Tjasa Owen. *Barn & the Studio.* Acrylic on canvas, 24″ × 36″.

As the understanding of the pathophysiology of myelofibrosis evolves, so does the development of novel therapies such as JAK inhibitors.

Advances in the Management of Myelofibrosis

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Background: Myelofibrosis (MF) is a rare and serious hematologic malignancy classified as a Philadelphia chromosome-negative myeloproliferative neoplasm (MPN). The disease is more common in males and in older individuals. Of the MPNs, MF presents with the most severe morbidity and greatest mortality. Although the cause of MF is unknown, it is thought to occur from acquired mutations that target the hematopoietic stem cell.

Methods: We reviewed the current literature pertaining to the pathophysiology, clinical presentation, diagnosis, risk stratification, and treatment of MF. The strengths and limitations of present treatment options as well as the emerging clinical experience with Janus kinase 2 (JAK2) inhibitors are explored.

Results: Diagnosis is often one of exclusion and is facilitated using the World Health Organization or International Working Group for Myelofibrosis Research and Treatment criteria, depending on whether primary or secondary MF is suspected. Treatment is complicated by a lack of disease familiarity of general practitioners and the advanced age of presenting patients. Although allogeneic stem cell transplant offers a potential cure, most treatments for this condition are limited to symptomatic management, with little to no effect on survival. Appropriate patient assessment and risk stratification are essential for predicting outcomes and allowing treating physicians to tailor therapy accordingly.

Conclusions: Significant advances have been made in understanding the pathophysiology of MF, leading to novel therapeutic approaches. The discovery of the JAK2 mutation and the development of JAK2 inhibitors provide clinicians with a new effective treatment option. Ruxolitinib is the first JAK1/2 inhibitor approved by the Food and Drug Administration (FDA) for the treatment of patients with intermediate- or high-risk MF. In clinical studies, ruxolitinib produced a significantly greater reduction in spleen size and improved quality of life compared with placebo or best available therapy. Several future therapies, including combination therapies with ruxolitinib, are currently under investigation.

Introduction

Myelofibrosis (MF) is a rare, serious hematologic malignancy classified as one of the Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs).[1] Given the rarity of the malignancy (0.41 to 1.46 cases per 100,000 persons),[2,3] community practitioners do not routinely encounter patients suffering from this malady. As a result, diagnosis and prompt treatment may be delayed. Patients are typically of more advanced age at the time of diagnosis,[2] further complicating disease management. Patients of more advanced age often have multiple comorbidities and are more susceptible to adverse drug events, resulting in a reduced viable pool of pharmacotherapeutic options.

With the exception of allogeneic stem cell transplant (ASCT) as a potential cure, treatments for MF have been limited to symptomatic management. Further, although ASCT is potentially curative, morbidity and mortality associated with this modality are high, and only a small proportion of patients are eligible candidates.

In the recent past, tremendous advances have been made in understanding the pathophysiology of MF. In particular, the genetic basis of the disease has been better defined following the discovery of mutations in *Janus kinase 2 (JAK2)*.[4] Almost half of the patients with MF have an exon 14 mutation in the JAK homology 2 (JH2) domain of *JAK2V617F* gene, which normally encodes a noncatalytic pseudokinase with autoinhibitory properties.[5,6] This past year marked the first Food and Drug Administration (FDA) approval of a treatment for MF, ruxolitinib, a *JAK1/2* inhibitor.

This article explores a number of facets of this rare hematologic malignancy to help clinicians better understand the diagnosis, risk stratification, and management of MPNs and MF. After covering the epidemiology and pathophysiology of MPNs, this review highlights key diagnostic and risk-stratification considerations. Then, the role and limitations of current treatment options are discussed. *JAK1/2* inhibitor therapy is examined in detail and future treatment strategies highlighted. Practical considerations are addressed to help clinicians improve their ability to diagnose, classify, and incorporate established and new treatments into the management of patients with MF.

Understanding MF: Epidemiology, Terminology, and Pathophysiology

Epidemiology

The annual incidence of MF has been estimated to be 0.41 to 1.46 cases per 100,000 individuals.[2,3] The prevalence of MF in the United States has been estimated at 16,000 to 18,500 persons.[7] MF is slightly more common in males and more common in older patients.[2] The median age of patients at the time of diagnosis is 67 years.[2] Among the Philadelphia chromosome-negative MPNs (eg, MF, polycythemia vera [PV], essential thrombocytopenia [ET]), MF is the most symptomatic and carries the worst prognosis.[8,9]

The major causes of death in MF include progressive marrow failure, transformation to acute myeloid leukemia (AML), infection, thrombohemorrhagic events, heart failure, and portal hypertension.[10,11] The median survival for patients with MF ranges from 3.5 to 5.5 years; however, it is highly variable, reaching 20 years in the lowest-risk patients.[12-15] In terms of thrombotic events (both fatal and nonfatal), patient age older than 60 years and the presence of *JAK2* mutation are associated with an increased risk.[16] The presence or absence of *JAK2* mutations has not been shown to affect survival or leukemic transformation.[13,14] Five-year transformation to leukemia is dependent on patient risk stratification, with transformation in high-risk patients reaching 21%.[17]

Terminology

MF is subdivided into primary MF (PMF) and secondary MF.[4] Secondary MF may arise from PV or ET.[18] As MF is a less common malignancy, community practitioners may not refer to it with standard terminology. Terms frequently used synonymously with PMF include chronic idiopathic MF, agnogenic myeloid metaplasia, MF with myeloid metaplasia, and idiopathic MF. Numerous other terms have been used synonymously with PMF, further contributing to the lack of standardization in nomenclature.[19,20]

The International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) has provided guidance on a standard definition of MF.[20] IWG-MRT has defined MF as either PMF (de novo presenting disease) or post PV or ET MF (MF transformation from prior PV or ET). Furthermore, patients with transformation to acute leukemia are referred to as PMF in blast phase (PMF-BP) or post PV/ET MF in blast phase.

Pathophysiology

Although the etiology of MF is unknown, its development has been linked to ionizing radiation (eg, in atomic bomb survivors) and benzene or toluene exposure.[21-25] Current understanding suggests that MF occurs secondary to acquired mutations that target the hematopoietic stem cell.[1] As a result, ineffective hematopoiesis and proliferation of dysfunctional megakaryocytes are commonly seen in MF.[19,26] The hallmark of the disease pathologically is bone marrow reticulin and collagen fibrosis, ineffective extramedullary hematopoiesis, and deregulated production of cytokines.

