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Management of Myelofibrosis: from Diagnosis to New Target Therapies

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Opinion statement

Myelofibrosis (MF) is a clonal disorder of the pluripotent hematopoietic stem cell, whose clinical manifestations can be extremely heterogeneous, including cytopenias, organomegaly, constitutional symptoms, and cachexia. Median survival ranges from approximately 3.5 to 5.5 years; while the most frequent cause of death is the evolution to acute myeloid leukemia, also other conditions such as progression without transformation, complications due to cytopenias including infections or bleeding, and cardiovascular events may be fatal. Myelofibrosis is still orphan of curative treatments: allogeneic hematopoietic stem cell transplant (HSCT), the only therapeutic approach that has clearly demonstrated an impact on disease progression, is associated with relevant morbidity and mortality and only a minority of patients is eligible for such an intensive procedure. While the discovery of the crucial role of *JAK2* mutations and the consequent clinical use of JAK inhibitors has led to a dramatic improvement of symptoms control and quality of life, yet these drugs do not significantly modify the natural history of the disease. A better understanding of the molecular pathogenesis will hopefully foster the development of new targeted therapies aimed at improving MF prognosis. Herein, we review the most recent advances about JAK inhibitors and other molecules which are under investigation.

Introduction

Myelofibrosis (MF) is a clonal disorder of the pluripotent hematopoietic stem cell [1], in which the abnormal stem cell population releases several cytokines and growth factors into the bone marrow microenvironment [2].

Myelofibrosis may present as a primary disorder (PMF) or evolve from another pre-existing *BCR-ABL1*-negative myeloproliferative neoplasm (MPN), such as polycythemia vera (PV) or essential thrombocythemia (ET), globally identified as secondary MF (SMF) [3••].

The diagnosis of PMF is currently based on the WHO 2016 criteria, which distinguishes a pre-fibrotic and an overt fibrotic stage [3]; the former might mimic ET in its presentation and it is prognostically relevant to distinguish between the two [4]. The diagnosis of post-PV/ET MF should adhere to the criteria of the International Working Group for MPN Research and Treatment (IWG-MRT) [5].

The presence of the *JAK2*V617F mutation, detected in 50–60% of all cases, is included in the diagnostic criteria [6–9], and mutations in genes other than *JAK2* such as *MPL* (frequency 5–10%) [10, 11] and somatically acquired mutations in the *CALR* gene (frequency 15–20%) [12, 13] have also been described. About 10% of MF patients do not develop any known mutation and are considered to have "triple-negative" MF [14]. Numerous "other" somatic mutations involving epigenetic processes (*EZH2*, *TET2*, *ASXL1*, and *DNMT3A*), spliceosome machinery (*SRSF2*, *SF3B1*, and *U2AF1*), and disease evolution (e.g., *TP53*, *IDH1/2*, and *IKZF*) have been identified and they might contribute to disease progression and leukemic transformation [15–18].

Splenomegaly-related symptoms such as abdominal distension and pain, early satiety, dyspnea, together with constitutional symptoms such as fatigue, night sweats, cachexia, pruritus, bone pain, weight loss, and fever are the dominant aspects of the clinical picture heavily affecting the functional status and quality of life (QoL) of MF patients. Other clinical manifestations may include portal hypertension and non-hepatosplenic extramedullary hematopoiesis causing cord compression, pleural effusion, and pulmonary hypertension. While the most frequent cause of death is the evolution to acute myeloid leukemia, also other conditions such as progression without transformation, cytopenias-related complications, and cardiovascular events may be fatal [19].

