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Unrelated umbilical cord blood transplantation in children: experience of the Hong Kong Red Cross Blood Transfusion Service

給兒童進行無血緣關係臍血移植：香港紅十字會輸血服務中心處理的病例

Key words:

Child;
Cord blood stem cell transplantation;
Graft vs host disease;
Leukemia

關鍵詞：

兒童；
臍血幹細胞移植；
移植抗宿主病；
白血病

Hong Kong Med J 2004;10:89-95

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Objective. To review the outcome of unrelated umbilical cord blood transplantation in children using cord blood from the Hong Kong Red Cross Blood Transfusion Service.

Design. Retrospective study.

Patients. Records of eight patients who received unrelated umbilical cord blood transplants between 1999 and 2003 were reviewed.

Main outcome measures. Engraftment of haematopoietic cells and graft-versus-host disease after transplantation.

Results. The median age of the patients was 4.9 years (range, 1.0-9.4 years). Five patients had acute leukaemia, one had non-Hodgkin's lymphoma, one had X-linked adrenoleukodystrophy, and one had mucopolysaccharidosis. The infused umbilical cord blood units contained a median of 6.7×10^7 /kg nucleated cells and 4.0×10^5 /kg CD34-positive cells. Neutrophil engraftment was achieved at a median of 13 days (range, 11-19 days) and, for seven patients, platelet engraftment was achieved at a median of 39 days (range, 24-98 days). Acute graft-versus-host disease occurred in all patients (grades I to III). One of the patients died because of encephalitis; of the other seven, five developed chronic graft-versus-host disease of the skin. At a median follow-up of 2 years, the four patients with leukaemia and the one with non-Hodgkin's lymphoma remained in continuous complete remission; the patient with adrenoleukodystrophy showed stabilisation of neurological condition.

Conclusion. The Hong Kong Red Cross Blood Transfusion Service Cord Blood Bank stored cord blood units of good quality for transplantation, the outcome of which was comparable to that of bone marrow transplantation.

目的：檢討使用紅十字會輸血服務中心提供的臍帶血給兒童進行無血緣關係臍血移植的成效。

設計：回顧研究。

患者：審視在 1999 年至 2003 年間，8 位患者接受無血緣關係臍血移植的病歷。

主要結果測量：造血細胞植活以及移植後出現的移植抗宿主病。

結果：8 位接受臍血移植的患者，年齡中位數為 4.9 歲 (分佈域為 1.0-9.4 歲)，其中有 5 位患急性白血病，餘下 3 位所患病症分別為非霍奇金淋巴瘤組織瘤、與 X 染色體有關的腎上腺白質營養不良，以及黏脂病。患者所輸入的臍血含有核細胞的中位數為 6.7×10^7 /kg、CD⁺₃₄ 的細胞中位數為 4.0×10^5 /kg。中性粒細胞順利植入所需時間的中位數為 13 天 (分佈域為 11-19 天)，此外，有 7 位患者的血小板順利植入所需時間的中位數為 39 天 (分佈域為 24-98 天)。所有患者都出現移植抗宿主病的急性病症，嚴重程度從第 I 級至第 III 級不等。1 位患上腦炎而死亡，其餘 7 位中，有 5 位患上皮膚的慢性移植抗宿主病。其後中位數為兩年的隨訪期內，非霍奇金淋巴瘤組織瘤患者和 4 位急性白血病患者，症狀完全得到緩解，而患有腎上腺白質營養不良的病者，神經病學的情況則保持穩定。

