Bone Marrow Transplantation (2003) 32, 341–342

www.nature.com/bmt

# Correspondence

## Homozygous α-thalassemia treated with intrauterine transfusions and postnatal hematopoietic stem cell transplantation

*Bone Marrow Transplantation* (2003) **32,** 341–342. doi:10.1038/sj.bmt.1704129

In malaria-endemic Southeast Asia, deletions in the α-globin gene cluster on chromosome 16 are common, with carrier rates for the most prevalent (–SEA) deletion ranging from 3.5 to 14%.[1] Homozygosity for this deletion is the most common cause of the hemoglobin Bart's ($\gamma_4$) hydrops fetalis syndrome.[1] Affected fetuses usually succumb to the effects of hypoxia in the third trimester. For the few surviving infants, supportive treatment has consisted of regular red cell transfusions and iron-chelation therapy.[2,3] In two previously reported instances, allogeneic hematopoietic stem cell transplantation (HSCT) has been performed.[4,5] Here, we present a patient with homozygous α-thalassemia diagnosed and treated *in utero*, who underwent successful HSCT from his HLA-matched sister at 23 months of age.

Our patient was born to Laotian parents. He was the product of his mother's fifth pregnancy. The previous four pregnancies had resulted in a spontaneous miscarriage at 12 weeks, intrauterine fetal demise at 25 and 28 weeks, and one normal delivery of a healthy female infant at term. In this pregnancy, diagnostic amniocentesis was performed at 16 weeks of gestation. Molecular genetic testing of parental blood and of cells from the amniotic fluid established that the fetus was homozygous for the –SEA deletion, confirming the diagnosis of homozygous α-thalassemia. The first of four intrauterine blood transfusions was administered at 26 weeks of gestation. Spontaneous labor occurred at 34 weeks. The patient weighed 4 lb 9 oz at birth, was vigorous and experienced no neonatal complications. Hypospadias was noted. From birth, he was transfused with red blood cells every 4 weeks. He thrived and developed normally. His sister was determined to be an HLA match, and demonstrated 64.4% HbA, 22.6% $HbA_2$/E, 10% HbF and 3% HbH/Bart's on hemoglobin electrophoresis, consistent with the presence of both α-thalassemia trait and hemoglobin E trait. A treatment plan of transfusions and iron monitoring was decided upon, with a view to elective HSCT at 24 months of age.

By 18 months of age, he had received 19 red cell transfusions, in addition to the four received *in utero*. At this time, his serum ferritin was 1681 ng/ml. A liver biopsy demonstrated pronounced iron overload: hepatic iron concentration, determined by atomic absorption spectrophotometry of more than 1 mg of nonparaffin-embedded tissue, was 15.4 mg/g dry weight. A central venous catheter was placed, and chelation therapy with deferoxamine was initiated. During 5 months of aggressive intravenous chelation therapy, he had three documented episodes of bacteremia.

At 23 months of age, he was admitted for HSCT from his 4-year-old HLA-matched sister. At the time of transplant, he was seronegative for hepatitis viruses. He was conditioned with cyclophosphamide (120 mg/kg) and fractionated total-body irradiation (14 Gy) and received a marrow graft containing $3.32 \times 10^8$/kg nucleated cells. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and short-course methotrexate. The early transplant course was complicated by mild hepatic veno-occlusive disease. A sustained neutrophil count exceeding $0.5 \times 10^9$/l was attained on day 27, a transfusion-independent platelet count exceeding $20 \times 10^9$/l on day 24, and his last red cell transfusion was administered on day 36. He was discharged on day 37 with no signs of acute GVHD.

At 4 months post transplant, his hemoglobin drifted to 7 g/dl without evidence of hemolysis. Hemoglobin electrophoresis revealed the donor-specific pattern. However, chimerism analysis by fluorescent *in situ* hybridization (FISH) with X- and Y-chromosome-specific probes determined 48% of circulating leukocytes to be male (recipient) and 52% to be female (donor). Serum erythropoietin was found to be inappropriately low at 50 mU/ml. Serum ferritin was 4137 ng/ml, and liver biopsy demonstrated residual hemosiderosis, mild portal fibrosis without bridging and an hepatic iron concentration of 12.3 mg/g dry weight. Tests for hepatitis B and C viruses remained negative. In an attempt to mobilize excess iron stores and to correct his anemia, therapy with recombinant human erythropoietin (rhEPO) was initiated at a dose of 100 U/kg thrice weekly. Within 6 weeks, the hemoglobin concentration rose to 9.6 g/dl. The rhEPO was weaned, and rhEPO-independent hemoglobin concentrations of 10–12 g/dl were maintained by 12 months post transplant.

Immunosuppression was weaned and discontinued 6 months post-transplant. The patient is now 5 years old, and 3 years out from his transplant. He has attained all appropriate developmental milestones, and is growing with normal velocity. He has no evidence of chronic GVHD. His hemoglobin is 12.3 g/dl. His serum ferritin is 1440 ng/ml. He remains a stable mixed chimera: 33.5% of circulating leukocytes are male (recipient) and 66.5% female (donor), by FISH.

