In a remarkable Editorial in BLOOD more than 60 years ago, Dameshek coined the term “Myelo-proliferative Syndromes” (MPS) to characterize an apparently diverse group of hematologic disorders characterized by myeloid hyperplasia with maturation. Based on the relative degree of erythroid, megakaryocytic and granulocytic proliferation all four of the major myeloproliferative neoplasms (MPN) come into view. Equally remarkable is the description of both primary (PMF) and secondary myelofibrosis (SMF) with speculation regarding a pre-fibrotic stage of PMF.

Over the next 50 years the treatment of MPN remained largely palliative. For patients with the two most deadly variants, chronic myelogenous leukemia (CML) and PMF, median survival was on the order of five years, with leukemic transformation being a major cause of death. For patients with CML, hydroxyurea was used to control leukocytosis and splenomegaly with the only disease modifying therapy being interferon which produced cytogenetic remissions in a small group of patients at the cost of substantial toxicity. For patients with PMF, hydroxyurea produced transient and incomplete control of systemic symptoms and splenomegaly, but at the cost of aggravating anemia and increasing transfusion requirements. While the anemia of PMF has been treated with androgens, erythropoietin, and IMIDs, transfusion requirements are improved in less than one-third of those treated. While the only potentially curative therapy for CML and PMF has been allogeneic stem cell transplantation, most patients either do not have matched donors or are too old to undergo dose-intensive therapy.

For patients with CML, this all changed in 2001 when Imatinib, the rationally designed tyrosine kinase inhibitor (TKI), became available. This agent produced rapid and complete hematologic remissions in nearly all patients with CML and complete cytogenetic responses in the large majority. This was accompanied by a delay in leukemic transformation with subsequent trials demonstrating median survival exceeding 10 years. The continued development of new more potent TKIs now raises the possibility of a normal life span for many patients with CML.

The success of molecularly targeted therapy in CML and the discovery in 2005 of the activating Jak-2 V617-F mutation in 50-60% of patients with PMF raised great hope that Jak inhibitors might change the natural history of this disease as well. However, the absence of this mutation in nearly half of all patients with PMF, and the presence of Jak-2 negative leukemic transformation in patients with Jak-2 positive PMF indicates that this mutation is a secondary event. Given this, the results of the Comfort I and II trials are not surprising—improvement in constitutional symptoms and splenomegaly with exacerbation of cytopenias and with little or no effect on survival, fibrosis, and allelic burden.

Many of these issues were addressed in the satellite symposium titled “Clinical Advances in the Management of Myelofibrosis,” held in February 2013 at the Tandem BMT meeting in Salt Lake City, Utah. Dr. Mesa started by providing a concise review of diagnosis, classification, and prognostic scoring systems. Dr. Gupta then provided a very timely review of the Comfort I and II trials with a discussion of investigational Jak1/2 inhibitors. Next, Dr. Hari provided an overview of current outcomes with stem cell transplantation in PMF. Last, Dr. Gupta returned to discuss individualized care plans in the era of Jak inhibitors and reduced intensity transplants.

Progress in the treatment of myelofibrosis is at hand, and future strides will depend upon reduction in transplant-related mortality, as well as advances in our understanding of the molecular pathogenesis of this terrible disease.
Be a part of a national organization established to promote education, research, and medical development in the field of blood and marrow transplantation.

Full Membership is open to individuals holding an MD or PhD degree with demonstrated expertise in blood and marrow transplantation as evidenced by either the publication of two papers on hematopoietic stem cell transplantation–related research as recorded by curriculum vitae, or documentation of two years of experience in clinical transplantation as recorded by curriculum vitae or letter from the director of a transplant center attesting to the experience of the candidate.

Associate Membership is open to individuals with an MD or PhD degree who otherwise do not meet the criteria for full membership.

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Symposium Report

Clinical Advances in the Management of Myelofibrosis

Adapted from a continuing medical education symposium presented at the 2013 BMT Tandem Meetings on February 16, 2013, in Salt Lake City, Utah. This program is supported by an educational grant from Incyte Corporation.

Faculty

Parameswaran Hari, MD, MS
Medical College of Wisconsin
Milwaukee, Wisconsin

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Mayo Clinic Cancer Center
Scottsdale, Arizona

Program Overview

This continuing education activity, targeted to clinicians caring for patients eligible for or planning to undergo stem cell transplantation and/or with myelofibrosis, will provide an overview of clinical advances in the management of myelofibrosis and strategies for optimizing and individualizing treatments, including the evolving role of allogeneic stem cell transplantation and Janus kinases inhibitors. During this activity, participants will learn about validated diagnostic, prognostic, and individual patient risk factors that will assist them in customizing treatment strategies that will maximize outcomes for myelofibrosis patients. Participants will learn how Janus kinase inhibitors should be incorporated into existing or novel therapeutic strategies, including incorporation into strategies for those eligible for allogeneic stem cell transplantation.

Learning Objectives

Upon completion of the program, participants should be able to:

- Incorporate information gained from this activity toward diagnosis, risk stratification, and classification of patients with myelofibrosis.
- Make therapeutic decisions for patients with myelofibrosis based on diagnosis, classification, prognosis, and individual patient-risk factors.
- Discuss the palliative value of JAK inhibitor therapy in patients that are not allogeneic SCT candidates and the controversy surrounding timing of these inhibitors in patients that are allogeneic SCT candidates.
- Integrate emerging evidence regarding JAK inhibitor and other novel therapies (eg, immunomodulatory agents, mTOR inhibitors, and HDAC inhibitors) in the establishment of treatment plans and goals for patients with intermediate- or high-risk myelofibrosis.

Target Audience

The program will be oriented to a targeted audience of physicians, nurses, pharmacists, and healthcare professionals specializing in oncology, hematology, and hematopoietic stem cell transplantation.

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The Medical College of Wisconsin is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Medical College of Wisconsin designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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Faculty Disclosures

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- John R. Wingard, MD, has no relevant financial relationships to disclose.
- Randy A. Brown has no relevant financial relationships to disclose.
- Parameswaran Hari, MD, MS (Chair) has no relevant financial relationships to disclose.
- Vikas Gupta, MD, FRCP, FRCPath, discloses that he is a Speaker and Consultant for Incyte Corporation, Novartis, and YM Biosciences. He is a member of an advisory board for Novartis and Sanofi.
- Ruben A. Mesa, MD, FACP, discloses that he has received research support from Incyte Corporation, MS Pharma, Genentech, Gilead, and Lilly.
Introduction

Myelofibrosis (MF) is a chronic myeloproliferative disorder characterized by bone marrow fibrosis, cytopenias, and spleen enlargement due to extramedullary hematopoiesis (EMH). Presently, allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative therapy for MF. Given the significant risk of regimen-related toxicity, graft failure, and graft-versus-host disease (GVHD), however, the appropriate role of HSCT in the management of MF remains controversial. In the era of JAK1/2 inhibitors, patients with MF have new options for reducing symptom burden, improving quality of life, and delaying transplantation. The selection of optimal therapy for MF requires an individualized assessment of each patient’s biological characteristics, comorbidities, and overall treatment goals. Future options may include novel therapeutic strategies and the combined use of JAK inhibition and allogeneic HSCT to optimize patient outcomes in MF.

Myelofibrosis: Diagnosis, Classification, Prognosis, and Molecular Etiology

Ruben A. Mesa, MD, FACP

The term myeloproliferative neoplasm describes a spectrum of abnormalities characterized by uncontrolled bone marrow proliferation in the presence of intact cellular differentiation. Diagnosis and treatment rely on accurate assessment of histologic, molecular, and clinical features, as well as individualized risk-stratification.

Natural History of Myelofibrosis

The natural history of primary MF can be described in 2 distinct phases (Figure 1). In the first phase, early primary MF can overlap with other myeloproliferative neoplasms, including essential thrombocytopenia (ET) and polycythemia vera (PV). This phase can persist for a period of 10 years or longer, during which the patient experiences only limited effects from the disease. The risk of vascular events, however, is elevated during early primary MF.

In the second phase, the patient progresses to overt primary, post-ET, and post-PV MF. This stage is characterized by 3 to 5 years of progressively worsening constitutional symptoms, organomegaly, EMH, and cytopenias. Patients with overt MF are at risk for leukemic transformation and premature death.

