Umbilical Cord Blood Transplantation in Children with Beta-Thalassemia Diseases

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To evaluate factors affecting the outcome of sibling and unrelated donor umbilical cord blood transplantation (CBT) in Thai children with beta-thalassemia diseases. The case-series study of all children undergoing such transplants in our institute was conducted. Six children with thalassemia major were diagnosed at a median age of 1.5 years and CBT was performed at a median age of 5.5 years (range 2-15). Six donors consisted of three HLA-identical siblings, one two-allele, one three-antigen mismatched sibling, and one one-allele mismatched unrelated cord blood. The median number of nucleated cells infused was 2.83 x 10^7/kg (range 1.49-5.3); the median number of CD34+ cells infused was 1.94 x 10^5/kg (range 0.2-5.3). In all, two patients had complete donor engraftment; three had mixed chimerism (MC); one patient died of cerebral thrombosis and neutropenic septicemia. Of the two complete donor-engrafted patients, two developed grade 2 acute graft-versus-host disease (GVHD) which responded well to immunosuppressive therapy. Of the three mixed-chimeric patients, two were clinically cured. With a median follow-up of 7 months (range 2-30), five children survived and have done well with transfusion-independent. Umbilical cord blood provides a reasonable option for hematopoietic stem cell source to transplant for beta-thalassemia diseases and the outcome in the present study was good.

Keywords: *Cord blood transplantation, Unrelated donor, Thalassemia*

J Med Assoc Thai 2004; 87 (Suppl 2): S62-7
e-Journal: *http://www.medassocthai.org/journal*

Beta-thalassemia major is a highly prevalent inheritable hematologic disorder in Thailand. Hematopoietic stem cell transplantation is the only curative treatment of this disease. Most of the reports worldwide are of bone marrow transplantation [1]. Recently umbilical cord blood transplantation (CBT) has been performed in a variety of malignant and non-malignant diseases [2,3]. With the establishment of the National cord blood bank at the National Blood Centre of Thai Red Cross Society, CBT can be now more conveniently performed in Thai children. The authors report their experience of CBT in beta-thalassemia major.

Patients and Method

Pre-transplant characteristics

From February 2002 to July 2004, all beta-thalassemia patients; who received either sibling or unrelated CBT at the pediatric stem cell transplant unit, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; were included in the study. Six patients were recruited; all were diagnosed with beta-thalassemia/hemoglobin E diseases by hemoglobin electrophoresis. The median age at transplant was 5.5 years (range 2-15 years). Liver biopsies were performed in all cases. Of six patients, one belonged to class 1 (no hepatomegaly; no hepatic fibrosis; adequate iron chelation), two to class 2 (no hepatomegaly but had hepatic fibrosis), and three to class 3 (hepatomegaly; hepatic fibrosis; inadequate iron chelation) according to Pesaro classification [4]. None of the patients had undergone splenectomy.

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Donors and UCB Collection

Five cord blood (CB) donors were siblings of the patients; of these, three were HLA-identical, two were 2-allele and 3-antigen mismatched with the patients. Chorionic villi sampling (CVS) and molecular gene mutation had been performed in all five sibling-fetuses; one fetus was normal, while the other four were heterozygous carriers. One CB unit used was from an unrelated 1-allele HLA-A mismatched neonate; its CB was also tested to be heterozygous carrier. The parents

of CB donors signed informed consent before donation. The babies were born by either normal vaginal deliveries or cesarean section; CB was collected by aseptic technique thereafter. The detail on CB collection method was previously described by Wacharaprechanont et al [5]. CB was then cryopreserved and stored in a liquid nitrogen storage tank. Informed consent for CBT was also obtained from the parents of patients before transplant.

