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Allogeneic Transplantation for Myelofibrosis: For Whom, When, and What are the True Benefits?

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Abstract

Purpose of review—Allogeneic hematopoietic stem cell transplantation (HSCT) is the only potentially curative therapy for myelofibrosis. Despite improved outcomes, morbidity and mortality of HSCT remain high. Here we examine recent data on patient selection, timing, and outcomes of HSCT in myelofibrosis.

Recent findings—While there is a general effort to restrict HSCT to transplant-eligible intermediate-2 and high risk patients, this group has comparatively worse HSCT outcomes, largely driven by their high transplant-related mortality (TRM). When adjusted for age, reduced-intensity conditioning (RIC) has shown superior outcomes compared to myeloablative conditioning (MAC), making RIC-HSCT a viable option for older patients. Emerging concepts include the use of ruxolitinib pre-transplant, optimizing MAC to decrease toxicity, and use of post-transplant *JAK2*-mutant allele burden to guide prophylactic immunotherapy to prevent relapse. The recognition of prognostic significance of somatic mutations in the *ASXL1*, *EZH2*, *SRSF2* and *IDH1/2* genes, and the improved assessment of risk of leukemic transformation have added a new dimension to risk stratification.

Summary—Improving our understanding of molecular genetics and leukemic transformation holds promise for more precise patient selection for HSCT. While RIC-HSCT may reduce TRM, further studies are needed to optimize conditioning regimens and to define the optimal timing of HSCT.

Keywords

Myelofibrosis; myeloproliferative neoplasms; bone marrow transplant; allogeneic hematopoietic stem cell transplantation

INTRODUCTION

Mr. T. is a 52-year-old gentleman presenting with progressive weight loss, abdominal distention, pain, night sweats and early satiety. On exam, he is cachectic with massive splenomegaly extending to the pelvic rim. Laboratory studies reveal a white blood cell count

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of $32.9 \cdot 10^3/\mu\text{L}$, left-shifted myeloid series with 8% circulating blasts, a hemoglobin of 13.0 g/dL, and platelets of $475,000/\mu\text{L}$. Lactate dehydrogenase (LDH) is elevated at 1857 units/L. JAK2 p.V617F mutation is detected. Bone marrow biopsy reveals a hypercellular, markedly fibrotic marrow, with megakaryocytic hyperplasia and atypia, morphologically consistent with primary myelofibrosis. Karyotype is normal. Ruxolitinib is started with rapid improvement in constitutional and spleen-related symptoms. The risks and benefits of HSCT are discussed, and HSCT is recommended. A stem cell donor search is initiated.

Myelofibrosis is a chronic myeloproliferative neoplasm (MPN), characterized by cytopenias and constitutional symptoms, megakaryocytic hyperplasia, reactive marrow fibrosis and extramedullary hematopoiesis (1). Myelofibrosis can occur as a primary disorder, primary myelofibrosis (PMF), or as a secondary disorder following a diagnosis of polycythemia vera (PV) or essential thrombocythemia (ET), post-PV or post-ET myelofibrosis (2). A recent epidemiologic study in the United States estimated an annual incidence of PMF at 1 per 100,000, and post-ET and post-PV myelofibrosis at 0.2 per 100,000 and 0.3 per 100,000, respectively (3). The median age at diagnosis of PMF is 62-66 years (3-5). HSCT, with its high morbidity and mortality, remains the only potentially curative treatment (Figure 1). The clinical course of myelofibrosis is markedly heterogeneous, ranging from months for the highest risk patients to over a decade for the low risk patients: it is this variability that makes decisions with respect to transplantation particularly arduous. This review examines recent data on patient selection, optimal timing, and outcomes of HSCT for myelofibrosis.

Transplantation for Myelofibrosis: For Whom?