Variable Symptom Profiles

The burden of cytopenias varies for individual patients. The most common cytopenia is anemia, with only 1 in 4 patients with MF having normal hemoglobin levels, defined as 13.5 g/dL for men and 12 g/dL for women. The remaining 75% of patients with MF will have some degree of anemia, including 25% who will be dependent on red blood cell (RBC) transfusions. Anemia can exacerbate the substantial fatigue that is normally associated with MF. Transfusions provide some symptomatic relief, but they do not return patients fully to normal energy levels. Anemia is also associated with dyspnea and organ dysfunction. Thrombocytopenia occurs less often, and is associated with an increased risk of hemorrhage. Leukopenia is a rare complication of MF, but when it does occur, it can increase the risk of infection.

Splenomegaly is the main physical finding of MF and a major cause of morbidity. In one multicenter study of 1,054 patients with primary MF, palpable splenomegaly was present in 89% of patients at diagnosis [1]. In another study of patients with MF, 64% presented with palpable splenomegaly [2]. The median spleen size in this patient cohort was 7.4 cm below the left costal margin (BLCM). Splenomegaly is associated with a range of symptoms and potential complications, including mechanical discomfort, pain, possible splenic infarction, early satiety adding to cachexia, and splenic sequestration and exacerbation of cytopenias. Splenomegaly may also delay engraftment in the setting of allogeneic HSCT. In addition, increased cytokine levels can cause debilitating constitutional symptoms such as night sweats, fevers, and muscle and bone pain.

As a result of these symptoms, patients with MF can experience a major erosion in quality of life. Several randomized studies have evaluated quality of life for patients with MF and other hematologic malignancies and solid tumors [3-5]. Patients with MF have composite quality of life scores that are similar to or worse than those in patients with chronic myeloid leukemia (CML), myeloma, and lung cancer. Moreover, patients with MF can have individual symptom scores for fatigue, pain, dyspnea, and insomnia that surpass the severity observed in patients with metastatic solid tumors.

Figure 1. Natural History of Myeloproliferative Neoplasms. EMH indicates extramedullary hematopoiesis; ET, essential thrombocytopenia; MF, myelofibrosis; PMF, primary myelofibrosis; PV, polycythemia vera.
Table 1. WHO Diagnostic Criteria for Primary Myelofibrosis [7]*

Major Criteria (All 3 Are Required)

1. Presence of megakaryocyte proliferation and atypia, usually accompanied by reticulin or collagen fibrosis, or in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (i.e., prefibrotic cellular-phase disease).

2. Not meeting WHO criteria for PV, BCR-ABL1 + CML, MDS, or other myeloid neoplasms.

3. Demonstration of JAK2V617F or other clonal marker (e.g., MPLW515L/K) or in the absence of a clonal marker, no evidence that the bone marrow fibrosis is secondary to infection, autoimmune disorder or other chronic inflammatory condition; hairy cell leukemia or other lymphoid neoplasm; metastatic malignancy; or toxic (chronic) myelopathies.

Minor Criteria† (At Least 2 Are Required)

1. Leukocytoclastosis
2. Increase in serum lactate dehydrogenase level
3. Anemia
4. Palpable splenomegaly

*WHO indicates World Health Organization; PV, polycythemia vera; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome.
† Requires the absence of BCR-ABL.
§ Secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies. It should be noted that patients with conditions associated with reactive myelofibrosis are not immune to primary myelofibrosis and the diagnosis should be considered in such cases if other criteria are met.
† Degree of abnormality could be borderline or marked.

Different clusters of MF symptoms and disease features can result in distinct symptomatic phenotypes [2]. In a recent study of 329 patients, 4 symptom clusters were identified, with disease features including leukopenia, thrombocytopenia, and spleen size varying significantly between clusters (P < .05) [2]. The most common symptomatic phenotype, affecting nearly half (46%) of all patients, was described as fatigue-dominant with few laboratory abnormalities. These patients had fatigue-dominant complaints and a relatively low prevalence of anemia (67%), thrombocytopenia (20%), or clinical deficiencies such as prior thrombosis (9%), prior hemorrhage (5%), or prior RBC transfusions (20%). The second most common phenotype, affecting 32% of patients, was associated with a high prevalence of cognitive complaints, including fatigue, sexual difficulties, insomnia, and inactivity, as well as the largest mean spleen size (8.7 cm BLCM). Additional phenotypes included “nighttime and cognitive complaints” (16%) and “severe fatigue with few end-organ complaints” (6%). The ability to identify distinct symptomatic phenotypes in patients with MF may aid in the selection of appropriate therapy.

Prevalence

Historically, limited epidemiologic data have been available to understand the prevalence and burden of MF. Some studies have attempted to estimate the prevalence of MF, with results ranging from 0.4 to 1.4 per 100,000 individuals. In 2012, Mesa and colleagues evaluated 2 major U.S. health insurance claims databases to estimate the current prevalence of MF and other myeloproliferative neoplasms [6]. Together, the databases included approximately 70 million enrollees, providing a representative sample of the U.S. population.

The results suggest that the prevalence and burden of MF is higher than has been reported in the past. Between 2008 and 2010, the prevalence of MF ranged from 3.6 to 5.7 per 100,000 patients. In addition, the prevalence of ET ranged from 39 to 57 cases per 100,000, and the prevalence of PV ranged from 45 to 57 cases per 100,000 patients.

Diagnosis of Myelofibrosis

To date, no single absolute marker for MF has been identified. Therefore, diagnosis relies on a mix of physical, laboratory, histologic, and molecular criteria. Table 1 summarizes the current World Health Organization (WHO) diagnostic criteria for primary MF, which include a mix of major and minor criteria [7]. A diagnosis of primary MF requires meeting all 3 major criteria and 2 minor criteria.

Histologic Findings

Several changes in bone marrow morphology are characteristic of MF. Megakaryocyte changes include dense clustering of small to large megakaryocytes, aberrant nuclear/cytoplasmic ratio, and hyperchromatic, bulbous, irregularly folded nuclei and dense clustering. The presence of megakaryocyte proliferation and atypia most often accompany reticulin/collagen fibrosis. If fibrosis is absent, however, megakaryocyte changes occur in the context of hypercellularity with granulocytic proliferation and decreased erythropoiesis [7].

Differential Diagnosis

Patients can become myelofibrotic as a consequence of early primary MF or from prior ET or PV. To clarify the distinction between these etiologies, the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) published diagnostic criteria for post-PV and post-ET myelofibrosis (Table 2) [8].

In 2011, Barbu and colleagues described the prognostic importance of distinguishing early primary MF from ET in an international study of 1,104 patients who were previously diagnosed as having ET [9]. All patients had undergone a pretreatment bone marrow biopsy at the time of diagnosis, or within 1 year of diagnosis in untreated patients. For the current analysis, all bone marrow biopsies underwent a central re-review to identify cases of early/prefibrotic primary MF based on
Table 2. IWG-MRT Diagnostic Criteria for Post-PV MF and Post-ET MF [8]*

<table>
<thead>
<tr>
<th>Required Criteria</th>
<th>Diagnostic Criteria for Post-PV MF</th>
<th>Diagnostic Criteria for Post-ET MF</th>
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<tbody>
<tr>
<td>1. Documentation of a previous diagnosis of ET or PV as defined by the WHO criteria</td>
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<td>1. Documentation of a previous diagnosis of ET or PV as defined by the WHO criteria</td>
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<td>2. Bone marrow fibrosis grade 2-3 (on a 0-3 scale) or grade 3-4 (on a 0-4 scale)</td>
<td>* Additional Criteria (2 are required)</td>
<td>* Additional Criteria (2 are required)</td>
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<td>1. Anemia or sustained loss of requirement for either phlebotomy (in the absence of cytoreductive therapy) or for cytoreductive treatment for erythrocytosis</td>
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<td>2. A leukoerythroblastic peripheral blood picture</td>
<td>2. A leukoerythroblastic peripheral blood picture</td>
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<td>3. Increasing splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly</td>
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<td>4. Development of ≥1 of 3 constitutional symptoms: &gt;10% weight loss in 6 months, night sweats, unexplained fever (&gt;37.5°C)</td>
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<td>5. Development of ≥1 of 3 constitutional symptoms: &gt;10% weight loss in 6 months, night sweats, unexplained fever (&gt;37.5°C)</td>
</tr>
</tbody>
</table>

*IWG-MRT indicates International Working Group for Myelofibrosis Research and Treatment; PV, polycythemia vera; MF, myelofibrosis; ET, essential thrombocythemia; WHO, World Health Organization.

