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# A successful booster umbilical cord blood transplantation for a 10-year-old patient with beta-thalassemia major in India

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## Abstract:

Beta-thalassemia major is characterized by a genetic deficiency in synthesis of beta-globin chains, resulting in reduced levels of functional hemoglobin. It is characterized by anemia, hepatosplenomegaly, and iron overload due to repeated blood transfusion. Hematopoietic stem cell transplantation is currently the only known curative treatment. We present a case of a 10-year-old girl with beta-thalassemia major who was successfully cured with allogeneic booster umbilical cord blood (UCB) transplantation with outcome data after 3 years of transplantation, in India. Postdiagnosis, she was on regular once-a-month blood transfusion until the age of 10 years, with no improvement. No serious adverse events occurred in the patient post-UCB transplantation. Chronic graft versus host disease was limited and was managed by medicines. Signs of primary graft rejection were also not seen.

## Keywords:

Beta-thalassemia major, human leukocyte antigen-matched sibling, umbilical cord blood transplantation

## Introduction

Beta-thalassemia major (Cooley's anemia or homozygous beta-thalassemia), a clinically severe disease, results from mutation in two beta-thalassemia alleles, one on each chromosome.<sup>[1]</sup> These patients require sequential blood transfusions without which they may develop severe skeletal deformities along with hepatosplenomegaly.<sup>[2]</sup> Continuous transfusions may not be feasible for all owing to cost and associated complications.

Stem cell transplant is the only curative treatment option for these patients. The first umbilical cord blood (UCB) transplant for this was performed in 1993.<sup>[3]</sup> Since then, it has

emerged as a superior source of hematopoietic stem cells (HSCs). Mesenchymal stem cells present in UCB help lower the risk of graft versus host disease (GvHD).<sup>[4]</sup> Age is a critical factor that determines success of UCB transplant.<sup>[5]</sup> Hence, this report presents a case of a 10-year-old girl with beta-thalassemia major.

## Case Report

The patient was a 10-year-old girl with symptomatic beta-thalassemia major, diagnosed at 3 months. Her parents were diagnosed with beta-thalassemia minor gene (intervening sequence 1–5 [G-C] mutation) using amplification refractory mutation system polymerase chain reaction (PCR) analysis. Thus, the fetus could have beta-thalassemia minor, but her condition was confirmed by hemoglobin

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electrophoresis to be beta-thalassemia major. She then underwent once-a-month blood transfusion regularly until the age of 10 years, with no improvement. Her parents planned a second baby hoping to treat her with UCB preservation and transplant from her younger sibling (a probable donor). Accordingly, they preserved the UCB with Biocell®, a cord blood bank run by Regrow Biosciences Pvt. Ltd in September 2012 when their second baby, a female, was born and approximately 60 ml UCB was collected within 24 h and sent to the Biocell® laboratory for processing (double sedimentation spin method), and it was cryopreserved successfully.

Later, this UCB was analyzed for hematology, viability, and other factors [Supplementary Table 1] and was recorded free from infectious agents [Supplementary Table 2]. Human leukocyte antigen (HLA) testing and matching at low resolution by PCR showed a complete 6/6 match for HLA-A, HLA-B, and HLA-DRB1 phenotypes; high-resolution sequence-based typing from Applied Biosystems-Life Technologies, USA (National Accreditation Board for Hospital and Healthcare Providers-accredited lab) showed a complete 10/10 match for HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 between both siblings.

Therefore, physicians requested retrieving the cryopreserved UCB for allogeneic HSC transplantation. Approval from the Institutional Committee for Stem Cell Research on July 13, 2016, was received and communicated to the National Apex Committee for Stem Cell Research and Therapy on July 15, 2016, and transplant was done on July 29, 2016. Table 1 describes the details of the stem cell product at the time of cryopreservation and transplantation. Parents consented retrieval and release of cord blood unit for the planned therapy. The patient was not splenectomized prior transplantation, and Pesaro risk classification was not performed, as pretransplantation liver biopsy was not a routine procedure at the treating hospital. Owing to high ferritin level and liver size >5 cm below costal margin, the patient was deemed Lucarelli Class III.

**Table 1: Characteristics of stem cell product**

Parameter	Value
At the time of cryopreservation	
TNCC	6.04×10 <sup>8</sup> /unit
CD 34	10.5×10 <sup>5</sup> /unit
TNC viability	93.73%
Post thaw (37°C water bath)	
TNCC	3.86×10 <sup>8</sup> /unit
CD 34	9.25×10 <sup>5</sup> /unit
TNC viability	75%

TNCC=Total nucleated cell count, TNC=Total nucleated cell

Blood components helped maintain hemoglobin (80 g/L) and platelets (20 × 10<sup>9</sup>/L). For prophylaxis against fungal infections and cytomegalovirus (CMV) reactivation, fluconazole 5 mg/kg daily and acyclovir, respectively, were prescribed from day 1 post transplant. Cotrimoxazole was given for pneumocystis jiroveci infection on day + 14 post transplant. Acyclovir and cotrimoxazole were continued up to day 180 until T-cell function was restored. Quantitative CMV PCR before transplantation was negative. Parenteral nutrition was given during anorexia.

