Treatment of Myelofibrosis: Old and New Strategies

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ABSTRACT: Myelofibrosis (MF) is a *BCR-ABL1*–negative myeloproliferative neoplasm that is mainly characterised by reactive bone marrow fibrosis, extramedullary haematopoiesis, anaemia, hepatosplenomegaly, constitutional symptoms, leukaemic progression, and shortened survival. As such, this malignancy is still orphan of curative treatments; indeed, the only treatment that has a clearly demonstrated impact on disease progression is allogeneic haematopoietic stem cell transplantation, but only a minority of patients are eligible for such intensive therapy. However, more recently, the discovery of *JAK2* mutations has also led to the development of small-molecule *JAK1/2* inhibitors, the first of which, ruxolitinib, has been approved for the treatment of MF in the United States and Europe. In this article, we report on old and new therapeutic strategies that proved effective in early preclinical and clinical trials, and subsequently in the daily clinical practice, for patients with MF, particularly concerning the topics of anaemia, splenomegaly, iron overload, and allogeneic stem cell transplantation.

KEYWORDS: Myeloproliferative neoplasms, myelofibrosis, *JAK2* inhibitors, ruxolitinib, momelotinib, allogeneic stem cell transplantation

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Introduction

Myelofibrosis (MF) belongs to the category of myeloproliferative neoplasms (MPNs) and may present as a primary disorder (primary myelofibrosis [PMF]) or evolve from polycythaemia vera (PV) or essential thrombocythaemia (ET) to post-PV or post-ET MF.[1] It is characterised by the clonal proliferation of a pluripotent haematopoietic stem cell,[2] in which the abnormal stem cell population releases several cytokines and growth factors into the bone marrow microenvironment, thus leading to an increase in bone marrow fibrosis, stromal changes, involvement of extramedullary organs such as the spleen and liver, and consequent clinical manifestations.[3]

Myelofibrosis has an incidence of about 0.58 new cases per 100 000 person-years, but a higher prevalence of 6 per 100 000 person-years because of its chronic and disabling course.[4] Median age at diagnosis is 67 years, without any significant difference in distribution between the sexes.

The diagnosis of MF is currently based on the World Health Organization 2016 criteria, which include the *JAK2*V617F mutation that is detected in 50% to 60% of all cases.[5–8] Mutations in genes other than *JAK2* such as *MPL* mutations (frequency: 5%-10%)[9,10] and somatically acquired mutations in the *CALR* gene (frequency: 15%-20%)[11,12] have also been described. However, about 10% of patients with MF do not develop any known mutation and are considered to have 'triple-negative' MF.[13] In addition to these 3 driver mutations, numerous other somatic mutations involving epigenetic processes (*EZH2*, *TET2*, *ASXL1*, and *DNMT3A*), spliceosome machinery (*SRSF2*, *SF3B1*, and *U2AF1*), and disease evolution (eg, *TP53*, *IDH1/2*, and *IKZF*) have been identified in MF.[14–16] Some of these mutations, such as those in *DNTM3A*[17] or *TET2*,[18] have not been shown to correlate with survival outcome. Conversely, mutations in *ASXL1*, *SRSF2*, and *EZH2* predicted short survival in a large cohort of patients. More specifically, a report by Tefferi et al[19] points to the *CALR−/ASXL1+* profile as the most detrimental mutation profile in PMF. Nevertheless, the genetic trigger of MF remains unknown.

The symptoms mainly include those associated with splenomegaly (abdominal distension and pain, early satiety, splenic infarction, dyspnoea, and diarrhoea) and constitutional symptoms such as fatigue, cachexia, pruritus, bone pain, weight loss, and fever; these worsen patients' role functioning and quality of life (QoL). Median survival ranges from approximately 3.5 to 5.5 years,[20,21] and the most frequent cause of death in patients with MF is transformation to acute myeloid leukaemia (20%), but most patients die because of other disease-related events, such as progression without transformation, infections, and thrombo-haemorrhagic complications.[20]

Prognosis is currently based on 3 different prognostic scoring systems, which mainly refer to age, constitutional symptoms, anaemia, white blood cell counts, and percentage of peripheral blood blasts: International Prognostic Scoring System (IPSS), which is applicable at diagnosis[20]; Dynamic International Prognostic Scoring System (DIPSS)[22]; and DIPSS-plus, which can be applied at any time during follow-up. The last incorporates 3 additional independent risk factors: red blood cell (RBC) transfusion requirement, platelet counts of $<100 \times 10^9$/L, and an unfavourable karyotype (Table 1).[23]

Until recently, MF has remained orphan of curative treatments: the only treatment that has a clearly demonstrated impact on disease progression is allogeneic haematopoietic stem cell transplantation (allo-HSCT), but treatment-related mortality is high and only a minority of patients are eligible for

Table 1. Scoring systems for primary myelofibrosis.