Cytogenetic abnormalities originating on the progenitor cell level are well described in MF, particularly deletions of chromosomes 13q and 20q; trisomy 8; and abnormalities in chromosomes 1, 7, and 9.[13,27] Several molecular mutations have been identified to date. A mutation in the gene encoding the JAK2 tyrosine kinase, at position *V617F,* was described in 2005.[28] The *JAK2V617F* mutation is present in 50% to 65% of patients with MF and is seen in the other Phila-

delphia chromosome-negative MPNs (96% in PV and 55% in ET).[4,28,29] Although JAK2V617F murine models can recapitulate a myelofibrotic myeloproliferative disease, intricate sequencing experiments done on PMF patient samples suggest that this mutation may not be a disease-initiating event in humans, but it is rather a "second hit" in the disease evolution. Other molecular mutations, present to a lesser extent, have been reported in the following genes: *myeloprolif-erative leukemia virus (MPL), LNK, Casitas B-lineage lymphoma (CBL), ten-eleven-translocation 2 (TET2), additional sex-combs-like 1 (ASXL1), isocitrate dehy-drogenase (IDH) 1* and *2, IKAROS family zinc finger-1 (IKZF1),* and *enhancer of zeste homolog 2 (EZH2).*[30,31]

JAK2 and *MPL* mutations and *LNK* loss of function result in the activation of *JAK* and signal transducer and activator of transcription (*STAT*) and induction of MPN-like disease in mice.[28,32,33] An activated JAK-STAT pathway promotes the transcription of a plethora of proproliferative and antiapoptotic genes.[34-36] MF is also characterized by bone marrow changes induced by cross-communication among clonal stem cells, megakaryocytes, and monocytes with stromal cells, leading to inappropriate cytokine release, myelopro-liferation, neoangiogenesis, and fibrosis.[27] Excessive release of cytokines may further result in JAK-STAT activation, resulting in the propagation of the cycle.[37]

Clinical Presentation, Diagnosis, and Risk Stratification
Clinical Presentation
Table 1 highlights the clinical features of MF. Symp-toms may be classified as either spleen-related or non–spleen-related.[38] Owing to ineffective extramedullary hematopoiesis,[8,9,20] splenomegaly is a well-established clinical feature of MF, with 85% or more of patients with MF presenting with palpable sple-nomegaly at the time of diagnosis.[39,40] Spleen-related symptoms include abdom-inal discomfort, early satiety, and pain under the left ribs; they are reported in 60% to 80% of patients with MF.[9,38] Portal hypertension and variceal bleeding can be morbid complications of splenomegaly.

Non–spleen-related symptoms are also common, occurring in up to 50% to 60% of patients.[9] These symptoms include pruritus, night sweats, and bone/muscle pain. Cytopenia could dominate the course of the disease, es-pecially at the advanced stage. One third of patients may have anemia at diagnosis. The development of anemia in MF rang-es in severity from mild to transfusion-dependent. Patients with MF are also at risk for developing thrombohemor-rhagic complications secondary to leu-kocytosis and/or thrombocytosis.[8] Other potential symptoms and complications include hepatomegaly, ascites, portal hypertension, lymphadenopathy, pleural effusions, nerve or cord compression, osteosclerosis, hypertrophic osteoar-thropathy, and periostitis.[41]

Characteristic laboratory findings in MF may in-clude peripheral blood leukoerythroblastosis, dac-ryocytosis, tear drop-shaped red blood cells, circulat-ing immature myeloid cells, increased serum lactate dehydrogenase levels, increased vitamin B_{12} levels, and hyperuricemia. The characteristic bone marrow aspirate and biopsy findings may be limited by the inability to collect an adequate bone marrow aspirate or "dry tap." The clustering of atypical megakaryo-cytes, which often may be mistaken as dysplasia by an inexperienced pathologist, is a pathologic hall-mark of myeloproliferative syndromes.[17] Reticulin staining demonstrates an increased deposition of reticulin fibers. Collagen fibrosis can be appreci-ated and may be more disease specific compared with reticulin staining. In some early cases of MF, the bone marrow could be hypercellular, with no evidence of fibrosis.[13] Fig 1 illustrates typical bone marrow findings in MF.

Circulating levels of CD34+, hematopoietic stem cells, and progenitors are high in patients with MF compared with healthy patients as well as patients with other Philadelphia chromosome-negative MPNs.[42] Higher levels of cytokines have been reported in pa-tients with PMF compared with healthy controls.[43] Specifically, patients with PMF have higher levels of interleukin 6 (IL-6), tissue inhibitor of metalloprotein-ase (TIMP-1), macrophage inflammatory protein-1b (MIP-1b), and insulin-like growth factor binding pro-tein 2 (IGFBP-2).[43] The increased levels of cytokines are likely to contribute to a hypercatabolic state and cytokine-mediated constitutional symptoms.[44]

Table 1. — Clinical Features of Myelofibrosis

Signs and Symptoms	Mechanism
Abdominal pressure, peripheral edema	Portal hypertension/ascites
Acute left upper quadrant pain, fever, nausea	Splenic infarct
Bleeding, bruising	Thrombocytopenia/platelet dysfunction
Bone and musculoskeletal pain	Hypertrophic osteoarthropathy, periostitis
Dyspnea, palpitations, light-headedness	Anemia
Fatigue, weight loss, nocturnal sweating, pruritus	Hypercatabolic state
GI bleeding	Esophageal varices/hemorrhoids
Monoarticular arthritis, nephrolithiasis	Hyperuricemia
Pain, early satiety, diarrhea	Splenomegaly
Tumor mass effect (lung, GI tract, GU system, CNS, spine/vertebral column)	Ectopic myeloid metaplasia
CNS = central nervous system, GI = gastrointestinal, GU = genitourinary.	