No serious adverse events (AEs) were observed post transplantation. She was engrafted promptly with 100% donor chimerism that was persistent until final follow-up. Absolute neutrophil count exceeded 0.5 × 10<sup>9</sup>/L on day 17 (14–25 days). She became red cell- and platelet-independent on days 32 and 36, respectively. No signs of graft rejection were seen. Mild hepatic veno-occlusive disease, acute Grade 2 GvHD, and CMV interstitial pneumonia were observed. Methylprednisolone and mycophenolate were given to manage chronic GvHD. No other AEs occurred during follow-up.

Posttransplant follow-up was at 3 years posttransplant. Cumulative reports showed improvement in blood cells, and serum ferritin levels (standard: 4.63–204.00 ng/ml) normalized (633.0 ng/ml) against prior-to-implant levels (2451.18 ng/ml) that clinically correlated with reduced iron overload by transfusion. Liver profile also improved when correlated clinically. At 3.5 years (February 21, 2020), she was well and did not require transfusion.

## Discussion

This case describes successful allogeneic booster UCB transplantation in a 10-year-old girl diagnosed at 3 months with beta-thalassemia major. She received UCB from her younger sibling. No posttransplant serious AEs were notified within follow-up and signs of primary graft rejection were absent. She reported well with improved liver profile and no requirement for transfusion 3.5 years post transplantation.

Current regimen for these patients includes RBC transfusions (suppresses endogenous hematopoiesis) and deferoxamine (parenteral chelation therapy). Splenectomy is appropriate upon increased transfusion requirements for normal growth. Bone marrow transplant (BMT) is the only curative therapy when performed early-on,<sup>[6,7]</sup> and only <30% of patients have HLA-matched siblings who can be donors,<sup>[8]</sup> significantly limiting BMT utility. Moreover, after HLA-identical sibling BMT, the incidence of acute

GVHD grade II is considerably high of about 15%–30% in pediatric nonmalignant disorders.<sup>[9]</sup> Thus, we need alternative sources of stem cells for curative therapy of beta-thalassemia major.

Allogeneic UCB transplantation from related/unrelated donors are increasingly used for treating children with malignant/non-malignant diseases.<sup>[7,9]</sup> Several studies highlighted their advantages, including rapid donor availability, tolerance of less-stringent HLA matching, reduced viral contamination and incidence, and severity of acute and chronic GvHD.<sup>[7-9]</sup> Compared to other HSC sources, cell dosing correlates with clinical outcomes rather than HLA matching in patients transplanted with UCB. We used booster UCB to complement BMT (UCB plus stem cells) and adding UCB stem cells increases the amount of infusion hematopoietic progenitors. Moreover, booster UCB also reduces the volume of bone marrow stem cells required for transplantation to achieve adequate number of MNCs in the graft without placing the donor at the same risk as that for standard stem cell collection.<sup>[10]</sup> Although it is reported that prognosis of beta-thalassemia worsens with age, in this case report, we overcame most limitations and successfully performed UCB and stem cell transplant in a 10-year-old girl using UCB from her 3-year-old HLA-matched sibling. Thus, this report shows that patients >10 years of age can be successfully cured with allogeneic booster cord blood transplantation rather than performing a regular BMT.

#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parents have given consent for the patient's images and other clinical information to be reported in the journal. The patient's parents understand that name of the patient and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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#### Conflicts of interest

There are no conflicts of interest.

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## Supplementary Tables

**Supplementary Table 1: Results of the processed umbilical cord blood sample at the time of cryopreservation**

Test	Methodology	Results
Total nucleated cell count	Automated hematology analyzer	6.04×10 <sup>8</sup> cells
Cell viability	Flow cytometry	93.73%
CD34 <sup>+</sup> cell count	Flow cytometry	10.5×10 <sup>5</sup> cells
Hematopoietic colony forming cells assay	Pour plate method	CFU-GM: 2.42×10 <sup>5</sup> CFU BFU-E: 4.23×10 <sup>5</sup> CFU
Sterility method	Automated microbial detection system	No growth
Blood grouping	Agglutination test	A, Rh-positive

CFU=Colony-forming unit, GM=Granulocyte-monocyte, BFU-E=Burst-forming unit-erythroid, Rh=Rhesus

**Supplementary Table 2: Infectious disease testing results of maternal blood sample**

Test	Methodology	Results
HIV I and II	ELISA	Negative
HBs Ag		Nonreactive
Anti-HBc		Nonreactive
Anti-HCV		Nonreactive
Anti-HTLV I and II		Negative
CMV IgM		Negative
CMV IgG		Immune
Malarial parasite	Slide method	Not detected
Syphilis antibodies	Tube method	Nonreactive

HIV=Human immunodeficiency virus, HBs Ag=Hepatitis B surface antigen, Anti-HBc=Antibody to Hepatitis B core antigen, Anti-HCV=Antibody to hepatitis C virus, Anti-HTLV=Antibody to human T-cell lymphotropic virus, CMV=Cytomegalovirus, ELISA=Enzyme-linked immune sorbent assay, IgM=Immunoglobulin M, IgG=Immunoglobulin G