

# CLINICAL UPDATE

Advances in the Treatment of Myelofibrosis

## Recent Advances in the Management of Myelofibrosis



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### H&O Could you provide some background on myelofibrosis?

**RM** The myeloproliferative neoplasm myelofibrosis afflicts an estimated 18,000 patients in the United States, with an annual incidence of approximately 1 to 2 cases per 100,000 people. It has a mixed prognosis. Survival can range from 2 years to more than 10 years, depending on many factors. Splenomegaly or symptoms such as fatigue or anemia can lead to the diagnosis of myelofibrosis.

### H&O What are the potential complications?

**RM** Myelofibrosis can impact patients in 4 main ways. First, splenomegaly can cause a variety of symptoms, such as pain, discomfort, abdominal fullness, and early satiety. Second, patients are at risk of cytopenias, most commonly anemia and less commonly thrombocytopenia. Third, there are disease-associated symptoms that tend to be hypercatabolic, leading to sequelae such as fatigue, weight loss, night sweats, bone pain, and itching. Fourth, patients with myelofibrosis are at risk of progressing to acute myeloid leukemia.

### H&O How can prognostic risk and symptom burden be used to assess and predict the disease course?

**RM** As with many other diseases, the symptomatic factors of myelofibrosis can be suggestive of the prognosis. Increasing weight loss, night sweats, and bone pain indicate a worse prognosis. Other important prognostic factors include significant anemia, significant leukocytosis,

and increasing age. Movement toward acute leukemia can be suggested by blasts in the bloodstream or abnormal cytogenetics.

### H&O What are some recent insights into the molecular mechanisms of myelofibrosis?

**RM** There have been a tremendous amount of advances in the understanding of the molecular mechanisms of myelofibrosis. The 3 most prevalent key driver mutations are Janus kinase 2 (*JAK2*) V617F, calreticulin, and the myeloproliferative leukemia (*MPL*) gene. Almost 80% of patients with myelofibrosis will have one of these mutations. In addition, this group of patients can have other mutations seen in myeloid disorders, some of which have negative prognostic implications, such as additional sex combs-like 1 (*ASXL1*), enhancer of zeste homolog 1 (*EZH1*), and enhancer of zeste homolog 2 (*EZH2*).

### H&O What is the goal of treatment?

**RM** The goal of treatment is somewhat individualized. There are 2 different paths. A curative path can include stem cell transplant. However, less than 10% of myelofibrosis patients undergo stem cell transplant owing to factors such as older age, comorbidities, high risk of disease, lack of an available donor, and personal choice.

Another treatment path is to alleviate suffering and extend survival with medical therapy. Success in this area is measured by improvements in splenomegaly, decreases in symptom burden, avoidance of progression toward acute myeloid leukemia, improvements in cytopenias, and, hopefully, longer survival.

## H&O What types of medical therapy are used?

**RM** The standard of care for myelofibrosis is ruxolitinib (Jakafi, Incyte), which is the only therapy approved by the US Food and Drug Administration for the disease. Ruxolitinib inhibits JAK1 and JAK2, and it can be effective regardless of which molecular mutations a patient has. The data show that ruxolitinib will improve splenomegaly in most patients. In approximately half of patients, this improvement will meet the response criteria from the International Working Group for Myelofibrosis. Most patients will also experience improvement in other symptoms. Additionally, clinical trials demonstrate that ruxolitinib increases survival, when accounting for crossover. That being said, ruxolitinib is not considered a curative therapy. A limitation of ruxolitinib is that it typically does not improve anemia or thrombocytopenia.

There are other therapies in testing. Two unmet needs in myelofibrosis are to better identify which therapies should be used in patients with very early disease or very advanced disease.

## H&O Is ruxolitinib being evaluated as a component of combination regimens?

**RM** Ruxolitinib has been tried in at least 10 different combinations to date. Those studies are largely ongoing, so there are no final conclusions. At this time, there are no clear data to support the use of a particular combination outside of a clinical trial.

## H&O When should treatment with ruxolitinib be initiated?

**RM** Ruxolitinib should be considered in patients with splenomegaly or other symptoms, in whom the benefits are clear. There likely is benefit in using ruxolitinib earlier to try to avoid disease progression, but that approach remains experimental.

## H&O What do data suggest about the use of pacritinib?

**RM** Pacritinib is an oral tyrosine kinase inhibitor (TKI) with activity against JAK2 and FMS-like tyrosine kinase 3 (FLT3). I presented results from the phase 3 PERSIST-1 trial (A Randomized Controlled Phase 3 Study of Oral Pacritinib Versus Best Available Therapy in Patients With Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis) at the 2015 meeting of the American Society of Clinical Oncology. Pacritinib showed positive results when compared with best alternative therapy

among patients with myelofibrosis who had not received previous treatment with JAK2 inhibitors. The trial enrollment criteria had no minimum threshold for the platelet count, so the population included patients with high blast counts and with very advanced disease moving toward acute leukemia.

A phase 2 study, PERSIST-2, was evaluating pacritinib as second-line therapy. In February 2016, the FDA placed a full clinical hold on pacritinib in order to more closely examine the deaths that occurred among patients in the trial. It is not clear that the deaths seen on the study are a side effect of pacritinib, and the toxicity profile had been favorable. Ongoing analysis is attempting to discern whether the deaths could be attributable to adverse patient selection, or whether they represent a true safety concern with pacritinib. For some patients who benefited from pacritinib in clinical trials, access to the drug has been continued through the single-patient Investigational New Drug protocol.

## H&O Are there other ongoing clinical trials in myelofibrosis?

**RM** Two important phase 3 studies are comparing ruxolitinib vs momelotinib, with the aim of improving anemia. SIMPLIFY-1 (A Phase 3, Randomized, Double-Blind Active-Controlled Study Evaluating Momelotinib vs. Ruxolitinib in Subjects With Primary Myelofibrosis [PMF] or Post-Polycythemia Vera or Post-Essential Thrombocythemia Myelofibrosis [Post-PV/ET MF]) is for first-line therapy and SIMPLIFY-2 (A Phase 3, Randomized Study to Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects With Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis Who Were Treated With Ruxolitinib) is for second-line therapy.

There are several studies in patients with relapsed or refractory disease after treatment with ruxolitinib. A phase 2 trial is evaluating imetelstat, a telomerase inhibitor, at doses found to have activity in a phase 1 trial. Another phase 2 study is evaluating PRM-151, an antifibrosing agent.

## H&O What are some other areas of research in myelofibrosis?

**RM** There are several important areas of research. Investigators are evaluating whether early intervention can reduce the risk of progression. There are also efforts to understand how the interactions of molecular mutations can impact patient progression, and whether these mechanisms can be targeted in a more effective way. Much

research is focused on patients with advanced disease who are moving toward acute leukemia. The high mortality in this phase of the disease continues to be difficult to overcome. Finally, I would like to highlight a new national study initiated in response to a request from the Centers for Medicare & Medicaid Services so that Medicare patients with myelofibrosis can undergo transplant in the setting of a clinical trial.

### Disclosure

*Dr Mesa is a consultant for Novartis, AOP, Shire, Ariad, and Galena. He has performed research for Incyte, Gilead, CTL, Promedior, and Celgene.*

### Suggested Readings

Cervantes F, Vannucchi AM, Kiladjian JJ, et al; COMFORT-II Investigators. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. *Blood*. 2013;122(25):4047-4053.

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