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Momelotinib Usage Within Our Current Canadian Myelofibrosis Armamentarium

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Introduction

Myelofibrosis (MF) can be categorized as primary MF (PMF), or secondary MF, which comprises post-polycythemia MF (PPV) and post-essential thrombocythemia (PET).[1] Activating mutations in *JAK2*, *CALR*, or *MPL* are the main driver mutations resulting in abnormal signalling that promotes cell proliferation and survival, leading to secretion of inflammatory cytokines causing myeloproliferation, bone marrow fibrosis, and extramedullary hematopoiesis in MF.[2]

The current treatment landscape for MF consists of strategies to reduce spleen volume and improve MF-related symptoms with less effective results in improving cytopenias. Mainstay therapies have included hydroxyurea (HU) and Janus kinase inhibitors (JAKi), as well as curative allogeneic stem cell transplant (ASCT), though fewer patients are eligible for this treatment. Several JAKi have been approved in Canada for first-line treatment, including ruxolitinib, fedratinib, and most recently, momelotinib. Approximately 40% of patients with MF have anemia at diagnosis, and nearly 25% are red blood cell (RBC) transfusion-dependent (TD). Many patients with MF struggle with symptoms related to chronic anemia, and anemia often progresses with time, leading to transfusion dependence for many patients.[3] Anemia of any severity negatively impacts MF survival and is highlighted as a negative prognostic factor among most validated MF scoring systems.[4-8] Anemia results in increased patient fatigue and lower quality of life (QoL), which results in increased healthcare utilization. Severe anemia results in a 2-fold increased healthcare resource utilization compared to mild anemia.[9] This review focuses on the current treatment approaches for MF, with particular focus on MF-related anemia and the targeted role of newer JAKi, such as momelotinib.

Treatment

Currently available MF treatments are non-curative, except for ASCT. Thus, it is important to first identify patients who are ASCT-eligible to provide these patients with curative treatment.

ASCT referral and access to JAKi therapy is based on MF risk stratification. Various prognostic scoring systems **(Table 1)** have evolved with the International Prognostic Scoring System (IPSS) model introduced in 2009.[10] Dynamic IPSS (DIPSS) models can be used throughout the course of disease with additional features included within the DIPSS+ model, such as cytogenetics and RBC transfusions.[4,5] Molecular IPSS (MIPSS) scores include myeloid gene mutations, (MIPSS 70 model) and are used for transplant-eligible patients.[6,7] Patients with secondary MF are best prognosticated using the MYelofibrosis SECondary to PV and ET prognostic model (MYSEC-PM).[8] Patients classified as intermediate- or high-risk based on prognostic scoring models are eligible for first-line JAKi treatment.

Lower-risk patients often remain under observation but may require cytoreduction with HU or pegylated-interferon therapy (in cases of extreme thrombocytosis, leukocytosis, or for symptom control).[11] For patients who are transplant-eligible, transplant is offered to those with intermediate- or high-risk, which often requires JAKi treatment as a bridge to ASCT. Spleen size reduction and symptom resolution were used as primary endpoints, leading to the approval of current JAKi therapies. Standardized symptom assessments are performed most commonly using a myeloproliferative neoplasm (MPN)-10 Total Symptom Score (TSS) to quantify the 10 most clinically relevant MF symptoms.[12]