VARIABLES	IPSS[20]	DIPSS[22]	DIPSS-plus[23]
Age >65 y	1	1	1
Constitutional symptoms	1	1	1
Hb <10 g/dL	1	2	1
WBC count >25 × 10^9/L	1	1	1
Peripheral blood blasts ⩾1%	1	1	1
PLT count <100 × 10^9/L	—	—	1
RBC transfusion need	—	—	1
Unfavourable karyotype (+8, –7/7q–, i(17q), –5/5q–, 12p–, inv(3), 11q23)	—	—	1

Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; Hb, haemoglobin; IPSS, International Prognostic Scoring System; PLT, platelets; RBC, red blood cell; WBC, white blood cell.
IPSS: 0, low risk; 1, intermediate-1 risk; 2, intermediate-2 risk; ⩾3, high risk. DIPSS: 0, low risk; 1 or 2, intermediate-1 risk; 3 or 4, intermediate-2 risk; more than 4, high risk. DIPSS-plus: 0, low risk; 1, intermediate-1 risk; 2 or 3, intermediate-2 risk; ⩾4, high risk.

such intensive therapy.[24] The previously used treatments were palliative and have only limited benefits in QoL and symptom control. However, the discovery of *JAK2* mutations, which has established that dysregulation of the *JAK-STAT* signalling pathway is a major contributor to the pathogenesis of MPNs, has also led to the development of small-molecule *JAK1/2* inhibitors, the first of which (ruxolitinib) has been approved for the treatment of MF in the United States and Europe.

In this article, we report on old and new therapeutic strategies that proved effective in early preclinical and clinical trials and subsequently in the daily clinical practice for patients with MF, particularly concerning the topics of anaemia, splenomegaly, iron overload (IO), and allo-HSCT.

Anaemia

The management of anaemia can be one of the most challenging aspects of treating patients with MF (Table 2). Blood transfusion is the standard therapy for symptomatically anaemic patients, and the transfusion target should be assessed individually.

Corticosteroids (eg, prednisone 0.5 mg/kg/day) may be temporarily effective in treating anaemia and constitutional symptoms and are usually used in combination with other therapies.[25]

Erythropoiesis-stimulating agents (ESAs) are worth trying in MF patients with moderate, nontransfusion-dependent anaemia and a low serum erythropoietin level (<125 IU/L), although rapid spleen enlargement during treatment has occasionally been reported. Response rates vary from 23% to 60% in different studies, with no clear evidence favouring darbepoetin-alfa over conventional recombinant erythropoietins. Furthermore, responses are usually short-lived (<1 year), and as no prospective randomised study of the value of ESAs has yet been published, they are not indicated in anaemic subjects with established transfusion dependency.[26]

If there are no contraindications, androgen preparations or danazol (a semisynthetic attenuated androgen) can be used. They have been shown to stimulate erythropoiesis in patients with refractory anaemia, leading to increased haemoglobin (Hb) levels, reticulocytosis, and a decreased need for RBC transfusions[27]; however, documentation of their efficacy as single agents is largely restricted to retrospective studies. One of these reported responses in 11 of 30 patients with MF, including 8 with a complete response,[28] with a lack of transfusion dependence and higher pretreatment Hb levels predicting response. In another retrospective study, responses were observed in 17 of 39 patients with MF taking danazol, including 8 (21%) with an increase in Hb of ⩾1.5 g/dL, Hb levels of >10 g/dL, and transfusion independence for ⩾8 weeks.[29] However, there were no identifiable patients' characteristics (such as transfusion dependency, baseline Hb level, or cytogenetic results) that influenced outcome. These findings have been confirmed in a recent series of 50 patients with MF[30]; the slightly lower rate of anaemia response (30%) should be attributed to the use of more stringent response criteria.[31] In terms of predicting response, the only pretreatment variable showing a trend for an association with response to danazol was transfusion dependency, with only 18.5% of the responders in this subgroup of patients against 43.5% in the subgroup not requiring transfusions. The main limitations of using danazol are toxicities, including fluid retention, increased libido, liver function test abnormalities, headache, and virilisation. All patients receiving danazol should therefore be monitored using monthly liver function tests during initial therapy and periodic liver ultrasound examinations to detect any hepatic malignancy. Men should also be screened for prostate cancer before and during treatment.