Diagnosis

The differential diagnosis of MF should include bone marrow fibrosis associated with non-neoplastic and neoplastic conditions, including but not limited to chronic myeloid leukemia (CML), myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), lymphoma, or AML. The presence of *JAK2* or *MPL* mutation is a reliable screen to rule out reactive bone marrow fibrosis or a nonmyeloid malignancy. The presence of a +9 or 13q– cytogenetic abnormality is suggestive of PMF.[1] The diagnosis of PMF is facilitated by using the World Health Organization criteria, whereas the diagnosis of post PV or post EF MF is based on the IWG-MRT criteria (Table 2).[18,45]

Risk Stratification

MF is a progressive hematologic disease, with its prognosis depending on several factors. The International Prognostic Scoring System (IPSS) estimates survival from the time of diagnosis using the following risk factors: (1) age 65 years or older, (2) anemia (hemoglobin level < 10 g/dL), (3) presence of constitutional symptoms, (4) leukocytosis (white blood cell count > 25 × 10⁹/L), and (5) circulating blasts of at least 1%.[46-48] Patients presenting with more than two of these prognostic factors of MF have a median survival of less than 3 years, whereas patients without any of the factors have a median survival of more than 10 years.[46] The presence of 0, 1, 2, and ≥ 3 factors using
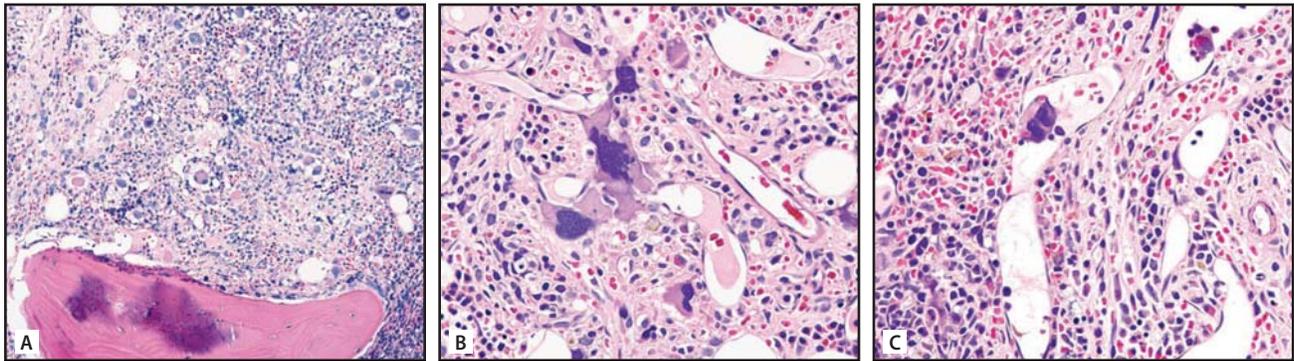

Fig 1. — Typical bone marrow findings in myelofibrosis. (A) Low-powered view of a bone marrow core biopsy sample, which shows increased marrow fibrosis, decreased hematopoiesis, and clustering of megakaryocytes (hematoxylin and eosin [H&E], ×100). (B) High-powered view illustrating clustering of megakaryocytes, many with bizarre nuclear irregularity (H&E, ×400). (C) High-powered view showing a megakaryocyte abnormally localized within a dilated sinus (H&E, ×400). From Klco JM, Vij R, Kreisel FH, et al. Molecular pathology of myeloproliferative neoplasms. *Am J Clin Pathol*. 2010;133(4):602-615. Reprinted with permission by the American Society of Clinical Pathology.

Table 2. — Diagnostic Criteria for Primary and Secondary Myelofibrosis

WHO Criteria: Primary MF	IWG Criteria: Post ET MF and Post PV MF
Major Criteria (all required): • Megakaryocyte proliferation and atypia – Reticulin or collagen fibrosis • Does not meet criteria for other myeloid disorders (eg, PV, CML, MDS) • Clonal marker (eg, *MPL*W515K/L, *JAK2*V617F) or no evidence of secondary marrow fibrosis	**Major Criteria** (all required): • Previous diagnosis of ET or PV • Grade 2–3 bone marrow fibrosis (on 0–3 scale) or grade 3–4 bone marrow fibrosis (on 0–4 scale)
Minor Criteria (must meet 2): • Increase in serum lactate dehydrogenase (LDH) level • Palpable splenomegaly • Leukoerythroblastosis • Anemia	**Minor Criteria** (must meet 2): • An increase ≥ 5 cm in palpable splenomegaly or new splenomegaly • Leukoerythroblastosis • One or more constitutional symptoms • Increase in serum LDH level (post ET MF only) • Anemia with a decrease in hemoglobin level ≥ 2 mg/mL from baseline (post ET MF only) • Anemia or sustained loss of requirement for either cytoreductive treatment or phlebotomy (post PV MF only)

CML = chronic myeloid leukemia, ET = essential thrombocytopenia, IWG = International Working Group, MDS = myelodysplastic syndromes, MF = myelofibrosis, post ET MF = post essential thrombocythemia myelofibrosis, post PV MF = post polycythemia vera myelofibrosis, PV = polycythemia vera, WHO = World Health Organization.

A portion of this research was originally published in *Blood*. Tefferi A, Thiele J, Orazi A, et al. Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. *Blood*. 2007;110(4): 1092-1097. © the American Society of Hematology. A portion of this research was adapted from Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. *Leukemia*. 2008;22(2):437-438. © Nature Publishing Group.

the IPSS defines low-, intermediate 1-, intermediate 2-, and high-risk disease.

A karyotype abnormality is also prognostic of survival. In a retrospective review of 200 patients with MF, in comparison with trisomy 8 or a complex karyotype, patients with 13q and 20q deletions and trisomy 9 had an improved survival and no leukemia transformation.[49] In an update to the IPSS, the Dynamic IPSS (DIPSS) was modified using the same prognostic factors from the IPSS.[47] Unlike the IPSS, the DIPSS may be used at any time during the course of disease to estimate survival. Most recently, the DIPSS was updated to the DIPSS-plus, which incorporates three more prognostic factors: the need for red blood cell transfusion, platelet count < 100 ×10^9/L, and presence of an unfavorable karyotype (Fig 2).[48] In addition to the prognostic factors in the IPSS and DIPSS-plus, increased levels of IL-8, IL-10, IL-15, or IL-2 receptor have also been associated with reduced overall survival and leukemia-free survival.[50]

The ability to prognosticate and stratify the severity of disease is critical in effectively counseling patients regarding expected outcome and defining the most appropriate treatment strategies. Risk stratification allows clinicians to identify high-risk patients who may benefit from intensive therapy such as ASCT, where benefit outweighs the risk. Lower-risk patients with MF or patients with MF who are not transplant candidates should be managed based on symptoms.

