Current Therapies for the Treatment of Myelofibrosis

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MediCom recently spoke with a leading expert to discuss the wide spectrum of symptom burden and other disease manifestations in the presentation of myelofibrosis, and the need to appropriately risk stratify each patient.

What are the first steps one should take when encountering a patient with newly diagnosed myelofibrosis?

Dr. Vachhani: Myelofibrosis (MF) can present with a wide spectrum of symptom burden and other disease manifestations, so the first thing we need to do when patients are diagnosed with MF is to stratify them according to risk. This can help us get a better sense of how good or bad their overall prognosis is, as well as select optimal treatment and supportive therapy. As discussed in the first newsletter of this series, the MIPSS version 2.0 (MIPSSv2.0)[1] is the most recent version of the original International Prognostic Scoring System (IPSS)[2] that was developed in 2009 for this purpose. The MIPSSv2.0 scores nine components – 5 genetic and 4 clinical – to determine whether a patient has high-risk or low-risk disease. This determination provides the framework for future therapy.

It is also important to accurately assess symptom burden, regardless of risk status. The National Comprehensive Cancer Network (NCCN) recommends the MPN-SAF TSS (Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score).[3] This score assesses fatigue, abdominal discomfort, bone pain, and other symptoms of MF.

What treatments are available for patients with symptomatic MF who are not candidates for stem cell transplant?

The goal of front-line treatment for MF is to alleviate symptoms. We do this by inhibiting the Janus kinase/signal transducer and activator of transcription proteins (JAK/STAT) pathway, which is upregulated in MF patients. There are currently 4 FDA-approved JAK inhibitors for MF: ruxolitinib, fedratinib, pacritinib, and momelotinib, which was very recently approved in

September 2023. Ruxolitinib was the first JAK inhibitor to be approved for MF based on the landmark COMFORT-I and COMFORT-II trials. In COMFORT I, 42% of patients achieved the primary endpoint, which was a reduction of spleen volume by at least 35% (SVR35%), compared to 0.7% in the placebo arm.[4] COMFORT-II compared ruxolitinib with best available therapy (BAT) and showed that SVR35% was achieved in 28% of patients in the ruxolitinib group compared to 0% in the BAT group.[5]

Fedratinib is a JAK2/FLT3 inhibitor that was approved by the FDA for intermediate-2 or high-risk MF in patients who are either ruxolitinib-naïve or -resistant based on the JAKARTA and JAKARTA-2 trials. In the phase 3 JAKARTA trial, 36% and 40% of patients receiving 400mg and 500mg of fedratinib, respectively, achieved SVF35% at 24 weeks compared to 1% in the placebo group.[6,7] In the phase 2 JAKARTA-2 trial, which included patients who were resistant or intolerant to ruxolitinib, 55% achieved SVR35%. An additional phase 3 trial – the FREEDOM trial - investigated fedratinib in patients with a >3 month history of ruxolitinib treatment, with primary analysis revealing that 26% of patients achieved SVR35% by the end of cycle 6 (enrollment was capped early due to the COVID-19 pandemic).[8]

One challenge that became apparent over the course of these trials was the association between JAK inhibition and grade 3/4 anemia, which occurred in 42.0%-45.2% of those in the COMFORT-I and -II trials, respectively, and 38%-58% of those in JAKARTA and JAKARTA-2 [4,5,6,7] Anemia is a common finding in newly diagnosed MF patients, with 38% of patients having a hemoglobin (Hb) >10g/dL at diagnosis.[9] Anemia is a negative prognostic indicator in MF that also decreases quality of life (QOL). The combined risk of anemia associated with both MF and JAK inhibitor therapy poses a significant barrier to improved outcomes for those with this hematologic malignancy.