結論：香港紅十字會輸血服務中心臍血庫儲存優質臍血供血液移植之用，效果媲美骨髓移植。

Introduction

Bone marrow transplantation (BMT) is a well-established treatment modality for children with relapsed cases of leukaemia or fatal metabolic diseases.¹ In communities with small family sizes, however, it is difficult to find a sibling who is identically matched for human leukocyte antigen (HLA). An unrelated bone marrow donor is an alternative source of stem cells for BMT. There are many national registries of unrelated bone marrow donor worldwide, including in Hong Kong.² However, unrelated BMT is associated with high morbidity and mortality because of the much higher incidence of severe graft-versus-host disease (GVHD), compared with when the donor is a relative.³ The first umbilical cord blood (UCB) transplantation was performed in 1989 for a child with Fanconi's anaemia.⁴ Since then, UCB transplantation involving a sibling donor (eg a newborn sibling) has become an accepted mode of transplantation for children. When a newborn sibling who is HLA-compatible with the patient is not available, use of a cord blood bank is an alternative option, because cord blood donated from the public can be stored for use in an unrelated-UCB transplantation. Several large public cord blood banks have been set up in Europe and the United States.^{5,6} The Hong Kong Red Cross Blood Transfusion Service (HKRCBTS) set up its public cord blood bank in 1998, and between 1999 and 2003, eight units of cord blood were supplied to a single institution for unrelated-UCB transplantation. This report describes the clinical course and outcome of the eight children who received the transplants.

Patients and methods

The HKRCBTS established the unrelated-UCB bank in 1998. Pregnant women attending antenatal care clinics at two public hospitals (the Kwong Wah Hospital and the Tsan Yuk Hospital) were invited to donate cord blood after delivery. The cord blood was collected by gravity via a closed system into a collection bag containing anticoagulant while the placenta was still in utero or ex utero. The cord blood was tested for the nucleated cell count, number of CD34-bearing cells (CD34 is a marker on early progenitor cells), blood group, sterility, and infectious disease markers (hepatitis B surface antigen and antibodies to hepatitis C, human immunodeficiency viruses 1 and 2, cytomegalovirus, and syphilis). For each cord blood unit, HLA typing for A and B antigens was also conducted. The units were stored for 24 hours at -80°C in a freezer, then transferred to a programmable freezer set at -140°C, and then to the vapour phase of a liquid nitrogen tank. After the absence of infectious disease markers had been confirmed, the units were placed in the liquid phase at -196°C for long-term storage. When a request for a unit of UCB was received, a computer search was initiated to identify any units that closely matched the HLA status of potential recipients. Then, HLA-DR typing and confirmation by DNA-based methods were performed

on the identified units. The transplantation team decided the acceptability of the unit on the basis of the HLA typing results and the cell number per kilogram of body weight of the recipient. The approved cord blood unit was then transferred to the transplantation centre in a dry-shipping container pre-chilled with liquid nitrogen. The transplantation team inspected the integrity of the cord blood unit before storing it in the liquid nitrogen tank at the transplantation centre and starting the chemoradiotherapy preparative regimen.

From November 1999 to October 2003, a total of 9 units were delivered to two hospitals for transplantation of paediatric patients who had no HLA-compatible family donors and for whom matched unrelated bone marrow donors could not be found. Eight unrelated-UCB units were sent to the Prince of Wales Hospital and one unit was sent to another hospital for transplantation. Unrelated-UCB transplantation was performed after written informed consent; the procedure was approved by Ethics Committee of The Chinese University of Hong Kong.

On the day of the transplantation, the frozen unit was put into a sterile plastic bag and immersed in a 37°C water bath, agitated continuously, and gently massaged to break up ice clumps during thawing. The thawed UCB unit was diluted with half its volume each of 5% (w/v) human albumin (HKRCBTS) that had been precooled to 4°C and dextran 40 (B. Braun, Irvine, US) with continuous mixing for 5 minutes. After the mixture was centrifuged at 400 g for 10 minutes, the supernatant was removed and the sedimented cells were resuspended in the albumin and dextran solution. This washing procedure was repeated. Cells were finally resuspended in a fresh solution of albumin and dextran to a volume appropriate for infusion into the patient. Flow cytometry of CD34-bearing cells and clonogenic assay of colony forming units were performed as previously described.⁷

The details of all patients' characteristics are shown in Table 1. Patient 1 was an 8-year-old boy with X-linked adrenoleukodystrophy, which had been diagnosed when he was aged 7 years after his parents had noticed a deterioration in handwriting and poor school performance. Neuropsychological assessment showed impaired eye-hand coordination. Biochemical tests showed a markedly increased level of very-long-chain fatty acids (C24/C22 and C26/C22 ratios), which is diagnostic of X-linked adrenoleukodystrophy. Magnetic resonance imaging (MRI) of the brain showed typical demyelination changes involving predominantly the occipital lobes. The patient received an unrelated-UCB transplant before he developed rapid neurological deterioration. Most adrenoleukodystrophy patients develop motor and intellectual deterioration within 1 to 2 years after diagnosis and become bed-ridden and succumb soon.

