Are transplant indications changing for myelofibrosis?

Jeanne Palmer
Division of Hematology/Medical Oncology, Mayo Clinic, Phoenix, AZ

Myelofibrosis is a devastating myeloid malignancy characterized by dysregulation of the JAK-STAT pathway, resulting in splenomegaly, constitutional symptoms, anemia, thrombocytopenia, leukocytosis, and an increased likelihood of progression to acute leukemia. The only curative option is allogeneic stem cell transplantation. The numbers of transplants have been increasing every year, and although there have been improvements in survival, there remain many unanswered questions. In this review, we will evaluate patient selection and appropriate timing for transplantation. We will cover the current prognostic scoring systems, which can aid in the decision of when to move forward with transplant. We will also review the different donor options, as well as the conditioning regimens. The peritransplant management of splenomegaly will be reviewed. We will discuss management of posttransplant complications such as loss of donor chimerism or disease relapse. Finally, we will review what is known about the outlook of patients who have undergone allogeneic stem cell transplant with regards to quality of life and long-term survival.

LEARNING OBJECTIVES

- Compare the different prognostic scoring systems for patients who have myelofibrosis when considering allogeneic stem cell transplant
- Evaluate different donor sources and conditioning regimens
- Compare different methods of management of splenomegaly in the peritransplant setting
- Apply concepts to management of posttransplant issues such as disease relapse, as well as long-term outlook

CLINICAL CASE

The patient is a 57-year-old woman with primary myelofibrosis (PMF) diagnosed when she presented with anemia and leukocytosis in 2018. At the time of diagnosis, she had a hemoglobin of 12 g/dL and white blood cell (WBC) count of 15×10^9/L with leukoerythroblastosis but no peripheral blasts. Her spleen was palpable at 3 cm below the left costal margin. She had mild night sweats and weight loss. Bone marrow biopsy specimen showed 3/3 reticulin fibrosis and no increase in blasts. She had a *JAK2* mutation (variant allele frequency [VAF] 35%) and *TET2* mutation (VAF 26%). She was started on ruxolitinib with improvement of her spleen, as well as symptoms. After 3 years, she started to have worsening (hemoglobin 10 g/dL), and WBC count increased to 29×10^9/L. She had 2% blasts in her peripheral blood. Her spleen was palpable at 7cm below the left costal margin. Bone marrow biopsy specimen showed ongoing fibrosis and no increase in blasts. Cytogenetics showed a new trisomy 8, and next-generation sequencing (NGS) showed *JAK2* mutation (VAF 43%), *TET2* (VAF 40%) mutation, and a new *ASXL1* (VAF 45%) mutation. She was referred to a bone marrow transplant specialist.

Allogeneic stem cell transplant (ASCT) is the only curative treatment for patients with myelofibrosis (MF). Although the benefit of transplant is well established, there are still many questions as to timing of transplant. Myelofibrosis is a disease that can span over many years; therefore, identifying the correct time in the disease course is critical.

When approaching a patient who has MF, there are 2 critical aspects to review with the patient: first, whether they desire a transplant once they understand the risks and benefits of a transplant and, second, what their disease risk is. The patient's perception of transplant for MF can vary significantly and in many cases can be a barrier to transplantation. In an Internet-based survey, of 129 patients, only 41 patients were referred for transplant, and of those, only 16 patients intended on proceeding with transplant.[1] In another study of 116 transplant-eligible patients, only 102

decided to proceed with human leukocyte antigen typing, 41 patients went to upfront transplant, and of those who did not, only 15 went to a salvage transplant.[2] For this reason, I feel it is important that patients are referred to transplantation early in the disease course, to allow for time to process the information and make an educated decision.