Grade 2-3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3-4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

Below the reference range for appropriate age, sex, gender, and altitude considerations.

Figure 2. Survival by Subtype of Myeloproliferative Neoplasm [10]. ET indicates essential thrombocythemia; MPN NOS, myeloproliferative neoplasm not otherwise specified; PMF, primary myelofibrosis; PV, polycythemia vera.
characteristic histologic patterns misdiagnosed as ET. Bone marrow morphology in early/prefibrotic primary MF tends to be hypercellular, with prominent clustering of megakaryocytes, abnormally hypolobulated (cloud-like) and hyperchromatic nuclei, and granulocytic proliferation. By comparison, histologic findings in patients with ET show normocellular bone marrow with dispersed large to giant megakaryocytes.

The re-review of bone marrow specimens led to a diagnosis of early/prefibrotic primary MF in 180 patients (16%) and ET in 891 cases (81%) [9]. The remaining 33 cases (3%) were qualitatively inadequate or represented reactive occurrences. Patients with early primary MF had a much higher rate of progression to the more problematic form of the disease (P = 0.04). The cumulative incidence of overt MF in patients with ET and early/prefibrotic primary MF was 0.2% versus 2.3%, respectively, at 5 years; 0.8% versus 12.3% at 10 years, and 9.3% versus 16.9% at 15 years. These findings reinforce the importance of differential diagnosis in understanding prognosis, as the natural histories of primary MF and ET are distinct.

Prognosis in Myelofibrosis

Myeloproliferative neoplasms (MPNs) are associated with reduced overall survival compared with the general population, although prognosis varies with individual disorders.

In 2010, Hultcrantz and colleagues reported findings from a long-term, population-based study to determine the causes of death in patients with myeloproliferative disorders [10]. Researchers analyzed data from the national Swedish Cancer Registry to identify all cases of MPN diagnosed between 1973 and 2008. A total of 9,384 cases were identified, including patients with PV (n = 4,389), ET (n = 2,359), primary MF (n = 1,048), and MPN not otherwise specified (n = 1,288). The median age at diagnosis was 71 years, and 47% of patients were men.

Survival outcomes differed according to MPN subtype (Figure 2). Patients with PV fared the best. Compared with the general population, the relative survival ratio (RSR) for patients with PV was 0.83 at 5 years and 0.64 at 10 years. For patients with ET, the RSR at 5 and 10 years was 0.80 and 0.68, respectively. Patients with primary MF had the worst survival outcomes, with RSRs of 0.39 at 5 years and 0.21 at 10 years.

The most common causes of death were hematologic malignancy (27%), cardiac disease (27%), solid tumors (12%), and vascular events such as thromboembolism and bleeding (9%). Regardless of MPN subtype, older age at diagnosis predicted worse survival. The RSR at 10 years was 0.86 for patients diagnosed at age <50 years, compared to 0.35 for those diagnosed at age ≥80 years (P < 0.001). Survival was also better for female patients than for male patients, as measured by an excess mortality rate ratio of 0.72. Although survival for patients with MPNs has steadily improved over time, mortality rates were significantly higher than those in the general population during all calendar periods.

Prognostic Scores in Myelofibrosis

Several prognostic tools have been developed to facilitate risk-assessment and therapeutic decision-making for patients with primary MF [1,11-13]. The different scoring systems provide specific information about patient prognosis. For example, the International Prognostic Scoring System (IPSS) is utilized to estimate survival from the time of diagnosis, whereas the dynamic IPSS (DIPSS) model is used for estimating survival from any point in the disease course [1,12]. The DIPSS-plus scoring system is an extension of the DIPSS methodology that incorporates additional disease information to predict both overall survival and leukemia-free survival [13]. Each scoring
system relies on a core set of prognostic variables, such as cytopenias, age, circulating blasts, symptoms, karyotype, and need for RBC transfusions (Table 3) [1,11-13]. As the number of adverse prognostic factors increases, patient prognosis worsens.

The IPSS illustrates the correlation between prognostic factors and survival [1]. The IPSS uses 5 risk factors to estimate survival: age > 65 years, hemoglobin < 10 g/dL, leukocyte count > 25 × 10⁹/L, circulating blasts ≥ 1%, and presence of constitutional symptoms. Patients are classified into 4 risk groups based on the number of risk factors present: low (0 risk factors), intermediate-1 (1 risk factor), intermediate-2 (2 risk factors), and high risk (≥ 3 risk factors). The median overall survival for patients in the low, intermediate-1, intermediate-2, and high risk groups is 135 months, 95 months, 48 months, and 27 months, respectively (P < .001).

**Molecular Etiology**

Myelofibrosis is closely related in molecular etiology to CML and other chronic myeloid neoplasms, although it presents with a unique clinical phenotype. Figure 3 illustrates the complex interactions that contribute to the pathogenesis of MF [14]. Chromosomal abnormalities are detected in approximately half of patients with MF, although no signature cytogenetic defect has been identified to date [14]. Beginning in 2005, progress in the understanding of the genetic basis of MPDs began to accelerate. That year, 4 research groups independently identified a single gain-of-function mutation in the Janus kinase 2 (JAK2) gene in a large number of patients with myeloproliferative disorders [15-18]. The JAK2 V617F mutation is an acquired mutation that arises in multipotent progenitor cells in the myeloid lineage but is absent in T-cells. The JAK2 V617F mutation results in constitutively active JAK2 tyrosine kinase and signal transducer and activator of transcription (STAT)-mediated transcription.

**Novel Treatment Options for Myelofibrosis**

**Vikas Gupta, MD, FRCR FRPath**

Current treatment options for patients with MF are extensive, ranging from simple pharmacotherapies to transplantation-based strategies. The challenge is selecting the appropriate therapy for individual patients. Historically, clinicians have used conventional therapies to address the manifestations of MF. For instance, erythropoietin, corticosteroids, androgen therapy, and immunomodulatory drugs (IMiDs) such as thalidomide have been used to manage anemia. For splenomegaly, treatment approaches may include hydroxyurea, splenectomy, and low-dose irradiation.

Conventional therapies, however, are limited by poor efficacy and a lack of prospective clinical data in patients with MF. Without strong consensus on the effective use of these therapies, treatment practices are highly variable. Moreover, with the exception of allogeneic HSCT, most traditional treatment approaches are palliative, and do not address the underlying disease process in myelofibrosis.

The JAK-STAT signaling pathway is an attractive target for therapeutic intervention in myelofibrosis. Approximately 50% of patients with primary MF have the JAK2 V617F gain-of-function mutation, and other mechanisms of direct and indirect JAK pathway activation have been identified in this patient population. The proinflammatory cytokines and growth factors that play a major role in the pathogenesis of myelofibrosis communicate via the JAK-STAT signaling pathway. Regardless of the mutational status of JAK2, dysregulation of the JAK-STAT signaling pathway appears to be a major pathogenic component in myelofibrosis.

**Ruxolitinib**

Ruxolitinib is an orally bioavailable, potent, and selective inhibitor of JAK1 and JAK2. The U.S. Food & Drug Administration (FDA) approved ruxolitinib for the treatment of intermediate- and high-risk myelofibrosis on the basis of 2 randomized phase III clinical trials, the Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment (COMFORT)-I and COMFORT-II studies [21,22].

**COMFORT-I and COMFORT-II Study Design**

COMFORT-I was a randomized, double-blind, placebo-controlled phase III trial that enrolled 309 patients with intermediate-2 or high-risk myelofibrosis [21]. At the time of enrollment, all patients had myelofibrosis that was refractory to available therapies, had side effects requiring discontinuation, or were not candidates for available therapies. Patients were randomly assigned to treatment with ruxolitinib 15 mg or 20 mg twice daily (n = 155) or placebo (n = 154). The primary end point was the proportion of patients with a reduction of ≥ 35% in spleen volume from baseline at week 24, as assessed by magnetic resonance imaging (MRI). Patients with progressive disease were eligible to crossover to ruxolitinib.