Patient 6 was born to a Pakistani couple after consan-

Table 1. Patient characteristics

Patient No.	Sex	Age of transplant	Diagnosis	Age of diagnosis	Pretransplantation status
1	M	8 years	X-linked adrenoleukodystrophy	7 years	Demyelination of white matter, impaired eye-hand coordination
2	M	9.4 years	ALL*, B-lineage of common ALL subtype, cytogenetically normal	20 months	1st bone marrow relapse at 5 years, 2nd bone marrow relapse at 8.5 years, 3rd bone marrow relapse at 9 years, transplantation at 4th remission
3	F	30 months	AML†, FAB‡ M5a, t(9;11)(p22;q23)	12 months	1st bone marrow relapse at 27 months, transplantation at 2nd remission
4	M	12 months	ALL, early pre-B subtype, 46XY, del(11)(q23)	6 months	Hyperleukocytosis (white blood cells, 1326×10^9 /L) at presentation with poor steroid response, transplantation at 1st remission
5	F	8.2 years	ALL, B-lineage of common ALL subtype, complex cytogenetic abnormalities	5.5 years	1st bone marrow relapse at 8 years, transplantation at 2nd remission
6	F	12 months	Mucopolipidosis II (I-cell disease)	1 month	Failure to thrive, multiple dysmorphic features, developmental delay
7	M	22 months	AML, 46XY, inv(16)(p13q22)	8 months	1st bone marrow relapse at 19 months, transplantation at 2nd remission
8	M	7 years	T-cell lymphoblastic lymphoma stage IV, 46XY, t(9)(q10)	3.5 years	1st relapse at 6.5 years, 2nd relapse at 7 years, transplantation in partial remission

* ALL acute lymphoblastic leukaemia

† AML acute myeloid leukaemia

‡ FAB French-American-British

guineous marriage. She was noticed to have a dislocated hip and dysmorphic features at the age of 1 month. Her plasma enzyme levels (arylsulphatase A, α -mannosidase, β -galactosidase) were markedly increased, and intracellular enzyme levels in white blood cells were slightly lower than normal. These signs were consistent with mucopolipidosis type II (I-cell disease), which is the diagnosis that her cousin had received 2 years previously. The patient received the unrelated-UCB transplant at the age of 1 year.

The other six patients had haematological malignancies: three had acute lymphoblastic leukaemia, two had acute myeloid leukaemia, and one had T-cell lymphoblastic non-Hodgkin's lymphoma. These patients had one or more relapses before transplantation, except patient 4, who nevertheless had a very high risk of treatment failure and relapse: a very young age at diagnosis (6 months), a white blood cell count of 1326×10^9 /L at presentation, cytogenetic findings of a chromosome 11 deletion—namely, del(11)(q23)—and poor response to initial steroid treatment. Bone marrow transplantation during the first complete remission was thus indicated for patient 4.

The cord blood characteristics and HLA typing are shown in Table 2. Patients 1, 5, and 8 had lymphoid malignancies and were prepared for transplantation with total-body irradiation and cyclophosphamide treatment. Patient 4 was only 1 year old at the time of transplantation and was prepared with chemotherapy using busulphan, etoposide, cyclophosphamide, and antithymocyte globulin. The two patients with acute myeloid leukaemia and the two patients with metabolic disease received busulphan, cyclophosphamide, and antithymocyte globulin. Prophylaxis for GVHD was intravenous cyclosporin ($3 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ from day -1) and intravenous methylprednisolone ($1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$

from day 7). A course of granulocyte colony-stimulating factor at $5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ was started from day 7 after transplantation. Each patient's post-transplantation course was monitored for early complications, such as cytomegalovirus infection, acute GVHD, and graft rejection, as well as for late complications, such as chronic GVHD, late infection, and relapse. Haematopoietic cells were tested for donor or recipient origin (chimerism study) by fluorescent in-situ hybridisation analysis if the donor and recipient were sex-mismatched, or by DNA variable number tandem repeat analysis if they were sex-matched. Chimerism studies were performed at 1 month and then every 3 months for the following 2 years.