Conditioning Regimen and Graft-versus-Host Disease Prophylaxis

For thalassemia, conditioning was busulfan 16 mg/kg total given orally divided 4 times per day for 4 days in four cases; and 20 mg/kg in two of Pesaro class 3 cases; and cyclophosphamide 50 mg/kg per day given intravenously for 4 days. For unrelated CBT, intravenous fludarabine 200 mg/m^2 divided over 5 days was added. Anti-thymocyte globulin (ATG) was given routinely to all patients for prevention of graft rejection. Graft-versus-host disease **(**GVHD) prophylaxis regimen was intravenous cyclosporin 3 mg/kg per day from day -1 and methylprednisolone 2 mg/kg per day beginning from day -5 in two patients; only cyclosporin in four patients. Methylprednisolone was tapered by 0.2 mg/kg per week from day 19 or the first day when the absolute neutrophil count (ANC) exceeded 0.5 x 10^9/L and discontinue by day 100 if there is no GVHD. Cyclosporin was administered orally when the patients could tolerate oral feeding. It was gradually tapered starting on day 50 and discontinued by day 180 if there was no GVHD.

The patients were nursed in isolated laminar airflow rooms and given a low-microbial diet. Sulfamethoxazole-trimethoprim was administered from day -10 to day -2. Oral fluconazole was given as antifungal prophylaxis. Empiric antibiotics for bacterial or fungal infection were started as clinically indicated. Granulocyte colony-stimulating factor (G-CSF) at 5 microgram/kg/day given intravenously was started from 4 hours after cord blood infusion and continued once daily until the day when the ANC exceeded 2.0 x 10^9/L for 2 consecutive days. Heparin 100 units/kg/day, in a continuous intravenous infusion, was given as hepatic veno-occlusive disease (VOD) prophylaxis in the first 3 patients. All cellular blood products were filtered and also irradiated to 2,500 cGy.

Outcome parameters included treatment-related complications-namely VOD [6], GVHD [7,8], transplant-related mortality, overall survival (OS), and event-free survival (EFS). Events were defined as death or graft rejection. All continuous variables were expressed as median and range.

Results

The median number of nucleated cells infused was 2.83 x 10^7/kg (range 1.49-5.3); the median number of CD34+ cells infused was 1.94 x 10^5/kg (range 0.2-5.3). The stem cell values for individual patients are shown in Table 1. There were no adverse reactions during stem cell infusion. Febrile neutropenia was common in the early post-transplant period but no patients really had positive blood culture for bacteria. Four patients developed hepatic VOD (tender hepatomegaly, fluid retention, weight gain, and elevated serum bilirubin) that was supportively treated and subsequently resolved. One patient (No.3) who is the oldest in this series and of Pesaro class 3, died of cerebral thrombosis and non-engrafted septicemia on day 22 post-transplant. In the remaining 5 patients, the ANC of > 0.5 x 10^9/L was achieved on day 22 (median; range 17-27). The platelet count of > 20 x 10^9/L was achieved on day 46 (median; range 39-73). The outcome of CBT is shown in Table 2.

The engraftment studies for the 5 surviving patients were done by chimerism analysis via microsatellite technique and, if there were sex-mismatches, by karyotyping for X- and Y-chromosomes. Complete

Table 1. Patient and cord blood characteristics

No.	Sex	Age at Transplant	Weight (kg)	Pesaro Class	HLA Matching	Donor	Nucleated cells (x 10^7/kg)	CD34+ cells (x 10^5/kg)
1	M	3y 6m	16	2	6/6	sibling	2.75	0.28
2	M	7y 6m	21	3	3/6	sibling	4.95	2.38
3	M	15y	30	3	4/6	sibling	5.3	1.5
4	F	5y 9m	19.6	3	6/6	sibling	1.49	0.2
5	M	2y 1m	13	1	6/6	sibling	2.9	5.3
6	M	7y 7m	22.6	2	5/6	unrelated	2.15	3.0

