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ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR PATIENTS WITH MYELOFIBROSIS

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Abstract

Purpose of review—Hematopoietic cell transplantation (HCT) offers potentially curative therapy for patients with myelofibrosis. What is the current status?

Recent Findings—Changes in transplant strategies allow offering HCT to patients who, because of age or comorbid conditions, were not considered transplant candidates in the past. The omission of high-dose total body irradiation, adjusting doses of busulfan to achieve defined target levels, using fludarabine instead of cyclophosphamide as an immunosuppressive agent, the addition of melphalan, and the incorporation of anti-thymocyte globulin, all appear to have contributed to better tolerability of new regimens. Reduced-intensity conditioning regimens are associated with a decrease in non-relapse mortality and allow for successful HCT even in patients 60–70 years of age. Some 50–75% of patients are cured by HCT. Emerging concepts include new prognostic scoring systems and novel molecular markers such as Janus kinase (JAK) 2 mutations, which may aid in making treatment decisions and assess remission status.

Summary—Modifications of transplant conditioning regimens have reduced transplant-related mortality and allow carrying out successful HCT in increasingly older patients. The selection of patients who should be transplanted, the optimal timing for transplantation, and pre- and post-transplant strategies remain challenging problems.

Keywords

Myelofibrosis; allogeneic hematopoietic cell transplantation; relapse; non-relapse mortality

INTRODUCTION

Primary myelofibrosis (PMF) (also referred to as myelofibrosis with myeloid metaplasia [MMF] or chronic idiopathic myelofibrosis [CIFM]) is one of the Philadelphia chromosome-negative clonal myeloproliferative disorders (MPDs). PMF is characterized by the proliferation mainly of megakaryocytic and granulocytic elements in the bone marrow, which is associated with deposition of connective tissue (reticulin and collagen) due to a response of marrow fibroblasts to signals derived from the hematopoietic clone. Typical additional features are circulating immature hematopoietic cells and extramedullary hematopoiesis. A similar picture of myelofibrosis may develop in patients originally diagnosed with polycythemia vera (PV) or essential thrombocythemia (ET) and is termed post-PV or post-ET MF [1**]. Recently, a proposal for a revision of the World Health Organization (WHO) diagnostic criteria for the chronic MPDs PV, ET, and PMF was published [2], and algorithms based on those diagnostic

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criteria, including newly identified genetic abnormalities, in particular, the mutation V617F in the JAK2 tyrosine kinase, were developed [3*].

The only currently available treatment modality with curative potential for patients with MPDs is hemopoietic cell transplantation (HCT). However, PMF occurs most commonly in older individuals, and transplant-related morbidity and mortality tend to be high in that age group. Modified transplant regimens are aimed at reducing toxicity to make HCT available to older patients. Secondly, as PMF may evolve over many years, and the course may vary considerably between patients, the timing of HCT has remained controversial, although certain prognostic scoring systems are helpful in deciding upon the optimum treatment strategy [4]. Thirdly, novel non-transplant strategies, including those aimed at the newly identified molecular abnormalities, may stabilize hematologic parameters, improve the quality of life, and, in subgroups of patients, induce remissions for variable periods of time.

Allogeneic HCT with conventional (myeloablative) conditioning

The extensive marrow fibrosis associated with PMF was initially considered a contraindication for HCT. However, despite earlier concerns that marrow fibrosis may hinder hematopoietic recovery following allogeneic HCT [5,6], multiple reports on small numbers of patients have shown that engraftment is obtained consistently and that extensive fibrosis (and even osteosclerosis) is completely reversible with successful allogeneic HCT [7,8]. Those results were subsequently confirmed in larger series. Guardiola et al. [9] reported in 1999 combined results from several European and American transplant centers. Another report presented by Deeg et al. in 2003 [10] summarized results from the Fred Hutchinson Cancer Research Center in Seattle. In the two cohorts of 55 and 56 PMF patients, the median age at HCT was 42 and 43 years, respectively, treatment-related mortality (TRM) was 27% and 33%, and 5-year survival 47% and 58%, respectively. The 5-year probability of treatment failure due to relapse or persistent disease after HCT was 36% [(28% for patients receiving an unmanipulated human leukocyte antigen (HLA)-matched related transplant] in the report by Guardiola et al. [9]. In the Seattle study [10] the incidence of failure of sustained engraftment, occurring solely in patients receiving transplants from alternative donors, was 10%.

