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Novel therapeutics for myelofibrosis

Sung-Eun Lee

Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

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Correspondence to
Sung-Eun Lee, M.D., Ph.D.
Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
E-mail: lee86@catholic.ac.kr

Abstract

Myelofibrosis (MF) includes primary MF, post-essential thrombocythemia MF, and post-polycythemia vera MF. MF is a progressive myeloid neoplasm characterized by ineffective clonal hematopoiesis, extramedullary hematopoiesis, a reactive bone marrow environment resulting in reticulin deposition and fibrosis, and a propensity for leukemia transformation. The identification of driver mutations in *JAK2, CALR,* and *MPL* has contributed to a better understanding of disease pathogenesis and has led to the development of MF-specific therapies, such as JAK2 inhibitors. Despite the fact that ruxolitinib and fedratinib have been clinically developed and approved, their use is limited due to adverse effects such as anemia and thrombocytopenia. Recently, pacritinib has been approved for a group of thrombocytopenic patients with significant unmet clinical needs. In symptomatic and anemic patients with prior JAK inhibitor exposure, momelotinib was superior to danazol in preventing exacerbation of anemia and in controlling MF-associated signs and symptoms, such as spleen size. Although the development of JAK inhibitors is remarkable, modifying the natural course of the disease remains a priority. Therefore, many novel treatments are currently under clinical development. Agents targeting bromodomain and extra-terminal protein, anti-apoptotic protein Bcl-xL, and phosphatidylinositol-3-kinase delta have been studied in combination with JAK inhibitors. These combinations have been employed in both the frontline and "add-on" approaches. In addition, several agents are being studied as monotherapies for ruxolitinib-resistant or -ineligible patients. We reviewed several new MF treatments in the advanced stages of clinical development and treatment options for cytopenic patients.

Key Words Myelofibrosis, JAK2 inhibitors, Cytopenia, Novel therapy

INTRODUCTION

Myelofibrosis (MF) includes primary MF, post-essential thrombocythemia MF, and post-polycythemia vera MF. MF is a progressive myeloid neoplasm characterized by ineffective clonal hematopoiesis, extramedullary hematopoiesis, a reactive bone marrow (BM) environment resulting in reticulin deposition and fibrosis, and a propensity for leukemia transformation [1]. The identification of driver mutations in *JAK2, CALR,* and *MPL* has contributed to our understanding of the pathogenesis of MF. Additionally, the near-universal upregulation of JAK-STAT signaling pathway has been implicated in the development of this disease [2]. Dysregulated signaling leads to uncontrolled myeloproliferation and elevated proinflammatory cytokine production. Mouse model studies have provided evidence that myeloproliferation and cytokine production are associated with the development of BM fibrosis, which manifests as anemia, splenomegaly, and debilitating symptoms [2].

The goals of MF treatment are to reduce the symptom burden and splenomegaly and improve survival by reducing the risk of leukemic transformation. JAK inhibitors (JAKis) are valuable therapies for patients with MF who have splenomegaly and/or disease-related symptoms [3-5]. Although approved JAKis such as ruxolitinib and fedratinib can lead to spleen and symptom improvements, their use can be limited by side effects, including anemia and thrombocytopenia [4-9]. Disease-related or treatment-exacerbated cytopenia may require a dose reduction or discontinuation of JAKis. Therefore, cytopenia limits the treatment efficacy and is associated with poor survival rates [10]. To address this issue, pacritinib has recently been approved for a group of thrombocytopenic patients with a significant unmet clinical need (baseline platelet count $<50\times10^9$/L) [1]. In addition, for symptomatic and anemic patients with previous JAKi ex-

posure, momelotinib has been shown to be superior to danazol in preventing the exacerbation of anemia and in controlling MF-associated signs and symptoms, such as spleen size [1].

