ManagingMPN

Shared Decision-Making with Patients and Caregivers

What second line treatment options are available, referral to clinical trials; how to choose?

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After so many years of limited treatment options for myelofibrosis (MF), both clinicians and patients are faced with more complex treatment decision making. To effectively guide discussions with patients, clinicians must understand current literature, guidelines, and treatment standards.

"Treatment decision making for patients with MF who have progressed or who are intolerant of frontline therapy requires a systematic approach to defining progression or intolerance and vigilance in reviewing clinical trials data, including the study design, inclusion and exclusion criteria, primary and secondary endpoints, efficacy, and safety data."

This is particularly critical with the robust pace of scientific discovery and the growing pipeline of novel agents.

The first step in the process of treatment decision making is risk stratification, which should be repeated at each point of progression or intolerance. The most common risk stratification tools used in second-line treatment decision making are the Dynamic International Prognostic Scoring System Plus (DIPSS-Plus) and the newer mutation and karyotype enhanced tools that are adjusted for age 70 or less (MIPPS-70), or age greater than 70 years (MIPSS-70+ version 2), or the MYSEC prognostic model (MYSEC-PM) for post polycythemia vera or post essential thrombocythemia MF. Importantly, molecular testing at each point in the disease trajectory is essential to accurate risk stratification as driver mutations can be acquired over time.[1-5] Although peripheral blood may be sent for next generation sequencing (NGS) and flow-cytometry, a bone marrow biopsy and aspirate is recommended to include bone marrow blasts, chromosomal analysis, and evaluation of bone marrow fibrosis for full assessment of response or progression.[3]

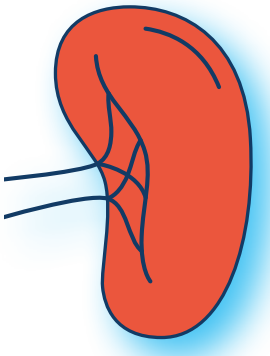
"Risk stratification is essential to effectively setting goals of care based on the variability in survival across risk groups, particularly older or frail patients that are not eligible for an allogenic stem cell transplant (alloSCT)."

For example, a patient in the highest risk group using the MIPPS-70 has an estimated median overall survival of 2.3 years (95% CI, 1.9 to 2.7 years) and a risk of death of 81% at 5 years, and a patient in the highest risk group for the MIPPS70+ with an estimated 5-year overall survival of just 7%.[2] Conversely, patients in the lowest risk groups may not require immediate cytoreductive therapy in the absence of progressive proliferative changes or increasing symptom burden and have an estimated 5-year median overall survival exceeding 90%.[2,6] Understanding estimated survival is essential to tailoring treatment decision making conversations and setting expectations for each patient.

"Once risk stratification is complete, it is helpful to frame the treatment decision making process by reviewing evolving treatment options, including new drug combinations and available clinical trials with a look back at recent drug approvals."

The first in class Janus kinase (JAK) inhibitor, ruxolitinib, was approved in November of 2011 and was the only targeted cytoreductive therapy available for treatment of MF until subsequent approvals of fedratinib in August of 2019 and pacritinib in March of 2022.

Fedratinib, a potent selective JAK2 and FLT3 inhibitor, was approved based on results of the phase III JAKARTA trial in patients not previously treated with ruxolitinib and subsequent phase II JAKARTA-2 trial in ruxolitinib-resistant or ruxolitinib-intolerant intermediate-1, intermediate-2, or high-risk MF.[7] In both trials, fedratinib met the primary endpoints of >35% spleen volume reduction (SVR) and the secondary endpoint of >50% reduction in total symptom score (TSS) when compared to placebo in the JAKARTA trial and in patients previously treated with ruxolitinib in the single arm JAKARTA-2 trial.[6] FDA approval of fedratinib was delayed largely due to a concern for the rare neurological disorder, Wernicke encephalopathy (WE), reported in only one case of a patient treated in the JAKARTA-2 trial and subsequently determined not to be associated with fedratinib, but rather underlying hepatic encephalopathy.[6] In this same analysis of 670 patients treated with fedratinib across both solid tumors and myeloproliferative neoplasms, the incidence of WE were <1%, consistent with the prevalence of WE in the general US population.



