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CRITICAL REVIEW

Innovative strategies to improve hematopoietic stem cell transplant outcomes in myelofibrosis

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Abstract

Myelofibrosis (MF) is a clonal myeloproliferative neoplasm characterized by inflammation, marrow fibrosis, and an inherent risk of blastic transformation. Hematopoietic allogeneic stem cell transplant is the only potentially curative therapy for this disease, however, survival gains observed for other transplant indications over the past two decades have not been realized for MF. The role of transplantation may also evolve with the use of novel targeted agents. The chronic inflammatory state associated with MF necessitates pretransplantation assessment of end-organ function. Applying the transplant methodology employed for other myeloid disorders to patients with MF fails to acknowledge differences in the underlying disease pathophysiology. Limited understanding of the causes of poor transplant outcomes in this cohort has prevented refinement of transplant eligibility criteria in MF. There is increasing evidence of heterogeneity in molecular disease grade, beyond the clinical manifestations which have traditionally guided transplant timing. Exploring the physiological consequences of disease chronicity unique to MF, acknowledging the heterogeneity in disease grade, and using advanced prognostic models, molecular diagnostics and other organ function diagnostic tools, we present an innovative review of strategies with the potential to improve transplant outcomes in this disease. Larger, prospective studies which consider the impact of molecular-based disease grade are needed for MF transplantation.

1 | INTRODUCTION

Myelofibrosis (MF) is a clonal myeloproliferative neoplasm (MPN) characterized by inflammation, marrow fibrosis, and an inherent risk of blastic transformation. It can arise de novo, as primary myelofibrosis (PMF), or secondary to antecedent polycythemia vera or essential thrombocythemia. The median age at diagnosis of PMF is around 65–70 years,[1,2] with an annual population incidence of 0.4–1.5 per 100 000.[3–5] Survival is variable, with a median of around 5–7 years.[3,6,7] Multiple prognostic systems refine survival estimates, such as the Dynamic International Scoring System (DIPSS) and Mutation-Enhanced International Prognostic Scoring System (MIPSS).[7,8] The only potentially curative treatment is allogeneic hematopoietic stem cell transplantation (HCT), with prospective studies[9,10] and multiple retrospective analyses confirming a long term survival advantage of HCT compared to non-transplant therapy.[11,12]

Clinical gains can be attained with use of JAK inhibitors (JAKi); however, in responding patients the desire to delay HCT due to high nonrelapse mortality (NRM) must be balanced by the risk of disease progression and age and disease-related procedural tolerability. Moreover, the disease-modifying potential of JAKi therapy is limited.[13] Retrospective data shows that patients transplanted while exhibiting a splenic response to JAKi have improved overall survival (OS) compared to those who never showed or no longer show a response.[14] Responding patients also had a lower NRM and relapse risk. These findings were confirmed in a large European Bone Marrow Transplant (EBMT) retrospective analysis,[15] suggesting that transplantation should not be delayed due to JAKi response.

2 | CURRENT RECOMMENDATIONS

HCT is recommended by the American Society of Transplant and Cellular Therapy and the EBMT-European LeukaemiaNet (ELN) guidelines for patients aged under 70 years with intermediate-2 or high-risk disease based on IPSS, DIPSS, or DIPSS+.[16–18] The ELN additionally considers HCT for intermediate-1 disease with adverse genetics, transfusion dependence or >2% circulating blasts. Patients ineligible for HCT may be offered a JAKi, clinical trial, transfusion support, splenectomy, or splenic irradiation. The optimal timing of HCT remains uncertain with the evolution of novel nontransplant therapies.[19,20] If anything, the decision of whom, and when, to transplant for MF has only become more complex.[21]

3 | CURRENT OUTCOME DATA

Despite high NRM, a significant number of patients achieve long term survival and "cure" following HCT for MF. Retrospective evidence supports transplant in DIPSS intermediate-2 and high-risk MF patients, and recently Markov modeling was also shown to support this approach.[11,22,23] Recent data from the Center for International Blood and Marrow Transplant Research (CIBMTR), including 187 DIPSS intermediate-2 or high-risk patients showed a 2-year OS of approximately 50%, compared to >75% among low-risk patients. Importantly, the lead time to realize a transplant survival advantage was most protracted in the low-risk patient group, such that transplant is not currently recommended in this population based on low-risk DIPSS alone.[11] Further criteria, such as donor type and conditioning, have been associated with improved outcomes. In one study, recipients of matched sibling donor (MSD) reduced intensity conditioned (RIC) HCT had OS as high as 80% at 3 years.[24] Furthermore, 2-year OS of 91% has been reported in patients with enduring response to ruxolitinib, compared to 54% in those with stable or progressive disease at transplant.[14] Outcomes following HCT in patients with ruxolitinib exposure is summarized in Table 1. While disease heterogeneity explains some of the difference in OS outcomes due to relapse risk, NRM in the setting of advanced disease remains high.

4 | TARGETS FOR IMPROVED TRANSPLANT OUTCOMES FOR MF

Despite improving OS trends for transplantation, there has been relatively little change in MF HCT outcomes.[12] This is reflected in a recent Australasian retrospective analysis comparing outcomes of a recent cohort to an earlier group from 1993 to 2005. The 5-year OS was 57% and to 53%, respectively.[12] CIBMTR data indicates 3-year OS in all acute myeloid leukemia (AML) is 53%, 48% for myelodysplastic syndrome (MDS) and 55%–65% for the matched related MF subset.[25] While NRM posttransplant for AML is around 20% at 5 years, it is 18%–25% at only 1 year,[12,26,27] and around 35% at 5 years in MF.[28] A recent large retrospective analysis documented a high mortality in the first 12 months posttransplant, followed by a plateau in OS, with high variability in survival stratified by DIPSS.[11] The authors conclude that high early mortality was largely due to upfront NRM, which increased with clinical disease stage. This observation provides insight to guide transplant timing, however may also reflect the accrual of organ dysfunction with disease progression—a potential target to improve patient selection and transplant outcomes. While explanations for high NRM (such as the disease's inflammatory milieu and extramedullary hematopoiesis [EMH]) have been offered, there has been little done to address these issues in transplantation.

5 | NRM: CONTRIBUTING FACTORS AND POTENTIAL STRATEGIES FOR IMPROVEMENT

Many uncertainties remain in MF HCT, namely, the optimal patient selection, influence of secondary end-organ pathology on NRM, optimal integration of nontransplant therapies and pretransplant management of splenomegaly, and donor and conditioning choice. A review in 2014 noted "the need to optimize patient-related factors that can impact NRM,"[30] however, there has been no significant progress in this area in the last decade. There are many potentially modifiable

TABLE 1 Transplant studies involving patients with exposure to JAK inhibitors

	Trial design	NRM	OS	RR	DFS	Graft failure	Molecular clearance	aGVHD Grade 2–4	cGVHD	CMV reactivation	Ruxolitinib
Robin 2021	Prospective $n = 59$	42%/46% at 1/2 years	55% at 1 years	3%	52/46% at 1/2 years	2%	NR	66% ($n = 39$)	33% at 12 months 37% at 24 months	NR	Ruxolitinib for 6 months pre, and abrupt cessation with conditioning
Morozova 2021	Prospective $n = 20$	15% at 2 years	85% 2 years	NR	72% at 2 years	6% (1/18)	NR	25%	Mod 20%, no severe	30%	Pre-Tx rux until d-2. Rux 15 mg bd +5 to +100 PTCy
Kroger 2018	Prospective $n = 12$	0% at 1 year	100% at 1 year	8% at 1 year	NR	0% at d100	Driver mut cleared in 10/12	8% ($n = 1$)	Unknown	41%	5 mg bd until stable engraftment
Kröger 2021	Retrospective ($n = 551$)	At 1 year	At 2 years	At 2 years	At 2 years	NR	NR		At 2 years		Transplantation in ruxolitinib responsive patients resulted in lower relapse rate and better EFS
	No pre-HSCT ruxolitinib exposure ($n = 274$)	22.9%	63.2%	19.1%	53.7%			28.9%	41.7%	26.8%	
	No or lost response to ruxolitinib pre-HSCT ($n = 104$)	25.5%	57.5%	15.7%	49.9%			27.5%	55.7%	36.6%	
	Ongoing ruxolitinib response at transplant ($n = 91$)	14.8%	70.0%	8.1%	68.9%			27.0%	50.7%	36.6%	
Gowin 2020	Retrospective $n = 551$		49% at 10 years	NR	NR	NR	NR	NR	NR	NR	<30% of patients had prior use of ruxolitinib
Gupta 2019[29]	Prospective $n = 21$	28% at 2 years	63% at 2 years	10.5%	59%	16%	NR	43%	76% at 2 years	NR	Pretransplant ruxolitinib in all
Shanavas 2016	Retrospective $n = 100$	28% at 2 years	61% at 2 years	17% at 2 years	NR	4%	NR	37%	48% at 2 years	NR	Pretransplant ruxolitinib in all
Kunte 2021	Retrospective ($n = 69$)	21% at 2 years	72% at 3 years	31% at 3 years	NR	6%	NR	10% (Grade 3–4)	29% at 2 years	NR	58% of patients had received JAK inhibitor therapy prior to transplant

Abbreviations: aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; DFS, disease-free survival; HSCT, hematopoietic stem cell transplant; NR, not reported; NRM, nonrelapse mortality; OS, overall survival; PTCy, posttransplant cyclophosphamide; RR, relapse rate.

risks in MF HCT requiring further evaluation, as summarized in Table 2.

