

# Myelofibrosis-associated complications: pathogenesis, clinical manifestations, and effects on outcomes

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**Abstract:** Myelofibrosis (MF) is a rare chronic *BCR-ABL1* (breakpoint cluster region-Abelson murine leukemia viral oncogene homologue 1)-negative myeloproliferative neoplasm characterized by progressive bone marrow fibrosis, inefficient hematopoiesis, and shortened survival. The clinical manifestations of MF include splenomegaly, consequent to extramedullary hematopoiesis, cytopenias, and an array of potentially debilitating abdominal and constitutional symptoms. Dysregulated Janus kinase (JAK)-signal transducer and activator of transcription signaling underlies secondary disease-associated effects in MF, such as myeloproliferation, bone marrow fibrosis, constitutional symptoms, and cachexia. Common fatal complications of MF include transformation to acute leukemia, thrombohemorrhagic events, organ failure, and infections. Potential complications from hepatosplenomegaly include portal hypertension and variceal bleeding, whereas extramedullary hematopoiesis outside the spleen and liver – depending on the affected organ – may result in intracranial hypertension, spinal cord compression, pulmonary hypertension, pleural effusions, lymphadenopathy, skin lesions, and/or exacerbation of abdominal symptoms. Although allogeneic stem cell transplantation is the only potentially curative therapy, it is suitable for few patients. The JAK1/JAK2 inhibitor ruxolitinib is effective in improving splenomegaly, MF-related symptoms, and quality-of-life measures. Emerging evidence that ruxolitinib may be associated with a survival benefit in intermediate- or high-risk MF suggests the possibility of a disease-modifying effect. Consequently, ruxolitinib could provide a treatment backbone to which other (conventional and novel) therapies may be added for the prevention and effective management of specific MF-associated complications.

**Keywords:** extramedullary hematopoiesis, JAK inhibitor, myelofibrosis, myeloproliferative neoplasm, ruxolitinib

## Introduction

Myelofibrosis (MF) is a chronic *BCR-ABL1* (breakpoint cluster region-Abelson murine leukemia viral oncogene homologue 1)-negative stem cell myeloproliferative neoplasm (MPN) characterized by bone marrow fibrosis, ineffective hematopoiesis, extramedullary hematopoiesis (EMH), splenomegaly, shortened survival and progressive abdominal and constitutional symptoms, as well as other general chronic debilitating complaints.<sup>1,2</sup> The MF-associated consequences and medical complications often result in premature death from infection, thrombohemorrhagic events, cardiac or pulmonary failure, and leukemic transformation.<sup>3,4</sup> MF is an uncommon malignancy. Recent estimates of MF prevalence in the USA range from 3.6 to 5.7 per 100,000 persons, whereas estimates of MF incidence range from 1.7 to 2.4 per 100,000 persons.<sup>5</sup>

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Although the etiology of MF is unknown, environmental factors may well be relevant since MF has been linked in a small number of patients to radiation and exposure to petrochemicals such as benzene and toluene.<sup>6–8</sup> MF can be primary (termed “primary myelofibrosis” [PMF]; formerly termed “idiopathic MF,” “agnogenic myeloid metaplasia,” or “myeloid metaplasia with MF”) or secondary, developing from polycythemia vera (PV; currently termed “post-PV MF” [PPV-MF]) or essential thrombocythemia (ET; currently termed “post-ET MF”).<sup>9</sup> The past decade has witnessed considerable progress in the understanding of the cellular and molecular biology of MPNs, and this has recently resulted in the addition of the Janus kinase (JAK) 1 and JAK2 inhibitor ruxolitinib to our therapeutic armamentarium.<sup>10</sup> Ruxolitinib is highly effective in the clinical management of patients with intermediate- or high-risk MF, particularly in those with disease-related symptoms and splenomegaly.<sup>11–13</sup> Importantly, recent updates from two prospective, randomized, Phase III studies showed that patients with MF treated with ruxolitinib had improved survival over placebo and best available therapy, suggesting an overall survival benefit.<sup>14,15</sup> However, the overall prognosis for advanced MF remains guarded, owing to a potentially remaining substantive burden of disease-related morbidities. The basis for these morbidities is the emergence of a remarkably broad array of general medical complications associated with this rare – and, until recently, rather therapeutically neglected – malignancy. Some of these complications are directly linked to excessive clonal myeloproliferation (the end result of which is leukemic transformation); however, most MF-associated complications are of more protean nature and deserve a deeper discourse. Here, we discuss some of the important issues related to the diagnosis and management of these complications.

## Definition and pathogenetic features of MF

The current diagnostic criteria for PMF were defined by the World Health Organization in 2008 and are depicted in Table 1.<sup>16</sup> Available evidence indicates that PMF is a bona fide clonal stem cell malignancy.<sup>17</sup> MPNs comprise clonal hematologic diseases that are thought to arise from a transformation of a hematopoietic stem cell. The notion of “clonality” gained popularity in 1974 due to the astute seminal observations of Prchal and Axelrad,<sup>18</sup> and thereafter was confirmed by Fialkow et al,<sup>19,20</sup> as well as various other investigators.<sup>21</sup> Currently, in contrast to our detailed understanding of chronic myeloid leukemia pathogenesis, which is defined by a single causative molecular lesion, the *BCR-ABL1* fusion gene, we