Present Treatment Options: Strengths and Limitations

Treatment should be individualized, with careful evaluation of the risk versus benefit of a treatment option. Current treatment options short of ASCT are not curative for MF.[1] Fig 3 illustrates a suggested treatment algorithm for PMF. Based on risk stratification, treatments include ASCT in selected higher-risk eligible patients to alter the natural history of the disease or management of disease-related symptoms/complications (eg, anemia, splenomegaly, extramedullary hematopoiesis, thrombosis) using various conventional agents and novel agents (namely *JAK2* inhibitors) in the majority of patients (Fig 4).

Selection of therapy should be based on risk stratification. Consideration of patient parameters (eg, comorbidities, life expectancy, concomitant medications) is critical when formulating a treatment plan.
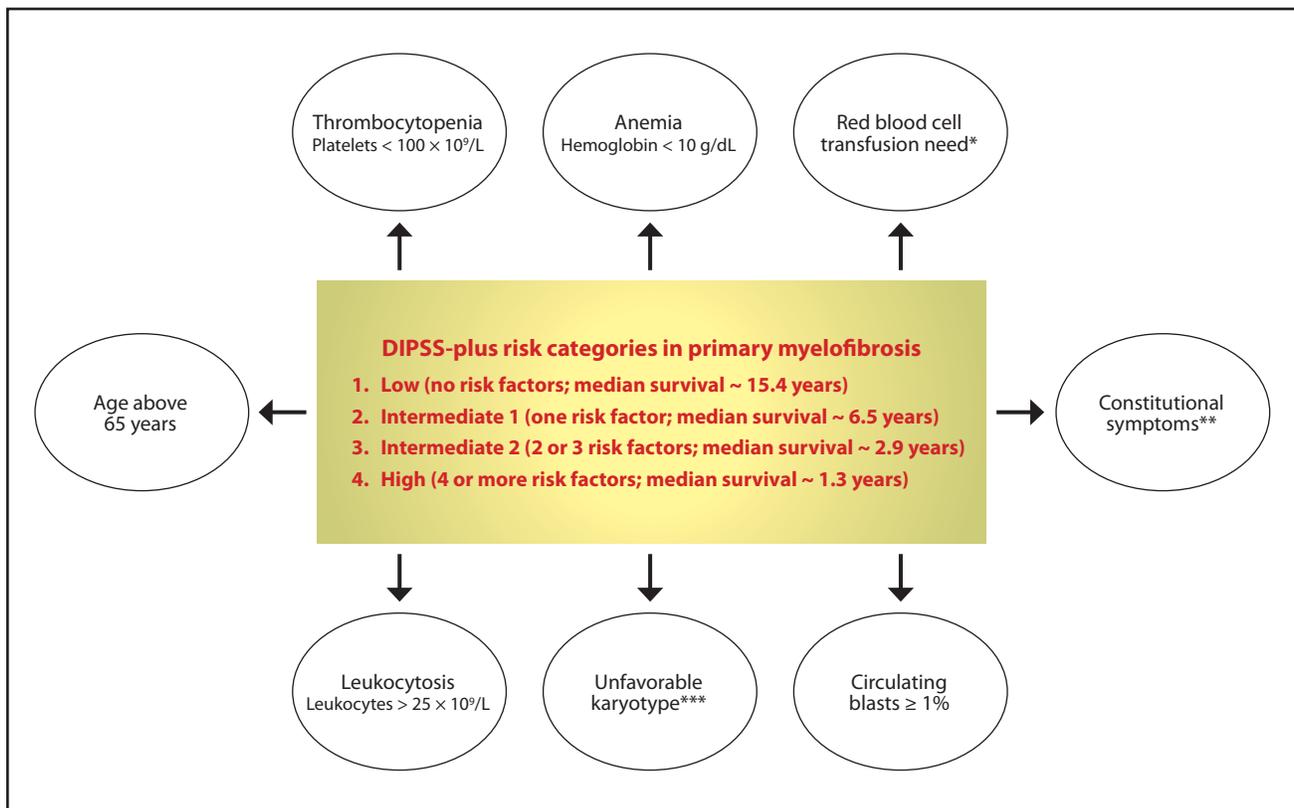

Fig 2. — The Dynamic International Prognostic Scoring System (DIPSS)-plus prognostic model for primary myelofibrosis (PMF). The DIPSS-plus prognostic model for PMF uses 8 risk factors for inferior survival: age > 65 years, hemoglobin level < 10 g/dL, leukocyte count > 25 × 10^9/L, circulating blasts ≥ 1%, presence of constitutional symptoms, presence of an unfavorable karyotype, platelet count < 100 × 10^9/L, and the need for red blood cell transfusion.

*Note that a transfusion-dependent patient automatically has 2 risk factors because of transfusion need (1 risk point) and hemoglobin level < 10 g/dL (1 risk point).

**Constitutional symptoms constitute weight loss > 10% of baseline value in the year preceding diagnosis, unexplained fever, or excessive sweats persisting for > 1 month.

***Unfavorable karyotype constitutes complex karyotype or sole or 2 abnormalities that include +8, −7/7q−, i(17q), inv(3), −5/5q−, 12p−, or 11q23 rearrangement.

From Tefferi A. How I treat myelofibrosis. *Blood*. 2011;117(13):3494-3504. *Blood*: journal of the American Society of Hematology by American Society of Hematology; HighWire Press Copyright 2011. Reproduced with permission of AMERICAN SOCIETY OF HEMATOLOGY (ASH) in the format republish in a journal via Copyright Clearance Center.