Prognosis is currently based on three different scoring systems, which mainly refer to age (>65 years), constitutional symptoms, anemia (hemoglobin <10 g/dL), white blood cell count (>25×10^9/L), and percentage of peripheral blood blasts (>1%). While the International Prognostic Scoring System (IPSS) is applicable only at diagnosis [19], the Dynamic International Prognostic Scoring System (DIPSS) [20] and the DIPSS-plus can be applied also at any time during follow-up; the last one incorporates three additional independent risk factors, namely red blood cell (RBC) transfusion requirement, platelet counts of <100×10^9/L, and an unfavorable karyotype [21]. More recently, the increasing knowledge of MF molecular landscape has led to the development of genetically based prognostic scoring systems (i.e., MIPSS70, MIPSS70+ version 2.0, and GIPSS), requiring however the characterization of subclonal mutations [22, 23, 24••]. As these pieces of information are available only in a limited number of laboratories, a new simple prognostic scoring system has been recently proposed to define PMF prognosis at diagnosis, i.e., an integrated International Prognostic Scoring System (I-IPSS) which combines IPSS, grade of bone marrow fibrosis, and driver mutations profile [25]. Notably, it can be easily applicable worldwide, being based on information derived from the "good clinical practice" management of PMF patients. For SMF, due to the recently acknowledged differences from PMF in terms of genetics, phenotype, and prognosis, a specific prognostic tool, the Myelofibrosis Secondary to PV and ET Collaboration-Prognostic Model (MYSEC-PM), has been developed [26••].

The MF therapeutic algorithm according to the ELN recommendations [27••] is reported in Fig. 1. While allogeneic hematopoietic stem cell transplant (HSCT), the only therapeutic approach with a clear impact on disease progression, is associated with relevant morbidity and mortality and only a minority of patients is eligible for such an intensive procedure [28••, 29], yet the discovery of the *JAK2* mutations and the development of JAK inhibitors (JAKi) have significantly changed the therapeutic outcome of MF as far symptoms control and patients' QoL are concerned. Unfortunately, the natural history of the disease remains unaffected also by these targeted drugs; a better understanding of the molecular pathogenesis will hopefully foster the development of new therapies aimed at improving MF prognosis. Herein, we review the most recent advances about JAKi and other molecules which are under investigation.

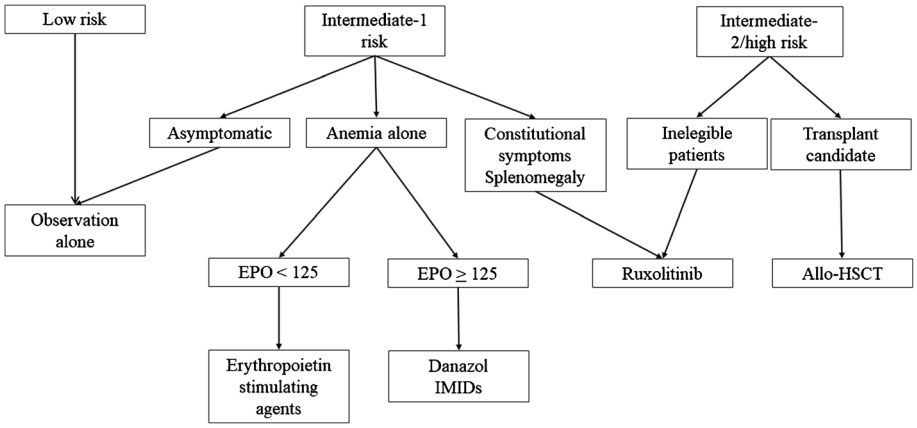

Fig. 1. Treatment algorithm for MF patients according to ELN recommendations.

Ruxolitinib

Ruxolitinib (Jakavi) was the first JAKi to become commercially available for MF treatment [30]. It is approved in the USA for the treatment of splenomegaly in subjects with intermediate-/high-risk disease, and in Europe for the treatment of splenomegaly and/or constitutional symptoms in intermediate-2/high-risk MF patients [31].

