CHAPTER 24

HSCT for myeloproliferative disorders in adults

P. Guardiola

1. Introduction

This Chapter will consider the indications for, and the results of, haematopoietic stem cell transplant (HSCT) in myeloproliferative disorders (MPD) other than chronic myeloid leukaemia (CML). These include myeloid metaplasia with myelofibrosis (MMM), myelofibrosis secondary to polycythemia vera (PV) and essential thrombocythopenia (ET).

2. Indications for transplantation

Factors that have to be considered for choosing the optimal timing of transplantation in non CML-MPD, are the prognostic factors for disease outcome when non-transplant approaches are used, and those associated with a worse outcome following allogeneic transplantation. In non-transplanted patients with MMM, the main prognostic factors identified are: leukocytes <4 x 10^9/L or >30 x 10^9/L haemoglobin level <10 g/dL, abnormal karyotype, peripheral blood blasts, night sweats and weight loss. In low-risk patients with none of these prognostic factors, the expected median survival is longer than 5 years. Therefore, allogeneic transplantation should only be considered in patients with either intermediate- or high-risk prognostic scores (according to the classifications of Dupriez et al. or Cervantes et al. (1)) since their expected median survival is less than 2 years. In patients with PV or ET, occurrence of marrow fibrosis is the main criterion that should lead to consideration of allogeneic transplantation.

In MMM, factors associated with a worse outcome following allogeneic transplantation are the same as those that predict poor outcome in non-transplanted patients, i.e. a low haemoglobin level, the need for red blood cell transfusions, a low platelet count, presence of severe marrow fibrosis and abnormal karyotype, and also older age at transplantation (in the setting of myeloablative preparative regimens only) (2–5). On the other hand patients without any of these poor-risk features can survive many years without any treatment and the risks of transplant would not be justified in early disease. Therefore the most appropriate time for HSCT is when one of these poor prognosis features appears, i.e. when life expectancy with classical treatments is usually around 2 years or less,

Presence or new occurrence of any of these poor-prognostic factors, and especially inefficient erythropoiesis, should lead to consideration of allogeneic transplantation in patients who have a suitable donor and can tolerate the procedure.

3. Disease specific preparative regimens

In the setting of myeloablative preparative regimens, retrospective studies favour non-total body irradiation-based regimens, since they are associated with a lower

incidence of grade II-IV acute graft-versus host disease (GvHD) and less transplant-related mortality (TRM) (3–5).
The fact that patients with MMM are most often diagnosed at an age greater than 50 years, and that a high TRM has been reported with myeloablative regimens, suggests that reduced-intensity preparative regimens might be appropriate for a majority of MMM patients. However, data about this approach are limited and the follow-up is still too short to give "a firm recommendation" regarding the type of reduced-intensity preparative regimen to use.

4. Role and outcome of autologous transplantation

The role of autologous transplantation in patients with MMM or myelofibrosis secondary to PV or ET is not clearly defined. The main objective of this non-curative strategy is to restore efficient haematopoiesis while reducing the tumour burden, i.e. splenomegaly and/or hepatomegaly, with an acceptable toxicity. Anderson et al. in 2001 reported the largest series of autologous transplants performed in patients with advanced MMM or myelofibrosis secondary to PV or ET (6). Since this publication, which included 27 patients, only limited data have been reported. From the Fred Hutchinson Cancer Research Center study, it appeared that G-CSF mobilisation of haematopoietic progenitor cells and leukapheresis were feasible and safe. Toxicity of the oral busulfan-only preparative regimen was acceptable (n=21 patients undergoing the transplant procedure), with a 3-year survival of 61% and three patients dying of non-relapse causes. Haematopoietic recovery was delayed as compared to autologous PBPC transplantation performed in lymphoma or myeloma patients (median time to neutrophil recovery 21 day; range: 10–96), five patients requiring subsequent back-up PBPC infusions. More than 50% of the patients experienced improvement in either erythroid (10 of 17 anaemic patients) or platelet (4 of 8 patients) response, and a reduction in symptomatic splenomegaly (n=7 of 10 patients). Despite these first encouraging results, development of reduced-intensity allogeneic transplantation and the risk of pancytopenia after autologous transplantation have made this approach less attractive.

