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Editorial
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Is Treatment for Cytopenic Myelofibrosis Still an Unmet Clinical Need?

Madeline J. Caduc[1,2], Steffen Koschmieder[1,2]

Correspondence: Steffen Koschmieder (skoschmieder@ukaachen.de).

Philadelphia-negative myeloproliferative neoplasms (MPN), including essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF), are a group of clonal hematological disorders driven by mutated hematopoietic stem cells. MF, as de novo myeloid malignancy (primary MF: PMF) or secondary to an antecedent MPN (post-ET-MF or post-PV-MF), is a life-threatening condition associated with shortened survival and risk of leukemic transformation in about 20% of the patients.[1] Clonal expansion of malignant myeloid stem- and progenitor cells and stromal changes along with increased proinflammatory cytokines production drive the remodeling of the bone marrow (BM) microenvironment and disrupt physiological hematopoiesis. Clinical manifestations of MF-associated progressive BM failure, such as cytopenia (anemia, thrombocytopenia), hepatosplenomegaly, constitutional symptoms (eg, weight loss, fever, night sweating), significantly impact patients' quality-of-life (QoL) and correlate with poor prognosis for overall survival (OS).[2,3]

The identification of a constitutive JAK–STAT pathway activity and underlying somatic driver mutations in the *janus kinase 2 (jak2)*, *calreticulin (calr)*, *and thrombopoietin receptor (mpl)* genes has revolutionized the therapeutic landscape with the development of JAK inhibitors (JAKi).

Ruxolitinib, a dual JAK1/JAK2 inhibitor, was the first JAKi approved for treatment in patients with intermediate- or high-risk MF (U.S. Food and Drug Administration [FDA]) or MF with disease-associated splenomegaly or symptoms (European Medicines Agency [EMA]) and remains the standard of care. However, although 2 phase 3 clinical trials, COMFORT-I and –II, demonstrated that ruxolitinib induces rapid spleen volume reductions (SVR) as well as symptom improvement, treatment discontinuations are frequent (up to 60% in 3 y),[4] because of grade of ≥3 cytopenia, and resulting in suboptimal symptom control, risk of disease relapse, and decreased survival.[5–7]

Nearly a decade later, the selective JAK2 and FMS-like tyrosine kinase 3 (FLT3) inhibitor fedratinib was approved for the treatment of intermediate and high-risk MF (FDA) or MF with disease-associated splenomegaly or symptoms (EMA). Although fedratinib was active in untreated patients but also patients with documented progression during ruxolitinib or intolerance to ruxolitinib, fedratinib induced comparable myelosuppression with anemia and thrombocytopenia as the most common causes for treatment discontinuation. Thus, although the development of JAKi has significantly improved MF treatment, cytopenic myelofibrosis still presents a significant unmet medical need.

Pacritinib, a potent JAK2 and interleukin-1 receptor associated kinase 1 (IRAK1) inhibitor, received FDA-approval for use in MF patients with platelet counts of $\leq 50 \times 10^9$/L, based on the results of the PERSIST-1 and PERSIST-2 studies. The efficacy and safety of pacritinib compared with physician's choice of therapy (including ruxolitinib) is currently being further investigated in MF patients with severe thrombocytopenia in the phase 3 study PACIFICA (NCT03165734). Interestingly, a post hoc analysis of the PERSIST-2 study showed an anemia benefit in patients treated with pacritinib, which was attributed to activin A receptor type 1 (ACVR1) inhibition.[8] However, further investigations are needed to unravel the detailed biological mechanisms involved, including the role of IRAK1 inhibition.

The pathophysiology of MF-related anemia has not been fully deciphered. In addition to progressive reticulin deposition, dysregulation of iron homeostasis has emerged as a pivotal process for disruption of normal erythropoiesis. Hepcidin, a key regulator of iron metabolism, was discovered to be elevated in MF patients, and this upregulation proved to be unresponsive to ruxolitinib treatment.[9] Interestingly, the combined JAK1/2 inhibitor, Momelotinib (MMB), also inhibits ACVR1 and thereby decreases hepcidin, emerging as a promising therapeutic alternative for patients with MF-related anemia. MMB was assessed as treatment of intermediate- or high-risk MF patients in 2 phase 3 trials, SIMPLIFY-1 and SIMPLIFY-2. Although MMB met the primary endpoint in the SIMPLIFY-1 trial (noninferiority to ruxolitinib regarding spleen volume response), the key secondary endpoint was not met (noninferiority to ruxolitinib regarding symptom response). However, MMB activity demonstrated consistent anemia benefits including conversion to transfusion-independence (TI), SVR, and QoL improvement, when compared with baseline.[10] The SIMPLIFY-2 trial evaluated the superiority of MMB over the best available therapy (BAT) in MF patients who had previously received ruxolitinib treatment. The defectiveness of currently available therapies for cytopenic MF was emphasized by the fact that 89% of the BAT patients continued treatment with ruxolitinib. However, the primary endpoint (superiority of MMB versus BAT regarding spleen volume reduction at week 24 [SVR24]) was not met, although the MMB group demonstrated a higher rate of conversion to TI, emphasizing its anemia-alleviating potential when compared with BAT.[11] Of note, the lack of JAKi washout period before MMB-treatment start might have influenced the results.