Once it is determined that the patient is interested in transplant, it is important to perform an optimal disease risk assessment. Many prognostic scoring systems can be applied, including a dynamic international prognostic scoring system (DIPSS), DIPSS plus, a molecularly annotated international prognostic scoring system 70 (MIPSS70), MIPSS70 plus v2.0, and MYelofibrosis SECondary to PV and ET–Prognostic Model (MYSEC-PM) (see Table 1). The most commonly used one is the DIPSS, a prognostic scoring system for patients with PMF, which takes into account laboratory factors such as hemoglobin less than 10 g/dL, WBC count greater than 25×10^9/L, and peripheral blasts ≥2%, as well as clinical factors such as age and constitutional symptoms. Each factor gives a score of 1 except anemia, which conveys a higher risk, so it has a score of 2 points. The DIPSS stratifies patients into low, intermediate 1 (Int-1), intermediate 2 (Int-2), and high-risk categories, corresponding to a median overall survival (OS) of not reached, 14.2 years, 4.0 years, and 1.5 years, respectively.[3] Generally speaking, transplant is reserved for Int-2 and high-risk disease.[4] The use of DIPSS Int-2 risk disease as a cutoff was validated in a retrospective study that compared patients who had ASCT vs retrospective comparators from a 14-center registry between 2000 and 2014. There were 551 patients who underwent transplant and 1377 who underwent nontransplant management. The median time for follow-up was 72 months (3-193) for the transplanted patients and 63 months (<1-208) for the nontransplanted patients. It is notable that only 10% of the patients who underwent transplant were exposed to ruxolitinib as compared to 30% who were not exposed to ruxolitinib.[5] There was a survival advantage appreciated in Int-1, Int-2, and high-risk patients, although in the Int-1 risk patients, that benefit was not observed for a number of years, and there was a high rate of early mortality.[5] More refined scoring systems are needed to determine which patients with Int-1 risk disease will benefit from transplant. It is important to acknowledge that the DIPSS and DIPSS plus are validated in PMF but not secondary MF. MYSEC-PM, a score designed for secondary MF, is more predictive for outcomes following transplant for MF but still does not perform well.[6] Further, the same comparative studies evaluating survival with and without transplant have not been done with the MYSEC-PM.

Over the past decade, the genetic landscape of patients with MF has been under intense study. With regard to the driver mutations associated with MF, patients with type 1 *CALR* mutations have the most favorable prognosis, and patients who do not have a driver mutation, also known as triple negative, have the worst prognosis.[7] Additionally, several other mutations have been associated with a higher-risk prognosis, including *ASXL1*, *IDH1/2*, *EZH2*, *SRSF2*, and *U2AF1*.[7] To account for the impact of the somatic mutations, a novel scoring system, the mutation enhanced international prognostic scoring system, was created: MIPSS 70 and MIPSS70 plus 2.0. These scoring systems take into account similar data as the DIPSS but also include driver mutation, grade fibrosis, NGS, and cytogenetics (in MIPSS70 plus 2.0). In the MIPSS70, there are 3 risk categories, including low risk, intermediate risk, and high risk; the MIPSS70 plus 2.0 creates 4 risk categories: low, intermediate, high, and very high.[7] These scoring systems place heavy consideration on both the mutational landscape as well as the cytogenetics. It is critical to acknowledge that patients may stay in a given risk category for years and, based on laboratory variations, may fluctuate between risk levels. It is important to

Table 1. Prognostic scoring systems for myelofibrosis

	DIPSS[3]	DIPSS plus[38]	MIPSS70[7]	MIPSS70 plus	MYSEC[39]
Age	☑	☑	☑	☑	☑
Anemia (hemoglobin <10)	☑	☑	☑	☑	☑
WBC >25	☑	☑	☑		
Blast %	☑	☑	☑	☑	☑
Constitutional symptoms	☑	☑	☑	☑	☑
Platelets <100		☑	☑		☑
Red cell transfusion dependent		☑			
Unfavorable karyotype*		☑		☑	
Bone marrow fibrosis grade			☑		
High-risk molecular mutations (1)			☑	☑	
High-risk molecular mutations (≥2)			☑	☑	
Type 1 *CAL-R* absence			☑		☑
Scoring	Low risk: 0	Low: 0	Low: 0–1	Low: 0–2	Low: <11
	Int-1: 1–2	Int-1: 1	Intermediate: 2–4	Intermediate: 3	Int-1: 11–13
	Int-2: 3–4	Int-2: 2–3	High: ≥5	High: 4–6	Int-2: 14–16
	High risk: 5–6	High risk: 4–6		Very high: ≥7	High: >16

*Unfavorable karyotype: Complex karyotype or one or two abnormalities that include +8, −7/7q−, i(17q), −5/5q−, 12p−, inv(3), or 11q23. High-Risk molecular mutations: *ASXL1, IDH1/2, EZH2, SRSF2*, and *U2AF1*.

monitor the trend of labs and have ongoing discussions with the patient regarding their disease risk.