The antiangiogenic and immunomodulatory properties of thalidomide, lenalidomide, and pomalidomide make them potentially effective medical therapies for MF, with some

Table 2. Treatment strategies for anaemia.

DRUGS	DOSAGE	PROS	CONS
Corticosteroids (eg, prednisone)[25]	0.5 mg/kg/day	Commonly used in combination with other therapies	Only temporarily effective
Erythropoiesis-stimulating agents (eg, darbepoetin-alfa)[26]	150 µg/wk	Are worth trying in patients with MF with moderate, nontransfusion-dependent anaemia	A low serum erythropoietin level (<125 IU/L) is required. Are not indicated in anaemic subjects with established transfusion dependency
Danazol[27–30]	600 mg daily for patients weighing up to 80 kg and 800 mg daily for those weighing >80 kg	Stimulate erythropoiesis in patients with refractory anaemia, leading to increased haemoglobin level and decreased need for transfusions	Toxicities include fluid retention, increased libido, liver function test abnormalities, headache, and virilisation
Thalidomide[32]	50 mg/day	Some responses in patients with anaemia, thrombocytopenia, and splenomegaly	High incidence of neuropathy. Not usually selected for first-line management of anaemia
Lenalidomide[33–35]	10 mg/day (5 mg/day if platelet count is <100 × 10^9/L) in 28-day cycles on a 21-day on/7-day off schedule	More effective than thalidomide-based therapy. Longer response duration in patients receiving lenalidomide plus prednisone	Toxicities mainly include cytopenias
Pomalidomide[37]	0.5 mg/day	Significantly better platelet response	No advantage in anaemia response

responses in patients with anaemia, thrombocytopenia, and splenomegaly; potential modifications to the bone marrow microenvironment; and a possible reduction in bone marrow fibrosis.

The combination of thalidomide and prednisone has been evaluated in 21 patients with MF, 62% of whom showed an anaemia response.[32] However, the high incidence of neuropathy associated with thalidomide limits its usefulness. Furthermore, because of the risk of thrombosis, prophylaxis with aspirin is recommended in all patients with a platelet count of >50 × 10^9/L. This combination is therefore not usually selected for the first-line management of anaemia.

A phase II clinical trial (NCT00227591) assessed the therapeutic efficacy of lenalidomide combined with prednisone in 42 patients with MF. Clinical improvements in anaemia and splenomegaly were observed in, respectively, 19% and 10% of the subjects. Similar to thalidomide, lenalidomide was burdened by toxicity, including cytopenia (at least 1 grade 3-4 event in 88% of patients) and nonhaematologic toxicity (at least 1 grade 3-4 event in 45% of patients).[33] A second study of lenalidomide plus prednisone in 40 patients with intermediate-risk or high-risk MF led to an overall response rate based on International Working Group criteria of 30% for anaemia and 42% for splenomegaly, with a median time to response of 12 weeks. However, grade 3 and 4 adverse events (AEs) were reported, mainly cytopenia.[34] A recently updated report of this study after a median follow-up of 9 years[35] showed that treatment responses improved over time, with 14 patients (35%) responding overall. More specifically, 39% of the patients showed a response in terms of reduction in spleen size, and the overall anaemia response rate was 32%. However, there was no significant difference in baseline characteristics between the patients who responded and those who did not.

An analysis combining the results of 3 phase II trials indicated that lenalidomide-based therapy may be more effective than thalidomide-based therapy, and fewer patients treated with lenalidomide plus prednisone discontinued therapy due to toxicity than those receiving thalidomide-based therapy. In addition, there was no significant difference in the response to lenalidomide alone and lenalidomide plus prednisone; however, response duration was significantly longer in patients who received lenalidomide plus prednisone.[36]

Pomalidomide, a more potent immunomodulatory drug, has been evaluated in a multicentre, double-blind, placebo-controlled phase III study (NCT01178281).[37] However, the study failed to meet the primary endpoint as an equal proportion of patients with MF in the pomalidomide (n = 152) and placebo arm (n = 77) achieved an anaemia response (16% vs 16%, $P = 1$). On the contrary, the platelet response was significantly better in patients who received pomalidomide (22% vs 0%).