These approvals were based on the results of COMFORT-I and COMFORT-II phase III trials [32, 33]. Overall, more than 90% of enrolled patients experienced a spleen volume response (SVR) which in most subjects remained stable after a median follow-up of 5 years [34, 35••]. Differently from conventional drugs, ruxolitinib therapeutic effect was not limited to SVR, being also efficacious in relieving constitutional symptoms; reducing abdominal discomfort, appetite loss, itching, fatigue, night sweats; and improving QoL. As the drug activity is independent of *JAK2* mutational status, response rate was similar in patients with and without the *JAK2*V617F mutation because of its anti-*JAK1*-mediated effect.

The phase II ROBUST trial evaluated ruxolitinib in intermediate-1-risk MF. Fifty-seven percent of enrolled subjects achieved a treatment success (50% SVR and/or a ≥50% decrease in total symptoms score (TSS)); the most common hematological adverse events (AEs) were anemia and thrombocytopenia [36••]. In the phase IIIb expanded-access JUMP trial, the majority of patients achieved a ≥50% SVR and approximately 50% of subjects experienced clinically significant improvements. Safety and efficacy profiles in intermediate-1-risk patients were consistent with those recorded in the overall JUMP population and with the ones previously reported in intermediate-2- and high-risk subjects [37].

Given these promising results, ruxolitinib was also exploited as a therapeutic bridge to HSCT. Furthermore, several reports described the bone marrow (BM) morphologic changes occurring in ruxolitinib-treated patients, mostly focusing on modifications in BM fibrosis grade [38–42], a prognostic parameter both in PMF and SMF [43, 44].

The main toxicity of ruxolitinib is hematological due to the non-selective inhibition of JAK-STAT signaling, an essential pathway for normal hematopoiesis. In both COMFORT trials, thrombocytopenia was the dose-limiting toxicity, while anemia was the most common hematological AE. In this context, low-dose thalidomide represents a useful potential partner as it could offset both ruxolitinib-dependent anemia and thrombocytopenia [45].

Due to its impairing activity on immune response, ruxolitinib may favor an increased incidence of both opportunistic and non-opportunistic infections [46–48]. Despite warnings about this risk [49–51], a recent update of the JUMP study reported a low incidence of infections, with no hepatitis B (HBV) reactivation and treatment discontinuation for grade ≥3 pneumonia in 0.5% of patients [37].

Nevertheless, since MF patients are predisposed to infections [52] and the long-term risk of ruxolitinib treatment is still unknown, patients should be carefully monitored and prophylaxis for Herpes zoster or other infections should be considered on a case-by-case basis, depending on local risk. Serological screening for identifying prior Herpes zoster infection before ruxolitinib administration is generally not recommended since it does not add any valuable information on the subsequent risk of reactivation. On the contrary, all the patients should be evaluated for previous HBV (see Fig. 2) or tuberculosis exposure and referred to the infectivologist for further assessment and treatment when required [53].

Recently, a concern has been raised about an increased risk of aggressive B cell lymphomas in ruxolitinib-treated patients. Porpaczy et al. first reported an association between JAKi and lymphoma development in MPN subjects; 626 patients were evaluated, including 69 with MF treated with JAKi. B cell lymphomas were detected in 5.8% of subjects receiving JAKi compared with 0.36% of conventionally treated cases corresponding to a 16-fold increased risk [54].