In the following sections we review existing evidence and propose directions for future study of these potentially outcome-modifying variables. Levels of evidence and grade of recommendation are applied based on the Infectious Diseases Society of America United States Public Health Service grading system,[31] as shown in Table 3.

TABLE 2 Levels of evidence and grade of recommendations

Pretransplant • Assessment of disease-related risk to guide transplant timing • Early referral for transplantation, including those with ruxolitinib responsiveness • Evaluation of secondary organ dysfunction (endoscopy, echocardiogram, EMH screening, hepatic Doppler ultrasound, MRI for iron overload) • Conventional medical therapies for MF - JAK inhibitors, iron chelation, interferon • Role of splenectomy or splenic radiation • Experimental therapies for MF - investigational agents including novel JAK inhibitors, BCL-2 inhibitors, BET-inhibitors, telomerase inhibitors, MDM2 inhibitors, LSD1 inhibitors, and interferon
Transplant procedure • Donor selection—MSD superior to MUDs and haploidentical • Conditioning toxicity • GVHD prophylaxis • JAK inhibitor continuation through conditioning and peritransplant period
Posttransplant • Optimal timing and frequency of chimerism and MRD monitoring • Optimal management of posttransplant relapse • DLI vs. nontransplant therapies vs. second allograft

Abbreviations: DLI, donor lymphocyte infusion; EMH, extramedullary hematopoiesis; GVHD, graft-versus-host disease; MF, myelofibrosis; MSD, matched sibling donor; MUD, matched unrelated donor.

TABLE 3 Disease and treatment considerations to improve transplant outcomes

Levels of evidence	
I	Evidence from at least one properly randomized, controlled trial
II	Evidence from at least one well designed clinical trial without randomization, from cohort or case–control analytic studies from multiple time-series studies or from dramatic results in uncontrolled experiments
III	Evidence from opinions or respected authorities, based on clinical experience, descriptive studies or reports of expert committees
Grades of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use

5.1 | Secondary organ dysfunction

Secondary organ dysfunction in MF may contribute to high NRM, however, the incidence and significance of this is currently unknown. Comprehensive screening during transplant work-up is not universally performed, and studies correlating secondary organ damage with NRM have therefore not been reported. Evidence to guide optimal management of organ dysfunction is lacking, however, organ-specific management and intervention strategies utilized in the non-MF population should be considered in MF patients planned for transplantation. Pretransplant investigations may allow clinicians to medically or surgically optimize their patient prior to transplant. Where this is not possible, clinicians may still be better placed to anticipate and manage peritransplant complications. Importantly, such investigations will allow future correlative outcome studies which might establish the significance of these comorbid issues, and potentially influence future patient selection for transplant.

5.1.1 | Portal hypertension

Portal hypertension (poHTN) has been reported in up to 18% of patients with MPN.[32] Splanchnic thrombosis is a common cause, particularly in *JAK2*-mutated MPNs, however hepatosplenic EMH may also contribute.[32] A retrospective study identified gastroesophageal varices by CT in 3.6% of MF patients, in the absence of established cirrhosis.[33] The effect of noncirrhotic poHTN on transplant outcomes is unknown, but varices may confer a significant bleeding risk both peri- and posttransplant.

Screening for poHTN and varices may allow for pretransplant clinical optimisation, or even assist in patient eligibility determination. Several studies have suggested that CT is a sensitive method for detection of high-risk varices, however, the validity of this modality in noncirrhotic variceal disease is unknown.[34,35] *While endoscopic screening in asymptomatic MPN patients is not routinely recommended,*[36] *it is a reasonable undertaking prior to HCT for prophylactic banding of high-grade varices, given the significant bleeding risk and the difficulty of intervention peritransplant. Screening for noncirrhotic poHTN using imaging modalities such as Doppler ultrasound or MRI angiography, with liver elastography (e.g., FibroScan) to exclude cirrhosis in suspected cases is recommended.*[37]

Level III Grade C.

5.1.2 | Liver dysfunction

Compared to HCT for MDS, increased rates of transaminitis and veno-occlusive disease are reported for MF.[38] In addition to poHTN, both iron overload and splanchnic thrombosis were associated with peri-HCT hepatotoxicity, predicting a reduced 12-month OS due to higher NRM. Pretransplant chelation for those with significant hepatic siderosis may reduce hepatotoxicity, but this requires further evidence.

Screening MRI to assess liver iron burden, if available, is recommended pretransplant where iron overload is suspected. In the event of

significant iron overload, an individualized risk assessment must be performed (based on disease risk, patient comorbidities, and presence of other veno-occlusive disease risk factors) to determine whether transplant delay for chelation might be indicated. Knowledge of iron overload status may also inform peritransplant medication choices such as selection of antifungal agent if excess hepatotoxicity is anticipated.

Level III Grade C.

5.1.3 | Pulmonary hypertension

Pulmonary hypertension (pHTN) may occur in patients with MF, through mechanisms including cardiac failure, pulmonary EMH, thrombotic disease and cytokine-mediated effects. Rates of pHTN up to 30% are reported in MF, however it is not routinely assessed in many centers.[39] pHTN tends to associate with conventional cardiac risk factors, as well as elevation of either hematocrit or N-terminal pro-brain natriuretic peptide.[40] Evidence suggests that the majority of cases occur secondary to left-sided heart disease. In patients with MF undergoing HCT, rates of pHTN have been reported at up to 50%, and pHTN has been shown to predict higher NRM and reduced OS.[41] A significant reduction in pulmonary artery pressure has been reported in some patients following HCT, indicating at least partial reversibility. pHTN is thus not necessarily a barrier to transplant—indeed HCT may ultimately be a therapy.

Right heart catheterisation is the gold standard for diagnosis of pHTN, however, there is insufficient evidence to recommend invasive screening prior to HCT. We propose pretransplant NT-proBNP and troponin levels, and pulmonary pressure estimate by echocardiogram for all transplant candidates. The need for invasive investigation should be guided by screening results, however, it is likely indicated where left heart disease is not apparent and vasoreactivity testing is warranted to determine therapeutic options. In patients with significant pHTN review by a cardiologist or respiratory physician specializing in pHTN should be undertaken, to facilitate individualized pre-transplant medical optimisation. Where no optimisation is viable, knowledge of pHTN may nonetheless inform management of haemodynamic complications arising during transplant.

Level III Grade C.

5.1.4 | Extramedullary hematopoiesis

While hepatosplenic EMH is common in MF, EMH can occur in any organ. A study of SPECT–CT screening reported pulmonary EMH in 45% of MF patients, more than half of whom also had pHTN (mostly asymptomatic).[42] The effect of EMH on NRM is unknown, however, it is hypothesized that the combination of tissue involution secondary to conditioning, and thrombocytopenia may lead to atypical bleeding complications due to the classically friable nature of EMH tissue.

Several radiologic modalities (FDG-PET-CT, ^{99m}Tc-colloid scintigraphy) reliably identify EMH, although the effect of EMH on NRM is unknown. We recommend screening patients with one of these imaging modalities prior to HCT if possible. Where a significant burden of EMH is identified, or high-risk sites such as gastrointestinal and pulmonary are involved, targeted radiotherapy should be considered on an individualized basis as EMH is generally exquisitely sensitive. The role of pre-transplant screening and incorporation of low dose irradiation in conditioning are areas for further investigations.

Level III Grade C.

5.1.5 | Iron overload

Hemosiderosis exacerbates the ineffective erythropoiesis of MF, due to reactive oxygen species toxic to the marrow microenvironment.[43] The implications of this on HCT outcomes in MF are unknown. In HCT for non-MF indications, hepatic iron overload on MRI does not predict OS, NRM, relapse, or GVHD.[44] Hyperferritinemia is associated with higher NRM and reduced OS in non-MF HCT.[45] Critically in MF, many patients exhibit an inflammatory hyperferritinemia rather than true iron overload, and delineation may be important. The strong correlation between hyperferritinemia, comorbidity scores and performance status in MF likely indicates the prognostic significance of inflammation, regardless of iron overload.[46]

It is hypothesized that reduction in marrow toxicity by free iron may improve engraftment and hematopoiesis. We recommended MRI screening for hepatic and cardiac iron overload (where available) in at-risk patients (generally transfusion of more than 15 units of RBC). In the absence of contraindication, we recommend pretransplant chelation for iron overload. We cannot recommend routine delay of transplant for the purposes of chelation, however this may be appropriate in certain cases, for example, with iron overload cardiomyopathy or hepatotoxicity.

Level II Grade B (Figure 1).

