Optimizing the Care of Patients With Higher-Risk Myelofibrosis

PRESENTED BY JULIE HUYNH-LU, MPAS, PA-C, and LINDSEY KALHAGEN, MMS, PA-C

From [1]MD Anderson Cancer Center, Houston, Texas; [2]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, Illinois

Presenters' disclosures of conflicts of interest are found at the end of this article.

https://doi.org/10.6004/jadpro.2025.16.2.16

Abstract

Higher-risk myelofibrosis is a complex disease requiring individualized care. At JADPRO Live 2024, presenters reviewed pathophysiology, diagnosis, risk assessment, and symptom management strategies for myelofibrosis. They also explored treatment options for higher-risk myelofibrosis, balancing benefits and risks while considering patient preferences and goals.

Myelofibrosis (MF) is a rare but serious myeloproliferative neoplasm. At JADPRO Live 2024, Julie Huynh-Lu, MPAS, PA-C, of MD Anderson Cancer Center, and Lindsey Kalhagen, MMS, PA-C, of Robert H. Lurie Comprehensive Cancer Center of Northwestern University, discussed the latest evidence in diagnostic criteria, risk assessment, emerging therapies, and side-effect management in MF.

PATHOPHYSIOLOGY AND DIAGNOSIS

Myelofibrosis is a BCR-ABL1-negative myeloproliferative neoplasm (MPN) that can be either primary or secondary, evolving from polycythemia vera (PV) or essential thrombocythemia (ET). The disease is characterized by disruption in the JAK-STAT signaling pathway, leading to excessive inflammatory cytokine production, resulting in bone marrow fibrosis, extramedullary hematopoiesis, and myeloproliferation. These pathophysiologic changes contribute to clinical manifestations, including cytopenias, hepatosplenomegaly, and systemic symptoms such as fatigue, weight loss, and night sweats.

"Splenomegaly is one of the most common features, sometimes at diagnosis or certainly with progression," noted Ms. Kalhagen.

DIAGNOSIS AND RISK STRATIFICATION

The International Consensus Classification (ICC) and the World Health Organization (WHO) updated the diagnostic criteria for MF in 2022. A diagnosis requires the presence of three major criteria—including bone marrow fibrosis, megakaryocytic proliferation, and a clonal mutation (*JAK2, CALR, MPL*, or others)—along with at least one minor criterion, such as anemia, splenomegaly, or elevated lactate dehydrogenase (LDH).

J Adv Pract Oncol 2025;16(suppl 2):36–38

Risk stratification plays an important role in determining prognosis and treatment options. The Mutation-Enhanced International Prognostic Scoring System (MIPSS-70) is preferred for patients younger than 70 years old. Other models are the Dynamic International Prognostic Scoring System (DIPSS) and Myelofibrosis Secondary to Essential Thrombocythemia and Polycythemia Vera Prognostic Model (MYSEC-PM).

There are profound differences between prognosis for low- to high-risk MF, with median overall survival at 27 or more years for low risk vs. only 2.5 years for high risk.

There can be considerable variability in symptom presentation among patients with MF. Some patients may be asymptomatic at diagnosis, while others present with profound, life-altering symptoms that significantly impact their quality of life. Patients may experience fatigue, early satiety, weight loss, night sweats, bone pain, and itching.

"Fatigue is probably the most commonly reported symptom for MF," noted Ms. Kalhagen.

To assess and document these symptoms, the presenters recommended using tools such as the MPN Symptom Assessment Form and the Brief Fatigue Inventory.

"Many of us as APPs are the ones assessing symptoms not only upfront but also at follow-up visits. It is important to document these symptoms and any changes to the best of our ability," commented Ms. Kalhagen.

TREATMENT

For higher-risk MF, the main treatment decision is whether the patient is eligible for allogeneic stem cell transplantation (ASCT)—the only potentially curative therapy. However, many patients are not transplant candidates due to age, comorbidities, or personal preference.