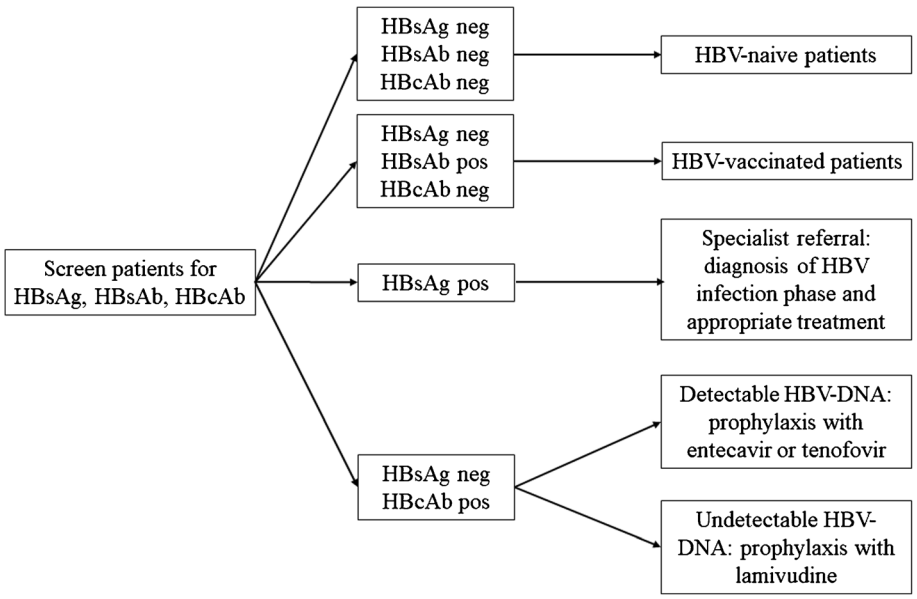

Fig. 2. Algorithm for HBV prophylaxis according to previous viral exposure.

Patients at risk are those with a preexisting B cell clone in the BM. In subjects candidate to ruxolitinib treatment, a thorough BM investigation by means of PCR technique for detection of immunoglobulin gene rearrangement and flow cytometry immunophenotyping is therefore advisable. In the absence of a clonal B cell population, ruxolitinib treatment can be safely started closely monitoring the patient, while the therapeutic decision becomes problematic in the opposite case [55••].

Unfortunately, at some point, patients on ruxolitinib will experience a relapse of symptoms and splenomegaly, worsening cytopenias, or progression to the accelerated or blast phase; as an example, in the COMFORT-II study, responding patients had a <50% chance of maintaining response at 5 years [34]. Furthermore, patient survival after ruxolitinib discontinuation is poor, particularly if it occurs while in the blast phase. Salvage therapies can improve outcomes, emphasizing the need for novel treatments [56].

Other JAK inhibitors

As reported in Table 1, three new investigational agents have been tested in phase III randomized controlled trials: momelotinib, fedratinib, and pacritinib.

Momelotinib

Based on promising "in vitro" findings [57, 58], momelotinib, a selective JAKi, entered clinical testing. A phase I/II study was performed in subjects with intermediate-/high-risk MF, consisting of a dose-escalation study at 100, 150, 200, 300, and 400 mg once-daily followed by a dose-confirmation phase with an expansion of the 150 mg once-daily, 300 mg once-daily, and 150 mg twice-daily cohorts. While on therapy, 95 patients achieved a clinical improvement, 69 had a stable disease, and one subject had a progressive disease. Seventy-five percent of transfusion-dependent patients became transfusion-independent and 28.2% with hemoglobin levels <10 g/dL achieved a hemoglobin response. Thrombocytopenia and peripheral sensory neuropathy were the most common AEs leading to treatment discontinuation in 13.3% of enrolled subjects [59, 60]. The impact of genomic alterations on the outcome of MF patients treated with momelotinib has also been investigated. While SVR was independently associated with *CALR*-mutated and *ASXL1*-unmutated status, anemia response was not correlated with mutational status or baseline karyotype; the absence of *CALR* and the presence of *ASXL1* or *SRSF2* mutations were associated with inferior survival [61, 62]. Efficacy and tolerability of momelotinib were further investigated in a similar series of MF patients treated at a dose of 200 mg twice-daily. At 24 weeks of therapy, anemia response was 45% and SVR was 72% by palpation and 45.8% by MRI; MF symptoms were improved in most subjects. Diarrhea, peripheral neuropathy, thrombocytopenia, and dizziness were the most common AEs [63].