Splenomegaly

Cytoreductive agents have been the treatment of choice for most MF patients with symptomatic splenomegaly (Table 3).

Hydroxyurea (HU), an S-phase cell cycle–specific nucleotide-depleting agent that inhibits ribonucleotide reductase,[38] is one of the most widely used medical therapies for patients with appreciably symptomatic splenomegaly,[39,40] although it induces only modest responses at higher doses (1-2 g daily) and mainly in subjects with nonmassive splenomegaly (<15

Table 3. Treatment strategies for splenomegaly.

DRUGS	DOSAGE	PROS	COS
Hydroxyurea[38-40]	0.5-2 g/day	Only modest responses. Mostly in subjects with nonmassive splenomegaly	Exacerbation of cytopenias frequently limits treatment
Oral alkylating agents[41,46]	Melphalan: 2.5 mg/3 times/wk Busulfan: 2-4 mg/day	Improve splenomegaly and other symptoms of disease	Exacerbate cytopenias. Possibly increase the frequency of leukaemic transformation
Interferon-alfa[43]	Recombinant interferon alfa-2b (500. 000-1 million units, 3 times weekly, progressively increased to 2-3 million units, 3 times weekly). Pegylated recombinant interferon alfa-2a (45-90 μg weekly)	In vitro data suggested that it might be effective in reducing bone marrow fibrosis	Only minimal clinical effect in reducing splenomegaly
Methotrexate[48,49]	5-25 mg/wk	Effective in controlling haematologic parameters, systemic symptoms, and splenomegaly	Toxicity is mainly haematologic
Ruxolitinib[53]	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 twice a day, to optimise safety and efficacy for each patient	Toxicity is mainly haematologic. Another important issue is the incidence of infections

cm).[45] Although HU is generally well tolerated, the modest improvement in symptoms is temporary, and exacerbated cytopenia frequently limits treatment.

In patients who do not respond to HU, it has been shown that the oral alkylating agents, melphalan and busulfan, improve splenomegaly and other disease symptoms, but they may also exacerbate cytopenia and possibly increase the frequency of leukaemic transformation. Furthermore, they are mainly used in older patients as they are relatively manageable insofar as frequent laboratory monitoring is not required, unlike in the case of HU or other cytoreductive agents.[41,46]

In cases of massive refractory splenomegaly, it has been found that monthly courses of intravenous cladribine (2-chlorodeoxyadenosine) lead to a response in up to 50% of patients, with severe but reversible cytopenia being the main toxicity.[42]

Interferon-alfa (standard and pegylated versions) has proved to have only a minimal clinical effect in reducing splenomegaly, and therefore, its use is not generally recommended.[43]

Hypomethylating agents, such as azacitidine and decitabine, have also been studied in MF, but currently play only a limited role in its treatment.[47]

More recently, Thomas et al[48] demonstrated that methotrexate (MTX) may act as an inhibitor of the *JAK-STAT* pathway and that this activity is likely to be specific and not related to a general effect on protein phosphorylation: the drug's in vitro activity was observed at a concentration equivalent to that used in patients taking low-dose MTX (5-25 mg/wk). What is important is that its efficacy in controlling haematologic parameters, systemic symptoms, and splenomegaly has been confirmed in vivo in 2 recent case reports.[49]

Splenectomy is a palliative debulking measure used in patients with MPNs. Its indications are mainly symptomatic massive splenomegaly, symptomatic portal hypertension with oesophageal varices and/or bleeding, profound cachexia, transfusion-dependent anaemia, and/or severe hypercatabolic symptoms. Removal of the spleen improves mechanical symptoms (ie, early satiety and pain) in most cases and is often followed by weight gain in cachectic patients, but it is usually not effective against other constitutional symptoms. Improvements in anaemia and thrombocytopenia after splenectomy have been reported in, respectively, 50% and <30% of patients.

Progressive hepatomegaly sometimes follows splenectomy, probably due to the migration of haematopoiesis, and a markedly enlarged liver is a contraindication to splenectomy. Current data concerning an increased rate of leukaemic transformation after spleen removal are still discordant.[44,50] However, given the high complication rate and limited benefit of splenectomy, appropriate patient selection is crucial.[51]

Splenic radiotherapy, on a fractioned basis, at a daily dose of 0.4 to 1 Gy, with weekly evaluation of spleen size and haematologic values until therapeutic effect is achieved or haematologic toxicity develops, can be used to treat MPNs with an adequate platelet count (>50 × 10^9/L), as extramedullary haematopoiesis has proved to be considerably sensitive to external beam radiotherapy in patients with MF. However, it leads to only transient benefits and may exacerbate cytopenia, particularly thrombocytopenia.[50] It also has to be remembered that radiation can also cause local fibrosis with splenic adhesions to surrounding tissues that make a subsequent splenectomy technically more complicated and increase the morbidity and mortality of the procedure.