Although the development of JAKis has been remarkable, modifying the natural course of the disease remains a priority. Therefore, many novel treatments are currently in clinical development. For example, agents targeting the bromodomain and extra-terminal (BET) protein, the anti-apoptotic protein Bcl-xL, and phosphatidylinositol-3-kinase delta, have been studied in combination with JAKis, as front-line or second-line "add-on" approaches. In addition, several investigational agents have been studied as monotherapies for patients who are resistant or ineligible for ruxolitinib. We reviewed several new MF treatments in the advanced stages of clinical development and treatment options for patients with cytopenia.

THERAPEUTIC OPTIONS FOR CYTOPENIC MF

MF is characterized by biological and clinical heterogeneity; some patients present with features of myeloproliferation, whereas others exhibit myelodepletion. Cytopenia in patients with MF has been associated with a poor prognosis. Patients with mild [hemoglobin (Hb) ≥10 g/dL and less than the sex-adjusted lower limit of normal], moderate (Hb ≥8 and <10 g/dL), and severe (Hb <8 g/dL or transfusion-dependent) anemia experienced shortened median survival of 4.9, 3.4, and 2.1 years, respectively [11]. In general, MF-associated anemia management includes red blood cell (RBC) transfusions, erythropoiesis-stimulating therapy, corticosteroids, androgens such as danazol, immunomodulatory drugs, and splenectomy [12-15]. However, these strategies have shown only modest and transient clinical benefits. MF-associated anemia is the result of a multifactorial process, including displacement of medullary erythropoietic tissue by fibrotic stroma, ineffective erythropoiesis in the spleen and other extramedullary sites, splenic sequestration and destruction of circulating RBCs, and an increase in plasma volume. The upregulation of inflammatory cytokines in the BM of patients with MF has been associated with the upregulation of circulating hepcidin, which can interfere with iron metabolism and utilization in a manner similar to that of chronic disease anemia [14]. Therefore, the development of new classes of erythroid progenitor drugs targeting chronic inflammation and iron restriction is necessary [16].

Thrombocytopenia (platelet count <50,000/mL) is a major characteristic of the myelodepletive phenotype [17]. Severe thrombocytopenia is associated with a poor prognosis [18]. To evaluate the significance of a low platelet count, Masarova *et al.* [18] compared 145 patients with a platelet count $<50\times10^9$/L, 179 patients with a platelet count between 50×10^9/L and 100×10^9/L, and 948 patients with a platelet count $>100\times10^9$/L at presentation. They showed that patients with a platelet count $<50\times10^9$/L were the most anemic and transfusion-dependent and had higher blast and unfavorable karyotype counts. Moreover, their overall and leukemia-free survival were the shortest, with median times of 15 and 13 months, respectively.

Momelotinib

Momelotinib is a first-in-class oral inhibitor of activin A receptor type 1 (ACVR1)/activin receptor-like kinase 2, and an inhibitor of JAK1 and JAK2 [19-21]. Preclinical studies have demonstrated that inhibiting ACVR1-mediated hepcidin production can increase serum iron availability and stimulate erythropoiesis. In the SIMPLIFY-1 trial of JAK inhibitor-naïve patients, momelotinib was found to be non-inferior to ruxolitinib in reducing spleen volume by 35% from baseline at week 24, which was the primary endpoint [19]. Furthermore, compared with patients who received ruxolitinib, those who received momelotinib had a higher week-24 transfusion independence rate, an increased Hb level, and approximately half the transfusion burden. However, momelotinib did not demonstrate non-inferiority to ruxolitinib in reducing the total symptom score (TSS) by at least 50% at week 24 compared with baseline [19].

In the SIMPLIFY-2 study of patients previously treated with ruxolitinib, additional symptom responses were observed after momelotinib treatment. However, the superiority of momelotinib in providing additional SV reductions of at least 35% without washout immediately following ruxolitinib treatment was not demonstrated in SIMPLIFY-2 [20]. Therefore, the beneficial effects of momelotinib on anemia, splenomegaly, and constitutional symptoms were assessed in a phase 3 randomized, double-blind MOMENTUM trial of momelotinib versus danazol in symptomatic, anemic patients with MF who previously received JAKi [22]. Compared to danazol, momelotinib treatment resulted in significant improvements in MF-associated symptoms, anemia measures, and spleen responses at week 24. The latest findings from the MOMENTUM study, which evaluated patients for up to 48 weeks, were promising. These results included improved symptom maintenance, transfusion independence, and spleen responses, with continued good survival and safety in the ITT analysis set, and in those with low platelet counts. These findings suggest that momelotinib may address a critical unmet need, particularly in anemic patients with MF, including those with severe thrombocytopenia [23].

