REVIEW

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Hematopoietic cell transplantation for chronic myeloproliferative disorders

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Abstract

Myeloproliferative disorders, including chronic idiopathic myelofibrosis (CIMF), polycythemia vera (PV), essential thrombocythemia (ET), and chronic myelomonocytic leukemia (CMML), are clonal diseases of hematopoietic stem or precursor cells. They often show a protracted or chronic course; however, all have the potential of progressing to severe marrow failure, associated with myelofibrosis, or of transforming into acute leukemia. At that point, hematopoietic cell transplantation (HCT) is the only current treatment strategy with curative potential. If transplantation is being considered and a suitable donor is available, HCT should be carried out before leukemic transformation has occurred, as the success rate of HCT declines steeply in patients who have evolved to leukemia. As many as 75–80% of patients with the original diagnoses of PV or ET, about 65–70% with CIMF, and 45% of patients with CMML are surviving long term after allogeneic HCT using conventional transplant regimens, with follow-up now extending to 15 years. Results with HLA-identical related and unrelated donors are comparable. Major risk factors for the outcome after HCT are the disease stage, the presence of comorbid conditions, and patient age. The development of reduced-intensity conditioning regimens has allowed for successful HCT even for older patients and patients with comorbid conditions. Studies on disease mechanisms, including the recent characterization of an activating mutation in JAK2, may provide additional prognostic guidance and are likely to lead to the development of novel treatment strategies, which will require continuous reassessment as to the optimum timing of HCT.

Key words: hematopoietic cell transplantation, myeloproliferative disorders, myelofibrosis, polycythemia vera, essential thrombocythemia.

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INTRODUCTION

Chronic myeloproliferative disorders, initially classified by William Dameshek in 1951, are a diverse group of malignant bone marrow conditions that originate in a transformed multipotential hematopoietic progenitor cell or pluripotential stem cell [5, 29]. The major entities in this broad classification include essential thrombocythemia (ET), polycythemia vera (PV), chronic idiopathic myelofibrosis (CIMF, previously referred to as agnogenic myeloid metaplasia), and a genotypically distinct entity with BCR-ABL gene rearrangement, chronic myeloid leukemia (CML, a well-defined disease that will not be discussed here). In addition, we will consider here chronic myelomonocytic leukemia (CMML), which was recently reclassified by the WHO as a "Myelodysplastic/Myeloproliferative Disorder" [34]. The natural course of these diseases varies widely. Patients may have indolent disease over many years, but all are at risk of developing progressive marrow fibrosis or evolving to acute leukemia.

Chronic myeloproliferative disorders are predominantly disorders of older patients with a median age at diagnosis of 55–65 years [2, 24]. The incidence is estimated at 0.5 cases/100,000 individuals/year. Advanced age is an important factor to be considered, as the probability of co-morbidities increases with age, and older patients often do not tolerate aggressive therapy well.

GENERAL CONSIDERATIONS FOR HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplantation (HCT) is an established procedure for many malignant and nonmalignant hematopoietic disorders [32], although the indi-

cations for HCT are in flux for various disorders, including chronic myeloproliferative disorders. Most patients receive conservative and supportive treatment for extended periods of time. However, once the tempo of the disease accelerates, treatment options are limited. As these diseases are hematopoietic stem cell disorders, they should be amenable to HCT, and in fact, HCT is currently the only therapeutic approach with curative potential [17, 31]. Because the clinical course of these disorders is highly variable, a careful assessment of the prognosis is essential before deciding on treatment strategies, in particular HCT [30]. The Lille score [9] and the recently published addition of criteria from the Mayo Clinic [8] provide useful prognostic information and guidance to counsel patients in regard to treatment strategies. For patients with CMML, the M.D. Anderson Cancer Center group has proposed a separate classification system [20].

Initial transplant trials raised concerns of engraftment failure in patients with severe marrow fibrosis (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) [22]. However, these results may have been related to patient selection and the fact that patients with various primary diagnoses (including CML) were included. In a large retrospective study comparing data on more than 200 patients with hematopoietic disorders and marrow fibrosis who underwent autologous or allogeneic HCT, there was no significant difference in engraftment endpoints between patients with and without marrow fibrosis [26]. There was, nevertheless, a non-significant delay in the kinetics of hematopoietic recovery: 33 patients who had severe marrow fibrosis reached platelet transfusion independence 7 days later and red blood cell transfusion independence two days later than patients without marrow fibrosis. In patients with marrow fibrosis who underwent successful HCT, splenomegaly generally regressed and the bone marrow showed remodeling towards a normal architecture [6, 25].