In the patient described above, when initially seen, she would have been considered Int-1 risk, only scoring a point for constitutional symptoms. It would be appropriate to have her meet with a transplant specialist at the initial time point, as starting discussions with the transplant physician earlier can be beneficial for the patient. However, based on current recommendations, she would not be considered a transplant candidate at that point. When she started to progress through ruxolitinib, she would be still be considered Int-1 risk based on DIPSS but would be considered high risk based on MIPSS70 and MIPSS70 plus 2.0. Additionally, she has progressed through ruxolitinib, which is associated with a median survival of about 14 months.[8] Therefore, she is at a time when it would be very appropriate to consider ASCT.

Other factors that should be accounted for when considering transplant include age and hematopoietic cell transplant comorbidity index. Patients older than 55 years have a increased risk of mortality in the setting of transplant for MF.[4,9] There has not been a direct comparison in recent years of patients older vs younger 65 years of age, but in a recent analysis of patients older than 65 years, the 5-year survival was 40%, as compared to 50% in a recent analysis including all age groups.[10] The upper age limit has not been established. The European LeukemiaNet (ELN)–European Society for Blood and Marrow Transplantation (EBMT) recommendations from 2015 suggest 70 years is the upper age limit for transplant,[4] but many centers have higher upper age limit cutoffs, and the aforementioned study included patients up to 75 years of age. In unadjusted multivariate analysis, age less than or greater than 68 did not impact outcome.[10] Another predictive model can be employed at this time, the Myelofibrosis Transplant Scoring System, at this time point. This scoring system takes into account factors such as patient age, mutation status (non-*CAL-R/MPL* driver mutation and presence of *ASXL1*), platelets, WBC count, patient performance status, and donor status (matched related/unrelated vs mismatched unrelated donor).[11] This scoring system accounts for variables at the time of transplant and is applicable to both PMF and secondary MF.[11]

Patient has no siblings but does have 2 adult children. An unrelated donor search was done, which showed one 10/10 matched unrelated donor (MUD) and several 9/10 mismatched unrelated donors (MMUDs). Her adult children are both haploidentical, and she does not have any donor-specific antibodies. Choice of donor for ASCT has evolved over the past 10 years. Over time, the donor pool has expanded in that MMUD and haploidentical donors can be considered. In the setting of transplant for MF, there appears to be increased intolerance of mismatches, particularly in the unrelated donor setting, where a 9/10 donor is thought to be associated with inferior outcomes as compared to a MUD or a matched related donor (MRD), with 5-year survival around 38% to 48% (see Table 2).[12-14] Until recently, there were very little data evaluating the use of a haploidentical donor in the setting of MF, but recently, Kunte et al[14] published a multicenter retrospective analysis of haploidentical transplant for MF and found 3-year survival of 72% (95% CI, 59%-81%). Another retrospective study done using the EBMT registry of patients undergoing haploidentical transplant showed a 2-year survival of 57%.[15] It is important to note, in the United States, any patient who has Medicare must participate in the Myelofibrosis Medicare Study. In this study, the donor must have a fully matched related or unrelated donor. If