Pacritinib

Pacritinib is an oral JAK2/IRAK1/ACVR1 inhibitor that has demonstrated clinical activity against MF in two phase 3 studies (PERSIST-1 and PERSIST-2) and a phase 2 dose-finding study. The PERSIST studies demonstrated clinical benefits, such as significant spleen volume responses (SVRs) and improvements in MF-associated symptoms, in a substantial proportion of patients, including those with severe baseline thrombocytopenia and those who had previously received ruxolitinib. However, owing to concerns regarding high-grade cardiac and bleeding events in these studies, a phase 2 dose-finding PAC203 study was designed. At 24 weeks, 17% of patients with MF and severe thrombocy-

topenia who received 200 mg twice daily achieved a SVR ≥35% [24].

In general, patients with MF and severe thrombocytopenia (platelet count $<50\times10^9$/L) are older and have more advanced disease, an increased risk of bleeding, higher rates of anemia, unfavorable cytogenetics, and poor prognoses [17]. Approved JAKis for treating MF in patients with severe thrombocytopenia are limited due to potential adverse effects on blood cell counts. As a result, the recent approval of pacritinib in the United States has prompted the initiation of a phase 3 clinical trial (PACIFICA) that is currently enrolling patients from other countries. In this study, pacritinib was evaluated in comparison with physicians' therapeutic choices (low-dose ruxolitinib, hydroxyurea, danazol, or steroids) in patients with advanced MF and severe thrombocytopenia [25].

Luspatercept

Luspatercept (activin receptor-ligand trap enhancing late-stage erythropoiesis) is a first-in-class erythroid maturation agent that has been shown to increase Hb levels while decreasing transfusion burden in patients with myelodysplastic syndromes [26] and β-thalassemia [27]. A phase 2 study of luspatercept in patients with MF-associated anemia was performed in four cohorts. Patients not receiving concomitant ruxolitinib at study entry or RBC transfusions comprised Cohort 1, and those receiving 2–4 RBC units 28 days into the 12 weeks prior to treatment comprised Cohort 2. Patients on a stable dose of ruxolitinib for at least 16 weeks who did not receive RBC transfusions comprised Cohort 3A, and Cohort 3 B patients were similar to cohort 3A patients, except for the receipt of a transfusion. In the cohort of RBC transfusion-dependent, patients treated with ruxolitinib and luspatercept, 46% achieved a reduction of ≥50% in RBC transfusions over 12 weeks. In addition, 36% of the patients achieved RBC transfusion independence over 12 consecutive weeks [28]. A pivotal phase 3 trial (INDEPENDENCE) was recently launched to assess the efficacy of luspatercept in patients with MF and myeloproliferative neoplasm (MPN)-associated anemia, who were concurrently treated with ruxolitinib and required RBC transfusions.

NOVEL THERAPIES IN MF

Following FDA approval of the JAK1/2 inhibitor ruxolitinib in 2011 and the JAK2 inhibitor fedratinib in 2019, unprecedented clinical benefits, including improvement of quality of life in patients with MF, have precipitated their widespread use. Allogeneic stem cell transplantation remains the only curative treatment for MF; however, the use of this therapy is typically limited by age-related comorbidities and is associated with high treatment-related mortality. Therefore, a better understanding of the molecular pathogenesis of the disease and potential new therapies to address major unmet medical needs is necessary. These requirements include management of anemia and thrombocytopenia, the prevention of the progression of MF to leukemia, prevention of suboptimal responses or resistance to ruxolitinib [29], and extension of the short overall survival (OS) [10, 30].

Table 1. Combination treatments with ruxolitinib being studied in clinical trials.

