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Role of Hematopoietic Stem Cell Transplantation in Patients with Myeloproliferative Disease

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Synopsis

Myeloproliferative neoplasms (MPN), including primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocythemia (ET) are clonal hematopoietic stem cell disorders. While some patients have an indolent course, all, to a lesser or greater extent, are at risk of progressing to severe marrow failure or of transforming into acute leukemia. Allogeneic hematopoietic cell transplantation (allo-HCT) is the only potential curative therapy. If transplantation is being considered and a suitable donor is available, allo-HCT should be carried out before leukemic transformation has occurred, as the prognosis is poor, even with allo-HCT, in patients who have evolved to leukemia. Survival following allo-HCT ranges from 30% to 70% at 5 years. The development of reduced-intensity conditioning regimens has allowed for successful allo-HCT even for older patients and patients with comorbid conditions. Results with high intensity/ myeloablative (MAC) and reduced intensity conditioning (RIC) are comparable. Major pre-transplant risk factors for the outcome after allo-HCT are the disease stage of the MPN, the presence of comorbid conditions and the use of HLA non-identical donors. The pre-transplant use of JAK-2 inhibitors, which may be effective in down-staging a patient's disease and decreasing comorbidities, may improve the outcomes following allo-HCT. Ongoing research is directed at determining the role of novel non-transplant strategies into the overall treatment algorithm.

Keywords

Myeloproliferative Neoplasms (MPN); Myelofibrosis; Polycythemia Vera; Essential Thrombocythemia; Hematopoetic Stem Cell Transplantation; Ruxolitinib

Introduction

Myelofibrosis (MF) can present as de novo primary myelofibrosis (PMF) or evolve from other myeloproliferative neoplasms (MPN), such as polycythemia vera (PV) or essential thrombocythemia (ET)[1,2]. Regardless of the etiology, MF is characterized as a clonal stem cell disorder associated with dysregulated Janus kinase/signal transducers and activators of transcription (JAK-STAT) signaling and elevated levels of pro-inflammatory and pro-angiogenic cytokines such as TNF alpha, IL-6 and IFN gamma, resulting in a bone marrow

stromal reaction that includes varying degrees of reticulin and collagen fibrosis and osteosclerosis[3–5]. Clinically, MF is typified by progressive anemia, leukopenia or leukocytosis, thrombocytopenia or thrombocythemia and multi-organ extramedullary hematopoiesis. It frequently involves the spleen, resulting in massive splenomegaly, severe constitutional symptoms, a hypermetabolic state and cachexia[6,7]. The median age at diagnosis is 60 to 65 years[8]. The clinical course is heterogeneous, ranging from indolent disease and survival for decades, to aggressive disease in other cases with survival measured in months[9]. The most common causes of death are progressive marrow failure leading to infection or hemorrhage, transformation to acute myelogenous leukemia and complications of portal hypertension.

Patient Evaluation Overview

Prognosis of MF varies with the presence or absence of specific risk factors. Historical prognostic scoring systems, such as the Lille or Dupriez classification, focused primarily on blood cell counts as the major prognostic factor.[10] In 2009, Cervantes et al published a multi-center analysis of risk factors and their impact on prognosis in patients with myelofibrosis.[6] Age greater than 65 years, presence of constitutional symptoms, including weight loss, fever, or night sweats, anemia (hemoglobin < 10 g/dL), leukocytosis (white blood cells (WBC) > 25 × 109/L), and a circulating blast percentage ≥ 1% were identified as most predictive of outcome. Median survival among patients with no risk factors (low-risk group) was 135 months, compared to 95 months among patients with one risk factor (intermediate-1 risk), 48 months among those with two risk factors (intermediate-2 risk), and 27 months among those with 3 or more risk factors (high-risk). [6] This risk stratification is referred to as the international prognostic scoring system (IPSS) (see Table 1).