Careful monitoring for safety and efficacy is essential to minimize adverse drug effects. The use of the IWG-MRT criteria (Table 3) is a critical tool to gauge treatment response and represents a standard method in clinical trials to evaluate treatment efficacy.[26]

Currently the only potential cure for MF, ASCT has been shown to prolong disease remission in select patients; however, treatment-related morbidity and mortality are high.[51,52] In one published report summarizing a 20-year experience with ASCT, the cumulative 1-year and 3-year incidences of transplant-related mortality were 35% and 43%, respectively.[53] Further, the 3-year overall and relapse-free survival rates after ASCT were 42% and 35%, respectively.[53] ASCT may not be appropriate in patients with DIPSS-plus low- or intermediate 1-risk disease, as the morbidity and mortality associated with transplant likely dwarf the potential benefits.[1] ASCT may be more appropriate in patients with DIPSS-plus intermediate 2- or high-risk disease, particularly those younger than 40 to 50 years of age.[1] Conventional intensity conditioning regimens are reserved for younger patients with a
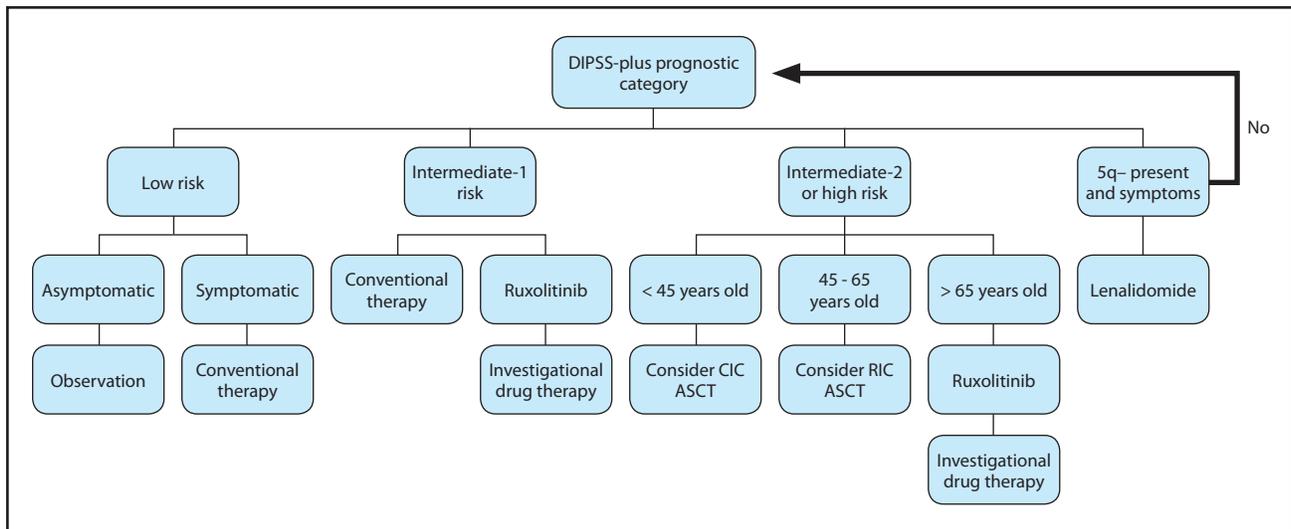

Fig 3. — Treatment algorithm for risk-adapted therapy in primary myelofibrosis. ASCT = allogeneic stem cell transplant; CIC = conventional intensity conditioning; DIPSS-plus = Dynamic International Prognostic Scoring System Plus model for primary myelofibrosis; RIC = reduced intensity conditioning. Adapted from Tefferi A. How I treat myelofibrosis. *Blood*. 2011;117(13):3494-3504. Blood: journal of the American Society of Hematology by American Society of Hematology; HighWire Press Copyright 2011. Reproduced with permission of AMERICAN SOCIETY OF HEMATOLOGY (ASH) in the format republish in a journal via Copyright Clearance Center.

Anemia:
Androgens
Corticosteroids
Danazol
ESAs
Lenalidomide
Thalidomide

Symptomatic Splenomegaly:
Azacitidine
Busulfan
Cladribine
Decitabine
Hydroxyurea
Immunomodulatory agents*
Interferon-α
Melphalan
Radiotherapy
Ruxolitinib
Splenectomy

Extramedullary Hematopoiesis:
Radiotherapy

Thrombosis:
Aspirin
Hydroxyurea

Fig 4. — Available conventional and novel treatment options for myelofibrosis in patients not suitable for allogeneic stem cell transplant based on clinical need. Ruxolitinib is a novel therapeutic option, which has emerged as the most efficacious treatment for splenomegaly and/or constitutional symptoms in patients with intermediate- or high-risk MF. Data from reference 1, 8, and 40. ESAs = erythropoiesis-stimulating agents.

*Thalidomide, lenalidomide, and pomalidomide.

relatively high performance status, whereas a reduced intensity conditioning regimen may be considered for older patients.[54]

Symptomatic splenomegaly is managed using a variety of strategies, and treatment selection is based on patient parameters. Appropriate management of splenomegaly is critical, as this complication of MF has a significant impact on patients' quality of life. Splenectomy has not been shown to improve survival or alter the disease course.[40] In one retrospective review, durable responses in constitutional symptoms were achieved in 67% of patients; however, complication rates in the first 45 days were as high as 30.5% (27.9% of which were fatal events).[55] Thrombohemorrhagic complications are a significant concern post splenectomy; platelet apheresis and cytoreductive therapies such as hydroxyurea may help mitigate some of these complications.[8,40,56] Given the significant risks associated with splenectomy, this procedure should be considered only in select patients with substantial and

Table 3. — IWG-MRT Treatment

Response	Criteria
1. Complete remission (CR)	i. Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly. ii. Peripheral blood count remission defined as hemoglobin level at least 110 g/L, platelet count at least 100×10^9/L, and absolute neutrophil count at least 1.0×10^9/L. In addition, all 3 blood counts should be no higher than the upper normal limit. iii. Normal leukocyte differential including disappearance of nucleated red blood cells, blasts, and immature myeloid cells in the peripheral smear, in the absence of splenectomy.[a] iv. Bone marrow histologic remission defined as the presence of age-adjusted normocellularity, no more than 5% myeloblasts, and an osteomyelofibrosis grade no higher than 1.[b]
2. Partial remission (PR)	Requires all of the above criteria for CR except the requirement for bone marrow histologic remission. However, a repeat bone marrow biopsy is required in the assessment of PR and may or may not show favorable changes that do not however fulfill the criteria for CR.
3. Clinical improvement (CI)	Requires one of the following in the absence of both disease progression (as outlined below) and CR/PR assignment (CI response is validated only if it lasts for no fewer than 8 weeks): i. A minimum increase of 20 g/L in hemoglobin level or becoming transfusion independent (applicable only for patients with a baseline hemoglobin level of less than 100 g/L).[c] ii. Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes nonpalpable.[d] iii. A minimum 100% increase in platelet count and an absolute platelet count of at least $50,000 \times 10^9$/L (applicable only for patients with a baseline platelet count below 50×10^9/L). iv. A minimum 100% increase in ANC and an ANC of at least 0.5×10^9/L (applicable only for patients with a baseline ANC below 1×10^9/L).
4. Progressive disease (PD)	Requires one of the following[e]: i. Progressive splenomegaly that is defined by the appearance of a previously absent splenomegaly that is palpable at greater than 5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5 cm to 10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of greater than 10 cm. ii. Leukemic transformation confirmed by a bone marrow blast count of at least 20%. iii. An increase in peripheral blood blast percentage of at least 20% that lasts for at least 8 weeks.
5. Stable disease (SD)	None of the above.
6. Relapse	Loss of CR, PR, or CI. In other words, a patient with CR or PR is considered to have undergone relapse when he or she no longer fulfills the criteria for even CI. However, changes from either CR to PR or CR/PR to CI should be documented and reported.

