Do all patients with myelofibrosis need treatment?

Myelofibrosis is a serious myeloproliferative disorder that has no cure aside from allogeneic stem cell transplant. Treatment early in the disease course—before symptoms arise—has never been shown to improve outcomes. Therapies are aimed at relieving symptoms when they occur.

The Dynamic International Prognostic Scoring System (DIPSS) can be used to predict which patients with primary myelofibrosis are most likely to experience symptoms and require treatment. Factors that increase this risk include age older than 65 years, white blood cell count greater than 25,000/μL, hemoglobin less than 10 g/dL, the presence of circulating blasts in peripheral blood, and constitutional symptoms such as weight loss and unexplained fever or sweating. Based on some basic values from a complete blood count, physical examination, and medical history, we can determine whether the patient is at low risk, intermediate 1 risk, intermediate 2 risk, or high risk for mortality.

Stratification of these patients is important because many of them need only observation and supportive care for years, and sometimes more than a decade. Patients whose disease progresses earlier will require earlier treatment.

More recently, with the advent of molecular testing, we have started to use the DIPSS-plus score. In addition to the clinical factors from the DIPSS, this score includes karyotype, platelet count, and transfusion status.

Molecular testing also may reveal mutations in the additional sex combs-like 1 (ASXL1) gene, which is associated with a very poor prognosis, and other genes that may play a role in myelofibrosis. These high-risk patients should be treated sooner rather than later.

A recently described entity is triple-negative myelofibrosis, which refers to patients who do not have mutations in Janus kinase 2 (JAK2), calreticulin (CALR), or myeloproliferative leukemia virus (MPL). This is considered a very difficult subset of myelofibrosis, with an adverse prognosis.

What is the preferred treatment for patients with myelofibrosis?

Treatment depends on the specific needs of the patient. Myelofibrosis can produce a broad variety of effects, so one patient may develop splenomegaly, another may develop leukocytosis, and another may develop anemia and thrombocytopenia. Symptoms may include B symptoms such as fatigue, shortness of breath, severe weight loss, cachexia, and poor appetite. Treatment is individualized based on the patient’s presentation and the goals of therapy. A patient with anemia and thrombocytopenia but without splenomegaly, for example, may benefit from agents such as erythropoietin, the hyperandrogenic agent danazol, or even thalidomide or lenalidomide (Revlimid, Celgene).

Prednisone in combination with either thalidomide or lenalidomide has been shown to produce response rates
of 30% to 40% in patients with anemia or thrombocytopenia, as shown in studies by Mesa and colleagues in Blood and in the Mayo Clinic Proceedings, and some patients also experience a reduction in spleen size.

In contrast, hydroxyurea can be very helpful in patients with splenomegaly or leukocytosis, although it does not have much of an effect on symptoms. We previously used anagrelide in these patients, but this has been mostly supplanted by hydroxyurea.

The JAK2 inhibitor ruxolitinib (Jakafi, Incyte Pharmaceuticals), which is excellent at reducing spleen size and controlling symptoms, was approved in 2011 for patients with myelofibrosis. People often have a significant reduction in splenomegaly with ruxolitinib, which leads to improved appetite, weight gain, and feeling better in general. I would say that approximately half of patients with myelofibrosis are being treated with ruxolitinib now that physicians are more aware of it and comfortable with it. Recent data by Vannucchi and colleagues have even suggested an improvement in overall survival with ruxolitinib compared with best-available therapy.

Patients who have a high blast count or a high white cell count and are progressing to acute myeloid leukemia (AML) may be candidates for chemotherapy-based approaches, specifically the hypomethylating agents azacitidine or decitabine. These agents are approved for use in myelodysplastic syndrome, and have been shown to be effective at reducing spleen size and sometimes improving blood counts in patients with myelofibrosis. They are particularly useful for reducing blast counts in patients who have an especially high blast count in the peripheral blood, and for those with “accelerated” myelofibrosis that is transforming to AML.

Finally, if the treatment goal is cure using allogeneic stem cell transplant—which is often an option for younger, fit patients—treatment with chemotherapy, hypomethylating agents, or ruxolitinib may be needed to get the disease under control.

H&O Which studies have established the efficacy of ruxolitinib in myelofibrosis?

TMK The 2 biggest studies of ruxolitinib in patients with myelofibrosis have been COMFORT-I (Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment) and COMFORT-II (Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment-II).

COMFORT-I was a randomized double-blind study of ruxolitinib vs placebo in 309 patients with intermediate 2–risk or high-risk myelofibrosis. Patients received either ruxolitinib twice daily at the standard dose or a placebo. After 24 weeks, patients who were assigned to the ruxolitinib group were more likely to have a reduction in spleen volume of at least 35% than those who were assigned to the placebo group (41.9% vs 0.7%). Adverse events led to discontinuation of the study drug in 11.0% of patients in the ruxolitinib group and 10.6% of those in the placebo group. Anemia and thrombocytopenia were the most common adverse events with ruxolitinib. Patients in the ruxolitinib arm also had a significantly greater improvement in the total symptom score and in overall survival compared with placebo.

The COMFORT-II trial by Harrison and colleagues was similar in design, but 309 patients were randomly assigned 2:1 to either ruxolitinib or best-available therapy rather than placebo. Best-available therapy was whatever the treating physician decided to use, with the exclusion of investigational therapy. At 48 weeks, there was a 35% or more reduction in spleen size among 28% of the patients in the ruxolitinib group vs none of the patients in the best-available therapy group. This trial also suggested an improvement in leukemia-free survival and progression-free survival with ruxolitinib.