Table 2. Donor source and outcomes

Reference	N	TRM	OS
Kröger et al. 2009[13]	**103 PMF, post-ET MF, post-PV MF** HLA matched: 82 HLA mismatched: 21	**At 1 y** MRD: 10% MUD: 13% MMUD: 38%	**At 5 y** MRD/MUD: 74% MMUD: 38% *P*=.03
Rondelli et al. 2014[40]	**66 PMF, post-ET MF, post-PV MF** MRD: 30 Haplo: 2 MUD: 25 MMUD: 9	MRD: 22% MUD: 59%	MRD: 75% MUD: 32%
Gupta et al. 2014[41]	**233 PMF** MRD: 79 MUD: 104 MMUD: 50	**At 1 y: 18%** **At 5 y: 24%** MUD: 3.92 MMUD: 9.37 (*P*<.0001)	**Adjusted OS at 5 y** MRD: 56% MUD: 48% MMUD: 34% (*P*=.002)
Raj et al. 2019[15]	**PMF 42, secondary MF 14** 56 MMRD	**35% (95% CI, 22%-48%) @ 1 y**	**61% (95% CI, 48%-74%) @ 1 y**
McLornan et al. 2021[42]	**4142 patients** **PMF 3239, post-ET MF 494, post-PV MF 409** MRD: 1430 MUD: 1554 MMRD: 226 MMUD: 537 CB: 31	**NRM hazard ratio:** MRD: 0 MUD: 1.3 (1.11–1.54), *P*=.001 MMRD: 1.76 (1.32–2.36) *P*≤.001 MMUD: 1.9 (1.56–2.31), *P*≤.001	**OS hazard ratio** MRD: 0 MUD: 1.21 (1.06–1.38), *P*=.005 MMRD: 1.51 (1.16–1.97), *P*=.002 MMUD: 1.67 (1.41–1.97), *P*≤.001
Kunte et al. 2022[14]	**69 patients** **PMF 35, post-ET MF 19, post-PV MF 15**	**@ 1 y: 21% (95% CI, 12%-32%)** **@ 3 y: 23% (95% CI, 14%-34%)**	**@ 1 y: 74% (95% CI, 61%-83%)** **@ 3 y: 72% (95% CI, 59%-81%)**

CB, cord blood; ET, essential thrombocythemia; HLA, human leukocyte antigen; MMRD, mismatched related donor; NRM, non-relapse mortality; PV, polycythemia vera; TRM, treatment-related mortality.

neither of them are available, a haploidentical donor may be used (Medicare Clinical Trials, cibmtr.org). Therefore, in this case, if the MUD did not work out, I would likely consider a haploidentical donor over a 9/10 donor, using a posttransplant cyclophosphamide-based graft-versus-host disease prophylaxis.

Conditioning regimen has also been an area of debate in the field of transplantation. In the situations where a myeloablative regimen is preferred, busulfan-based regimens can be considered, pairing it with fludarabine or cyclophosphamide.[16] Reduced intensity conditioning (RIC) regimens, such as fludarabine/melphalan, or fludarabine/8 to 10 mg/kg busulfan have been used.[17] A recent publication evaluating over 800 patients with MF who underwent ASCT suggest that both myeloablative and RIC regimens including busulfan and fludarabine appear to have improved outcomes as compared to busulfan/cyclophosphamide and fludarabine/melphalan regimens, respectively.[18] In those patients who can tolerate a myeloablative regimen, it is unclear whether an ablative regimen is superior to an RIC regimen. A retrospective analysis done by EBMT did not see a significant difference between those transplanted with RIC or myeloablative conditioning regimens, but there was a trend toward decreased risk of relapse in patients who underwent MA transplant.[19]

Another factor that must be considered prior to ASCT is management of an enlarged spleen. Several studies have suggested outcomes of transplant in patients with a spleen >15 cm are associated with worse outcomes.[20,21] There are increasing data that use of ruxolitinib prior to transplant is not only safe but also may provide improved outcomes (see Table 2).[22,23] JAK inhibition can be continued until the time of the conditioning regimen,[24] but some studies have used it up until engraftment,[25] day 30,[22,25] or even up to 1 year.[22] In this case, where there has been clear progression through ruxolitinib, one of the newer generation of JAK inhibitors such as fedratinib and pacritinib can be considered,[26,27] although there are limited data of their use in this setting. In the setting where JAK inhibition is contraindicated or not tolerated, both splenic radiation and splenectomy can be considered. Splenic irradiation has been studied in the pretransplant setting and appears to be safe, but whether it provides an advantage over splenectomy or no treatment is not clear.[28,29] In an analysis by the EBMT, they found that in patients whose spleen was greater than 15 cm below the left costal margin (LCM), improved survival was appreciated in patients who underwent splenectomy.[21] However, substantial morbidity and mortality are associated with splenectomy,[30] and this analysis only included patients who survived the splenectomy to make it to transplant, so it is possible that patients who would otherwise be transplant candidates may be unable to receive a transplant once they have undergone splenectomy (Table 3).

