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Symposium Report

Risk Factors and New Methods of Treatment of Myelofibrosis: Transplantation in the Era of JAK Inhibitors

Adapted from a continuing medical education symposium presented at the 2015 BMT Tandem Meetings on February 14, 2015, in San Diego, California.

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Statement of Need

The goal of this educational program is to equip transplant specialists, oncologists, hematologists, and other healthcare professionals involved in the treatment of hematologic malignancies with the up-to-date clinical knowledge and tools they need to best treat their patients with Myelofibrosis.

Myelofibrosis (MF) is a rare myeloproliferative neoplasm (MPN), which are diseases of the blood and bone marrow where an excess number of blood stem cells become platelets red blood cells or white blood cells. An important feature of MF is the production of too many megakaryocytes, giant cells in the marrow that break up into fragments and produce hundreds to thousands of platelets. This leads to the release of cytokines in the marrow. The cytokines stimulate the development of scar tissue in the marrow, called fibrosis. The platelets' normal function is to stick to the site of a blood vessel injury and form a clot to seal off the injured blood vessel to stop bleeding. The body makes new platelets to replace used platelets. The megakaryocytes can become so abnormal that platelet production decreases in some patients.

MF occurs mostly in the elderly population, specifically between 60-70 years of age. The prevalence of MF is estimated at between 0.1 to 1 in 100,000 people per year, according to a European study by Moulard et al. Additionally, in 10-15% of MF cases, the disease arises from other myeloproliferative diseases like polycythemia vera (PV) or primary/essential thrombocythemia (ET). When MF follows another myeloproliferative disease, it is secondary MF whereas MF starting on its own is called primary myelofibrosis (PMF).

For most people who have myelofibrosis (MF), there are no obvious risk factors why they developed the disease. The disease starts as one of two other myelo-proliferative diseases, either polycythemia vera or primary thrombocythemia, in about 10 percent to 15 percent of people with MF. Physicians do not fully understand the cause of MF. MF results from a mutation in a stem cell in the bone marrow, which leads to uncontrolled

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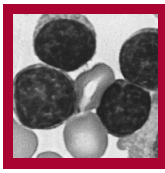

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blood cell production. Abnormal cell production gradually overtakes production of normal red cells, white cells and platelets. Too few red cells are made, and usually too many platelets and white cells are made. Eventually, there are more abnormal cells in the marrow than there are normal cells.

About 50% of MF patients have a mutation in the JAK2 kinase called V617F. The discovery of the JAK2 mutation in the pathogenesis of MF and other diseases led to the idea that the JAK pathways are good targets for drug therapy in MF. A new class of drugs has been created based on this discovery: oral JAK2 inhibitors. Despite the value shown by use of JAK2 inhibitors, currently, the only treatment for MF that has shown to have curative qualities is hematopoietic stem cell transplantation (HCT). When a patient is diagnosed with PV or ET, it can progress to myelofibrosis or acute myeloid leukemia. However, allogeneic stem cell transplantation (ASCT) can prevent this progression, which involves a transplant from a donor. In some cases, survival rates with ASCT are between 40-60%. ASCT is more effective in certain patients, and the new findings with JAK inhibitors could work well in combination with transplants in eligible patients. More research on this is likely to shed light on this new combination therapy.

Learning Objectives

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

1. Identify the Risk Factors and Optimal Timing of HCT for Myelofibrosis
2. Evaluate the Benefits of Non-transplant Treatment Options
3. Assess the Increased Use of Stem Cell Transplantation in Combination with JAK inhibitor Treatment

Target Audience

This activity has been developed and is intended for transplant specialists, oncologists, hematologists, and other healthcare professionals involved in the treatment of myelofibrosis.

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John R. Wingard, MD, has no relevant financial relationships to disclose.

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Myelofibrosis: To JAK and Back?

Randy A. Brown, M.D. and John R. Wingard, M.D.

Although myelofibrosis (MF) is the least common of the myeloproliferative neoplasms, it is the most lethal with a median survival of only 3-5 years. Cytopenias and leukemic transformation are the major causes of death. For many years palliation of symptoms with alkylating agents or hydroxyurea was the only therapy available and this had little or no effect on the survival of patients with MF.

Stem cell transplantation was the first major step forward in the treatment of this disease. Early retrospective analysis using myeloablative preparative regimens demonstrated that 40-50% of patients achieved 3-5 year disease-free survival with late relapse being uncommon. However, transplant related mortality (TRM) was as high as 50% so that this procedure was limited to younger patients without major comorbidity's. Given that the median age of patients with MF is around 65 years, transplant was applicable to a small minority of patients.

Limited therapeutic options and the hope of developing highly effective targeted therapy led to great excitement when, in 2005, the JAK-2 V617F mutation was described in the majority of patients with MF. Ruxolitinib, a selective inhibitor of JAK 1 and 2 entered clinical trials soon thereafter. Two pivotal, randomized trials (COMFORT 1 and 2) were carried out and demonstrated that durable reduction in spleen volume and symptom scores were significantly more common with ruxolitinib compared with the control arms. Based on these results, ruxolitinib became the first FDA approved treatment for MF in 2011.

Unlike imatinib in CML however, ruxolitinib does not produce remission in patients with MF and there is no evidence that this drug alters the course of the disease. Cytopenia often worsens, fibrosis persists and there is no evidence that the risk of leukemic transformation is reduced. In the COMFORT trials, with a median follow-up of 3 years, only 50% of all patients remained on the drug due to toxicity or progression. In short, while ruxolitinib may be more effective at relieving symptoms than hydroxyurea, it is nonetheless palliative care. Further, for MF patients with high-risk features and for those with severe cytopenias, we are "back" to transplant as the most effective approach.

The current issue of *Blood and Marrow Transplantation Reviews* provides a concise review of current therapeutic options for MF in the era of JAK-2 inhibitors. Dr. Gupta starts by reviewing prognostic models that allow physicians to make decisions about the optimal timing of transplant in patients with MF. Next, Dr. Michaelis examines risk stratification tools in the context of novel conventional therapies. Finally, Dr. Hari addresses current approaches to stem cell transplantation in MF, including the role of reduced intensity preparative regimens and the use of novel agents to improve outcomes.

Introduction

Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) characterized by debilitating constitutional symptoms, bone marrow fibrosis, cytopenias, and marked spleen enlargement resulting from extramedullary hematopoiesis. Among the MPNs, MF is associated with the greatest symptom burden and worst prognosis. Historically, treatment has focused on controlling the clinical manifestations of MF with conventional therapy. Erythropoietin, corticosteroids, androgens, and immunomodulating drugs (IMiDs) such as thalidomide, lenalidomide, and pomalidomide have been used to manage anemia. For splenomegaly, treatment approaches have included hydroxyurea, splenectomy, and low-dose irradiation.

Most conventional therapies, however, are limited by poor efficacy and a lack of prospective clinical data in patients with MF. Moreover, these approaches are largely palliative and do not address the underlying disease process in MF. In current practice, allogeneic hematopoietic stem cell transplant (HSCT) is the only curative therapy for MF. However, transplantation is associated with significant risks of toxicity, graft failure, and graft-versus-host disease (GVHD), and transplant-related mortality (TRM). Although the potential benefits of HSCT outweigh the risks for patients with severe disease, the appropriate role of HSCT remains controversial for patients with lower-risk disease.

Dysregulation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway is a hallmark of the underlying pathogenesis of MF. With the advent of JAK inhibitor therapy, patients with MF have new options for reducing symptom burden, improving quality of life, and delaying the need for transplant. JAK inhibitor therapy is not curative, however, and treatment does not reduce the risk of leukemic transformation. Selecting upfront therapy for MF requires an individualized assessment of each patient's biological characteristics, symptom burden, and overall treatment goals. Future treatment strategies may include new approaches for targeting the JAK/STAT signaling pathway, agents with novel mechanisms of action, and the combined use of JAK inhibitors and allogeneic HSCT to optimize patient outcomes in MF.