Agent (class)	Drug class	Phase (NCT number)	Official title
CPI-0610	BET inhibitor	2 (NCT02158858)	A phase 1/2 Study of CPI-0610, a small molecule inhibitor of BET proteins: phase 1 (in patients with hematological malignancies) and phase 2 (dose expansion of CPI-0610 with and without ruxolitinib in patients with myelofibrosis)
		3 (NCT04603495)	A phase 3, randomized, double-blind, active-control study of pelabresib (CPI-0610) and ruxolitinib vs. placebo and ruxolitinib in JAKi treatment naive MF patients (MANIFEST-2)
Navitoclax	BCL-2/BCL-xL antagonist	2 (NCT03222609)	A phase 2 open-label study evaluating tolerability and efficacy of navitoclax alone or in combination with ruxolitinib in subjects with myelofibrosis (REFINE)
		3 (NCT04472598)	A randomized, double-blind, placebo-controlled, phase 3 study of navitoclax in combination with ruxolitinib vs. ruxolitinib in subjects with myelofibrosis (TRANSFORM-1)
		3 (NCT04468984)	A randomized, open-label, phase 3 study evaluating efficacy and safety of navitoclax in combination with ruxolitinib vs. best available therapy in subjects with relapsed/refractory myelofibrosis (TRANSFORM-2)
Parsaclisib	PI3Kδ inhibitor	2 (NCT02718300)	A phase 2 study of the safety, tolerability, and efficacy of INCB050465 in combination with ruxolitinib in subjects with myelofibrosis
		3 (NCT04551066)	A phase 3, randomized, double-blind, placebo-controlled study of the combination of PI3Kδ inhibitor parsaclisib and ruxolitinib in participants with myelofibrosis (LIMBER-313)
		3 (NCT04551053)	A randomized, double-blind, placebo-controlled study of the PI3Kδ inhibitor parsaclisib plus ruxolitinibin participants with myelofibrosis who have suboptimal response to ruxolitinib (LIMBER-304)

Many researchers have focused on developing new monotherapies and rational combination treatments that exhibit complementary activity or act synergistically with ruxolitinib (Table 1) [31, 32]. Novel investigational agents may target biological pathways other than JAK/STAT, and/or enhance the efficacy of ruxolitinib.

Combination treatments with ruxolitinib being studied in clinical trials

Targeting the BET protein: BET proteins regulate key oncogenic pathways, including NF-κB and transforming growth factor β (TGFβ) signaling pathways, which are important drivers of proinflammatory cytokine expression and BM fibrosis, respectively. Preclinical studies suggest that the use of a combination of CPI-0610 (pelabresib), a selective and potent small-molecule BET inhibitor, and JAKi can result in synergistic reduction of splenomegaly, BM fibrosis, and mutant cell burden [33].

In a phase 2 study, CPI-0610+ruxolitinib provided clinical benefits to patients with MF who were JAKi-naive or had a suboptimal response to ruxolitinib alone. In addition, CPI-0610+ruxolitinib can lead to improved anemia and BM fibrosis, suggesting its potential for disease modification [34, 35]. The response rate to CPI-0610+ruxolitinib was especially encouraging in JAKi-naïve patients with MF. 68% and 60% of the patients achieved SVR35 at week 24 and 48, respectively. Furthermore, at weeks 24 and 48, 56% and 43% of patients , respectively, demonstrated TSS improvements of >50% [34]. These percentages were higher than those previously noted for ruxolitinib in pivotal phase 3 trials, suggesting the potential synergistic efficacy of CPI-0610+ruxolitinib. The global phase 3 MANIFEST-2 trial of CPI-0610+ruxolitinib versus placebo +ruxolitinib in JAKi-naïve patients with MF is ongoing [36].

