Bone marrow transplantation for beta-thalassemia

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Marrow transplantation from HLA-identical siblings has been increasingly adopted for therapy of non-malignant conditions.

The first successful transplant in β-thalassaemia, was performed by Thomas et al. in 1981[1] in an untransfused 14-months old child. This patient, now aged 18 years, is the longest surviving patient who is definitely cured from a genetic disease by bone marrow transplantation. At the same time a 14-year old thalassemic patient who had recived 150 cell transfusions was transplanted in Pesaro but he had recurrence of thalassemia after rejection of the graft.

Since then, a large clinical experience has been achieved in this setting: it can be calculated that about 1,000 bone marrow transplant have been performed in Italy by three B.M.T. Centers (Pesaro, Percara and Cagliari).[2] Numerous others centers worldwide have reported the results of clinical trials. In the U.S.A and U.K. there has been an increasing interest in recent years in the field of bone marrow transplant in thalassemia and sickle-cell anemia.[2] The results of marrow transplantation have remarkably improve since first reports, due to use of cyclosporine, more effective treatment of cytomegalovirus infection, improvement of aseptic techniques, and evolution of systemic antibiotic therapy.

Three classes of patients have been identified on the basis of the inadequacy of iron chelation therapy, the presence of liver fibrosis and hepatomegaly: patients in Class I have non of this characteristics, patients in Class II have one or two, and patients in Class III have all three characteristics. These risk factors have been found to significantly influence the post-transplant outcome.[3-5] Among Class I (low risk) children, transplanted early in the course of the disease, disease-free survival is 90-93% with a risk of transplant mortality of 3-8%.[3-6] The results of centers that mainly perform transplant in patients with similar characteristics compare accordingly.[2] Survival rate and disease-free survival are 86-87% and 82-83% for Class II patients (intermediate risk group),[2] 62% and 51% for Class III (high risk group).[7] In this last category of patients, the introduction of conditioning regimes containing less than 200 mg/kg of Cyclophosphamide resulted in a significant decreased of transplant-related mortality, with a concomitant increased risk of graft rejection: in a group of 95 patients examined, survival rate is 74%, disease-free survival 49%, rejection rate 35% and non-rejection mortality 24% with a maximum follow-up of 6 years.[7] Adult patients (aged 16 years old) have survival rate and a disease-free survival after transplant of 65% and 62% respectively.[8] Persistence of residual host hematopoietic cells (RHC), normally referred as mixed chimerism (M.C.) has been described after marrow transplantation in b-thalassemia.[9] Between 30 and 60 days after the transplant. M.C. was detected in 98 out of 351 (27.9%) β-thalassemia transplanted patients investigated by DNA-based techniques (restriction fragment length polymorphism-variable number of tandem repeats) of fluorescence in situ hybridization analysis of the Y chromosome. After one-two years from transplant, M.C. was still present in a proportion of 13.6% and 9.2% respectively. The incidence of M.C. was influenced by the kind of pre-transplant treatment used. Reduction of the doses of both Busulfan (BU) or Cyclophosphamide (CY) in the conditioning regimes produced higher rates of M.C. The presence of R:H:C: in a transplant patient represents a risk factor for graft failure. None of the patients showing full donor engraftment rejected the transplant, while 29% of the patients with M.C. rejected the graft within 2 years from the marrow infusion.

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Analysis of the results demonstrated a direct correlations between the occurrence of graft failure and the amount of R.H.C. present in the recipient. For levels of R.H.C. less than 25% the rejection rate was 12.9% while it was 90% in patients with R.H.C. over 25%. Nevertheless a condition of long-term persistent mixed chimerism has been observed after BMT in thalassaemia. In fact 14 patients, transfusion independent and in good clinical conditions, have been persisted mixed chimeras for more than two years from the transplant. In particular, three of these patients showing an amount of R.H.C. equal to 50% both in the marrow and in the peripheral blood have now a follow-up of over five years.[1]

This study clearly demonstrates the possibility of the co-existence of both donor and host marrow cells, as a mutual tolerance has been induced. These observations may have important implications in graft modulation, immunology and gene therapy.

A current limitation of the general applicability of this therapy is the availability of a related HLA-matched donor. There is a one-in-four chance that any given sibling will be HLA identical. For patients who lack a bone marrow donor, a transplant form related donors mismatched for one or more HLA-A, B or DR loci has been tempted, however, resulting in high risk of mortality and graft-versus-host disease.[10]

An alternative approach is the use of unrelated phenotypically matcher donors.[11,2] Although the clinical experience is still very limited, the improve results of unrelated transplants in malignancies and the advances in the knowledge of the HLA region suggest further exploration of this therapeutical option: at least for patients who have a poor outlook with conventional treatment and using a careful selection of donors with an extensive DNA study of Class II antigents. This is the aim of and ongoing pilot study recently approved by the Italian Bone Marrow Donor Registry (IBMDR).

The post-transplant clinical follow-up of these patients is of particular importance not only within the first year, when careful attention is necessary in monitoring hematologic and engraftment parameters, infectious complications and GVHD. A long-term follow-up is of particular interest in monitoring the evolution of the multisystem problems (iron overload, pubertal development, growth, endocrine deficiencies) that are related to the disease. A number of specific reports show that iron overload,[12,13] chronic hepatities,[14] cardiac function[15] and endocrine deficiencies[16,17,2] can be more easily managed after BMT, and sometimes permit healing of the damage organs. For this reason it has been suggested that BMT shoul be performed at an early stage of the disease, before complications and organ damage (cardiac and hepatic above all) become evident.

Bone marrow transplantation represents today the only possibility of "cure" of the genetic disease for patients who have an HLA identical donor within the family; new developments in transplant immunology and clinical practice will provably increase the number of potential candidates and may further diminish the risk related to this procedure. Unrelated bone marrow transplants, cord blood transplans,18 in utero transplants of hemopoietic stem cells, represent interesting fields of research.

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