Variables (weight)	DIPSS	DIPSS+	MIPSS70	MIPSS-70+version 2.0	MYSEC-PM*
Clinical	Age >65 yrs (1) Constitutional sx (1)	Age >65 yrs (1) Constitutional sx (1) RBC transfusions (1)	Constitutional sx (1)	Constitutional sx (2)	Age (0.15 x yrs of age) Constitutional sx (1)
Lab	Hgb <100g/L (2) WBC >25 × 10^9/L (1) PB Blasts ≥1% (1)	Hgb <100g/L (1) WBC >25 × 10^9/L (1) PB Blasts ≥1% (1) Plt <100 × 10^9/L (1)	Hgb <100g/L (1) WBC >25 × 109/L (2) PB Blasts ≥2% (1) Plt <100 × 10^9/L (2) BM fibrosis grade ≥2 (1)	Hgb <90 g/L (women) or <80 g/L (men) (2) Hgb 80-99 g/L (women) or 9-109 g/L (men) (1) PB Blasts ≥2% (1)	Hgb <110g/L (2) PB Blasts ≥3% (2) Plt <150 × 10^9/L (1)
Mutation status			Absence CALR type 1/like (1) 1 HMR (1) 2 or more HMR (2)	Absence CALR type 1/like (2) 1 HMR included U2AF1Q157 (2) 2 or more HMR included U2AF1Q157 (3)	Absence CALR (2)
Cytogenetics		Unfavourable ** (1)		Unfavourable± (3) Very high-risk ∞ (4)	
Risk group (score), median survival	Low (0), NR Int-1 (1-2), 14.2 yrs Int-2 (3-4), 4 yrs High (5-6), 1.5 yrs	Low (0), 15.4 yrs Int-1 (1), 6.5 yrs Int-2 (2-3), 2.9 yrs High (≥4), 1.3 yrs	Low (0-1), NR Int (2-4), 6.3 yrs High (≥5), 3.1 yrs	Very Low (0), NR Low (1-2), 16.4 yrs Int (3-4), 7.7 yrs High (5-8), 4.1 yrs Very High (≥9), 1.8 yrs	Low (<11), NR Int-1 (11-13), 9.3 yrs Int-2 (14-15), 4.4 yrs High (≥16), 2 yrs

Table 1. Current prognostic models to predict survival for myelofibrosis; *courtesy of Sonia Cerquozzi, MD, FRCPC*

Abbreviations: BM: bone marrow; **BMF:** bone marrow fibrosis; **CALR:** calreticulin; **DIPSS:** Dynamic International Prognostic Scoring System; **DIPSS+:** Dynamic International Prognostic Scoring System Plus; **MIPSS-70/apexV2:** Mutation-Enhanced International Prognostic Scoring System; **MYSEC-PM:** Myelofibrosis Secondary to polycythemia vera and essential thrombocythemia-Prognostic Model; **Hgb:** hemoglobin; **HMR:** high molecular risk (ASXL1, EZH2, SRSF2, or IDH1/2); **Int:** intermediate; **MIPSS:** Mutation-Enhanced International Prognostic Score System; MYSEC-PM* used for secondary MF; **NR:** not reached; **PB:** peripheral blood; **PLT:** platelets; **RBC:** red blood cells; **sx:** symptoms; **WBC:** white blood cells; **yrs:** years.

** Complex karyotype or sole or 2 abnormalities including +8, −7/7q-, i(17q), −5/5q-, 12p-, inv(3) or 11q23 rearrangement.
± Chromosomal abnormalities except "very high-risk" (see below) or sole 13q-, +9, 20q-, chromosome 1 translocation/duplication or sex chromosome alterations including -Y.
∞ Single/multiple abnormalities of −7, i(17q), inv(3)/3q21, 12p-/12p11.2, 11q-/11q23, +21, or other autosomal trisomies except +8/9.

Anemia In MF

One of the biggest challenges facing MF is the presence or emergence of anemia, which can be the result of the clinical phenotype of MF or an off-target effect of JAKi therapy. Patients are generally symptomatic from anemia, and transfusions to treat it require additional bloodwork and appointments, leading to poorer patient QoL accompanied by potential complications of iron overload and risks of transfusion-related reactions.

Although variable, 35-54% of patients with MF have been reported to have anemia (hemoglobin [Hgb] <100 g/L) at the time of diagnosis.[3-5,10] MF-related anemia results from reduced erythropoiesis, splenomegaly, and inflammatory cytokines with functional iron deficiency due to inflammatory upregulation of hepcidin and iron-restricted anemia.[13,14] Ultimately, it is important to understand the etiology of anemia and to evaluate for any contributing factors.

