; these mutations serve as markers for clonal hematopoiesis, and reliably exclude reactive bone marrow fibrosis or a non-myeloid malignancy. Unlike chronic myeloid leukemia, where BCR-ABL1 is the central pathogenetic lesion, the disease-initiating mutation in MF is unknown. In addition to *JAK2 V617F* and MPL mutations, a minority of MF patients harbor *LNK*, *CBL*, *TET2*, *ASXL1*, *IDH*, *IKZF1*, *DMT3A*, *EZH2*, and/or *SF3B1* mutations. These mutations are neither disease-specific nor mutually exclusive, and likely constitute secondary events with a complex clonal hierarchy. However, given that *JAK2 V617F* is the most frequent mutation observed in MF patients, it is reasonable to consider it as a potential drug target.

H&O What are some common features of various JAK2 inhibitors that have emerged from clinical trials?

AP Although JAK2 inhibitors clearly have palliative value in MF, they have not been shown to induce complete or

partial remissions. Also, there appear to be significant differences in the therapeutic activity and side effect profile of currently available JAK inhibitor drugs, and it is too early to determine which of these drugs will prove to be best-in-class. Furthermore, although treatment-emergent anemia can be anticipated based on the lack of selectivity of these drugs for mutant versus wild-type JAK2, certain JAK inhibitors appear to paradoxically improve anemia in a subset of MF patients. Finally, the mechanism of action of JAK inhibitors appears to differ, based on the degree to which they downregulate circulating proinflammatory cytokines versus the inhibition of clonal myeloproliferation. This difference is likely exemplified by the varying degree by which the different JAK inhibitor drugs decrease the *JAK2 V617F* allele burden during therapy.

H&O What are some available data regarding ruxolitinib (INCB018424) in MF treatment?

AP Ruxolitinib (INCB018424) is the furthest along of the JAK inhibitors in clinical development for MF therapy. It has been evaluated in 2 phase III studies. In COMFORT-I (Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment), intermediate-2 or high-risk MF patients were randomized to receive either a placebo or ruxolitinib at 15 mg (platelet count 100–200 × 10⁹/L) or 20 mg (platelet count >200 × 10⁹/L) twice daily. The primary endpoint of the study was spleen response (>35% volume reduction by imaging) at 24 weeks. A total of 309 patients were randomized, and at a median of 32.2 weeks, the spleen response rate was approximately 42% for ruxolitinib versus less than 1% for placebo. In addition, approximately 46% of patients treated with ruxolitinib experienced substantial improvement in constitutional symptoms. There was no significant difference between groups in the number of deaths, whereas notably more patients receiving ruxolitinib became anemic (31% vs 13.9%) or thrombocytopenic (34.2% vs 9.3%). In the trial known as COMFORT-II, ruxolitinib was compared to “best available therapy” in patients with intermediate-2 or high-risk MF. The primary endpoint was a greater than 35% spleen volume reduction by imaging at 48 weeks. The study included 219 patients. Spleen responses were better with ruxolitinib (28.5% vs 0%), and the median duration of response was 48 weeks. However, ruxolitinib therapy was associated with higher incidences of thrombocytopenia (44.5% vs 9.6%), anemia (40.4% vs 12.3%), and diarrhea (24.0% vs 11.0%). The number of deaths was similar between the 2 arms.

Long-term follow-up of 51 MF patients at the Mayo Clinic who were treated with ruxolitinib in a phase I/II trial showed modest responses by conventional criteria: 29% for spleen, 21% for anemia, and 63% for constitu-

tional symptoms. Treatment discontinuation rates at 1, 2, and 3 years were 51%, 72%, and 89%, respectively. Side effects included thrombocytopenia of grade 2 or above (26%) and anemia (33%). During drug discontinuation, serious adverse events that necessitated hospitalization occurred in at least 5 cases (10%), and constituted acute relapse of symptoms, rapid and painful enlargement of the spleen, and acute hemodynamic decompensation that occasionally led to a septic shock–like syndrome. There were no significant differences in survival between the ruxolitinib-treated patients and a cohort of primary MF patients receiving standard treatment and matched for disease risk.

Ruxolitinib has significant activity against MF-related symptoms and thus improves patient quality of life. Symptom improvement is correlated with a downregulation of proinflammatory cytokines. The spleen and anemia responses, however, are modest. Ruxolitinib is generally well-tolerated. Aside from thrombocytopenia and anemia, some patients may develop a ruxolitinib withdrawal syndrome following treatment interruption or cessation that requires close monitoring, and that may be attenuated via a drug taper.

H&O How might newer JAK inhibitors suggest a broader spectrum of activity?