The COMFORT-II trial was a randomized, open-label, phase III trial that compared ruxolitinib with the best available therapy (BAT) in 279 patients with primary MF, post-PV MF, or post-ET MF [22]. Patients were randomly assigned to treatment with ruxolitinib 15 mg or 20 mg twice daily (n = 146) or BAT (n = 73). Within the BAT group, 49 (67%) patients received one or more BAT medications, while 24 (33%) patients received no medication. Among those who received BAT medications, antineoplastic agents were the most commonly used (51%), followed by hydroxyurea (47%) and glucocorticoids (16%). The primary end point was a reduction in spleen volume of ≥ 35% at 48 weeks, as assessed by MRI or...
computed tomography (CT). Crossover to ruxolitinib was also permitted for patients with progressive disease.

Reduction in Spleen Volume

Both clinical trials met the primary end point of spleen volume reduction of ≥35% with ruxolitinib (Figure 2) [21,22]. In the COMFORT-I trial, 41.9% of patients in the ruxolitinib group and 0.7% of patients in the placebo group had a reduction of ≥35% in spleen volume by week 24 (P < .001) [21]. In COMFORT-II, 28.3% of patients treated with ruxolitinib had a reduction in spleen volume of ≥35% by week 48, compared with 0% of patients in the BAT group (P < .001) [22]. Patients in both studies showed rapid responses to ruxolitinib treatment, with reductions in spleen volume and palpable spleen length within weeks [21,22]. In the COMFORT-II trial, the median time to first observation of a reduction of ≥35% in spleen volume was 12.3 weeks [22].

Treatment with ruxolitinib was superior to placebo across all patient populations, with no subgroup showing diminished response. A subgroup analysis of the COMFORT-I trial showed a consistent benefit of ruxolitinib with regard to spleen volume reduction across all subgroups, including those defined by patient age, type of myelofibrosis, IPSS risk category, and baseline hemoglobin level and platelet count [23]. Importantly, patients also benefited from treatment with ruxolitinib regardless of JAK2 V617F mutational status, demonstrating that the activity of JAK inhibition is not mutation-specific.

Reduction in Other Symptoms

Beyond reduction in spleen volume, treatment with ruxolitinib showed a substantial benefit in addressing patient symptoms, as measured by the secondary endpoint of total symptom score. The total symptom score reflected the sum of individual scores for night sweats, itching, abdominal discomfort, pain under the ribs on the left, early satiety, muscle or bone pain, and activity. In the COMFORT-I trial, 45.9% of patients in the ruxolitinib group, compared with 5.3% of patients in the placebo group, experienced a decrease in their total symptom score of 50% or more from baseline to week 24 [21]. Further, an analysis of individual symptom scores showed a consistent improvement in all individual symptoms for patients treated with ruxolitinib, as well as a consistent increase in symptom burden for patients in the placebo group.

Table 1. Adverse Events Observed in at Least 10% of Patients in COMFORT-I [21]

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ruxolitinib (n = 155), % with Adverse Event</th>
<th>Placebo (n = 151), % with Adverse Event</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>All Grades 3/4</td>
<td>Grade 3</td>
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<tr>
<td>Hematologic</td>
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<tr>
<td>Anemia</td>
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</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69</td>
<td>13</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
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<tr>
<td>Fatigue</td>
<td>25</td>
<td>5</td>
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<tr>
<td>Diarrhea</td>
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<td>2</td>
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<tr>
<td>Peripheral edema</td>
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<tr>
<td>Eczymosis</td>
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<tr>
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<td>1</td>
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<tr>
<td>Dizziness</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
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<td>0</td>
</tr>
<tr>
<td>Headache</td>
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<td>0</td>
</tr>
<tr>
<td>Constipation</td>
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<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
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<td>1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

Safety

Hematologic toxicities were the most common adverse events associated with ruxolitinib in the COMFORT-I trial (Table 1) [21]. In particular, anemia and thrombocytopenia occurred more frequently in the ruxolitinib group than in the placebo group. Treatment discontinuation because of anemia and thrombocytopenia, however, was rare, occurring in only 1 patient in each treatment group for each event.

Most non-hematologic adverse events occurred with similarly low frequency in both treatment groups. Exceptions included ecchymosis, dizziness, and headache, which were more common in the ruxolitinib group. Abdominal pain was more common in the placebo group, grade 3-4 abdominal pain was reported by 11% of patients in the placebo group compared with 3% of patients in the ruxolitinib group.

Overall Survival

At the 2012 American Society of Hematology (ASH) annual meeting, Verstovsek and colleagues presented additional long-term findings from the COMFORT-I trial [24]. In the updated analysis, all patients initially in the placebo arm completed crossover to ruxolitinib or discontinued treatment within 3 months of the primary analysis. The median follow-up duration in the ruxolitinib group was 102 weeks. In an unplanned, intent-to-treat analysis, overall survival was significantly better in the ruxolitinib group compared with placebo (hazard ration [HR], 0.58; P = 0.028).

Overall survival favored ruxolitinib across all patient subgroups, including those defined by baseline risk factors and on-study ruxolitinib dose. Patient age was the only baseline variable that differed between treatment groups; the median age in the ruxolitinib group was 66 years, compared with 70 years in the placebo group (P < .05) [22]. The age-adjusted HR for overall survival was 0.61, favoring ruxolitinib (P = 0.040) [24].

Durability of Spleen Response

Investigators evaluated the duration of spleen response to ruxolitinib in a long-term analysis of the COMFORT-II trial [25]. The updated analysis included a median follow-up of 112 weeks. Within the ruxolitinib group (n = 136), 132 patients (97%) experienced a clinical benefit with some degree of reduction in spleen volume. This includes 70 patients (48%) who achieved a ≥35% reduction from baseline in spleen volume at any time during the study. Reductions in spleen volume of ≥35% were sustained with continued ruxolitinib treatment, with the median duration of response not yet reached. The probability of maintaining a spleen response was 75% at week 48 and 58% at week 84.

Abrupt discontinuation of ruxolitinib treatment is not recommended. In the COMFORT-I study, interrupted dosing resulted in a return to baseline myelofibrosis symptoms over a period of approximately 7 days [26]. Although a small number of patients used a tapering strategy to discontinue ruxolitinib, most treatment interruptions occurred at total daily doses of ≥10 mg twice daily. Regardless of the ruxolitinib dose at which treatment interruption occurred, however, both the total symptom score and the worst single daily symptom score returned to baseline levels within 1 week of discontinuation.

JAK1/2 Inhibitors in Development

Several investigational JAK1 and JAK2 inhibitors are currently in development (Table
2). SAR302503 is a JAK2-selective inhibitor that showed clinically meaningful reductions in spleen size and improvements in constitutional symptoms in a phase II study of 31 patients with primary MF, post-PV MF, or post-ET MF [27]. The ongoing phase III JAKArTA trial will evaluate SAR302503 in patients with intermediate-2 and high-risk primary MF, post-PV MF, or post-ET MF with splenomegaly [28].

### Other Investigational Agents in Myelofibrosis

Although JAK inhibitors represent a major advance in the use of targeted therapy for MF, these agents are not curative, and they do not reduce the risk of leukemic transformation. Effective control of symptoms, including constitutional symptoms and symptoms related to splenomegaly, may require the use of novel agents with mechanisms of action that are complementary to JAK inhibition. Investigational classes with a potential role in the treatment of myelofibrosis include immunomodulators, histone deacetylase (HDAC) inhibitors, interferons (IFNs), mammalian target of rapamycin (mTOR) inhibitors, and agents with other novel mechanisms of action (Table 3). Many of these agents are being evaluated in combination with JAK inhibitors to improve the clinical efficacy of current therapy.

### Stem Cell Transplantation in the Era of JAK Inhibition: Putting the Pieces Together

**Parameswaran Hari, MD, MS**

In current clinical practice, allogeneic HSCT is the only curative treatment for patients with MF. In addition to eradicating or reducing the malignant clone with allogeneic HSCT, there is evidence of a graft-versus-leukemia (GVL) effect in MF, similar to that observed in other chronic hematologic malignancies [29]. Despite the potential benefits of HSCT, however, MF is a rare indication for transplantation, and even major transplantation centers perform a limited number of allogeneic HSCT procedures for patients with MF [29].