Anemia management begins with RBC transfusions, initial assessment, and correction of associated factors. Erythropoiesis-stimulating agents (ESAs) have been used off-label. Those with anemia and low EPO levels (<125 mU/mL) at baseline should be considered for this treatment. In routine practice, those with EPO levels <500 mU/mL can attempt an ESA trial for 12 weeks. Suggested starting doses of 40,000 units per week of recombinant erythropoietin or darbepoetin 150 µg/week (or 500 µg/3 weeks) with dose escalation to 80,000 units or 300 µg per week, respectively, if required after 6–8 weeks.[11,15] ESA anemia responses were observed in 53% of patients, more specifically in 29% of transfusion-dependant (TD) and in 57% of transfusion-independent (TI) patients, with a median duration of response (DOR) of 19 months with or without JAKi concomitant usage.[16] Anabolic steroids such as danazol have been shown to be effective in ~30% of patients (18% of TD vs. 43% of TI).[17] Immunomodulatory agents (IMiDs), such as thalidomide and lenalidomide, have also been studied and were shown to have more limited benefits, with TI rates of 11% vs. 16%, respectively.[18]

Luspatercept, a SMAD2/3-pathway ligand trap, is currently under evaluation vs. placebo in the Phase 3 INDEPENDENCE trial (NCT04717414). While the Phase 2 results were promising, this treatment is not yet accessible for clinical use.[19]

The ACE-536-MF-001 trial enrolled patients with MF (n = 95) into four cohorts: patients in two cohorts who were TI (TI) and had anemia, and patients in two cohorts who were TD. Each cohort had one subcohort in which patients had been on stable ruxolitinib treatment before and during the study. The primary endpoint was the anemia response rate, which in this study was defined as a ≥15 g/L increase from baseline for TI, or achieving transfusion independence over any 12-week period during the primary treatment period (weeks 1-24) for TD. In both TI cohorts, those with and without ruxolitinib, 27% and 50% of patients, respectively, had an anemia response. Among TD patients, ~50% had a ≥50% reduction in transfusion burden.[20]

JAK Inhibitors

Ruxolitinib was the first approved *JAK1/JAK2* inhibitor. The COMFORT I/II studies revealed that ruxolitinib was associated with prolonged survival in patients with MF compared to controls, regardless of baseline anemia status. The median duration of response (DOR) in both trials was ~3 years.[21,22] Ruxolitinib remains a standard first-line option for patients with MF with a platelet count >50 × 10^9/L, although treatment-related anemia is a disadvantage. Dose-dependent anemia and thrombocytopenia occur with this therapy.[23,24] Typically, anemia occurs in the first 12 weeks of therapy and can be managed with dose adjustments and/or transfusions. Mean hemoglobin levels have been shown to reach a nadir at 8–12 weeks with near baseline level recovery by week 24.[23,25] In a pooled exploratory analysis of both COMFORT studies, 61% (99 out of 162) of patients in the ruxolitinib group without baseline anemia developed anemia on treatment, and 69% (93 out of 134) of those with baseline anemia experienced worsening anemia. Exploratory analyses showed that while MF-related anemia is associated with reduced overall survival (OS), new or worsening anemia that occurred during and possibly as a result of ruxolitinib therapy had no effect on OS.[21] Fedratinib, a *JAK2/FLT3* inhibitor, was the second *JAK2* inhibitor approved for use in intermediate-2 and high-risk MF based on the JAKARTA and JAKARTA-2 trials. Similarly, fedratinib was also shown to result in anemia at 12-16 weeks, which partially recovered over time.[26] Fedratinib is an option and accessible for patients with ruxolitinib intolerance and has been shown to result in

comparable spleen and symptom reduction with similar treatment-related anemia effects as ruxolitinib.

