



Annotated Bibliography

XII. Sickle Cell Disease and Thalassemia ii. Thalassemia



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C. Umbilical Cord Blood Transplantation

1. **Innovative approaches to hematopoietic stem cell transplantation for patients with thalassemia.** Locatelli F, De Stefano P. *Haematologica*. 2005;90:1592-4.

Hundreds of patients with thalassemia have been cured of their disorder by allogeneic HSCT, in most cases using stem cells from an HLA-identical family donor. The risk of dying of transplant-related complications has been shown to be mainly dependent on patient age, iron overload and viral liver infections. In class 1 pediatric patients, the probability of survival following HSCT is over 90%, whereas for class 3 patients, the probability is in the order of 60%.

In recent years, **two innovative approaches have been tried to increase the number of patients treatable with HSCT**, namely (1) cord blood transplantation (CBT) and (2) BMT using unrelated volunteers selected using high-resolution molecular typing of HLA-loci.

In regard to CBT, a recent Eurocord cooperative group study (see [citation #6](#)) analyzed the outcomes of 33 patients, mainly children in class 1 and class, who were given CBT from a sibling who was HLA-identical in 30 cases and with a single HLA-disparity in 3. No patient died of transplant-related complications; 7 did not have sustained engraftment, although 2 of these did obtain sustained engraftment after subsequent allogeneic BMT from the same donor. Patients who did not receive methotrexate as part of GVHD prophylaxis and who were treated with thiotepa during the preparative regimen had a remarkably better probability of thalassemia-free survival (above 90%), **indicating that CBT under optimal conditions offers a probability of success at least as good as that of BMT**. Also, the incidence of both grade II-IV acute and chronic GVHD were negligible. However, few data are available regarding the role of CBT from an unrelated donor.

In recent years more precise characterization of HLA alleles using high-resolution molecular typing for both class I and class II loci has allowed to reduce the risk of both immune-mediated complications and fatal events. A recently published study (see [ii. Thalassemia, B. Bone Marrow and PBSC Transplantation, citation #8](#)) suggests that both the risk of death and that of developing severe chronic GVHD are limited and do not exceed the level already largely accepted when using a family donor, provided that stringent criteria of compatibility are employed for selecting the donor. This approach, however, does limit the number of suitable donors; indeed, only about one-third of thalassemia patients who started a search found a suitable donor.

Other approaches were mentioned: *In vitro* fertilization and pre-implementation selection of compatible, healthy embryos is feasible. T-cell depleted HSCT from an HLA-partially matched relative is not routinely advisable due to the substantial risk of serious, often fatal, infectious complications. Haplo-identical, T-cell depleted HSCT can be considered in extreme situations.

2. **Rapid and Complete Donor Chimerism after Unrelated Mismatched Cord Blood Transplantation in 5 Children with beta-Thalassemia Major.** Jaing TH, Hung IJ, Yang CP, Chen SH, Sun CF, Chow R. *Biol Blood Marrow Transplant*. 2005;11:349-53. [Abstract](#)

Five consecutive patients with β -thalassemia major underwent transplantation with an umbilical cord blood (UCB) graft between October 2003 and August 2004. High-resolution molecular HLA typing demonstrated that 2 recipient/donor pairs had 2-loci mismatches, and the remaining 3 pairs had a mismatch at 1 locus. The cell dose determined at the time of cryopreservation was $3.25 - 11.83 \times 10^7/\text{kg}$ total nucleated cells and $2.31 - 3.75 \times 10^5/\text{kg}$ CD34+ cells. The authors used a myeloablative preparative regimen that did not involve total body irradiation. The preparative regimen consisted of oral busulfan 3.5 mg/kg/d (day -9 to -6), intravenous cyclophosphamide 50 mg/kg/d (day -5 to -2), and antithymocyte globulin 30 mg/kg/d (day -4 to -1). Patients received phenytoin for prophylaxis against seizures during treatment. Mesna 50 mg/kg was administered intravenously on the days of cyclophosphamide infusion. Graft-versus-host disease prophylaxis comprised cyclosporine (2.5 mg/kg intravenously every 8 hours) from day -3 with a course of methylprednisolone (1 mg/kg intravenously every 12 hours on days 5 to 19, decreasing 25% thereafter every other day). The cyclosporine dose was tapered beginning at least 60 days after demonstration of engraftment and full donor chimerism by short tandem repeat (STR) analysis.