The *Dynamic* IPSS (DIPSS), which was subsequently developed uses the same 5 variables but can be used at any time in the disease course. However, unlike the IPSS, Hb < 10 g/L receives a score of 2 points. The risk groups are scored as follows: Low risk (score = 0), Intermediate 1 (score = 1), Intermediate 2 (score = 2 or 3) or High risk (score = 4 – 6) with corresponding median survivals of 185, 78, 35 and 16 months, respectively[11]. The DIPSS *plus* scoring system includes an additional 3 risk factors: transfusion dependence, unfavorable cytogenetics (+8, -7/7q-, i (17q), inv (3), -5, 5q-, 12p-, 11q23 and complex karyotype) and platelet count <100 × 10^9/l.[12]

Indications for Transplantation

IPSS, DIPPS or DIPPS-plus risk classifications, comorbidities and donor availability should be used to identify patients who are candidates for allo-SCT[13]. Current recommendations imply that the potential risk of transplant-related complications is justified in transplant-eligible patients with < 5 years expected survival if not transplanted[14]. Based on DIPSS data, this would include patients in the Intermediate 2 and High risk groups. Those are, indeed, the patients included in most clinical transplant trials; however, lower risk patients actually have better outcome following allo-HCT, raising questions as to the most appropriate selection of patients and timing for allo-HCT[15]. Published data from the Fred Hutchinson Cancer Research Center (FHCRC) on 170 patients, median age 51.5 years, with

myelofibrosis showed that the 6 year post-allo-HCT survival for Low, Intermediate 1, Intermediate 2 and High risk patients was 80%, 67%, 54% and 38%, respectively, validating the DIPSS as an accurate prognosticator for post-allo-HCT outcome in MF.[16]

Tefferi et al recently completed an analysis of 884 patients aimed at identifying risk factors associated with a greater than 80% 2-year mortality. Poor prognostic features included monosomal karyotype, inv (3)/i(17q) abnormalities, or any two of the following factors: peripheral blast percentage > 9%, WBC > 40×10^9/L or other unfavorable karyotypes.[17] Those patients meeting performance status and donor criteria for allo-HCT should be referred directly to allo-HCT rather than undergo conventional treatment. In another study, which characterized 793 patients with PMF using DIPSS-plus criteria, the only two risk factors for leukemic transformation were unfavorable karyotype and platelet count $<100\times10^9$/L; the 10-year risk of leukemic transformation was 12% in the absence of these two risk factors and 31% in the presence of one or both risk factors. [12] As is becoming evident for overall survival, leukemia-free survival is also significantly compromised in patients carrying certain mutations, including ASXL1, *IDH1/2*, *EZH2* and *SRSF2*.[18,19,20]

Transformation into acute leukemia occurs in 10–20% of patients and is associated with a median 5 months survival.[21,22] Previous studies have shown that postponing transplantation in myelofibrosis until patients are at a more advanced stage of disease resulted in worse outcome.[16,23] In a study performed by the MPN subcommittee of the chronic myeloid leukemia workimg party (CMWP) of the European Bone Marrow Transplant (EBMT) group looking at 46 patients with leukemic transformation of PMF or post ET/PV MF, 3 year overall survival (OS) and progression-free survival (PFS) were 33% and 26%, respectively.[24] Only remission status was significantly predictive for OS and PFS (69% vs 22%; p =0.0008). However, the survival benefit of patients transplanted in complete remission (CR) was due to significantly lower treatment-related mortality (TRM) while relapse incidence was identical. The consensus by the EBMT/ELN working committee in 2014 is that patients with leukemic transformation should receive cytoreductive therapy and be considered for transplantation only after achieving a partial or complete remission of leukemia.[25]

Timing of and Preparing Patients for Transplant

Although allo-HCT remains the only known curative therapy for myelofibrosis, any treatment that improves the patient's performance status and reduces the individual transplant-specific risk should be considered in the pre-transplant phase[25]. In the past, drug therapies including hydroxyurea, busulfan, 6-mercaptopurine, anagrelide, thalidomide, lenalidomide, interferon, corticosteroids, androgens, and erythropoiesis stimulating agents or other growth factors were used as the first line treatment of MF[26,27]. These treatments may be helpful for palliation of symptoms, but responses typically are of short duration, usually less than 1 year. Ruxolitinib, a selective JAK-1/2 inhibitor, was recently FDA approved for treatment of primary and secondary MF. JAK-2 inhibitor therapy (ruxolitinib or others) is indicated in patients with a spleen extending more than 5 cm from the left costal margin and patients with constitutional symptoms. The drug should be administered for a minimum of one month but tapered off before transplant conditioning[25]. Impressive symptom control in

MF patients on ruxolitinib treatment is predominantly mediated by profound suppression of pro-inflammatory and pro-angiogenic cytokines.[28] Reduction of cytokine levels is typically accompanied by a substantial decrease in spleen size. Patients should be treated to best response.