Identifying the Risk Factors and Optimal Timing of HCT Myelofibrosis

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Given the risks associated with allogeneic HSCT, appropriate patient selection is of paramount importance. Transplant eligibility for patients with MF is based on multiple criteria that may differ across treatment centers. Historically, the typical candidate for allogeneic HSCT has been younger (eg, aged <70 years) with reasonable performance status and no prohibitive comorbidities. The ideal age range for transplantation in MF varies by institution, and some centers forgo defining any specific age threshold for transplant eligibility.

Identifying Candidates for Transplantation

In the absence of standardized clinical guidelines, risk-assessment tools such as the Dynamic International Prognostic Scoring System (DIPSS) are often used to understand the natural history of disease. Patients with DIPSS intermediate-2 and high-risk disease are considered appropriate transplant candidates, given the poor prognosis within this group. The median survival for patients with intermediate-2 and high-risk disease by DIPSS is approximately 4 years and 2.3 years, respectively [1].

Transplantation is a controversial treatment option for MF patients with less advanced disease, including those with intermediate-1 risk according to DIPSS. Within this cohort, allogeneic HSCT is generally reserved for patients with features such as high-risk cytogenetics. Transplantation may be appropriate for severely cytopenic patients, including those who are transfusion-dependent and refractory to conservative treatment options. Patients with severe thrombocytopenia (eg, platelet count < 50 x 109/L) are also potential candidates for allogeneic HSCT, given the inability to administer sufficient doses of JAK inhibitor therapy in these patients. The presence of high-risk mutations also favors more aggressive treatment. Patients with MF who harbor the ASXL1 mutation, particularly in combination with wild-type calreticulin (CALR) status, have a poor prognosis [2].

Benefit of Transplantation in Intermediate-2 and High-Risk Patients

Allogeneic HSCT offers a potential survival benefit for select patients with intermediate-2 and high-risk MF. In 2014, Kröger and colleagues presented findings from a retrospective analysis of MF patients aged 65 years or younger treated with allogeneic HSCT (n = 190) or conventional therapy (n = 248) in the pre-ruxolitinib era [3]. The survival analysis compared ASCT with non-transplant approaches according to baseline DIPSS risk score (Table 1).

In patients with low-risk disease, transplantation was associated with an increased risk of death compared with conventional therapy. Conversely, patients with intermediate-2 and high-risk disease according to DIPSS appeared to benefit from undergoing allogeneic HSCT at some point during their disease history. The optimal treatment approach was unclear for patients with intermediate-1 risk disease, highlighting the importance of individualized risk assessment and treatment planning in this risk group.

Algorithm for Upfront Therapy Selection

In the current JAK inhibitor era, the selection of upfront treatment for patients with MF should be based on a careful assessment of individual patient, disease, and transplant factors (Figure 1) [4]. In addition, the potential benefits of upfront therapy should be weighed against the potential risks of treatment. In the context of patient factors such advanced age, poor performance status, and prohibitive comorbidities, treatment with JAK-inhibitor therapy or referral for a clinical

Table 1. Risk of Death Following Allogeneic Stem Cell Transplantation Versus Conventional Therapy by DIPSS Category in Patients Younger than 65 Years with Primary Myelofibrosis [3]

DIPSS Risk Category	10-Year Survival		RR of Death (95% CI)	*P* Value
	Allogeneic HSCT	Conventional Therapy		
Low risk	60%	92%	5.6 (1.7-19)	.0051
Intermediate-1 risk	41%	63%	1.6 (0.79-3.2)	.19
Intermediate-2 risk	32%	11%	0.55 (0.36-0.83)	.005
High risk	27%	1%	0.37 (0.21-0.66)	.0007

DIPSS = Dynamic International Prognostic Scoring System; HSCT = hematopoietic stem cell transplantation; RR = relative risk.

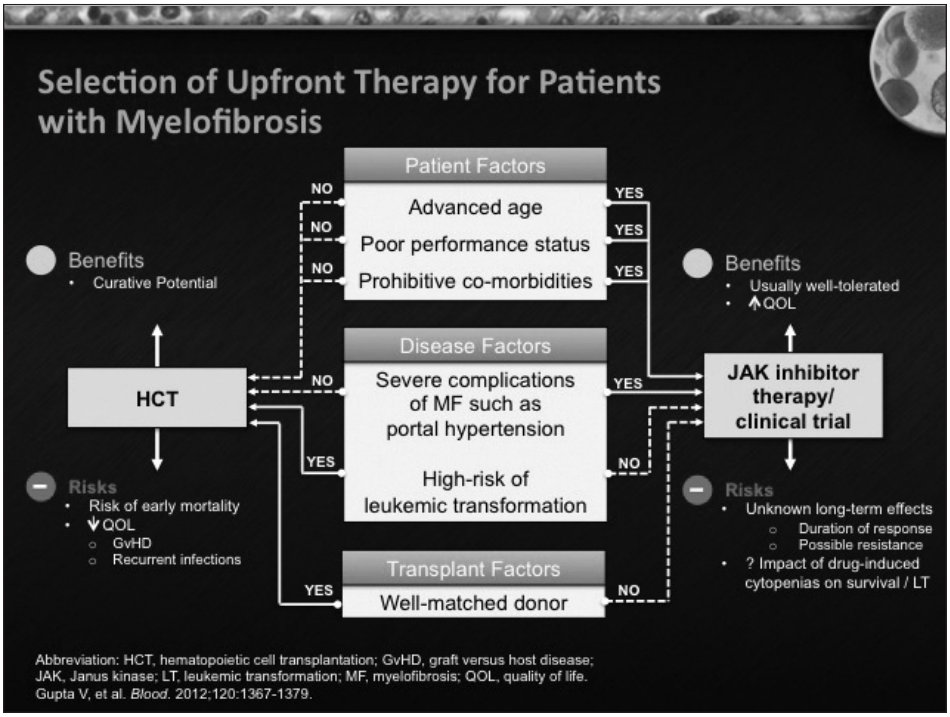

Figure 1. Selection of upfront therapy for patients with myelofibrosis [4].

trial may be preferred. Upfront JAK inhibitor therapy or clinical trial referral may also be preferred for patients with severe complications such as portal hypertension. In contrast, factors such as a high risk of leukemic transformation and the availability of an HLA well-matched donor favor the selection of allogeneic HSCT.

Recent findings from the Center for International Blood and Marrow Transplant Research (CIBMTR) underscore the importance of donor type as a key consideration for transplant eligibility in patients with MF [5]. The CIBMTR analysis evaluated survival following allogeneic HSCT with reduced-intensity condition (RIC) in patients with primary MF according to donor type: HLA-matched sibling donor (n = 79), HLA well-matched unrelated donor (n = 104), and partially matched/mismatched donor (n = 50). The adjusted probabilities of 5-year survival in these patient cohorts were 56%, 48%, and 34%, respectively (P = .002).

The CIBMTR findings indicate that allogeneic HSCT with RIC is a potentially curative option for select patients with primary MF, with the best survival outcomes observed in patients with HLA-matched sibling donors and HLA well-matched unrelated donors [5]. For patients with a mismatched donor, an alternative approach involves upfront treatment with JAK1/2 inhibition or via referral to a clinical trial. This treatment strategy allows allogeneic HSCT to be delayed until first-line treatment failure, if needed.

Optimal Timing of Allogeneic HSCT in Myelofibrosis

For patients with MF who have initiated upfront treatment with JAK inhibitor therapy, choices around the use and timing of transplantation are complex. In general, there are three potential time points within the natural history of MF that may be most appropriate for HSCT [6]. The first option involves initiating HSCT while patients are experiencing their peak response to JAK inhibitor therapy. This includes patients who meet the standard International Working Group (IWG) criteria for clinical response or stable disease.

