

High incidence of haemophagocytic syndrome following umbilical cord blood transplantation for adults

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Summary

Umbilical cord blood transplantation (CBT) is widely accepted, but one critical issue for adult patients is a low engraftment rate, of which one cause is haemophagocytic syndrome (HPS). We aimed to identify the contribution of HPS to engraftment failure after CBT, following preparative regimens containing fludarabine phosphate, in 119 patients (median age, 55 years; range; 17–69 years) with haematological diseases. Graft-versus-host disease prophylaxis comprised continuous infusion of a calcineurin inhibitor with or without mycophenolate mofetil. Of the 119 patients, 20 developed HPS within a median of 15 d (cumulative incidence; 16.8%) and 17 of them did so before engraftment. Donor-dominant chimaerism was confirmed in 16 of 18 evaluable patients with HPS. Despite aggressive interventions including corticosteroid, ciclosporin, high-dose immunoglobulin and/or etoposide, engraftment failed in 14 of 18 patients. Of these 14 patients, four received second rescue transplantation and all resulted in successful engraftment. Overall survival rates significantly differed between patients with and without HPS (15.0% vs. 35.4%; $P < 0.01$). Univariate and multivariate analysis identified having fewer infused CD34⁺ cells as a significant risk factor for the development of HPS ($P = 0.01$ and 0.006, respectively). We concluded that engraftment failure closely correlated with HPS in our cohort, which negatively impacted overall survival after CBT.

Keywords: cord blood transplantation, reduced-intensity chemotherapy, haemophagocytic syndrome, engraftment failure.

Umbilical cord blood transplantation (CBT) is an alternative allogeneic haematopoietic stem cell transplantation (HSCT) strategy for patients with haematological diseases who do not have a matched related or unrelated donor and who need urgent transplantation. The value of CBT using myeloablative preparative regimens has already been confirmed among paediatric and adult patients (Laughlin *et al*, 2004; Rocha *et al*, 2004; Takahashi *et al*, 2004). However, conventional myeloablative preparative regimens are associated with significant morbidity and mortality, particularly in

older patients or in those who have experienced extensive prior therapy or organ dysfunction associated with transplantation-related mortality. Various reduced-intensity preparative regimens that have been applied to such patients by several groups, including the authors of the present study, have proven feasible (Barker *et al*, 2003, 2005; Chao *et al*, 2004; Jacobsohn *et al*, 2004; Miyakoshi *et al*, 2004, 2007; Yuji *et al*, 2005; Misawa *et al*, 2006; Ballen *et al*, 2007; Brunstein *et al*, 2007; Komatsu *et al*, 2007; Uchida *et al*, 2008).

Engraftment failure is a critical problem that can arise after CBT. The limited doses of infused total nucleated and CD34⁺ cells contained in umbilical cord blood are thought to influence the rate and kinetics of haematopoietic recovery. In order to overcome engraftment failure, various kinds of strategies, such as multiple unit or *ex-vivo* expanded CBT, and co-infusion of peripheral blood stem cells, have been employed (Shpall *et al*, 2002; Fernandez *et al*, 2003; Barker *et al*, 2005).

Several recent reports have described HPS that arose after autologous and allogeneic HSCT followed by engraftment failure (Sokal *et al*, 1987; Levy *et al*, 1990; Reardon *et al*, 1991; Nagafuji *et al*, 1998; Sato *et al*, 1998; Takahashi *et al*, 1998; Ishikawa *et al*, 2000; Fukuno *et al*, 2001; Abe *et al*, 2002; Tanaka *et al*, 2004, 2007; Kishi *et al*, 2005a; Boelens *et al*, 2006; Ostronoff *et al*, 2006; Ishida *et al*, 2007; Koyama *et al*, 2007). In a reduced-intensity conditioned CBT (RI-CBT) setting, we experienced one patient who failed to achieve engraftment due to HPS following HSCT (HSCT-HPS). Following this case, several similar cases were observed in our institute. We postulated that HPS could play a critical role in engraftment failure after CBT. This report describes the characteristics of 20 patients with HSCT-HPS among 119 who underwent CBT.

