

Stem Cell Transplantation in Thalassemias

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Although advances in the supportive care of thalassemias and hemoglobinopathies such as aggressive transfusion therapy and iron chelation have improved the quality of life and decreased the morbidity and mortality rates associated with these diseases,^(1,2) at present stem cell transplantation is the only curative treatment for these diseases. Furthermore, hypertransfusion and iron chelation are expensive in developing countries and require life-long management. Stem cell transplantation programmes for severe thalassemias have now been established in most parts of the world where the disease is prevalent, although in many countries it is only a minority of affected patients who have access to such specialized care. Since the first successful bone marrow transplant (BMT) in a thalassaemic patient was reported in 1982⁽³⁾ more than 1000 patients have been treated with BMT around the world⁽⁴⁾. The outcome of these transplants from centres in Europe, North America and Asia were presented at the Third International Symposium on BMT in Thalassemia (1997) held recently in Pesaro, Italy⁽⁵⁾. Overall around 80% of patients survive long term and of these nearly 90% are cured of their diseases. Updated information on stem cell transplantation in thalassemias was reported at the 7th International Conference on Thalassemia and Hemoglobinopathies (1999) recently held in Bangkok, Thailand⁽⁶⁾.

Sources of stem cells

The majority of stem cell transplantations in thalassemias were performed by using HLA-compatible sibling donor bone marrow. In recent years, the source of stem cells has been extended to include peripheral blood stem cells (PBSC) and cord blood stem cells (CBSC) for transplantation. Since the first successful transplantation of CBSC in a patient with Fanconi's anemia⁽⁷⁾, more than 600 cord bloods have been used as a source of hematopoietic stem cells for transplantation to treat a variety of malignant and nonmalignant hematologic disorders⁽⁷⁻¹⁰⁾.

The first successful cord blood stem cell transplantation in a thalassemia patient was reported in 1995⁽¹¹⁾. Since then approximately 20 CBSCT have been performed in thalassaemic patients worldwide.

Prognostic factors for outcome after BMT

The largest series of transplanted thalassaemic patients is that from Professor Lucarelli's group in Pesaro, Italy. Multivariate analysis of the outcome of the first 222 patients showed that the risks of BMT using an HLA-identical sibling donor could be predicted according to the presence or absence of only three criteria: hepatomegaly, evidence of portal fibrosis in the liver on biopsy, and inadequate iron chelation

therapy⁽¹²⁾. Patients with none of these risk factors were categorized as class I, with any one or two of the risk factors as class II, and with all three risk factors as class III. In this analysis disease-free survival was 94%, 77% and 53% in class I, II and III, respectively⁽¹²⁾.

Conditioning regimens

Most BMT centers use a combination of busulfan and cyclophosphamide for the conditioning regimen, with cyclosporin +/- short course methotrexate as graft-versus-host disease (GVHD) prophylaxis. The most widely used regimen is a total dose of 14 mg/kg of busulfan given over 4 days, followed by 200 mg/kg of cyclophosphamide over the next 4 days^(12,13). This regimen is the most appropriate for patients with class I and II disease. For those higher risk patients in class III (particularly for patients > 17 years), a lower dose of cyclophosphamide (120-160 mg/kg) is recommended in order to reduce transplant-related mortality,⁽¹⁴⁾ although this is likely to be at the expense of an increased chance of graft rejection. On the other hand, to overcome the risk of graft rejection in poor-risk class III patients, some centers use either 16 mg/kg or 600 mg/m² of busulfan especially in children with markedly expanded abnormal erythropoiesis^(15,16). The addition of antilymphocyte globulin (ALG)/antithymocyte globulin (ATG) or Campath to the pre-BMT preparative regimen effectively reduced the rate of graft rejection in many trials^(13,17-19).

Outcome

The largest series of BMT for thalassemias remains that of Lucarelli's groups in Pesaro, which reached 826 transplants by April 1997⁽¹³⁾. The ages of the patients at the time of the transplant ranged between 1 and 35 years. Eight hundred patients received marrow from an HLA-identical donor (25 parents and 775 siblings), 25 from 1 HLA-partially matched donor, and one from an HLA-identical unrelated donor. Overall results revealed probabilities of survival and of event-free survival as 78% and 72%, respectively. Updated results obtained in 119 class I and 291 class II patients aged less than 17 years showed survival rate of 93% and 87% and disease-free survival 91% and 83%, respectively. Update of results obtained in 126 class III patients aged less than 17 years using busulfan 14 mg/kg and cyclophosphamide 120-160 mg/kg, are 79% survival and 58% disease-free survival with 28% graft rejection⁽²⁰⁾. In 115 adult thalassaemics (age > 17 years), the results of BMT revealed a 66% survival rate and 62% disease-free survival. These data reflect the impact of reducing the intensity of conditioning in high-risk patients; the major complication being graft rejection with recurrent thalassemia rather than trans-

planted-related fatal events. Fourteen ex-thalassemics after BMT are transfusion independent and in good clinical condition, showing a persistent mixed chimerism more than 2 years post transplant. The outcome of bone marrow transplantation in thalassemia performed in many other centers around the world was reported at the Third International Symposium on Bone Marrow Transplantation in Thalassemia held in Pesaro in September 1996⁽⁵⁾. An update of the results of BMT in thalassemia from Pesaro, Italy and some centers in Asia were reported also at the 7th International Conference on Thalassemia and the Hemoglobinopathies held in Bangkok in June 1999⁽⁶⁾ as shown in **Table 1**. The overall results from Asian countries are comparable with those obtained in developed countries but at lower expense in most centers.