y =years, m = months

Table 2. Outcome of umbilical cord blood transplantation

No.	Day ANC $>0.5x10^9/L$	Day Platelet $>20x10^9/L$	VOD	Acute GVHD grade	Engraft-ment	Latest Status
1	22	46	yes	0	MC	EFS 30m
2	27	73	no	0	MC	improved anemia, alive 24m
3	not achieved	not achieved	yes	-	No	died of sepsis 22d
4	23	48	yes	2	CC	EFS 7m
5	17	45	yes	0	MC	EFS 6m
6	19	39	no	2	CC	EFS 2m

m = months, d = days, ANC = absolute neutrophil count, GVHD = graft-versus-host disease, VOD = veno-occlusive disease, CC = complete donor chimerism, MC = mixed chimerism, EFS = event-free survival

donor chimerism occurred in two patients (No.4, 6). They achieved normal hemoglobin level, no longer required blood transfusion and were documented for cure. Of the three patients with mixed chimerism (MC); two (No.1, 5) achieved normal hemoglobin level and their enlarged livers and spleens became smaller towards normal size; one (No.2) remained anemic with hepatosplenomegaly but improved average base-line hemoglobin level from 6 to 8.5 g/dL. He has done fairly well and is no longer transfusion-dependent. Patient no.5 could be assessed for the proportion of donor (XX): recipient (XY) cells to be 40:60 approximately because he was sex-mismatched with a sister-donor. Meanwhile, patient no.1, 2 could be checked only by qualitative microsatellite technique because they and donors had similar gender so the exact proportion of cells could not be counted. The MC status persisted up to report time. There was no relation between the various degrees of MC and base-line hemoglobin level post-transplant.

Of the five patients with engraftment, two (No.4, 6) developed generalized erythroderma and slightly increased bilirubin that was assessed as grade 2 acute GVHD by Seattle criteria [7]. These occurred in a case of matched-sibling and a case of one-allele mismatched unrelated CBT. They responded to methylprednisolone dose up to 2-4 mg/kg/day and increment of cyclosporin dosage. No patients developed secondary graft rejection; no one developed chronic GVHD to date. No patients developed cardiac disease or irreversible hepatic impairment after transplant. The median follow-up time was 7 months (range 2-30 months). The OS and EFS of all six patients were the 83.3% and 66.7%, respectively.

Discussion

Since the first report of successful allogeneic bone marrow transplantation for thalassemia major in 1982[9], there have been more than 1,800 transplants reported in the literature [10-19]. Lucarelli et al reported long-term event-free survival rates of 85%, 80%, and 53% for class 1, 2, and 3 patients, respectively [4]. Hematopoietic stem cell or bone marrow transplantation is now recommended by most centers as the treatment of choice for young patients if a compatible sibling donor is available. If not, the effort to find a suitable HLA-compatible unrelated donor must be made. The first successful unrelated donor bone marrow transplantation for thalassemia was reported in 1994 [20].

Umbilical cord blood has been utilized as an alternative source of hematopoietic stem cell for transplantation worldwide to treat many fatal diseases. CBT for thalassemia from an HLA-identical sibling was first reported in 1995 [21]. Since then, there have been up to 50 children with thalassemia major, reported to have undergone CBT [22-27]. In Thailand there was a previous report by Suvatte et al [23] regarding the result of bone marrow, peripheral blood, and cord blood transplantation from related donors. They demonstrated the outcome in 29 thalassemic children revealing 23 (79.4%) were cured, whereas three (10.3%) remained alive with disease and the other three (10.3%) died.

When an HLA-identical sibling is not available, unrelated donor search and selection is now realistic option. With increasing settlement of standard cord blood banks worldwide as well as in Thailand, the opportunity to use unrelated cord blood is rising. The present report is the first published on successful unrelated cord blood transplantation for thalassemic patients in Thailand, using the cord blood unit from the National cord blood bank.

Umbilical cord blood with sufficient stem cell dose has a potential to engraft despite one- or two-antigen disparity, and to develop less incidence and severity of GVHD. The authors believe, in unrelated CBT setting, minimal requirement of CD34+ cell dose should be not less than 1.5×10^5/kg for successful result [28].