5.2 | Graft function

5.2.1 | Delayed engraftment, graft failure, and poor graft function

Delayed engraftment likely contributes to early and high rates of NRM following MF HCT, as has been noted in cord transplant recipients in whom delayed engraftment is also a challenge.[47]

5.2.2 | Graft failure and poor graft function

Graft failure (GF) and poor graft function (PGF) are significant challenges in MF HCT. Differentiation from relapse, when both may manifest as cytopenias, is based on chimerism and clonality.

The marrow niche in MF is thought to be hostile to donor cells due to inflammation, with markedly elevated proinflammatory cytokines, fibrosis, and often osteosclerosis. Furthermore, splenic sequestration may reduce stem cell localization to the marrow.[16] Advanced fibrosis is linked to poor transplant outcomes in some, but not all studies.[48]

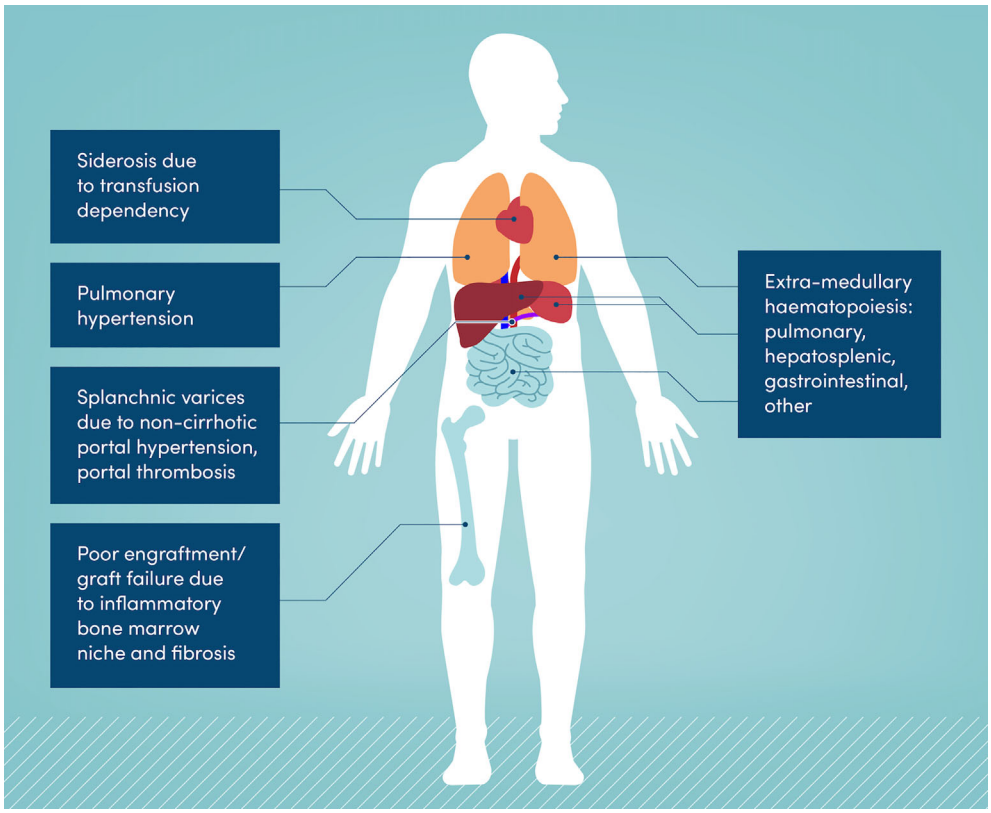

FIGURE 1 Factors potentially contributing to poor transplant outcomes [Color figure can be viewed at wileyonlinelibrary.com]

Furthermore, dynamic reversal of fibrosis following transplant occurs in many patients, with one study suggesting near or complete resolution in 59% of patients by day + 100 and 90% by day + 180. Early resolution of fibrosis has been associated with improved OS.[49,50]

A lack of universal criteria for PGF, GF, and disease response assessment has been a barrier to progress. New EBMT consensus guidelines define PGF as mild/moderate cytopenia in ≥2 cell lines, for ≥2 weeks despite full donor chimerism. It is a diagnosis of exclusion requiring the absence of severe GVHD, viral infection or myelosuppressive medications. Alignment of clinical trial design with these consensus definitions will facilitate consistent reporting and outcome comparisons. Known risk factors for PGF are largely unmodifiable—age, disease grade, prior HLA sensitization, and donor characteristics (unrelated donor, low CD34+ dose, major ABO mismatch). Further elucidation of factors affecting GF and PGF is required, with the hope that this may lead to improved management options as well in cases where it cannot be prevented.

5.3 | Disease-related risk assessment: Stage versus grade

Multiple risk stratification models have been developed, recently including molecular risk factors, in an effort to improve patient selection for HCT. Despite this the decision to transplant remains challenging. Early NRM leads to delayed survival advantage for MF HCT. Stratified by DIPSS, the time to survival benefit is more than 9 years for low-risk patients, compared to 4 years in intermediate-2 or high-risk patients, highlighting the importance of patient selection.[11] NRM is also lower in DIPSS low-risk patients. Thus the decision to delay

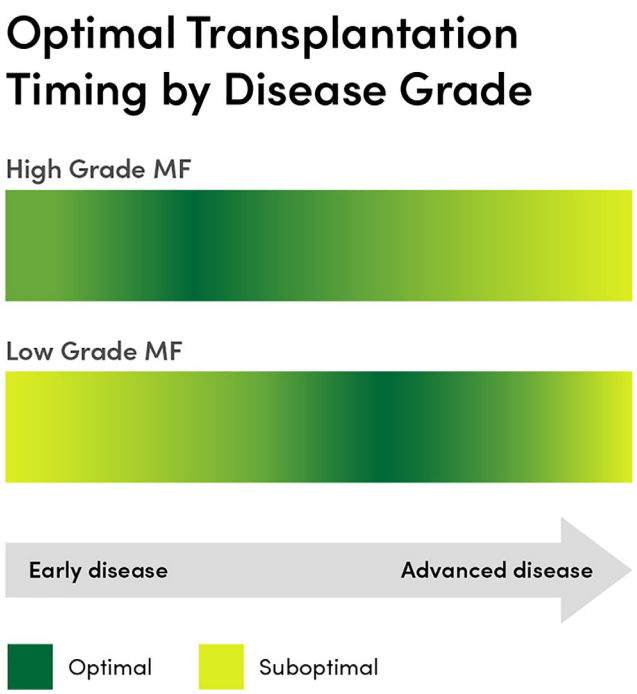

FIGURE 2 Optimal transplant timing based on disease grade and stage [Color figure can be viewed at wileyonlinelibrary.com]

HCT in low-risk patients may result in a later, higher risk transplant. It must be noted that although NRM may be lower when HCT is performed earlier in the disease course, it is not negligible, nor is the risk of GVHD.

Molecular-based risk stratification identifies disease "grade," in addition to disease stage models, such as the DIPSS. The "mutation-enhanced" MIPSS70 or MIPSS70+ considers the presence of high-risk mutations (ASXL1, SRSF2, EZH2, IDH1/2, or *U2AF1*) as well as the favorable *CALR*-type 1 mutation, and both are validated for HCT.[51] A survival advantage has been shown in DIPSS low-risk patients.[11] Whether this reflects a more benign underlying disease process or transplantation at an earlier stage in the natural history of disease requires evaluation. Refined guidelines on transplant timing are needed, and a model incorporating genetic heterogeneity may be useful, as is depicted in the schematic below (Figure 2).

Current evidence pertains to superseded prognostic models.[11,12,14,24] The DIPSS incorporates age, constitutional symptoms, anemia, leukocytosis, and peripheral blast count.[7] When applied to the transplant setting, high scores unsurprisingly portend increased relapse rate (RR), reduced progression-free survival (PFS), and less GVHD-free and relapse-free survival.[11] The DIPSS largely measures clinical disease "stage." By contrast, models such as the DIPSS+, Genetically Inspired Prognostic Scoring System (GIPSS), and MIPSS assign disease "grade" based on high-risk genetic lesions. One might predict that patients with early-stage high-grade disease would be most likely to benefit from HCT, however evidence to support this is currently lacking.