Anemia is not a contraindication for JAKi usage, although novel dosing strategies for ruxolitinib were used and shown to be effective in the Phase 2 REALISE trial **(Figure 1)**. It has been suggested to use a lower starting dose of ruxolitinib (10 mg PO BID) for patients with MF with Hgb <100 g/L, which is followed by up-titration after 12 weeks, based on platelet count and efficacy, to a maximum dose of 25 mg PO BID. This dosing regimen resulted in 70% of patients reaching a 50% spleen volume reduction (SVR50%) and stable hemoglobin levels compared to baseline.[27] However, in assessing the response to ruxolitinib after 6 months, lowering the dosage and RBC transfusions were both negative risk factors for survival.[28]

Momelotinib is an oral inhibitor of *JAK1/JAK2* and *ACVR1*. The additional targeted inhibition of ACVR1 downregulates hepcidin expression, a pivotal regulator of iron homeostasis, which facilitates erythropoiesis, resulting in anemia benefits.[29] Given the treatment-related anemia associated with current JAKi's, momelotinib was designed to relieve symptoms and spleen burden while preventing and/or improving anemia. In the first Phase 3 non-inferiority SIMPLIFY-1 trial, symptomatic intermediate-1, intermediate-2, and high-risk MF patients were assigned to 200 mg PO daily momelotinib vs. 20 mg PO BID ruxolitinib, allowing for crossover to momelotinib after 24 weeks. SVR35% was achieved in 27% vs. 29% of momelotinib and ruxolitinib groups (non-inferior p=0.11), respectively, with TSS50% failing to meet non-inferiority. Transfusion independence was met in 67% of patients in the momelotinib arm vs. 49% in the ruxolitinib arm (p<0.001), with fewer dose reductions required in the momelotinib arm (26% vs. 56%) and grade 3/4 anemia of 5.6% in the momelotinib arm vs. 23% in the ruxolitinib arm.[30] Mean hemoglobin levels decreased with ruxolitinib with a plateau below 100 g/L, but improved in patients who crossed over to momelotinib after week 24. In subgroup analysis, where patients with mild anemia at baseline (Hgb ≥100 to <120 g/L) were for the large majority TI (90% in momelotinib vs 87% in ruxolitinib arms), 93% of patients in the momelotinib arm had stable or reduced transfusion intensity versus only 51% of patients in the ruxolitinib arm.[31] This highlights momelotinib's ability to preserve hemoglobin and avoid treatment-related anemia. The SIMPLIFY-2 trial included patients with MF who had used ruxolitinib prior to comparing momelotinib to best available treatment (BAT); 89% were on ruxolitinib. Here, the momelotinib group needed fewer RBC transfusions with TI rates of 43% vs. 21% at week 24 (p=0.0012).[32] In a subgroup analysis of TD patients at baseline, dose-reduced ruxolitinib was used in 59% (17 of 29) of patients in the BAT arm (10 mg PO BID or less), with further dose reductions noted by week 24. Additional supportive use of ESAs with ruxolitinib occurred in 4/5 patients, but these patients did not achieve TI by week 24.[33]

The MOMENTUM Phase 3 trial included symptomatic (TSS ≥10) patients with MF with baseline Hgb <100 g/L and prior JAKi exposure for