Four of the patients received 1 UCB unit, whereas 1 patient received 2 units. However, the DNA of only 1 of the 2 donors was detectable after engraftment. The UCB units had been cryopreserved as whole blood; they were thawed in a 37°C waterbath with gentle agitation and without further processing before infusion into the patients. GCSF 10 $\mu\text{g}/\text{kg}/\text{d}$ was given intravenously on day 1 after transplantation and on each day thereafter until the neutrophil count remained $>1.0 \times 10^9/\text{L}$ for 3 consecutive days.

Neutrophil engraftment occurred at a median of 12 days (range, 12-17 days) after transplantation. The median number of days to achieve a platelet count of $>20 \times 10^9/\text{L}$ was 46 days (range, 43-55 days). The engraftment was sustained in all patients. Serum immunoglobulin levels were in the reference range 6 months after transplantation. All patients developed acute GVHD (grade I or II in 4 patients, and grade III in one patient); none developed extensive chronic graft-versus-host disease. Asymptomatic CMV reactivation was detected in 2 patients on posttransplantation days 27 and 62, respectively. All patients were alive at a median follow-up of 303 days after transplantation, with complete donor chimerism and transfusion independence.

The authors emphasized that they selected **cord blood units containing high cell doses** and that all of the patients were classified as Lucarelli class I. They commented that the success of UCB transplantation in their study suggests that **ideal candidates are young patients without underlying complications of their disease or transfusional iron overload**.

(Comment: Recent publications indicate that, with modern supportive therapy, 32% of patients with thalassemia major will die by the age of 35 (See ii. Thalassemia A. Clinical Aspects citations #1 and #3). The question that immediately comes to mind is, "If 100 children with beta-thalassemia major were to be transplanted at an early age, would 32 be dead at the age of 35?" As illustrated in this report by Jaing et al, transplants of young children using stem cell products from related or unrelated donors has a mortality much less than 32%. These data make a strong case for transplanting young children with beta-thalassemia major. It is doubtful that many parents of patients with thalassemia major in the United States are provided the option of an unrelated cord blood transplant at a young age for their children. Should this change?)

3. **Unrelated umbilical cord blood transplantation for an infant with beta-thalassemia major.** Hall JG, Martin PL, Wood S, Kurtzberg J. *J Pediatr Hematol Oncol.* 2004;26:382-5. [Abstract](#)

This report describes the successful transplantation of a 2-month-old infant with β -thalassemia major using partially HLA-matched unrelated umbilical cord blood. After cytoreduction with busulfan, cyclophosphamide, and antithymocyte globulin (ATG), the patient underwent transplantation at the age of 2 months with a 4/6 HLA matching umbilical cord blood unit from an unrelated donor.

The patient engrafted promptly with 100% donor chimerism. His only major complication was an autoimmune hemolytic anemia that resolved 2 years after transplantation. He is currently surviving, event-free, 5 years after transplantation with normal growth and cognitive development and full donor chimerism without evidence of β -thalassemia.

The authors state that umbilical cord blood transplantation from related and unrelated donors should be considered for patients with β -thalassemia major who lack traditional bone marrow donors. As most newborns undergo screening for hemoglobinopathies, those with disease could be transplanted early in life before experiencing the morbidity and mortality caused by transfusion therapy, alloimmunization, and iron overload, increasing the likelihood of successful transplantation therapy.

