Myelofibrosis (MF) is a complex hematologic disorder that requires a tailored approach to treatment. At the NCCN 2023 Annual Congress: Hematologic Malignancies, Andrew T. Kuykendall, MD, Assistant Member, Department of Malignant Hematology, Moffitt Cancer Center, and member of the NCCN Guidelines Panel for Myeloproliferative Neoplasms, discussed recent updates in the management of MF, particularly regarding the use of JAK inhibitors.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) currently stratify patients into lower- and higher-risk categories based on a number of clinical and genetic factors. The patient’s risk category mainly serves to identify patients in whom a transplant evaluation would be appropriate. Although risk status has been used as an inclusion criteria for most registrational clinical trials, Dr. Kuykendall argued that the treatment approach for this malignancy should hinge upon clinical presentation and symptom burden more so than risk.

Treating Lower-Risk MF
After being separated by risk category, patients with lower-risk MF are further divided into asymptomatic and symptomatic subgroups. Asymptomatic patients may undergo observation or surveillance over time until symptoms or cytopenias develop, which can then be addressed with current treatments. For symptomatic lower-risk patients, JAK inhibitors such as ruxolitinib are often first-line treatment. However, in some cases, pegylated interferon or hydroxyurea may be considered, focusing on cytoreduction.

“What’s worth noting in patients with a lower risk is that clinical trials are really the preferred approach, because this is a group and a disease in which we feel we need to do better in terms of the treatments offered,” said Dr. Kuykendall.

Treating Higher-Risk MF
Patients with higher-risk MF are most often stratified by platelet count. Those with markedly low platelet counts (<50 × 10⁶/L) tend to have very high-risk disease and therefore, transplantation should be considered for appropriate patients. For those who cannot undergo transplantation (as is the case for many patients with MF), the JAK inhibitor pacritinib may be considered, as it has received accelerated FDA approval for use in this patient population. Patients with platelet counts ≥50 × 10⁶/L who are not candidates for immediate transplantation may be prescribed other approved JAK inhibitors. Dr. Kuykendall noted that pacritinib has a category 2B indication in this setting, because it has been studied in patients with higher platelet counts, although its accelerated approval was not granted for this indication.

He added that the higher-risk subset of patients who present with anemia alone and are not eligible for transplantation—but lack splenomegaly/symptoms—may not benefit greatly from JAK inhibition and should focus on anemia management, although the approval of pacritinib and momelotinib—JAK inhibitors with favorable impacts on anemia—may specifically benefit this group of patients.

Anemia Management in MF
The management of MF-associated anemia involves addressing alternative causes of anemia (eg, nutritional deficiencies, hemolysis) and stratifying patients based on their baseline erythropoietin levels. Patients with low levels may benefit from erythropoiesis-stimulating agents, whereas those with higher erythropoietin levels may explore other options, such as danazol, lenalidomide, thalidomide, or luspatercept.

“This certainly is an area of unmet need, and one we’re striving to improve,” Dr. Kuykendall said. The NCCN Guidelines for the management of MF-associated anemia are outlined in Figure 1.

According to Dr. Kuykendall, patients with MF often present with either anemia, splenomegaly/symptoms, or...
a combination of both. “This dictates what agents we have available,” he added. “But none of our agents are disease-modifying in the truest sense; many of them are symptomatic or palliative therapies aiming to improve certain aspects of the patient’s clinical condition.”

Although the treatment recommendations in the NCCN Guidelines should be followed to arrive at the “end result,” he added, another type of treatment algorithm based less on risk and more on clinical presentation has proven helpful in his practice (Figure 2).

Dr. Kuykendall commented: “Clinical trials are always an acceptable preferred option in both the first and second lines, regardless of symptoms, and allogeneic stem cell transplantation should always be considered for appropriate patients, because it offers the only curative option for MF”

Ruxolitinib: A Mainstay Treatment

Approved since 2011, ruxolitinib has been a mainstay of treatment for patients with MF. According to Dr. Kuykendall, its impact in this malignancy should not be understated.

Ruxolitinib is well-known for its benefits in regard to spleen volume and symptoms, often with “striking” rapidity and durability of benefit, he noted. It is also generally well tolerated, he added, as seen in the COMFORT-I and COMFORT-II trials, which led to its approval.

Newer data also showed that overall survival in MF may be improved in the era of ruxolitinib. Compared with patients who received investigational therapy or “other” treatments, patients treated with ruxolitinib had better outcomes. Additionally, those diagnosed after ruxolitinib approval are living longer than those diagnosed in the pre-ruxolitinib era, regardless of treatment. “This really [highlights] the benefit JAK inhibitors have had in this space,” he commented.

Dr. Kuykendall emphasized the importance of differentiating between the terms “symptoms” and “risk” when treating these patients. “Ruxolitinib has largely been approved for patients with intermediate- to high-risk disease. However, I don’t think that approach is necessarily appropriate, as we know ruxolitinib is very good at improving disease-related symptoms, and symptoms don’t always correlate with disease risk,” he explained.