Several prognostic algorithms were developed in order to identify patients with high risk disease, in whom the risks of HSCT could be justified (Tables 1A-B). The International Prognostic Scoring System (IPSS)(6), validated for PMF patients at diagnosis, remains widely used and has largely overtaken the older Lille/Dupriez system (7). IPSS stratifies patients into four prognostic categories based on five risk factors: age > 65 years, hemoglobin > 10 g/dL, leukocyte count over $25 \cdot 10^3/\mu\text{L}$, circulating blasts $\geq 1\%$ and constitutional symptoms. Two modified versions of IPSS, validated for PMF patients longitudinally over their disease course, are the Dynamic-IPSS (DIPSS), which places a higher emphasis on anemia (8), as well as the DIPSS-Plus, which incorporates transfusion dependence, platelet count under $100,000/\mu\text{L}$ and unfavorable karyotype (9). Increased hepcidin (> 3 standard deviations of normal) and ferritin levels (>500 $\mu\text{g/L}$) were found to predict inferior overall survival (OS) independent of the DIPSS-plus category (10). Additional high-risk features predictive of dismal prognosis were reported by several groups: blasts $\geq 10\%$ in peripheral blood or bone marrow, platelet count < $50,000/\mu\text{L}$, and chromosome 17 abnormalities were each associated with a median survival of under 12 months (11). A monosomal karyotype, presence of i17q and inv (3) abnormalities, or any two of peripheral blasts >9%, leukocyte count > $40 \cdot 10^3/\mu\text{L}$, or other unfavorable karyotype predicted a 2-year mortality of 80% (12).

Leukemic transformation (LT) of myelofibrosis is associated with poor outcomes (13), and remains the most feared complication of myelofibrosis. DIPSS Intermediate-2 and High risk groups have an increased risk of LT, with a hazard ratio (HR) of 7.8 and 24.9 (14),

respectively. Additional prognostic models further refined the LT risk-stratification. Tefferi *et al.* identified high risk karyotype (monosomal karyotype or i17q/inv(3)), circulating blasts 2%, and a platelet count < 50,000/ μ L as factors predictive of low, intermediate, or high 3-year LT risk of 3%, 10%, and 34%, respectively (15). Bone marrow blasts >10% and high risk karyotype (del 17p, -5, -7 or complex) were predictive of a 1-year LT rate of 13% (16). Barbui *et al.* reported an alternative prognostic system for LT, using high-sensitivity C-reactive protein 7mg/L, age 65 years, and peripheral blasts 1% to stratify patients into three risk groups with an eight-year leukemia-free survival of 88%, 48%, and 32%, respectively (17).

Undoubtedly, these clinical variables have clonal molecular underpinnings. There is growing evidence that many mutations affect prognosis, some independent of the clinical risk category (18). Vannucchi *et al.* evaluated the prognostic significance of somatic mutations in *ASXL1*, *SRSF2*, *EZH2*, *TET2*, *DNMT3A*, *CBL*, *IDH1*, *IDH2*, *MPL* and *JAK2* in a European cohort of myelofibrosis patients; mutations in *ASXL1*, *EZH2*, *SRSF2* and *IDH1/2* were associated with poor outcomes. Mutationally high-risk patients, defined as carrying at least one mutation in these four genes, had a worse OS and a higher risk of LT than patients without these mutations, independent of their IPSS risk. In a validation cohort from Mayo clinic, mutations in *ASXL1*, *SRSF2*, and *EZH2* were associated with worse OS, and mutations in *IDH1* and *SRSF2* with LT (18). In a multivariate analysis, mutations in *ASXL1*, had negative prognostic significance, independent of the IPSS and DIPSS-plus category (18). Mechanistically, *ASXL1* loss-of-function mutations appear to promote myeloid transformation by dysregulation of Polycomb-mediated gene silencing (19). Adverse prognostic significance of the *EZH2*, *IDH*, and *SRSF2* mutations, independent of the risk category, was previously reported (20–22).

In summary, emerging data on prognostic importance of somatic mutations and factors predictive of LT add a new dimension to risk-stratification for myelofibrosis. It has been generally accepted that myelofibrosis patients with a predicted overall survival of less than 5 years (corresponding to the IPSS and DIPSS Intermediate-2 and High categories) should be considered for a HSCT (23). In our practice, we also integrate age and symptom burden of disease in the risk-benefit assessment: i.e. a 66-year-old with incidentally discovered, asymptomatic Intermediate-2 disease and a hemoglobin of 12 g/dl is not someone for whom we recommend immediate transplantation, while a person in their forties with transfusion-requiring anemia but only Intermediate-1 disease may strongly want to consider HSCT. While the clinical prognostic scoring systems (IPSS, DIPSS and DIPSS-plus) remain the cornerstone of risk assessment, recognition of adverse significance of molecular markers (*ASXL1*, *EZH2*, *SRSF2* and *IDH1/2*) and the increasing appreciation of clinical factors associated with very poor prognosis and LT, may tip the balance in borderline cases.

