What are the signs and symptoms indicating that a patient with myelofibrosis requires treatment?

According to standard practice, there are typically 3 indications for therapy in patients with myelofibrosis: significant anemia, significant general systemic symptoms leading to quality-of-life issues, and symptomatic splenomegaly. Approximately 80% of patients with myelofibrosis will develop a very large spleen, and 40% will develop a large liver. Symptomatic splenomegaly can lead, for example, to fullness in the abdomen, abdominal pain and distension, and inability to bend. General systemic symptoms can include night sweats, low-grade fevers, bone aches and pains, fatigue, weakness, and weight loss.

When managing anemia, the goal of therapy is to prevent blood transfusions by improving blood cell counts and eliminating anemia-related symptoms. There are no drugs specifically approved by the US Food and Drug Administration (FDA) to reach this goal. The medications used in this setting include prednisone; anabolic steroids; immunomodulatory inhibitory drugs, such as thalidomide and lenalidomide; and erythropoietin-stimulating agents. None of these agents work well in many patients, and the efficacy is of limited duration.

Most patients with myelofibrosis are symptomatic to some degree. There is no standard tool available in everyday practice to help decide when treatment is needed. Guidelines from the National Comprehensive Cancer Network recommend using the MPN-10 questionnaire for this purpose. In theory, it is preferable to treat all patients who develop symptoms. A common question, however, is how to assess the need for treatment. For example, is treatment necessary if a patient reports symptom severity of 2 on a scale of 0 to 10? Or would it be better to wait until the symptoms are worse?

I believe there is no reason to allow symptoms of any degree to persist if there are medications to control them. My usual approach is to initiate treatment if the patient develops any symptoms that interfere with quality of life. Without a quality-of-life questionnaire that would be part of electronic medical records and would objectivize symptoms, treatment decisions are guided by the physician's perception of their severity. In many cases, management consists of observation rather than treatment because the patient is not “sick enough.” This is my main concern as a specialist in myeloproliferative neoplasms. I prefer to intervene early so that patients do not have to deal with symptoms that interfere with their quality of life too much.

What are the current treatment options?

The Janus kinase (JAK) inhibitors ruxolitinib (Jakafi, Incyte) and fedratinib (Inrebic, Bristol Myers Squibb) are approved by the FDA for the treatment of myelofibrosis, and they are used to control symptomatic splenomegaly or systemic symptoms. Most patients with myelofibrosis receive ruxolitinib as a first choice to manage symptoms...
and improve quality of life. These drugs can worsen platelet counts, so they are not recommended for patients with a platelet count below 50,000/µL (50 × 10^9/L), in whom they could possibly lead to bleeding. In this setting (patients with platelets <50,000/µL), we are fortunate to now have a new JAK inhibitor, pacritinib (Vonjo, CTI BioPharma Corp), which is not myelosuppressive and can be safely given to these patients.

In clinical trials, ruxolitinib and fedratinib controlled symptoms related to splenomegaly and improved quality of life in approximately 40% to 45% of patients within 6 months. (Ruxolitinib and fedratinib have not been compared in a head-to-head study.) The response rates reported in trials may be lower than the overall clinical benefit seen in practice. This is because clinical trials followed certain strict response criteria to determine efficacy. In my experience, ruxolitinib and fedratinib improve signs and symptoms of myelofibrosis in 9 out of 10 patients.

In patients with less-advanced disease, lower-risk disease, and elevated blood cell counts (high counts of white blood cells and/or platelets) that require cytoreduction, one may choose to use hydroxyurea or interferon. This is also applicable to patients who have transformed from essential thrombocytopenia or polycythemia vera to myelofibrosis, who may still have high blood counts requiring reduction to decrease thrombotic risk. A new formulation of long-acting interferon, ropeginterferon alfa-2b-njft (Besremi, PharmaEssentia), was recently approved by the FDA as therapy for patients with polycythemia vera. I hope to see studies with this medication in patients with early-stage myelofibrosis.

One should not forget transplant as an option, although fewer than 10% of patients with myelofibrosis overall undergo this procedure. Transplant is typically reserved for patients with higher-risk disease, even in the up-front setting, before any intervention with medications.

**H&O** How do the JAK inhibitors work?

**SV** The JAK family of enzymes includes JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). JAK1 and JAK2 play a role in hematopoiesis, the immune system, and inflammation. JAK enzymes are integral signaling pathway proteins that attach from within the cell to receptors for different cytokines or growth factors.