The potential benefits of (surgical) splenectomy are a matter of debate. Data from Mayo Clinic on 314 MF patients undergoing splenectomy showed significant perioperative complications in 28% of patients and a mortality of 6.7%. [29] The report by Ballen et al in 2010 on 289 patients with MF failed to show a significant effect of prior splenectomy on graft failure or PFS.[30] Ciurea in 2008 noted that successful engraftment still was achieved even with massive splenomegaly.[31] Michallet et al showed in 2009 greater severity of GVHD in splenectomized patients.[32] A recent report from the MD Anderson Cancer Center demonstrated improvement in symptoms, such as anemia and thrombocytopenia, as well as abdominal discomfort at the cost of increased TRM.[33] However, there are also proponents for pre-allo-HCT splenectomy in myelofibrosis patients. Li et al showed in 2001 that splenectomized patients had faster neutrophil recovery and decreased transfusion requirements.[34] Robin et al, in a multivariate analysis of results in patients receiving peripheral blood stem cells, showed faster engraftment in patients without splenomegaly and those who had undergone splenectomy pre-transplant. [35] Kroger et al demonstrated a trend toward more rapid neutrophil engraftment in splenectomized vs non-splenectomized RIC allo-HCT patients. [36] However, in that study a higher rate of relapse at 3 years was seen in splenectomized patients. On the other hand, the retrospective analysis by Scott et al in 170 patients transplanted at the FHCRC, suggests that splenectomized patients had superior post-allo-HCT survival ($p=0.05$). [16] Bacigalupo et al suggested that a spleen size > 22 cm was an independent risk factor for survival.[37]

In summary, for patients with refractory, symptomatic splenomegaly, the evidence in support of splenectomy to improve transplant outcome is not sufficient to recommend splenectomy as a standard pre-transplant procedure[25]. Pre-transplant splenectomy in patients with refractory splenomegaly should be decided on an individual basis. If this procedure is performed, it should be in the setting of a clinical trial and at a center that performs many procedures per year and has a proven track record of success.

Autologous Stem Cell Transplant

Data on autologous stem cell transplantation for MPN are sparse. In a multicenter study, 27 patients with myelofibrosis in the setting of PMF, PV, or ET underwent autologous hematopoietic cell collection, and 21 underwent conditioning with busulfan only, followed by autologous HCT.[38] The median time to platelet and neutrophil recovery was 21 days (for both), with clinically significant responses seen in 10 of 17 patients with anemia, 4 of 8 patients with thrombocytopenia, and 7 of 10 patients with symptomatic splenomegaly. However, the study was closed because of graft failure or incomplete hematopoietic recovery in 5 patients (27%). The high graft failure rate was attributed to the fact that autologous hematopoietic cells had been collected late in the disease course, and the investigators speculated that engraftment might be improved if autologous cells had been harvested earlier. The benefit achieved with autologous cells was thought to be due to the

faster growth of normal stem cells than that of clonal malignant cells. To carry out autologous HCT for MPN with curative intent, purging of clonal hematopoietic cells from the harvested cells would be necessary, and currently no effective method to achieve this objective is available [39].