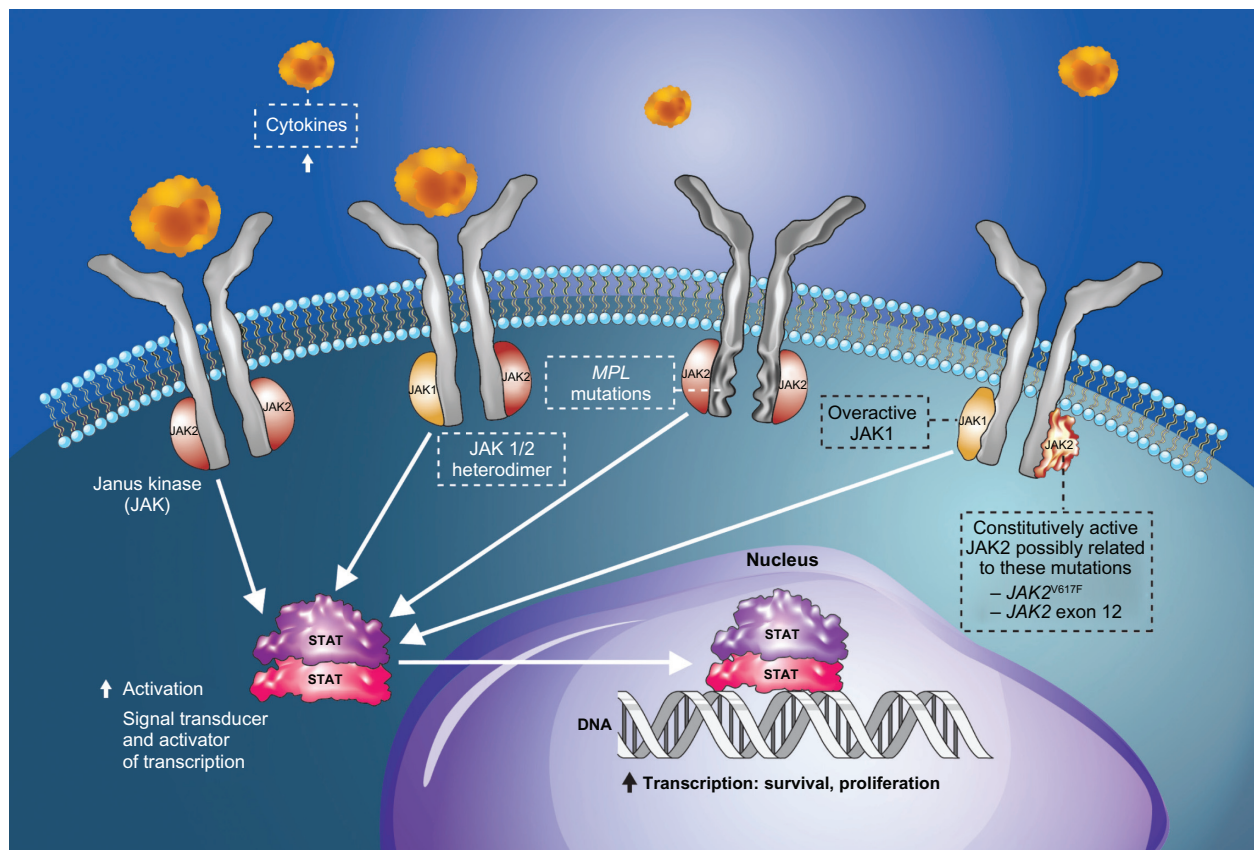
**Table 1** World Health Organization (WHO) diagnostic criteria for primary myelofibrosis (PMF)<sup>16</sup>

Major criteria	<ol style="list-style-type: none"> <li>1. Megakaryocyte proliferation and atypia<sup>a</sup> accompanied by either reticulin and/or collagen fibrosis, or in the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased bone marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis (ie, prefibrotic PMF)</li> <li>2. Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm</li> <li>3. Demonstration of <i>JAK2</i><sup>V617F</sup> or other clonal marker or no evidence of reactive bone marrow fibrosis</li> </ol>
Minor criteria	<ol style="list-style-type: none"> <li>1. Leukoerythroblastosis</li> <li>2. Increased serum LDH</li> <li>3. Anemia</li> <li>4. Palpable splenomegaly</li> </ol>

**Notes:** The diagnosis of PMF requires all three major criteria and two minor criteria to be met. <sup>a</sup>Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering. Adapted with permission of the American Society of Hematology from: The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Vardiman et al. *Blood*, 2009;114(5):937–951. Copyright © 2009. Permission conveyed through Copyright Clearance Center, Inc.

**Abbreviations:** CML, chronic myeloid leukemia; JAK, Janus kinase; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; PV, polycythemia vera.

