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Second bone marrow transplantation for patients with thalassemia: risks and benefits

A recent paper by Angelucci and Baronciani[1] discussed numerous aspects of thalassemia major with special attention to two dilemmas. The first is the choice between transplantation, which is still defined as the only curative treatment but bears chances of severe complications such as chronic extensive graft versus host disease (GVHD), and conservative treatment which will eventually lead to death. The second is the influence of the underdeveloped society setting on treatment possibilities. There is an additional unique group of patients that represent 10-20% of all transplanted patients, who to date have received little consideration in the literature: those who lost their graft. It seems that in these cases, marked erythropoietic hyperplasia contribute more to the graft failure than a robust host immune system. Gaziev *et al*. have shown improved results after a second BMT in thallasemic patients, with an improved overall survival (OS) of 49% in older series[2] and 79%[3] in a more recent cohort study.

Twenty-seven of our 107 thalassemic patients transplanted from 1981 to 2008 experienced graft failure. In 18 patients thalassemia recurred; in 10 of these cases autologous back-up stem cell infusion was given due to primary graft failure. Nine patients proceeded to a second allogeneic BMT using the same donor (Table 1). As we did not include routine liver biopsy in our pre-transplant evaluation, we cannot accurately stratify our patients according to the Pesaro risk classification system. However, all of these 9 patients had hepatomegaly and inadequate iron chelation and, therefore, could be stratified to at least class II risk group, while we cannot rule out that some of them belonged to a higher risk category.

Of 18 patients who did not undergo a second transplantation, 2 died: one from veno-occlusive disease, sepsis and disseminated intravascular coagulation (DIC), and one from brain toxoplasmosis; one patient suffered from a severe peritransplant complication requiring frontal lobectomy due to intracranial hemorrhage during post-transplant aplasia. Fourteen patients are alive, transfusion dependent, treated by chelation and in good clinical condition. Nine patients received additional allogeneic hematopoietic stem cell therapy for treatment of graft failure: median follow-up is 24 (2-98) months from the second BMT. Seven BMTs were performed as a second approach to establish normal hematopoiesis; in 2 other cases BMT were performed as an emergency in the context of graft failure. Of these 9, 3 patients died from early complications of the second BMT (aGVHD, DIC, pulmonary hemorrhage). Two of them underwent a second BMT within six months of the first. Six of the 9 patients developed grade II-IV aGVHD, which progressed in 2 cases to extensive chronic GVHD. Two patients of the 6 surviving experienced severe life-threatening events (LTE) (Table 2). One patient experienced thalassemia

Table 1. Transplantation details for the 9 patients receiving a second allogeneic transplant.

	1st BMT	2nd BMT
Donor	Sibling 6 MFD 3	Same 9
Graft, TNC×10^8 (X+SD)	11.3±12.3 BM-8, PBSC-1	14.2±12.7 (ns) BM-6, PBSC-3
Conditioning	TLIBuCy-5 BuCy-2 BuCyTT-1 FluBu(ATG)-1	Cy(HU)- 3 TLIBuCy-1 BuCyMit-1 CyMPC1H-1 FluBuTTATG-1 FluMelTTTBI-1 FluTBI-1

BMT: bone marrow transplantation; MFD: matched family donor; BM; bone marrow; PBSC: peripheral blood stem cells; TLI: total lymphoid irradiation; Bu: busulfex; Cy: cyclophosfamide; TT: thiotepa; Flu: fludarabine; ATG: anti-thymocyte globulin; HU: hydroxyurea; Mit: mitoxantrone; MP: methylprednisolone; C1H: campath-1H; TBI: total body irradiation; Mel: melphalane.

Table 2. Post-bone marrow transplantation course after second allogeneic transplantations.

Case n.	2nd BMT associated LTE	aGvHD (grade II-IV)	Late consequences	Chimerism (donor)	Transfusion independence	Last follow-up (days)	Outcome
1	Yes[1]	Yes				151	Dead
2	Yes[1]	Yes				107	Dead
3	Yes[1]					68	Dead
4	Yes[2]	Yes	Epilepsy, cGvHD	100%	Yes	400	Alive
5	Yes[3]	Yes		100%	Yes	1020	Alive
6	No			10%	No	7263	Alive
7	No			40%	Yes (except stress)	1500	Alive
8	No	Yes	cGvHD	100%	Yes	724	Alive
9	No	Yes		100%	Yes	712	Alive

BMT: bone marrow transplantation; GvHD: graft versus host disease; [1]Multiorgan failure; [2]Status epilepticus; [3]Septic shock, acute respiratory distress syndrome.

recurrence with gradually decreasing donor chimerism to 10% and development of blood transfusion dependence. Another transplant resulted in 40% stable donor chimerism and moderate anemia (Hb≥8 g/L), without bony deformities or persistent transfusion dependence. The rate of aGVHD (6 out of 9) and LTEs (5 out of 9) were high after the second allogeneic transplantation; of 9 patients undergoing second allogeneic transplant 6 are alive, 2 are suffering from chronic GVHD; only 4 are fully transfusion independent, and just one single patient (n. 9) had no LTE or chronic health problems (Table 2).

Successful BMT for patients with β-thalassemia is curative and results in better quality of life than conservative treatment.[4,5] In contrast, conservative treatment is still evolving;[1,5] recent advances in oral chelators, improved blood banking techniques, and aggressive endocrine management currently allow for prolonged, symptom free survival. Patients experiencing graft failure following BMT are candidates for a second BMT, but re-transplant is fraught with risks. Despite the relatively mild preparation regimens administered to our patients, mortality and morbidity were unacceptably high. Gaziev and colleagues[3] proposed using a more myelo- and immunoablative preparative regimen for second transplants, and reported a better overall survival rate: 79% *vs.* 70% in our series. However, re-transplant with its high risk of treatment-related mortality and irreversible life-threatening complications must be carefully considered in the light of the recent improvements in long-term conservative treatment in children and adults with thalassemia. Patients failing BMT with subsequent disease recurrence demonstrated better short-term survival and will likely have a better long-term prognosis (life expectancy and low rate of serious complications) despite their dependence on transfusion and chelation therapy.

Our impression is that a second BMT should be considered only after a sufficient interval has elapsed from the first transplant, and after the patient has adequately recovered from any adverse effects. As opposed to papers quoted by Angelucci and Baronciani, with one thalassemic patient described in each,[6,7] in our series of 20 patients transplanted using non-myeloablative conditioning, thalassemia free survival reached 80% with no TRM. Therefore, this approach must be considered as an option for the second BMT.[8] Undoubtedly, collection of additional data from an ongoing EBMT retrospective analysis and sharing of data between individual centers will help clinicians faced with the management of patients with graft failure following BMT for thalassemia.

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