Interpretation of molecular prognostic information in MF is complicated. Rapidly evolving methodology, use of partially overlapping gene panels of variable sensitivity, rarity of individual mutations, and the inherent heterogeneity of HCT studies contribute to this difficulty. Nonetheless, some patterns are emerging. *CALR* mutation subtype influences prognosis in the nontransplant setting, with inferior outcomes in those harboring a Type 2 mutation. As a result, the MIPSS70+ ascribes a favorable prognosis to the Type 1 mutation only.[51] In MF patients undergoing HCT, the presence of any *CALR* driver mutation is associated with more favorable outcomes (relative to patients with *JAK2*, *MPL* or "triple-negative" driver mutation status), with reduced NRM and increased OS.[52] Most, but not all, recent studies have shown similar findings.[51,53–55] The effect of CALR mutation type on prognosis appears to be overcome by HCT.[56]

Outside of transplant, the impact of additional "nondriver" mutations on survival in PMF has been demonstrated, however, robust data are still lacking in secondary MF and following HCT. Individual gene mutations affect OS (including CBL[51] and U2AF1[55]). ASXL1 and IDH2 mutations have been associated with reduced PFS.[54] *TP53* mutation following transformation to AML, unsurprisingly portends a very poor prognosis even with HCT.[57] The presence of ≥3 nondriver mutations has also been associated with increased risk of relapse and NRM post-HCT.[58]

To date the largest study exploring the impact of molecular lesions on OS post-HCT is the Myelofibrosis Transplant Scoring System (MTSS) study,[53] in which age ≥ 57 years, Karnofsky performance status <90%, leukocyte count >25 × 10^9/L, platelet count <150 × 10^9/L, *ASXL1* mutation, HLA antigen mismatched, unrelated donor and the presence of a non-*CALR/MPL* driver mutation predicted increased NRM and reduced OS. The effect of the MTSS on RR was not reported. The MTSS was highly predictive of 5-year NRM, which increased from 10% in the low-risk group to 66% in the very high-risk group. Importantly, peripheral blast percentage and anemia, which contribute to many risk scores, did not affect OS.

Until more clarity exists around optimal disease and transplantation risk calculation, we recommend use of a model incorporating molecular risk where possible, such as the GIPSS or MIPSS70+, the MIPSS70+, or DIPSS+ where only cytogenetic information is available, and the DIPSS or MIPSS70 where genetic information is unavailable. The MTSS is also of use in the prediction of NRM.

Level III Grade B.

6 | PRETRANSPLANT THERAPY

6.1 | JAK inhibitors

In the JAK-ALLO study, patients with DIPSS intermediate-2 or high-risk MF who were intended for transplant within 6 months were commenced on ruxolitinib 15 mg twice daily, and transplant outcomes evaluated. Due to several adverse outcomes with gradual weaning, abrupt cessation of ruxolitinib prior to conditioning was instituted.[59] All 64 transplanted patients achieved engraftment. Grade 2–4 acute GVHD was observed in 66% by day 100, and in 82% of mismatched unrelated donors (MMUDs). By contrast chronic GVHD was seen in 37% at 24 months, ranging from 11% in mismatched unrelated recipients to 75% of matched sibling recipients.[59] Although not a formal study endpoint, survival curves for MSD recipients and nontransplant ruxolitinib patients crossed just prior to 12 months, supporting HCT in patients with an available MSD.

There is limited evidence of a disease-modifying activity of JAKi therapy, with most patients failing to achieve molecular responses or regression of fibrosis. Acknowledging that the potential opportunity cost of using JAKi to delay transplant has not been prospectively studied, a 551 patient retrospective analysis by the EBMT reported superior outcomes in those transplanted while exhibiting ongoing ruxolitinib responsiveness, compared to those who no longer responded or had never responded to ruxolitinib. *We recommend that transplant eligible patients who have achieved maximal splenic response to ruxolitinib therapy should be considered for HCT without delay.*[14,15]

Level II Grade B.

6.2 | Pretransplant interferon

There are limited data on the use of interferon (IFN)-alpha to treat MF prior to HCT. The largest retrospective case series from the French MPN group included 62 patients of whom 7 proceeded to transplantation after IFN treatment: 5 of these 7 patients died from severe

GVHD.[60] IFN is known to have immunomodulatory effects, and historically IFN was associated with GVHD in CML patients proceeding to HCT.[61] Clinical responses have also been reported in some patients treated with the novel IFN, ropeginterferon.[62] There is hope that it may be a disease modifier in MF, as has been reported in polycythemia vera, but this remains an unproven and off license use.[63,64]

We recommend avoiding IFN in MF patients who are planned for HCT until further evidence is available or at least discontinue it a minimum of 3 months prior to HCT.

Level III Grade C.

6.3 | Experimental therapies

Other medical therapies are also being developed with the aim of having a greater impact on the natural history of MF, including the BCL-2 inhibitor navitoclax, bromodomain, and extraterminal inhibitors, such as pelabresib, and the telomerase inhibitor, imetelstat.[65–68] The place of these therapies within the armamentarium remains unknown.

6.4 | Splenectomy or splenic radiation

Splenomegaly is associated with delayed engraftment and increased rates of GF, leading to use of splenectomy or splenic irradiation pre-HCT in some centers. No prospective study has demonstrated that this alters HCT outcomes. Some studies have reported that splenectomy is associated with higher RR.[9] In the ruxolitinib era, higher RR following splenectomy or irradiation might be explained by selection bias for ruxolitinib refractory cases. Regardless, OS is not influenced by splenectomy in most studies,[65,69] although there are occasional reports of improved OS.[70,71] Lack of randomization, the introduction of JAKi therapy, and progression to transplant earlier in the natural history of the disease result in significant heterogeneity limiting the applicability of existing data to current patient populations, hence the role, if any, of splenectomy remains largely unknown.

Evidence supporting splenic irradiation or splenectomy in those with significant splenomegaly despite maximal response to ruxolitinib is lacking, however, this may be considered.

Level III Grade C.

7 | HOW TO TRANSPLANT

7.1 | Donor selection

Donor source impacts transplant outcome, with superior OS following MSD compared to other donor HCT.[9,72,73] Historically, this related to uniquely high rates of NRM following matched unrelated donor (MUD) transplant, however outcomes are improving, with a reduction in this high NRM among MUD recipients the primary contributor to this change.[74,75] The JAK-ALLO study reported significant variation in DFS at 24 months by donor type: 77% in MSD, 36% in MUD and 23% in MMUD. Similarly, 2-year NRM was higher in MUD and MMUD (50% and 77%, respectively) compared to MSD (23%). In this cohort, mortality differences were accounted for by hyperacute and Grade 3–4 acute GVHD, however of note only 73% of patients received antithymocyte globulin (ATG) as prophylaxis. All patients in this group were also ruxolitinib refractory prior to transplant.[59] Significant improvements in outcomes for MUD and haploidentical transplant have been reported. A retrospective study of 69 recipients of haploidentical transplant for MF in the era of posttransplant cyclophosphamide revealed a 72% 3-year OS, with 23% NRM over this time. RRs were relatively high at 31%, however Grade 3–4 acute GVHD was reported in only 10%, and extensive chronic GVHD in 8%.[76] GF occurred in 6%, but rates of PGF were not reported. With the general shift over the last decade away from umbilical cord donor transplant, there is limited research into the efficacy of cord transplant for MF. Earlier reports suggested similar survival outcomes regardless of marrow, peripheral blood or cord source,[77,78] however, prospective trials are lacking. MSDs remain the ideal donor when available.

An MSD is the preferred donor source, however evidence suggests outcomes are improving following MUD or haploidentical transplantation. In general, MMUD donors should be avoided due to inferior survival outcomes.

Level II Grade A.

7.2 | Conditioning

In AML and MDS myeloablative conditioning (MAC) is known to reduce the risk of relapse and improve survival, albeit at the cost of increased NRM. The optimal balance between conditioning intensity and NRM is unknown for MF. A prospective trial in patients with MF evaluated RIC versus MAC busulfan/fludarabine conditioning, finding a trend toward lower RR in the MAC group, without increased NRM.[79] A further large EBMT retrospective cohort analysis published in 2019 reported equivalent OS and NRM between recipients of RIC and MAC, with a trend toward reduced RR and improved GRFS in the MAC group.[28] Predictors of poorer outcomes following MAC were MUD, older age and reduced performance status. The authors concluded that MAC remained the preferred conditioning in the remaining population. Further prospective randomized trials are needed to better evaluate optimal conditioning intensity, however, there is evidence that RIC may be as effective with less toxicity even among young, MSD recipients.[80] In the last two decades, RIC has been used in around two-thirds of patients in European centers, although this is confounded by increasing age at transplant (median 49.4 vs. 59.3 years).[81] Comparison between the two commonly used regimens, consisting of fludarabine with either busulfan or melphalan, shows similar OS outcomes.[82] The busulfan-based regimen was associated with lower rates of Grade 3–4 acute GVHD, with a trend toward lower NRM. PFS at 7 years was significantly lower in the busulfan group (33% compared to 52% for the melphalan group), owing to significantly higher RR (hazard ratio 9.21, $p = .008$). Nonetheless, OS was similar in both groups.