HSCT for Myelofibrosis: When? “Sick enough to need it, but well enough to tolerate it”

Clinical heterogeneity and high TRM in myelofibrosis make the timing of HSCT particularly difficult. To date, there are no prospective studies evaluating the optimal timing of HSCT in myelofibrosis, nor are there decision analyses, such as for myelodysplastic syndrome (24), that rigorously compare outcomes of HSCT to non-transplant therapies in

patients with different disease risk. This is particularly problematic in light of the general gains in survival in myelofibrosis patients over the last decade, largely independent of HSCT outcomes (4, 25), as well as due to the significant improvements in quality of life and, perhaps, a modest survival advantage with ruxolitinib (26). Thus, the question of whether and to what degree high risk patients truly benefit from transplant is complicated and ultimately remains unanswered. The decision to transplant lower risk patients is similarly highly individualized.

Several studies have evaluated HSCT outcomes as predicted by the myelofibrosis prognostic scores and other potentially relevant variables. In a recent European study of 150 patients treated with reduced intensity conditioning (RIC) high risk patients, defined by IPSS and DIPSS, had significantly worse OS than Intermediate-2 patients. In contrast, there was no difference in OS between the Low/Intermediate-1 and Intermediate-2 prognostic groups (27). The Seattle group found however that among 170 patients transplanted with either MAC or RIC-HSCT, High and Intermediate-2 DIPSS risk patients had a significantly worse OS compared to the Low DIPSS risk patients (28). Notably, most of the difference was attributable to TRM, which was 3.41 times higher in the high risk compared to the low risk patients. While there was a correlation between the DIPSS risk and the HSCT co-morbidity index (HCT-CI)(29), the DIPSS category retained an association with HSCT outcomes even after adjusting for HCT-CI. Inferior OS after HSCT for Intermediate-2 and High risk patients compared to Low risk patients was confirmed in an independent study of 76 patients with myelofibrosis treated with MAC-HSCT (30). In both studies, in a multivariate analysis, the increased mortality in the higher risk categories was not associated with higher relapse rates. While several variables appeared to have independent prognostic significance in individual studies, overall there was no consistent relationship between HSCT outcomes and *JAK2* V617F mutation status, prior splenectomy, history of transfusions, degree of marrow fibrosis, or the patient's age (27, 28, 30). To date, there is no evidence that acquired molecular changes affect HSCT outcomes in myelofibrosis, although data are scant and this is an active area of investigation (31).

Taken together, available data indicate that Intermediate-2 and High risk myelofibrosis patients have inferior outcomes, largely accounted for by their increased TRM (27, 28, 30). We can speculate that this reflects the high catabolic state, cachexia, and increased cytokine levels in this patient population, which are not otherwise captured by current prognostic systems. Pre-transplant use of ruxolitinib has therefore been proposed as a possible strategy to improve transplant outcomes (32, 33) by improving performance status, reversing the catabolic state and reducing the spleen size, and is being investigated in an ongoing phase II study by the Myeloproliferative Disorder-Research Consortium.

HSCT for Myelofibrosis: What are the True Benefits?

The vast majority of data on HSCT in myelofibrosis comes from retrospective multicenter and registry analyses spanning three decades from the late 1970s through 2000s (Figure 2). The variety of conditioning regimens, inherent patient selection bias, and improvements in HSCT over time largely preclude meaningful comparisons across studies, and make it difficult to reliably identify transplant- or patient-specific factors that influence outcomes.

Here we present a synthesis of historical results with a focus on the most recent findings; for a more comprehensive overview we refer the reader to several recent in-depth reviews (33–35).