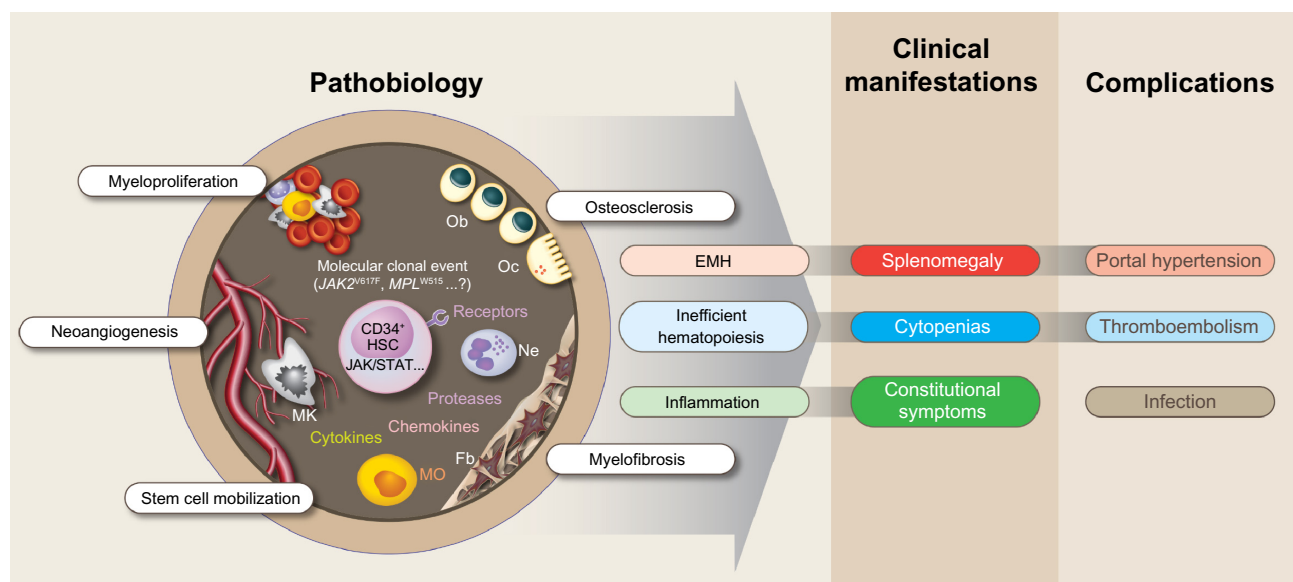
only have some essential clues to the molecular pathogenetic mechanisms for PV, ET, and PMF. A major clue was the recognition of increased signaling through the JAK-signal transducer and activator of transcription (STAT) pathway, comprised of JAKs and STATs, as well as through the phosphatidylinositol 3-kinase (PI3K)-AKT (also known as protein kinase B) pathway in erythroid and myeloid cells.<sup>22–24</sup> The most significant clue to date came in 2005 with the identification of the somatic mutation *JAK2*<sup>V617F</sup>.<sup>25–28</sup> This mutation in *JAK2* exon 14, which occurs in at least 95% of patients with PV and about 60% of those with PMF and ET, results in a valine (V) to phenylalanine (F) substitution at codon 617.<sup>29</sup> This codon is located in the JH2 pseudokinase domain of JAK2, and the mutation is generally considered to negatively affect the JH2-mediated auto-inhibitory functionality of the enzyme, resulting in constitutive activation of the tyrosine kinase function. This in turn results in dysregulation of JAK-dependent signal transduction and activation of multiple downstream effectors, including STAT3 and STAT5.<sup>13,30</sup> Dysregulated JAK-STAT signaling is now recognized as the central mechanism of MF pathobiology<sup>31</sup> beyond aberrant myeloproliferation (Figures 1 and 2). For example, the efficacy of JAK inhibitors appears to play a role, in large part, in the reversal of secondary disease-related phenomena, such as inflammation and cachexia,<sup>11,32</sup> that have no obvious relationship to myeloproliferation but are primary drivers of the MF symptom burden.



**Figure 1** Pathogenic mechanisms in myelofibrosis involving dysregulated JAK-STAT signaling. Mutations affecting cytokine receptor function (eg, *MPL* mutations causing ligand-autonomous activation of the thrombopoietin receptor) or *JAK2* mutations resulting in constitutive *JAK2* activity lead to over-activation of JAK-STAT signaling in hematopoietic stem cells, with consequent myeloproliferation and excess production of proinflammatory cytokines.<sup>108</sup>

**Note:** Reproduced with permission from Incyte Corporation (Wilmington, DE, USA).

**Abbreviations:** JAK, Janus kinase; *MPL*, myeloproliferative leukemia virus oncogene; STAT, signal transducer and activator of transcription.



**Figure 2** Pathobiology, main clinical manifestations, and common complications of myelofibrosis.

**Note:** Adapted with permission of the American Society of Hematology from: Does primary myelofibrosis involve a defective stem cell niche? From concept to evidence, Lataillade et al. *Blood*, 2008; 112(8):3026–3035. Copyright © 2008. Permission conveyed through Copyright Clearance Center, Inc.<sup>17</sup>

**Abbreviations:** CD34, cluster of differentiation 34; EMH, extramedullary hematopoiesis; Fb, fibroblast; HSC, hematopoietic stem cell; JAK, Janus kinase; MK, megakaryocyte; MO, monocyte; *MPL*, myeloproliferative leukemia virus oncogene; Ne, neutrophil; Ob, osteoblast; Oc, osteoclast; STAT, signal transducer and activator of transcription.

Although *JAK2*<sup>V617F</sup> is the most prevalent somatic mutation among patients with MF, a large proportion of patients with MF are *JAK2*<sup>V617F</sup> negative and, even in those who are *JAK2*<sup>V617F</sup> positive, the mutation is unlikely to be the disease-initiating event.<sup>33,34</sup> An increasing number of mutations that directly or indirectly affect JAK-STAT signaling are being implicated in the pathobiology of MPNs, including PMF,<sup>33–35</sup> revealing an unexpected genetic and epigenetic complexity of these neoplasms.<sup>29,36</sup> Notably, findings of multiple mutations in the same patient<sup>33</sup> are consistent with the notion that MPNs are multiclonal diseases with as yet poorly understood clonal hierarchies.<sup>37–39</sup>

