Myeloproliferative Neoplasms: Emerging Treatment Options for Myelofibrosis

Presented by Aaron T. Gerds, MD, MS

ABSTRACT

Myelofibrosis (MF) is a symptom-forward disease, and its treatment focuses on alleviating those symptoms, as well as improving survival. An initial disease risk assessment is critical for deciding on a course of therapy (and a number of models can be used depending on the available patient information), and anemia can be considered a special case within the treatment algorithms for MF. JAK-STAT inhibition is currently the cornerstone of treatment for MF, but these inhibitors are not perfect. Future research will focus on the microenvironment in reversing fibrosis, immunotherapies, proliferative signaling pathways, epigenetic regulators, and stem cells.

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Myelofibrosis (MF) is one of the classic Philadelphia chromosome (Ph)–negative myeloproliferative neoplasms (MPN), along with essential thrombocythemia and polycythemia vera. An estimated 13,000 patients have MF in the United States,¹ and although JAK inhibitors constitute the cornerstone of current treatment options, these patients can be treated with a number of different therapies.

“Treatments for MF focus on the symptoms of the disease,” said Aaron T. Gerds, MD, MS, Associate Professor of Medicine, Cleveland Clinic Taussig Cancer Institute/Case Comprehensive Cancer Center, at the NCCN 2020 Virtual Congress: Hematologic Malignancies. “This is a very symptom-forward disease.” Eighty percent of patients experience splenomegaly, whereas 70% of patients have symptoms driven primarily by cytokines, such as fevers and night sweats. Many patients also experience cytopenias, particularly anemia and thrombocytopenia.^{2,3} “And, of course, it is a disease that carries a shortened life expectancy, with an average time from diagnosis to death of approximately 5 to 6 years in all-comers,” he stated.

Disease Risk Assessment

Unlike many of the solid tumors represented in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), the classification of MF does not use a staging system. Instead, a risk model is used in which clinical pathologic variables are assigned points and put into a total score, and those scores are assigned a disease risk. The Dynamic International Prognostic Scoring System (DIPSS) is the most commonly used prognostic model in MF (Figure 1). “We’ve taken things further and introduced molecular data into these clinical pathologic

models, thus refining our ability to predict outcomes for patients,” he said. “By layering on all of these different variables, we’ve come up with a lot of different models, and this can get very confusing.”

According to Dr. Gerds, depending on the patient data available, providers can pick the best model to apply to each individual (Figure 2). For example, if molecular data are unavailable but cytogenetic data are available, the preferred model is DIPSS-plus. “The goal of treatment for lower-risk patients is careful observation, focusing on individual symptoms,” he said. “In higher-risk patients, we really are focusing on disease modification.”

Treating Anemia in MF

Anemia is a common consequence of MF, present in 30% to 40% of patients at the time of diagnosis, with an increasing incidence over time. Anemia is associated with shorter overall survival and is an independent prognostic risk factor for leukemic transformation in MF.^{4,5}

“Anemia is a big deal, especially when patients become transfusion-dependent,” he said. “That can be incredibly burdensome, not to mention the symptoms of anemia that make them feel tired or run down. This has a significant impact on patients.” Moreover, JAK inhibitors, the most commonly used treatment for MF, can worsen anemia in approximately 25% of patients.

According to Dr. Gerds, MF-associated anemia can be treated several different ways, illustrated in the NCCN Guidelines for MPN (Figure 3). The data in MF for recombinant erythropoietin show that patients who are anemic and treated with erythropoiesis-stimulating agents do experience response, and a number of different factors have been shown to predict response,

DIPSS Parameter	Points		
	0	1	2
Age	≤65 years	>65 years	
Constitutional symptoms	Absent	Present	
Anemia	≥10 g/dL		< 10 g/dL
Leukocytosis	≤25 × 10 ⁹ /L	>25 × 10 ⁹ /L	
Circulating blasts	<1%	≥1%	

DIPSS Risk Group	Points	Med Survival (y)	Incidence of BP MF (/100 pt-yrs)
Low	0	NR	0.3
Intermediate-1	1-2	14.2	0.7
Intermediate-2	3-4	4	2.6
High	5-6	1.5	8.6

Figure 1. DIPSS: Dynamic International Prognostic Scoring System.

Abbreviations: BP, blast phase; MF, myelofibrosis.

Data from Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood* 2010;115:1703–1708; and Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med* 2012;366:799–807.

including age, serum erythropoietin levels, and hemoglobin concentration prior to treatment.^{6,7} “These factors have been identified in the NCCN Guidelines for MPN, and help to provide guidance regarding when and when not to use erythropoiesis-stimulating agents,” he noted. Other agents used to improve anemia in patients with MF include danazol and lenalidomide.^{8,9} A randomized trial of pomalidomide in patients with MF did not improve anemia, and it is therefore not recommended in the NCCN Guidelines.

“We’re always trying to move things forward, and on the horizon is lusatercept, which is already approved for the treatment of anemia in patients with thalassemia, as well as myelodysplastic syndromes,” he said. In a phase II study of patients with MF, the most significant improvements in anemia were seen in patients receiving

lusatercept and ruxolitinib concurrently.¹⁰ That study is informing a phase III trial that will launch soon, looking specifically at patients with anemia on ruxolitinib.