The encouraging activity recorded in phase I/II trials led to the development of two phase III studies, SIMPLIFY-1 and SIMPLIFY-2. The SIMPLIFY-1 study was a non-inferiority comparison of momelotinib 200 mg once-daily vs ruxolitinib 20 mg twice-daily in 432 JAKi-naïve patients with intermediate-2-/high-risk or symptomatic intermediate-1 risk MF. Non-inferiority was achieved

Table 1. JAK inhibitors for the treatment of myelofibrosis

Drug	Dosage	Pros	Cons
Ruxolitinib	15 or 20 mg twice daily (based on baseline platelet counts of 100–200×10^9/L or >200×10^9/L, respectively)	• Can be titrated over the course of treatment, from a minimum of 5 mg bid to a maximum of 25 mg bid, to optimize safety and efficacy for each patient	• Hematological toxicity • Both opportunistic and non-opportunistic infections • Possible issue of lymphoproliferative disorders
Momelotinib	200 mg once daily (trials ongoing)	• Promising effect on hemoglobin levels, with the possibility of transfusion independence	• Thrombocytopenia • Peripheral neuropathy
Fedratinib	400 mg once daily (FDA-approved)	• Significant spleen response, with also some cases obtaining a reduction in *JAK2*V617F allele burden	• Anemia and thrombocytopenia • Nausea, vomiting, diarrhea • Possible issue of Wernicke's encephalopathy
Pacritinib	200 mg twice daily or 400 mg once daily (trials ongoing)	• Non-myelosuppressive due to the lack of effects on JAK1 • Significant rate of spleen volume reduction • Significant rate of transfusion independence	• Fatigue • Mild-to-moderate gastrointestinal toxicities • Possible issue of intracranial hemorrhage, cardiac failure, and cardiac arrest

for SVR, but not for TSS response. Transfusion rate, transfusion independence, and transfusion dependence were all improved by momelotinib. Treatment-emergent peripheral neuropathy occurred in 10% of patients treated with momelotinib and in 5% of cases receiving ruxolitinib [64].

The SIMPLIFY-2 study evaluated the activity of momelotinib vs best available therapy (BAT) in 156 MF subjects who previously had a suboptimal response or hematological toxicity with ruxolitinib. Patients were assigned to either BAT or momelotinib 200 mg once-daily for 24 weeks, after which all patients could receive extended momelotinib treatment. Since BAT besides chemotherapy, steroids, or no treatment included also ruxolitinib, 89% of patients randomly assigned to BAT continued to receive ruxolitinib. A 35% SVR at 24 weeks was achieved by 7% of subjects in the momelotinib group vs 6% in the BAT group, therefore stating the non-superiority of momelotinib in this subset of patients; reduction in TSS and in transfusion dependence was more frequent in the momelotinib group. Anemia and thrombocytopenia were the most common grade > 3 AEs [65].

Fedratinib

Fedratinib, a highly selective JAKi with minor effect on *JAK1*, *JAK3*, and *TYK2*, entered clinical evaluation in MF due to a promising activity on *JAK2*V617F-mutated cell populations both in vitro and in vivo in animal MPN models [66, 67]. These preclinical findings were confirmed by a multicenter phase I trial on 59 patients. Forty-seven percent of subjects obtained a SVR and leukocytosis and thrombocytosis were normalized in the majority of patients; a significant decrease in *JAK2*V617F allele burden was also observed. The recommended