In 2006, mutations in exon 10 of the thrombopoietin receptor gene *MPL* (myeloproliferative leukemia virus oncogene) were noted in some patients with *JAK2*<sup>V617F</sup>-negative MPNs,<sup>40</sup> and further work confirmed their pathogenicity.<sup>33</sup> In 2007, mutations within exon 12 of *JAK2* were also described in some patients with *JAK2*<sup>V617F</sup>-negative MPNs, but the precise role in the pathogenicity of MPNs remains enigmatic.<sup>41,42</sup> To date, mutations in at least 12 genes have been described that can be involved in MPN pathogenesis.<sup>43</sup> In addition, recent work has established the important contribution of STAT5 to the molecular pathogenesis of MPNs,<sup>44</sup> confirming the central role of the STAT family of phosphorylation-regulatable nuclear transcription factors in the induction and sustenance of excessive proliferation of clonal myeloid progenitor cells in these neoplasms, including MF. Clearly, much has been learned about the molecular biology of MPNs, but the precise causative (“initiator” culprit) lesion remains, for the moment, an enigma.<sup>34,45</sup>

## Natural history of MF

The evolution of bone marrow fibrosis, a cardinal feature of MF, is poorly understood. It is thought to represent a polyclonal reaction to several cytokines, particularly transforming growth factor- $\beta$ , basic fibroblast growth factor, epidermal growth factor, platelet-derived growth factor, vascular endothelial growth factor, and calmodulin.<sup>46</sup> These moieties are mostly locally produced from the malignant clone throughout its various stages of aberrant differentiation (megakaryocytes, monocytes, or both).<sup>47</sup> The effects of these growth factors are mainly para- and autocrine; however, in advanced MF, as well as advanced PV and ET, progression of fibrosis appears to involve increasingly altered crosstalk between hematopoietic and stromal cells, resulting in the liberation of fibrogenic cytokines and the escape of malignant stem cells in the circulation with consequent EMH.<sup>48,49</sup> Efforts are underway to thoroughly

study other candidate factors involved in the development of fibrosis in patients with MPNs. Results of a recent study suggest that the risk of patients with PV developing PPV-MF is increased significantly by high (>50%) *JAK2*<sup>V617F</sup> allele burden.<sup>50</sup>

Results of a recent study suggest that the bone marrow fibrosis grade (determined according to the European consensus on grading bone marrow fibrosis)<sup>51</sup> may have prognostic value in patients with PMF,<sup>52</sup> and thus may deserve attention during a patient’s risk assessment when allogeneic hematopoietic stem cell transplantation (allo-SCT) is considered. However, although allo-SCT may provide rapid regression of bone marrow fibrosis in some patients<sup>53</sup> and at present is the only potentially curative therapy,<sup>54</sup> it is also associated with high risks of relapse, morbidity, and mortality.<sup>55–57</sup>

Transformation into secondary acute leukemia occurs in a small minority of patients with MPNs; it typically involves the myeloid lineages (secondary acute myeloid leukemia [sAML]) but, rarely, lymphoid transformation (secondary acute lymphoid leukemia) also may occur. Patients who develop acute leukemia have a median survival time of less than 3 months.<sup>58</sup> Leukemic transformation is rare in patients with non-fibrotic MPNs<sup>59</sup> but common in patients with MF.<sup>3,58,60</sup> The 10-year risk of leukemic transformation for patients with PMF has been estimated at 12%–31%, depending on the presence of thrombocytopenia and/or unfavorable karyotype.<sup>61</sup> A peripheral blood blasts count of  $\geq 2\%$  has been identified as an independent predictor of poor leukemia-free survival.<sup>62</sup> The pathogenetic events leading to leukemic transformation are poorly understood, but the presence of *IDH* (isocitrate dehydrogenase) mutations has been shown to be a significant independent prognostic factor of leukemic transformation.<sup>35</sup> In contrast, the presence of *JAK2*<sup>V617F</sup> is not essential for nor prognostic of leukemic transformation,<sup>63,64</sup> with various case reports indicating that *JAK2*<sup>V617F</sup> allele burden may diminish or completely disappear during leukemic transformation of *JAK2*<sup>V617F</sup>-positive chronic-phase MF.<sup>63,65–67</sup> It has been shown that exposure to select cytoreductive agents may increase the risk of leukemic transformation, possibly by causing additional genetic and/or epigenetic lesions.<sup>68,69</sup>

## Clinical presentation and complications of MF

The median age of patients with MF at the time of diagnosis is approximately 65 years.<sup>3,60</sup> In the USA, MF appears to affect slightly more men than women.<sup>60</sup> Until recently, it was estimated that up to 21% of all patients with MF are



asymptomatic at the time of diagnosis, which is often made by the determination of an abnormal blood count, usually indicating anemia, or an abnormal peripheral blood smear demonstrating leukoerythroblastosis, or after a routine physical examination revealing splenomegaly and sometimes hepatomegaly.<sup>70</sup> However, the results of recently published, Internet-based symptom surveys among patients with MPNs showed that the great majority (ie, more than 80%) of patients with MF experienced at least one disease-related symptom at the time of the survey.<sup>71,72</sup> The most common presenting symptoms are constitutional symptoms and the consequences of ineffective hematopoiesis.<sup>2,73</sup> Fatigue is extremely common; it is often relentless, chronic, and profoundly debilitating, and is also seen in patients who do not have anemia.<sup>71</sup>