The second approach involves delaying HSCT while patients continue to derive a clinical benefit from JAK inhibitor therapy, and considering transplantation only when the patient's status begins to deteriorate [6]. Using this approach, transplant may be appropriate in patients who develop the following:

- Intolerable treatment-related side effects
- Worsening anemia or increased transfusion dependence
- Increased blast count (10% to 19%)
- Inadequate response or loss of response requiring a change in treatment

In the third approach, transplant is further delayed until the patient shows clear signs of disease progression on JAK inhibitor therapy [6]. Potential triggers for considering HSCT in this model may include:

- Progression of splenomegaly
- Need for splenectomy
- Blasts >20%

At present, there is limited clinical evidence to determine the optimal timing of transplantation in patients who have initiated JAK inhibitor therapy. Findings from ongoing observational studies of post-JAK inhibitor transplant in MF, expected within the next year, are eagerly awaited to provide clarity around these challenging treatment decisions.

Barriers to Successful Transplantation

Common barriers to successful outcomes for patients with MF undergoing allogeneic HSCT include regimen-related toxicities, graft failure, and graft-versus-host disease (GVHD).

Posttransplantation Hepatotoxicity

Patients with MF are predisposed to underlying liver injury and dysfunction. In 2012, Wong and colleagues described poor outcomes associated with early hepatotoxicity following allogeneic HSCT in patients with MF (n = 53) [7]. During the first 6 weeks after HSCT, 43% of patients with MF developed moderate or severe hyperbilirubinemia and 6% experienced a substantial increase in aspartate aminotransferase levels. Compared with patients without signs of liver injury, survival at 12 months was significantly worse for patients who developed early posttransplant hyperbilirubinemia or elevated transaminase levels (P = .02). Given the potential for posttransplant hepatotoxicity, patients with MF should be screened prior to transplant for risk factors such as asymptomatic portal hypertension, iron overload, and the presence of portal and splanchnic thrombi.

Graft Failure

To date, two prospective studies have examined the safety and efficacy of allogeneic HSCT in patients with MF [8, 9]. In a study from the European Group for Blood and Marrow Transplantation (EBMT), the rate of auto primary graft failure was 2%. In addition, 11% of patients required a stem cell boost [8]. In the Myeloproliferative Disorders Research Consortium (MPD-RC) study, the overall risk of primary and secondary graft failure was as high as 24% for patients undergoing allogeneic HSCT with an unrelated donor [9].

The underlying mechanisms driving graft failure in patients with MF are not well understood. Marrow fibrosis, significant splenomegaly, and transfusion dependency may contribute to an increased risk of graft failure. Proinflammatory cytokines, which are elevated in advanced MF, may also play a role in graft failure following transplantation [10]. In preclinical models of MPNs, tumor necrosis factor (TNF)-alpha had been shown to suppress the expansion and renewal of normal hematopoietic stem cells while facilitating the expansion of JAK2-expressing cells [10, 11]. In addition, bone marrow niche appear to contribute to graft failure [12].

Graft Versus Host Disease

In the recent CIBMTR analysis of transplant-related outcomes, the cumulative incidence of grade 3 and 4 acute GVHD at 100 days following allogeneic HSCT with RIC was 19% [5]. In a multivariate analysis, the use of an unrelated donor was associated with a significant increase in the risk of developing acute GVHD ($P = .02$). Compared with a matched sibling donor, the relative risk (RR) for acute GVHD was 1.98 for well-matched unrelated donors ($P = .006$) and 1.52 for partially matched/mismatched unrelated donors ($P = .18$).

As described above, proinflammatory cytokines have been implicated in the pathophysiology and clinical manifestations of MF. Future research may examine whether the underlying chronic inflammatory state of MF also contributes to the high incidence of severe acute GVHD following HSCT, even among patients undergoing RIC transplantation.

Current Role of JAK Inhibitors in Transplantation Protocols

Strategies to reduce the risk of graft failure, acute GVHD, and TRM are needed to improve outcomes for patients with MF undergoing allogeneic HSCT. Targeting the JAK/STAT signaling pathway has proven to be an effective approach to controlling some of the clinical manifestations of MF, particularly splenomegaly, and altering the natural history of the disease. Approximately 50% of patients with primary MF have the JAK2 V617F gain-of-function mutation. In addition, the proinflammatory cytokines and growth factors implicated in the pathogenesis of MF 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.

Table 2. JAK1/2 Inhibition in Transplant-Eligible Patients with Myelofibrosis

Study	No. Patients	Study Design	Results	Conclusions
Jaekel 2014 [14]	14	Retrospective	Engraftment in 13 patients (93%); graft fibrosis (n = 1) and treatment related sepsis (n = 1)	Tapering ruxolitinib until conditioning did not result in unexpected SAEs
Shanavas 2014 [15]	6	Retrospective	No adverse impact on early post-HSCT outcomes	Tapering ruxolitinib until conditioning did not result in unexpected SAEs
Stübig 2014 [16]	22	Retrospective	1-year OS of 100% in patients with a good response to ruxolitinib vs. 60% in others	Continuing ruxolitinib until conditioning without taper resulted in no unexpected SAEs
Lebon 2013 [17]	11	Retrospective	Good engraftment rates	Differing schedules of ruxolitinib tapering associated with high engraftment rates

HSCT, hematopoietic stem cell transplantation; OS, overall survival; SAE, severe adverse effect.

While the beneficial effects of JAK1/2 inhibitors on outcomes such as spleen size and quality of life are well documented, the potential effects of these agents on other endpoints is unclear. For instance, some evidence suggests that JAK1/2 inhibition may improve constitutional symptoms by reducing the activity of proinflammatory cytokines. The anti-cytokine effects of JAK1/2 inhibitor therapy may also reduce the risk of severe GVHD. Furthermore, achieving better performance status prior to HSCT may improve other transplant-related outcomes, including TRM.

Studies of JAK Inhibition in Transplant-Eligible Patients

Several research groups have explored the role of JAK inhibitor therapy in transplant-eligible patients with MF. The phase II JAK ALLO trial was designed to evaluate the effects of ruxolitinib in patients with intermediate- and high-risk MF who were candidates for allogeneic HSCT [13]. Recruitment stopped after 22 patients enrolled into the trial due to the development of unexpected severe adverse events in 3 patients, including tumor lysis syndrome (n = 1) and cardiogenic shock (n = 2). The implications of the JAK ALLO trial are difficult to interpret given the presence of confounding factors such as the use of splenectomy prior to transplantation.

On the contrary, preliminary findings from four other retrospective studies provide some insight into the potential use of JAK inhibitors prior to allogeneic HSCT in patients with MF (Table 2). In contrast to the JAK ALLO trial, these studies have found favorable outcomes that support the use of ruxolitinib in patients with MF who are candidates for transplantation [14-17].

For patients who initiate treatment with ruxolitinib prior to allogenic HSCT, abrupt discontinuation is not recommended. In the COMFORT-I study, interrupted ruxolitinib dosing was associated with a return of MF symptoms [18]. Although a small number of patients used a tapering strategy to discontinue ruxolitinib, most treatment interruptions occurred at total daily doses of ≥ 10 mg BID. Regardless of the ruxolitinib dose at the time of interruption, however, both the total symptom score and the worst single daily symptom score returned to baseline levels within 7 days of discontinuation.

The ongoing MPD-RC 114 is evaluating a combined treatment strategy that incorporates both JAK1/2-inhibitor therapy and allogeneic HSCT [19]. The 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 full-dose ruxolitinib for 56 days followed by 4 days of tapered dosing prior to the start of reduced-intensity fludarabine/busulfan conditioning followed by allogeneic HSCT. The primary endpoint is survival without graft failure at day 100 post-transplant. The MPD-RC 114 trial will also evaluate whether adding ruxolitinib to the pre-transplant regimen reduces spleen size, improves performance status, and reduces adverse events related to allogeneic HSCT.