Materials and methods

Patients

The study population consisted of 119 adult patients with haematological diseases, who underwent CBT as the first allogeneic HSCT at Toranomon Hospital, Tokyo, Japan between January 2004 and December 2006. All the patients were incurable using conventional approaches, lacked a human leucocyte antigen (HLA)-identical sibling or a suitable unrelated donor from Japan Marrow Donor Program. Most of the patients were considered inappropriate for conventional myeloablative allogeneic HSCT due to being >50 years and/or having organ dysfunction (cardiac ejection fraction <50%, forced expiratory volume 1.0 s % <80%, or serum creatinine > 1.5× upper limit of normal range). Written informed consent was provided by all patients in accordance with the Declaration of Helsinki. The Institutional Review Board of Toranomon Hospital approved the study.

Transplantation procedures

Cord blood units that were serologically matched for ≥4 of six HLA antigens and which contained at least 1.8×10^7 nucleated cells/kg of recipient body weight before freezing were obtained from the cord blood bank at the Japan Cord Blood Bank Network (Nishihira *et al*, 2003). The units were not depleted of T lymphocytes. All patients received purine analogue-based preparative regimens comprising fludarabine phosphate (125–180 mg/m²), melphalan (80–140 mg/m²) or busulfan (BU; 8–16 mg/kg) and 0–8 Gy of total body irradiation (TBI), as

decided by the treating physician. Graft-versus-host disease (GVHD) prophylaxis comprised a continuous intravenous infusion of either 0.03 mg/kg of tacrolimus (TAC) or 3 mg/kg of ciclosporin (CsA), starting on day-1, except eight patients who received 2 g/d of mycophenolate mofetil (MMF) starting on day-1 in addition to TAC.

Supportive cares

All the patients were treated in reverse isolation in laminar airflow-equipped rooms and received trimethoprim/sulfamethoxazole for *Pneumocystis jirovecii* prophylaxis. Fluoroquinolone and azole and acyclovir were administered to prevent bacterial, fungal and herpes virus infection, respectively. Neutropenic fever was managed according to the guidelines (Hughes *et al*, 2002). Cytomegalovirus pp65 antigenaemia was monitored weekly and preemptive therapy with foscarnet was initiated in the event of a positive result (Matsumura *et al*, 2007; Narimatsu *et al*, 2007a). Haemoglobin and platelet counts were maintained at >70 g/l and $10 \times 10^9/l$, respectively. Granulocyte colony-stimulating factor was administered intravenously from day 1 until neutrophil recovery became durable.

Assessment of engraftment, chimaerism, pre-engraftment immune reactions, disease risk and survival

Engraftment was defined as the first of three consecutive days in which white blood cell counts were $>1.0 \times 10^9/l$ or the absolute neutrophil counts were $>0.5 \times 10^9/l$. When the above definition was not met by day 28 without subsequent neutrophil recovery, the patient was considered to have primary engraftment failure. Delayed engraftment was defined as neutrophil engraftment after day 29. Secondary engraftment failure was defined as a decrease in the neutrophil count to $<0.5 \times 10^9/l$ for three consecutive days after successful engraftment. The date of platelet recovery was defined as the first of seven consecutive days during which the non-transfused platelet count was at least $20 \times 10^9/l$.

Chimaerism was assessed using fluorescent *in situ* hybridization (FISH) in sex-mismatched donor–recipient pairs. In sex-matched pairs, chimaerism was assessed using the polymerase chain reaction for variable numbers of tandem repeats with donor cells detected at 10% sensitivity (Thiede *et al*, 1999).

Pre-engraftment immune reactions (PIR) were diagnosed when febrile patients (body temperature $\geq 38.0^\circ\text{C}$) developed skin eruption, diarrhoea, jaundice (serum total bilirubin $>34.2 \mu\text{mol/l}$) or body weight gain of >10% of baseline, with no direct evidence of infection or adverse effects of medication, developing ≥ 6 d before engraftment (Kishi *et al*, 2005b).

Patients with acute myeloid leukaemia in first or second complete remission (CR) at the time of transplant, with acute lymphoblastic leukaemia in first or second CR, with chronic myeloid leukaemia in the chronic phase, with refractory

anaemia or refractory anaemia with ringed sideroblasts of myelodysplastic syndrome and with non-malignant diseases were defined as being at standard risk. All other patients were defined as being at high risk.