An update of the Seattle data included results in 104 patients (56 related and 45 unrelated allogeneic, and 3 syngeneic HCT). Diagnoses included PMF (n=62), post-ET MF (n=18), post-PV ET (n=12), or MF with unclassified myeloproliferative disorders (n=12) [11**]. Patient age was 18–70 (median 49) years, and the source of stem cells was bone marrow in 43 and G-CSF mobilized peripheral blood cells in 61 patients. Busulfan (BU) or total body irradiation (TBI)-based conventional conditioning regimens were used in 95 patients, and a reduced intensity regimen consisting of fludarabine (3×30 mg/m^2) plus 200 cGy of TBI in nine patients. The estimated 7-year survival was 61%, and nonrelapse mortality at 5 years was 34%. In a multivariate analysis, superior survival was observed among patients conditioned with targeted oral BU (steady state target levels 800–900 ng/ml) plus i.v. cyclophosphamide, 60 mg/kg/day × 2 (tBUCY), among younger patients, patients with a low comorbidity score as described by Sorror et al. [12], and in patients with platelet counts greater than 100×10^9/L at HCT. Data from five important studies are summarized in Table 1.

Thus, these results taken together show that in patients with myelofibrosis engraftment can be achieved consistently, and that more than 50% of patients survive long-term in remission, with follow-up extending currently beyond 15 years. However, results are unsatisfactory, particularly in patients more than 60 or 65 years of age, i.e. about the median age at the time of diagnosis.

Allogeneic hematopoietic cell transplantation following reduced-intensity conditioning

The introduction of reduced-intensity conditioning regimens is based on the concept of shifting the emphasis of eradication of tumor cells from high-dose chemo (or radio) therapy to the donor cell-mediated immunologically graft-versus-tumor effect. The potential advantages are low regimen-related morbidity and mortality, in general, and the applicability to older patients or patients with clinically significant comorbid conditions, in particular. Evidence for an immunologically mediated graft-versus-MF effect comes from reports on patients who relapsed after allogeneic HCT and showed remarkable reduction of bone marrow fibrosis after donor lymphocyte infusion [21,22]. As fibrosis is only a reactive process in response to clonal hematopoietic cells, an anti-hematopoietic cell effect of donor lymphocytes should lead to the eventual regression of fibrosis. The use of reduced-intensity conditioning regimens in patients with PMF was first reported by Devine et al. [15] and Hessling et al. [16]. Those preliminary reports indicated that reduced-intensity conditioning was well tolerated and provided effective therapy. Some important reports on reduced intensity conditioning in patients with myelofibrosis are summarized in Table 1.

In a retrospective registry study, including European and American institutions of the myeloproliferative disorders (MPD) Consortium, Rondelli et al. [17] reported on 21 patients (including updated results of four patients previously presented by Devine et al. [15]). The median age of the patients was 54 (range 27 to 68) years. All patients had intermediate or high severity scores according to Dupriez grading, which takes into account hemoglobin and white blood cell values [23]. No patient had evidence of acute transformation. Various conditioning regimens were used, most containing fludarabine. TRM was 10% and 2-year overall survival was 87%. Eighteen patients were alive 12–122 (median 31) months after HCT, and 17 were in remission (one after a second transplant); the relapse rate was 14%.