In summary, allogeneic HSCT is an appropriate option for select patients with MF. In particular, transplantation appears to improve outcomes in patients with high-risk or intermediate-2-risk disease according to DIPSS, and in patients with intermediate-1-risk disease with unfavorable cytogenetics or certain clinical features such as transfusion dependency. The decision to pursue allogeneic HSCT should be based on patient preferences as well as other individual patient-, disease-, and transplant-related factors. The use of JAK inhibitor therapy in the transplant setting may address some of the current barriers to successful allogeneic HSCT in patients with MF.

Evaluating the Benefits of Non-Transplant Treatment Options

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Given the challenging nature of treatment decisions for patients with MF in the pre-transplant setting, accurate risk stratification tools are essential to guide patient management. To date, three major risk-assessment tools that incorporate clinical and cytogenetic features of MF have been validated. Additional risk-assessment models that incorporate novel molecular prognostic factors are also emerging.

Risk-Stratification Models in Myelofibrosis

IPSS

In 2009, the International Prognostic Scoring System (IPSS) was the first tool designed to assess prognosis and facilitate therapeutic decision-making in patients with MF (Table 3) [20]. The IPSS accounts for the presence of 5 features associated with worse prognosis at the time of diagnosis: age > 65 years, presence of constitutional symptoms, hemoglobin level < 10 g/dL, leukocyte count > 25 x 109/L, and circulating blast cells ≥ 1%. Constitutional symptoms include > 10% weight loss over the past 12 months and fever or substantial night sweats for at least 1 month.

The IPSS categorizes patients into 1 of 4 risk groups based on the presence of 0 (low risk), 1 (intermediate risk-1), 2 (intermediate risk-2) or ≥ 3 (high risk) of these variables. In the IPSS validation cohort (N = 1054), the median survival in each risk group was 135 months, 95 months, 48 months, and 27 months, respectively.

Table 3. IPSS and DIPSS Prognostic Scoring Systems for Myelofibrosis

	IPSS [20]	DIPSS [1]
Parameters	Points	
Median hemoglobin, g/dL	1	2
Median leukocytes, x 109/L	1	1
Circulating blasts, %	1	1
Constitutional symptoms	1	1
Age > 65 years	1	1
Risk Category	Total Score	
Low	0	0
Intermediate-1	1	1-2
Intermediate-1	2	3-4
High	≥ 3	5-6

IPSS = International Prognostic Scoring System; DIPSS = Dynamic IPSS.

DIPSS

In 2010, Passamonti and colleagues described the DIPSS as a tool for assessing the same risk factors of the IPSS in a time-dependent manner (Table 3) [1]. In the DIPSS validation cohort (N = 525), the presence of anemia demonstrated a higher adverse impact on survival (roughly double) relative to the other risk factors. Therefore, although the DIPSS and IPSS utilize the same 5 risk factors, the DIPSS assigns anemia a score of 2. Based on a maximum total score of 6 points, the DIPSS classifies patients into low (0 points), intermediate-1 (1-2 points), intermediate-2 (3-4 points), and high-risk (5-6 points) categories [1].

DIPSS-Plus

Research on cytogenetics has revealed the heterogeneity of the stem cell niche in MF, as well as the importance of mutational complexity in understanding patient prognosis. The DIPSS-plus scoring system builds on the DIPSS by incorporating unfavorable cytogenetics as well as transfusion dependency and thrombocytopenia as additional adverse prognostic factors (Table 4) [21]. In this risk-assessment model, unfavorable cytogenetics is defined as a complex karyotype or abnormalities that include +8, -7/7q-, i(17q), inv(3), -5/5q-, 12p-, or 11q23 rearrangement. With 3 additional prognostic factors added to the 6-point DIPSS, the total maximum DIPSS Plus score is 9. The DIPSS-plus scoring system classifies patients into low (0 points), intermediate-1 (1 points), intermediate-2 (2-3 points), and high-risk (≥ 4 points) categories. In the DIPSS Plus validation cohort (N = 793), the median survival times for patients in the low, intermediate-1, intermediate-2, and high-risk groups were 15.4 years, 6.5 years, 2.9 years, and 1.3 years, respectively [21].

The IPSS should be used to assess survival from the time of diagnosis, whereas the DIPSS and DIPSS Plus can be used to assess survival from any point during the disease course in patients with MF [1, 20, 21].

Emerging Risk-Assessment Tools

As new prognostic factors in MF are identified, risk-assessment tools are evolving to provide a more precise estimate of overall survival. Monosomal karyotypes are associated with more resistant stems cells that are less susceptible to conventional therapy [22]. The presence of any 2 of the following features is also associated with poor prognosis: >9% circulating blasts, leukocytes > 40 x 109/L, and unfavorable karyotype [22].

Multiple somatic mutations are now recognized as important prognostic factors in MF [22]. Approximately 91% of patients with primary MF carry a mutation in the CALR, JAK2, or MPL genes, whereas only 9% are triple-negative for these mutations [23]. Regardless of DIPSS-plus risk category, patients with triple-negative MF and those who harbor an ASXL1 mutation in the presence of wild-type CALR (CALR-/ASXL1+) are considered to have high-risk disease due to very poor prognosis [23]. In one study, the median survival for patients with CALR-/ASXL1+ MF was 2.3 years, compared with 9.6 years for those with CALR+/ASXL1- disease (P < .0001) [23].

Two new scoring systems have emerged to account for a range of clinical, cytogenetic, and molecular features in patients with MF [24, 25]. The mutation-enhanced IPSS (MIPSS) incorporates 8 prognostic factors to stratify patient risk: age >60 years; symptoms; anemia; thrombocytopenia; triple-negative status for JAK2, MPL, and CALR; JAK2+ or MPL+; ASKL1+; and SRSF2+ [24 25]. The median survival times for patients classified as low, intermediate-1, intermediate-2, and high-risk

Table 4. DIPSS-Plus Scoring System for Prognosis in Myelofibrosis [21]

Parameters	Points	
DIPSS low risk	0	
DIPSS intermediate-1 risk	1	
DIPSS intermediate-2 risk	2	
DIPSS high risk	3	
Unfavorable karyotype (-8,-7,-5, i17q,12p-, inv3, 11q23 or complex)	1	
Platelets < 100 x 109/L	1	
Transfusion need	1	
DIPSS-Plus Risk Category	**Total Score**	**Median OS**
Low	0	15.4 years
Intermediate-1	1	6.5 years
Intermediate-1	2-3	2.9 years
High	≥ 4	1.3 years

DIPSS = Dynamic International Prognostic Scoring System; OS = overall survival.

according to MIPSS were 26.4 years, 9.7 years, 6.4 years, and 1.9 years, respectively.

The genetics-based prognostic scoring system (GPSS) also incorporates the mutational status of JAK2, MPL, CALR, ASKL1, and SRSF2 genes, as well as high-risk and very high-risk karyotypes, to define risk categories. Using the GPSS stratification system, the median overall survival times for patients with low, intermediate-1, intermediate-2, and high-risk disease were not reached, 9 years, 5 years, and 2.2 years, respectively [25].

At present, the DIPSS-plus remains the gold standard for risk-stratification in MF. In the future, however, repeat molecular testing may be helpful to clarify prognosis and understand whether patients with MF are acquiring risk over the course of their disease.

Risk Categories and Symptom Heterogeneity

In 2014, Geyer and colleagues described distinct clusters of symptomatology and physical and laboratory findings in a large international study of patients with MPNs (N = 1470) [26]. Using the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS), patients rated the severity of 10 symptoms most representative of MPNs on a scale from 0 (absent) to 10 (worst imaginable). The cluster analysis identified 4 distinct symptom phenotypes among patients with MF (n = 329), with significant variations in the presence and severity of disease features such as leukopenia, thrombocytopenia, and enlarged spleen (Table 5).