Historically, the perceived risk of graft failure was a major treatment barrier for patients with MF, resulting in low rates of referral to HSCT [29]. However, early studies demonstrated the feasibility of engraftment, as well as long-term disease control, in the setting of marrow fibrosis. Table 1 summarizes findings from early, nonrandomized, retrospective studies of allogeneic HSCT in MF, which included myeloablative conditioning strategies such as total body irradiation (TBI) or busulfan and high-dose cyclophosphamide.
Table 1. Early Studies With Myeloablative Conditioning for MF, 1979 to 2002*

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Median Age, y</th>
<th>Conditioning Regimen (%)</th>
<th>MRD</th>
<th>NRM</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guardiola [30]</td>
<td>55</td>
<td>42</td>
<td>TBI (63%)</td>
<td>90%</td>
<td>27% at 1 year</td>
<td>47% at 5 years</td>
</tr>
<tr>
<td>Deeg [31]</td>
<td>56</td>
<td>43</td>
<td>Bu/Cy (78%)</td>
<td>64%</td>
<td>14% at 3 months</td>
<td>58% at 3 years</td>
</tr>
<tr>
<td>Daly [32]</td>
<td>25</td>
<td>48</td>
<td>TBI (92%)</td>
<td>52%</td>
<td>48% at 1 year</td>
<td>41% at 2 years</td>
</tr>
<tr>
<td>Kerksy [33]</td>
<td>104</td>
<td>49</td>
<td>Bu/Cy (62%); RIC (9%)</td>
<td>50%</td>
<td>13% at 3 months; 35% at 5 years</td>
<td>61% at 5 years</td>
</tr>
<tr>
<td>Ballen [34]</td>
<td>289</td>
<td>47</td>
<td>Bu/Cy (43%); RIC (21%)</td>
<td>56%</td>
<td>35% (RD); 50% (URD) at 5 years</td>
<td>37% (RD); 30% (URD) at 5 years</td>
</tr>
</tbody>
</table>

*MF indicates myelofibrosis; MRD, matched related donor; NRM, non-relapse mortality; OS, overall survival; TBI, total body irradiation; Bu, busulfan; CY, cyclophosphamide; RIC, reduced intensity conditioning; RD, related donor; URD, unrelated donor.

(Bu/CY) [30-34]. The high rates of treatment-related mortality (TRM) associated with conventional myeloablative HSCT restricted its use in MF to younger and fitter patients. In these studies, the majority of patients (50% to 90%) had HLA-matched sibling donors [30-34]. In the largest analysis of myeloablative HSCT for patients with MF (n = 289), the 5-year overall survival was 37% for patients with matched sibling donors and 30% for those with unrelated donors [34]. Although findings from these studies performed more than 15 to 20 years ago are not applicable to modern clinical practice, they are sometimes used to justify reluctance to referral for transplantation for patients with MF [29].

Within the past decade, the treatment paradigm for HSCT in MF shifted to include reduced-intensity and nonmyeloablative conditioning regimens [29]. The conditioning regimens are predominantly fludarabine-based, and include the use of fludarabine in combination with TBI (Flu-TBI), melphalan (Flu-Mel), or busulfan (Flu-Bu) (Table 2) [35-38]. With this approach, non-relapsed mortality rates have ranged from 10% to 22% at 1 year, and overall survival rates have ranged from 43% to 67% at 5 years [35-38].

Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) show other recent trends in allogeneic HSCT for patients with MF [29]. Overall transplantation activity for MF has increased steadily across the different time periods of CIBMTR data analysis (1997 to 2000; 2001 to 2004; 2005 to 2008) [29]. Other recent trends include the increasing use of HSCT in older patients. For patients with MF, the median age at diagnosis is 67 years, with only 13% of patients younger than age 50 years at diagnosis. The myeloablative conditioning studies, however, show a median patient age of 42 to 47 years, which is clearly not reflective of the majority of patients with MF [30-34]. Data from CIBMTR also show a greater willingness to use unrelated donor transplants and peripheral blood stem cell grafts [29].

To date, no prospective studies have compared myeloablative versus reduced-intensity conditioning (RIC) for patients with MF. In retrospective, nonrandomized studies, reduced-intensity regimens have been restricted to older patients with significant comorbidities and poor performance scores, who are not candidates for myeloablative conditioning [29,39,40]. Despite the major differences in patient populations, however, these studies demonstrate the feasibility of RIC in patients with MF who are undergoing HSCT [29,39,40].

**Barriers to Successful Transplantation**

Clinical trials of allogeneic HSCT in the setting of MF have identified several major barriers to transplantation success. The incidence of graft failure is particularly high in MF (5% to 25%) and appears worse for recipients of unrelated grafts and in patients with elevated plasma cytokine levels [29]. Inflammatory cytokines may also exacerbate the risk of GVHD. Patients with poor performance status, as indicated by symptomatic splenomegaly, anemia, debilitating constitutional symptoms, also have worse transplantation outcomes. Treatment-related hepatotoxicity, posttransplantation relapse, and leukemic transformation are also significant barriers to treatment success.

**Splenomegaly**

Massive splenomegaly is common in patients with MF. Whether splenomegaly influences engraftment and posttransplantation morbidity and mortality is controversial, with conflicting data from small studies. To assess the true impact of spleen status on outcomes following allogeneic HSCT, the CIBMTR evaluated transplantation data from 9,683 myeloablative allograft recipients [41]. In this cohort, 7,440 patients had a normal spleen, 1,471 had splenomegaly, 472 had prior splenectomy, and 300 received splenic irradiation.

Long-term hematopoietic recovery at day 100 was comparable across all patients groups. However, compared with patients with normal

Table 2. Newer Conditioning Regimens for Allogeneic HSCT in MF, 2002 to Present*

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Median Age, y</th>
<th>Conditioning Regimen (%)</th>
<th>MRD</th>
<th>NRM</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rondelli [35]</td>
<td>21</td>
<td>54</td>
<td>Flu-TBI (28%); Flu-Mel (33%); Thiopeta-CY (33%)</td>
<td>85%</td>
<td>10% at 1 year</td>
<td>81% at 2.7 years</td>
<td>85% at 2.7 years</td>
</tr>
<tr>
<td>Kröger [36]</td>
<td>103</td>
<td>55</td>
<td>Flu-Bu (100%)</td>
<td>32%</td>
<td>10% at 1 year</td>
<td>51% at 5 years</td>
<td>67% at 5 years</td>
</tr>
<tr>
<td>Alchalby [37]</td>
<td>162</td>
<td>56</td>
<td>Flu-Bu (96%)</td>
<td>27%</td>
<td>22% at 1 year</td>
<td>46% at 5 years</td>
<td>62% at 5 years</td>
</tr>
<tr>
<td>Banigalalo [38]</td>
<td>46</td>
<td>51</td>
<td>Thiopeta-CY + Mel (100%)</td>
<td>65%</td>
<td>24% at 5 years</td>
<td>NR</td>
<td>45% at 5 years</td>
</tr>
</tbody>
</table>

*HSCT indicates hematopoietic stem cell transplantation; MRD, matched related donor; NRM, non-relapse mortality; PFS, progression-free survival; OS, overall survival; Flu, fludarabine; TBI, total body irradiation; Mel, melphalan; CY, cyclophosphamide; Bu, busulfan; NR, not reported.
spleens, patients with splenomegaly were significantly less likely to have hematopoietic recovery at day 14 (odds ratio [OR], 0.56; P < 0.001), neutrophil engraftment at day 21 (OR, 0.55; P < 0.001), and platelet engraftment at day 28 (OR, 0.82; P < 0.001). Conversely, compared with the normal spleen group, patients with prior splenectomy were more likely to have hematopoietic recovery at day 14 (OR, 3.26; P < 0.001), neutrophil engraftment at day 21 (OR, 2.25; P < 0.001), and platelet engraftment at day 28 (OR, 1.28; P < 0.001).