In general, traditional treatment options are limited and insufficient to address the morbidity and mortality associated with MF. However, as mentioned above, the discovery of

mutations leading to constitutive activation of the *JAK-STAT* signalling pathway raises hope that MF may be cured by selective *JAK1/2* inhibitors, as happens in the case of chronic myeloid leukaemia treated with *BCR-ABL1* tyrosine kinase inhibitors.

Ruxolitinib (Jakavi; Novartis, Basel, Switzerland) was the first *JAK1/2* inhibitor to become commercially available for the treatment of MF.[52] In preclinical *JAK2*V617F-positive MPN mouse models, it induced a considerable downregulation of *JAK*-dependent proinflammatory cytokines, reduced mouse splenomegaly, and showed antiproliferative and proapoptotic activities. It is the only *JAK* inhibitor approved in the United States for the treatment of splenomegaly in subjects with intermediate/high-risk MF and in Europe for the treatment of splenomegaly and/or constitutional symptoms in patients with intermediate-2/high-risk MF.[53]

These approvals were based on the results of 2 phase III randomised studies: COMFORT-I (ruxolitinib vs placebo) and COMFORT-II (ruxolitinib vs best available therapy [BAT]).[54,55] The primary endpoint of both studies was a >35% reduction in spleen volume after 24 (COMFORT-I) or 48 weeks of treatment (COMFORT-II), which was reached by, respectively, 41.7% and 28.5% of the patients treated with ruxolitinib, as against, respectively, 0.7% and 0% of the patients receiving placebo or BAT ($P < .0001$).[54,55] Overall, more than 90% of the patients enrolled in both studies experienced some reduction in spleen volume at some time during the follow-up, and the reduction remained stable in most of the patients after a median follow-up of 3 (COMFORT-I) and 5 years (COMFORT-II).[56,57]

The therapeutic success of ruxolitinib is not limited to reducing spleen volume because, unlike the drugs previously used to treat MF, it is efficacious in relieving constitutional symptoms; reducing abdominal discomfort, appetite loss, itching, fatigue, and night sweats; and improving the QoL of most treated patients. As the drug's activity is independent of *JAK2* mutational status and not specific for the neoplastic clone, the response rate is similar in patients with and without the *JAK2*V617F mutation because of its anti-*JAK1*–mediated effect.

Further studies have investigated the efficacy of ruxolitinib in patients at intermediate-1 risk. The UK, open-label, phase II ROBUST study evaluated its safety and efficacy in patients with MF, including those at intermediate-1 risk. The treatment was successful in 50% of the population as a whole and 57% of the intermediate-1–risk patients. Reduction in spleen length and symptoms was observed in all of the risk groups, and improvements in the Myelofibrosis Symptom Assessment Form Total Symptom Score were seen in 80% of intermediate-1, 72.7% of intermediate-2, and 72.2% of high-risk patients.[58] Similarly, the phase IIIb expanded-access JAK Inhibitor Ruxolitinib in Myelofibrosis Patients (JUMP) trial for patients with MF without access to ruxolitinib outside of a clinical study found that the drug's safety and efficacy profile in intermediate-1–risk patients was consistent with that in the study population as a whole and with that previously reported in intermediate-2–risk and high-risk patients.[59]

The toxicity of ruxolitinib treatment is mainly haematologic due to the drug's interference with an essential pathway for haematopoiesis, as demonstrated in the COMFORT studies; in both trials, thrombocytopenia was the dose-limiting toxicity, and anaemia was the most common haematologic AE.