Longer-term follow-up of these studies has suggested significant improvement in overall survival in patients who received ruxolitinib vs either placebo or best-available therapy. These 2 trials solidified the use of ruxolitinib, and established its efficacy in the treatment of myelofibrosis.

H&O What is the mechanism of action of ruxolitinib?

TMK Ruxolitinib is a JAK1/2 inhibitor. In the case of myelofibrosis, JAK2 inhibition is key. We do know that myeloproliferative neoplasms such as polycythemia vera, essential thrombocytopenia, and myelofibrosis have a constitutive upregulation of the JAK/signal transducers and activators of transcription (STAT) pathway. In many cases, this is related to mutations in this pathway, such as mutations in JAK2, MPL, or even CALR. Ruxolitinib works by inhibiting signaling in this pathway. What is interesting is that the agent inhibits both mutant and wild-type JAK2, so the patient does not have to be JAK2-mutated in order for ruxolitinib to work.

H&O What are the limitations and side effects of ruxolitinib?

TMK Ruxolitinib is very well tolerated overall. The main side effects that we see are cytopenias, predominantly thrombocytopenia and anemia. Cytopenia can be modified and controlled with dose reductions and dose interruptions. Patients also may experience some loose stools, fatigue, or rash.

H&O Which patients with myelofibrosis should not receive ruxolitinib?
TMK Oncologists should be judicious with the use of ruxolitinib in patients who have profoundly low platelet counts, in which case the agent might worsen thrombocytopenia or anemia. In addition, ruxolitinib is not the best first-line option for patients who have cytopenia as the main manifestation of their disease, and who do not have splenomegaly or severe B symptoms.

H&O Is ruxolitinib being studied in combination with other agents?

TMK Absolutely. In a study at MD Anderson that was published by Dave and colleagues, we looked at a combination of ruxolitinib and lenalidomide for patients with myelofibrosis. We found that combining these agents led to some responses but also to significant myelosuppression, so this would not be a recommended approach.

Ruxolitinib also has been combined with danazol, which led to clinical responses—especially in patients with cytopenias. In fact, in a trial that Kristina Gowin presented at the 2015 American Society of Hematology (ASH) annual meeting, 71% of patients experienced stable disease and 21% experienced clinical improvement, which included spleen responses.

A Dutch study presented by Stine Ulrik Mikkelsen at the 2015 American Society of Hematology (ASH) annual meeting that looked at a combination of ruxolitinib and interferon produced excellent responses in people with myelofibrosis. Approximately 57% to 66% of patients experienced an improvement in blood counts and splenomegaly, including complete remissions. The investigators also documented a decrease in the JAK2 allele burden in this trial, suggesting that interferon was at least partially responsible for the improvements.

H&O Are other JAK inhibitors being developed for use in myelofibrosis?

TMK The drug pacritinib, which is a JAK inhibitor that also has some FLT3 activity, was studied initially in PERSIST-1 (Oral Pacritinib Versus Best Available Therapy to Treat Myelofibrosis). This phase 3 trial compared pacritinib vs best-available therapy. Ruxolitinib was in use at the time PERSIST-1 was conducted, so some of the patients on best-available therapy would have been taking it.

This trial, which was presented at the 2015 annual meeting of the American Society of Clinical Oncology by Ruben Mesa, found that pacritinib was better than best-available therapy at reducing symptom burden and spleen size. Pacritinib was believed to cause slightly less cytopenia than ruxolitinib, which would make it an important drug for patients with myelofibrosis who have cytopenia.

However, the US Food and Drug Administration put a second study, PERSIST-2 (Oral Pacritinib Versus Best Available Therapy to Treat Myelofibrosis With Thrombocytopenia), on clinical hold in February of this year because of patient deaths from intracranial hemorrhage, cardiac failure, and cardiac arrest. A safety evaluation is ongoing. We do not know whether pacritinib will continue to be developed, but we hope to hear some news soon.

Additional JAK2 inhibitors are being studied in clinical trials, including momelotinib and lestaurtinib. Momelotinib is a JAK1/JAK2 inhibitor that demonstrated a spleen response rate of 39% and an anemia response rate of 53% in a phase 1/2 study of patients with myelofibrosis that Animesh Pardanani presented at the 2013 ASH annual meeting. Based on these encouraging results, momelotinib is currently being compared with ruxolitinib in a phase 3, randomized, double-blind study of patients with myelofibrosis (NCT01969838). The study is ongoing and the results are awaited. A phase 1 trial by Hexner and colleagues suggested some response with lestaurtinib, which is an inhibitor of both JAK2 and FLT3, and that work is continuing.

H&O What other agents are being developed for use in myelofibrosis?

TMK Researchers are looking at histone deacetylase inhibitors such as vorinostat (Zolinza, Merck), which is approved for use in cutaneous T-cell lymphoma. In addition, the small molecule second mitochondrial activator of caspase (SMAC) mimetic LCL-161 is being studied. Researchers also are looking at combinations of histone deacetylase inhibitors and JAK2 inhibitors for treatment of myelofibrosis.

H&O What other treatment modalities are used in myelofibrosis?

TMK One option that is used occasionally for a patient with highly symptomatic splenomegaly that is refractory to JAK2 inhibition or hydroxyurea is splenectomy. We previously used splenic radiation in some of these cases, but we use it less often now because it is minimally efficacious, the effects are transient, and it can lead to abdominal pain, nausea, and vomiting. Also, it has the potential to cause fibrosis to develop around the splenic bed, which could make a future splenectomy difficult.

We usually avoid the use of transfusions, but sometimes they are necessary as supportive care in patients who have cytopenia.

Suggested Readings


