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Successful engraftment in reduced-intensity cord blood transplantation (CBT) as a salvage therapy for graft failure after primary CBT in adults

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Accumulating evidences strongly support the efficacy of umbilical cord blood transplantation (CBT) in adults (*1*, *2*). This now becomes a standard alternative to bone marrow or peripheral blood stem cell transplantation for patients who lack an HLA-matched donor. However, surprisingly high incidence of graft failure (GF) after CBT (7-40%) has been reported (*2-4*). The second CBT could be a therapeutic strategy to rescue patients with GF, but very few cases of successful engraftment by the second CBT for patients with GF after primary CBT have been reported (*4-6*).

In a past few years, we performed the second CBT in four cases with primary GF after CBT and all cases successfully achieved engraftment as summarized in Table 1. In these salvage CBTs, we paid attention to following three points. First, we tried to make a confirmation of GF and decision to perform the salvage CBT as quickly as possible. The confirmation of GF was made by no donor chimerism in bone marrow cells on day 28 or by no sign of hematopoietic recovery until day 35 (week 5) after primary CBT. Finally, the salvage CBT was performed before day 42 (week 6). The earlier application of salvage CBT while patients still have better performance status without infection or organ toxicities may improve the engraftment and survival.

Second, considering toxicities of conditioning regimen used for primary CBT, reduced-intensity CBT was chosen for the second transplant to avoid regimen related

toxicity and mortality. Because strong immunosuppression has a clear advantage over engraftment, we used fludarabine-based preparative regimen. Subsequent conditioning therapy including fludarabine within a short duration after primary transplant and strong GVHD prophylaxis could cause a high risk of infection, particularly cytomegalovirus (CMV) in CBT. However, only sub-clinical CMV infection occurred, which was well controllable with pre-emptive administration of ganciclovir. Acute GVHD was also mild.

Third, to intensify the immunosuppression in combination with a key drug tacrolimus, we utilized mycophenolate mofetil (MMF) instead of methotrexate (MTX) which was used in the first CBT in case 1, 2 and 3 for following two reasons. 1) MMF has been reported to cause lower incidence of mucositis compared with MTX (*7*). 2) Although mechanism has not been elucidated, several reports have suggested that a GVHD prophylaxis regimen containing MMF after allogeneic transplantation is associated with faster engraftment (*7-10*). Our retrospective observation also shows the promotional effect of MMF in hematopoietic engraftment (data not shown), but further studies are necessary to decide the optimal dose of MMF for SCT.

We all have to recognize the fact that GF can possibly occur in approximately one third of adult CBT particularly in the case of low transplant cell number. It would be

important to make sure of a cord blood unit for salvage transplant as early as possible, and not to lose a chance to make a decision of the salvage CBT to avoid life-threatening complications. Further clinical studies are necessary to establish the reduced-intensity CBT as a salvage therapy for primary GF.

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Table1. Patient characteristics

	Case 1		Case 2		Case 3		Case 4	
Age/Sex	55/female		53/male		45/female		23/female	
Disease Status	ALL, 2nd CR		APL, 2nd CR		DLBL, 2nd CR		SAA-post CBT secondary GF	
Transplantation	1st	2nd	1st	2nd	1st	2nd	2nd	3rd
Conditioning regimen	TBI-CY	Flu-BU	TBI/CY	Flu-BU	TBI-CY	Flu-BU	TBI-Flu-Mel	TBI-Flu-Mel
HLA matching	5/6	5/6	4/6	4/6	4/6	5/6	4/6	4/6
Total cell dose ($\times 10^7$/kg)	2.81	2.44	2.07	2.01	4.01	2.28	2.41	4.1
$CD34^+$ cell dose ($\times 10^5$/kg)	3.7	0.43	0.77	0.52	0.63	1.16	0.63	1.64
GVHD prophylaxis	CyA+sMTX	FK506+MMF	CyA+sMTX	FK506+MMF	FK506+sMTX	FK506+MMF	FK506	FK506+MMF
Day of second transplant	day 37		day39		day39		day42	
Days to neutrophils>0.5×10^9/l	day42		day32		day31		day19	
Days to platelets >20×10^9/l	day129		Not reached		Not reached		day166	

Abbreviations. ALL: acute lymphoblastic leukemia; APL: acute promyelocytic leukemia; DLBL: diffuse large B-cell lymphoma; SAA: severe aplastic anemia; CR: complete remission; CBT: cord blood transplantation; GF: graft failure; TBI: total body irradiation; Flu: fludarabine; BU: busulfan; Mel: melphalan; GVHD: graft-versus-host disease; CyA: cyclosporine A; sMTX: short-term methotrexate; MMF: mycophenolate mofetil; FK506: tacrolimus