Fortunately, the next JAK inhibitor to be approved for MF – pacritinib – was shown to demonstrate an anemia benefit. Pacritinib is a JAK2/IRAK1 inhibitor that, unlike ruxolitinib and fedratinib, can be given in patients with severe thrombocytopenia (<50 x 10^9/L), which often co-occurs with severe anemia. In the PERSIST-1 and PERSIST-2 trials, pacritinib was effective in both JAK inhibitor-naïve and ruxolitinib-treated patients, demonstrating a significantly higher SVR35% compared to BAT (18% vs 3%, respectively) and a greater total symptom score improvement by greater than 50% (TSS50%) compared to BAT (25% vs 14%), although the difference was not statistically significant.[10] Importantly, improvements in Hb and reductions in transfusion burden were also observed in pacritinib-treated individuals.[10] Although the exact mechanism of action that allows pacritinib to maintain or even improve Hb levels is not clear, it is theorized to be related to ACVR1 inhibition, which is apparent in pacritinib-treated individuals but not in those treated with ruxolitinib or fedratinib.[10] Inhibition of ACVR1 has been found to reduce hepcidin transcription, which in turn increases available iron stores and subsequently increases Hb production.[11]

The recent approval of momelotinib for MF offers a new treatment choice with a positive effect on anemia due to this activity. Momelotinib is JAK1/JAK2/ACVR1 inhibitor that was approved in September 2023 based on the phase 3 MOMENTUM study, which enrolled patients with a

baseline Hb of <10g/dL and previous exposure to JAK inhibitor therapy.[12] Compared with danazol, momelotinib treatment conferred greater achievement of TSS50% (25% vs 9%) and SVR35% (23% vs 3%). In terms of anemia, transfusion independence (TI) was achieved by 31% of patients receiving momelotinib compared to 20% receiving danazol. It is also important to mention the SIMPLIFY-1 and -2 trials, which demonstrated increased rates of TI in association with momelotinib therapy (67% in SIMPLIFY-1 and 43% in SIMPLIFY-2) versus ruxolitinib therapy (49% and 21%, respectively).[13] These data show that momelotinib is a promising treatment option for patients with MF and anemia regardless of exposure to ruxolitinib.

How else can anemia be managed in MF patients?

Luspatercept is a recombinant activin receptor type IIB fusion protein that was designed to trap TGF-β superfamily ligands. This agent was recently approved for the treatment of anemia associated with transfusion-requiring beta thalassemia and low/intermediate-risk MDS with ring sideroblasts without (MDS-RS) or with (MDS-RS-T) thrombocytosis. Although not approved by the FDA for MF specifically, there is evidence that this agent can effectively treat anemia in MF patients. Recently, the phase 2 ACE-536-MF-001 study showed that luspatercept therapy improved the likelihood of TI regardless of baseline transfusion status or ruxolitinib therapy, with the greatest effect being observed in the setting of ruxolitinib therapy and transfusion dependence.[14]

Erythropoiesis-stimulating agents (ESAs) can also be used to manage anemia in MF patients with low serum erythropoietin (EPO) levels. Available ESAs, which include epoetin, darbepoetin, and methoxy polyethylene glycol-epoetin beta, are recombinant versions of EPO that are indicated in conditions associated with impaired red blood cell production. These agents are capable of improving anemia in 50% or more of anemic MF patients, as well as reducing spleen size in some individuals. These agents do not interfere with the activity of JAK inhibitors, making them a reasonable choice for the treatment of anemia in JAK inhibitor-treated patients.

How are these agents incorporated into current guidelines?

The NCCN guidelines for lower-risk, symptomatic MF recommend ruxolitinib, peginterferon alfa-2a, or hydroxyurea for lower risk symptomatic disease, and ruxolitinib (category 1), fedratinib (category 1), momelotinib, or pacritinib (category 2b) for higher risk symptomatic patients who are not candidates for stem cell transplant.[3] Loss of response can be managed with an alternate JAK inhibitor. Those with anemia symptoms only can be treated with supportive care consisting of red blood cell transfusion, momelotinib, danazol, lenalidomide ± prednisone, thalidomide ±prednisone, or luspatercept if serum EPO ≥500 mU/mL, or ESAs if serum EPO <500 mU/mL.

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