The early experience with HSCT for myelofibrosis relied on myeloablative conditioning, primarily TBI-based or using busulfan/cyclophosphamide (Bu/Cy), with targeted busulfan introduced in later years. Outcomes were poor, with the long-term OS of 30–60%, event-free survival (EFS) of 25–50%, and a sobering TRM of 30–40% (Figure 2). Recurrent factors associated with increased mortality were mismatched or unrelated donor, non-targeted busulfan dosing, older age (with a cut-off of 40–60 years among different studies (36–40)), poor performance status, and high risk or transformed disease.

The introduction of RIC-HSCT, with a significantly lower 1-year TRM of 12–25%, and as low as 12–13% for fully matched sibling and unrelated donor transplants (40, 41), both confirmed the concept that myelofibrosis is a reversible, immunoresponsive entity and expanded the option of transplantation to older patients. The long-term OS with RIC-HSCT ranges from a low of 31% in 24 patients treated with a predominantly fludarabine/melphalan (flu/mel)-based conditioning (42) to a high of 67–68% with largely fludarabine/busulfan (flu/bu)-based regimens (40, 43) (Figure 2). The largest, and the only published prospective multicenter study of RIC-HSCT in myelofibrosis, conducted by the European Group for Blood and Marrow Transplantation (EBMT), evaluated outcomes of 103 patients with PMF and post-PV/post-ET myelofibrosis treated with flu/bu conditioning in combination with antithymocyte globulin (ATG, Fresenius)(40). The median patient age was 54 years. The 1-year TRM was 16%, with a cumulative incidence of relapse at 3-years of 22%. The 5-year OS and EFS were 67% and 51%, respectively. Age over 55 years and a mismatched graft correlated with inferior outcomes. An alternative RIC-HSCT regimen of flu/mel ± ATG with a PBSC graft is being evaluated in an ongoing prospective phase II study (MPD-RC 101). An interim analysis of 42 patients with a median age of 54 years, revealed a low TRM of 13% in 23 MRD transplants, but an unexpectedly high TRM of 47% in the 19 MUD transplants (41).

While there are no prospective trials comparing myeloablative and RIC-HSCT, there are multiple retrospective analyses comparing outcomes of MAC- and RIC-HSCT in myelofibrosis (36, 38, 42–46). Despite being on average ten years older, patients transplanted with RIC have similar outcomes to patients transplanted with MAC (36, 38, 43–46). When adjusted for age, RIC had superior outcomes in a recent analysis of 92 patients from Nordic countries, where RIC patients had an estimated 5-year OS 78% compared to 52% for MAC for patients under 53 years, and a 5-year OS of 44% compared 38% for patients 53 years and older (38). Within the RIC group, outcomes were significantly better for patients under sixty with an estimated 5-year OS of 75% as compared to 20% for older patients. The poor outcomes in the older population in this study were worse than the previously reported 45% 3-year OS and 40% EFS in 30 patients aged 60 to 78 years (47).

Additional prospective studies are needed to generate more precise estimates of HSCT outcomes in myelofibrosis. Myelofibrosis patients are particularly susceptible to early hepatotoxicity after HSCT, including sinusoidal obstruction syndrome (SOS), which is

associated with TRM (48). In an effort to reduce toxicity of myeloablative conditioning, Rezvani and colleagues prospectively evaluated the use of intravenous cyclophosphamide followed by targeted busulfan (Cy/^tBu) in patients with hematologic malignancies, including twenty patients with myelofibrosis (49). The pharmacologic rationale was to reduce toxicity of cyclophosphamide by maximizing the stores of hepatic glutathione, necessary for cyclophosphamide detoxification and normally depleted by busulfan. Compared to historical controls treated with targeted busulfan followed by cyclophosphamide (^tBu/Cy), patients treated with Cy/^tBu had a significantly lower incidence of hepatotoxicity and SOS, and lower 100-day TRM (2% vs. 13%)(49). Although this small study found no significant difference in 2-year TRM or OS, this may be a promising approach for intensifying conditioning while limiting toxicity, and merits further study.

Can we monitor and intervene on persistent or minimal residual disease?