The optimal conditioning agents also remain unclear. Recently, an 872 patient retrospective CIBMTR analysis reported superior outcomes with fludarabine and busulfan conditioning in both MAC and RIC settings.[83] For MAC protocols, the comparator was busulfan and cyclophosphamide which was associated with significantly increased rates acute GVHD ($p < 0.01$), and reduced GRFS ($p < 0.01$). Fludarabine and melphalan were the comparator for RIC transplant and were associated with reduced OS ($p < 0.01$), higher NRM ($p = 0.01$) and increased acute GVHD ($p < 0.01$). A 60-patient randomized trial comparing fludarabine-busulphan with fludarabine–thiotepa found equivalence between the two regimens, with improved rates of donor chimerism at Day 100 in the fludarabine–thiotepa group.[84]

There is evidence suggesting that dual alkylating agent exposure may improve rates of donor chimerism and reduce relapse risk. A retrospective analysis of 120 patients conditioned with a single (fludarabine with either melphalan, busulphan, or thiotepa) or dual (fludarabine with busulphan and thiotepa) alkylating agents reported striking results with full donor chimerism achieved in 45% and 87% of patients, respectively, and RRs at 5 years of 43% and 9%. There were several covariables of note including reduced rates of prior splenectomy, higher rates of advanced disease (DIPSS), higher use of alternative donors and more frequent pretransplant ruxolitinib use in the dual alkylating agent group, highlighting the need for further research in this area.[85]

High NRM in MF transplant makes lower toxicity conditioning appealing. Noninferiority of treosulfan was shown in a European cohort of AML and MDS patients,[86] however, to date only small studies in MF have been performed. Retrospective analysis of a 20-patient cohort conditioned with fludarabine 150 mg/m^2, treosulfan 42 g/m^2 and in 7 patients 4 Gy TBI, was disappointing, with NRM of 45%, and 2-year OS of 40%. Patients were predominantly intermediate-2 or high risk on the DIPSS, with a median age at transplant of 62 years.[87]

Based on available evidence, we recommend fludarabine and busulfan conditioning regimen for MF transplant, while acknowledging the role for ongoing research into less commonly used agents such as thiotepa and treosulfan.

Level II Grade B.

7.3 | Role of CD34+ cell dose

A recent EBMT retrospective analysis reported improved rates of neutrophil and platelet engraftment in patients receiving a CD34+ cell dose of >7.0 $\times$ 10^6/kg,[88] with no evidence of adverse consequences from the higher dose. Of note, the presence of splenomegaly ≥5 cm compared to no splenomegaly or splenectomy remained a significant predictor of engraftment by multivariate analysis. This study represents the largest such analysis and is currently the only evidence to guide optimal cell dose in MF transplant. No association between high CD34+ doses and GVHD was reported in this analysis, however, this has been reported for other transplant indications requiring caution with higher doses.

We recommend use of high CD34+ doses between 7.0 and 10.0 $\times$ 10^6/kg in transplants for MF.

Level II Grade B.

7.4 | Role of T-cell depleting agents

The rate of GVHD following transplant for MF is higher than for other transplant indications. Robin et al. retrospectively assessed the impact of ATG on GVHD rates in 287 patients undergoing MSD transplant for MF. While ATG significantly reduced the incidence of aGVHD (26% vs. 41%) it did not alter rates of cGVHD, in contrast to the striking difference reported by Kröger et al. in the acute leukemia setting.[89] Importantly, the concern that ATG use might increase RR was not borne out.[90] Recent evidence for the efficacy of ruxolitinib in management of both acute and chronic GVHD raises questions about whether ruxolitinib may have a prophylactic role in MF patients posttransplant.

We recommend use of in vivo T-cell depletion with ATG, or post-transplant cyclophosphamide for haploidentical donors, in all MF transplants.

Level II Grade B.

7.5 | JAKi during the transplant

The role of the inflammatory milieu in MF in delayed engraftment, and potentially GF has been explored previously by Tiribelli et al.,[91] and tested in a 12 patient study of primarily intermediate-2 and high-risk patients who clinically responded to pretransplant ruxolitinib.[92] Therapy was continued from conditioning until day + 28. Only 8% of patients developed Grade 2–4 acute GVHD by day + 100. Early CMV reactivation occurred in five of six seropositive recipients (median 22 days). Two patients ceased ruxolitinib due to cytopenia. Late acute GVHD occurred in four patients following cyclosporin withdrawal, but 3/4 were less than grade 3. Although patient numbers were small, NRM was 0% at a median follow up of 17 months. A further 18 patient study has been performed, which identified tolerability and efficacy of ruxolitinib 10 mg twice daily dosing from day − 3 until day + 30, followed by a gradual wean.[93] Only 7 of the 12 patients treated with continuous 10 mg dosing were receiving ruxolitinib prior to study entry. All patients underwent RIC fludarabine melphalan conditioned matched transplants. Rates of Grade 2–4 acute GVHD were higher compared to the initial pilot study, 17% at Day 100. There were two deaths due to GVHD at 1 year, with a cumulative incidence of moderate to severe chronic GVHD of 24% at 1 year.

While acknowledging the paucity of evidence, and with caution regarding potential cytopenias, we recommend continuation of ruxolitinib at 10 mg bd, as tolerated, through conditioning and until stable engraftment.

Level II Grade C.

8 | POSTTRANSPLANT MONITORING AND MANAGEMENT

8.1 | JAKi posttransplant

The efficacy of ruxolitinib in glucocorticoid refractory GVHD has recently been established.[94,95] The role of ruxolitinib in GVHD prophylaxis, however, remains unclear, although early results hold promise.[96] Whether ruxolitinib may have a role in suppression of residual inflammation, particularly in the bone marrow microenvironment, is also unknown at present.

8.2 | CD34+ stem cell boost

PGF (persistent cytopenia despite full donor chimerism) leads to significant posttransplant morbidity. Reaching a diagnosis of PGF can be difficult, due to the need to exclude alternative causes. Once PGF is confirmed, measures such as growth factor and transfusion support can be utilized. Improved graft function is increasingly reported following CD34+ stem cell boost (SCB). With full donor chimerism, SCB rarely causes GVHD, and facilitates improvement in cytopenias in up to 76% of patients transplanted for hematological malignancy, although data in MF are limited.[97–99] Patients unresponsive to SCB may proceed to a second transplant. The optimal SCB cell dose and timing are unknown, and who will respond is unpredictable. However, since the SCB carries minimal risk it is increasingly trialed. It is important to note that it may take several months for transfusion independence following SCB. In those with persistent splenomegaly who are fit for surgery, improvement in cytopenias may occur following splenectomy.

We recommend use of CD34+ selected SCBs in patients with PGF, before considering second transplant.

Level III Grade C.

8.3 | Relapse

8.3.1 | Risk factors for posttransplant relapse and the role of MRD monitoring

There is little data guiding patient monitoring following transplant for MF. Optimal timing and frequency of bone marrow biopsy for assessment of cellularity, fibrosis, chimerism, and molecular status remains unknown. Furthermore, the value of bone marrow compared to peripheral blood tests in predicting relapse is unknown. Most relapses occur within 12 months posttransplant suggesting a critical monitoring period. The recently published EBMT guidelines introduced above suggests monitoring intervals including bone marrow biopsy at 100 days, and peripheral blood chimerism with concurrent MRD monitoring (where a suitable molecular marker exists), at 1, 3, 6, 9, and 12 months.

Driver mutation clearance is necessary for PFS. The median time to clearance of JAK2 V617F post-HCT is reportedly around 100 days, with persistence at day 180 associated with increased RR.[100] These findings have been confirmed and extended to include CALR and MPL mutations.[101] Interestingly, the proportion of patients with clearance of the driver mutation at day 100 was higher for CALR (92%) than for JAK2 (67%) and MPL (75%).

Data guiding "nondriver" mutation monitoring is limited. Some nondriver mutations are subclonal and might not be present at relapse.[55] In these patients, the detection of mixed myeloid chimerism is a reliable indicator of disease posttransplant.[102] Although quantification methods for nondriver mutations tend to be less sensitive than allele-specific PCR for driver mutations, novel methods can achieve higher sensitivity.[103] We recommend that the EBMT guidelines for post-HCT monitoring be used to improve homogeneity of data.

8.3.2 | Use of donor lymphocyte infusions

EBMT consensus guidelines recommend the use of pre-emptive donor lymphocyte infusion (DLI) in the setting of persistent MRD, molecular

TABLE 4 Recommendations

Pretransplant

Transplant eligibility

- Use of a prognostic model incorporating genetic risk
- Early referral in ruxolitinib responsive transplant eligible patients
- Avoid interferon pretransplant

Extended pretransplant assessment

- Endoscopy for variceal disease
- Doppler ultrasound or MRI angiography of the portal system
- Fiboscan in patients with suspected cirrhosis
- SPECT–CT or FDG-PET for extramedullary hematopoiesis
- Transthoracic echocardiogram for pulmonary hypertension
- ProBNP and troponin levels
- Right heart catheterisation in selected patients
- Cardiac and hepatic T2* MRI for siderosis assessment

Optimisation (where appropriate)

- Variceal banding
- Iron chelation
- Splenic irradiation
- Irradiation to extramedullary hematopoiesis

Transplant

- MSD preferred to MUD and haploidentical donor, avoid MMUD if possible
- Fludarabine and busulphan conditioning
- CD34+ cell dose >7.0 $\times$ 10^6/kg preferred
- Continue ruxolitinib at 10 mg bd (as tolerated) until stable engraftment
- Early consultation with Intensivist for patients with pulmonary hypertension
- Early consultation with gastroenterologist for patients with portal hypertension, siderosis, or cirrhosis
- In vivo T-cell depletion for all MSD, MUD and haploidentical transplants

Posttransplant

- Consideration of CD34+ selected stem cell boost in patients with poor graft function and full donor chimerism
- Consideration of DLI in patients with mixed or declining chimerism and no significant GVHD
- Consideration of second allograft in patients with poor graft function, graft failure or mixed chimerism

relapse, or loss of full donor chimerism.[16] Due to the high risk of GVHD, an escalating DLI dose program is recommended, with ongoing infusions guided by a predefined end point such as donor chimerism or clearance of MRD.