5. Role and outcome of HLA-identical sibling transplantation with myeloablative preparative regimens

Guardiola et al. reported the first large retrospective collaborative study of allogeneic transplantation using myeloablative regimens, initially including 55 patients with MMM, then 66 patients (2, 3). They showed that this strategy could lead to full engraftment and long-term complete histo-haematological remissions in a majority of patients (>15 years of follow-up), with complete disappearance

of marrow fibrosis during the first year after transplantation in responding patients (2, 4). Median time to achieve neutrophil recovery was 20 days (range, 11–50). Pre-transplant splenectomy, absence of osteomyelosclerosis, and a high number of nucleated cells infused were associated with faster neutrophil recovery. In patients receiving T-cell replete grafts from HLA identical related donors, the 5-year overall and event-free survivals were 54 and 48%, respectively. For patients transplanted since 1977, the 1-year transplant-related mortality was 22%, and the 5-year incidence of treatment failure, 28%. Factors associated with an improved outcome were: absence of severe marrow fibrosis, haemoglobin level >10 g/dL, no red blood cell transfusion, normal karyotype, and recipient age <45 years at transplantation. In patients who had haemoglobin level >10 g/dL and who had never received red blood cell transfusion before transplantation, the 5-year overall survival rate was greater than 75%, whereas it was below 25% in other patients. Similar results were reported by Deeg et al. (4), who also observed that patients prepared with a non-TBI regimen - targeted busulfan + cyclophosphamide - had an improved outcome, whereas those with low pre-transplant platelet counts had a worse survival. In this later study, no difference in term of outcome was observed according to the type of donor. Of note, Daly et al., in a series of 25 patients, reported a high TRM, i.e., 48%, which could be explained by the fact that 23 of these patients were prepared with a combination of total body irradiation and cyclophosphamide (7).

More recently, Kerbauy et al., reported the Seattle experience with myeloablative regimens (n=95) or a fludarabine plus 2 Gy total body irradiation regimen (n=9), in patients with either MMM (n=62) or myelofibrosis secondary to PV or ET (n=30) transplanted with HLA identical sibling (n=52), HLA matched unrelated donors (n=36) or other donor type (n=16) (5). Using a multivariable regression model, they found that use of targeted-busulfan plus cyclophosphamide as preparative regimen, high platelet count at transplantation for myelofibrosis secondary to PV or ET, younger patient age, and decreased comorbidity score were significantly associated with an improved survival. For instance, patients transplanted with targeted-busulfan plus cyclophosphamide had a 7-year survival of 68%.

6. Role and outcome of HLA matched unrelated transplantation with myeloablative preparative regimens

Because of the limited number of patients transplanted all over the world for non CML-MPD, reported studies so far have combined results from HLA identical siblings and alternative donors (2–5, 7). Deeg et al. reported a significantly increased risk of failure of sustained engraftment in patients transplanted with alternative donors

(n=25 of 56 patients), 14 being transplanted with HLA matched unrelated donors (4). Of note, all these patients received a bone marrow graft rather than PB, which was also identified as a risk factor for engraftment failure. However, the outcome of patients transplanted with alternative donors was not significantly different from that of patients receiving grafts from HLA matched related donors; acute GvHD incidence and severity as well as overall mortality rates being similar for HLA-identical related and alternative donor transplants. Similar results regarding overall survival were observed in a subsequent study from the Seattle group (5).

7. Role and outcome of allogeneic transplantation with reduced-intensity preparative regimens

Rondelli et al. reported a retrospective series of 21 MMM patients transplanted with reduced-intensity preparative regimens (intermediate risk, n=13; high-risk, n=8) (8). Median age was 54 years, with a range of 27 to 68 years. Eighteen of 21 received PBPC grafts from HLA matched related donors. Various preparative regimens were used. Full engraftment was observed in all but one case. Grade II to IV acute GvHD was observed in seven cases, and extensive chronic GvHD in about 50% of evaluable patients. With a median follow-up of 31 months, 17 patients were alive in remission. Encouraging results were also reported by Kroger et al. in a prospective trial including 21 patients, of whom 13 received PBPC grafts from unrelated donors (9). Full donor cell engraftment was observed in 20 cases. Grade II to IV acute GvHD occurred in about 50% of the cases, ands chronic GvHD in 55%. Transplant-related mortality was 16% by 1 year after transplantation. Complete histopathological remission was confirmed in 75% of the patients. With a median follow-up of 22 months, the 3-year overall and disease-free survivals were 84%.

These data suggest that in older patients with MMM, reduced-intensity preparative regimens could result in prolonged survival with a low TRM. However, incidence of either grade II-IV acute GvHD or chronic extensive GvHD remains high, and the follow-up of these studies is still short to confirm that this strategy will lead to persisting complete disease remission. Patients to be transplanted with reduced-intensity preparative regimens should be included in prospective trials, so that it will become possible to properly analyse results of this strategy.

8. Post-transplant treatment and monitoring

8.1. Nature and role of cellular or chemotherapy post-transplantation

Data from retrospective studies and short reports suggest that a graft-versus-disease effect could be induced in MMM, via either donor lymphocyte infusions (1)

or the occurrence of GvHD, which has been associated with a reduced incidence of treatment failures (2, 3).