APPROACHES TO HCT IN PATIENTS WITH CHRONIC MYELOPROLIFERATIVE DISORDERS

Autologous HCT

Autologous HCT uses stem cells harvested from the peripheral blood of patients. As patients with myelofibrosis typically have high concentrations of $CD34^+$ precursors circulating in the blood, it may in fact not be necessary to use a particular mobilization procedure, and sufficient cells can be harvested at "steady state".

In a multicenter study, 27 patients with myelofibrosis secondary to CIMF, PV, or ET underwent autologous hematopoietic cell collection and 21 underwent conditioning with busulfan only followed by autologous HCT. 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 [1]. 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. It appears that the palliative effect achieved with autologous cells was owing to the fact that the growth kinetics of clonal and non-clonal precursor cells differ, providing a temporary advantage to non-clonal cells. To carry out autologous HCT for myeloproliferative disorders with curative intent, purging of clonal hematopoietic cells from the harvested cells would be necessary, and currently no effective method to achieve this is available.

Allogeneic HCT

CIMF, PV, and ET. Several multi-institutional and single center studies have been reported. In one series including 28 centers and 55 patients (with an update that added 11 more patients) [12, 13], patients were followed for a median of three years, and the probability of 5-year survival was 47% for the entire group and 54% for patients receiving unmanipulated transplants from HLA-identical siblings. Hemoglobin levels below 100 g/l and the presence of osteomyelosclerosis, as well as the presence of clonal cytogenetic abnormalities and older age adversely affected outcome [12]. Survival at 5 years post-transplantation was 48% for all 66 patients; however, there was a significant effect of age, with only 14% of patients older than 45 years surviving compared with 62% for those younger than 45 years. The incidence of grades III and IV acute graft-versus-host disease (GvHD) was 53%, significantly associated with osteosclerosis and the use of total body irradiation (TBI) in the conditioning regimen. The risk of post--transplantation relapse was associated with increased patient age, longer time from diagnosis to transplant, presence of cytogenetic abnormalities, and the use of T cell depletion from the donor cells.

A report from the Fred Hutchinson Cancer Research Center (FHCRC) included 56 patients [6]. The majority of patients were conditioned with busulfan and cyclophosphamide (n=44) or TBI and cyclophosphamide (n=12). Patients were 10–66 (median: 43) years old and had had their disease for 3–312 (median: 33) months. The donors were related in 36 and unrelated in 20 patients; 33 patients received marrow and 23 granulocyte colony-stimulating factor mobilized peripheral blood progenitor cells as a source of stem cells. Treatment-related mortality was 27%. With a median follow-up of 2.8 years, the projected 3-year survival was 58%. While three patients failed to achieve sustained engraftment, 50 became complete donor chimeras and

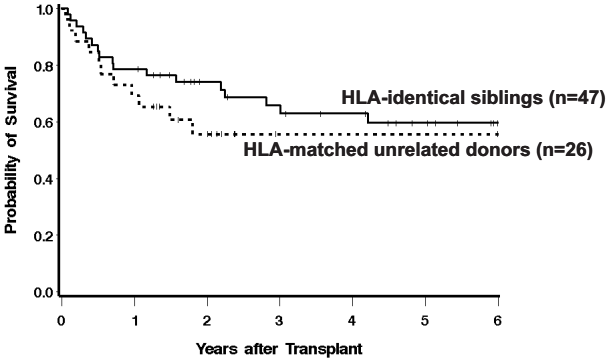

Fig. 1. Survival among patients with myelofibrosis without excess blasts transplanted from HLA-identical siblings (n=47) or HLA--matched unrelated donors (n=26). Surviving patients are indicated by tick marks (Deeg et al., updated from [6]).

three remained mixed chimeras at 26–86 months. The highest probability of survival, 76%, was achieved with a regimen that used targeted busulfan (plasma levels 800–900 ng/ml). Higher Dupriez score, clonal cytogenetic abnormalities, and advanced degrees of marrow fibrosis were the most significant risk factors for post--HCT mortality. There was no significant difference in outcome between patients transplanted from related and unrelated donors (Fig. 1). Patients aged >45-years (n=23) had a 3-year relapse-free survival of 48%, superior to that reported in the multi-institutional study. Targeted busulfan in the conditioning regimen may have been a relevant factor for the better outcome.

A very striking observation in patients with severe myelofibrosis, or even osteosclerosis, who underwent successful HCT has been the regression or complete resolution of marrow fibrosis with normalization of the marrow architecture (Figs. 2 and 3).