Targeting the anti-apoptotic protein Bcl-xL: The anti-apoptotic protein Bcl-xL is regulated by JAKs and the combined targeting of JAK2. Furthermore, Bcl2-xL has been shown to be synergistic in preclinical JAK2V617F MPN models and to overcome acquired resistance to ruxolitinib [37]. Navitoclax is an orally bioavailable inhibitor of the anti-apoptotic Bcl-2 family of proteins. Based on the results of preclinical studies, navitoclax in combination with ruxolitinib was assessed in patients with MF and platelet counts $\geq 100\times10^9$/L in a phase 2 clinical trial. Navitoclax was administered to patients who had received prior treatment with ruxolitinib, starting at a daily dose of 50 mg, which was increased to 300 mg per day based on individual tolerability. The drug combination was well tolerated and demonstrated significant clinical efficacy; 27% of patients exhibited SVR35, and 30% had >50% improvement in TSS. A reduction in BM fibrosis was observed. These findings suggest that apoptotic induction with navitoclax may be an important therapeutic option for patients with MF to prevent or reverse JAK2 resistance and modify MF biology.

Inflammatory cytokine analyses have revealed a direct correlation between changes in MF-associated cytokine levels and SV changes from the baseline [38]. At week 24, Cohort 3 of the aforementioned phase 2 study enrolled JAKi treatment-naïve patients with MF and SVR35 were observed in all poor prognosis subgroups: those related to age (≥75 yr, 50%), a high DIPSS score (intermediate-2, 63%; high, 33%), and a high-molecular-risk mutation (47%) [39]. The combination of navitoclax with ruxolitinib in patients with MF has been evaluated in two randomized phase 3 trials in JAKi-naïve (TRANSFORM-1) [40] and JAKi-resistant patients with MF (TRANSFORM-2) [41].

Targeting phosphatidylinositol-3-kinase delta: The phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) cascade integrates cellular growth and proliferation signals downstream of JAK-STAT, and constitutive activation of this pathway is central to MPN pathogenesis [42]. Preclinical studies have demonstrated that inhibitors targeting this pathway can reduce proliferation and induce apoptosis in $JAK2^{V617F}$/$MPLW^{515L}$ MPN cell lines and primary cells. These inhibitors have been shown to act synergistically with ruxolitinib or fedratinib, [42-44].

Parsaclisib is a potent and highly selective inhibitor of PI3Kδ, that was recently evaluated as an "add-on" medication to ruxolitinib at two different dosing schedules. One schedule consisted of parsaclisib 10 or 20 mg QD for 8 weeks and the same dose once weekly (QW) thereafter (QD/QW group). The second schedule was parsaclisib 5 mg or 20 mg QD for 88 weeks and 5 mg QD thereafter (all QD groups). These schedules were followed for patients with MF who had a suboptimal response to ruxolitinib treatment at a stable dose. The final results from the phase 2 study demonstrated that daily parsaclisib dosing appeared to be more efficacious in reducing SV and TSS [45]. The combination of parsaclisib with ruxolitinib will be further evaluated in two phase 3 trials in JAKi and PI3K inhibitor-naïve (LIMBER-313) patients with MF or those with suboptimal responses to ruxolitinib (LIMBER-304).

Novel agents under study as monotherapies

Telomerase inhibitor: Imetelstat is a first-in-class potent telomerase inhibitor that generates considerable excitement when it results in durable, complete, or partial responses in seven of 33 patients with MF. BM fibrosis was reversed in all four patients who had a complete response, as reported in a pilot study [46]. In a phase 2 study of two doses of imetelstat, a higher dose (9.4 mg/kg once every 3 wk) yielded a median OS of 29.9 months in patients with intermediate-2 or high-risk MF that had relapsed or was refractory to JAKis [47]. This median OS is in marked contrast to the 13–14 months reported in several groups of patients in whom ruxolitinib was discontinued [10, 30, 48].

Dose-dependent inhibition of telomerase with imetelstat results in on-target activity that is correlated with clinical benefits. These benefits include a dose-dependent reduction in the variant allele frequency (VAF) of MF driver mutations and an improvement in BM fibrosis [47]. Furthermore, VAF reduction and BM fibrosis improvement correlated with improved OS. Considering this promising result, a pivotal international phase 3 trial comparing imetelstat to the best avail-

able therapy (BAT) has been undertaken [49]. This trial enrolled patients with intermediate-2 or high-risk MF whose disease had either relapsed after, was refractory to, or were ineligible for further JAKi treatment. The primary objective of this trial was to assess the survival benefit associated with this treatment. This is an unprecedented trial endpoint for investigational MF [49].