Allogeneic Stem Cell Transplant

Allo-HCT remains the only curative therapy for myelofibrosis. Initial trials at the FHCRC showed that patients with *severe* marrow fibrosis were prone to experience engraftment failure (33% in a cohort of 15 patients), while engraftment was prompt in patients with mild or moderate fibrosis (6% failure in a cohort of 32 patients). [40] However, subsequently patients with severe myelofibrosis or even osteosclerosis, were shown to achieve sustained engraftment and regression or even complete resolution of marrow fibrosis with normalization of the marrow architecture following allo-HCT.[39]

Myleoablative Conditioning

While a broad range of conditioning regimens of different intensities has been developed, initial studies of allo-HCT for MF used high intensity MAC regimens, usually including total body irradiation (TBI) or Busulfan. For MAC regimens, graft failure rates of <5% to 30% have been reported, reflecting the heterogeneity in patient populations and specific conditioning regimens[41,42] Published TRM rates of 10–35% at 1 year and overall survival from 30% to 67% at 5 years have been reported (Table 2)[41,43–48].

One of the first studies reported by the EBMT, included 55 patients with a median age of 42 years and showed a 5-year overall survival of 47%. Anemia was a predictive factor for poor survival.[43] The largest study to date was reported from the Center for International Blood and Marrow Transplant Research (CIBMTR), analyzing data in 289 patients with PMF.[30] Patients were transplanted between 1989 and 2002 at 118 centers, with a variety of conditioning regimens. A total of 162 patients received an HLA-matched sibling transplant, 101 received HLA-matched unrelated donor (URD) transplants, and 26 received transplants from HLA non-identical related donors. The majority of patients received bone marrow as the stem cell source, and 83% were conditioned with an MAC regimen. The 100-day TRM was 18% for HLA-matched sibling patients, and 33% for the URD patients. The graft failure rate was 9% for HLA-matched sibling transplants, and 20% for URD transplants. Splenomegaly did not impact the graft failure rate. Graft versus host disease (GVHD) grades II – IV occurred in 43% of sibling patients, and 40% of the URD patients. The overall survival at 5 years was 37% for sibling transplants and 30% for URD transplants. Relapse-free survival at 5 years was 33% for recipients of an HLA-identical sibling allografts and 27% for recipients of a URD transplants. Positive predictors for survival included HLA-identical sibling donors, performance status > 90%, and absence of peripheral blood blasts at the time of transplantation.[30] Patients who had a poor Karnofsky score, peripheral blood blasts or were transplanted from an unrelated donor had a 15% probability of 3-year survival[49].

Other reports of allo-HCT for MF have confirmed the findings of the CIBMTR study. The Italian group analyzed results in patients from 26 centers; 48% received a MAC regimen.[50]

The risk of graft failure was 13%, and the 1-year TRM was 35%. The 5-year overall and PFS rates were 31% and 28%, respectively. Positive predictors for survival included an HLA-matched sibling donor, transplantation after 1995, and a short interval between diagnosis and transplantation[49].

A French group reported results in 147 patients with primary or secondary MF, who received an allo-HCT, 31% with MAC regimens, with similar results.[35] Sixty percent of patients received transplants from HLA-identical sibling donors. The 4-year OS was 39%, PFS 32%, and the non-relapse mortality 39%. In a multivariate analysis, neither the Lille nor the IPSS score predicted survival. Positive predictors for survival included prior splenectomy, female gender and transplantation from an HLA-identical sibling donor.

Our group at the FHCRC reported on 104 patients with myelofibrosis, either PMF or after PV or ET. [41] The survival at 7 years was 61% in patients conditioned with targeted IV busulfan and cyclophosphamide. The use of a targeted busulfan-based chemotherapy regimen, younger patient age, and a lower comorbidity score predicted for better survival. This was consistent with a prior report by Deeg et al in 2003 that demonstrated that patients conditioned with cyclophosphamide plus targeted busulfan had a higher probability of survival at 3 years (76%). [47] A more recent study demonstrated that administering cyclophosphamide, 120 mg/kg over 2 days *before* targeted busulfan for 4 days, conferred significantly less liver toxicity than busulfan *followed* by cyclophosphamide, [51] which translated into decreased early TRM.