When the symptom clusters were arranged by increasing mean MPN-SAF TSS, the proportion of patients with intermediate-2 or high-risk classification increased from 20.5% in the first cluster to 66.7% in the last (P = .001). Despite this correlation, however, the DIPSS was not effective in predicting high levels of symptom distress. Many patients with low and intermediate DIPSS scores experienced a significant symptomatic burden, suggesting that current prognostic scores are not ideal surrogates for symptom burden in MF. These findings underscore the heterogeneity of symptoms among patients with MF and the importance of assessing symptoms to clarify the goals of therapy.

Table 5. Symptom Clusters in Myelofibrosis [26]

Cluster	Prevalence in MF	DIPSS Risk Distribution	Cluster Description
Mild MF	46%	· Majority (79%) low risk (33%) or intermediate-1 risk (46%)	· Fatigue-dominant complaints · Shortest disease duration (<3 years in 61% of patients)
Moderate-I MF	32%	· Majority (77%) intermediate-1 risk (54%) or intermediate-2 risk (23%)	· Largest spleen size · Longest disease duration (>3 years in 50% of patients)
Moderate-II MF	16%	· Majority intermediate-1 risk (64%) · <5% low or high risk	· Many cognitive and nighttime-related complaints
High MF	4%	· Highest proportion of high-risk patients (33%) · No low-risk patients	· Most symptomatic group, with highest prevalence of cytopenias and prior thrombosis, hemorrhage, transfusions

DIPSS = Dynamic International Prognostic Scoring System; MF = myelofibrosis.

Table 6. Goals of Care in Myelofibrosis

Goals	Interventions	Considerations	Other
Cure	· Allogeneic HSCT	· High-risk, high-reward	· Limited eligibility
Control splenomegaly, prolong life	· JAK inhibitor therapy	· FDA-approved · Low toxicities · Symptom relief	· Duration of response not highly predictable · Cytopenias · Transient effects
Control splenomegaly, improve symptoms	· Referral to clinical trials	· Eligibilities · Access to newer medications	
Symptom management: anemia	· IMiDs · Hydroxyurea · Androgens · Steroids	· Specific to patient symptoms · No evidence of improved survival	· Combination therapies often lack data

FDA, Food & Drug Administration; HSCT, hematopoietic stem cell transplantation; IMiDs, immunomodulatory drugs; JAK, Janus kinase.

Current Therapies in Myelofibrosis

Goals of Care

Therapeutic decision-making in MF should incorporate patient preferences regarding the goals of care (Table 6). Educating patients and family members on treatment options and expectations can be critical for ensuring adherence to therapy. For many patients, allogeneic HSCT is not a realistic treatment strategy due to the presence of comorbidities, logistical considerations, or other concerns. Available interventions for controlling symptoms and prolonging life expectancy should also be discussed.

Ruxolitinib

Ruxolitinib is a selective inhibitor of Janus kinase 1 and 2 (JAK1/2), with potent clinical activity in patients with MF [27]. In 2011, ruxolitinib became the first agent to gain approval from the U.S. Food & Drug Administration (FDA) with a specific indication for MF. The approval of ruxolitinib was based on preliminary results from the phase III COMFORT-I and COMFORT-II studies [27 28]. To date, ruxolitinib remains the only agent approved for MF. Ruxolitinib was also approved recently for symptomatic PV that has failed optimal therapy with hydroxyurea and phlebotomy.

In 2015, investigators reported updated efficacy, safety, and survival data from the COMFORT-I study with a median follow-up of 3 years [29]. In the COMFORT-I trial, 309 patients with IPSS intermediate-2 or high-risk MF were randomly assigned to treatment with twice-daily oral ruxolitinib (n = 155) or placebo (n = 154). The primary efficacy endpoint was the proportion of patients with a reduction of spleen volume of ≥ 35% at 24 weeks as assessed by magnetic resonance imaging (MRI). In the updated 3-year analysis, approximately 50% of patients who were initially assigned to the ruxolitinib group remained on ruxolitinib treatment at the time of data cutoff. In addition, 100% of patients who were initially assigned to the placebo arm had either crossed over to ruxolitinib or discontinued therapy.

The long-term survival findings show a trend in favor of JAK1/2 inhibitor treatment. After a median follow-up of 149 weeks, 42 patients initially assigned to ruxolitinib had died, compared with 54 patients initially assigned to placebo. The hazard ratio favored

Table 7. Investigational JAK/STAT Inhibitors [30-32]

Name	Target	Efficacy	Possible Toxicity	Development Status
Pacritinib	JAK1, JAK2, JAK3, FLT3	Splenomegaly, symptoms, low risk of cytopenias	Gastrointestinal side effects	Phase III vs. best available therapy (PERSIST-1, PERSIST-2)
Momelotinib	JAK1, JAK2, JAK 3, JNK1, CDK2	Splenomegaly, symptoms, anemia	Neuropathy, thrombocytopenia	Phase III vs. ruxolitinib
NS-018	JAK2, SRC-family	Splenomegaly, anemia	Nausea, thrombocytopenia	Phase I/II
INCB039110	JAK1 selective	Symptoms, anemia	Fatigue, nausea	Phase II
Fedratinib	JAK1,2,3 TYK, FLT3, RET	Splenomegaly, symptoms	Wernicke's encephalopathy	Withdrawn

JAK = Janus kinase; STAT = signal transducer and activator of transcription.

patients originally assigned to ruxolitinib compared with those assigned to placebo (HR, 0.69; 95% CI, 0.46-1.03; P =.067). The high prevalence of crossover from placebo to ruxolitinib may have masked the true difference in survival between the treatment groups. In an exploratory analysis that corrected for the potential impact of crossover, the hazard ratio continued to favor treatment with ruxolitinib (HR, 0.36; 95% CI, 0.204-1.035).

Secondary efficacy endpoints such as splenomegaly may contribute to prolonged survival in the ruxolitinib group. At week 144, patients in the ruxolitinib group had a mean reduction in spleen volume of 34% and a mean reduction in palpable spleen length of 49% compared with baseline. The reduction in splenomegaly may be linked to survival through mechanisms such as improved lipid levels, reduced anorexia, and reduced risk of concomitant infections in the ruxolitinib group.

Myelosuppression is an expected class effect of JAK1/2 inhibition, given the key role of JAK2 in the erythropoietin and thrombopoietin signaling pathways. Among patients in the ruxolitinib group, the risk of developing grade 3 or 4 anemia or thrombocytopenia was highest during the first 6 months of treatment, followed by a substantial decrease over time. The mean hemoglobin levels and platelet counts also decreased within the first 8 to 12 weeks of ruxolitinib treatment. However, the anemia normalized over time, with hemoglobin levels reaching new steady-state levels by week 24. No new safety or tolerability issues with ruxolitinib arose during the long-term follow-up period.

An analysis of quality of life endpoints also favored long-term treatment with ruxolitinib. Initial improvements in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) scores, including scores in the individual domains of global health status/QOL, fatigue, role functioning, and physical functioning, were maintained through 144 weeks of follow-up. For patients with MF and severe fatigue, the improvements in fatigue and other quality of life outcomes may warrant continued treatment with ruxolitinib even in the absence of spleen response.

Overall, the updated COMFORT-I study showed durable reductions in spleen volume and meaningful improvements in quality of life measures among patients receiving ruxolitinib for a median of three years. The survival analysis also favored ruxolitinib treatment, despite substantial crossover from the placebo to active-treatment arms. These findings support the long-term use of ruxolitinib to improve outcomes in patients with MF.