Patient status prior to transplant is a very essential issue to be considered. Pesaro class 3 patients have a high risk of treatment-related mortality such as neutropenic septicemia, multiple vital organ failure, and hypercoagulable states. The new appropriate conditioning regimen for these high-risk patients should be considered for safer and better outcome. The authors recommend that class 3 patients younger

than 17 years old are eligible for bone marrow transplantation using the new protocol [29], but for CBT they need to have sufficient cord blood stem cell dose per kilogram body weight.

In the present study, all three mixed-chimera cases have done very to relatively well post-transplant; they have never developed GVHD. These mixed chimera states are probably due to the HLA disparity (one haploidentical CBT), the inadequacy of conditioning regimen, and also the intrinsic hyper-function residual marrow in the host of thalassemia major. MC in not unusual in transplanted thalassemic patients. Furthermore, MC may be transient when it evolves into complete chimerism or graft rejection, or persistent when the coexistence of donor and recipient cells is longer than 2 years, with hemoglobin levels sufficient for living without red blood cell transfusion [30,31].

Locatelli et al reviewed the Eurocord experience of CBT for thalassemia [22]. There was a relatively high rate of graft rejection, with 7 of 33 patients not having sustained donor engraftment. In the present series, all three patients who received HLA-identical CB successfully engrafted, as well as one patient who got one-allele mismatched unrelated CB. There has been no secondary graft failure to the report time. In a recent multicenter study, the addition of thiotepa or fludarabine appeared to achieve a higher engraftment rate [22]. The authors used fludarabine adding on conventional preparative regimen for CBT in unrelated setting for thalassemia. Fludarabine has a potent lympholytic effect but with relatively little toxicity to non-hematologic organs.

Veno-occlusive disease (VOD) of the liver is an important cause of transplant-related mortality in thalassemia major post-transplant. With the conditioning regimen based on usual dose of busulfan (total 16 mg/kg), the authors did not encounter any mortality from VOD. After reviewing Reiss et al [32] report of ineffectiveness of VOD prevention, the authors omitted routine heparin infusion as VOD prophylaxis after the first 3 cases. The authors found four patients who transiently suffered from VOD whether they had received heparin for prevention or not.

The CD34+ count has recently been suggested to be a more important factor for engraftment in CBT, with a higher probability of survival when the CB contains more than 1.5 x 10^5/kg, even with one or two mismatched antigens [28]. In the present series, however, two matched-sibling transplanted patients receiving CD34+ cell count as low as 0.2 x 10^5/kg still had satisfactory engraftment with good long-term results even though the initial neutrophil recoveries were quite delayed (day 22 and 23). The authors suggest thalassemia patients may require a higher number of stem cell doses to guarantee sustained donor engraftment and enhance rate of neutrophil and platelet recoveries. Early transplant is preferable for thalassemia major patients if possible, because their size and weight are not too much to keep stem cell doses per kilogram high, in particular for CBT; as well as younger patients have a lower risk of multiple vital organ dysfunction from chronic anemia or iron overload. Ex-vivo expansion of CB stem cells is another approach of increasing the cell dose, but this remains in the early stage of development.

The cost of CBT in the present series was appro-ximately 400,000 - 800,000 baht (40 baht = 1 US$) per recipient-donor pair. It varied upon the recipients' weight and complication. The more weight the patient had, the more expense it cost.

Conclusion

Either related sibling or unrelated umbilical cord blood transplantation could be performed and achieved the successful outcomes for many patients of beta-thalassemia major, as demonstrated. Umbilical cord blood provides an option for hematopoietic stem cell source beside bone marrow to transplant for these genetic diseases. Even one or two mismatched CBT can achieve satisfactory results in children. National cord blood bank of Thailand [5] can provide good-quality unrelated cord blood to be transplanted in Thai children with success.

Acknowledgements

The authors wish to thank Nattiya Hirankarn MD PhD, Department of Microbiology for evaluating the chimerism analysis, and Verayuth Praphanphoj MD, Rajanukul Institute for assessing fluorescent in-situ hybridization (FISH) of X- and Y-chromosomes in sex-mismatched cases.