8.3.3 | Second allograft

Repeat allogeneic transplant has shown reasonable success in eligible patients, and can be considered in the setting of both relapse and GF. Given the high NRM associated with transplant for MF, patients undergoing second allografts are highly selected, which likely contributes to the surprisingly favorable outcomes. In a study of patients who relapsed following transplant, and were DLI refractory, a second allograft with treosulfan-based conditioning was performed, with a 3-year OS of 59%, RR of 16%, and NRM of 31%.[104] These positive outcomes are unique to second transplant for MF, with incrementally poorer outcomes observed following second allograft for other hematological malignancies.[105]

We recommend use of DLI or second allograft in patients with mixed or declining chimerism. Second allograft is also recommended in suitable patients with persistent PGF following CD34+ selected SCB, as well as patients in frank relapse.

Level II Grade B (Table 4).

9 | CONCLUSION

With an active pipeline of nontransplant therapies for MF, incorporation of transplantation, the current standard of care for MF, in randomized trials is essential to inform optimal patient management. It is imperative that the transplant community seek to enroll MF patients in clinical trials wherever possible, with international collaboration to increase the power of research in this rare disease. Whether ruxolitinib might have a role in improving engraftment and in primary GVHD prophylaxis remains to be determined, however, it is a particularly appealing option in MF.

High NRM rather than relapse has limited gains in outcomes following MF HCT, but the reasons for this remain poorly understood. Use of less toxic conditioning is one potential way to improve outcomes. Standard patient transplant assessments have failed to identify those MF patients most at risk of NRM. Intensive investigation for secondary organ dysfunction prior to transplant offers a potential avenue to refine patient selection for transplant or institute pretransplant optimisation to reduce this risk. In this way, we may attempt to mitigate the effects of the unique chronic inflammatory state associated with this disease.

Prospective analyses of MF HCT are limited by patient number and heterogeneity, and further complicated by our evolving understanding of prognostic factors and the emergence of novel nontransplant therapies. Optimal splenic management, transplant prognostic modeling, conditioning regimen selection, optimal transplant timing, the impact of molecular disease grade, and the role of peritransplant JAKi remain active questions. Large prospective studies are needed to address these questions, with a focus on high yield questions including the role of treosulfan and ruxolitinib in conditioning and peritransplant prospectively. The challenge faced is in the design of such a trial to address as many clinical questions as possible while maintaining power, in the setting of so much uncertainty. Given the rarity of this disease, international multicenter research collaboration is essential to the advancement of our practice.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated.

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REFERENCES

1. Penna D, Lasho TL, Finke CM, et al. 20+ Years and alive with primary myelofibrosis: phenotypic signature of very long-lived patients. *Am J Hematol*. 2019;94(3):286-290.
2. Tefferi A, Lasho TL, Jimma T, et al. One thousand patients with primary myelofibrosis: the mayo clinic experience. *Mayo Clin Proc*. 2012;87(1):25-33.
3. Baade PD, Ross DM, Anderson LA, Forsyth C, Fritschi L. Changing incidence of myeloproliferative neoplasms in Australia, 2003-2014. *Am J Hematol*. 2019;94(4):E107-E109.
4. Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Vol 2. 4th ed. IARC; 2017.
5. Mesa RA, Silverstein MN, Jacobsen SJ, Wollan PC, Tefferi A. Population-based incidence and survival figures in essential thrombocythemia and agnogenic myeloid metaplasia: an Olmsted County study, 1976-1995. *Am J Hematol*. 1999;61(1):10-15.
6. Cervantes F, Dupriez B, Passamonti F, et al. Improving survival trends in primary myelofibrosis: an international study. *J Clin Oncol*. 2012;30(24):2981-2987.
7. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood*. 2010;115(9):1703-1708.
8. Tefferi A, Guglielmelli P, Lasho TL, et al. MIPSS70+ version 2.0: mutation and karyotype-enhaned international prognostic scoring system for primary myelofibrosis. *J Clin Oncol*. 2018;36:1769-1770.
9. Kroger N, Holler E, Kobbe G, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, mutlicenter study fo the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Blood*. 2009;114:5264-5270.

10. Rondelli D, Goldberg JD, Isola L, et al. MPD-RC 101 prospective study of reduced-intensity allogeneic hematopoietic stem cell transplantation in patients with myelofibrosis. *Blood*. 2014;124(7):1183-1191.
11. Gowin K, Ballen K, Ahn KW, et al. Survival following allogeneic transplant in patients with myelofibrosis. *Blood Adv*. 2020;4(9):1965-1973.
12. Lwin Y, Kennedy G, Gottlieb D, et al. Australasian trends in allogeneic stem cell transplantation for myelofibrosis in the molecular era: a retrospective analysis from the Australasian bone marrow transplant recipient registry. *Biol Blood Marrow Transplant*. 2020;26(12):2252-2261.
13. Harrison CN, Vannucchi AM, Kiladjian JJ, et al. Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis. *Leukemia*. 2016;30(8):1701-1707.
14. Shanavas M, Popat U, Michaelis LC, et al. Outcomes of allogeneic hematopoietic cell transplantation in patients with myelofibrosis with prior exposure to Janus kinase 1/2 inhibitors. *Biol Blood Marrow Transplant*. 2016;22(3):432-440.
15. Kröger N, Sbianchi G, Sirait T, et al. Impact of prior JAK-inhibitor therapy with ruxolitinib on outcome after allogeneic hematopoietic stem cell transplantation for myelofibrosis: a study of the CMWP of EBMT. *Leukemia*. 2021;35(12):3551-3560.
16. McLornan DP, Boluda JCH, Czerw T, et al. Allogeneic haematopoietic cell transplantation for myelofibrosis: proposed definitions and management strategies for graft failure, poor graft function and relapse: best practice recommendations of the EBMT Chronic Malignancies Working Party. *Leukemia*. 2021;35:2445-2459.
17. Kanate AS, Majhail NS, Savani BN, et al. Indications for hematopoietic cell transplantation and immune effector cell therapy: guidelines from the American Society for Transplantation and Cellular Therapy. *Biol Blood Marrow Transplant*. 2020;26(7):1247-1256.
18. Kröger NM, Deeg JH, Olavarria E, et al. Indication and management of allogeneic stem cell transplantation in primary myelofibrosis: a consensus process by an EBMT/ELN international working group. *Leukemia*. 2015;29(11):2126-2133.
19. Zhou S, Tremblay D, Hoffman R, et al. Clinical benefit derived from decitabine therapy for advanced phases of myeloproliferative neoplasms. *Acta Haematol*. 2021;144(1):48-57.
20. Shahin OA, Chifotides HT, Bose P, Masarova L, Verstovsek S. Accelerated phase of myeloproliferative neoplasms. *Acta Haematol*. 2021;144(5):484-499.
21. Tefferi A, Guglielmelli P, Nicolosi M, et al. GIPSS: genetically inspired prognostic scoring system for primary myelofibrosis. *Leukemia*. 2018;32:1631-1642.
22. Kröger N, Giorgino T, Scott BL, et al. Impact of allogeneic stem cell transplantation on survival of patients less than 65 years of age with primary myelofibrosis. *Blood*. 2015;125(21):3347-3350.
23. Cipkar C, Kumar S, Thavorn K, Kekre N. Optimal timing of allogeneic stem cell transplantation for primary myelofibrosis. *Transplant Cell Ther*. 2022;28:189-194.
24. Chhabra S, Narra RK, Wu R, et al. Fludarabine/busulfan conditioning-based allogeneic hematopoietic cell transplantation for myelofibrosis: role of ruxolitinib in improving survival outcomes. *Biol Blood Marrow Transplant*. 2020;26(5):893-901.
25. Phelan R Arora M, Chen M. Current Use and Outcome of Hematopoietic Stem Cell Transplantation: CIBMTR US Summary Slides. 2020.
26. Hernández-Boluda JC, Pereira A, Kröger N, et al. Determinants of survival in myelofibrosis patients undergoing allogeneic hematopoietic cell transplantation. *Leukemia*. 2021;35(1):215-224.
27. Jain T, Kunze KL, Mountjoy L, et al. Early post-transplantation factors predict survival outcomes in patients undergoing allogeneic hematopoietic cell transplantation for myelofibrosis. *Blood Cancer J*. 2020;10(3):36.
28. McLornan D, Szydlo R, Koster L, et al. Myeloablative and reduced-intensity conditioned allogeneic hematopoietic stem cell transplantation in myelofibrosis: a retrospective study by the chronic malignancies working Party of the European Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2019;25(11):2167-2171.
29. Gupta V, Kosiorek HE, Mead A, et al. Ruxolitinib therapy followed by reduced-intensity conditioning for hematopoietic cell transplantation for myelofibrosis: myeloproliferative disorders research consortium 114 study. *Biol Blood Marrow Transplant*. 2019;25(2):256-264.
30. Babushok D, Hexner E. Allogeneic transplantation for myelofibrosis: for whom, when, and what are the true benefits? *Curr Opin Hematol*. 2014;21(2):114-122.
31. Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis*. 1994;18(3):421.
32. Wanless IR, Peterson P, Das A, Boitnott JK, Moore GW, Bernier V. Hepatic vascular disease and portal hypertension in polycythemia vera and agnogenic myeloid metaplasia: a clinicopathological study of 145 patients examined at autopsy. *Hepatology*. 1990;12(5):1166-1174.
33. Lee J, Sung PS, Eom K, et al. Clinical characteristics of portal hypertension complicated by gastroesophageal varices in patients with myeloproliferative neoplasms. *Clin Mol Hepatol*. 2019;26:78-82.
34. Yu NC, Margolis D, Hsu M, Raman SS, Lu DSK. Detection and grading of esophageal varices on liver CT: comparison of standard and thin-section multiplanar reconstructions in diagnostic accuracy. *Am J Roentgenol*. 2011;197(3):643-649.
35. Perri RE, Chiorean MV, Fidler JL, et al. A prospective evaluation of computerized tomographic (CT) scanning as a screening modality for esophageal varices. *Hepatology*. 2008;47(5):1587-1594.
36. Yan M, Geyer H, Mesa R, et al. Clinical features of patients with Philadelphia-negative myeloproliferative neoplasms complicated by portal hypertension. *Clin Lymphoma Myeloma Leuk*. 2015;15:e1-e5.
37. Schouten JNL, Verheij J, Seijo S. Idiopathic non-cirrhotic portal hypertension: a review. *Orphanet J Rare Dis*. 2015;10:67.
38. Wong KM, Atenafu EG, Kim D, et al. Incidence and risk factors for early hepatotoxicity and its impact on survival in patients with myelofibrosis undergoing allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2012;18(10):1589-1599.
39. Tabarroki A, Lindner DJ, Visconte V, et al. Ruxolitinib leads to improvement of pulmonary hypertension in patients with myelofibrosis. *Leukemia*. 2014;28(7):1486-1493.
40. Lopez-Mattei J, Verstovsek S, Fellman B, et al. Prevalence of pulmonary hypertension in myelofibrosis. *Ann Hematol*. 2020;99:781-789.
41. Gupta R, Jamal F, Yang D, et al. Pulmonary arterial hypertension is associated with increased nonrelapse mortality after allogeneic hematopoietic cell transplantation for myelofibrosis. *Bone Marrow Transplant*. 2019;55:877-833.
42. Yang M, Roarke M, Nguyen B. Diagnosis of diffuse pulmonary Extramedullary hematopoiesis in myelofibrosis with technetium-99m sulfur colloid bone marrow scintigraphy. *J Nucl Med*. 2017;58-(supplement 1):596.
43. Isidori A, Borin L, Elli E, et al. Iron toxicity - its effect on the bone marrow. *Blood Review*. 2018;32:473-479.
44. Trottier BJ, Burns LJ, DeFor TE, et al. Association of iron overload with allogeneic hematopoietic cell transplantation outcomes: a prospective cohort study using R2-MRI measured liver iron content. *Blood*. 2013;122:1678-1684.
45. Sucak GT, Yegin ZA, Ozkurt ZN, Aki SZ, Yağci M. Iron overload: predictor of adverse outcome in hematopoietic stem cell transplantation. *Transplant Proc*. 2010;42:1841-1848.
46. Armand P, Kim HT, Virtanen JM, et al. Iron overload in allogeneic hematopoietic cell transplantation outcome: a meta-analysis. *Biol Blood Marrow Transplant*. 2014;20(8):1248-1251.
47. Ruggeri A, Labopin M, Sormani MP, et al. Engraftment kinetics and graft failure after single umbilical cord blood transplantation using a