A prospective study of 21 patients, median age of 53 (range 32–67) years, reported remarkably similar data [18]. One patient had accelerated disease with a blast count of 17% at the time of HCT, and two patients had secondary acute myeloid leukemia, but were in complete or partial remission at HCT. The conditioning regimen consisted of BU and in-vivo T-cell depletion with ATG. TRM was 16% at 1 year. Hematological responses were seen in 100%, and complete histopathological remission in 75% of the patients; 25% of the patients showed partial histopathological remission with a continuing decline in the grade of marrow fibrosis. No primary graft failure was observed and only one secondary graft failure was seen. After a median follow up of 22 (range 4–59) months, the 3-year estimated overall and disease-free survival was 84%. In this study, five of six patients who were 55 years or older (55, 58, 62, 63 and 64, respectively) received transplants from unrelated donors and survived 59+, 22+, 8+, 8 +, and 6 months, respectively.

A retrospective comparison between two conditioning regimens was performed in a small cohort of 27 patients transplanted between 1982 and 2004 by the Swedish Group for Myeloproliferative Disorders [19]. Treatment-related mortality was higher (30%) among 17 patients who received cyclophosphamide plus TBI (“high dose”) conditioning, compared to 10 patients given “reduced intensity” conditioning with a BU plus cyclophosphamide regimen (*P*=NS).

In a prospective trial of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation, 104 patients with PMF and a median age of 55 (range, 32–68) years were included. The risk distribution was as follows: low risk with constitutional symptoms (18%), intermediate risk (58%), and high risk (19%). All but three patients received peripheral blood stem cells either from related (n=31) or unrelated donors (n=69). Acute-graft

versus-host disease (GvHD) grades II–IV occurred in 19%, and severe acute GvHD (grades III/IV) in 7%, while chronic GvHD was seen in 32% of patients. Nonrelapse mortality at 1 year was 19% (95% CI, 11–27%) and was significantly lower for patients younger than 50 years of age (0 versus 27%; P=0.004) and for patients with low versus intermediate /high-risk disease (0 versus 27%; P=0.02). The 3-year overall survival and event-free survival was 70% (95% CI, 60–80%) and 55% (95% CI, 42–68%), respectively. Significant factors for superior survival were younger age and low risk disease, while cytogenetic abnormalities, JAK2 mutation status, and donor type (related versus unrelated) had no significant effect [24].

In another single center study (reported in abstract form) including 39 patients who received a dose-reduced conditioning consisting of thiotepa and cyclophosphamide, favorable factors for improved survival were human leukocyte antigen-identical donor, Karnofsky index of 100%, time from diagnosis to transplantation less than 1 year, and previous splenectomy [25].

Overall, the most commonly used regimens were BU/fludarabine or melphalan/fludarabine based. In comparison to studies with conventional conditioning, the median age of patients in studies using reduced-intensity regimens was more than a decade old. The nonrelapse mortality was less than 20%, and the overall survival after short follow-up was 55% to 85% [15–17, 18,19].

These results suggest that reduced-intensity conditioning regimens followed by related or unrelated allogeneic HCT may be associated with low TRM. It also seems that long-term control of the disease is achieved in a high proportion of patients. Transplantation from unrelated donors is associated with greater TRM, although not significantly so; clearly, however, results need to be confirmed in a larger number of patients. The reversal of disease manifestations or sequelae may not be complete, even in patients without hematologic relapse, as some degree of splenomegaly or marrow fibrosis may persist.

Splenectomy in patients with myelofibrosis undergoing allogeneic hematopoietic cell transplantation

Splenomegaly in PMF is a reflection of an expansion of the underlying malignant clone, and as such, splenectomy may help to debulk the disease and facilitate disease eradication. Moreover, splenomegaly leads to sequestration of donor cells after HCT, causing delayed engraftment, if not graft failure. Indeed, some reports have shown faster engraftment in splenectomized patients [9,10]. Li et al. [26] analyzed the impact of pretransplant splenectomy on posttransplant outcome in 26 patients. Posttransplant granulocyte recovery was faster among splenectomized patients, and the need for both red blood cell and platelet transfusions was greater among patients who had their spleens intact. The 3-year probability of disease-free survival was 73% for splenectomized patients and 64% for patients without splenectomy (P=NS). However, this was a retrospective analysis, and splenectomy, for various reasons, generally had occurred by the time the patient was referred to the transplant center.