daily dose for phase II studies was 400–500 mg [68]. In a phase II randomized trial on 31 JAKi-naïve patients with intermediate-2-/high-risk MF, fedratinib was given at 300, 400, or 500 mg once-daily in 4-week cycles; the mean SVR was 30.3%, 33.1%, and 43.3%, respectively, and the median duration of SVR was 255, 251, and 251 days. A ≥50% reduction of TSS at week 4 was achieved by 44%, 50%, and 50% of subjects, respectively. Anemia, fatigue, diarrhea, vomiting, and nausea were the most common grade 3/4 AEs; one case of Wernicke's encephalopathy was reported [69]. The clinical activity of fedratinib in MF at the daily dose of 400 mg was also investigated in the phase II JAKARTA-2 trial addressed to ruxolitinib-resistant or ruxolitinib-intolerant patients. Out of 83 assessable subjects, 55% achieved a ≥35% SVR at week 24, regardless of the baseline spleen size and platelet count. A ≥50% reduction of TSS was obtained by 26% of subjects. Anemia and thrombocytopenia were the most common AEs. Suspected cases of Wernicke's encephalopathy reported in other fedratinib trials led to early study termination [70]. In the phase III JAKARTA trial, 289 patients with intermediate-2-/high-risk MF were assigned to receive fedratinib at a daily dose of 400 mg, 500 mg, or placebo. The primary endpoint, i.e., ≥35% SVR at week 24 as determined by MRI or CT, was achieved by 36% and 40% of subjects in the fedratinib 400 mg and 500 mg groups vs 1% in the placebo group. A ≥50% reduction in TSS was obtained by 36%, 34%, and 7% of patients in the three abovementioned experimental groups; no significant change in *JAK2* allele burden was recorded. Anemia and gastrointestinal symptoms were the most common AEs and Wernicke's encephalopathy was detected in three patients [71]. In November 2013, the FDA placed a clinical hold on the drug's development which was removed in August 2017 owing to additional safety data showing that in nine fedratinib trials enrolling 670 patients with either MF or solid tumors, between three and five subjects experienced a Wernicke's syndrome, a prevalence inferior to that expected for a patient population of this size [72]. In August 2019, the FDA approved fedratinib (INREBIC) for adults with intermediate-2- or high-risk MF at the recommended daily dose of 400 mg orally.

Two clinical trials, FREEDOM (NCT03755518) and FREEDOM-2 (NCT03952039), are ongoing. FREEDOM is a phase IIIb trial with fedratinib at 400 mg once-daily in intermediate-/high-risk MF patients previously treated with ruxolitinib. The primary endpoint is the proportion of patients achieving a ≥35% SVR and the estimated completion date of the study is June 2022 [73]. FREEDOM-2 will enroll 192 subjects randomized to either fedratinib 400 mg daily or BAT; inclusion criteria and endpoints are the same as in the FREEDOM study. The study estimated completion date is May 2022 [74].

Pacritinib

Pacritinib is a potent JAKi, active also on *FLT3*, *CSF1R*, and IL-1R-associated kinase1, with the peculiarity of being non-myelosuppressive due to the lack of effects on *JAK1* [75]. Pacritinib was initially assessed in a phase I/II clinical trial. In the dose-escalation part, 43 subjects with advanced myeloid malignancies, including 33 with MF, were treated with 100 to 600 mg once-daily. Mild gastrointestinal toxicities were the most frequent AEs; 400 mg was the recommended daily dose for the phase II part of the study. Thirty-one adults with MF and any degree of cytopenia were treated; the primary endpoint, a ≥35% SVR at

week 24 as determined by MRI, was obtained by 23.5% of evaluable patients and a ≥50% decrease of TSS was recorded in 38.9% of subjects. Mild-to-moderate gastrointestinal toxicities and fatigue were the most common AEs. Grade 3/4 anemia and thrombocytopenia were found in 16.1% and in 9.7% of cases, respectively [76]. In a further phase II study, 35 MF subjects with poorly controlled splenomegaly and any degree of cytopenia were treated with pacritinib 400 mg once-daily in 28-day cycles. At week 24, 31% of evaluable patients achieved a ≥35% SVR as determined by MRI; median symptom improvement was ≥50%, except for fatigue. Grade 1/2 gastrointestinal toxicities were the most frequent AEs [77].