AP Data from the phase I/II study of TG101348 (now SAR302503) in 59 high- or intermediate-risk MF patients were recently reported. The drug was orally administered once daily, and patients with a platelet count above 50 × 10⁹/L were eligible. After 6 and 12 cycles of treatment, 39% and 47% of patients, respectively, had achieved a spleen response per conventional criteria. Response rates for constitutional symptoms were 89% for night sweats, 75% for cough, and 75% for pruritus. The majority of patients with leukocytosis or thrombocytosis at baseline achieved normalization of blood counts. A significant decrease in *JAK2 V617F* allele burden was observed at 6 months in mutation-positive patients, particularly in the subgroup with allele burden greater than 20%; the decrease was durable at 12 months. Effects on bone marrow pathology or plasma cytokine levels were unremarkable. Grade 3/4 adverse events included anemia (35% of the 37 patients who were not transfusion-dependent at baseline became transfusion-dependent), thrombocytopenia (24%), and neutropenia (10%). Nonhematologic adverse events (mostly grade 1/2) included nausea (70%), diarrhea (64%), and vomiting (35%). SAR302503 has significant activity in controlling leukocytosis, and its activity in improving splenomegaly and constitutional symptoms is broadly similar to that of ruxolitinib and another new JAK inhibitor, CYT-387. At higher doses

(>500 mg/day), there is a greater incidence of gastrointestinal toxicities and treatment-emergent anemia; these issues are being addressed in ongoing clinical trials using lower drug doses (300–500 mg/day). SAR302503 has demonstrated anti-clonal activity through a decrease in *JAK2 V617F* allele burden during treatment.

In an ongoing phase I/II study, over 150 MF patients have been treated with CYT387; interim results for the first 60 patients were recently reported. The study included patients with high- or intermediate-risk disease, and CYT387 was orally administered once daily. Per conventional criteria, the anemia response rate was 50% overall and 58% in transfusion-dependent patients. The median duration of anemia response was 20 weeks. The spleen response rate was approximately 45%, and the majority of patients experienced resolution of constitutional symptoms. Responses were also documented in patients who previously failed treatment with ruxolitinib, SAR302503, and pomalidomide. Approximately half of the patients experienced a first-dose effect (transient lightheadedness and hypotension), which was self-limited. Grade 3/4 thrombocytopenia occurred in 25% of patients. Nonhematologic adverse events included increased liver function tests, headache, and increased lipase. A mild, nonprogressive, grade 1 sensory peripheral neuropathy was observed in approximately 28% of patients.

CYT387 stands out from the other JAK inhibitors in terms of the anemia responses observed in preliminary data. It will be important to confirm anemia responses in a larger cohort of patients, as well as the durability of such responses. CYT387 is well-tolerated; thrombocytopenia and liver/pancreas test abnormalities have been observed, and the incidence and natural history of peripheral neuropathy will need to be monitored.

H&O What are some unresolved issues with JAK2 inhibitors?

AP JAK inhibitors have not yet shown disease-modifying activity, but they do produce significant symptom palliation in MF, which is a notable achievement in this patient population. An improved JAK inhibitor—such as one with better JAK2 mutant wild-type selectivity or less off-target kinase inhibition—may not, when used as monotherapy, fare better than currently available drugs, due to the molecular and clonal complexity of MF. However, there is room to improve the side effect profile of JAK inhibitors, particularly regarding myelosuppression. It

may be possible to attenuate treatment-emergent anemia by combining JAK inhibitors with other drugs (pomalidomide, androgenic agents, recombinant erythropoietin) that have erythropoietic activity, without overlapping toxicities. Removal of FLT-3 inhibitory activity from some drugs (CEP-701, SAR302503) could lessen gastrointestinal toxicities. Regarding an optimal starting dose, I favor a predefined, dynamic schedule that triggers dose changes based on specific response and toxicity criteria. Treatment can begin with an induction dose to maximize response (particularly splenomegaly), followed by a lower maintenance dose; this approach has led to alleviation of treatment-emergent anemia with SAR302503.

H&O What do you think is next in the treatment of MF?

AP Although the development of JAK inhibitors constitutes an important advance in MF therapy, one has to look beyond this class of drugs, given their inability thus far to achieve complete remission. Pomalidomide has shown significant anti-anemia activity in MF in preliminary studies, and an ongoing, phase III, randomized study of pomalidomide versus placebo should further clarify its activity for this indication. Other drugs under investigation for MF therapy include histone deacetylase (HDAC) inhibitors, PI3K/Akt/mammalian target of rapamycin (mTOR) inhibitors, hypomethylating agents, hedgehog pathway inhibitors, and others (eg, bevacizumab [Avastin, Genentech], plitidepsin [PharmaMar], GS-6624). Finally, new information on the prognostic value of specific plasma cytokines in primary MF, and the demonstration that clinical benefit with JAK inhibitor therapy is correlated with downregulation of proinflammatory cytokines (eg, ruxolitinib) support further evaluation of targeted anti-cytokine therapy.

Suggested Readings

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