CMML. Recent studies at the M.D. Anderson Cancer Center indicate that the median life expectancy for patients with CMML is in the range of 5 months to 2 years, dependent upon the presentation, in particular the hemoglobin values, circulating immature cells, the proportion of lymphocytes in peripheral blood, and the proportion of myeloblasts in the marrow [20]. Thus the term "chronic" is somewhat misleading. While chemo-

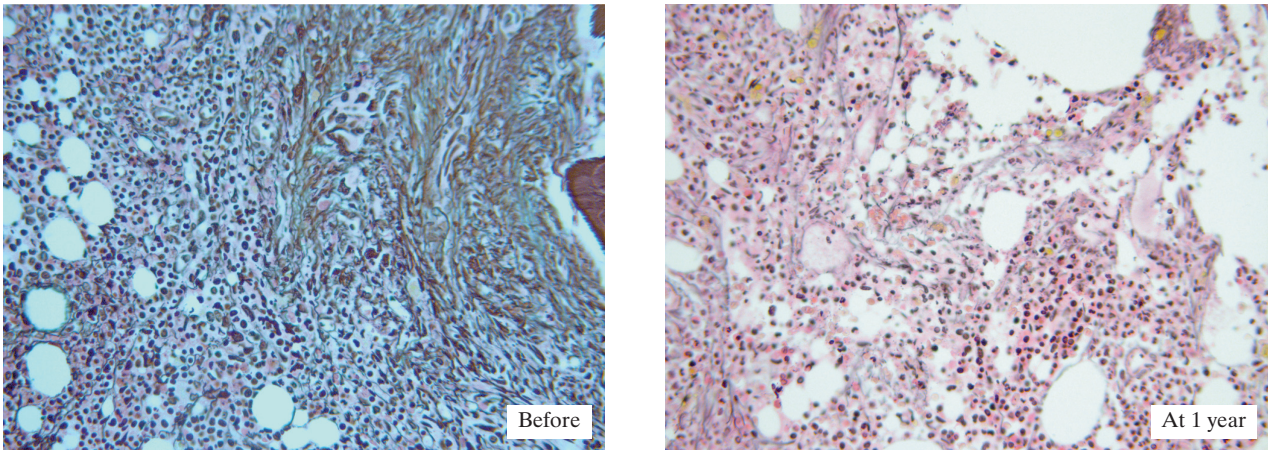

Fig. 2. Marrow biopsies from a patient with CIMF before and one year after HCT (Reticulin stain; original magnification ×300).

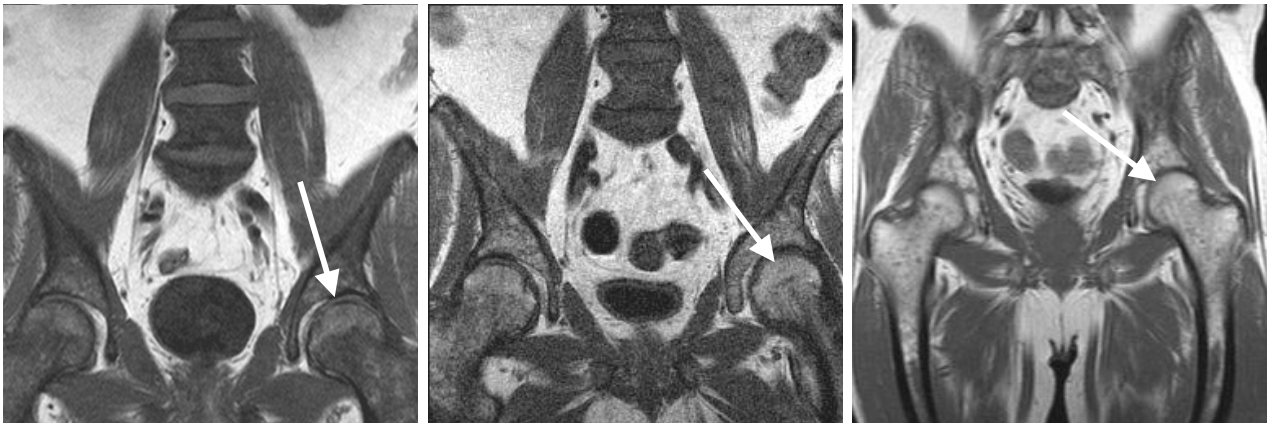

Fig. 3. Magnetic resonance imaging of myelofibrosis. Coronal T1 spin echo picture of the pelvis showing remodeling of bone, particularly prominent in the femur heads, from before HCT to one year after HCT.

therapy may induce remissions in 40–50% of patients, they are generally of short duration; HCT is the only modality shown to have curative potential. We recently presented results on 43 patients who were transplanted from related or unrelated donors. The projected relapse-free survival at 4 years was 41%, with the lead patient surviving at more than 14 years; outcome with related and unrelated donors was comparable. The major risk factors for mortality after HCT were pre-transplant comorbidities as described by Sorror and colleagues [14, 27]. Patients with a comorbidity score of 2 or less showed a survival of 54%, compared with 15% in patients with a score of 3 or higher. None of the currently used disease classification systems had a significant predictive value for post-HCT prognosis [11, 20, 34].