Results

Seven patients received HLA-mismatched UCB units with a disparity in two to three antigens, and one patient received an HLA-matched UCB unit. On the day of the transplantation, the UCB units were thawed and washed according to method described by Rubinstein et al.⁸ There was no adverse reaction to transplantation. All eight patients achieved neutrophil engraftment at a median of 13 days (range, 11-19 days) after transplantation, which was defined as a neutrophil count of more than 0.5×10^9 /L for 3 consecutive days. The neutrophil count increased to beyond 1.0×10^9 /L at 11 to 35 days. Platelet engraftment was defined as a platelet count of more than 20×10^9 /L, and was achieved in seven patients at a median of 39 days (range, 24-98 days). One patient was dependent on platelet transfusions until the day of death.

Acute GVHD occurred in all eight patients. Patients 1 and 8 developed grade-I skin GVHD, whereas patients 2, 4, 6, and 7 developed grade-II skin GVHD. Patient 3 devel-

Table 2. Cord blood characteristics

Patient No.	Duration of storage (months)	Donor's sex	Recipient's weight (kg)	Volume (mL)	Blood group (donor/recipient)
1	13	M	24	75	B/B
2	28	F	29.8	80	O/O
3	31	F	12.3	130	A/B
4	5	F	10	70	A/O
5	12	F	25	119	O/B
6	44	M	5.6	84	O/O
7	21	M	14.4	58	A/A
8	30	M	24	55	A/O

* Antigen mismatches are underlined

† GM-CSU granulocyte-macrophage colony-stimulating unit

Table 3. Outcome of cord blood transplantations

Patient No.	Day neutrophil $>0.5 \times 10^9/L$	Day platelet $>20 \times 10^9/L$	Acute GVHD* (onset time)	Chronic GVHD
1	13	39	Grade I: skin (day 43)	Limited skin, off GVHD treatment
2	18	98	Grade II: skin (day 7)	Extensive skin, off GVHD treatment
3	12	24	Grade III: skin, liver (day 6)	Extensive skin, given mycophenolate
4	14	41	Grade II: skin (day 10)	Extensive skin, given prednisolone and cyclosporin
5	19	Not achieved before death	Grade II: skin, liver, gut (day 8)	Not applicable
6	11	47	Grade II: skin (day 22)	Extensive skin, given prednisolone and cyclosporin
7	12	38	Grade II: skin (day 8)	Too early to evaluate
8	13	31	Grade I: skin (day 9)	Too early to evaluate

* GVHD graft-versus-host disease

† VLCFA very-long-chain fatty acid

oped grade-III GVHD involving the skin and liver, and patient 5 developed grade-II GVHD of the skin, liver, and gut. After treatment with methylprednisolone, seven patients showed a good response. However, one patient (patient 5) had refractory GVHD and was given anti-lymphocyte globulin and mycophenolate. For assessment of chronic GVHD at 3 months, two patients were just 2 months from transplantation and hence not evaluable for chronic GVHD, another patient died at day 60 because of encephalitis. Thus the other five patients surviving more than 3 months were evaluable for chronic GVHD and all later developed chronic GVHD. Patient 1 also developed lymphoproliferative disease in the tonsils at day 90 after UCB transplantation. This diagnosis was confirmed by excision biopsy, and the disease subsided after cyclosporin treatment was gradually discontinued. Chronic GVHD was limited to the skin in all patients and was controlled by combined treatment with prednisolone and cyclosporin. Two patients (patient 2, 3) were also given mycophenolate for the chronic GVHD.

Severe infection occurred in three patients. Patients 2 and 5 developed human herpesvirus 6 encephalitis at 17 and 20 days, respectively, after UCB transplantation. For treatment, they were given high-dose ganciclovir. Patient 2 responded to treatment and recovered, whereas patient 5 did not respond and her condition deteriorated despite the addition of foscarnet to her treatment. She subsequently died at day 60 because of multi-organ failure. Patient 6 developed coagulase-negative staphylococcus septicaemia on day 8, which was treated successfully with antibiotics.