Targeting JAK-STAT

“Targeting JAK-STAT has really been a centerpiece of treatment for MF. From low risk to high risk, from the top to the bottom of every algorithm, JAK inhibitors are everywhere,” Dr. Gerds said. Whether a patient has a *JAK2* mutation, a *calreticulin* mutation, or an *MPL* mutation, all lead to constitutive JAK-STAT activation, which can then lead to MF.¹¹

A flood of JAK inhibitors have been in development in recent years, with ruxolitinib and fedratinib now approved based on findings from the COMFORT-1 and COMFORT-2 studies of ruxolitinib and the JAKARTA and

Figure 2. What model to use and when?

Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; HCT, hematopoietic cell transplant; MF, myelofibrosis; MIPSS, Mutation-Enhanced International Prognostic Scoring System; MYSEC-PM, Myelofibrosis Secondary to PV and ET-Prognostic Model; PV, polycythemia vera.

^bIncludes RBC transfusion support, iron chelation therapy for patients who have received >20 transfusions and/or ferritin >2500 ng/mL in low/INT-1-risk patients. ESAs not effective for patients with RBC-TD anemia.
^cRuxolitinib or fedratinib may be continued for the improvement of splenomegaly and other disease-related symptoms.
^mProstate cancer screening for men and monitoring of liver function tests as well as concomitant medications such as statins are recommended.
ⁿPresence of del(5q) is associated with better response rates with lenalidomide.

MF-3

Figure 3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Myelofibrosis: Management of MF-associated anemia. Version 1.2020.

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JAKARTA-2 studies of fedratinib. Pacritinib and momelotinib are now in active late-phase development.

“The somewhat arbitrary response used in clinical trials for efficacy in MF is reduction in spleen volume of 35%, which roughly approximates to reducing the palpable spleen size by 50% on clinical examination,” he explained. In the COMFORT-1 study, ruxolitinib outperformed placebo at reducing spleen size, and later outperformed best available therapy in the COMFORT-2 study.^{12,13} Ruxolitinib also improved symptoms such as abdominal discomfort, bone or muscle pain, night sweats, and inactivity. Ruxolitinib was also associated with better median overall survival in the COMFORT trials: 5.3 years in the ruxolitinib arm versus 3.8 years in the control arm (without crossover to the experimental arm, however, survival was estimated to be 2.3 years in the control arm).¹⁴ “Even though it doesn’t kill MF cells, and we’re not seeing MF scores change in the bone marrow, patients who are on ruxolitinib are living longer,” he said.

Fedratinib has also displayed significant clinical activity in MF. In the randomized, placebo-controlled phase III JAKARTA study, fedratinib led to a significant reduction in spleen volumes at 24 weeks.¹⁵ In the JAKARTA-2 trial, 53% of patients with intermediate-/high-risk MF who were resistant to and 63% of patients who were intolerant to ruxolitinib had ≥35% reduction in spleen volume at week 24, providing a second-line indication for fedratinib.¹⁶

“The point I want to make is that no 2 JAK inhibitors are created equal,” Dr. Gerds said. Each of these drugs inhibit JAK1, JAK2, and JAK3 to varying extents, and carry with them different off-target effects. However, according

to Dr. Gerds, “there is room for all of these JAK inhibitors in the treatment of MF, because they all are a little bit different, and can be applied to different populations of patients.”

Where JAK Inhibitors Fall Short

JAK inhibitors do not cure patients. Median survival time on ruxolitinib in the COMFORT studies was approximately 3 years. “And if you look at smaller real-world analyses that are ongoing, that average is much shorter, closer to 1.5 to 2 years,” he said. Additionally, patients who discontinue ruxolitinib perform poorly—particularly those who are thrombocytopenic—and these patients have a short median survival.^{17,18}

“This is not chronic myeloid leukemia. We can’t fool ourselves into thinking there’s a single mutation we can hit with the magic imatinib or another tyrosine kinase inhibitor that will allow us to see long-term or indefinite control,” he said. “There are so many pathways activating this disease that need to be targeted in order to get to that. So we are looking forward, and we are looking at other pathways and different ways of attacking this disease.”

Looking Forward

Ongoing trials in MF are focusing on the microenvironment in reversing fibrosis, immunotherapies, proliferative signaling pathways, epigenetic regulators, and stem cell maintenance, survival, and differentiation.¹⁹

“While all of these pathways are exciting, I like to think about the treatment of MF in the construct of

where we are now, treatments that are close to becoming commercially available for patients, what's just a little further down the road, and, finally, what's on the horizon," he said. "And the treatments on the horizon are really only limited by our creativity."

Momelotinib and pacritinib will hopefully be available for patients in the very near future outside of a clinical trial. Down the road, PRM-151 shows promise in reversing fibrosis in the bone marrow, whereas trials of bromodomain inhibitors are ongoing in the upfront and post-JAK inhibitor settings. On the horizon are JAK2-type II inhibitors. "These target a different spot of the mutant *JAK2*, potentially knocking it out permanently and reducing the malignant clone," he said.

Future research will also focus on a mutant calreticulin protein trap, and preclinical models are exploring the role of CAR T cells in MF. According to Dr. Gerds, although JAK-STAT inhibition is currently the cornerstone of treatment, these inhibitors do fall short. "So we do need to keep pushing the field forward," he said.

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