Similar results were reported by Mittal et al. [19], while a relapse-free survival of only 18% at three years was observed by Elliott et al. [10]. As indicated above, comorbidities at the time of HCT have a major impact on transplant outcome and may be responsible for the observed differences.

Other chronic myeloproliferative disorders. Anecdotal cases of successful HCT for other chronic disorders such as mastocytosis, chronic neutrophilic leukemia, or hypereosinophilic syndrome have also been reported [3, 4, 15, 21, 33]. These reports show proof of principle, although it would be premature to draw firm conclusions from few reported cases.

Reduced-intensity HCT

The development of reduced-intensity conditioning (RIC) allogeneic HCT has rendered transplantation an attractive approach even for older patients and patients with comorbid conditions. Encouraging results were reported in 4 patients with myelofibrosis who were conditioned with fludarabine and melphalan and received transplants from HLA-identical siblings [7]. Rondelli et al. [23] expanded on this experience in a retrospective multicenter analysis describing 21 patients. The regimens included fludarabine plus TBI (200 or 400 cGy), fludarabine plus melphalan, thiotepa plus cyclophosphamide, and thiotepa plus fludarabine. Twenty patients achieved hematopoietic engraftment, with 18 patients reaching greater than 95% donor chimerism; two patients subsequently converted to full donor chimerism after donor lymphocyte infusion. Grades II–IV acute GvHD was seen in 7 patients. Extensive chronic GvHD occurred in 8 of 18 evaluable patients. At the time of reporting, 18 patients were alive from 12 to 122 (median: 31) months, 17 in remission.

In a prospective European study, 21 patients with myelofibrosis received RIC regimens consisting of fludarabine plus busulfan and ATG followed by allogeneic HCT; 13 patients had unrelated donors [16]. Outcome was remarkably similar to that in the report by Rondelli et al. [23], with an estimated 3-year disease-free survival of 84%. These are encouraging data, particularly since this trial was conducted prospectively. However, other studies have shown less encouraging data, due to graft failure and disease progression [28]. Prospective randomized trials would be desirable.

Splenectomy

Splenomegaly in chronic myeloproliferative disorders is a reflection of bone marrow damage and expansion of the underlying malignant clone; splenectomy might serve as a debulking procedure. Furthermore, splenomegaly may affect the pace of hematopoietic recovery after HCT [18]. However, the spleen is also part of the immune system and removal may compromise antibody responses to infectious organisms.

Li and Deeg [18] reported on the impact of pre-transplant splenectomy on post-transplant outcome in 26 patients with myelofibrosis treated at the FHCRC. Post-transplant neutrophil recovery was faster, with 14–51 (median: 18) days to reach 0.5×10^9/l in pre-transplant splenectomized patients compared with 19–85 (median: 23) days in non-splenectomized patients ($p=0.04$). The need of red blood cell and platelet transfusions was lower among splenectomized patients. However, the 3-year probability of disease-free survival was not significantly different. Whether splenectomy affects results after RIC remains to be determined.

To date there is no systematic study supporting pre-transplant splenectomy for chronic myeloproliferative disorders. In clinical practice it is rational to recommend splenectomy in patients with significant symptomatic splenomegaly, including splenic infarcts, refractory hemolytic anemia, severe thrombocytopenia, and portal hypertension and related complications. However, the operative mortality of splenectomy maybe in the range of 3–5% and must also be taken into consideration.

CONCLUSIONS AND FUTURE DIRECTIONS

Allogeneic HCT remains the only available therapy with curative potential for patients with chronic myeloproliferative disorders. Even though the criteria for HCT are in flux, it appears that patients with less advanced disease do better with allogeneic HCT than patients with far advanced disease and, presumably, more severe fibrosis in non-hematopoietic organs, or patients with leukemic transformation. With the development of non-TBI conditioning regimens, in particular with targeted busulfan, transplant-related toxicity has been reduced, and this appears to have been reflected in improved survival. The place of RIC allogeneic HCT is not yet clearly defined. Older patients (>60–65 years old) and patients with clinically significant co-morbid conditions are certainly candidates for RIC regimens. Pre-transplant splenectomy may lead to faster hematopoietic recovery after allogeneic HCT; the question has not been addressed in the RIC setting. Currently it is not clear whether mutations in JAK 2

(617) affect transplant outcome, nor do we know how potential targeted therapy aimed at JAK2 might affect the disease course and the indications for transplantation. Future investigations will also have to aim at the identification of additional prognostic parameters to aid in determining the optimal timing for HCT.

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