The overall survival (OS) of all of the patients was measured from the date of transplantation to the date of death from any cause.

Definition of haemophagocytic syndrome following haematopoietic stem cell transplantation

We modified the criteria proposed by others for diagnosing HPS after transplantation (Henter *et al*, 1991; Imashuku, 1997; Tsuda, 1997) and selected two major and four minor criteria. A diagnosis of HSCT-HPS required both major criteria, or one major and all four minor criteria. The first major criterion comprised engraftment failure, delayed engraftment, or secondary engraftment failure after HSCT and the second was histopathological evidence of haemophagocytosis. The four minor criteria comprised high grade fever, hepato-splenomegaly, elevated ferritin and elevated serum lactate dehydrogenase (LDH). Although progressive cytopenia has formed the backbone of the previous criteria, we excluded it considering the post-HSCT setting.

Statistical analysis

The cumulative incidences were estimated for neutrophil engraftment and the development of HSCT-HPS (Gooley *et al*, 1999). The probability of OS was estimated from the time of transplantation according to the Kaplan-Meier product limit method and outcomes were compared using the log-rank test. The following patient or transplant characteristics (baseline factors) were analysed using the Cox regression model to determine their impact on the development of HSCT-HPS: patient age, gender (matched or mismatched), blood type (matched or mismatched), disease (lymphoma or not), disease risk (standard or high), preparative regimen (reduced-intensity or myeloablative), GVHD prophylaxis (TAC alone or others), disparity of HLA-A, -B, -DR antigen (one or two mismatched antigens), and numbers of infused nucleated and CD34⁺ cells. A value of $P < 0.05$ was considered statistically significant. All data were statistically analysed using STAT-VIEW 5.0 and S-PLUS 2000 (Mathsoft, Seattle, WA, USA).

Results

Patient's characteristics

Table I summarizes the characteristics of the 119 patients and cord blood grafts. The median age was 55 years (range, 17–69); 103 patients (87%) had high risk diseases. The preparative regimen comprised fludarabine phosphate, melphalan and TBI in 91 patients (76%) and 106 patients (89%) received TAC alone as GVHD prophylaxis. MMF was administered in

Table I. Patients' characteristics and transplantation procedures.

Characteristic	Number
Age (years), median (range)	55 (17–69)
Gender (male/female)	78/41
<i>Primary diseases</i>	
Acute lymphoblastic leukaemia	10
Acute myeloid leukaemia	52
Chronic myeloid leukaemia	5
Adult T-cell leukaemia/lymphoma	11
Myelodysplastic syndrome	6
Malignant lymphoma	32
Aplastic anaemia	1
Chronic idiopathic myelofibrosis	1
Acute leukaemia of ambiguous lineage	1
<i>Preparative regimens</i>	
Flu (125–180 mg/m ²)/Mel (80–140 mg/m ²)/TBI (2–8 Gy)	91
Flu (125–180 mg/m ²)/Mel (80–140 mg/m ²)	7
Flu (125–180 mg/m ²)/BU (8–16 mg/kg)/TBI (4–8 Gy)	14
Flu (150–180 mg/m ²)/BU (8–16 mg/kg)	3
Others	4
<i>GVHD prophylaxis</i>	
CsA alone	5
TAC alone	106
TAC and MMF	8
<i>Cord blood cells</i>	
Number of infused nucleated cells, median (range), $\times 10^7$ /kg	2.52 (1.85–5.13)
Number of infused CD34 ⁺ cells, median (range), $\times 10^5$ /kg	0.766 (0.110–3.16)
<i>Sex match</i>	
Matched	24
Mismatched	95
<i>HLA match</i>	
6/6	2
5/6	14
4/6	103
<i>ABO-blood type match</i>	
Matched	36
Minor mismatched	31
Major mismatched	38
Bidirectional mismatched	14
<i>Disease risk</i>	
Standard/high	16/103

GVHD, graft-versus-host disease; BU, busulfan; CsA, ciclosporin; Flu, fludarabine phosphate; Mel, melphalan; MMF, mycophenolate mofetil; TAC, tacrolimus; TBI, total body irradiation; HLA, human leucocyte antigen.