Constitutional symptoms, including fever, night sweats, pruritus, and weight loss, are thought to result from the abnormal production of cytokines.<sup>13</sup> Such symptoms not only tend to have a negative impact on a patient's quality of life (QOL)<sup>71</sup> but also have been firmly associated with a poor prognosis for overall survival.<sup>3</sup> Both hepatomegaly and splenomegaly are considered fundamentally characteristic of MF and to be largely, although not exclusively, due to EMH. Splenomegaly may result from splenic sequestration of immature myeloid cells or other ill-defined mechanisms. Indeed, palpable splenomegaly (of any degree, from merely palpable to massive) has been noted in more than 80% of non-selected patients with MF<sup>3</sup> and can lead to a range of physical complaints, including generalized abdominal discomfort, left upper quadrant/subcostal pain, and early satiety. As splenomegaly worsens, it is not uncommon to witness patients developing severe generalized abdominal pain and sometimes an "acute abdomen"-like clinical picture; some patients may also experience splenic infarcts.<sup>74</sup>

Progressive bone marrow fibrosis leads to a "myelophthitic" phenotype with worsening cytopenias, particularly thrombocytopenia and anemia.<sup>70,75,76</sup> The latter typically results in fatigue, weakness, palpitations, compensatory tachycardia, bone pain, and dyspnea (either exertional or at rest), and may lead to (or exacerbate) symptoms of tissue hypoxia in patients with vasculopathies, such as atherosclerotic cardio-, cerebro-, and renovascular disease, or in those with pre-existing heart failure (combination of hypoxxygenation and hypoperfusion).<sup>77</sup> Anemia also can negatively affect pulmonary function parameters in patients with various pre-existing lung diseases.<sup>78</sup> The above considerations are clinically meaningful and important because patients with MF tend to have significant general medical comorbidities owing to their (on average) advanced age. The consequences

of thrombocytopenia, which may include bleeding of any grade/severity, can be compounded by acquired platelet dysfunction and sometimes a state of low-grade disseminated intravascular coagulation, resulting occasionally in a complex thrombohemorrhagic picture.<sup>79</sup> These latter manifestations may be catastrophic and are potentially life-threatening, particularly in the presence of portal hypertension. Moreover, MF is associated with an increased susceptibility to infections (viral, bacterial, and atypical),<sup>70,76</sup> even if there is no evidence of frank leukopenia/neutropenia.<sup>80</sup>

Hepatomegaly, which in various studies has been observed in 39%–65% of patients with MF at diagnosis,<sup>3,4,76</sup> may result in abnormal liver function tests, coagulopathy, and increased abdominal complaints.<sup>81</sup> MF is the most common cause of massive splenomegaly<sup>82</sup> and, with increased hepatic blood flow (or intrahepatic venous obstruction/stasis), marked splenomegaly may result in portal hypertension.<sup>83</sup> This complication is noted in about 7% of patients with MF<sup>84</sup> and may present with ascites and esophageal or gastric varices; bleeding in these varices may lead to catastrophic hemorrhage. Splanchnic (portal, mesenteric, or splenic) vein thrombosis and associated complications (eg, Budd–Chiari syndrome) also may occur in MF, although they do so less often in MF than in PV or ET.<sup>85</sup> Interestingly, although hyperplasia of Kupffer cells has been detected in MF, neither hepatic stellate cell activation nor hepatic parenchymal fibrosis are features of this malignancy.<sup>86</sup> In addition, EMH can result in a wide range of complications other than hepatosplenomegaly, depending on the specific organ involved, with potentially life-threatening consequences. EMH affecting the central nervous system may lead to intracranial hypertension, which in turn may result in chronic headaches, delirium, photophobia, papilledema, gait instability, alterations in the level of consciousness and, rarely, coma, paralysis, and/or death. In cases in which EMH develops in a paraspinal location, spinal cord compression may ensue, occasionally presenting as acute cord or spinal root/nerve compression syndrome.<sup>87</sup> Involvement of lymph nodes by this process can lead to generalized lymphadenopathy and, in advanced cases, lymphoceles. Pleural infiltration by EMH may result in pleural effusions and hemothorax.<sup>88</sup>

EMH in the gastrointestinal tract manifests itself as exacerbation of already existing abdominal pain and/or intestinal lumen obstruction. Rarely, obstructive uropathy may result from EMH infiltration of the kidneys, ureters, and the bladder neck,<sup>84</sup> which may lead to renal failure. Other very rare secondary complications of EMH include gastric outlet obstruction, bile duct obstruction, acalculous cholecystitis

from gallbladder infiltration, arthritis from synovial involvement, and renal colic from intrarenal or intra- or periureteric obstruction. Skin manifestations of EMH are quite rare and may include erythematous plaques, nodules, ulcers, bullae, myeloid leukemic-like infiltrates, and even neutrophilic dermatosis (Sweet's syndrome).<sup>87,89</sup> The risk of thromboembolic events in patients with MF (particularly PMF) appears to be considerably lower than that in patients with PV or ET. Nonetheless, cardiovascular, thromboembolic, and hemorrhagic complications are common in patients with MF,<sup>70,76</sup> and several investigators reported thrombohemorrhagic events to be among the principal causes of death in patients with MF.<sup>3,4</sup> The risk of leukemic transformation (mainly to sAML) appears to increase with time, and patients with sAML have a grim prognosis.<sup>58,61</sup> Very seldom, leukemic transformation can present with granulocytic sarcomas (also known as "chloromas" in the earlier literature) at any anatomical site.<sup>90,91</sup>