For non-transplant candidates, JAK inhibitors are aimed at reducing spleen size, alleviating systemic symptoms, and improving patient quality of life. Currently, there are four FDA-approved JAK inhibitors: ruxolitinib (Jakafi), fedratinib (Inrebic), pacritinib (Vonjo), and momelotinib (Ojjaara; Table 1).

"The great thing is that in the past 13 years, so much has been developed and changed in a disease that's as rare as MF," commented Ms. Huynh-Lu.

Ruxolitinib, the first JAK inhibitor approved for MF, is considered first-line therapy for patients with symptoms and splenomegaly, provided their platelet count is above 50,000. The drug has been shown to reduce spleen volume and improve symptoms significantly. However, it can cause cytopenias, particularly in the first 8-12 weeks of treatment.

Fedratinib, approved in 2019, is another JAK inhibitor used in both JAK inhibitor-naive patients and those who have developed resistance to ruxolitinib. It has been associated with gastrointestinal toxicities and a risk of Wernicke's encephalopathy, requiring thiamine supplementation.

Pacritinib, approved in 2022, is particularly useful for patients with thrombocytopenia, as it is indicated for those with platelet counts below 50,000. The drug has shown efficacy in reducing spleen volume and improving symptoms, but it carries risks of QTc prolongation and hemorrhaging.

Momelotinib, the most recently approved JAK inhibitor, is unique in its ability to address anemia, a common and challenging complication of MF. "Momelotinib is considered second-line therapy if patients have symptoms with or without splenomegaly, regardless of platelet count," Ms. Huynh-

Table 1. JAK Inhibitors for Higher-Risk Myelofibrosis

Drug	FDA approval	Mechanism of action
Ruxolitinib	Intermediate/high-risk MF	JAK1/JAK2 inhibitor
Fedratinib	Intermediate-2/high-risk primary or secondary MF in JAK inhibitor naive or ruxolitinib resistant patients	JAK2/FLT3/BRD4 inhibitor
Pacritinib	Intermediate or high-risk primary or secondary MF with platelets < 50K/uL	JAK2/IRAK1/FLT3/ACVR1 inhibitor
Momelotinib	Intermediate or high-risk primary or secondary MF in adults with anemia	JAK1/JAK2/ACVR1 inhibitor

Lu noted. "It's particularly beneficial for patients with anemia, as it can help them achieve transfusion independence."

Anemia is a major challenge in MF treatment. It can stem from the disease itself, JAK inhibitor therapy, or nutritional deficiencies or inflammation. Other options for managing anemia include erythropoiesis-stimulating agents (ESAs), which are effective in patients with erythropoietin levels below 500. Danazol, an androgen therapy, can be beneficial for some patients, though it is not ideal for those with a history of prostate cancer. Another emerging option is luspatercept (Reblozyl), which targets ineffective erythropoiesis, although it has not yet received FDA approval for use in MF.

MANAGING TREATMENT-RELATED SIDE EFFECTS

JAK inhibitors come with various adverse effects, necessitating careful monitoring and dose adjustments. One of the most significant challenges is cytopenias, including anemia and thrombocytopenia, which are managed through dose reductions, blood transfusions, or switching to momelotinib.

Infections are another concern, with patients at increased risk for shingles, bacterial, and fungal infections. To mitigate this, using prophylactic antivirals such as valacyclovir and vaccinations are recommended.

Gastrointestinal toxicities are common with fedratinib and pacritinib, often causing diarrhea and nausea. These side effects can be managed with medications like loperamide and ondansetron.

Additionally, ruxolitinib is associated with weight gain and metabolic issues, including increased cholesterol and triglycerides, and therefore requires regular lipid monitoring.

"High-risk MF is difficult to treat, especially when patients develop anemia and thrombocytopenia," Ms. Huynh-Lu concluded. "It's important to use risk assessment tools, monitor for adverse events, and document symptom burden to guide your treatment decisions."

Disclosure

Ms. Huynh-Lu has served on an advisory board for GSK and on speakers bureaus for GSK and Incyte. Ms. Kalhagen has served on speakers bureaus for Curio and Incyte.