Table 8. Novel Agents Under Evaluation in Myelofibrosis

Category	Activity	Efficacy	Possible Toxicity	Development Status
Telomerase inhibitors	Infusional, targets RNA template of telomerase reverse transcriptase	Fibrosis reversal; molecular response	Liver, intracranial hemorrhage	Imetelstat: phase II → phase III
Hedgehog inhibitors	Inhibition of smoothened (SMO)	Unknown	Unknown	· Phase I/II LDE-225 + ruxolitinib · PF04449913 in MF
Anti-fibrosing agents	Inhibits development of fibrocytes (SAP2)	Reduction of anemia, thrombo-cytopenia, and fibrosis in ruxolitinib combination	Unknown	· Simtuzumab + ruxolitinib · PRM-151 ± ruxolitinib
PI3K inhibitors/AKT inhibitors	Blocks PI3K/AKT/ pathway	Reduction of splenomegaly in ruxolitinib combination	Unknown	· Everolimus phase II trial · Ruxolitinib + BKM-120 phase II

mTOR = mammalian target of rapamycin; PI3K = phosphoinositide 3-kinase.

Future Non-Transplant Therapies in Myelofibrosis

Multiple investigational agents that target the JAK/STAT signaling pathway are currently under evaluation for the treatment of MF in phase II and III clinical trials (Table 7) [30, 31]. These include agents with broad activity against JAK, STAT, and other molecular targets (eg, pacritinib, momelotinib), as well as highly selective JAK1 inhibitors (eg, INCB039110) [30, 31]. Several novel therapies that alter the natural history of MF through alternate mechanisms of action are also under evaluation in clinical trials (Table 8) [32]. These include telomerase inhibitors, hedgehog inhibitors, anti-fibrosing agents, and inhibitors of the PI3K/AKT signaling pathway [32].

Several combination regimens are also being evaluated to address the molecular complexity and heterogeneity of MF. The goal of ruxolitinib-based combination therapy is to enhance the therapeutic benefits of JAK inhibition while attenuating its side effects. To date, researchers have reported preliminary data examining the use of ruxolitinib in combination with a range of currently available agents and investigational therapies, including:

- Danazol [33]
- IMiDs [34, 35]
- Hypomethylating agents [36]
- Antifibrotic agents [37]
- Mammalian target of rapamycin (mTOR)/AKT/phosphoinositide 3-kinase (PI3K) inhibitors [38]
- Hedgehog inhibitors [32]
- Histone-deacetylase inhibitors [39]

New therapeutic combinations are also needed to offset anemia and other class-specific adverse effects of JAK inhibition. In a pooled analysis of 2 consecutive trials, pomalidomide with or without prednisone was associated with an overall anemia response rate of 27%

[40]. The anemia response rate increased to 53% in JAK-positive patients with <10 cm palpable splenomegaly and <5% circulating blasts [40]. Treatment with lenalidomide also induces a hematologic response in patients with MF, especially those with chromosome 5q deletion [41]. Conventional therapies for correcting anemia, such as danazol and interferon, may be particularly effective in patients in the myeloproliferative phase of MF [42].

Summary

Although the overall prognosis for most patients with MF is poor, it is also variable. In current clinical practice, the management of MF should begin with a comprehensive risk assessment (Figure 2) [30]. Although the DIPSS-plus risk score remains the current standard of care, cytogenetic and molecular stratification may play an increasingly prominent role in future treatment decisions. For patients with asymptomatic low-risk disease, watchful waiting or initial treatment with interferon may be an appropriate management strategy. Patients with symptomatic low-risk or intermediate-1 risk disease may benefit from treatment with ruxolitinib or referral to a clinical trial as appropriate, depending on further genotyping.

The management of patients with intermediate-2 or high-risk MF depends on eligibility for transplantation. For patients who are eligible for allogeneic HSCT, the choice of induction regimen is critical for optimizing transplant-related outcomes. For patients who are not eligible for allogeneic HSCT, appropriate management options may include JAK inhibitor therapy, referral for clinical trial participation, and/or palliative care. Managing patients in blast crisis remains a difficult clinical challenge with poor response to classical induction chemotherapy. New treatment approaches are urgently needed to improve outcomes at each stage of the natural history of MF.

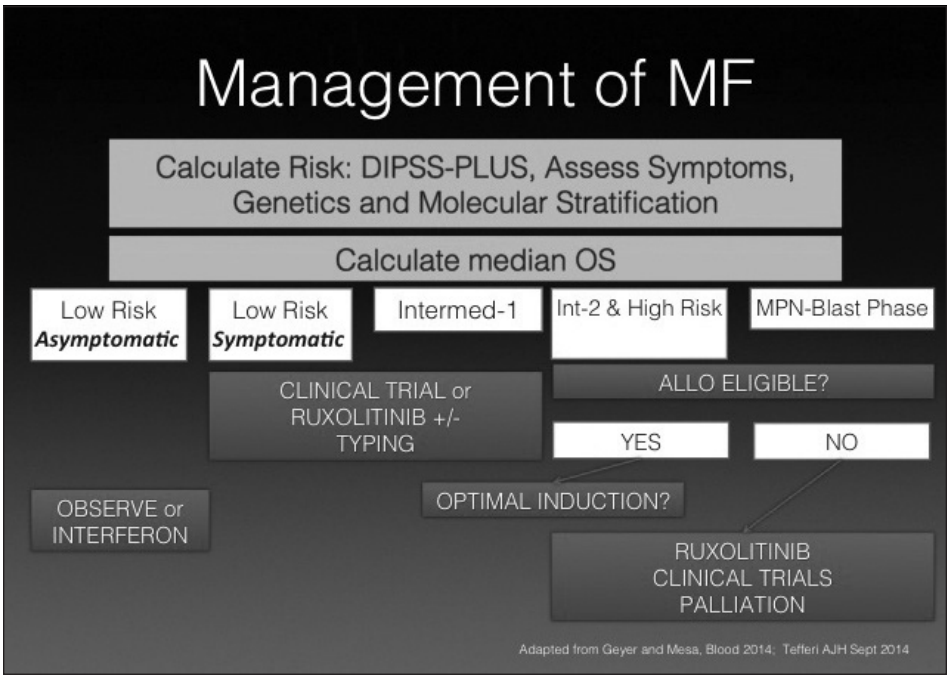

Figure 2. Management of myelofibrosis. (Adapted from presentations by Ruben Mesa, MD.)

Transplantation for Myelofibrosis in the JAK Inhibitor Era

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The standards of care for allogenic HSCT in patients with MF are evolving. Historically, conventional myeloablative HSCT was restricted to younger and fitter patients due to the high risk of TRM. Moreover, the perceived risk of graft failure was a major treatment barrier for patients with MF, resulting in low rates of referral to HSCT [4]. Indeed, MF is a rare indication for transplant, and even major transplant centers perform a limited number of allogeneic HSCT procedures for patients with MF [4]. With the availability of reduced-intensity regimens, however, more patients may be considered appropriate candidates for transplantation.

Discussing the options for MF treatment within the context of a patient case can illustrate the complexities of patient management in the JAK inhibitor era.

Case Presentation

A 47-year-old man presented in March 2000 with thrombocytosis (platelet count, 865 x 109/L). After a bone marrow biopsy he was diagnosed with essential thrombocytopenia, which was treated with aspirin alone. Once a diagnostic assay for the JAK2617F 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 (WBC) count, 17.9 x 109/L with left shift; platelet count, 216 x 109/L. There were no circulating peripheral blood blasts.

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. The most recent bone marrow biopsy, performed in 2012, showed 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.

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 inconvenience

of having 2 units of red cells every 4 weeks.

Case Discussion: Treatment Selection

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

Among available therapies used for symptom management, the patient has already failed a trial of erythropoietin. IMiDs 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. 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.

As this case discussion illustrates, choosing between upfront allogeneic HSCT and JAK-inhibitor therapy requires an individualized assessment of the patient's disease history and prognosis. Treatment goals, whether curative or palliative, should be based on patient preferences and a comparison of the potential risks and benefits of each therapeutic option.