Reduced Intensity Conditioning

TRM has generally been high in older patients and those with comorbidities. To improve outcomes in those patient groups, several small studies of older patients with MF, transplanted after RIC have reported encouraging results with decreased TRM. Early RIC studies for myelofibrosis included reports by Devine et al and Rondelli et al.[52,53] Kroger et al (2005) treated 21 patients with PMF or MF post-PV or ET with RIC regimens consisting of fludarabine, 180 mg/m2, and busulfan, 10mg/kg, plus ATG followed by related donor or URD allo-HCT and observed no graft failures and no day 100 TRM.[54] One year TRM was 16%. At 3 years, the PFS was 84%, and 78% of patients became JAK2 mutation PCR negative. A follow-up report included 103 patients, median age of 55 yrs. Among these, 33 had HLA-matched sibling donors, and 60 had URD of which 30% were mismatched [36]. Engraftment occurred in 98%, and acute GVHD grades II – IV in 27% of patients. The incidence of relapse at 3 years was 22%; patients with a low Lille score had a lower incidence of relapse, 14% versus 34%, suggesting that patients transplanted earlier in the course of their disease fared better. The 5-year PFS was 51%. Younger patients and those with HLA-matched donors did better. Thus, these results are comparable to those obtained with MAC regimens.[49]

The CIBMTR study by Ballen et al. (described above) included 60 patients who received RIC (or non-myeloablative) regimens.[30] Graft failure occurred in 7 patients, none of whom survived. TRM rate at 1 year was 15% for HLA matched sibling transplants, and 49% among those transplanted from URD. RFS at 3 years was 39% for matched sibling allo-HCT, and 17% with URD. [55] A more recent retrospective analysis by the CIBMTR included

233 patients undergoing RIC HCT for PMF. In this study 12% of patients were low risk, 49% of patients were intermediate-1, 37% were intermediate-2 and 15 were high risk by DIPSS. Probability of OS at 5 years was 47%. In a multivariate analysis donor type was the only factor associated with survival. [56]

With the use of RIC regimens, older patients with higher comorbidities have been transplanted successfully. However, results from these small, retrospective studies must be interpreted with great caution because of selection bias.

A comparison of outcomes by the Nordic MPD study group in 2009 revealed that when adjustments were made for age, survival after RIC vs MAC was significantly better ($p = 0.0003$).[57] A follow-up study by the same group published results of 92 patients undergoing MAC vs RIC in 2012.[58] Patients in the RIC arm had an estimated 5 year OS of 78% compared with 52% in the MAC arm for patients under the age of 53 years, and a 5-year OS of 44% compared with 38% for patients 53 years and older. Within the RIC group, outcomes were significantly better for patients under 60 years, with an estimated 5 year OS of 75% as compared with 20% for older patients. However, the poor outcome in the older population was worse than in prior publications comparing the two strategies. Discordantly, in a study by Stewart et al. in which 27 patients were treated with MAC and 24 patients with RIC, there was no difference in non-relapse mortality, OS or PFS between the two intensity groups. [59]

Donor Selection and Stem Cell Source

Only 30% of patients have HLA-matched sibling donors, and it is often difficult for African Americans and other minorities to find suitably matched URDs. Alternative stem cell sources for these patients include umbilical cord blood (UCB) or HLA- haploidentical donors - child, parent or HLA half-matched sibling. Because of the delayed engraftment often seen after UCB transplantation (UCBT), transplant physicians have been reluctant to extend UCBT to patients with myelofibrosis. However, a recent report by Takagi et al. suggests that successful engraftment can be achieved after RIC with UCBT in patients with myelofibrosis.[60] Fourteen patients with myelofibrosis, including several whose disease had transformed to acute myelogeneous leukemia, underwent UCBT following RIC, mostly consisting of fludarabine, 125 mg/m2, melphalan 80 mg/m2, and TBI 4Gy. Neutrophil engraftment occurred in 92% of patients (n =13) at a median of 23 days, and platelet engraftment in 43% of patients at a median of 56 days. Complete donor chimerism was achieved in all evaluable patients. Estimated 4-yr survival was 28.6%. Preliminary data by a French Group presented as an abstract at ASH 2013 looking at MAC and RIC followed by UCBT for PMF, ET and PV (12 patients had transformed to AML) demonstrated only 64% engraftment but 44% 2-yr survival. [61]

Alternative donor sources, such as HLA-mismatched unrelated donors, UCB or HLA-haploidentical donors may be effective, but the actual success rates and the incidence of complications such as graft-failure, and GVHD remain to be determined. The ELN/EBMT International Working Group concluded that patients with DIPSS intermediate 2- or high-risk disease lacking HLA matched sibling or unrelated donors, should be enrolled in prospective clinical trials using HLA non-identical donors[25]. The Working Group also

agreed on considering peripheral blood as the most appropriate source of hematopoietic stem cells for HLA-matched sibling and unrelated donor transplants[25].