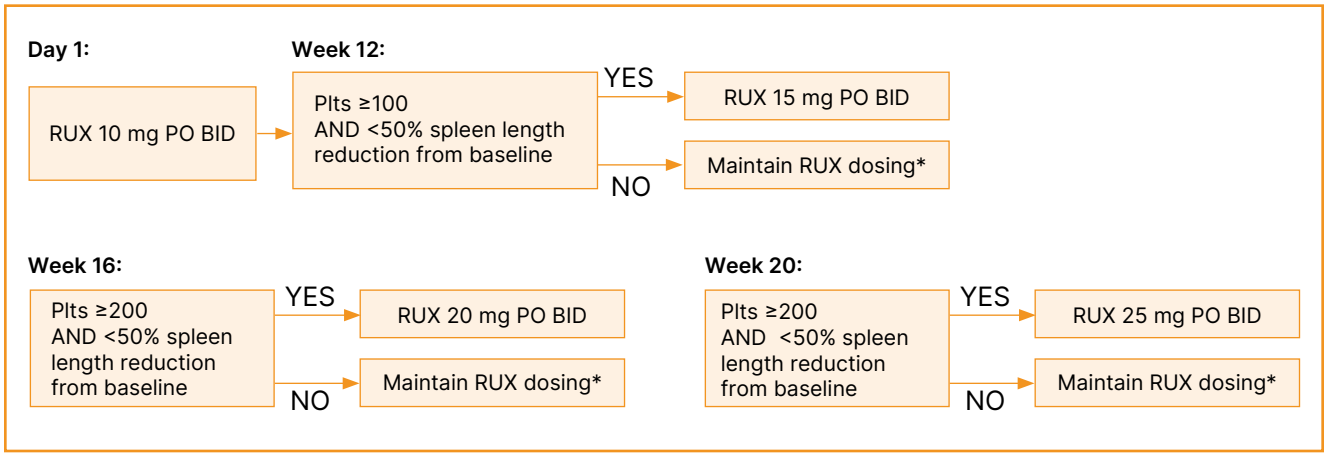

Figure 1. Ruxolitinib dosing strategy for MF patient with anemia based on the REALISE study[27]

Abbreviations: MF: myelofibrosis; **RUX:** ruxolitinib; **PO:** oral; **BID:** twice daily; **Plts:** platelets.

* Dose increase is optional in the setting of attaining platelet target level with >50% spleen length reduction from baseline, if required for patient symptom management and clinician preference.

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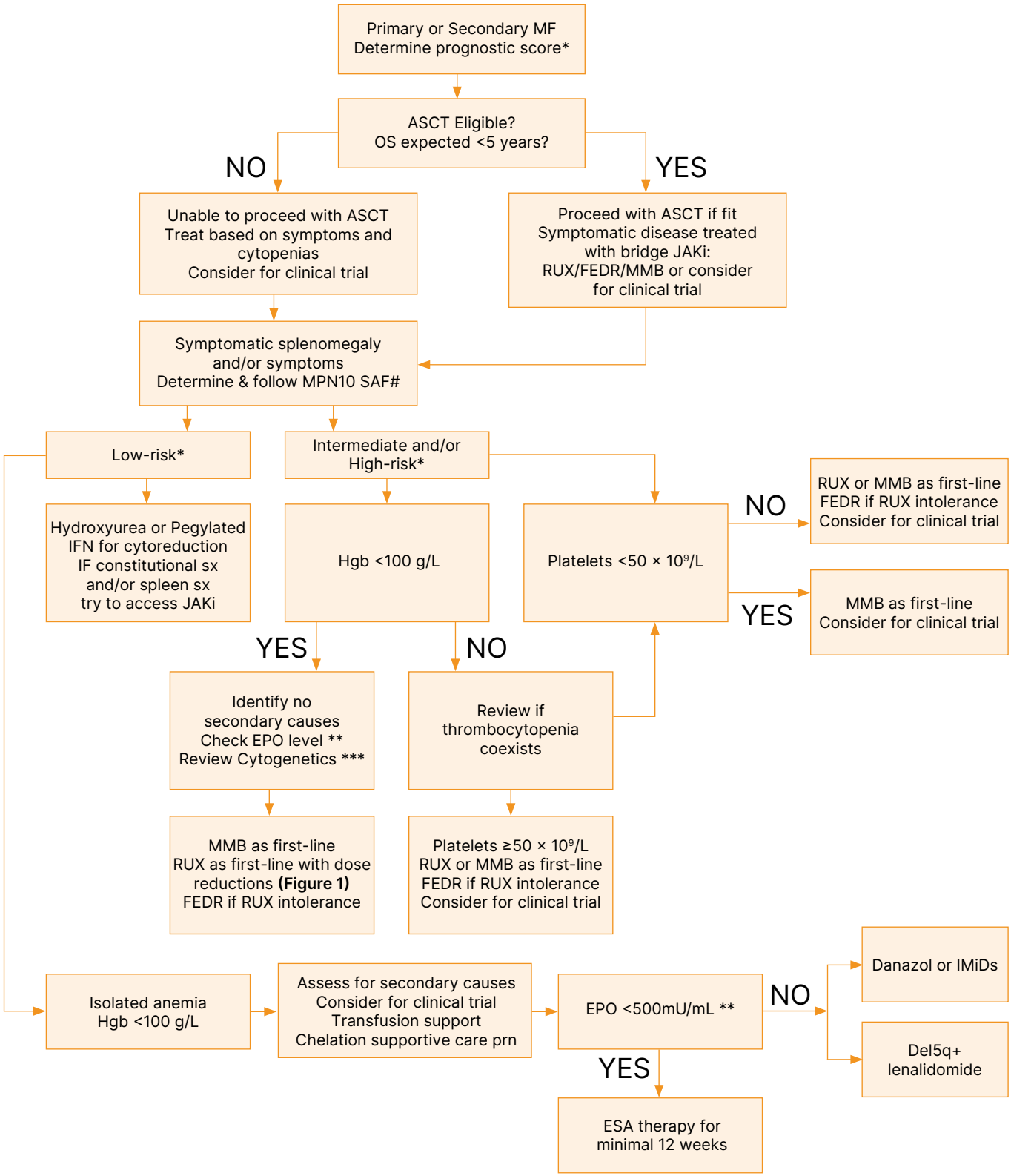