Emerging areas of investigation include the use of *JAK2* p.V617F allele burden in patients with *JAK2*-mutated myelofibrosis to identify patients at a higher risk of relapse (50, 51). Lange *et al.* reported that *JAK2* p.V617F allele burden of 1% on day 28 after MAC- or RIC-HSCT was predictive of relapse in a cohort of thirty patients with *JAK2*-mutated MPN (50); future studies are needed to validate the predictive value of early post-HSCT *JAK2* mutation burden in myelofibrosis patients with a more defined conditioning regimen. Donor lymphocyte infusion (DLI) has shown promise as a salvage therapy in the setting of relapse, minimal residual disease, and graft rejection (40, 52, 53) and proves definitively the immunoresponsiveness of myelofibrosis. We hope that additional biologic insights will inform novel studies of cellular therapy for myelofibrosis.

Conclusion

Despite improvements in outcomes in HSCT for myelofibrosis, TRM remains high, underscoring the importance of judicious patient selection and appropriate HSCT timing. Our recommended approach is to consider HSCT in patients with Intermediate-2 and High Risk disease as defined by DIPSS or DIPSS-plus criteria, and to incorporate prognostic information from the known adverse molecular markers (*ASXL1*, *EZH2*, *SRSF2* and *IDH1/2*) and LT risk factors, as well as age and symptom burden as guidance in borderline cases. In all transplant-eligible patients, we advocate identifying available donor options early, even if no immediate recommendation for HSCT is made, so that patients can move efficiently towards transplant should their disease evolve. With respect to the timing of HSCT, the available data indicate the need to optimize patient-related factors that can impact TRM. We advocate for a shared decision making approach, with a discussion of risks and benefits as well as the uncertainties with the patient. Patients with very high risk disease or those at high risk of LT should be considered for early transplantation. In contrast, it may be reasonable to closely monitor selected Intermediate-2 risk patients who remain minimally symptomatic with a good performance status, with a plan for expeditious transplant at disease progression.

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Abbreviations

DIPSS Dynamic International Prognostic Scoring System

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Key points

1. The recognition of prognostic significance of somatic mutations has given promise of more precise risk assessment in myelofibrosis.
2. Intermediate-2 and High risk myelofibrosis patients have worse HSCT outcomes than patients with Low risk disease; the difference is largely accounted for by their increased TRM.
3. When adjusted for age, RIC-HSCT has shown better outcomes compared to myeloablative transplantation; additional studies are needed.
4. Current data provide greatest support for flu/bu-based conditioning for the majority of patients.
5. Emerging concepts include the use of ruxolitinib pre-transplant, optimizing myeloablative regimens to decrease toxicity, and use of post-transplant *JAK2*-mutant allele burden to guide prophylactic immunotherapy to prevent relapse.

Figure 1. Resolution of Fibrosis Following Reduced-Intensity HSCT for Myelofibrosis

Pre-Transplantation: H&E stained sections (5× and 20×) demonstrate the typical features of advanced myelofibrosis: decreased myelo- and erythropoiesis, megakaryocytic atypia, grade 3 reticulin fibrosis, and osteosclerosis. Post-Transplantation (1 Year): H&E stained sections (5× and 20×) show reversal of fibrosis with restoration of trilineage hematopoiesis.

Source: original

Figure 2. Summary of Outcomes of Allogeneic Hematopoietic Cell Transplantation in Myelofibrosis

The timeline depicts outcomes of major studies of HSCT in myelofibrosis from 1999 to 2013 (28, 30, 36, 38–40, 42–44, 47, 49, 54–57), grouped by the conditioning regimen: primarily myeloablative (“MAC and mixed”, left side) and reduced-intensity (“RIC”, right side); within each group, the studies are listed chronologically according to the beginning of patient enrollment. Individual studies are labeled below the x-axis, with the corresponding outcomes shown in the plot above. Blue diamonds, overall survival (OS); red squares, event-free survival (EFS); green triangles, non-relapse mortality (NRM). *Unless otherwise indicated in individual study notations below the graph, the outcomes are for 5-year OS, 5-year EFS, and 1-year NRM.