Post-transplant monitoring

In patients transplanted in the presence of splenomegaly, monitoring of spleen size with ultrasound after allo-SCT is recommended.[25] Persistence of splenomegaly in the early post-transplant phase should be considered the normal process of disease clearance and does not need specific management, unless there is pancytopenia. If patients have persistent splenomegaly (and complete donor cell chimerism), splenectomy may be a therapeutic option. JAK-2 inhibition in this setting has not been tested so far, and may contribute to cytopenias. Persistence of splenomegaly late after transplantation, when associated with incomplete donor chimerism, is typically a sign of disease persistence or recurrence[25]. Treatment may consist of reduction of immunosuppression, donor lymphocyte infusion (DLI), or both. JAK2 inhibitors alone may reduce the spleen size and persistent constitutional symptoms, but will not increase donor cell chimerism or clear minimal residual disease. Splenomegaly appearing after allo-SCT should raise the suspicion of hepatic veno-occlussive disease, post transplant lymphoproliferative disorders, infections or relapse[25].

In the presence of poor graft function, bone marrow assessment by biopsy to assess cellularity and persistence of fibrosis and osteosclerosis as well chimerism determination should be performed[25]. Chimerism studies on peripheral blood CD3+ cells and unfractionated bone marrow cells are necessary to establish the degree of donor cell engraftment and may assist in the decision regarding withdrawal of immunosuppression. In patients with poor graft function, use of growth factors may be useful. In patients with a late decline in graft function who have full donor chimerism and no evidence of active GVHD, an infusion of additional donor hemopoietic stem cells is recommended[25]. In patients with graft failure and no autologous reconstitution, the only available option is a second transplant.

Management of relapses after transplantation

Disease-specific markers such as JAK2V617, CALR, and MPL mutations have been shown to be beneficial in detecting minimal residual disease after allo-SCT[62]. Those molecular markers can be monitored by PCR or by direct sequencing. In patients who relapse after allo-SCT and do not have severe GVHD, reduction of immunosuppressive drugs or DLI are currently considered the treatment strategies of choice. In patients who fail to achieve complete remission despite these measures, a second allo-HCT may be considered. Patients relapsing with constitutional symptoms or splenomegaly may benefit from treatment with a JAK-2 inhibitor.

Novel therapies and their integration in transplantation

Presently, ruxolitinib is the only FDA approved JAK2 inhibitor for MF, and the only non-HCT therapy to date associated with a survival benefit. In a phase I/II study of ruxolitinib therapy at MD Anderson Cancer Center, OS was significantly superior in ruxolitinib treated

patients compared to a historical cohort in an analysis adjusted for IPSS. [63] Spleen volume reduction alone was associated with a survival advantage in ruxolitinib treated patients; 63% of patients achieved >50% reduction in spleen volume with a median duration of approximately 2 years. Patients with >50% reduction in splenomegaly had superior survival when compared to patients with < 25% spleen size reduction ($p < 0.0001$). Furthermore, the finding of superimposable survival curves for high-risk and intermediate-2 risk patients treated with ruxolitinib suggested that ruxolitinib therapy may down-grade an individual's prognostic score category and improve predicted survival. [63]

Using JAK2- inhibitors to reduce spleen size pre-HCT may be useful in improving engraftment. In a study by a German group, 14 patients received allo-HCT following a median of 6.5 months treatment with ruxolitinib.[64] Under ruxolitinib therapy, spleen size was reduced in 64% of patients, and engraftment was achieved in 93% of patients. TRM was 7% and survival 79%, but the median follow-up was only 9 months. Another German group reported a retrospective analysis of results in 22 patients with PMF or post ET/PV MF who had received a median of 97 days of ruxolitinib prior to allo-HCT.[65] At the time of transplant 86% had improvement in constitutional symptoms, and 41% had a major response in spleen size. With a median follow-up of 12 months, 1 year OS was 81% and PFS 76%. Whether Jak2 inhibitor treatment prior to HCT can consistently improve patient performance status and the degree of splenomegaly and lead to more favorable outcomes is an important area of ongoing investigation. A prospective study (JAK-ALLO) is ongoing in France on behalf of SFGM-TC to evaluate the role of ruxolitinib before allo-HCT and a similar trial is under way at the FHCRC.