In the CIBMTR study, splenomegaly was associated with delayed engraftment following allogeneic HSCT, whereas splenectomy prior to transplantation appeared to facilitate early engraftment [41]. However, there was no survival advantage associated with either splenectomy or splenic irradiation in patients undergoing allogeneic HSCT. Overall survival was similar across all patient groups. In an earlier trial, splenectomy was associated with a significantly increased risk of relapse at 3 years (HR, 3.98; P = 0.06) in patients with MF who underwent allogeneic HSCT after RIC [39]. Based on current evidence, many transplantation centers avoid splenectomy immediately prior to transplantation due to the potential for surgical complications.

### Posttransplantation Hepatotoxicity

Patients with MF are predisposed to underlying hepatocellular injury and liver dysfunction [42]. In 2012, Wong and colleagues described the high risk of early hepatotoxicity following allogeneic HSCT in patients with MF and the adverse impact of liver injury on posttransplantation survival [42]. The retrospective case-control analysis compared acute hepatic complications occurring after HSCT in a cohort of 53 patients with MF and a control group of 53 patients with MDS.

During the first 6 weeks after HSCT, patients with MF were significantly more likely than patients with MDS to develop moderate or severe hyperbilirubinemia (44% versus 21%; P = 0.02) or veno-occlusive disease (36% versus 19%; P = 0.05). Patients with MF who had a history of portal hypertension, hepatic iron overload, or portal/splanchic vein thrombosis were significantly more likely than patients without these risk factors to develop moderate/severe hyperbilirubinemia (P = .02). Furthermore, survival at 12 months was significantly worse for patients who developed acute hepatocellular injury with moderate/severe hyperbilirubinemia or transaminitis (P = .02). These findings have led to a change in practice at many transplantation centers. Prior to allogeneic HSCT, patients with MF are now carefully screened for asymptomatic portal hypertension, iron overload, and the presence of portal and splanchic thrombi to identify risk factors for posttransplantation hepatotoxicity.

### Risk of Relapse after Transplantation

Disease relapse following allogeneic HSCT is a challenging issue for patients with MF. In 2012, Klyuchnikov and colleagues described an effective salvage strategy in a study of 30 patients with relapse (n = 27) or graft rejection (n = 3) after reduced-intensity allografting [43]. The 2-step salvage strategy included donor lymphocyte infusions (DLIs) and/or a second allogeneic HSCT.

During the first 6 weeks after HSCT, patients with MF were significantly more likely than patients with MDS to develop moderate or severe hyperbilirubinemia (44% versus 21%; P = 0.02) or veno-occlusive disease (36% versus 19%; P = 0.05). Patients with MF who had a history of portal hypertension, hepatic iron overload, or portal/splanchic vein thrombosis were significantly more likely than patients without these risk factors to develop moderate/severe hyperbilirubinemia (P = .02). Furthermore, survival at 12 months was significantly worse for patients who developed acute hepatocellular injury with moderate/severe hyperbilirubinemia or transaminitis (P = .02).

The 2-step salvage strategy included donor lymphocyte infusions (DLIs) and/or a second allogeneic HSCT for non-responding or ineligible patients. A total of 26 patients received a median of 3 DLIs escalated to a median dose of 40 106 T-cells/kg. Of these 10 patients (39%) achieved a complete response to DLI. The 13 non-responders to DLI underwent a second allogeneic HSCT, as did 4 patients who were ineligible for DLI due to graft rejection or leukemia transformation. In this group, the overall response rate to second HSCT was 80%, including 9 patients with a complete response and 3 with a partial response. For the full cohort of 30 patients, the 2-year progression-free survival was 67%, and 2-year overall survival was 70%. Therefore, the use of DLIs and/or second allogeneic HSCT appears to be an effective salvage strategy for patients with MF who experience disease relapse or graft rejection following reduced-intensity HSCT.

### Leukemic Transformation

The risk of leukemic transformation in patients with MF has been well described [44,45]. In a retrospective review of 2,333 consecutive patients who were treated for MF at the Mayo Clinic in Rochester, Minnesota, 91 fulfilled the criteria for transformation to acute myeloid leukemia (AML). Prognosis was poor, with a median overall survival of 2.6 months [44]. Treatment with AML-like induction chemotherapy was associated with reversion to chronic-phase MF in 41% of patients. In this group, the risk of treatment-related mortality was 33%, and the median overall survival was 3.9 months.

Another retrospective analysis evaluated 74 patients with Philadelphia chromosome (Ph)-negative myeloproliferative neoplasms that underwent leukemic transformation [45]. The median overall survival in this cohort was 5 months from the date of blast transformation. Induction chemotherapy was associated with a complete response in 46% of patients, but the response was not durable. Among responders, the median progression-free survival was 5 months. In summary, evidence to date demonstrates that leukemic transformation in patients with MF typically occurs in advanced disease and is associated with poor response to current treatment options [44,45]. The best opportunity for overall success appears to reside in the effective treatment of chronic-phase disease.

### Utility of Risk Scoring Prior to Transplantation

Risk-assessment tools can facilitate the identification of patients with MF who are mostly likely to benefit from allogeneic HSCT or investigational therapies. Another goal of prognostic assessment is minimizing treatment-related risks for patients whose disease characteristics suggest favorable prognosis without potentially risk therapeutic interventions.

The Lille scoring system has been studied extensively in patients with MF undergoing HSCT. Studies evaluating the prognostic usefulness of DIPSS scoring prior to transplantation, however, have shown mixed results [46,47]. At the Fred Hutchinson Cancer Research Center, a
trial of 170 patients undergoing allogeneic HSCT showed that pretransplantation DIPSS scores correlated with posttransplantation outcomes [46]. On the contrary, another study of 150 patients undergoing RIC showed DIPSS discriminated poorly between intermediate-1 and intermediate-2 risk populations [47].

At the 2012 ASH annual meeting, Gupta and colleagues reported findings from a comparison of the Lille and DIPSS scoring systems in predicting mortality and other outcomes following RIC allogeneic HSCT [48]. Using the CIBMTR database, investigators analyzed patient factors, disease characteristics, and transplantation-related factors in 222 patients with primary MF who underwent HSCT using RIC. The Lille risk score detected a 2-fold increase in overall mortality between patients with high-risk and low-risk disease (relative risk [RR], 2.22; P = .02). However, the DIPSS was not able to distinguish a difference in mortality risk between low/intermediate-1 and intermediate-2 high risk groups (P = .10). These findings demonstrate the need for a transplantation-specific scoring system to improve risk assessment for patients undergoing HSCT with RIC.

The CIBMTR database analysis revealed additional factors associated with posttransplantation outcomes in patients undergoing RIC HSCT for MF. In a multivariate analysis, donor type significantly predicted overall mortality (P = .001). Compared with HLA-identical sibling donors or other related donors, the relative risk of mortality increased to 1.53 (95% confidence interval [CI], 1.01 to 2.53) with partially matched donors and to 2.61 (95% CI, 1.57 to 4.36) with partially matched or mismatched unrelated donors. A comparison of conditioning regimens also showed a trend toward reduced mortality with Flu-Mel when compared to Flu-Bu (RR, 0.56; 95% CI, 0.33 to 0.92; P = .11) or other regimens (RR, 0.51; 95% CI, 0.26 to 0.99; P = .11).

Recent Prospective Multicenter Trials of Reduced-Intensity Allogeneic HSCT

European Group for Blood and Marrow Transplantation (EBMT) Study

Two recent prospective, multicenter, phase II studies provide insight into the modern era of reduced-intensity allogeneic HSCT in patients with MF (Table 3). At the 2011 ASH annual meeting, Alchalby and colleagues reported long-term findings from prospective multicenter study conducted by the MDS subcommittee of the Chronic Leukemia Working Party of the EBMT [36,49]. The EBMT trial enrolled 103 patients with primary (n = 63) or post-ET/PV MF (n = 40) from 17 international transplantation centers. The median patient age was 55 years (range, 32 to 68 years). By Lille scoring, 17% of patients were classified as low risk with constitutional symptoms. The conditioning regimen included busulanan 10 mg/kg orally or 8 mg/kg intravenously, fludarabine 180 mg/m², and antithymocyte-globulin (ATG). All but 3 patients received peripheral stem cells sourced from either related (n = 33) or unrelated (n = 70) donors. The median follow-up was 60 months.