Another important issue during ruxolitinib treatment is the incidence of infections. A number of studies have shown that ruxolitinib affects many cytokines and interferes with the immune process necessary for the pathogenesis of MPNs, but it also affects the function of various immune cells and may therefore favour an increased incidence of opportunistic and nonopportunistic infections.[60,61] For example, ruxolitinib impairs natural killer cell differentiation and function and inhibits dendritic cell activation and migration, and antigen-specific T-cell responses in a dose-dependent manner in vitro and in vivo. However, despite warnings about this increased risk,[62–64] a recent update of the JUMP study described a low incidence of infections: the all-grade infections observed in ⩾1% of patients included nasopharyngitis (6.3%), urinary tract infection (6%), pneumonia (5.3%), bronchitis (4.2%), herpes zoster (3.6%), influenza (3%), upper respiratory tract infection (2.9%), cystitis (2.5%), gastroenteritis (1.8%), respiratory tract infection (1.8%), and oral herpes (1.6%). Other infections included tuberculosis in 3 patients (0.3%) and *Legionella* pneumonia in 1 patient (0.1%). No hepatitis B reactivation was reported, and only 6 patients (0.5%) discontinued treatment because of grade ⩾3 pneumonia.[59]

The patients receiving ruxolitinib in the COMFORT-II study experienced higher rates of viral and bacterial infection than those receiving conventional therapy, but most of the infections were grade 1 or 2 and did not lead to any dose reductions or the discontinuation of trial medication. Furthermore, the rates of infection tended to decrease with longer exposure to the drug. However, as patients with MF are already predisposed to infections[65] and the long-term risks of ruxolitinib treatment are still unknown, treated 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.

Given its promising results, a further indication for ruxolitinib treatment is as a therapeutic bridge to allo-HSCT. Furthermore, an increasing number of reports appeared in the literature, describing the morphologic changes in the bone marrow occurring in ruxolitinib-treated patients, mostly focusing on modifications in bone marrow fibrosis degree.[66–70]

By the beginning of 2014, a number of other *JAK2* inhibitors were being tested: fedratinib,[71] pacritinib,[72] LY2784544,[73] and momelotinib.[74] However, the clinical trials of fedratinib and pacritinib were soon discontinued because of safety problems: Wernicke encephalopathy (fedratinib) and bleeding (pacritinib).

Momelotinib (formerly known as CYT387) is a small-molecule, adenosine triphosphate–competitive inhibitor of *JAK1* and *JAK2*. Its kinase profiling indicates that it has good selectivity over other *JAK* family kinases (*JAK3, TYK2*) and excellent selectivity over other tyrosine and serine/threonine kinases.[75] The preclinical data provide a rationale for the use of momelotinib in *BCR-ABL1*–negative MPNs, and a multicentre phase I/II trial involving 166 patients with intermediate/high-risk MF showed that the drug is well tolerated at oral doses of 150 or 300 mg once daily or 250 mg twice daily and led to improvements in splenomegaly, constitutional symptoms, and transfusion requirement.[74] Of particular interest are the transfusion independence responses, which were observed in more than half of the RBC transfusion–dependent subjects with a maximum transfusion-free period exceeding 2 years. In addition, the percentage of all subjects requiring RBC transfusions substantially decreased over the treatment period. More precisely, the overall anaemia response rate was 54% in transfusion-dependent patients with a median time to a confirmed anaemia response of 12 weeks (range: 84-293 days). As has been previously reported, treatment with momelotinib led to a rapid and sustained reduction in splenomegaly in approximately 31% of all cases, with a median time to response of 15 days, and the constitutional symptoms of most of the patients disappeared within 6 months. In terms of safety, about 20% of the patients experienced a first-dose effect (dizziness, flushing, and hypotension) that was self-limited. Grade 3/4 haematologic and nonhaematologic AEs were infrequent with the exception of thrombocytopenia, which occurred in approximately 17% of patients. Grade 3/4 nonhaematologic laboratory AEs included hyperlipasaemia (4%) and increased liver enzymes (grade 3 and 4 increase in aspartate aminotransferase in, respectively, 1% and <1% of the patients; a grade 3 increase in alanine aminotransferase in 2%). Mainly, grade 1 treatment–related sensory peripheral neuropathy was reported, but there were no treatment-related deaths.

In brief, momelotinib seems to lead to a significant and lasting improvement in anaemia, splenomegaly, and constitutional symptoms at doses of 150 or 300 mg/day or 150 mg twice daily. The efficacy and AEs of momelotinib will be further evaluated in 2 currently ongoing phase III trials: a randomised BAT-controlled study of MF patients with anaemia and thrombocytopenia previously treated with ruxolitinib and a randomised study comparing momelotinib and ruxolitinib in patients with MF (NCT02101268-NCT01969838).