Thus, the role of splenectomy before allogeneic HCT remains controversial. A compelling reason against routine use of splenectomy is an operative mortality rate of 5–8% [24,27,28]. In clinical practice splenectomy typically is undertaken in patients who are symptomatic from splenomegaly, patients with refractory hemolytic anemia, or those with complications of portal hypertension [29].

Evaluation for residual disease after allogeneic transplantation

Recently, mutations of JAK2, particularly V617F, have been identified in about 50% of patients with PMF [30,31], about 60% of patients with ET, and nearly 100% of patients with PV [28]. In a longitudinal prospective study by Barosi et al. [32] the presence of JAK2 mutations, present in 63% of 174 cases, independently predicted progression toward large splenomegaly and leukemic transformation. Confirmation by others, however, is lacking. Methods such as real-time PCR allow for monitoring of treatment responses at the molecular level [33]. The impact of JAK2 mutations and outcome after allogeneic HCT remains to be determined. In one study of 30 patients, the JAK2 mutation status did not appear to influence outcome after allografting [34]. However, JAK2 mutation screening with highly sensitive PCR should prove useful in assessing the level of remission after allografting and should aid in defining complete remission in patients with myelofibrosis, especially after allogeneic HCT. The criteria for complete remission recently proposed by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) include the disappearance of disease-related symptoms, peripheral blood levels of hemoglobin of 110 g/L (11 g/dL) or higher, and platelet counts of 100×10^9/L or higher [35]. After allogeneic HCT, the hematologic parameters may be influenced by poor graft function, GvHD, or infections, and cannot be used as valid remission parameters. On the other hand, normal blood cell counts and disappearance of disease-related symptoms do not exclude residual disease.

In one study by Kroger et al. [36] among 21 JAK2 (V617f)-positive patients with myelofibrosis, 78% became PCR-negative after reduced-intensity conditioning and allogeneic HCT. In 15 of 17 patients tested (88%), no JAK2 mutation was detectable after a median follow-up of 20 months. JAK2 negativity was achieved after a median of 89 days following HCT (range, 19–750 days). A significant inverse correlation was seen for JAK2 positivity and donor-cell chimerism (r:− 0.91, $P< 0.001$). Four of 5 patients who never reached JAK2 negativity during the entire follow-up nevertheless fulfilled all criteria for complete remission as proposed by the IWG. In one case, residual JAK2-positive cells were successfully eliminated by donor lymphocyte infusion (DLI). Thus, JAK2 measurement is likely to determine the depths of remission, similar to what has been shown for the abl/bcr transcript in patients with chronic myeloid leukemia [37]. These results show that allogeneic HCT after dose-reduced conditioning can induce high rates of molecular remission in JAK2-positive patients with myelofibrosis, and quantification of JAK2(V617F) mutation by real-time PCR allows the detection of minimal residual disease that may guide adoptive immunotherapy.

In another study, Steckel et al. [38] evaluated 25 patients with PMF for the JAK2 mutation prior to allogeneic HCT and monitored them in long-term follow up of 4–125 (median 15) months after transplant. Results were correlated with the chimerism status. The JAK2 gene mutation was detected in 15 of 25 patients pre-transplant. Three patients who were again positive for JAK2 after HCT concurrently also had mixed chimerism status. These three patients relapsed with their disease shortly after the JAK2 mutation was detected for the first time after transplantation. These data suggest that JAK2 gene mutation as determined by real-time PCR is useful as a minimal residual disease marker after HCT.

