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Successful Salvage Unrelated Umbilical Cord Blood Transplantation with Two Units After Engraftment Failure with Single Unit in Severe Aplastic Anemia

Severe aplastic anemia (SAA) patients without an HLA-matched sibling donor need alternative treatment options. Umbilical cord blood transplantation (UCBT) has become an alternative means for treating various diseases, but it has not been proved to be a satisfactory method to treat SAA. Here, we report the case of a girl who underwent successful two-unit UCBT after engraftment failure with a single unit. Two-unit UCBT is proposed to have better engraftment potential and to offer a better chance of survival, according to some reports. Increased cell dose and graft-*versus*-graft reaction could contribute to these advantages. With this promising result, two-unit UCBT could be an alternative treatment option for patients with SAA without an HLA-matched donor.

Key Words : *Anemia, Aplastic; Cord Blood Stem Cell Transplantation; Two-unit*

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INTRODUCTION

Bone marrow transplantation (BMT) from an HLA-matched related donor is the treatment of choice for children and young adults with severe aplastic anemia (SAA). Patients without an appropriate sibling donor usually receive immunosuppressive therapy, and those who fail it, undergo BMT from an HLA-matched unrelated donor. Umbilical cord blood transplantation (UCBT) has become an alternative option in various diseases since the first transplantation to treat a patient with Fanconi anemia was successful in 1988 (1). However, unrelated donor UCBT has not yet been recommended for SAA patients due to the high risk of graft failure and complications (2). Here we report the case of a girl who successfully underwent two-unit UCBT after engraftment failure with a single unit.

CASE REPORT

A 3-yr-old girl, whose blood type was A+, was admitted to our hospital for easy bruisibility. Her initial peripheral blood cell count showed 3.28×10^9/L white blood cell (WBC) with 2% neutrophils, 96% lymphocytes, 1% monocyte and 1% eosinophil, 7.0 g/dL hemoglobin with 19.2% hematocrit, 0.8% reticulocyte and 5×10^9/L platelet. A bone marrow study revealed hypocellular marrow (10% to 20% cellularity) with a marked decrease of normal hematopoietic cells. This led to the diagnosis of SAA. As the patient had no siblings, she underwent immunosuppressive therapy with anti-lymphocyte globulin and cyclosporine A for six months without response. Then she received oxymetholone and prednisolone for three years with intermittent transfusions of more than 30 units of packed red blood cell (RBC) and 30 units of plateletpheresis. However, oxymetholone was stopped because she developed a hepatic adenoma. At seven years of age, a single-unit UCBT from an AB+ male donor was performed with 5/6 HLA-matched unit, which contained 2.06×10^7/kg nucleated cells with 0.64×10^5/kg $CD34^+$ cells (Table 1). The conditioning regimen was composed of fludarabine (180 mg/m^2), busulfan (6.4 mg/kg), anti-thymocyte globulin (10 mg/kg) and total lymphoid irradiation (2 Gy). Graft-*versus*-host disease (GVHD) prophylaxis was done with cyclosporine A and methylprednisolone. The first UCBT failed due to an engraftment failure.

Three months after the first UCBT, two-unit UCBT was

Table 1. Cell doses and HLA types of cord blood units

Blood type/sex		First UCBT	Second UCBT	
			Engrafted unit	Disappeared unit
		AB+/male	A+/male	B+/male
HLA match		5/6 HLA matched	6/6 HLA matched	5/6 HLA matched
Cell dose	NC (/kg)	2.06×10^7	2.27×10^7	2.21×10^7
	$CD34^+$ (/kg)	0.64×10^5	0.57×10^5	1.15×10^5

UCBT, umbilical cord blood transplantation; NC, nucleated cell.

conducted. Two units of cord blood were infused after conditioning with fludarabine (180 mg/m^2), busulfan (6.4 mg/kg) and total body irradiation (4 Gy). She received GVHD prophylaxis with cyclosporine A and methylprednisolone. Other supportive care was performed according to the guidelines for stem cell transplantation at our center (3, 4). The engraftment was achieved with 6/6 HLA-matched unit containing 2.27×10^7/kg nucleated cells and 0.57×10^5/kg $CD34^+$ cells. But the other 5/6 HLA-matched unit containing 2.21×10^7/kg nucleated cells with 1.15×10^5/kg $CD34^+$ cells disappeared (Table 1). The engrafted unit came from an A+ male donor, while the other was from a B+ male. The number of days required to reach an absolute neutrophil count more than 0.5×10^9/L and 1.0×10^9/L was 18 days and 22 days, respectively. Spontaneous platelet recovery to more than 20×10^9/L and 50×10^9/L required 112 and 123 days, respectively. Complete donor chimerism was confirmed through the analysis of short tandem repeat regions and fluorescence *in situ* hybridization (FISH) of XY chromosome (Table 2).

After transplantation, grade II acute GVHD developed and was controlled with a steroid. She was also treated with ganciclovir for cytomegalovirus antigenemia detected on routine examination. Hepatic adenoma has been routinely followed up with abdomen sonography and α-fetoprotein without interval change. Up to two years and seven months after the two-unit UCBT, complete donor chimerism has been maintained with a normal blood cell count.

DISCUSSION

Since the first successful UCBT to treat a patient with Fanconi anemia in 1988 (1), UCBT has become an alternative option to treat a number of malignant or nonmalignant hematologic diseases. UCBT has the advantage of rapid availability and low risk of severe acute GVHD. However, it has been proposed that UCBT is limited by graft cell dose. Wagner et al. (5) demonstrate the importance of graft $CD34^+$ cell dose in determining the outcome after unrelated donor UCBT. To augment infused cell dose, *ex vivo* expansion of hematopoietic stem cells and transplantation of multiple umbilical cord blood units has been attempted.

Table 2. BM results and donor chimerism reports after two-unit UCBT

	BM cellularity (%)	STR (%)			FISH XX (%)/ XY (%)
		Recipient	Engrafted donor	Disappeared donor	
1 mo	11-20	0	100	0	0.2/99.8
3 mo	21-30	0	100	0	0/100
6 mo	ND	0	100	0	0/100
2 yr	ND	0	100	0	0/100

UCBT, umbilical cord blood transplantation; BM, bone marrow; STR, short tandem repeat; FISH, fluorescence *in situ* hybridization; ND, not done; mo, month.

In some studies, two-unit UCBT is proposed to have better engraftment potential and to offer a better chance of survival than single unit UCBT (4, 6). Recently, there was a report of a successful second transplantation with two unrelated cord blood units for early graft failure after first hematopoietic stem cell transplantation (7). The mechanisms of these additional advantages of two-unit UCBT are not fully understood. Increase of the cell dose could be a contributing factor, and graft-*versus*-graft reaction between two units also could be another factor. In previous reports on two-unit UCBT, results showed the dominancy of one unit in most of the cases. The mechanism of determining the dominancy is not known yet, but the number of $CD3^+$ cells and degree of HLA mismatch has been reported as related factors (4, 6).

In our case, the patient underwent a successful two-unit UCBT after engraftment failure with a single-unit UCBT. With this promising result, two-unit UCBT could be an alternative treatment option in SAA patients without an HLA-matched donor. Also, further investigation about the mechanism of engraftment in two-unit UCBT may extend the field of stem cell transplantation.

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