## Prognosis and MF-associated complications

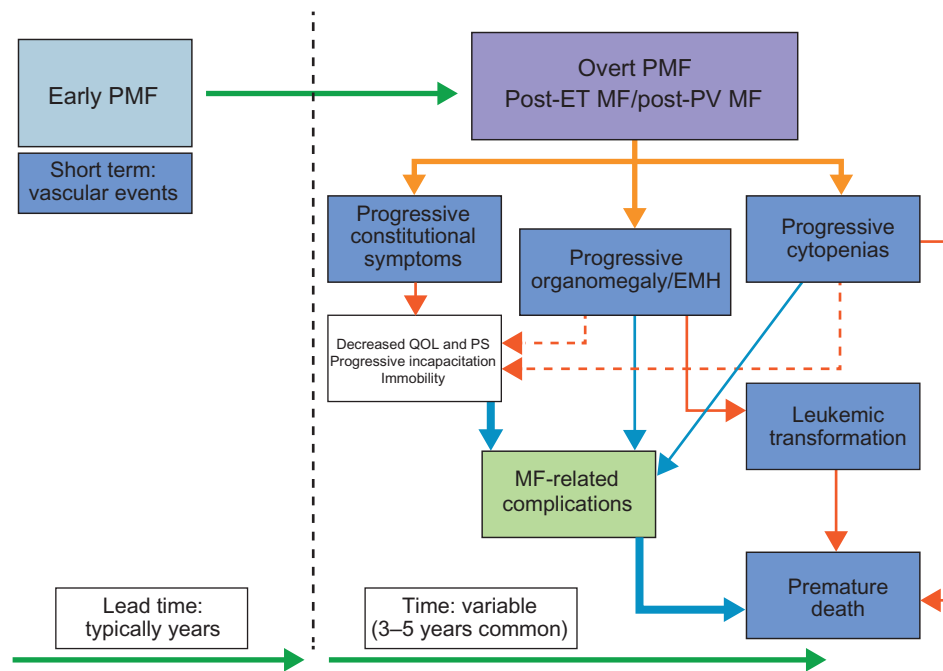
MF is clearly associated with substantial and increasingly burdensome morbidity, which has a very significant negative impact on patients' QOL and is associated with a substantial long-term risk (which increases over time) of developing potentially life-threatening complications. Because the median age of patients with MF is around 65 years at diagnosis, disease-associated complications are often compounded by concurring medical conditions such as diabetes, hypertension, atherosclerotic or pulmonary disease, and obesity. Current estimates suggest an overall survival of about 5 years for patients with intermediate-risk disease, and less than 2 years for those with high-risk disease.<sup>61</sup> Some patients, in particular those with low-risk disease, may survive for longer periods, but as the disease progresses, they often experience relentlessly progressive debilitating symptoms, inexorably worsening QOL, and increasing disability. Therefore, it is prudent to assess individual patients carefully and devise a treatment plan commensurate with each individual patient's risk stratification and symptoms. The only treatment that can accord long-term remission and possible cure is allo-SCT. This treatment is available to a small minority (around 3%) of eligible patients with MF and carries significant risks and complications.<sup>54,74</sup>

Over the past two decades, efforts have been made to identify clinical and laboratory parameters that are independently associated with prognosis in MF.<sup>3,4,61</sup> The principal candidate prognostic parameters have been age at diagnosis, constitutional symptoms, abnormal karyotype,

anemia, thrombocytopenia, low reticulocyte count, peripheral blood CD (cluster of differentiation) 34<sup>+</sup> progenitor cells, monocytosis, and peripheral blood blasts. Interestingly, the presence of hepatosplenomegaly has not been included in these prognostication systems. The most widely accepted prognostic scale so far is based on the 2009 International Working Group for Myelofibrosis Research and Treatment initiative and is known as the "International Prognostic Scoring System" (IPSS).<sup>3</sup> The IPSS validated the following parameters at diagnosis to be associated with a worse prognosis: age >65 years, presence of constitutional symptoms, hemoglobin <10 g/dL, leukocyte count >25 × 10<sup>9</sup>/L, and ≥1% circulating blasts.<sup>3</sup> Compared with the IPSS, the Dynamic International Prognostic Scoring System gives more prognostic weight to the presence of disease-related anemia and is valid not only at diagnosis but at any time during disease progression.<sup>4</sup> Recent efforts have established the additional value of abnormal karyotype as an independent negative prognostic factor for overall and leukemia-free survival.<sup>61</sup> Conversely, patients with a normal karyotype seem to have a very low risk of transformation to acute leukemia. Nonetheless, even for these patients, substantial residual risk of shortened overall survival remains, suggesting that multiple and diverse clinical events (other than leukemic transformation) contribute to the morbidity and, indeed, the mortality associated with MF. Some of the mechanisms responsible for the emergence of complications in patients with MF (as delineated here) are summarized in Figure 3.

## Management of MF-associated complications

Until recently, best available pharmacotherapy for MF consisted of the use of conventional agents that generally had limited and non-lasting efficacy and were often poorly tolerated, including cytoreductive agents such as hydroxyurea (hydroxycarbamide), and immunomodulatory agents.<sup>92</sup> Thus, treatment of MF was essentially palliative, without durably effective options for the alleviation of major clinical manifestations such as splenomegaly and MF-associated symptoms. The discovery of the essential role of dysregulated JAK-STAT signaling in the pathobiology of MF led to the development of JAK inhibitors as novel targeted therapies. The recent approval of ruxolitinib in MF in many countries – including the USA, where it is approved for the treatment of intermediate- or high-risk MF – is a validation of JAK inhibitor therapy in MF and a milestone in the development of targeted therapies for this disease. In light of the complexity of MF pathogenetics, experimental therapies targeting additional disease mechanisms are likely to have future roles



**Figure 3** Mechanisms of the emergence of complications in patients with myelofibrosis (MF).

**Note:** Patients with major clinical manifestations of MF (EMH, constitutional symptoms, and/or cytopenias) typically die prematurely from secondary acute leukemia or bone marrow failure as a consequence of disease progression (symbolized by blue boxes and orange arrows), or from an array of potential disease-related complications (green box, blue arrows), such as infections, thrombohemorrhagic events, or organ failure. Progressive constitutional symptoms have (solid dark orange arrows) and other clinical manifestations may have (dashed dark orange arrows) a strong negative effect on QOL and PS.