CLINICAL CASE (continued)

Patient undergoes ASCT from a 10/10 MUD. Her transplant course is unremarkable. At her day 100 analysis, she was noted to have 10% JAK2 positivity in her peripheral blood; CD33 sorted chimerism showed 90% donor, 10% recipient, but otherwise no evidence of MF.

Relapse remains a problem in transplant for MF; between 15% and 45% of patients will experience a relapse.[4] Definition of relapse may also be a challenge following transplant. Determination cannot be made by the presence of fibrosis of the bone marrow as it may take up to 2 years for fibrosis to resolve.[31] Molecular relapse includes persistence of the driver mutation at 3 to 6 months and loss of donor chimerism.[32] Overt relapse is characterized by increasing fibrosis or cellularity, as well as reappearance of megakaryocyte atypia.[33] Although the literature is fairly consistent in the increased risk of relapse in loss of myeloid chimerism,[32] persistence of JAK2 mutation following transplant is not as clearly associated with relapse.[32,34] In a large retrospective review done by EBMT, different approaches to relapse were compared, and there was no significant difference between donor lymphocyte infusion (DLI) alone, chemotherapy + DLI, or DLI and second transplant.[35] In this case, I would proceed with a DLI.

CLINICAL CASE (continued)

Patient was given a DLI and cleared the JAK2, and CD33 sorted chimerism returned to 100% donor. She wants to better understand her long-term outlook.

Although there is a high rate of treatment-related mortality with transplant, the long-term outlook is encouraging. With regards to quality of life, 61% of patients report feeling better at 1 year posttransplant as compared to pretransplant.[36] Long-

Table 3. JAK inhibitor prior to allogeneic stem cell transplantation

Reference (first author)	Prospective/ retrospective	Conditioning	N	Spleen response	Ruxolitinib discontinuation	Graft failure	GVHD II-IV	TRM	OS
Kröger 2018[24]	Pros	RIC	12	50%	Day +28	0%	8%	0% 17 mo	100% @ 17 mo
Kadir 2018[43]	Retro	RIC	46	39%	Varied	4%	37%	23% @ 2 y	72.7 @ 2 y
Gupta 2019[44]	Pros	RIC	21	45%	Prior to conditioning	16%	47%	28% @ 2 y	66% @ 2 y
Salit 2020[23]	Pros	RIC/MAC	28	NR	Prior to conditioning	0	78%	23% @ 1 y	86% @ 2 y
Kröger 2021[45]	Retro	RIC/MAC	277	56%	NR	NR	29%	26% @ 1 y	66% @ 1 y
Robin 2021[46]	Pros	RIC	59	46%	Prior to transplant—varied	3%	66%	42% @ 1 y	68% @ 1 y
Ali 2022[25]	Pros	RIC	18	NR	Day +30	0%	45%	23% @ 1 y	77% @ 1 y

GVHD, graft-versus-host disease; MAC, myeloablative conditioning; NR, not reported; Pros, prospective; Retro, retrospective.

