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LETTER TO THE EDITOR

Cotransplantation of umbilical cord MSCs to enhance engraftment of hematopoietic stem cells in patients with severe aplastic anemia

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A recent issue of *Bone Marrow Transplantation* reported that BM-derived MSCs (BMMSCs) could promote engraftment in pediatric recipients of unrelated donor umbilical cord blood.[1] Resnick *et al*.[2] found that intraosseous injection of BMMSCs could improve hematopoietic engraftment. Previous studies have also demonstrated that cotransplantation of BMMSCs and hematopoietic stem cells (HSCs) can enhance engraftment, prevent GVHD, accelerate lymphocyte recovery and reduce the risk of graft failure.[1,3] However, harvesting BMMSCs involves an invasive and painful procedure. Umbilical cords are rich with MSCs, which can be easily obtained and cultured.[4] Therefore, umbilical cords may represent a viable alternative source of MSCs. Friedman *et al*.[5] found that human umbilical cord-derived MSCs (UCMSCs) can accelerate human hematopoietic engraftment in SCID mice. In this study, we report two children receiving infusion of culture-expanded UCMSCs during PBSC transplantation, and both patients achieved rapid hematopoietic recovery without infusion-related toxicity.

The two patients were teenage girls diagnosed with severe aplastic anemia (SAA), who received immunosuppressive therapy, including CsA, methylprednisolone and antithymoglobulin, for 6 months. The treatment response was poor and they remained severely pancytopenic and transfusion dependent. No matched sibling donor existed for either patient; cotransplantation of UCMSCs and PBSCs from matched unrelated donors was performed after informed consents obtained from the parents.

Umbilical cords were processed within 24 h after delivery, and UCMSCs were isolated from Wharton's jelly as previously described.[6] In *in vitro* culture, UCMSCs showed a uniform spindle-shaped morphology. They were positive for CD13, CD29, CD44, CD73, CD90 and CD105, but negative for CD14, CD31, CD34, CD45 and HLA-DR. After identification and proof negative for bacteria, fungi and mycoplasma, these cells were cryopreserved in 10% DMSO at UCMSC bank. Approximately 3 weeks before cotransplantation, suitable UCMSCs were requested from the bank. These cells were thawed and *in vitro*-expanded sufficiently for cotransplantation, then cryopreserved. After being tested once again for the absence of pathogenic contamination, culture-expanded UCMSCs were thawed, washed and infused into the patient. PBSCs were infused 4 h after the completion of UCMSC infusion. The Institutional Review Board of China Medical University Hospital approved the procedures.

No adverse events occurred during or after the procedures. Both patients achieved hematopoietic engraftment; the time needed to achieve neutrophil engraftment was 9 and 10 days, and platelet engraftment was 13 and 15 days, respectively. At 30 days after cotransplantation, blood cells achieved 100% donor chimerism assessed with short tandem repeat method. No acute and chronic GVHD were detected. Both patients have been doing well without signs of ectopic tissue formation on imaging studies.

In our previous experience, among 11 SAA children receiving PBSC transplantation from matched unrelated donors without UCMSC infusion, one patient experienced graft failure and subsequently died. The other 10 patients achieved neutrophil and platelet engraftment at an average of 17.1 and 25.7 days, respectively. Four patients had acute GVHD, and two experienced chronic GVHD. The characteristics of the two SAA patients receiving cotransplantation and the ten receiving PBSC transplantation alone are summarized in Table 1.

MSCs have an important role in providing the specialized BM microenvironment.[7] Chemotherapy and/or radiotherapy before transplantation damage the marrow stroma. In addition, our previous study, as well as other studies, have provided evidence for MSC defects in SAA patients.[8,9] Therefore, BM reconstitution is more difficult in SAA patients after transplantation. Furthermore, MSCs possess immunomodulatory effects; they could suppress immune function in recipients and enhance engraftment of donor HSCs.[10] Concomitant infusion of abundantly normal MSCs at the time of HSC transplantation seems to be reasonable in SAA patients.

Harvesting BMMSCs is invasive, and UCMSCs are found to promote engraftment in mice.[5] This is the first description of cotransplantation of UCMSCs and HSCs in SAA children. Compared with the ten SAA patients receiving PBSC transplantation alone, the two patients achieved faster engraftment without infusion-related toxicity and GVHD. UCMSCs seem to accelerate engraftment safely and reduce the incidence of GVHD in SAA patients. A large study in a randomized trial is warranted to draw a more solid conclusion.

Conflict of interest

The authors declare no conflict of interest.

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Table 1 Characteristics of the two patients receiving cotransplantation and the ten patients receiving PBSC transplantation alone

Patients with severe aplastic anemia	*Patients receiving cotransplantation of UCMSCs and PBSCs (n = 2)*		*Patients receiving PBSC transplantation alone with engraftment (n = 10)*
	Patient 1	*Patient 2*	
Age (years)/gender	13/F	11/F	11.3 ± 3.6/M:F = 4:6
HSC source	MUD/PBSC	MUD/PBSC	MUD/PBSC
MSC source	5/6 HLA-MUD/UCMSC	5/6 HLA-MUD/UCMSC	
UCMSC passage	3	3	
UCMSC dose	4.2×10^6/kg	4.3×10^6/kg	
Conditioning	Flu + CY + ATG	Flu + CY + ATG	Flu + CY + ATG
GVHD prophylaxis	CsA + MTX	CsA + MTX	CsA + MTX
Days to ANC $\geqq 0.5 \times 10^9$/L	9	10	17.1 ± 3.1 (range, 12–23)
Days to platelet count $\geqq 20 \times 10^9$/L	13	15	25.7 ± 7.6 (range, 17–38)
Acute GVHD	None	None	4/10
Chronic GVHD	None	None	2/10
Outcome	Alive and well, 39 months after cotransplantation	Alive and well, 37 months after cotransplantation	Alive, 35.3 ± 6.7 months after PBSC transplantation

Abbreviations: ATG = antithymoglobulin; F = female; Flu = fludarabine; HSC = hematopoietic stem cell; M = male; MUD = matched unrelated donor; UCMSC = umbilical cord-derived MSC.

Y-H Chao[1,2], C Tsai[3], C-T Peng[4,5], H-P Wu[6,7], C-K Chan[8,9], T Weng[4] and K-H Wu[4,10]

[1]*Department of Pediatrics, Chung Shan Medical University Hospital, Taichung, Taiwan;*
[2]*School of Medicine, Chung Shan Medical University, Taichung, Taiwan;*
[3]*Bionet Corp, Taipei, Taiwan;*
[4]*Department of Pediatrics, Children's Hospital and School of Chinese Medicine, China Medical University and Hospitals, Taichung, Taiwan;*
[5]*Department of Biotechnology and Bioinformatics, Asia University, Taichung, Taiwan;*
[6]*Department of Pediatrics, Buddhist Tzu-Chi General Hospital, Taichung Branch, Taichung, Taiwan;*
[7]*Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan;*
[8]*Graduate Institute of Clinical Medical Science, Chang Gung University, Taoyuan, Taiwan;*
[9]*Department of Pediatrics, Taoyuan General Hospital, Taoyuan, Taiwan and*
[10]*Stem Cell Research Laboratory, Department of Medical Research, China Medical University Hospital, Taichung, Taiwan*
E-mail: m9683013@kimo.com

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