Trends in Allogeneic HSCT in Myelofibrosis

Over the past 30 years, trends from retrospective studies suggest a modest increase in overall and event-free survival following allogeneic HSCT in patients with MF. However, given the limitations of interpreting data from single-institution or small multicenter observational studies, advances in transplant-related outcomes are not well understood. In the absence of large prospective trials, findings from the CIMBTR database provide important insight on transplant trends in the U.S. in patients with MF [43].

According to CIMBTR data, the annual rate of allogeneic HSCT procedures for MPNs increased from < 200 per year in 2003 to approximately 350 procedures per year during the 2011-2012 observational period [43]. Of note, the marked increase in annual transplant rate appears to correspond with the availability of JAK1/2 inhibitor therapy. Over the same period, there has also been a steady increase in the proportion of transplants performed in older patients (aged ≥ 65 years) and in patients with unrelated donors.

Preferences regarding conditioning regimens have also changed over time. Prior to 2006, myeloablative regimens were used more commonly than reduced-intensity and nonmyeloablative conditioning. By 2007, the balance had shifted in favor of reduced-intensity and nonmyeloablative regimens over myeloablative conditioning. At present, the most frequently used conditioning regimens are fludarabine/melphalan (20%) and RIC fludarabine/busulfan (20%). The choice of regimen intensity does not appear to influence survival. Following treatment with RIC and ablative conditioning regimens, respectively, survival rates are similar at 100 days (86% vs. 85%; P = .74), 1 year (66% vs. 65%; P = .75), and 3 years (51% vs. 55%; P = .13).

Overall survival appears to be improving for patients with MF undergoing allogeneic HSCT. The 1-year overall survival rates by year of HSCT were 61% (2003-2006), 66% (2007-2010), and 68% (2011-2013). The 3-year overall survival rate has held steady at 52% in the 2003-2006 and 2007-2010 cohorts. Long-term follow-up data are not yet mature for patients treated with allogeneic HSCT in the JAK inhibitor era.

Insight from Prospective Trials of Reduced-Intensity Allogeneic HSCT

Limited prospective data are available to guide the use of RIC allogenic HSCT in patients with MF. In retrospective trials, reduced-intensity regimens were often given to older patients with significant comorbidities and poor performance scores, who are not candidates for myeloablative conditioning [4, 44, 45]. To date, only two prospective multicenter trials have examined the use of RIC allogeneic HSCT in patients with MF (Table 9) [8, 9].

The EBMT trial enrolled 103 patients with primary (n = 63) or post-ET/PV MF (n = 40) from 17 international transplant centers [46]. By Lille scoring, 17% of patients were classified as low risk. Patients underwent conditioning with busulfan 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 donors (n = 70). The overall survival was 68% at 5 years. The cumulative risk of non-relapse mortality (NRM) and relapse-related death at 3 years were 21% and 22%, respectively. 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.

The MPD-RC 101 trial was the first prospective phase II trial of RIC allogeneic HSCT in patients with primary MF in the U.S. [9, 47]. The trial included 66 patients who received transplants from a related (n = 32) or unrelated (n = 34) donor following RIC with fludarabine/melphalan with or without ATG. The median patient age was 54-55 years. Most patients (n = 63) were at intermediate/high risk by Lille scoring. The MPD-RC 101 trial is notable for the

Table 9. Prospective Studies of Reduced-Intensity Transplantation in Myelofibrosis

	European Group for Blood and Marrow Transplantation (EBMT) Study [8] (N = 103)	Myeloproliferative Diseases Research Consortium (MPD-RC) Study [9] (N = 66)
Conditioning	Flu-Bu + ATG	Flu-Mel +/- ATG
Low-risk patients, %	17%	4.5%
URD, %	68%	52%
Survival, %	68% at 5 years	75% at 25 months (RD); 32% at 25 months (URD)
NRM vs. relapse death %	21% vs. 22% at 3 years	22% vs. 4% at 25 months (RD); 59% vs. 3 % at 25 months (URD)
Leukemia-free survival, %	40% at 5 years	NR
Overall graft failure, %	2%; 11% needed stem cell boost	6% (RD); 36% (URD)

ATG = antithymocyte-globulin; Bu = busulfan; Flu = fludarabine; Mel = melphalan; NR = not reported; NRM = non-relapse mortality; RD = related donor; URD = unrelated donor.

high rate of primary (24%) and overall (36%) grafts failure in the unrelated donor group, leading to a high rate of transplant-related mortality (TRM) [9]. The risk of NRM was more than 2.5-fold higher among unrelated donors compared with related donors (59% versus 22%), although the risk of relapse-related mortality was similar (3% versus 4%). Furthermore, overall survival was 75% at 25 months in the unrelated group, compared with 32% at 25 months in the related group. Therefore, findings from the MPD-RC 101 trial support the use of Flu/Mel conditioning when sibling donors are available, but suggest that an alternate conditioning regimen may be preferable for unrelated transplants.

Ongoing Challenges in Transplantation

Pre-Transplant Splenomegaly

Massive splenomegaly is common in patients with MF [48, 49]. In 2010, Bacigalupo and colleagues identified spleen size >22 cm as an independent risk factor for unfavorable transplant-related outcomes among patients with MF undergoing allogeneic HSCT [48]. The risk of TRM was 9% and 27% for patients with small and large spleens, respectively (P = .02).

Whether splenomegaly influences engraftment and post-transplant morbidity and mortality is controversial, with conflicting data from multiple small studies. To assess the impact of spleen status on outcomes following allogeneic HSCT in a large patient cohort, Akpek and colleagues evaluated CIBMT transplant data from 9,683 myeloablative allograft recipients [49]. In this cohort, 7,440 patients had a normal spleen, 1,471 had splenomegaly, 472 had prior splenectomy, and 300 received splenic irradiation. Splenomegaly was associated with delayed engraftment following allogeneic HSCT, whereas splenectomy prior to transplantation appeared to facilitate early engraftment. However, there was no survival advantage associated with either splenectomy (RR, 1.01; P = .847) or splenic irradiation (RR, 1.05; P = .526) in patients undergoing allogeneic HSCT. Overall survival was similar across all patient subgroups defined by spleen status. Furthermore, there were no differences in survival according to spleen status in the subgroup of patients with MPNs.

Treatment with a JAK1/2 inhibitor is another approach to reducing spleen size prior to transplantation. In 2014, Hanif and colleagues described findings from a retrospective analysis of 10 patients with MF undergoing allogeneic HSCT who received pretreatment with ruxolitinib [50]. At the time of enrollment, 9 patients had splenomegaly. Beginning 6 days prior to Flu-BU conditioning, all patients were slowly transitioned from a steady-state dose of ruxolitinib (maximum of 25 mg BID) to 5 mg once daily, with the last dose given 48 hours prior to conditioning. Five patients had a reduction in spleen size attributed to ruxolitinib, while one patient (10%) experienced rebound splenomegaly after discontinuing treatment. All patients achieved engraftment, with a median time to engraftment of 17 days (range, 13 to 22 days). No serious adverse events associated with ruxolitinib pretreatment were observed. These findings demonstrate a beneficial effect on spleen size with the administration of ruxolitinib before allogeneic HSCT in patients with MF and splenomegaly.

HSCT After Leukemic Transformation

Transformation to acute leukemia occurs in up to 20% of patients with MF and is associated with poor outcomes. Several retrospective studies have examined the curative potential of induction chemotherapy and allogeneic HSCT in these patients [51-53]. In 2005, Mesa and colleagues identified 91 patients with MF who fulfilled the criteria for transformation to AML. Prognosis was poor in this cohort, with a median overall survival of 2.6 months [51]. Treatment with AML-like induction chemotherapy was associated with reversion to chronic-phase MF in 41% of patients. In this group, the risk of TRM was 33%, and the median overall survival was 3.9 months.