In the updated analysis of the EBMT trial, the overall survival was 68% at 5 years [49]. Mortality risk plateaued beginning at 5.3 years of follow-up, such that overall survival at 8 years was 65%. At 3 years, the cumulative incidence of relapse was 22%, and non-relapse mortality was 21%. The estimated 3-year disease-free survival was 40%. Of 28 patients with relapsed disease, 21 were treated with donor-lymphocyte infusions (DLI) and/or a second allogeneic transplantation. With adoptive immunotherapy, a second remission with long-term survival was induced in approximately 50% of relapsed patients. After a median follow-up of 46 months, beginning from the time of relapse, the estimated overall survival of all relapsed patients was 55%. Thus, the EBMT study shows that reduced-intensity allogeneic SCT from related or unrelated donors is a reasonable and potential curative treatment approach, even for older patients with primary MF or post-PV/ET MF.

Building on data from the EBMT study, Alchalby and colleagues developed a risk-prediction model by evaluating risk factors and treatment outcomes in 150 patients with MF [47]. In a multivariate analysis, 3 factors significantly predicted worse overall survival: wild-type JAK2 V617F (HR, 2.02), age ≥ 57 years (HR, 2.43), and constitutional symptoms (HR, 2.80). The hazard ratio for death associated with the presence of 1, 2, or 3 of these prognostic factors was 3.08, 4.70, and 16.61, respectively (P < .001).

MPD-RC 101 Trial

Also at the 2011 ASH annual meeting, Rondelli and colleagues presented findings from the Myeloproliferative Diseases Research Consortium (MPD-RC) 101 trial [50]. The MPD-RC 101 trial was the first U.S. prospective phase II trial of allogeneic HSCT in patients with primary MF. The trial enrolled 66 patients who received allogeneic transplantsations from a related (n = 32) or unrelated (n = 34) donor following RIC with fludarabine and melphalan with or without ATG. The median patient age was 54 to 55 years. Most patients (n = 63) were at intermediate/high risk by Lille scoring, and 3 patients were low risk but had thrombocytopenia.

Recipients of unrelated transplantsations had a high rate of primary graft failure (26%), leading to a high rate of transplantation-related mortality. Indeed, non-relapse mortality was more than 3-fold higher in the unrelated donor group compared with the related donor group (53% versus 17%), although the risk of relapse-related mortality was similar (3% versus 4%). Furthermore, overall survival was 44% at 1 year in the unrelated group, compared with 78% at 2 years in the related group. Therefore, findings from the MPD-RC 101 trial suggest that while the Flu/Mel regimen was effective in patients with MF transplanted from related donors, a different conditioning regimen may be required for unrelated transplantsations.

Reduction Barriers to Transplantation Success

Known barriers to transplantation success include graft failure, non-relapse mortality, GVHD, hepatotoxicity, and late referral. Several other patient- and disease-related factors contribute to these barriers, and therefore may represent opportunities for improvement. For instance, bone marrow fibrosis, significant splenomegaly, and a heavy transfusion history increase the risk of graft failure.

Non-relapse mortality is higher in patients with poor performance scores and higher symptom burdens. This suggests that improving the patient’s performance status and reducing the burden of symptoms prior to transplantation may also reduce the risk of non-relapse mortality. The use of RIC regimens also appears to reduce the risk of early transplantation-related mortality. Strategies to reduce circulating cytokine levels—for example, via the use of JAK inhibition—may reduce the risk of GVHD. Other approaches to improving transplantation success may involve reducing posttransplantation hepatotoxicity via better screening for portal hypertension and other risk factors.

Determining the optimal time for HSCT in patients with MF requires a careful assessment of the potential benefits and risks of transplantation. Ideally, transplantation is performed in younger patients with earlier disease and...
better prognostic scores. These are the patients with the best chance for transplantation success, yet they are equally likely to achieve successful outcomes with non-transplantation options. Indeed, given the high risk of nonrelapse mortality and transplantation-related morbidity, HSCT may serve only to shorten lifespan and erode the quality of life for these patients. Delaying transplantation until the disease progresses, however, carries its own risks. As transplantation is delayed, the patient may develop splenomegaly, portal hypertension, iron overload, and other risk factors for poor transplantation outcomes. Timely referral to HSCT is important to reduce the incidence of leukemic transformation. Restricting allogeneic HSCT for use only in older patients and those with advanced disease, worse prognostic scores, and/or constitutional symptoms will result in a high risk of transplantation failure.

The ideal treatment algorithm for patients with MF is a work in progress. Important considerations include survival time, potential loss of life-years with each treatment strategy, the cost of quality-adjusted life years, and the risks of treatment delay. Modeling studies are currently comparing early, late, and risk-adapted transplantation algorithms. New data to support clinical decision-making are expected soon.

**Summary**

Recent evidence shows a slow increase in HSCT activity for patients with MF. Reduced-intensity transplantation is now widely practiced, with Flu-Bu and Flu-Mel among the most common conditioning regimens. Special risk situations related to advanced disease remain a treatment challenge, but ongoing studies are attempting to better understand these patients. The ideal prognostic classification system for MF remains undefined, although the Lille and DIPSS-plus scoring systems are useful tools in both the research and clinical practice settings.

The place of allogeneic HSCT for patients with MF remains unclear, particularly in the era of molecular targeted therapy with JAK1/2 inhibition. In the absence of stronger clinical evidence, the selection of patients with MF for HSCT falls more into the realm of art than science.

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**Designing Individualized Care Plans for Patients with Myelofibrosis: JAK1/2 Inhibition versus Stem Cell Transplantation**

**Vikas Gupta, MD, FRCP, FRCPath**

With the development of JAK1/2 inhibitor therapy, patients with MF have new options for decreasing symptom burden, reducing splenomegaly, relieving constitutional symptoms, and improving quality of life. Despite these potential benefits, however, JAK1/2 inhibition is not curative, and does not reduce the risk of leukemic transformation. Determining optimal treatment for patients with MF requires an individualized assessment of the potential benefits and limitations of each therapeutic option.

**Selection of First-Line Treatment in Myelofibrosis**

The first step in treatment selection is prognostic assessment and risk stratification using DIPSS or, if cytogenetic information is available, DIPSS-plus. Figure 1 illustrates suggested approaches to selecting first-line treatment with transplantation or JAK1/2 inhibitor therapy in patients with MF by risk classification [29,51]. Separate algorithms are suggested for patients with intermediate-1/low-risk MF and for those with intermediate-2/high-risk MF. Patients who fall into the intermediate-2/high-risk category have a median survival of approximately 1.5 to 4 years (Table 1) [12]. For these patients, discussing treatment options can facilitate the selection of curative versus palliative therapy. Patients who prioritize symptom control are appropriate candidates for JAK1/2-inhibitor therapy, which may include treatment with ruxolitinib as the current standard of care or referral to a clinical trial. Additional treatment modalities can address individual symptoms, such as anemia, splenomegaly, and constitutional symptoms. Watchful waiting is an appropriate option for patients with asymptomatic disease.

For patients with low/intermediate-1 risk disease, treatment selection requires careful evaluation of symptoms and risk factors, including the risk of leukemic transformation.

**Table 1. Estimated Median Survival by DIPSS Risk Group**

<table>
<thead>
<tr>
<th>DIPSS Risk Group</th>
<th>Score</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>Not reached</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>1-2</td>
<td>14.2 years</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>3-4</td>
<td>4 years</td>
</tr>
<tr>
<td>High</td>
<td>5-6</td>
<td>1.5 years</td>
</tr>
</tbody>
</table>

* DIPSS indicates Dynamic International Prognostic Scoring System for primary myelofibrosis.

Asymptomatic patients with a low risk of leukemic transformation can be followed conservatively, with a follow-up evaluation every 3 to 4 months and a recalculation of the DIPSS or DIPSS-plus risk score at each visit. For patients who are symptomatic and have a low risk of leukemic transformation, treatment with current JAK1/2-inhibitor therapy or referral to a clinical trial is an appropriate treatment option.

For patients who are deemed to be at high risk of leukemic transformation, transplantation is the reasonable treatment option, even if they fall into the intermediate-1 risk group. Patients in this category tend to be heavily transfusion-dependent with unfavorable cytogenetics and severe thrombocytopenia.