Ruxolitinib inhibits both JAK1 and JAK2, whereas fedratinib is more specific for JAK2. The inhibition of JAK2 reduces the production of blood cells. Therefore, ruxolitinib has antiproliferative effects; lowers counts of white blood cells, platelets, and red blood cells; and reduces the size of the spleen and liver. Ruxolitinib is also anti-inflammatory, based on the combined inhibition of JAK1 and JAK2. Ruxolitinib decreases the cytokines in the body that cause inflammation and contribute to the characteristics of myelofibrosis disease biology and the associated symptoms. This is why symptoms such as weight loss, the ability to walk, fatigue, weakness, night sweats, and bone aches and pains all resolve to a significant degree during treatment with ruxolitinib. Ruxolitinib does have some effect on the immune system and, in rare cases, patients may develop an atypical infection.

Fedratinib works somewhat differently. This drug does not inhibit JAK1 very much, but rather it is more specific for JAK2. Fedratinib is antiproliferative. The improvement in quality of life seen with fedratinib to a significant degree reflects the reduction in spleen size. As fedratinib decreases the number of malignant cells in the body, the patient feels better.

**H&O** What are the toxicity profiles of the JAK inhibitors?

**SV** There are some differences in the toxicity profiles. Ruxolitinib can lead to shortness of breath, low-grade diarrhea, and easy bruising in patients with low platelet counts. Ruxolitinib can worsen anemia and thrombocytopenia. Fedratinib can also worsen the counts of red blood cells and platelets. In approximately two-thirds of patients, fedratinib causes gastrointestinal (GI) adverse events, including nausea, vomiting, and diarrhea. These adverse events are low grade, but they may require treatment. Fedratinib appears to interfere with the uptake of thiamine from the GI tract into the body, which can lead to exceptionally rare cases of encephalopathy. Pacritinib may also cause some GI irritation, but unlike other JAK inhibitors, it does not cause significant reductions in blood cell counts.

**H&O** What are your considerations when selecting treatment?

**SV** The considerations include specific clinical needs and the characteristics of the drugs. Management decisions are tailored to each individual case, based on the disease characteristics and whether treatment is needed for anemia vs symptoms, or both. The JAK inhibitors are not good therapy for anemia, which they can worsen (not the case with pacritinib). These agents can provide symptomatic relief, decrease the sizes of the spleen and liver, and improve body habitus. Treatment with JAK inhibitors allows the patients to gain weight. The patients are able to walk more. They change their perspective on life. Ruxolitinib can change the body metabolism and increase levels of protein and cholesterol, which are low in patients with advanced myelofibrosis. Fedratinib can be used successfully after ruxolitinib. Pacritinib is the main...
choice for patients with low platelets.

Another consideration is the treatment’s adverse events. In a patient with preexisting GI conditions, it might be better to avoid a treatment that can exacerbate such issues.

**H&O** Is it possible to use JAK inhibitors sequentially?

**SV** For patients who develop progression in the spleen and symptoms while receiving one of the JAK inhibitors, it is possible to switch to the other one. Loss of response is not attributable to acquisition of different mutations in the \textit{JAK2} gene. There are other biological correlates that explain why these drugs may stop controlling signs and symptoms of the disease.

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**H&O** What are the benefits of early treatment?

**SV** Earlier intervention can better control symptoms, better reduce an enlarged spleen, and possibly lead to a longer life. If treatment is delayed, the disease can affect other parts of the body, such as the liver, kidney, and lungs. Over time, the bone marrow does not work that well, so patients become more anemic. Patients may have more thrombocytopenia (their platelet counts may be low), and their spleen may be much bigger. Delaying treatment will lead to a sicker patient who has more symptoms, a bigger spleen, lower platelets, and a lower red blood cell count. In this advanced setting, it can be difficult to eliminate or adequately control these patient characteristics.

The presence of anemia or thrombocytopenia interferes with the proper dosing of ruxolitinib. (This is not the case for fedratinib and for the newly approved agent pacritinib.) For example, the dose of ruxolitinib must be adjusted based on the patient’s platelet counts. Earlier intervention in patients with less anemia and thrombocytopenia can allow optimal dosing of ruxolitinib. A higher dose of ruxolitinib leads to better symptomatic response, longer duration of overall benefit, and longer survival.