Disease risk considers clinical and genetic factors, as it primarily predicts overall mortality. Restricting JAK inhibitor therapy to high-risk patients may exclude those with lower-risk disease but significant symptoms; these lower-risk patients may be missing out on substantial benefit from ruxolitinib, Dr. Kuykendall explained. At the same time, treating all high-risk patients, including those without prominent splenomegaly/symptoms (ie, those with “cytopenic MF”), may also be an inappropriate intervention, as it might worsen their quality of life, he added. Clinical trials suggest that early intervention with ruxolitinib in patients with intermediate-1-risk disease may lead to better spleen responses with fewer cytopenias.

“This is an area where we might see improved outcomes when treating patients with less-complex disease and fewer cytopenias,” he said. “These cytopenias are important, because developing cytopenias—specifically
anemia—is one of the main reasons patients come off therapy and discontinue ruxolitinib.”

Dr. Kuykendall argued that “perhaps we can do better” for patients with anemia. “Historically, we’ve kind of punted anemia, started at a high dose and transfused through it,” he acknowledged. “But we know that in the real world, that doesn’t necessarily play out, and patients often come off the drug.”

The phase II REALISE study demonstrated that a modified dosing strategy may potentially mitigate the impact of anemia in patients with MF. A reduced starting dose followed by up-titration, as tolerated, resulted in spleen and symptom responses occurring in the setting of stable hematologic parameters (70% and 46%, respectively), suggesting this may be an optimal dosing strategy for patients who present with some degree of anemia.

Although the short-term side effects of JAK inhibitors are generally well tolerated, long-term use of these agents may lead to issues such as weight gain, an increased risk of nonmelanoma skin cancers, and immunosuppression. Patients receiving long-term ruxolitinib therapy should be monitored carefully for those side effects, Dr. Kuykendall advised.

**Fedratinib and Pacritinib: Efficacy and Safety**

Fedratinib, the second JAK inhibitor approved for use in patients with MF in August 2019, has shown efficacy in improving splenomegaly and symptoms, both in the first line compared with placebo and in the second line after treatment with ruxolitinib. However, its side-effect profile is potentially more concerning than that of ruxolitinib, Dr. Kuykendall noted. Gastrointestinal (GI) side effects require careful management in these patients; however, data suggest these toxicities may be mitigated with supportive care consisting of prophylactic antiemetic and antidiarrheal medications.

Notably, fedratinib has a black box warning for encephalopathy, including Wernicke encephalopathy. “Although this remains a concern, the focus should be on ensuring these patients do not have significant GI toxicity,” Dr. Kuykendall stated. “Patients should have adequate thiamine levels going into treatment with fedratinib—perhaps supplementing with thiamine—and should receive supportive care if they do develop GI toxicity.”

Pacritinib gained accelerated approval in February 2022 for patients with marked thrombocytopenia, based on data from the PERSIST-2 trial. Compared with best available therapy (eg, ruxolitinib), pacritinib led to improvements in spleen volume and symptoms in this thrombocytopenic patient population. Another study directly comparing pacritinib and ruxolitinib in patients with marked thrombocytopenia showed activity in the endpoints of spleen volume, symptom improvement, and Patient Global Impression of Change score in those treated with pacritinib.

Pacritinib (like momelotinib) exhibits potent ACVR1 inhibition, suggesting it may have benefit outside the markedly thrombocytopenic patient population and may
be appropriate for those with anemic MF. Pacritinib has also demonstrated favorable rates of transfusion independence compared with best available therapy in pivotal studies. However, similar to fedratinib, pacritinib has the potential to cause significant GI side effects, and patients should be carefully monitored.

**Momentum With Momelotinib**

The JAK1/JAK2 inhibitor momelotinib recently gained FDA approval for the treatment of intermediate- or high-risk MF, including primary or secondary MF (post–polycythemia vera and post–essential thrombocythemia), in adults with anemia. It has demonstrated substantial activity in treating MF and appears to be a valuable addition to the treatment armamentarium for MF.

In the pivotal MOMENTUM study, which enrolled patients previously treated with ruxolitinib and who were symptomatic and anemic and had enlarged spleens, momelotinib was demonstrated to be superior to danazol in terms of symptom responses, with 25% of patients achieving a symptom response compared with 9% of those in the danazol group. Spleen responses also occurred much more frequently with momelotinib than with danazol, and momelotinib was associated with higher rates of transfusion independence compared with best available therapy in pivotal studies.

Although there was no significant difference in overall survival, there was certainly a trend toward an improved benefit of receiving momelotinib in this patient population, he added.

Improvement in anemia was also seen immediately after transitioning from ruxolitinib to momelotinib in the SIMPLIFY-1 study of patients with JAK inhibitor–naïve disease. In this head-to-head study versus ruxolitinib, momelotinib demonstrated noninferiority in terms of spleen reduction, but it did not meet noninferiority criteria in terms of symptom response. Furthermore, momelotinib has shown activity in patients with thrombocytopenia, making it a potential choice for those with low platelet counts.

Ultimately, patient-specific factors and prior therapies play a significant role in determining the best JAK inhibitor for individuals with MF.

**References**