More recently, the efficacy and safety of 3 dose levels of a potent and selective oral *JAK1* inhibitor, INCB039110, have been evaluated in an open-label phase II study, resulting in clinically meaningful symptom relief, modest spleen volume reduction, and limited myelosuppression.[76] In particular, only 1 patient discontinued for grade 3 thrombocytopenia, whereas nonhaematologic AEs were largely of grade 1 or 2 and most commonly represented by fatigue.

Iron Overload

Nearly 40% of patients with MF are anaemic at the time of diagnosis, including 25% who are already transfusion dependent,[77,78] and more than 60% will develop clinically significant anaemia during the course of follow-up.[49] The clinical impact of IO and its potential relationship to the heightened inflammatory response of patients with MF warrant consideration not only because potential liver dysfunction, cardiac disease, and other complications of IO probably contribute to patient morbidity and mortality but also because the growing evidence of impaired haematopoiesis attributable to bone marrow haemosiderosis suggests a viable therapeutic target.[79,80]

Each unit of RBC contains 200 to 250 mg of iron, and as the reticuloendothelial system can clear approximately 10 to 15 g (corresponding to 50 RBC units), any excess is deposited in tissues and leads to organ damage.[81] Iron overload is a concern when treating patients with MF, which is why iron chelation therapy (ICT) has been used to counteract its potentially negative effects. However, it has to be admitted that there is a lack of prospective, randomised, controlled trials of the use of ICT in patients with MF. One small retrospective study of 10 patients with MF demonstrated an erythroid response in 40% of cases receiving oral ICT with deferasirox (DFX), thus allowing these patients to reduce their transfusion requirement; it also revealed a trend towards better overall survival in the responding patients.[82] Other data coming from a number of reported case studies[79,80,83,84] also indicate that ICT improves anaemia and decreases transfusion dependence in patients with MF. Finally, a recent retrospective, multicentre analysis of 28 patients with MF and IO secondary to transfusion dependence found that 11 patients (42.3%) achieved a stable and consistent reduction in ferritin levels (<1000 ng/mL), and 6 of 26 patients (23%) showed a persistent (>3 months) increase in Hb levels to >1.5 g/dL, with the disappearance of transfusion dependence in 4 cases. However, comparison of the baseline characteristics of the patients who achieved an erythroid response and those who did not achieve did not reveal any significant differences that could be considered predictive.[85]

Deferoxamine (Desferal) is a linear ligand that forms 1:1 complexes with iron that maintain a net charge, allow for membrane permeability, and provide access to intracellular iron stores[86] that are then excreted primarily in urine.[87,88] It is administered in the form of an intravenous or subcutaneous infusion, and because of its short plasma half-life, the efficacy of the treatment correlates with the duration of infusion, and it is only effective if administered at high doses between 5 and 7 times per week.[89] When administered as a continuous 24-hour infusion for 6 to 7 days per week in patients with high-risk β-thalassemia, it can reverse iron-induced cardiac dysfunction and increase long-term survival.[90] However, treatment-related side effects include infusion site discomfort (nearly 100%, with the development of local erythema or induration in some cases),[91] visual changes (0%-10%), generally transient auditory

neurotoxicity (20%-25%),[92,93] increased serum creatinine levels (22%), vomiting (16%), abdominal discomfort (14%), constipation (14%), arthralgia (14%), nausea (11%), rash (5%), and diarrhoea (5%).[94]

Deferasirox is an oral iron chelator frequently used in clinical practice in the United States and Europe that has a long half-life of 8 to 16 hours and can be administered once daily.[89] It forms a 2:1 complex with iron,[95] which is then excreted largely in the bile and faeces (much less in urine).[96,97] Unlike other iron chelators, it is thought that DFX also affects haematopoietic stem cell differentiation by means of a reactive oxygen species–mediated mechanism, which may underlie the erythropoeitic response seen in some DFX-treated patients.[95] The most frequently reported adverse effects are gastrointestinal toxicity (21%-64%), diarrhoea (46%), abdominal pain (15%-28%), nausea (24%), vomiting (21%), and constipation (10%).[94,98–101] Patients have also been reported to experience renal dysfunction (10%-64%, usually nonprogressive at the start of treatment and improving after a dose reduction), skin rash (4%-39%), arthralgia (15%),[94] and transaminitis (4%-70%),[81,98–101] and there have been rarer reports of auditory neurotoxicity (1%-6%) as a potential side effect.[100,101]

It is not entirely clear whether ICT can reverse the ill effects of IO, and there are no completed studies that provide prospective evidence of a beneficial impact in terms of the restoration of normal haematopoiesis or outcomes in patients with MF. Consequently, treatment decisions concerning the use of ICT in patients with MF continue to be extrapolated from the data of myelodysplastic syndromes.