4. **Unrelated peripheral blood and cord blood hematopoietic stem cell transplants for thalassemia major.** Tan PH, Hwang WY, Goh YT, Tan PL, Koh LP, Tan CH, Quah TC. *Am J Hematol.* 2004;75:209-12. [Abstract](#)

The authors point out that life-long transfusion and intensive iron chelation therapy are expensive, disruptive and that compliance is difficult. Also, in many developing countries, the safety of the blood supply is questionable. Further, even with optimal medical management a normal life span has not been achieved. They report two successful cases of unrelated hematopoietic stem cell transplants (HSCTs) in thalassemia major, one of which was performed using umbilical cord blood. That patient presented at age 5 1/2 years and was transfusion dependent and had received subcutaneous desferrioxamine via a pump 5 times a week since age 1 year. Both liver and spleen were 3 cm below the respective costal margins, but liver function tests were normal and liver biopsy did not show any peri-portal fibrosis. A cord blood sample fully matched in the direction of rejection but two-antigen mismatched in the direction of graft-versus-host was used. Conditioning was with busulfan (18 mg/kg p.o.), cyclophosphamide (120 mg/kg/ i.v.) and anti-thymocyte globulin. He received 6×10^7 nucleated cells per kg and 4.8×10^5 CD34+ cells/kg. Post transplant GVHD prophylaxis was with cyclosporine A and a short course of methotrexate. Myeloid engraftment was on day +19 and he became independent of platelet transfusion on day +38. 100% donor chimerism was documented by day +100, only mild GVHD was observed in the form of a skin rash. He is currently 2 years posttransplant and is well with a good hemoglobin level and has not received a RBC transfusion since the transplant. The authors suggest that the unusually large cell doses used could be an important contributory factor for their success, and pointed out that the patient was young had no significant organ damage. They state that graft failure is a major problem in transplantation of patients with thalassemia but that they believe that this may be overcome by using large cell doses and a more intensive conditioning regimen.

5. **Umbilical cord blood transplantation in Chinese children with beta-thalassemia.** Fang J, Huang S, Chen C, Zhou D, Li CK, Li Y, Huang K. *J Pediatr Hematol Oncol.* 2004;26:185-9. [Abstract](#)

This publication from the Peoples Republic of China describes 9 children with thalassemia major who received a cord blood transplant from a sibling donor. None of the children were Lucarelli class 1 and three of the sibling donors were mismatched. Two of the three patients receiving mismatched cord blood did not achieve engraftment and had autologous marrow regeneration; the other one engrafted but developed grade IV acute GVHD and died as a result. Two patients developed secondary graft rejection and had autologous marrow regeneration before day 60 posttransplantation. Eight patients survived and four patients became transfusion-independent. The authors suggested that a more intensive conditioning than the variety of regimens tried in this study might be required for more favorable results.

6. **Related umbilical cord blood transplantation in patients with thalassemia and sickle cell disease.** Locatelli F, Rocha V, Reed W, Bernaudin F, Ertem M, Grafakos S et al. *Blood* 2003; 101:2137-2143. [Abstract](#)

Forty-four children with hemoglobinopathies (thalassemia, n = 33; sickle cell disease, n = 11) received cord blood transplants from related donors (most receiving full matched grafts; three were 1-locus mismatched grafts). The median number of nucleated cells infused was 4.0×10^7 /kg. Engraftment was obtained in 86.4% of transplants; median time to neutrophil and platelet engraftments were 23 and 39 days, respectively. No patient died, and 36 of 44 children remain free of disease, with a median follow-up of 24 months (range 4-76 months). No grade III-IV acute GVHD occurred; 2 of 36 patients at risk developed limited chronic GVHD. The authors concluded that related cord blood transplantation offers a good probability of success and is associated with a low risk of GVHD.

(NOTE: Laughlin indicates that the low incidence of GVHD in this study compares favorably with the 15-25% incidence of chronic GVHD observed in children receiving HLA-matched sibling allogeneic bone marrow grafts. Thalassemia and sickle cell disease are among the most common genetic disorders, affecting several million children and young adults worldwide. **(UCB allogeneic transplantation for hemoglobinopathies.** Laughlin M. *Blood* 2003;101: 2077-2078.

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