myeloablative conditioning regimen. *Haematologica*. 2014;99(9):1509-1515.
48. Alchalby H, Yunus D-R, Zabelina T, et al. Risk models predicting survival after reduced-intensity transplantation for myelofibrosis. *Br J Haematol*. 2012;157:75-85.
49. Kröger N, Zabelina T, Alchalby H, et al. Dynamic of bone marrow fibrosis regression predicts survival after allogeneic stem cell transplantation for myelofibrosis. *Biol Blood Marrow Transplant*. 2014;20(6):812-815.
50. Kröger N, Thiele J, Zander A, et al. Rapid regression of bone marrow fibrosis after dose-reduced allogeneic stem cell transplantation in patients with primary myelofibrosis. *Exp Hematol*. 2007;35(11):1719-1722.
51. Ali H, Aldoss I, Yang D, et al. MIPSS70+ v2.0 predicts long-term survival in myelofibrosis after allogeneic HCT with the flu/Mel conditioning regimen. *Blood Adv*. 2019;3(1):83-95.
52. Panagiota V, Thol F, Markus B, et al. Prognostic effect of calreticulin mutations in patients with myelofibrosis after allogeneic hematopoietic stem cell transplantation. *Leukemia*. 2014;28(7):1552-1555.
53. Gagelmann N, Ditschkowski M, Bogdanov R, et al. Comprehensive clinical-molecular transplant scoring system for myelofibrosis undergoing stem cell transplantation. *Blood*. 2019;133(20):2233-2242.
54. Kröger N, Panagiota V, Badbaran A, et al. Impact of molecular genetics on outcome in myelofibrosis patients after allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2017;23(7):1095-1101.
55. Tamari R, Rapaport F, Zhang N, et al. Impact of high-molecular-risk mutations on transplantation outcomes in patients with myelofibrosis. *Biol Blood Marrow Transplant*. 2019;25(6):1142-1151.
56. Christopeit M, Badbaran A, Zabelina T, et al. Similar outcome of calreticulin type I and calreticulin type II mutations following RIC allogeneic haematopoietic stem cell transplantation for myelofibrosis. *Bone Marrow Transplant*. 2016;51(10):1391-1393.
57. Gupta V, Kim S, Hu ZH, et al. Comparison of outcomes of HCT in blast phase of *BCR-ABL*$^{-}$ MPN with de novo AML and with AML following MDS. *Blood Adv*. 2020;4(19):4748-4757.
58. Stevens EA, Jenkins IC, Beppu LW, et al. Targeted sequencing improves DIPSS-plus prognostic scoring in myelofibrosis patients undergoing allogeneic transplantation. *Biol Blood Marrow Transplant*. 2020;26(7):1371-1374.
59. Robin M, Porcher R, Orvain C, et al. Ruxolitinib before allogeneic hematopoietic tranplantation in patients with myelofibrosis on behalf of SFGM-TC and FIM groups. *Bone Marrow Transplant*. 2020;56:1888-1899.
60. Ianotto JC, Chauveau A, Boyer-Perrard F, et al. Benefits and pitfalls of pegylated interferon-α2a therapy in patients with myeloproliferative neoplasm-associated myelofibrosis: a French intergroup of myeloproliferative neoplasms (FIM) study. *Haematologica*. 2018;103(3):438-446.
61. Morton AJ, Gooley T, Hansen JA, et al. Association between pretransplant interferon-α and outcome after unrelated donor marrow transplantation for chronic myelogenous leukemia in chronic phase. *Blood*. 1998;92(2):394-401.
62. Palmer JM, Kosiorek HE, Dueck AC, Camoriano J, Zimmerman C, Mesa R. Ropeginterferon demonstrates safety and efficacy in myelofibrosis: pilot study results. *Blood*. 2020;136(supplement 1):23.
63. Greenfield G, McMullin MF, Mills K. Molecular pathogenesis of the myeloproliferative neoplasms. *J Hematol Oncol*. 2021;14(1):103.
64. Gisslinger H, Klade C, Georgiev P, et al. Evidence for superior efficacy and disease modification after three years of prospective randomized controlled treatment of polycythemia Vera patients with Ropeginterferon Alfa-2b vs. HU/BAT. *Blood*. 2018;132(supplement 1):579.
65. Tremblay D, Schwartz M, Bakst R, et al. Modern management of splenomegaly in patients with myelofibrosis. *Ann Hematol*. 2020;99:1441-1451.
66. Mascarenhas J, Harrison C, Luptakova K, et al. MANIFEST-2, a global, phase 3, randomized, double-blind, active-control study of CPI-0610 and ruxolitinib vs. placebo and ruxolitinib in JAK-inhibitor-naive myelofibrosis patients. *Blood*. 2020;136(supplement 1):43.
67. Tefferi A, Lasho TL, Begna KH, et al. A pilot study of the telomerase inhibitor imetelstat for myelofibrosis. *N Engl J Med*. 2015;373(10):908-919.
68. Harrison CN, Garcia JS, Mesa RA, et al. Results from a phase 2 study of Navitoclax in combination with Ruxolitinib in patients with primary or secondary myelofibrosis. *Blood*. 2019;134:671.
69. Polverelli N, Mauff K, Kroger N, et al. Impact of spleen size and splenectomy on outcomes of allogeneic hmatopoietic cell transplantation for myelofibrosis: a retrospective analysis by the chronic malignancies working part y on behalf of European society for blood and marrow transplantation (EBMT). *Am J Hematol*. 2020;96(1):69-79.
70. Lwin Y, Kennedy G, Gottlieb D, et al. Australiasian trends in allogeneic stem cell transplantation for myelofibrosis in the molecular era: a retrospective analysis from the Australasia Bone Marrow Transplant Recipient Registry. *Biol Blood Marrow Transplant*. 2020;26:2252-2261.
71. Robin M, Zine M, Chevret S, et al. The impact of splenectomy in myelofibrosis patients before allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2017;23(6):958-964.
72. Guardiola P, Anderson JE, Bandini G, et al. Allogeneic stem cell transplantation for agnogenic myeloid metaplasia: a European Group for Blood and Marrow Transplantation, Socit Franaise de Greffe de Moelle, Gruppo Italiano per il Trapianto del Midollo Osseo, and Fred Hutchinson Cancer Research Center Collaborative Study. *Blood*. 1999;93:2831-2838.
73. Rondelli D, Goldberg JD, Isola L, et al. MPD-RC101 prospective study of reduced-intensity allogeneic hematopoietic stem cell transplantation in patients with myelofibrosis. *Blood*. 2014;124(7):1183-1191.
74. Bregante S, Dominietto A, Ghiso A, et al. Improved outcome of alternative donor transplantations in patients with myelofibrosis: from unrelated to haploidentical family donors. *Biol Blood Marrow Transplant*. 2016;22(2):324-329.
75. Robin M, de Wreede LC, Wolschke C, et al. Long-term outcome after allogeneic hematopoietic cell transplantation for myelofibrosis. *Haematologica*. 2019;104(9):1782-1788.
76. Kunte S, Rybicki L, Viswabandya A, et al. Allogeneic blood or marrow transplantation with haploidentical donor and post-transplantation cyclophosphamide in patients with myelofibrosis: a multicenter study. *Leukemia*. 2021;36:856-864.
77. Murata M, Nishida T, Taniguchi S, et al. Allogeneic transplantation for primary myelofibrosis with BM, peripheral blood or umbilical cord blood: an analysis of the JSHCT. *Bone Marrow Transplant*. 2014;49(3):355-360.
78. Robin M, Giannotti F, Deconinck E, et al. Unrelated cord blood transplantation for patients with primary or secondary myelofibrosis. *Biol Blood Marrow Transplant*. 2014;20(11):1841-1846.
79. Popat U, Mehta RS, Bassett R, et al. Optimizing the conditioning regimen for hematopoietic transplant in myelofibrosis: long-term results of a phase II clinical trial. *Biol Blood Marrow Transplant*. 2020;26(8):1439-1445.
80. Mannina D, Zabelina T, Wolschke C, et al. Reduced intensity allogeneic stem cell transplantation for younger patients with myelofibrosis. *Br J Haematol*. 2019;186(3):484-489.
81. McLornan D, Eikema DJ, Czerw T, et al. Trends in allogeneic haematopoietic cell transplantation for myelofibrosis in Europe between 1995 and 2018: a CMWP of EBMT retrospective analysis. *Bone Marrow Transplant*. 2021;56(9):2160-2172.
82. Robin M, Porcher R, Wolschke C, et al. Outcome after transplantation according to reduced-intensity conditioning regimen in patients