All eight patients showed production of blood cells of complete donor-cell origin and did not have early- or late-stage graft rejection. The patients with leukaemia underwent repeated bone marrow tests including cytogenetic tests, which showed that remission had persisted. Patient 1, however, showed initial neurological deterioration that affected her vision in the first 6 months after transplantation. The patient's visual acuity worsened rapidly and he required placement in a school for blind

Human leukocyte antigen typing (recipient/donor)*	Nucleated cells (x10 ⁷ /kg)	CD34-positive cells (x 10 ⁵ /kg)	GM-CSU [†] (x 10 ⁴ /kg)
A 2, <u>31</u> / A 2, <u>2</u> B 60 / B 60 DR 12, <u>12</u> / DRB1 <u>0901</u> , 12	2.46	2.8	4.38
A 2, <u>2</u> / A 2, <u>2</u> B 13, <u>6701</u> / B 13, <u>60</u> DRB1 12, <u>14</u> / DRB1 12, <u>16</u>	2.6	0.72	4.58
A 1101, 33 / A 1101, 33 B 5801, <u>39</u> / B <u>5201</u> , 5801 DRB1 03, <u>04</u> / DRB1 03, <u>1410</u>	11.2	10.3	18.0
A <u>23</u> , 33 / A <u>24</u> , 33 B 5801, <u>39</u> / B 5801, <u>51</u> DRB1 <u>15</u> , 13 / DRB1 <u>08</u> , 13	16.4	27.4	3.37
A 02, 1101 / A 02, 1101 B 4001, <u>5603</u> / B <u>1502</u> , 4001 DRB1 12, <u>0901</u> / DRB1 12, <u>15</u>	7.37	2.2	5.47
A 24, <u>33</u> / A 24, <u>1101</u> B 35, <u>44</u> / B 35, <u>5801</u> DRB1 <u>07</u> , 14 / DRB1 <u>03</u> , 14	24.7	5.73	31.2
A 02, <u>33</u> / A 02, <u>1101</u> B 13, 4001 / B 13, 4001 DRB1 15, <u>12</u> / DRB1 15, <u>16</u>	6.04	3.97	6.75
A 02, 33 / A 02, 33 B 5801, 4601 / B 5801, 4601 DRB1 0301, 0901 / DRB1 0301, 0901	4.58	4.02	2.1

Complications (onset time)	Donor cell engraftment	Outcome
Acinetobacter septicaemia (day 91), Epstein-Barr-virus associated lymphoproliferative disease in tonsils (day 90)	100%	Visual deterioration in 1st 6 months, then static neurological status for 4 years, decreasing VLCFA [†] ratio
Human herpesvirus 6 encephalitis (day 17)	100%	Leukaemia in remission for 4 years
None	100%	Leukaemia in remission for 3 years
None	100%	Leukaemia in remission for 2 years
Human herpesvirus 6 encephalitis (day 20)	100%	Died of encephalitis on day 60
Coagulase-negative staphylococcus septicaemia (day 8)	100%	1 year after transplantation and too early to assess outcome
None	100%	2 months' post-transplantation in complete remission
None	100%	2 months' post-transplantation in complete remission

students. He was tested serially for neuropsychological function. There was no deterioration of intelligence and performance quotients, except for those to do with vision. His motor function remained normal and he could walk independently for up to 4 years after transplantation. The level of very-long-chain fatty acids showed gradual improvement and approached normal values, with the C26-to-C22 ratio decreasing from a pretransplantation level of 0.087 to 0.030 at the most recent follow-up visit (normal ratio, <0.022). The serial MRI scans of the brain showed static demyelination changes without progression. Patient 6 was tested for plasma enzyme levels, which were still elevated; hence, longer follow-up was deemed necessary. The post-transplantation outcomes of the eight patients are summarised in Table 3.