Stem Cell Transplantation

Allogeneic haematopoietic stem cell transplantation is still the only intervention that has been shown to be a potential cure for MF or a means of prolonging the survival of these patients. Data from the most recent studies suggest that the expected 3-year progression-free survival rate is in the range of 40% to 50%.[102]

The adoption of reduced intensity conditioning regimens has recently made allo-HSCT applicable to a larger proportion of patients.[103] However, decisions concerning allo-HSCT are based on inductive reasoning and require a considerable professional experience. Key questions include patient selection, donor selection, pre- and posttransplant management, conditioning regimen, and prevention and management of posttransplant relapses.

International prognostic scoring systems (ie, IPSS, DIPSS, and DIPSS-plus)[20,22,23] are the most comprehensive means of risk stratification currently available to guide therapeutic decision making, although the influence of driver mutations and the acquisition of additional mutations during the natural course of the disease may further refine this process. All patients with MF aged <70 years with IPSS, DIPSS, or DIPSS-plus intermediate-2–risk or high-risk disease and a reasonable performance status, and without any significant competing comorbid conditions, should be considered potential candidates for allo-HSCT. Patients aged <65 years with intermediate-1–risk disease should only be considered candidates if they present with refractory, transfusion-dependent anaemia or >2% of peripheral blood blasts, or adverse cytogenetics (as defined by the DIPSS-plus classification). Finally, patients with low-risk disease should not undergo allo-HSCT.[104]

Individual transplant-specific prognostic factors should be considered in every candidate for allo-HSCT to be able to make individualised decisions. In this context, the transplant-specific high-risk factors include a spleen extending more than 22 cm below the costal margin, having been transfused with more than 20 RBC units, having received a transplantation from an HLA nonidentical donor, a poor performance status (an Eastern Cooperative Oncology Group status of >2), a high comorbidity index (a haematopoietic cell transplantation comorbidity index score of >3), and the presence of portal hypertension.

Completely matched rather than mismatched donors should be selected because, as reported in the European Blood and Marrow Transplantation registry, the cumulative incidence of nonrelapsed mortality after 1 year is, respectively, 12% and 38% and is not different between HLA-identical siblings and 10/10 matched unrelated donors (10% vs 13%).[105] However, haploidentical related donors are an attractive alternative source of haematopoietic stem cells.[106]

It is important to note that peripheral blood is considered the most appropriate source of haematopoietic stem cells in the case of HLA-matched sibling and unrelated donors.

When splenectomy is performed before allo-HSCT, it may facilitate disease eradication. Some reports have also shown faster engraftment in splenectomised patients; however, the pretransplant use of splenectomy remains controversial as no study has yet prospectively evaluated the effect of protocol-based splenectomy before transplantation.

In the case of older patients and/or those with comorbidities, a less intense conditioning regimen is more appropriate, whereas patients with advanced disease and a good performance status should undergo a more intensified regimen.[104]

Finally, in patients relapsing with constitutional symptoms or splenomegaly, *JAK1/2* inhibitor treatment is recommended but remains experimental. To address this question, ruxolitinib is being administered to eligible patients with MF for 60 days before definitive allo-HSCT in a prospective multicentre phase II study conducted by the Myeloproliferative Disorders Research Consortium (NCT01790295).

Conclusions

Traditional MF treatments are primarily palliative and have proved to be inadequate to address the considerable morbidity and mortality associated with this disabling disease. More specifically, concerning anaemia, there have been various

therapeutic attempts, but RBC transfusions still remain the most frequently used approach, even though IO represents an increasingly frequent clinical challenge. Considering instead splenomegaly, besides HU, ruxolitinib, as well as other investigational *JAK1/2* inhibitors, offers new hope for these patients as they have been shown to lead not only to significant reduction in splenomegaly but also to the palliation of disease-related symptoms. However, allo-HSCT is still the only intervention that has evidence indicating it is potentially curative. Obviously, in such a context, participation into a clinical trial should be encouraged whenever possible, with the purpose of making new drugs available.

Author Contributions

AI and DC revised the literature and wrote the manuscript. AI revised and approved the final version of the manuscript.

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