**Abbreviations:** EMH, extramedullary hematopoiesis; ET, essential thrombocythemia; PMF, primary myelofibrosis; PS, performance status; PV, polycythemia vera; QOL, quality of life.

in MF disease management.<sup>92</sup> Table 2 is a summary of current management options for MF-associated complications that highlights the benefits of JAK-targeted therapy.

Ruxolitinib is currently the only approved treatment for patients with MF that has been shown in pivotal randomized clinical trials to be highly effective in alleviating symptom burden and splenomegaly.<sup>11,12</sup> In addition, ruxolitinib has been shown to reduce hepatomegaly in patients with prior splenectomy,<sup>93</sup> to mitigate cachexia-related weight loss and hypocholesterolemia in MF,<sup>32</sup> and to reduce the levels of cytokines driving systemic inflammation in this malignancy.<sup>11,13</sup> Preliminary data for experimental therapies suggest that a number of JAK inhibitors currently in development also have the capacity to reduce splenomegaly.<sup>94–96</sup> Although hydroxyurea may reduce splenomegaly in some patients with mostly non-massive splenomegaly, its benefit is usually of short duration and tolerability is poor.<sup>97</sup> Results of a randomized Phase III study showed that best available therapy, including the use of hydroxyurea in 47% of the patients, was significantly less effective than ruxolitinib in reducing MF-associated splenomegaly or improving several cardinal indices of health-related QOL.<sup>12</sup> Splenectomy is an option for patients with refractory symptomatic splenomegaly and/or portal hypertension but should only be considered if the qualifying patient has an adequate life

expectancy.<sup>98</sup> Palliative splenic irradiation may be indicated for patients with highly symptomatic splenomegaly and adequate platelet count; however, the benefits are usually transient and, in some cases, profound and prolonged cytopenias may develop.<sup>98</sup>

Currently available therapies have no or limited efficacy in the treatment of MF-related anemia. Thus, management of anemia largely depends on supportive care and the use of androgens or erythropoietin-stimulating agents. Immunomodulators, such as thalidomide and lenalidomide, may be effective in select patients but are generally poorly tolerated in the long term. A recent study of pomalidomide in patients with MF and significant anemia found that dosing was severely limited by tolerability, and treatment at tolerable doses was only moderately effective.<sup>99</sup> In addition, the manufacturer of pomalidomide recently announced in a press release that a Phase-3 double-blind, placebo-controlled study of pomalidomide in persons with myeloproliferative-neoplasm-associated myelofibrosis and red blood cell (RBC)-transfusion-dependence myelofibrosis and RBC-transfusion-dependence (RESUME)<sup>100</sup> did not meet its primary end point.<sup>101</sup> JAK inhibitors, with the possible exception of CYT387,<sup>96</sup> appear to have no beneficial effect on MF-related anemia, and, currently, no therapies in development clearly demonstrate efficacy in mitigating MF-related thrombocytopenia. Treatment of additional complications of MF,

**Table 2** Management of complications associated with myelofibrosis (MF)

Complication	General supportive care	"Best available" anti-MF therapy addressing a given complication	Specific treatment for complication	Novel anti-MF therapy with targeted agents
EMH: splenomegaly Hepatomegaly	Pain control (as needed)	Hydroxyurea (rarely, cladribine has been considered)	Splenectomy Splenic radiotherapy	JAK inhibitor (may decrease spleen/liver volume of EMH tissue)
Anemia	RBC transfusions Dyspnea symptomatic relief (eg, oxygen therapy) Hypo-oxygenation/hypoperfusion symptomatic relief (eg, nitrates for angina, anti-CHF Rx for cardiac failure, etc) Control of active bleeding Platelet transfusions	Immunomodulators (IMiDs)	Androgens ESAs	JAK inhibitor: If ruxolitinib therapy is being considered or has been initiated: → Individualization of choice of initial dose, aggressive Hb level follow-up, and subsequent dose modification If a JAK inhibitor other than ruxolitinib is being administered in a clinical study setting: Dose modification as per study protocol JAK inhibitor: If ruxolitinib therapy is being considered or has been initiated: → Individualization of choice of initial dose, aggressive platelet count follow-up, and subsequent dose modification If a JAK inhibitor other than ruxolitinib is being administered in a clinical study setting: Dose modification as per study protocol N/A
Thrombocytopenia		Immunomodulators (IMiDs) (possibly helpful therapy in select circumstances)	N/A	
Thrombohemorrhagic complications	Pain control (as needed) Appropriate levels of ambulation (eg, after DVT)	N/A	Aspirin ± clopidogrel (or other P2Y12 inhibitors) Heparin and heparinoids (arterial thrombosis) Warfarin; heparin (VTE) Stent placement as needed CAD/CVD/PAD care Embolectomy DIC-directed measures (eg, FFP administration; as needed) Specific (pathogen-directed) anti-infectives Abscess evacuation N/A	
Infections	Antipyretics (as needed) Systemic infection General medical care NSAIDs	N/A		N/A
Inflammation	Corticosteroids Antipyretics (as needed) Nutritional supplementation (hyper-alimentation) Multivitamins	N/A		JAK inhibitor: May reduce levels of proinflammatory cytokines and acute-phase reactants JAK inhibitor: May improve the profound catabolic state, may reverse hypocholesterolemia
Cachexia/sarcopenia (muscle loss)/general debilitation		N/A	Orexigens (eg, megestrol, mirtazapine, or cannabinoids)	