Based on these results, two large phase III clinical trials, PERSIST-1 and PERSIST-2, were designed. In the PERSIST-1 study, 327 patients were randomly assigned to receive either oral pacritinib 400 mg once-daily or BAT, excluding *JAK2* inhibitors. A significantly greater proportion of patients treated with pacritinib achieved the primary endpoint of ≥35% SVR at week 24 with a median duration of 34.4 weeks. The key secondary endpoint, a TSS reduction of ≥50%, was obtained by 36% of subjects in the pacritinib group vs 14% in the BAT group. Notably, in the pacritinib group, 25.7% of RBC transfusion-dependent patients became transfusion-independent vs none in the BAT group. The most common grade 3/4 AEs were anemia, thrombocytopenia, and diarrhea in the pacritinib group and anemia, thrombocytopenia, dyspnea, and hypotension in the BAT group. Cardiac failure (2%) was also recorded in patients treated with pacritinib [78].

The PERSIST-2 study was addressed at MF patients with platelet count $<100\times10^9$/L comparing two pacritinib doses, 200 mg twice-daily and 400 mg once-daily, with BAT; prior therapy with JAKi was allowed and BAT could include ruxolitinib. Out of 311 subjects, only 221 could be included in the intention to treat (ITT) population owing to a "full clinical hold" on the pacritinib development program placed by the FDA in February 2016 due to an excess of mortality related to intracranial hemorrhage, cardiac failure, and cardiac arrest in both PERSIST-1 and PERSIST-2 trials. While a significantly higher proportion of subjects in the pooled pacritinib groups than in the BAT group achieved at week 24 a ≥35% SVR as assessed by MRI or CT, a non-significantly greater rate of ≥50% TSS reduction was recorded. However, when considering only the twice-daily dosing group, pacritinib was significantly superior over BAT for both the primary endpoints and also for improvement of hemoglobin levels and reduction of transfusion requirement. Grade 3/4 cardiac events were recorded in 13% of patients treated with pacritinib once-daily, 7% treated with pacritinib twice-daily, and 9% treated with BAT [79].

In January 2017, the FDA repealed the clinical hold on pacritinib recommending new trials aimed at identifying the lowest dose with clinical efficacy. Following this request, the study NCT03165734 "Dose-Finding Study of Pacritinib in Patients With Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis Previously Treated With Ruxolitinib" was designed. Patients are randomized in three treatment groups receiving pacritinib at 100 mg once-daily, 100 mg twice-daily, or 200 mg twice-daily. Spleen volume response was selected as the primary efficacy parameter while safety outcomes include the percentage of patients with grade ≥3 cardiac and hemorrhagic AEs, grade ≥4 thrombocytopenia, and anemia [80, 81].

Other, selected, single-agent treatments

JAK inhibitors have dramatically changed the clinical outcome of MF patients mostly in terms of symptoms control and QoL without having, however, a real impact on the natural history of this disease. As a consequence, research aimed at the discovery of more effective drugs is extremely active.

Bromodomain and extraterminal protein (BET) inhibitors, such as CPI-0610, are another class of compounds being developed in MPNs [82]. In preclinical models of MPN, BET inhibition reduced inflammatory cytokine production and BM fibrosis [83, 84]. In the phase II MANIFEST study, CPI-0610 was given as monotherapy or with ruxolitinib, to 48 patients with refractory/intolerant advanced MF. Spleen volume response was observed in 94% and TSS improvement in 93% of subjects. Reduction of BM fibrosis was reported in 58% of patients; most common ≥3 grade AEs were anemia and thrombocytopenia [85]. CPI-0610 in combination with ruxolitinib was also assessed in 11 JAKi-naïve MF subjects. All four patients on treatment for ≥12 weeks achieved a ≥35% SVR and a ≥50% TSS improvement. Anemia, fatigue, and non-cumulative reversible thrombocytopenia were the most common AEs [86].

Sotatercept is an activin receptor IIA ligand trap that improves anemia by sequestering transforming growth factor-b (TGF-b) superfamily ligands. In a phase II study, 35% of MF patients with anemia treated with sotatercept alone had a hemoglobin response vs 12.5% of subjects treated with sotatercept and ruxolitinib [87]. A phase II study of luspatercept alone or in combination with ruxolitinib in anemic MF patients is near to completion (NCT03194542).