In another retrospective analysis, Tam and colleagues evaluated 74 patients with Philadelphia chromosome (Ph)-negative MPNs who underwent leukemic transformation [52]. In this cohort, the median overall survival was 5 months from the date of blastic 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.

A recent analysis of the EBMT registry identified 46 patients who underwent allogeneic HSCT for transformed AML involving MF [53]. Overall survival at 3 years was 33%. Complete remission prior to HSCT was the only independent predictor of survival, and only 8 of 46 patients (17%) achieved complete remission. At 3 years, overall survival was 69% for complete responders and 22% for nonresponders (P = .008). Together, these findings underscore the poor prognostic implications of leukemic transformation in MF, and suggest a curative role for allogeneic HSCT among patients with a complete response to induction chemotherapy.

Limitations of Risk Stratification Tools

Current risk-assessment tools can provide valuable prognostic insight regarding overall survival in patients with MF. To date, however, these tools show limited utility in identifying which patients are mostly likely to benefit from allogeneic HSCT. In 2012, Gupta and colleagues evaluated the Lille and DIPSS scoring systems as potential predictors of mortality and other outcomes in 222 patients with primary MF who underwent RIC allogenic HSCT [54]. The Lille risk score detected a 2-fold increase in overall mortality between patients with high-risk and low-risk disease (RR, 2.22; P = .02), but transplant outcomes for patients with intermediate risk were varied. Furthermore, the DIPSS was not able to distinguish a difference in mortality risk between low/intermediate-1 and intermediate-2/high risk groups (P = .10).

In the MPD-RC 101 trial, neither the Lille score nor the DIPSS risk categories correlated with mortality in patients undergoing allogeneic HSCT (Table 10) [9]. Moreover, factors such as donor HLA compatibility and the presence of the JAK2 V617F mutation failed to predict 2-year survival. These findings support the need for a transplant-specific scoring system to improve risk assessment among patients with MF being considered for allogeneic HSCT.

Building on data from the EBMT prospective study, Alchalby and colleagues developed a risk-prediction model by identifying novel risk factors that correlated with treatment outcomes in 150 patients with MF [55]. 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).

Another emerging prognostic factor involves somatic CALR mutations, which occur in up to 35% of all MF cases and up to 88% of JAK2/MPL-negative patients. The presence of a CALR mutation corresponds with favorable outcomes following allogeneic HSCT

Table 10. MPD-RC 101 Trial: 2-Year Survival in Sibling and Unrelated Donor Groups [9]

	Sibling Donors			Unrelated Donors		
	n (%)	2-year survival	P value	n (%)	2-year survival	P value
Lille score						
0/1	23 (72%)	73%	.81	23 (68%)	35%	.88
2	9 (28%)	78%		11 (32%)	36%	
DIPSS						
Low-risk/int-1	18 (56%)	71%	.67	19 (56%)	42%	.14
Int-2/high-risk	11 (34%)	82%		12 (53%)	17%	
Donor HLA						
Matched	30 (94%)	72%	.42	25 (74%)	40%	.33
Mismatched	2 (6%)	100%		9 (26)	22%	
Baseline JAK2 V617F mutational status						
Positive	12 (38%)	76%	.68	18 (53%)	28%	.29
Negative	17 (53%)	64%		16 (47%)	44%	

DIPSS = Dynamic International Prognostic Scoring System.

[56]. Future risk-assessment models are likely to incorporate CALR mutational status and other emerging prognostic factors to determine the potential benefit of transplantation in patients with MF [56].

Fibrosis Regression

Regression of bone marrow fibrosis is also emerging as a marker of favorable post-transplant outcomes in patients with MF. Indeed, Kröger and colleagues recently demonstrated that the speed of fibrosis regression correlates with survival and transfusion dependency, irrespective of IPSS risk category [57]. In a study of 57 patients undergoing RIC allogeneic HSCT for MF, 78% had a baseline myclofibrosis (MF) score of MF-3 and 28% were classified as MF-2. Within 30 days of engraftment, 21% of patients had complete (MF-0) or near-complete (MF-1) regression of bone marrow fibrosis. After 100 days, 54% of patients achieved MF-0/MF-1 status. There was no association between IPSS score at the time of transplant and fibrosis status on day 100.

The overall survival rate on day 100 was 96% among patients with MF-0/MF-1, compared with 57% for those with MF-2/MF-3 (P = .04). Patients who achieved MF-0/MF-1 status by day 100 were also less likely than those with MF-2/MF-3 disease to be transfusion dependent for red blood cells (P = .104) or platelets (P = .018). These findings suggest that rapid regression of bone marrow fibrosis predicts favorable outcomes, regardless of IPSS score at the time of transplant.

Relapse After Transplant

Disease relapse following allogeneic HSCT is a challenging issue for patients with MF. Treatment options following relapse include donor lymphocyte infusion (DLI) and repeat transplant. In general, DLI is an effective strategy for patients who experience morphologic or molecular relapse. By comparison, repeat allogeneic HSCT is preferable for those with blast phase relapse or post-DLI failure. Regardless of the initial salvage approach, a second round of DLI is recommended for additional residual disease.

In 2012, Klyuchnikov and colleagues demonstrated the utility of this 2-step salvage strategy among 30 patients with relapse (n = 27) or graft rejection (n = 3) after reduced-intensity allogenic HSCT [58]. Among 26 patients who received a median of 3 DLIs each, 10 patients (39%) achieved a complete response. 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 leukemic transformation. With this protocol, the 2-year overall and progression-free survival rate from the time of relapse was 70% and 67%, respectively. 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.

Summary

Trends from the CIBMTR database indicate a steady increase in allogeneic HSCT activity for patients with MF. Reduced-intensity transplantation is now widely practiced, with fludarabine/melphalan and fludarabine/busulfan among the most commonly used conditioning regimens. However, evidence from the MPD-RC 101 study suggests that fludarabine/melphalan should be avoided in the context of unrelated donors due to the high risk of non-engraftment. Special risk situations such as portal hypertension and splenomegaly related to advanced MF are particularly challenging, but ongoing studies are attempting to better understand these patients.

The use of JAK inhibitor therapy in the transplant setting may address some of the traditional complications of HSCT in patients with MF. In particular, ruxolitinib administered with a tapered dosing schedule appears to be a safe and effective approach to reducing spleen size in carefully selected patients prior to allogeneic HSCT. The ideal prognostic classification system for MF remains undefined, although the DIPSS-Plus scoring remains the standard of care in current clinical practice. In the absence of stronger evidence from prospective clinical trials, the selection of patients with MF for allogeneic HSCT in the era of JAK inhibitor therapy falls more into the realm of art than science.

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1. Which scoring system incorporates cytogenetic features to estimate patient prognosis?
A. Lille scoring system
B. International Prognostic Scoring System (IPSS)
C. Dynamic IPSS (DIPSS)
D. DIPSS-Plus

2. Which of the following predicts a more favorable prognosis in MF?
A. Circulating blasts >9%
B. Monosomal karyotype
C. Triple-negative status for the CALR, JAK2, and MPL mutations
D. Wild-type ASXL1 in the presence of mutated CALR (CALR+/ASXL1-)

3. JAK1/2 inhibitor therapy is associated with which of the following in patients with MF?
A. Increased risk of splenomegaly
B. Prevention of leukemic transformation
C. Improved quality of life
D. Reduced risk of anemia

4. In patients undergoing allogeneic HSCT, abrupt discontinuation of ruxolitinib is preferable to tapered ruxolitinib dosing prior to initiating the conditioning regimen.
A. True
B. False

5. In the phase II MPD-RC 101 study of fludarabine/melphalan RIC followed by allogeneic HSCT, the rates of graft failure and non-relapse morality were highest in which patient group?
A. Patients who received unrelated grafts
B. Patients with HLA-matched related donors
C. Patients with wild-type JAK2 V617F
D. Patients with the highest baseline symptom burden

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