Patterns of global migration mandate heightened awareness of common, formerly geographically isolated, diseases such as homozygous α-thalassemia. The early obstetric history of our patient's mother betrays a failure by health professionals to identify her potential risks, consistent with observations that over a recent 8-year period in Ontario, only 10–30% of at-risk pregnancies were identified and provided with counseling and diagnostic services.[1]

Intrauterine blood transfusions have been administered before to fetuses with homozygous α-thalassemia and other hematologic disorders associated with fetal demise.[6,7] It is rare for nontransfused fetuses to survive postnatally; reported survivors have generally required resuscitation at birth.[2–5] Once a patient is stabilized on a chronic

transfusion regimen, the medical issues are comparable to those of children with $\beta$-thalassemia major. With optimal iron chelation therapy, more than 90% of chronically transfused children with $\beta$-thalassemia major may now be expected to survive beyond 30 years of age.[8] However, poor compliance with chelation therapy reduces the chance of long-term survival to 10–20%.[8] The most recent HLA-matched sibling donor transplant data from Pesaro and the UK attest to long-term survival and thalassemia-free survival rates in excess of 90 and 80%, respectively, among pediatric patients, irrespective of Pesaro classification.[8,9] Attention to excess iron stores is an important component of the post-transplant management of these patients. Our patient is unquestionably iron-overloaded. In a stable mixed chimera of this age, the optimal approach to management is somewhat controversial. However, in view of his negligible risk for progression of hepatic fibrosis in the short term,[10] we have elected to adopt a watch-and-wait approach. We plan to re-evaluate his hepatic iron concentration and histology at intervals.

There are two other reports of HSCT in children with homozygous $\alpha$-thalassemia.[4,5] Neither child was diagnosed antenatally, and both required cardiopulmonary resuscitation perinatally. Chik *et al*[4] obtained a bone marrow graft from an HLA-identical sibling, whereas Zhou *et al*[5] used cord blood obtained from a sibling mismatched at one MHC locus. Busulfan, cyclophosphamide and antithymocyte globulin were used in both the cases as conditioning therapy. Both transplants resulted in a functional hematologic 'cure', despite the presence of mixed hematopoietic chimerism in one patient. Intrauterine HSCT has been attempted in fetuses with homozygous $\alpha$-thalassemia without success.[6]

To conclude, the incidence of homozygous $\alpha$-thalassemia in Europe and North America will continue to rise because of the ongoing migration from Southeast Asia. This case highlights the potential for successful treatment of this lethal disorder through the delivery of supportive care *in utero* and definitive curative therapy postnatally.

I Thornley[1,2]
L Lehmann[1,2]
WS Ferguson[3]
I Davis[1,2]
EN Forman[3]
EC Guinan[1,2]

[1]*Department of Pediatrics, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA;*
[2]*Division of Hematology/Oncology, Children's Hospital, Harvard Medical School, Boston, MA, USA; and*
[3]*Division of Pediatric Hematology/Oncology, Hasbro Children's Hospital, Brown University School of Medicine, Providence, RI, USA*

## References

1 Chui DH, Waye JS. Hydrops fetalis caused by alpha-thalassemia: an emerging health care problem. *Blood* 1998: **91**: 2213–2222.
2 Beaudry MA, Ferguson DJ, Pearse K *et al*. Survival of a hydropic infant with homozygous alpha-thalassemia-1. *J Pediatr* 1986: **108**: 713–716.
3 Bianchi DW, Beyer EC, Stark AR *et al*. Normal long-term survival with alpha-thalassemia. *J Pediatr* 1986: **108**: 716–718.
4 Chik KW, Shing MM, Li CK *et al*. Treatment of hemoglobin Bart's hydrops with bone marrow transplantation. *J Pediatr* 1998: **132**: 1039–1042.
5 Zhou X, Ha SY, Chan GC *et al*. Successful mismatched sibling cord blood transplant in Hb Bart's disease. *Bone Marrow Transplant* 2001: **28**: 105–107.
6 Hayward A, Ambruso D, Battaglia F *et al*. Microchimerism and tolerance following intrauterine transplantation and transfusion for alpha-thalassemia-1. *Fetal Diagn Ther* 1998: **13**: 8–14.
7 Remacha AF, Badell I, Pujol-Moix N *et al*. Hydrops fetalis-associated congenital dyserythropoietic anemia treated with intrauterine transfusions and bone marrow transplantation. *Blood* 2002: **100**: 356–358.
8 Vassiliou G, Amrolia P, Roberts IA. Allogeneic transplantation for haemoglobinopathies. *Best Pract Res Clin Haematol* 2001: **14**: 807–822.
9 Lucarelli G, Andreani M, Angelucci E. The cure of thalassemia by bone marrow transplantation. *Blood Rev* 2002: **16**: 81–85.
10 Angelucci E, Muretto P, Nicolucci A *et al*. Effects of iron overload and hepatitis C virus positivity in determining progression of liver fibrosis in thalassemia following bone marrow transplantation. *Blood* 2002: **100**: 17–21.