Notes:

[a] Because of subjectivity in peripheral blood smear interpretation, CR does not require absence of morphologic abnormalities of red blood cells, platelets, and neutrophils.

[b] In patients with CR, a complete cytogenetic response is defined as failure to detect a cytogenetic abnormality in cases with a preexisting abnormality. A partial cytogenetic response is defined as 50% or greater reduction in abnormal metaphases. In both cases, at least 20 bone marrow- or peripheral blood-derived metaphases should be analyzed. A major molecular response is defined as the absence of a specific disease-associated mutation in peripheral blood granulocytes of previously positive cases. In the absence of a cytogenetic/molecular marker, monitoring for treatment-induced inhibition of endogenous myeloid colony formation is encouraged. Finally, baseline and posttreatment bone marrow slides should be stained at the same time and interpreted at one sitting by a central review process.

[c] Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the past month for a hemoglobin level of less than 85 g/L that was not associated with clinically overt bleeding. Similarly, during protocol therapy, transfusions for a hemoglobin level of 85 g/L or more is discouraged unless it is clinically indicated.

[d] In splenectomized patients, palpable hepatomegaly is substituted with the same measurements.

[e] It is acknowledged that worsening cytopenia might represent progressive disease, but its inclusion as a formal criterion was avoided because of the difficulty in distinguishing disease-associated from drug-induced myelosuppression. However, a decrease in hemoglobin level of 20 g/L or more, a 100% increase in transfusion requirement, and new development of transfusion dependency, each lasting for more than 3 months after the discontinuation of protocol therapy, can be considered disease progression.

ANC = absolute neutrophil count, IWG-MRT = International Working Group for Myelofibrosis Research and Treatment.

This research was originally published in *Blood*. Tefferi A, Barosi G, Mesa RA, et al. International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT). *Blood*. 2006;108(5):1497-1503. © the American Society of Hematology.

refractory symptomatic splenomegaly or refractory cytopenias or in those with evidence of portal hypertension and varices.[40] Other considerations should include adequacy as a surgical candidate, failure of at least one medical therapy (including *JAK* inhibition), an adequate performance status, and a life expectancy of more than 1 year.[40]

Radiotherapy may be used in patients with MF for palliation. Frequently irradiated sites include the lungs, paraspinal masses, and spleen.[1] Reported response rates with splenic radiotherapy range from 59% to 95%; however, response is typically transient.[40,57-59] Myelosuppression may be severe and treatment-limiting. Splenic radiotherapy may be a palliative measure in patients who are not appropriate candidates for splenectomy and have a short expected survival.

For most patients with splenomegaly and/or constitutional symptoms, hydroxyurea is considered the first-line therapy for decreasing splenomegaly, and the estimated patient response rate is less than 50%.[40] Limitations with hydroxyurea include lack of sustained improvement, rarity in inducing complete remission, the need for high doses to induce a response, and the potential for cytopenias.[40] Although the oral alkylating agents such as melphalan and busulfan may alleviate splenomegaly, they are not without risk.[40,60] Ruxolitinib has emerged as a treatment option for splenomegaly and/or constitutional symptoms in patients with intermediate- or high-risk MF.

Another strategy for management of splenomegaly is the use of immunomodulatory agents, such as thalidomide, lenalidomide, and pomalidomide (currently in clinical trials), alone or in combination with corticosteroids. An important benefit of these agents involves the palliation of cytopenias. Significant responses in anemia (62%), thrombocytopenia (75%), and splenomegaly (19%) have been reported with low-dose thalidomide combined with a prednisone taper.[61] Lenalidomide produced similar results in a separate study and was better tolerated than thalidomide (indirect comparison) in patients with adequate baseline levels of neutrophils and platelets.[62] Overall responses to immunomodulatory agents are in the range of 30%. Patients with a chromosome 5q deletion appear to have the best response to lenalidomide, and thus this agent may be preferred in this population.[63] Other agents that have been used to manage splenomegaly include cladribine, azacitidine, and decitabine.[40]

Interferon-α has been evaluated in patients with MF; however, its toxicity prohibits its use in many cases (eg, worsening cytopenias).[64,65] It had been suggested that interferon may alter the natural history of the disease and reverse fibrosis in vitro.[66] Although many clinical studies in PMF have been disappointing,[64,65,67-69] results of a recent prospective study of 17 low- and intermediate 1-risk patients treated with interferon-α reported that > 80% of patients had either a response or stable disease (2 complete remissions and 7 partial remissions).[70] Interferon-α

may be considered in young lower-risk patients and is the treatment of choice in women of childbearing age contemplating pregnancy. Pegylated interferon may be an appealing choice to study further, given its toxicity profile.[71,72]

As with splenomegaly, there are limited options available to clinicians for managing anemia. In the absence of splenomegaly, erythropoietin-stimulating agents (ESAs; epoetin alfa, darbepoetin alfa) are a viable treatment option in patients with hemoglobin levels less than 10 mg/dL. Patients who are transfusion-dependent or those with erythropoietin levels higher than 125 U/L are unlikely to benefit from ESAs.[8,73,74] Other options for managing anemia include corticosteroids, androgens, and danazol. The response rate with these treatments appears to be similar (approximately 20%), and the response duration is estimated at 1 year.[1] As a result, selection of therapy should be based on patient characteristics. For patients who have symptomatic anemia and splenomegaly, the immunomodulating agents may be preferred.