Figure 2. Suggested management approach for Myelofibrosis; *courtesy of Sonia Cerquozzi, MD, FRCPC*

Abbreviations: ASCT: allogeneic stem cell transplantation; **RUX:** ruxolitinib; **FEDR:** fedratinib; **IFN:** interferon; **MMB:** momelotinib; **sx:** symptoms; **EPO:** erythropoietin; **ESA:** erythropoietin-stimulating agent; **Hgb:** hemoglobin; **IMiDs:** immunomodulatory drugs (eg lenalidomide); **JAKi:** Jak inhibitor; **MF:** myelofibrosis; **OS:** overall survival; **prn:** as needed.

* Based on Prognostic score options: DIPSS- Dynamic International Prognostic Scoring System) or MIPSS-70/PLUSV2 (Mutation-Enhanced International Prognostic Scoring System) or MYSEC-PM (Myelofibrosis Secondary to polycythemia vera and essential thrombocythemia-Prognostic Model).

MPN10SAF TSS items were designated as "moderate" if symptoms were rated as ≥4 of 10 or ≤6 of 10 and as "severe" if symptoms were rated as ≥7 of 10.

** A trial of ESA therapy for patients with EPO level <500 mU/L can be considered for 12 weeks, optimal response observed if EPO level <125 mU/L.

*** Use of lenalidomide for Del5q deletion suggested

either >90 days or >28 days with complications such as TD anemia and/or grade 3/4 anemia, thrombocytopenia, or bleeding.[34] Unlike the SIMPLIFY-2 trial, washout of prior JAKi was required for a minimum of 14 days. At enrollment, ~50% of patients were transfusion-dependent. The study enrolled 195 patients, who were randomized to 24-week treatment of 200 mg PO daily of momelotinib or danazol (a National Comprehensive Cancer Network [NCCN]-designated MF anemia treatment).[35] The SVR35% was 22% for momelotinib vs. 3% for danazol (superiority, two sided p=0.0011), with similarly significant TSS50% benefits for momelotinib, showing TI at 24 weeks was achieved in 30% of momelotinib vs. 20% of danazol users (non-inferiority, one-sided p=0.0116). Subsequent superiority testing found a treatment difference of 10% (p=0.1265.).[34] Only 20% and 17% of patients in the momelotinib and danazol arms were TI at baseline, respectively. Of those, 92% retained this TI status on momelotinib vs. only 64% with danazol. Among those who were TD at baseline, 21% vs. 7% became transfusion-free during treatment. Overall, 65% in the momelotinib arm had improvements in RBC transfusion intensities from baseline compared to 52% in the danazol arm.[36] A trend toward improved OS over the entire study period was observed in the momelotinib arm compared to the danazol arm (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.38-1.41, p=0.35). Based on the high rates of crossover, long-term OS and leukemia-free survival (LFS) effects could not be accurately predicted.[34, 37]