Summary/Discussion

Considering the lack of long-term effective drug therapies for patients with MF, the potential risk of transplant-related complications appears justified in patients with DIPSS-plus High or Intermediate-2 risk disease as well as those with either unfavorable karyotype or a platelet count of $<100 \times 10^9$/L. Currently, TRM is too high to justify pursuing allo-HCT systematically in lower risk patient populations, even though the data indicate that those patients have a much higher probability to benefit from HCT. As we modify our treatment regimens and enhance peri-transplant strategies for supportive care, transplant results are improving. Increasing success rates are being reported with RIC as well as with regimens historically designated as MAC. The JAK-2 inhibitor era provides a unique opportunity to begin to incorporate novel agents into the transplant algorithm for high risk patients. Clinical trials, which examine the best way to use these agents in concert with allo-HCT and the optimal timing will be the key to providing the best therapy for patients.

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Key Points

Allogeneic stem cell transplantation remains the only curative therapy for MPN. Transplantation following reduced intensity conditioning provides survival equivalent to that with high intensity (myeloablative) regimens. Alternative stem cell sources, including umbilical cord blood are acceptable for patients without HLA-matched siblings. JAK2 inhibitors (Ruxolitinb) may provide beneficial adjuvant therapy in patients undergoing allo-HCT.

Table 1

Prognostic Score Systems Developed for Patients with Primary Myelofibrosis

Variable	IPSS	DIPSS	DIPSS-plus
Age>65 years	X	X	X
Constitutional Symptoms	X	X	X
Hb<100g/L	X	X	X
WBC>25 × 10^9/L	X	X	X
Circulating Blasts>1%	X	X	X
Platelets <100 ×10^9/L			X
RBC Transfusion need			X
Unfavorable Karyotype			X
	1 point each	1 point each but Hb=2	1 point each

Table 2

Selected transplant studies in patients with Primary and Secondary Myelofibrosis

Study	N	Conditioning	Age (yrs)	1-yr TRM	5-year OS %	5-yr PFS
[30]Ballen et al. 2010	229	MAC	47	27% (Sib) 43% (URD)	37% (sib) 30% (URD)	33% (Sib) 27% (URD)
[50] Patriarca et al	100	MAC	49	35%	31%	28%
[41]Kerbauy et al 2007	104	MAC	49	27%	61% (7 yr)	
[47]Deeg et al 2003	56	MAC	43	35%	58%	
[43]Guardiola et al. 1999	55	MAC	42	27%	47%	
[58]Abelsson et al 2012	40 52	MAC RIC	46 55		49% 59%	
[35]Robin et al 2011	46 101	MAC RIC	53	29% (4 yr)	39% (4 yr)	32% (4 yr)
[59]Stewart et al 2010	27 24	MAC RIC	38 54	41 (3 yr) 32 (3 yr)	44 (3 yr) 31 (3 yr)	44 (3 yr) 24 (3 yr)
[36]Kroger et al 2009	103	RIC	53	16%	67%	51%
[30]Ballen et al 2010	60	RIC		15%		39%
[37]Bacigalupo et al 2010	46	RIC	51	24%	45%	43%
[23]Alchaby et al 2012	150	RIC	57		60%	
[53]Rondelli et al 2005	21	RIC	54	10%	85% (2.5 yr)	
[56]Gupta et al 2014	233	RIC	55	24% (5 yr)	47%	27%

PMF=Primary Myelofibrosis, ET=Essential Thrombocythemia, PV=Polycythemia Vera, RIC =Reduced Intensity Conditioning, MAC=Myeloablative Conditioning, TRM= treatment related mortality, OS=overall survival, PFS=progression free survival