After conventional conditioning and allogeneic HCT, about 50% of patients with myelofibrosis are considered cured, and bone marrow fibrosis generally regresses by 6–12 months after HCT [9,10]. Recent data show that similar results are achieved with reduced-intensity conditioning [39]. In that series of 24 patients with either fibrosis grade 2 (MF-2, n=13) or fibrosis grade 3 (MF-3) (n=11), complete (MF-0) or nearly complete (MF-1), regression of fibrosis was seen in 59% of patients by day 100, in 90% by day 180, and in 100% by day 360.

Monitoring of marrow composition by magnetic resonance imaging (MRI) has also been shown to accurately assess the pattern and extent of myelofibrosis and disease status, correlating with biopsy findings after HCT [40].

Prognostic scoring systems and the decision on allogeneic hematopoietic cell transplantation

Since allogeneic HCT is increasingly used as curative treatment option even in older patients, the ever-present morbidity and mortality must be carefully balanced with the patient's life expectancy without HCT in order to offer optimal management. Several risk scores for myelofibrosis have been developed. The most widely used risk-assessment model is the Lille (or 'Dupriez') score [23], which distinguishes low, intermediate and high risk with median life expectancies of 13 to almost 100 months, dependent upon hemoglobin levels and white blood cell counts. The Mayo group has recently added a platelet count below 100×10^9/L as an additional high risk factor [41].

Another scoring system (Cervantes score) [42] includes hemoglobin (<10g/dL), circulating blasts and constitutional symptoms, and distinguishes low risk (none to one adverse factor: median survival, 176 months), and high risk (two to three adverse factors: median survival, 33 months).

The Mayo team has proposed yet another risk-assessment score for patients with PMF [40*], adding monocytes $\geq 1 \times 10^9$/L to the criteria proposed earlier. With no risk factor, the median survival was 173 months, compared to 61 months with one risk factor, and 26 months with two or more risk factors [43,44].

A peripheral blood blast percentage ≥ 3% in addition to a low platelet count may be independent predictors of leukemic transformation in patients with PMF [45]. Vener et al. [46] reported a prognostic model for overall survival (OS) based on the WHO criteria and marrow fibrosis grading by European consensus in 113 patients with chronic MPDs (98 with PMF and 15 with post-PV MF), and compared the findings with other prognostic scoring systems. The results showed that the model was significantly associated with overall survival and, unlike the other prognostic scoring systems, clearly discriminated the overall survival of intermediate-risk and high-risk patients (fibrosis grade 0 versus 3, P=0.0011; grades 1–2 versus 3, P=0.0029).

The different prognostic scoring models are listed in Table 2, and the scores may be helpful in reaching a decision about allogeneic HCT. However, additional factors such as comorbidities or cytogenetic abnormalities may also be relevant.

Conclusions

As PMF progresses, the prognosis worsens. Unfortunately the success rate with HCT, using conventional or reduced intensity conditioning, is also inferior with more advanced disease. Clearly, the optimum timing for HCT still remains to be determined. Nevertheless, the various classification systems do provide guidance. Close monitoring of disease evolution, including a decline in platelet counts or hemoglobin or changes in the peripheral white blood cell counts and differential, should alert patient and physician to changes in the disease kinetics that my call for 'action' in the form of HCT. The optimum conditioning regimen is likely to depend on patient age and comorbid conditions. Further, the prediction of outcome after HCT may not be the sole element to be taken into account when considering transplantation in PMF patients. Since the risk of adverse outcomes is up front for patients undergoing HCT, while it is delayed for those receiving conventional therapy, risk aversion or risk taking by a given patient must also be taken into account. To what extent recent insights into the role of activating mutations

in the tyrosine kinase JAK2 or mpl-1 in patients with MPD, and the development of therapeutic compounds aimed at those mutations will affect treatment decisions remains to be determined.

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