[1]Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation, Medical Faculty, RWTH Aachen University, Germany
[2]Center for Integrated Oncology Aachen Bonn Cologne Düsseldorf (CIO ABCD), Germany

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Recently, MMB-induced anemia benefit was further investigated in the double-blind, (2:1) randomized clinical trial of MMB versus danazol, the MOMENTUM trial. This trial enrolled MF patients with failure to JAKi treatment, moderate-to-severe anemia (hemoglobin <10 g/dL), and a total symptom score (TSS) ≥10. The primary endpoint, a ≥50% reduction in the mean TSS at week 24, was met, as well as key secondary endpoints, including TI rate at week 24 and SVR24. Importantly, several of the symptoms were not directly correlated with anemia (eg, early satiety, abdominal discomfort, bone pain, and night sweats). Thus, inferiority of danazol might not be surprising. However, at the time of the study, danazol treatment was in alignment with the guidelines of the National Comprehensive Cancer Network and the European Society of Medical Oncology for the management of MF-associated anemia.

In the present *HemaSphere* issue, Mesa et al[12] present novel data from the MOMENTUM trial, bridging the knowledge gap of how MMB impacts MF-associated symptoms. In line with the results of SIMPLIFY-1 and -2, MMB improved anemia and led to a higher proportion of patients achieving TI compared to the danazol group. Interestingly, some patients experienced fatigue relief without attaining TI. Although some anemia benefits might have not been captured by the strict TI endpoint of the study, these findings underscore the multifactorial pathogenesis of fatigue. Thus, MMB treatment–associated benefits may well extend beyond its proerythrogenic activity with the reduction of cytokines production as a possible mechanism for the reported TSS improvement. However, as pointed out by the investigators, although patient-reported fatigue was a secondary endpoint of MOMENTUM, the trial was not designed to explore the relationship between anemia and symptoms. Further investigations will be needed.

In addition to anemia and RBC transfusion–dependency, recent surveys emphasized severe thrombocytopenia (platelet count $\leq 50 \times 10^9$/L) as a critical negative prognostic factor, with higher rates of both hemorrhagic and thrombotic complications, as well as a higher risk for leukemic transformation.[13] Furthermore, fatigue as a multifactorial and burdensome MF-symptom with significant repercussion on patients' cognitive, physical, and social functioning was shown to be significantly increased in thrombocytopenic MF patients.[14]

In a second publication in this *HemaSphere* issue, Kiladjian et al[15] present data from their post hoc combined analysis of the SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM trials on the efficacy and safety of MMB in patients with thrombocytopenia. All patients with baseline platelet counts of $<100 \times 10^9$/L were included and defined as the "sub-100 group." Of note, patients with severe thrombopenia ($<50 \times 10^9$/L) were not analyzed separately because of low patient numbers but were integrated within the sub-100 group. Overall, platelet counts were stable or increased in the MMB treated sub-100 group, enabling continuous adequate dosing beyond the initial 24-week-treatment period. Interestingly, this retrospective analysis of the SIMPLIFY trials indicates a reduced ruxolitinib effectiveness in patients with platelet counts below 100×10^9/L. The numerically higher TSS reduction, SVR, and conversation rate to TI in the MMB group may be because of a higher myelosuppressive activity of ruxolitinib, leading to more frequent dose reductions and treatment discontinuations. Thus, this post hoc analysis suggests that MMB may be superior to ruxolitinib, BAT, and danazol in patients with low platelet counts, without altering the safety profile. However, because of the descriptive nature of this analysis, prospective real world data will be required to confirm these results.

In summary, the new results of the SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM trials underline the potential of MMB to expand our treatment options for MF patients, particularly those with symptomatic and/or RBC transfusion–dependent anemia. MMB has recently been approved by the FDA for the treatment of intermediate- or high-risk MF in adults with anemia.

In addition, several new therapeutic agents are presently under clinical investigation, either as monotherapy or as add-on therapies to JAK inhibitor. Much of their success will depend on their ability to target the underlying disease pathophysiology, to lead to clinically meaningful long-term eradication of the malignant clone and cure of the patients from MF. Thus, the unmet clinical need for the treatment of cytopenic MF is lessened, but it still exists.

AUTHOR CONTRIBUTIONS

MJC and SK conceptualized, wrote, and finalized the article.

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