Discussion

The unrelated bone marrow donor registries in different parts of the world together have a donor pool of more than 8

million.⁹ However, some patients still cannot find an HLA-compatible bone marrow donor. The process of identifying a good, matched, unrelated marrow donor may take many months or years. Some patients may run a rapid downhill course and die before a donor is available. Since 1989, many sibling UCB transplants have been performed for different diseases, mainly leukaemia.^{10,11} The advantages of having a cord blood bank are the immediate availability of suitable units for transplantation, and the fact that HLA typing and infectious disease markers have already been tested at time of collection. Another advantage of UCB is the less stringent criteria for HLA typing. Because the UCB stem cells are immunologically naïve, the risk of severe GVHD is much lower.¹²⁻¹⁴ The likelihood of grade II-to-IV acute GVHD after unrelated-UCB transplantation is about 35%, whereas the likelihood after unrelated-donor BMT is about 60%. In our series, seven patients were mismatched with the donors by two to three HLAs; only one patient was HLA-matched with the donor. Grade-II acute GVHD was confined to the skin in four patients, whereas GVHD involved the skin,

liver, and gut in two. The GVHD was, however, quite easily controlled with steroid treatment. The incidence of chronic GVHD after unrelated-UCB transplantation was also lower compared with that of unrelated-donor BMT—20% versus 45%. Even when as many as two to three antigens are mismatched, the GVHD is still manageable in most cases. In our series, the five patients who survived more than 3 months developed chronic GVHD; however, disease was limited to the skin, did not involve any other organs, and was readily managed with immunosuppressive treatment. Unrelated bone marrow donor transplants require very strict HLA compatibility with the recipient, because severe GVHD is one of the major causes of transplantation-related mortality. Finding a suitable donor unit is more likely in cord blood transplantations than in unrelated bone marrow donor transplantations because the HLA matching is less stringent. In Hong Kong, the HKRCBT cord blood bank has stored only about 1200 units and has already provided 9 units for transplantation in 4 years.

Umbilical cord blood transplantation also has some limitations. The number of stem cells collected is finite and also quite variable. The success of UCB transplantation depends on two main factors: the cell dose and the HLA disparity.^{13,14} Earlier published reports have shown that nucleated cell counts of more than 3.7×10^7 /kg are associated with an increased incidence of neutrophil and platelet engraftment. More recently, CD34-positive cells of more than 1.7×10^5 /kg have been associated with a high probability of survival when there is a two-antigen mismatch.¹⁴ Umbilical cord blood transplantation is associated with a high incidence of deaths from infection due to prolonged neutropenia, and the early treatment-related mortality was reported to be up to 30%.^{15,16} Selection of units with a higher cell dose can achieve neutrophil recovery at an increased pace. In our series, the median number of CD34-positive cells was 4.0×10^5 /kg, and only one patient received less than 1.7×10^5 /kg. The neutrophil engraftment was rapid, taking a median of 13 days. This engraftment period is much shorter than that found in most of the published reports: 23 to 32 days. Platelet engraftment in our series of patients was also rapid, taking a median of 39 days. The reported platelet engraftment period is usually 80 days.^{15,16} In our study, human herpesvirus 6 encephalitis developed in two patients, one of whom died. Whether this type of infection is more prevalent during UCB transplantations needs further study.

The case number of our series is small. However, the three leukaemia patients surviving the first 3 months have remained in complete remission for 2 years or more. The likelihood of experiencing a relapse after 2 years is rather low. The relapse rate after UCB transplantation was reported to be similar to BMT. Unrelated-UCB transplantation may retain a good anti-leukaemia effect.¹³ The patient with adrenoleukodystrophy has had the longest survival, of 4 years, and also has normalised biochemical markers. Thus, this patient has benefited from transplantation,

because disease has not progressed. The timing of transplantation for metabolic disease is critical, and the procedure must be done early to prevent irreversible organ damage.¹⁷ The advantage of UCB transplantation is the rapid identification of a suitable donor, which allows transplantation to occur within a very short period. Young paediatric patients are particularly amenable to UCB transplantation due to their small size.

In conclusion, the establishment of a public local cord blood bank provides an alternative source of haematopoietic stem cells for transplantation, especially for children of small size and patients who need an urgent transplant. The transplantation outcome seems to be comparable to that of other forms of haematopoietic stem cell transplantation.

Acknowledgements

We thank the expert care from the nursing staff of BMT Unit of Lady Pao Children's Cancer Centre. We also thank 'S.K. Yee Medical Foundation' for support of the special enzyme assay for metabolic diseases.

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