Murine double-minute 2 inhibitor: Preclinical studies have shown that *JAK2*^{V617F} leads to overexpression of murine double minute 2 (MDM2) in MPN [50], and upregulation of MDM2 protects clonal hematopoietic stem cells that drive the disease from apoptosis. KRT-232 is a first-in-class, potent, and bioavailable inhibitor of MDM2, which is a key negative regulator of p53. In a phase 2 study, KRT-232 showed promising clinical efficacy and tolerability in *TP53*-wild-type patients with MF who failed ruxolitinib treatment [51]. A randomized phase 3 trial comparing KRT-232 (240 mg on days 1–7 of a 28-day cycle) to BAT in patients with MF that is refractory to or resistant to JAKis has also been launched [52].

OTHERS

Pentraxin-2, also known as serum amyloid P, is an endogenous protein that participates in the innate immune response and regulates wound healing [53, 54]. In an animal model of fibrosis, pentraxin-2 inhibits the differentiation of monocytes into fibrocytes and macrophages. PRM-151, a recombinant pentraxin-2 molecule, was evaluated in patients with MF in a phase 2 study. An open-label extension study was conducted to evaluate PRM-151 treatment in 18 patients, with 9 receiving PRM-151 alone and the remaining 9 receiving PRM-151 in combination with ruxolitinib. The results of the study have been reported. The median study was 30.9 months, and the drug was well tolerated. The mean best percent change (by palpation) in spleen size from baseline was -37%, with a median percent reduction of -26.1%. The mean best percentage improvement in the MPN-SAF TSS was -54%, with a median percentage reduction in TSS of -64%. In addition, overall improvements in BM reticulin and collagen fibrosis grades have been observed [55].

TGF-β1 is secreted by megakaryocytes in the BM of patients with MF. TGF-β1 levels are higher in the BM of patients with MF than in normal controls [56], and TGF-β1 promotes BM fibrosis and collagen deposition in these patients. Galunisertib, a small-molecule inhibitor of the TGF-β receptor 1 kinase ALK5, inhibits excessive collagen production in mouse models of *JAK2*^{V617F} and *MPLW*^{515L} [57]. Treatment with AVID200, a TGF-β1 trap that binds to TGF-β 1 and TGF-β3 but not TGF-β2, led to increased hematopoietic and progenitor cells in the BM, decreased splenic hematopoietic cells, and reduced fibrosis in a GATA1^{low} murine model of MF. In a phase 1 study of 12 patients with MF who were resistant to, intolerant of, or ineligible for ruxolitinib, no dose-limiting toxicities occurred; SVR was noted in 2 patients, and >50% improvement in TSS was noted in 5 patients. Sotatercept and luspatercept, which are receptor type IIA ligand traps designed to sequester natural ligands of the TGF-β receptor, have been used to target other members of the TGF-β superfamily in patients with anemia and MF. These treatments inhibit signaling by sequestering natural ligands of the TGF-β receptor. These agents are currently being tested in clinical trials of anemic patients with MF [58, 59].

CONCLUSIONS

Over the past decade, treatment with ruxolitinib has improved splenomegaly and its associated symptoms, regardless of the patient's driver mutation status. In addition, ruxolitinib is associated with a survival advantage in patients with intermediate-2- and high-risk MF. However, drug-related cytopenia and refractory or resistant responses to ruxolitinib after 2–3 years of therapy can lead to disease progression [48, 60]. Therefore, beyond the use of JAK1/2i monotherapies for MF, promising novel medications targeting various biological mechanisms have been developed. These include inhibitors of BET, MDM2, BCL-2/BCL-XL, and telomerase. In addition, several highly promising candidates are currently being evaluated in phase 3 clinical trials in front- and second-line settings. These studies may lead to the approval of novel medications that can significantly improve the current MF treatment paradigm.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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