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การปลูกถ่ายเลือดจากสายสะดือรักษาโรคเบต้าธาลัสซีเมีย

ปรีดา วาณิชยเศรษฐกุล, ธีระ วัชรปรีชานนท์, รัชนี โอเจริญ, ปัญญา เสกสรรค์, ภาวิณี คุปตวินทุ

เพื่อประเมินปัจจัยที่มีผลต่อการรักษาด้วยการปลูกถ่ายเลือดจากสายสะดือจากน้องของผู้ป่วยหรือจากทารกผู้บริจาคในเด็กไทยที่ป่วยด้วยโรคเบต้าธาลัสซีเมีย จึงทำการศึกษาข้อมูลของผู้ป่วยเด็กที่ได้รับการปลูกถ่ายเลือดจากสายสะดือในโรงพยาบาลจุฬาลงกรณ์ พบว่าเป็นผู้ป่วยเด็กโรคเบต้าธาลัสซีเมียฮีโมโกลบินอี 6 ราย ได้รับการวินิจฉัยเมื่ออายุเฉลี่ย 1.5 ปี และได้รับการปลูกถ่ายเลือดจากสายสะดือเมื่ออายุเฉลี่ย 5.5 ปี (พิสัย 2-15) โดยแหล่งที่มาของเลือดจากสายสะดือประกอบด้วย จากทารกที่เป็นน้องที่มี HLA ตรงกัน 3 ราย น้องที่มี HLA ต่างกัน 2 ตำแหน่ง 1 ราย น้องที่มี HLA ต่างกัน 3 ตำแหน่ง 1 ราย และจากทารกผู้บริจาคที่มี HLA ต่างกัน 1 ตำแหน่ง 1 ราย ค่าเฉลี่ยของจำนวน nucleated cells ที่ให้ผู้ป่วยเท่ากับ 2.83 x 10^7 ต่อกิโลกรัม (พิสัย 1.49-5.3) ค่าเฉลี่ยของจำนวน CD34+cells ที่ให้กับผู้ป่วยเท่ากับ 1.94 x 10^5 ต่อกิโลกรัม (พิสัย 0.2-5.3) ผลการปลูกถ่ายพบว่า ผู้ป่วย 2 ราย มีการปลูกติดเซลล์ของผู้บริจาคอย่างสมบูรณ์ ผู้ป่วย 3 รายมีการปลูกติดเซลล์ของผู้บริจาคปะปนกับเซลล์เดิมของผู้ป่วย ผู้ป่วย 1 ราย เสียชีวิตเนื่องจากเส้นเลือดในสมองอุดตันและติดเชื้อรุนแรงขณะเม็ดเลือดขาวนิวโตรฟิลต่ำ ในกลุ่มผู้ป่วยที่ปลูกถ่ายติดอย่างสมบูรณ์ ผู้ป่วยทั้ง 2 รายเกิดภาวะแทรกซ้อนเป็น GVHD แบบเฉียบพลันเกรด 2 ซึ่งรักษาได้ผลต่อยากดภูมิต้านทาน ในกลุ่มผู้ป่วยที่ปลูกถ่ายติดไม่สมบูรณ์ ผู้ป่วย 2 รายหายขาดจากอาการโลหิตจาง จากการติดตามผู้ป่วยเป็นระยะเวลาเฉลี่ย 7 เดือน (พิสัย 2-30) พบว่าผู้ป่วย 5 รายมีชีวิตรอด โดยปราศจากอาการป่วย สบายดี และไม่จำเป็นต้องได้รับเลือดทดแทนอีก เลือดจากสายสะดือเป็นทางเลือกที่สำคัญของแหล่งของเซลล์ต้นกำเนิดเม็ดโลหิตเพื่อการปลูกถ่ายรักษาโรคเบต้าธาลัสซีเมีย และพบว่าผลการรักษาได้ผลดี