8.2. Nature and role of minimal residual disease monitoring after transplantation

Using a real-time PCR approach, Kroger et al. have shown that quantification of the JAK2-V617F mutation, which occurs in about 50% of patients with myelofibrosis, was feasible after allogeneic transplantation, and that it could be used to monitor minimal residual disease in the setting of transplantation prepared with reduced-intensity regimens (10). In all but one responder (n=17 of 22 patients), PCR negativity was achieved during the first six months following transplantation. This real-time PCR has also been used as a decision-making analysis tool to guide immunomodulation in the post-transplant period, especially regarding timing of donor lymphocyte infusion. In this setting, this highly sensitive PCR (10^{-4}) was also useful to monitor minimal residual disease following donor lymphocyte infusions and assess their efficacy.

References

1. Cervantes F, Rovira M, Urbano-Ispizua A, et al. Complete remission of idiopathic myelofibrosis following donor lymphocyte infusion after failure of allogeneic transplantation: Demonstration of a graft-versus-myelofibrosis effect. Bone Marrow Transplant 2000; 26: 697-699.
2. Guardiola Ph, Anderson JE, Bandini G, et al. Allogeneic stem cell transplantation for agnogenic myeloid metaplasia: A European Group for Blood and Marrow Transplantation, Société Française de Greffe de Moelle, Gruppo Italiano per il Trapianto del Midollo Osseo, and Fred Hutchinson Cancer Research Center collaborative study. Blood 1999; 93: 2831-2838.
3. Guardiola Ph, Anderson JE, Gluckman E. Myelofibrosis with myeloid metaplasia. N Engl J Med 2000; 343: 659-660.
4. Deeg HJ, Gooley TA, Flowers MED, et al. Allogeneic hematopoietic stem cell transplantation for myelofibrosis. Blood 2003; 102: 3912-3918.
5. Kerbauy DMB, Gooley TA, Sale GE, et al. Hematopoietic cell transplantation as curative therapy for idiopathic myelofibrosis, advanced polycythemia vera, and essential thrombocythemia. Biol Blood Marrow Transplantation 2007; 13: 355-365.
6. Anderson JE, Tefferi A, Craig F, et al. Myeloablation and autologous peripheral blood stem cell rescue results in hematologic and clinical responses in patients with myeloid metaplasia with myelofibrosis. Blood 2001; 98: 586-593.
7. Daly A, Song K, Nevill T, et al. Stem cell transplantation for myelofibrosis: A report from two Canadian centers. Bone Marrow Transplantation. 2003; 32: 35-40.
8. Rondelli D, Barosi G, Bacigalupo A, et al. Allogeneic hematopoietic stem-cell transplantation with reduced-intensity conditioning in intermediate- or high-risk patients with myelofibrosis with myeloid metaplasia. Blood 2005; 105: 4115-4119.

9. Kroger N, Zabelina T, Schieder H, et al. Pilot study of reduced-intensity conditioning followed by allogeneic stem cell transplantation from related and unrelated donors in patients with myelofibrosis. Br J Haematol 2005; 128: 690-697.
10. Kroger N, Badbaran A, Holler E, et al. Monitoring of the JAK2-V617F mutation by highly sensitive quantitative real-time PCR after allogeneic stem cell transplantation in patients with myelofibrosis. Blood 2007; 109: 1316-1321.

Multiple Choice Questionnaire

To find the correct answer, go to http://www.esh.org/ebmt-handbook2008answers.htm

1. Which one of the following criteria does *not* help in deciding the optimal timing for allogeneic transplantation in non CML-MPD?

a) Haemoglobin level ☐
b) White blood cell count ☐
c) Spleen size ☐
d) Abnormal karyotype ☐

2. Which one of the following criteria helps in deciding the optimal timing for allogeneic transplantation in non CML-MPD?

a) Presence of dacryocytes on blood smear ☐
b) Presence of erythroblasts in the peripheral blood ☐
c) Haemoglobin level ☐
d) Gender of the patient ☐

3. In retrospective studies assessing the results of allo-HSCT in non-CML MDP patients, splenectomy performed before the transplantation procedure has been associated with which one of the following?

a) Faster neutrophil recovery ☐
b) Improved overall survival ☐
c) Reduced transplant-related mortality ☐
d) Decreased post-transplant incidence of disease relapses ☐

4. In retrospective studies assessing the results of allo-HSCT in non-CML MPD patients, myelo-ablative conditioning regimens using total body irradiation have been associated with which one of the following?

a) An improved overall survival . . . . . ☐
b) A reduced risk of disease relapse after transplantation . . . . . ☐
c) A decreased risk of grade II to IV acute graft-versus-host disease . . . . . ☐
d) An increased risk of transplant-related mortality . . . . . ☐

---

5. Which is one of the following sentences is wrong?

a) Marrow fibrosis is a reversible process that can disappear following allo-HSCT . . . . . ☐
b) Detection of the JAK2 mutation by quantitative PCR can be used to monitor minimal residual disease in non-CML MPD disorders after allo-HSCT . . . . . ☐
c) Spleen size before transplantation is correlated with the outcome of patients undergoing allo-HSCT . . . . . ☐
d) A "graft-versus leukaemia" effect has been observed in non-CML MPD . . . . . ☐