**H&O** What is known about how to optimize the dose of ruxolitinib?

**SV** At the start of therapy, the dose of ruxolitinib should be adjusted based on the patient’s platelet count. In up to half of patients, treatment with ruxolitinib may lead to anemia. Dose adjustments and use of anemia-targeting drugs is the standard approach if anemia arises. For patients with anemia at the start of therapy, use of an alternative dosing regimen that can optimize the delivery of ruxolitinib while limiting myelosuppression has become a priority. In 2021, the phase 2 REALISE study showed that starting ruxolitinib at a lower dose and increasing the dose based on the patient’s tolerance may be superior to starting at a higher dose and then decreasing when toxicity arises. This strategy provides excellent overall benefit, but with a lower risk of side effects.

**H&O** How has the use of JAK inhibitors changed the goals of management?

**SV** In the past, treatments for myelofibrosis aimed to decrease spleen size and increase blood production to improve anemia. With the advent of the JAK inhibitors, symptom control became a valid goal of therapy. Currently, the goals for any therapy are to alleviate symptoms, control the bone marrow production of red blood cells, improve anemia, and decrease the size of the spleen or liver. The clinical trials of ruxolitinib focused on the drug’s main purposes: to decrease spleen size and improve quality of life. The efficacy of ruxolitinib in these areas was viewed favorably by the regulatory bodies and led to approval from the FDA for the treatment of myelofibrosis.

Development of the JAK inhibitors led to an increased focus on quality of life in patients with myelofibrosis. Researchers properly objectivized the quality-of-life issues and developed questionnaires to measure the benefits of JAK inhibitors. It is valuable for patients and clinicians to be able to pinpoint these concerns and to know how treatment can improve them. In my experience, ruxolitinib improves quality of life and reduces spleen size to some degree in nearly all patients. Efficacy varies according to factors such as patient characteristics, time to intervention, and perhaps differences in disease biology, beyond just the hyperactivity of the JAK-STAT pathway that is uniformly present.

**H&O** Are there data on overall survival from clinical trials or real-world analyses?

**SV** The phase 3 COMFORT-1 and COMFORT-2 trials compared ruxolitinib vs placebo and best supportive care, respectively. Results from these trials led to the approval...
of ruxolitinib approximately 10 years ago. These trials included follow-up analyses. Some modifications to the study design were made to document survival. Although these studies followed a randomized, crossover design, analyses showed that treatment with ruxolitinib improved survival by 1.5 years to 3 years vs the control. In 2014, the FDA adjusted the label for the use of ruxolitinib, adding information about the drug’s ability to prolong life.

Subsequently, many studies, such as retrospective chart reviews, prospective observational studies, and an analysis of a large federal database of real-world data showed that ruxolitinib has a significant potential to extend overall survival. Now that patients have been exposed to ruxolitinib for many years, several sources have shown an improvement in overall survival. Among the patients who respond to treatment, efficacy lasts for a long time. Life extension is now recognized as a full-fledged benefit of ruxolitinib.

H&O Why might ruxolitinib increase overall survival?

SV Ruxolitinib, or any of the other treatments for myelofibrosis, does not eliminate the disease. Control of proliferation and inflammation allows patients to live longer. With the antiproliferative effect, the spleen size decreases. In a way, ruxolitinib debulks the disease. The size of the liver decreases. Anti-inflammatory effects lead to changes in metabolism. Levels of albumin increase, and levels of cholesterol normalize. Patients gain weight, and they walk more. Their performance status improves. Some studies also report that kidney function improves. Control of these signs and symptoms allow patients to live with the disease for several years longer than patients who do not receive ruxolitinib.

Disclosure
Dr Verstovsek has received research support for conduct of clinical studies from Incyte Corporation, Roche, NS Pharma, Celgene, Gilead, Promedior, CTI BioPharma Corp., Genentech, Blueprint Medicines Corp., Novartis, Sierra Oncology, PharmaEssentia, AstraZeneca, Italfarmaco, and Protagonist Therapeutics. He has performed consulting for Constellation, Sierra, Incyte, Novartis, Celgene, and BMS.

Suggested Readings
Harrison CN, Schaap N, Vannucchi AM, et al. Fedratinib induces spleen responses and reduces symptom burden in patients with myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF) and low platelet counts, who were either ruxolitinib-naive or were previously treated with ruxolitinib [ASH abstract 668]. Blood. 2019;134(suppl 1).