Long-term analysis of pooled data from Phase 3 studies of momelotinib (MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2 trials), showed that of the 725 patients with MF who received momelotinib, 12% remained on therapy for ≥5 years, with a median treatment exposure of 11.3 months (range, 0.1-90.4 months). The most common non-hematologic treatment-emergent adverse event (TEAE) was diarrhea (any grade, 27%; grade ≥3, 3%). A distinct adverse event (AE) of peripheral neuropathy occurred in 12% of patients. Any-grade thrombocytopenia, anemia, and neutropenia occurred in 25%, 23%, and 7% of patients, respectively. Thrombocytopenia was the most common AE resulting in momelotinib dose modification (10.5%), while treatment discontinuation (3.7%) was minimal. Despite ongoing treatment, the incidence of hematologic AEs decreased or remained stable over time.[37]

Importantly, the platelet limit for enrollment into the MOMENTUM trial was 25 × 10^9/L, and a starting dose of 200 mg daily was used, irrespective of baseline platelet level. Dose reduction for thrombocytopenia is required during treatment.[34] Momelotinib's efficacy on spleen reduction, symptom control, and improvement of anemia persisted even in patients with thrombocytopenia based on the pooled data from the SIMPLIFY studies.[37]

Choosing JAKi therapy for intermediate and high-risk symptomatic MF should be strategized based on the presence of concomitant anemia and thrombocytopenia **(Figure 2)**. In this setting, momelotinib can be considered as first-line or as second-line therapy. It has been suggested that dosing should be lowered when treating MF-related anemia with ruxolitinib.[27]

All current JAKi are approved for patients with platelet counts >50 × 10^9/L, with ruxolitinib preferred as first-line therapy given its clinical comfort and understanding of its long-term use and effectiveness. Ruxolitinib and fedratinib dosing is not recommended in patients with platelet counts <50 × 10^9/L. Momelotinib is effective and approved for patients with MF with platelet counts <50 × 10^9/L. For patients with severe thrombocytopenia or a platelet count <50 × 10^9/L, momelotinib is suggested for first-line use and is reported to be safe. In cases of borderline platelet levels (50-100 × 10^9/L) and associated anemia (Hgb <100 g/L), it would be important for the clinical provider to consider momelotinib as first-line treatment, given the anticipation of therapy-related anemia and thrombocytopenia with ruxolitinib usage. In cases of JAKi-related anemia or development on therapy, ESA therapies and/or lowering ruxolitinib dosing are options; however, it is suggested to switch to momelotinib as a second-line treatment to avoid ongoing anemia-related symptoms and/or transfusion dependency if cytopenias do not ameliorate.

Conclusion

MF is a heterogenous disease that can be treated with JAKi. However, these treatments have several limitations, including dose-limiting cytopenias that may lead to drug failure, loss of response, and/or high rates of treatment discontinuation. Anemia results in a substantial burden on survival, QoL, and healthcare costs. Disease-specific factors are essential for

identifying the most appropriate therapy, with momelotinib being a select JAKi favoured for symptomatic patients with MF who have concomitant anemia (Hgb <100 g/L) and/or thrombocytopenia (platelets <50 × 10^9/L). Evidence supports the use of momelotinib as first-line therapy to avoid or correct transfusion dependence, and it has similar efficacy in the second-line setting in addressing patients who have developed anemia. Here, we provide a suggested treatment approach based on current MF therapeutics. Further longitudinal studies and/or real-world data are anticipated for momelotinib. Ongoing research to optimize treatment in MF, including combination therapies and/or alternative targeted therapies, is highly anticipated.

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