Subsequent re-analysis of the JAKARTA-2 data using more stringent definitions of ruxolitinib failure, confirmed benefit in SVR and symptom response rates (SRR), albeit less robust than described in the JAKARTA-2 trial confirming the role of fedratinib in patients with prior ruxolitinib exposure.[6] The more stringent criteria for relapse/progression required exposure to

ruxolitinib for at least 3 months with regrowth of the spleen, defined as <10% SVR or <30% decrease in spleen volume from baseline following an initial response.[8] Ruxolitinib refractory MF was defined as exposure to ruxolitinib for at least 3 months with <10% SVR or <30% decrease in spleen volume, and ruxolitinib intolerance was defined as exposure to ruxolitinib >28 days complicated by transfusion dependence (>2 units of RBCs/month for 2 months), or grade >3 thrombocytopenia, anemia, hematoma/hemorrhage while on ruxolitinib.[8]

Based on these data, and the updated safety profile, fedratinib carries a category 1 recommendation for treatment of high-risk MF by the National Comprehensive Cancer Network (NCCN) in patients with prior ruxolitinib exposure.[9] Fedratinib does carry a boxed warning for the risk of WE with recommended guidelines for evaluating baseline thiamine levels on all patients being considered for treatment with correction of thiamine deficiency prior to treatment initiation.[9]

Pacritinib, a JAK2, FLT3, and IRAK1 inhibitor, received accelerated approval based on results of the PERSIST-1 and PERSIST-2 trials for the treatment of intermediate or high-risk MF with a platelet count <50 x10^9.[9] Thrombocytopenia is common in patient with MF, occurring in approximately 20% of patients over the course of their disease and in higher percentages for patients on active treatment.[10] Dosing of ruxolitinib is based on baseline platelet counts and thrombocytopenia presents a challenge in continuing treatment with ruxolitinib in sufficient doses to maintain efficacy in selected patients with higher risk MF.[11]

The PERSIST-1 trial did not allow for prior JAK2 inhibitor exposure and had no exclusion for baseline platelet counts, whereas the PERSIST-2 trial, that compared two doses of pacritinib to best available therapy (BAT), including 95 of the 221 patients enrolled who were previously exposed to ruxolitinib.[12] In both studies, patients were allowed to cross over to the pacritinib arm from the BAT arm at 24 weeks or at the time of progression on BAT. In the PERSIST-1 trial, at a median of 25 weeks, 84% of the patients on BAT crossed over to the pacritinib.[12] Importantly, as with most drugs approved under accelerated approval, continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).[13]

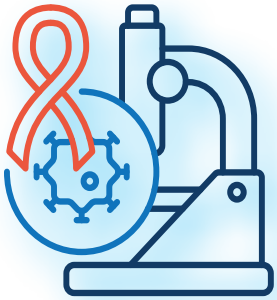
"Evaluating each patient with MF for clinical trial participation should be a consideration at each treatment decision making interval."[9]

Clinical trial participation remains limited across all disease states, particularly in older patients, yet all currently FDA approved agents are a result of clinical trials.[13]

This requires familiarity with resources to locate local or regional clinical trial centers with trials open to MF

patients. Many of these centers also offer alloSCTs. The open and maturing clinical trials are also summarized in the literature and at national and international hematology and oncology meetings. The National Institutes of Health site for clinical trials allows a search for open and enrolling trials with a brief summary of inclusion and exclusion criteria at https://clinicaltrials.gov/.

There are numerous ongoing clinical trials for MF. Importantly, many of these introduce agents with a novel mechanism of action, including the activin A receptor/activin receptor like kinase (ACVR1/ALK2) and JAK1/2 inhibitor momelotinib which has been studied in the recent phase III MOMENTUM trial evaluating patients previously treated with ruxolitinib who were symptomatic and anemic.[14] The primary endpoint, TSS response rate at 24 weeks; and secondary endpoints of transfusion independence (TI) and spleen response rate (SRR) were met and superior to danazol in this analysis. Like thrombocytopenia, anemia is prevalent in patients with MF across the disease trajectory with most patients developing anemia within a year of diagnosis and virtually all patients requiring RBC transfusions over the course of their disease.[10]



Additional agents in established clinical trials that have had data presented at recent national or international meetings include imetalstat, a telomerase inhibitor; parsaclisib, a PI3K inhibitor in combination with ruxolitinib; and navitoclax, a BCL2/BCLX inhibitor being evaluated as a single agent or in combination with ruxolitinib. There are numerous other ongoing trials. Additionally, supportive, and palliative care strategies and specifics will be summarized in the third installment of this series to round out the considerations in patient centric and tailored treatment decision making.

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