The major limitations of all the conventional treatments involve three core considerations: (1) the lack of sustained effectiveness, (2) the risk for toxicity, and (3) the lack of activity against the genetic basis of the disease. Furthermore, the aforementioned therapies are not curative. As discussed, ASCT has the potential to cure disease; however, experience with this therapeutic approach suggests high morbidity and mortality.[52]

The Advent of *JAK* Inhibition: Clinical Experience, FDA Approval, and Practical Considerations

With the discovery of the *JAK2* mutation, a significant stride has been made in identifying a molecular basis for disease and discovery of agents targeting this basis. Several *JAK* inhibitors are in clinical development (Table 4).

Ruxolitinib, an oral *JAK1* and *JAK2* inhibitor, was approved by the FDA for the treatment of intermediate- and high-risk MF in November 2011. The starting dose of ruxolitinib is dependent on the baseline platelet count. For patients with a platelet count higher than 200×10^9/L, a dose of 20 mg twice daily is indicated; for patients with a platelet count between 100×10^9/L and 200×10^9/L, a dose of 15 mg twice daily is indicated. Although there are no known contraindications to the use of ruxolitinib, experience with its use in patients with platelet counts lower than 100×10^9/L is limited and subject to investigational trials. It is prudent to use ruxolitinib in such patients at the reduced dose, eg, 10 mg twice a day as a starting dose. A complete blood cell count at baseline and at 2 to 4 weeks (depending on patient response) will help guide therapy. If thrombocytopenia develops, the dosage should be reduced. The dosage may be increased to a maximum of 25 mg twice daily, depending on patient response. If no reductions in splenomegaly or symptoms are observed after 6 months, therapy should be discontinued. Ruxolitinib

Table 4. — Overview of *JAK* inhibitors

Compound	Mechanism of Action	Manufacturer	Phase
AZD1480	*JAK2* inhibitor	AstraZeneca (Wilmington, DE, USA)	I/II
BMS911543	*JAK2* inhibitor	Bristol-Myers Squibb (Princeton, NJ, USA)	I/II
CYT387	*JAK1/2*, TYK inhibitor	YM Biosciences (Mississauga, Ontario, Canada)	I/II
LY2784544	*JAK2* inhibitor	Eli Lilly (Indianapolis, IN, USA)	I
NS-018	*JAK2* inhibitor	Nippon Shinyaku (Kyoto, Japan)	I/II
Pacritinib	*JAK2* inhibitor	Cell Therapeutics, Inc. (Seattle, WA, USA)	I/II
Ruxolitinib	*JAK1/2* inhibitor	Incyte Corporation (Wilmington, DE, USA); Novartis Pharmaceuticals (East Hanover, NJ, USA)	FDA-approved
SAR302503	*JAK2* inhibitor	Sanofi (Paris, France)	III

FDA = Food and Drug Administration, TYK = tyrosine kinase.

Adapted from Tefferi A. How I treat myelofibrosis. *Blood*. 2011;117(13):3494-3504; Verstovsek S. Therapeutic potential of Janus-activated kinase-2 inhibitors for the management of myelofibrosis. *Clin Cancer Res*. 2010;16(7):1988-1996; Verstovsek S. Therapeutic advances in myelofibroproliferative neoplasms: the role of new small molecule inhibitors. *Am Soc Clin Oncol Ed Book*. 2012;406-410.

is nonspecific for *JAKV617F* mutation; therefore, it may be useful in patients with MF for whom no approved therapy exists.[75]

The safety and efficacy of ruxolitinib have been evaluated in two phase III clinical trials. The Controlled Myelofibrosis Study with Oral *JAK1/2* Inhibitor Treatment I and II (COMFORT-I and COMFORT-II) studies provided evidence that ruxolitinib therapy leads to reduction in splenomegaly, improvements in signs and symptoms, and improved quality of life in patients with MF.[76,77]

COMFORT-I is a randomized, double-blind, placebo-controlled study that enrolled 309 adults in the United States, Canada, and Australia. Patients were enrolled if they had palpable splenomegaly and had an IPSS classification of intermediate 2- or high-risk primary or secondary MF and were randomized 1:1 to receive either placebo or ruxolitinib 15 mg by mouth twice daily.

Significantly more patients treated with ruxolitinib achieved a spleen volume reduction of at least 35% vs placebo at week 24 of treatment (41.9% vs 0.7%, respectively; $P < .001$) Of the ruxolitinib-treated patients who achieved a spleen volume reduction of at least 35%, 67% of the patients maintained the reduction for 48 weeks or more. In addition, patients receiving ruxolitinib had a significant mean improvement in the Total Symptom Score (TSS; measured using the modified Myelofibrosis Symptom Assessment Form [MFSAF] v2.0) of 46.1%, whereas in the placebo group, TSS worsened by a mean of 41.8% ($P < .001$). The MFSAF is a validated tool that measures the symptoms reported by > 10% of patients with MF and includes a measure of quality of life.[38] Ruxolitinib-treated patients had similar improvements in splenomegaly and TSS regardless of the MF subtype, IPSS risk category, age, baseline hemoglobin level, baseline palpable spleen length, and *JAK2V617F* mutation status.

COMFORT-II is an open-label phase III study evaluating ruxolitinib 15 mg to 20 mg by mouth twice daily vs best available treatment (as determined by the investigator) in 219 patients with palpable splenomegaly and IPSS intermediate 2- or high-risk PMF, PV-MF, and ET-MF. None of the patients who received the best available treatment achieved at least a 35% reduction in spleen volume from baseline at week 24 or 48. On the contrary, 31.9% and 28.5% of patients treated with ruxolitinib achieved this endpoint at weeks 24 and 48, respectively ($P < .001$). At a median of 12 months, 80% of patients continued to have a response. Similar to COMFORT-I, subgroup analysis did not find significant variation in response rates in any one individual group. Patients treated with ruxolitinib experienced significant improvements in quality of life, as measured by the European Organization for Research and Treatment of Cancer (EORTC-QLQ-C30) and the Functional Assessment of Cancer Therapy Lymphoma (FACT–Lym).