Source: original

Table 1

A. Prognostic Scoring Systems in Myelofibrosis

Standard Prognostic Scoring Systems		
IPSS (6)		
Clinical Feature	Points	
Age > 65 years	1	
Constitutional Symptoms ¹	1	
Hgb < 10g/dl	1	
WBC count > 25 x 10 ⁹ /L	1	
Peripheral blasts ≥ 1%	1	
Prognostic Category	Points	Median Survival (mo)
Low	0	135
Intermediate-1	1	95
Intermediate-2	2	48
High	≥3	27
DIPSS (8)		
Clinical Feature	Points	
Age > 65 years	1	
Constitutional Symptoms ¹	1	
Hgb < 10g/dl	2	
WBC count > 25 x 10 ⁹ /L	1	
Peripheral blasts ≥ 1%	1	
Prognostic Category	Points	Median Survival (mo)
Low	0	not reached
Intermediate-1	1-2	170
Intermediate-2	3-4	48
High	5-6	18
DIPSS Plus (9)		
Clinical Feature	Points	
DIPSS-Low	0	
DIPSS-Int-1	1	
DIPSS-Int-2	2	
DIPSS-High	3	
PLUS		
Unfavorable Karyotype ²	1	
Transfusion Dependence	1	
Platelet <100,000/ul	1	
Prognostic Category	Points	Median Survival (mo)
Low	0	185
Intermediate-1	1	78
Intermediate-2	2-3	35
High	4-6	16
Markers of Very High Risk and Accelerated Phase Disease		
Very High Risk (Over 80% 2-Year Mortality) (12)		
Clinical Feature	Points	
Monosomal Karyotype	1	
inv(3)/i(17q)	1	
Other Unfavorable Karyotype ³	0.5	
Peripheral blasts > 9%	0.5	
WBC ≥40 ⁹ /L	0.5	
Prognostic Category	Points	Median Survival (mo)
Very High Risk	≥1	9
Accelerated Phase (Median Survival ≤12 Months) (11)		
Clinical Feature	Points	
Any abnormality of Chr 17	1	
Blood/bone marrow blasts ≥ 10%	1	
Platelets < 50,000/ul	1	
Prognostic Category	Points	Median Survival (mo)
Accelerated Phase	≥1	≤12

B. Prognostic Scoring of Leukemic Transformation and Adverse Molecular Markers

Prognostic Scoring Systems of Leukemic Transformation

LT (DIPSS-Plus) (9)

Clinical Feature	Points
Platelets < 50,000/ul	1
Unfavorable Karyotype ²	1

Prognostic Category	Points	LT rate (5-year, 10-year)
Low Risk	0	6%, 12%
High Risk	≥ 1	18%, 31%

LT (Tefferi *et al.*) (15)

Clinical Feature	Points
Very High Risk Karyotype ⁴	2
Blasts ≥2%	1
Plt ≤ 50,000/ul	1

Prognostic Category	Points	LT rate (3-year)
Low	0	3%
Intermediate	1	10%
High	≥ 2	35%

LT (Quintás-Cardama *et al.*) (16)

Clinical Feature	Points
Worst Karyotype ⁵	1
Blasts ≥10%	1

Prognostic Category	Points	LT rate (1-year)
Low Risk	0	2%
High Risk	≥ 1	13%

LT (Barbui *et al.*) (17)

Clinical Feature	Points
Blasts > 1%	4
Age > 65	2
hs-CRP >7mg/L	2

Prognostic Category	Points	8-Year Leukemia-Free Survival
Low	0	88%
Intermediate	2-4	43%
High	6-8	32%

Clonal Molecular Changes of Adverse Prognostic Significance in Myelofibrosis (18)

Mutations in: *ASXL1, EZH2, SRSF2, IDH1, IDH2*

¹ Constitutional symptoms: weight loss > 10% of the baseline value in the year preceding PMF diagnosis and/or unexplained fever or excessive sweats persisting for more than 1 month).

² Unfavorable karyotype: complex karyotype or single or two abnormalities including +8,-7/7q-, i(17q),-5/5q-, 12p-, inv(3) or 11q23 rearrangement.

³ Other unfavorable karyotype: non-monosomal complex karyotype or single or two abnormalities including +8,-7/7q-, i(17q),-5/5q-, 12p-, inv(3) or 11q23 rearrangement.

⁴ Very High Risk Karyotype: monosomal karyotype or inv(3)/i(17q).

⁵ Worst Karyotype: del17p, -5, -7, and/or complex.