Cord blood transplantation for thalassemia

For thalassemias and hemoglobinopathies, transplantation of stem cells from cord blood has several theoretical advantages (IU), including the feasibility of prenatal diagnosis of thalassemia and HLA typing, enabling directed donation of only the unaffected cord blood that is compatible. In addition, the availability of a suitable cord blood collection may allow the transplant to be carried out 1-2 years earlier and spares the donor the discomfort and risks of bone marrow donation. As compared with hematopoietic stem cells from adults, hematopoietic stem cells in cord blood have distinctive proliferative advantages, including the capacity to form more colonies in culture, a higher cell-cycle rate, autocrine production of growth factors, and longer telomeres. All these properties should favor the engraftment and growth of cord-blood hematopoietic stem cells. Moreover, the relative immaturity of lymphocytes in cord blood may reduce the risk and severity of GVHD, which in turn could permit more HLA mismatching between donor and recipient than is usually acceptable in bone marrow transplantation^(8,9). In the largest single-centre experience reported from Bangkok, Thailand, HLA-matched sibling donor cord blood transplants were carried out on ten patients with thalassemias, six of whom survived free of disease⁽²¹⁾. No GVHD was observed. In Hong Kong, CBSCTs were performed in five patients with transfusion-dependent thalassemia. All five cases became transfusion independent with

follow-up duration ranging from 3 to 48 months (median: 10 months)⁽²²⁾. In addition, HLA-mismatched CBSCT were performed in three severe thalassemias, two in Bangkok and one in Hong Kong, with encouraging results. Two out of three patients survive disease-free and in good health. Although grade II acute GVHD occurred in both surviving cases, it resolved with steroids and ATG.^(22,23)

Long-term consequences

For thalassemic patients who have undergone BMT and acquired normal hematologic status post transplant, the term "ex-thalassemic after transplant" has been proposed by Lucarelli⁽⁵⁾. The long-term consequences in these ex-thalassemics include both the complications associated with the underlying disease and those that arise from the allogeneic stem cell transplantation. Virtually all "ex-thalassemic" patients have moderate-severe iron overload⁽²⁴⁾. In order to prevent progressive cardiac and hepatic damages in patients who maintain high levels of iron overload, it is now recommended that these "ex-thalassemic" patients should have their total iron burden reduced towards normal levels by regular venesection or desferrioxamine administration. The effect of BMT on growth and development in "ex-thalassemics," particularly on fertility, is still not clear. Thalassemic children transplanted early in the history of their disease (< 8 years) regain a normal growth rate after BMT, while older children and children in class III, especially those who developed chronic GVHD, often have severely impaired growth⁽⁵⁾. There is evidence that gonadal function of some patients who have undergone BMT for thalassemia is impaired, but it is not clear how much of this effect is a result of previous iron overload or a consequence of the preparatory regimen⁽²⁵⁾. Indeed, successful pregnancy following BMT for thalassemia, as well as following BMT for other hematological disorders using busulfan/cyclophosphamide conditioning, has been reported, and no increase in congenital anomalies of the resultant offspring has yet been seen⁽²⁶⁾.

Conclusion

The beneficial results of stem cell transplantation from HLA-identical family members for patients with severe thalassemia are clear. Class I patients have a very high probability of cure with a very low early and late morbidity and mortality. Delay of transplantation until the patient is in a risk category beyond class I substantially reduces the probability of transplant success and jeopardizes the reversibility of liver and cardiac damage. It is reasonable to suggest that patients with β -thalassemia who have HLA-identical donors should be transplanted as soon as possible. Umbilical cord blood (UCB) has been shown to be capable of reconstituting the bone marrow of the patient with thalassemia after myeloablated pre-conditioning treatment. The major advantage of UCB over other sources of stem cells is the ability to cross HLA barriers, and there is evidence of less GVHD. The use of related-donor UCB stem cells with HLA mismatches at one to three antigens needs to be considered.

Table 1. Reported transplants for thalassemia and probabilities of survival and disease-free survival in various Asian Transplant Centers⁽⁶⁾.

Center	No. Patients	Survival (%)	Disease-free survival (%)
Vellore	93	86	71
Hong Kong	52	86	83
Taiwan	43	80	50
Bangkok	48	89	76
Malaysia	44	86	75

We suggest that prospective studies to evaluate the role of UCB stem cell transplantation in the treatment of the thalassemias and hemoglobinopathies are indicated

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