The most common adverse drug effects with ruxolitinib in COMFORT-I and COMFORT-II included thrombocytopenia and anemia. The rates of grade 3 or 4 anemia and thrombocytopenia were higher in ruxolitinib-treated patients than in the placebo group (45.2% and 12.9% vs 19.2% and 1.3%, respectively) in COMFORT-I. Similarly, in COMFORT-II, patients treated with ruxolitinib vs best available therapy experienced more grade 3 or 4 anemia and thrombocytopenia (42% and 8% vs 31% and 7%, respectively). In COMFORT- I, the mean hemoglobin level reached a nadir of 95 g/L after approximately 8 to 12 weeks of therapy, with an increase by week 24 to a new steady state of 101 g/dL. Interestingly, based on IWG-MRT response criteria in the COMFORT-I study, 41.2% of ruxolitinib-treated patients who were transfusion-dependent at baseline changed their classification to transfusion-independent; however, the same change to transfusion-independence

was recorded in 46.9% of placebo-treated patients, strongly suggesting inadequacy of the response criteria in this instance. Nonhematologic adverse drug effects included ecchymosis, dizziness, and headache. MF-related symptoms typically returned after 1 week of ruxolitinib discontinuation.

Although the COMFORT-I and COMFORT-II study results have been extremely encouraging, there have been concerns raised regarding the durability of treatment, survival benefits, and adverse drug events. One of the centers involved with the early phase I/II trial noted that in a follow-up analysis of 51 patients, responses (particularly spleen size reduction) may not have been enduring, treatment did not enhance survival, and adverse events were of concern.[78] On the other hand, an analysis of data from the 107 patients in the phase I/II trial from MD Anderson Cancer Center compared with historic controls found that survival was longer with ruxolitinib and that this treatment may have the potential to change the natural progression of MF in patients with advanced disease.[79] Additionally, in a post hoc analysis in the COMFORT-I study, with a follow-up of 52 weeks in the ruxolitinib arm and 51 weeks in the placebo arm, a significant reduction in the risk of death was observed in ruxolitinib-treated patients (hazard ratio, 0.50; 95% confidence interval, 0.25–0.98; $P = .04$).[80] These data suggest that ruxolitinib may provide a survival benefit in patients with advanced MF.

There have been concerns raised regarding discontinuation syndrome upon ruxolitinib withdrawal. However, no pattern of adverse events supporting this concern was identified in the COMFORT-I randomized study.[81] Discontinuation of ruxolitinib was associated with the return of MF-related symptoms.

When evaluating outcomes with novel agents, it is critical not only to assess their efficacy in terms of survival, but also their ability to improve symptoms, which often dramatically impact patients' quality of life. The MFSAF is an inventory designed to measure symptom burden in MF.[9] In future clinical studies, the use of this inventory may help decipher which treatment options improve patients' quality of life to the greatest extent.

The importance of quality of life in this patient population is underscored by a post hoc analysis of the COMFORT-II study.[82] The analysis demonstrated that on average, health-related quality of life and MF symptoms improved in ruxolitinib-treated patients, whereas these measures remained the same or worsened in patients treated with best available therapy. In a separate analysis, severe disease-related symptoms were found to be associated with a diminished health-related quality of life.[83] Improving symptoms and in turn quality of life is an important consideration in patients' well-being. Thus, optimizing control of symptoms and improving quality of life may help patients to tolerate adjuvant/alternative therapies.

Future Horizons in the Management of MF

In addition to *JAK* inhibitors, several novel compounds are under investigation for the treatment of MF, including histone deacetylase (HDAC) inhibitors, hedgehog inhibitors, lysyl oxidase homolog 2 (LOXL2) humanized monoclonal antibody, mammalian target of rapamycin (mTOR) inhibitors, and other immunomodulating agents (Table 5).[84] These agents hold promise for improving the care of patients with MF.

Non-*JAK2* therapies on the horizon for MF include panobinostat, peginterferon alfa-2a, pomalidomide AB0024, NS-018, SAR302503, SB939, and TAK-901. Panobinostat, an HDAC inhibitor, has demonstrated a 30% median reduction in spleen size in a phase I study. Pomalidomide, a thalidomide derivative, is targeted to improve MF-associated anemia. Although pomalidomide was well tolerated in preliminary trials, this immunomodulatory agent did not produce a sustained increase in hemoglobin levels. However, ongoing clinical trials with this agent will address its possible role.

Table 5. — Overview of Novel Therapies in Development for Myelofibrosis

Compound	Mechanism of Action	Manufacturer	Phase
Everolimus (RAD-001)	mTOR inhibitor	Novartis Pharmaceuticals (East Hanover, NJ, USA)	I/II
Givinostat (ITF2357)	HDAC inhibitor	Italfarmaco (Milan, Italy)	IIA
GS6624 (AB0024)	LOXL2 humanized monoclonal antibody	Gilead Sciences (Foster City, CA, USA)	II
Panobinostat (LBH-589)	HDAC inhibitor	Novartis Oncology (Basel, Switzerland)	I/II
Plitidepsin	Marine cyclic depsipeptide	PharmaMar (Madrid, Spain)	II
Pomalidomide	Immunomodulating agent	Celgene Corporation (Summit, NJ, USA)	III
Pracinostat (SB939)	HDAC inhibitor	S*BIO (Singapore, Thailand)	II
Saridegib (IPI-926)	Hedgehog inhibitor	Infinity Pharmaceuticals (Cambridge, MA, USA)	II

HDAC = histone deacetylase, LOXL2 = lysyl oxidase homolog 2, mTOR = mammalian target of rapamycin.
Adapted from Verstovsek S. Therapeutic advances in myeloproliferative neoplasms: the role of new small molecule inhibitors. *Am Soc Clin Oncol Ed Book*. 2012;406-410.

Other promising advances in therapy include the combination of ruxolitinib with other therapies. Ruxolitinib is under investigation in combination with lenalidomide and also with panobinostat. Another potential application of ruxolitinib is in pretreatment of candidates for ASCT. Ruxolitinib may facilitate achievement of an improved performance status, thereby making ASCT possible. Ultimately, controlled clinical trials are needed to evaluate whether these approaches are safe and effective.

Conclusions

MF is a rare hematologic malignancy, with a variable prognosis and major disease morbidity. Prompt identification, risk stratification, and treatment initiation are imperative. Until recently, treatments were targeted at symptom management, with only ASCT as a potential cure. With the discovery of the *JAK2* mutation, treatments such as ruxolitinib are positioned to target the molecular basis of disease, the dysregulated JAK-STAT pathway. Experience with ruxolitinib has been encouraging, with significant improvements in MF-related symptoms and overall survival in high-risk patients. Treatments that significantly alleviate disease burden and improve patients' quality of life are important steps to improving patient care and outcomes. In addition to treatment, the ability to prognosticate and individualize patient management continues to progress. As the understanding of the pathophysiology of MF evolves, so does the development of novel therapies.

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