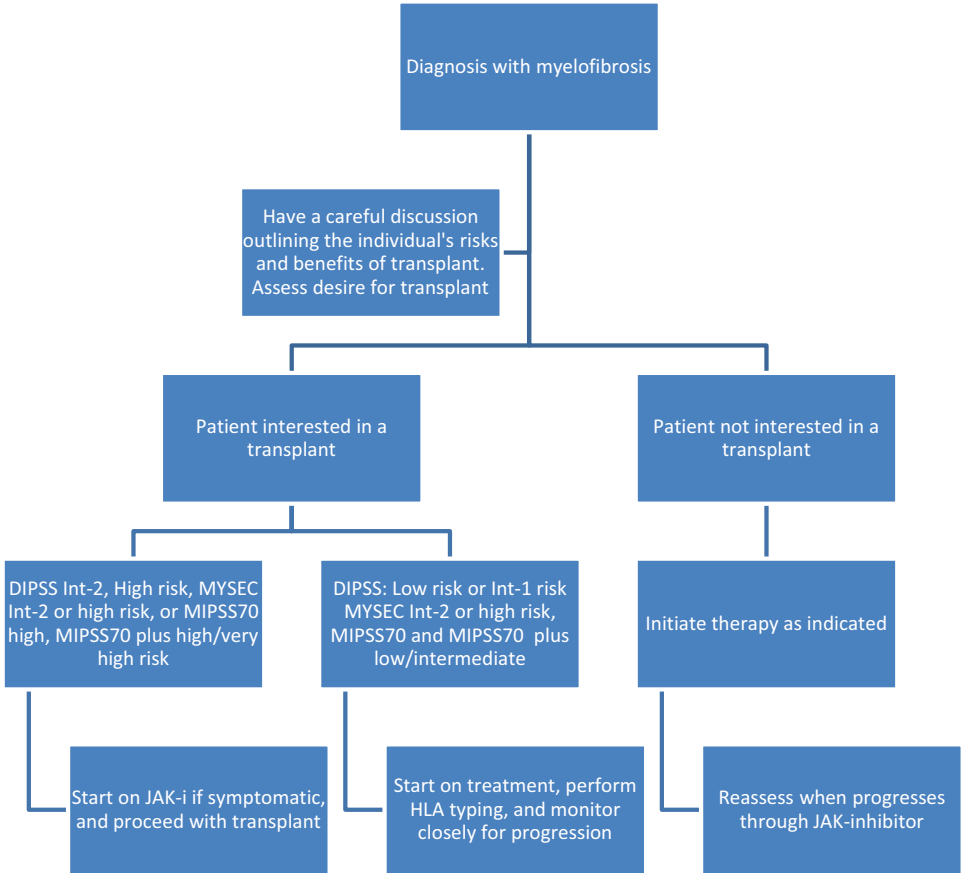

Figure 1. Approach to myelofibrosis. This table outlines an approach for patients with myelofibrosis when considering transplant. It is important to highlight the importance of the initial discussion needed prior to assessing interest in proceeding with transplant.

term survival was assessed in an EBMT registry study doing a landmark analysis on patients who were alive at 2 years following transplant. Of 2,459 patients who received first allo transplant between 1995 and 2014, 1,055 were alive at 2 years, and 10-year OS and disease-free survival for 2-year survivors were 74% (71%-78%) and 64% (60%-68%), respectively.[37] Factors that are associated with a higher risk of late mortality include older age, secondary MF, male sex, and no graft-versus-host disease prior to the landmark date.[37]

In summary, ASCT is a curable therapy for patients with MF. It is important to be methodical when approaching a patient with MF (see Figure 1). Decision on timing of transplant is a careful evaluation of age, patient preference, and careful risk assessment with the available risk calculators. Donor choice should be MRD > MUD > haploidentical donor > MMUD. If there is splenomegaly, ideally the patient should be treated with a JAK inhibitor prior to transplant, but whether the JAK inhibitor should be continued following transplant is not clear. Splenectomy or splenic irradiation may be an option for the appropriately selected patient. Following transplant, it is important to monitor chimerism and driver mutation as a means of determining relapse and consider DLI. Looking forward, once a patient has survived the first year or 2 following transplant, long-term outlook is far more optimistic.

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Off-label drug use

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Correspondence

Jeanne Palmer, 5881 E Mayo Blvd., Phoenix, AZ 85054; e-mail: palmer.jeanne@mayo.edu.

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