Portal hypertension	Ascites care	Splenectomy	Portosystemic shunt	JAK inhibitor:
Leukemic transformation (secondary AML)	Abdominal pain/distension control Acute leukemia general medical care	Radiotherapy N/A	Local GI care for varices Cytarabine (Ara-C) plus anthracycline combination Decitabine Allogeneic SCT	May decrease spleen volume/intrasplenic/portal pressure N/A

**Abbreviations:** AML, acute myeloid leukemia; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cerebrovascular disease; DIC, disseminated intravascular coagulation; DVT, deep venous thrombosis; EMH, extramedullary hematopoiesis; ESAs, erythropoiesis-stimulating agents; FFP, fresh frozen plasma; GI, gastrointestinal; Hb, hemoglobin; IMiDs, immunomodulatory drugs; JAK, Janus kinase; MF, myelofibrosis; N/A, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; PAD, peripheral arterial disease; RBC, red blood cell; Rx, prescription; SCT, (hematopoietic) stem cell transplantation; VTE, venous thromboembolism.

such as thrombosis, bleeding, portal hypertension, infections, chronic inflammation, and sAML consists mostly of supportive care and/or palliative therapies that are specific for the type of complication.

Because of the essential role of JAK2-STAT signaling in definitive hematopoiesis, decreases in blood cell counts are an expected effect of JAK2 inhibition. Thus, thrombocytopenia, and to a lesser extent anemia, are the most common adverse events associated with ruxolitinib therapy. However, the frequency and severity of these treatment-related cytopenias can be reduced by careful individual patient management. Consequently, the rates of grade 3 and 4 events of thrombocytopenia or anemia tend to be highest within the first 8–12 weeks of therapy,<sup>11</sup> and, in the two Phase III studies, cytopenias were rarely a cause for discontinuation of ruxolitinib therapy.<sup>11,12</sup> Effective management of ruxolitinib-related thrombocytopenia requires initial dose titration, monitoring of platelet counts, and appropriate dose adjustments based on serially tested platelet counts.<sup>10</sup> Treatment-related decreases in hemoglobin level usually occur within the first 8–12 weeks after treatment initiation. However, hemoglobin levels generally recover with appropriate dose modifications and/or the use of RBC transfusions, on average returning to near baseline values by week 24 of therapy.<sup>11</sup>

## Conclusion

Many efforts since the seminal description of the mutations affecting JAK2 and the enhanced understanding of the universal presence of a dysregulated JAK-STAT signaling pathway in MF (even in the absence of a JAK2 mutation) have led to a wide array of therapeutic agents being studied clinically in this malignancy, ranging from adenosine triphosphate-competitive inhibitors of JAKs (eg, ruxolitinib) to immunomodulatory agents (eg, lenalidomide) and other novel approaches.<sup>92</sup> Current experience confirms the notion that treating patients with intermediate- and high-risk MF (either primary or secondary) with the JAK1 and JAK2 inhibitor ruxolitinib has an overall favorable benefit–risk profile. Robust clinical trial data<sup>11–13</sup> have led to the drug receiving regulatory approval in health authorities in many countries, including the USA,<sup>10</sup> Canada,<sup>102</sup> and the European Union.<sup>103</sup> The drug has a notable clinical impact on the management of patients with intermediate- or high-risk MF, with the majority achieving durable symptomatic responses and reduction of splenomegaly. Moreover, recent updates from two prospective, randomized, Phase III studies showed that patients with MF treated with ruxolitinib had improved survival over placebo (Controlled MyeloFibrosis study with ORal JAK inhibitor

Treatment: The COMFORT-I Trial [COMFORT-I])<sup>14,104</sup> and best available therapy (CONtrolled MyeloFibrosis study with ORal Janus-associated kinase [JAK] inhibitor Treatment-II: The COMFORT-II Trial [COMFORT-II]),<sup>15,105</sup> suggesting an overall survival benefit. The median follow-up period for data reported to date remains relatively short for either trial (approximately 2 years), and there are indeed numerous challenges, both clinical and scientific, that need further elucidation, including the precise mode of action of ruxolitinib in this malignancy.

Interestingly, recent data from an exploratory analysis of bone marrow trephine biopsies in patients with MF treated at the MD Anderson Cancer Center who participated in the Phase I/II trial of ruxolitinib<sup>10,106</sup> raise the possibility that JAK inhibitor therapy with ruxolitinib for a minimum of 2 years may retard the progression of bone marrow fibrosis in some patients.<sup>107</sup> Long-term hydroxyurea therapy had no comparable benefit in a European cohort of patients with MF. Data from randomized controlled studies are needed to substantiate a positive effect of ruxolitinib therapy on bone marrow fibrosis.

In conclusion, given the clinical efficacy and safety profile of ruxolitinib treatment in intermediate- and high-risk MF and with several other candidate agents of the same class currently under development,<sup>92</sup> the focus of the treating clinician should now be the prompt identification and effective preventive management of MF-associated complications.

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