PRM-151 is a recombinant form of pentraxin 2, an endogenous protein that regulates the differentiation of monocytes into fibrocytes that has been shown to reverse fibrosis formation in preclinical models. In a phase II study on PRM-151 given alone or in combination with ruxolitinib, 23.1% of subjects had a BM fibrosis response [88]. The long-term follow-up showed a sustained improvement in BM fibrosis grade, as well as spleen and symptom responses.

Another possible molecular target is represented by aurora kinase A (AURKA), a signaling pathway overexpressed in MF hematopoietic cells. In a phase I study on higher-risk MF patients, treatment with the AURKA inhibitor alisertib led to a SVR in 29%, transfusion independence in 8%, and > 50% symptom improvement in 23% of cases [89].

The oligonucleotide imetelstat is a potent telomerase inhibitor, being evaluated in a phase II study on 107 MF patients previously treated with a JAKi [90]. With a median treatment duration of 6.2 months, 10% of patients had a SVR and 38% had a symptom response at week 24. Of note, the survival of this high-risk population was longer than expected based on historical controls, and the SVR rate was higher in patients with high-risk mutations (*ASXL1*, *EZH2*, *SRSF2*, or *IDH1/2*), suggesting a peculiar efficacy in this specific MF subgroup.

An inhibitor of the hedgehog pathway, glasdegib, was evaluated in MF patients in a phase I/II study, showing only modest activity when used as a single agent [91]. On the contrary, when ruxolitinib was combined with sonidegib in 27 JAKi-naive MF patents, 56% achieved a > 35% SVR at any time on treatment [92].

Inhibitors of phosphatidylinositol 3-kinase (PI3K), AKT, and mTOR have been investigated in the preclinical and clinical settings. In particular, the phase I HARMONY study evaluated the combination of ruxolitinib and the pan-PI3K inhibitor buparlisib in MF patients [93]. The SVR rate, about 40%, was the same as with ruxolitinib alone. An ongoing study is evaluating the addition of the selective PI3Kd inhibitor parsaclisib to ruxolitinib as an add-back strategy to regain response in the setting of ruxolitinib failure [94].

Another class of promising molecules is represented by the histone deacetylase inhibitors: in phase I/II trials, panobinostat was shown to be safe and tolerable and demonstrated clinical activity in approximately a third of treated patients [95–97]. Combination therapy with ruxolitinib displayed a synergistic activity in a preclinical MF model, which prompted clinical evaluation of this combination in both ruxolitinib-naïve and ruxolitinib-treated patients. In a phase I trial in 15 MF subjects, ruxolitinib and panobinostat combination maintained a stable disease in the majority of patients and 40% of cases attained a clinical improvement. Furthermore, this combination treatment proved to be safe and tolerable without dose-limiting thrombocytopenia [98].

Conclusions

Traditional MF treatments were primarily palliative and inadequate to address the considerable morbidity and mortality associated with this disabling disease. The discovery in recent years of MF driver mutations has led to a better understanding of the pathogenesis of this disease and the consequent clinical development of JAKi has offered new hope to MF patients allowing to achieve significant advances in terms of SVR, symptoms control, QoL, and survival. Allogeneic hematopoietic stem cell transplant remains the only therapeutic approach that can fully modify the natural history of MF, preventing leukemic evolution; unfortunately, only a minority of patients is eligible for such an aggressive procedure and curative options for transplant-ineligible patients are still lacking. In such a context, participation in clinical trials should be encouraged whenever possible. Most of them are currently finalized to improve overall response rate, targeting cytopenias, complete resolution of splenomegaly, and BM fibrosis. Therefore, patients' populations should firstly include suboptimal responders to ruxolitinib or ruxolitinib-failing subjects.

Compliance with Ethical Standards

Conflict of Interest

Alessandra Iurlo declares that she has no conflict of interest. Daniele Cattaneo declares that he has no conflict of interest. Cristina Bucelli declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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