**Case Presentation**

A 61-year-old gentleman presented in March 2000 with thrombocytosis (platelet count, 865 10⁹/L). After a bone marrow biopsy, he was diagnosed with essential thrombocythemia, which was treated with aspirin alone. Once a diagnostic assay for the JAK2V617F mutation was available, he was tested and was found to be positive. In 2008, 8 years after diagnosis, a palpable spleen was noted on clinical examination. Over time, a slowly progressive increase in spleen size was documented, and by December 2012 the spleen size was 16 cm below the costal margin. He had also been experiencing a progressive decline in hemoglobin (Hb). In September 2012, a complete blood count showed the following: Hb, 9 g/L; white blood cell count, 17.9 10⁹/L with left shift; platelet count, 216 10⁹/L. There were no circulating peripheral blood blasts. A trial of erythropoietin was performed with no response. The most recent bone marrow biopsy, performed in December 2012, shows grade 2/3 fibrosis and normal cytogenetics (46, XY). At this time, a diagnosis of post-ET MF was made according to the IWG-MRT criteria.

The patient started his first RBC transfusion in December 2012. Within 3 months, it was established that his transfusion need is 2 units...
of red cells every 4 weeks. A donor evaluation revealed that he does have an HLA-matched sibling donor available. The patient has excellent performance score and no other comorbidities. He is a very motivated individual. He experiences infrequent night sweats but no other significant constitutional symptoms. His only symptom is abdominal discomfort from the spleen and the nuisance of having 2 units of red cells every 4 weeks.

Based on the patient's history and current presentation, what treatment approach is recommended?
- Carefully watch and wait
- Hydroxyurea
- JAK1/2 inhibitor therapy, reserving HSCT for failure of JAK therapy
- Upfront HSCT using the matched sibling donor
- Other options

**Case Discussion: Treatment Selection**

Anemia appears to be the only risk factor for this patient. Utilizing the DIPSS criteria, this patient falls into the intermediate-1 risk category, which is associated with a median survival of 14.2 years (Table 1) [12]. Under the DIPSS-plus criteria, however, transfusion dependency is counted as second risk factor. Applying this scoring system, the patient falls into the intermediate-2 risk category, which has a median overall survival of 2.9 years [13]. Therefore, this case highlights the occasional gross discrepancy between the DIPSS and DIPSS-plus risk-stratification tools.

Estimating the risk of leukemic transformation is helpful to further understand patient prognosis. In 2012, Tefferi and colleagues described a risk model for predicting leukemic transformation in patients with MF [51]. The model assigns points to 3 risk factors: very high-risk karyotype (2 points), peripheral BP blast ≥ 2% (1 point), and platelet count ≤ 50 109/L (1 point). In this model, the very high-risk cytogenetic category included patients with monosomal karyotypes and inv(3) or i(17q) abnormalities. Based on total points, risk of transformation at 3 years is 3%, 10%, and 35%, respectively. In the current case, the patient has no risk factors (0 points) and falls into the low-risk category for leukemic transformation.

**Figure 1. Suggested Approach to First-Line Treatment for Myelofibrosis by Risk Classification [48,51].** *Risk of LT according to IWG-MRT criteria using cytogenetics, thrombocytopenia and PB blast %. BMT indicates bone marrow transplantation; HCT, hematopoietic cell transplantation; Int-1, intermediate-1; Int-2, intermediate-2; JAK, Janus kinase; LT, leukemic transformation; MF, myelofibrosis.

**Case Discussion: Risk Assessment**

Anemia appears to be the only risk factor for this patient. Among therapies used for symptom management, the patient has already failed a trial of erythropoietin. Immunomodulators are an option, although these agents typically are not effective in reducing splenomegaly. Hydroxyurea may exacerbate the patient's transfusion dependence.

The patient has an HLA-matched sibling donor available, which is an important consideration for transplantation. According to recent CIBMTR data, the median 5-year overall survival rate is 58% for patients with MF who undergo reduced-intensity allogeneic HSCT with HLA-matched sibling donor grafts [29]. Another option is upfront treatment with JAK1/2 inhibition with currently available therapy or via referral to a clinical trial. This strategy allows allogeneic HSCT to be delayed until first-line treatment failure, if needed.

Figure 2 illustrates another approach to upfront treatment selection for patients with MF based on an assessment of patient, disease, and transplant factors [29]. In the context of patient factors such as advanced age, poor performance status, and prohibitive comorbidities, treatment with JAK1/2-inhibitor therapy may be preferred. Upfront treatment with JAK1/2 inhibition may also be appropriate for patients with severe complications such as portal hypertension. Factors such as a high risk of leukemic transformation and the availability of well-matched donor, however, favor the use of allogeneic HSCT.

In summary, as illustrated by this case discussion, choosing between upfront allogeneic HSCT and JAK1/2-inhibitor therapy for MF requires the development of a personalized treatment plan. Treatment goals, whether curative or palliative, should be established based on a careful assessment of patient preferences and a comparison of the potential benefits and risks of each therapeutic option. For some patients, access to therapy is a barrier that must be considered and addressed. Physician preferences may also influence decisions regarding upfront treatment for MF.

**Combination Treatment with JAK1/2 Inhibition and HSCT**

There is increased interest in the potential role of a combination strategy that incorporates both JAK1/2-inhibitor therapy and allogeneic HSCT. Investigators are currently evaluating this approach in the MPD-RC 114 trial [52]. This ongoing phase II trial will include patients with advanced primary MF or post-PV/ET MF who are eligible for transplantation. All
patients will be treated with ruxolitinib for 60 days prior to the start of standard Flu/Bu RIC and allogeneic HSCT. Patients with unrelated donors will also receive treatment with ATG.

The primary endpoint is survival without graft failure at day 100 posttransplantation. An additional goal of the MPD-RC 114 trial is to determine whether adding ruxolitinib to the pretransplantation regimen will reduce spleen size, improve performance status, and reduce adverse events related to allogeneic HSCT.

**Summary**

In the JAK1/2 inhibitor era, allogeneic HSCT remains an appropriate first-line treatment option in selected patients with MF. Most of the patients selected for HSCT have intermediate-2/high-risk disease, although transplantation is also reasonable for those with intermediate-1 disease with transfusion dependency or unfavorable cytogenetics. The selection between allogeneic HSCT and JAK1/2-inhibitor therapy should be individualized on the basis of patient preference as well as other patient-, disease-, and transplant-related factors. In the future, the combined use of JAK1/2-inhibitor therapy in the transplantation setting may help in overcoming some of the current issues with allogeneic HSCT in patients with MF.

**References**

Clinical Advances in the Management of Myelofibrosis

CME Assessment Test

1. Which of the following is required to meet the World Health Organization (WHO) diagnostic criteria for primary myelofibrosis (MF)?
   A. Anemia
   B. Palpable splenomegaly
   C. Presence of megakaryocyte proliferation
   D. Elevated serum lactate dehydrogenase

2. Which of the following prognostic scoring systems incorporates information on cytogenetic abnormalities in patients with MF?
   A. Lille scoring system
   B. International Prognostic Scoring System (IPSS)
   C. Dynamic IPSS (DIPSS)
   D. DIPSS-Plus

3. JAK1/2-inhibitor therapy is beneficial only in patients with MF who harbor the JAK2 V617F mutation.
   A. True
   B. False

4. Which of the following is NOT associated with JAK2/2 inhibitor therapy in patients with MF?
   A. Reduction in spleen volume
   B. Prevention of leukemic transformation
   C. Reduction in total symptom score
   D. Hematologic adverse events

5. In patients with MF undergoing allogeneic hematopoietic stem cell transplantation (HSCT), asymptomatic portal hypertension is a risk factor for:
   A. Graft rejection
   B. Delayed engraftment
   C. Posttransplantation relapse
   D. Posttransplantation hepatotoxicity

6. In the phase II Myeloproliferative Diseases Research Consortium (MPD-RC) 101 study of reduced intensity conditioning (RIC) with fludarabine/melphalan followed by allogeneic HSCT, the risk of non-relapse mortality was highest in which patient group?
   A. Patients with related donors
   B. Recipients of unrelated grafts
   C. Patients with wild-type JAK2 V617F
   D. Patients with baseline constitutional symptoms
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