undergoing transplantation for myelofibrosis. *Biol Blood Marrow Transplant*. 2016;22(7):1206-1211.
83. Guru Murthy GS, Kim S, Estrada-Merly N, et al. Superior outcomes with fludarabine-busulfan (flu/Bu) based conditioning for allogeneic hematopoietic cell transplantation in myelofibrosis—a comparative analysis by CIBMTR. *Blood*. 2021;138(supplement 1):912.
84. Patriarca F, Masciulli A, Bacigalupo A, et al. Busulfan- or thiotepa-based conditioning in myelofibrosis: a phase II multicenter randomized study from the GITMO group. *Biol Blood Marrow Transplant*. 2019;25(5):932-940.
85. Chiusolo P, Bregante S, Giammarco S, et al. Full donor chimerism after allogeneic hematopoietic stem cells transplant for myelofibrosis: the role of the conditioning regimen. *Am J Hematol*. 2021;96(2):234-240.
86. Beelen DW, Trenschel R, Stelljes M, et al. Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic haematopoietic stem cell transplantation for older patients with aute myeloid leukaemia or myelodysplastic syndrome (MC-FludT.14/L): a randomised, non-inferiority, phase 3 trial. *Lancet Haematol*. 2019;7:e29-e39.
87. Claudiani S, Lunghi F, Giglio F, et al. Treosulfan based myeloablative regimen provides high rate of allogeneic engraftment and low toxicity in patients with advanced myelofibrosis. *Blood*. 2013;122(21):5504.
88. Czerw T, Iacobelli S, Malpassuti V, et al. Impact of donor-derived CD34+ infused cell dose on outcomes of patients undergoing Allo-HCT following reduced intensity regimen for myelofibrosis: a study from the chronic malignancies working party of the EBMT. *Bone Marrow Transplant*. 2022;57(2):261-270.
89. Kroger N, Solano C, Wolschke C, et al. Antilymphocyte globulin for prevention of chronic graft-versus-host disease. *N Engl J Med*. 2016;374:43-53.
90. Robin M, Chevret S, Koster L, et al. Antilymphocyte globulin for matched sibling donor transplantation in patients with myelofibrosis. *Haematologica*. 2019;104:1230-1236.
91. Tiribelli M, Palandri F, Sant'Antonio E, Breccia M, Bonifacio M. The role of allogeneic stem-cell transplant in myelofibrosis in the era of JAK inhibitors: a case-based review. *Bone Marrow Transplant*. 2020;55(4):708-716.
92. Kröger N, Abd Kadir SSS, Zabelina T, et al. Peritransplantation ruxolitinib prevents acute graft-versus-host disease in patients with myelofibrosis undergoing allogenic stem cell transplantation. *Biol Blood Marrow Transplant*. 2018;24(10):2152-2156.
93. Ali H, Tsai NC, Synold T, et al. Peritransplant ruxolitinib administration is safe and effective in patients with myelofibrosis: a pilot open-label study. *Blood Adv*. 2022;6(5):1444-1453.
94. Zeiser R, Polverelli N, Ram R, et al. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *New Engl J Med*. 2021;385(3):228-238.
95. Zeiser R, von Bubnoff N, Butler J, et al. Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. *New Engl J Med*. 2020;382(19):1800-1810.
96. Morozova EV, Barabanshikova MV, Moiseev IS, et al. A prospective pilot study of graft-versus-host disease prophylaxis with post-transplantation cyclophosphamide and ruxolitinib in patients with Myelofibrosis. *Acta Haematol*. 2021;144(2):158-165.
97. M. Cuadrado M, Richard MS, Mike W, et al. Predictors of recovery following allogeneic CD34+-selected cell infusion without conditioning to correct poor graft function. *Haematologica*. 2019;105(11):2639-2646.
98. Stasia A, Ghiso A, Galaverna F, et al. CD34 selected cells for the treatment of poor graft function after allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2014;20(9):1440-1443.
99. Klyuchnikov E, El-Cheikh J, Sputtek A, et al. $CD34^{+}$-selected stem cell boost without further conditioning for poor graft function after allogeneic stem cell transplantation in patients with hematological malignancies. *Biol Blood Marrow Transplant*. 2014;20(3):382-386.
100. Alchalby H, Badbaran A, Zabelina T, et al. Impact of JAK2V617F mutation status, allele burden, and clearance after allogeneic stem cell transplantation for myelofibrosis. *Blood*. 2010;116(18):3572-3581.
101. Wolschke C, Badbaran A, Zabelina T, et al. Impact of molecular residual disease post allografting in myelofibrosis patients. *Bone Marrow Transplant*. 2017;52(11):1526-1529.
102. Srour SA, Olson A, Ciurea SO, et al. Mixed myeloid chimerism and relapse of myelofibrosis after allogeneic stem cell transplantation. *Haematologica*. 2021;106(7):1988-1990.
103. Stahl T, Rothe C, Böhme MU, Kohl A, Kröger N, Fehse B. Digital PCR panel for sensitive hematopoietic chimerism quantification after allogeneic stem cell transplantation. *Int J Mol Sci*. 2016;17(9):1515.
104. Atagunduz IK, Klyuchnikov E, Wolschke C, et al. Treosulfan-based conditioning regimen for second allograft in patients with myelofibrosis. *Cancers*. 2020;12(11):3098.
105. Moukalled NM, Kharfan-Dabaja MA. What is the role of a second allogeneic hematopoietic cell transplant in relapsed acute myeloid leukemia? *Bone Marrow Transplant*. 2020;55(2):325-331.

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