addition to TAC for eight patients (7%). The median numbers of infused total nucleated and CD34⁺ cells were 2.52×10^7 (range, 1.85–5.13) and 0.766×10^5 cells/kg (range, 0.110–3.16), respectively. The donor–recipient pairs had serological

mismatches at two HLA loci, a gender mismatch and an ABO blood-type mismatch in 103 (87%), 95 (80%) and 83 (70%) patients, respectively. Among 103 patients who survived beyond 28 d after CBT, neutrophil engraftment was achieved in 89 of them at a median of day 20 (range, 11–45). The cumulative incidence of neutrophil engraftment at day 60 was 85.6%. Secondary engraftment failure occurred in four of these 89 patients. Eleven patients were diagnosed with 'delayed engraftment' according to our definition. The direct causes of death in 16 patients who died within 28 d of CBT included sepsis ($n = 10$), haemorrhage ($n = 2$), relapse of primary disease ($n = 2$), thrombotic microangiopathy (TMA) ($n = 1$), and central nervous system complication ($n = 1$). Chimaerism data was obtained from 111 patients. Chimaerism analysis was performed in 58 patients in the peripheral blood and in 53 patients in the bone marrow. One hundred (90.1%) of them had achieved complete donor chimaerism by day 60. The median length of time required to complete donor chimaerism was 18 d (range, 9–93). Chimaerism was analysed in 10 of 16 patients who died within 28 d of CBT. All except one had complete donor chimaerism before neutrophil engraftment. Seventy-three (61.3%) of the 119 patients developed PIR. By day 100 after CBT, 55 patients had developed bacteraemia at a median of 10 d (range, 3–89 d). Of these 55 patients, 33

developed bacteraemia within 14 d of transplantation. Cytomegalovirus (CMV) was reactivated in 60 patients at a median of 33 d (range, 3–101 d). Ten patients developed histologically confirmed CMV enterocolitis. Eleven patients developed limbic encephalitis caused by human herpes virus 6 (HHV-6) at a median of 20 d of transplantation (range, 13–33 d).

HSCT–HPS patients' characteristics

Table II shows the characteristics of the 20 of 119 patients who had clinical features of HPS according to our diagnostic criteria. The cumulative incidence of HPS after CBT was 16.8% (Fig 1). HPS occurred within 4 weeks of transplantation and the median day of diagnosis was 15 d post-transplant (range, 10–27 d). The 20 patients comprised 13 men and seven women, with a median age of 52 years (range, 23–69 years); 17 patients had high risk disease. None of them had evidence of HPS before transplantation. The preparative regimen comprised fludarabine phosphate, melphalan and TBI for 15 patients and 19 patients received TAC alone as GVHD prophylaxis. MMF was administered in addition to TAC for one patient. The median numbers of infused total nucleated and CD34⁺ cells were 2.40×10^7 cells/kg (range, 1.98–5.13) and 0.52×10^5 cells/kg (range, 0.18–3.10), respectively. The

Table II. Characteristics of HSCT–HPS patients.

Patient	Age (years)/gender	Disease	Status	TNC ($\times 10^7$ /kg)	CD34 ⁺ ($\times 10^5$ /kg)	Gender match	HLA match	Blood type match	Preparative regimen	GVHD prophylaxis
117	68/M	ALL	RL1	2.64	0.74	Match	4/6	BD MM	F125/M80/TBI4	TAC
157	38/M	AML	PIF	2.39	0.31	MM	4/6	Minor MM	F125/M80/TBI4	TAC
161	69/M	NHL	RL1	2.54	0.99	Match	4/6	Major MM	F125/M80/TBI4	TAC
164	48/F	ATLL	PR	5.13	3.10	MM	4/6	Minor MM	F125/M80/TBI4	TAC
171	23/M	AML	RL2	2.30	0.52	MM	5/6	Minor MM	F180/B8/TBI8	TAC
181	62/M	AML	CR2	1.94	0.18	MM	4/6	Major MM	F125/M80/TSP	TAC
194	61/M	CML	BC	2.25	1.47	MM	5/6	Match	F125/M80/TBI4	TAC
198	56/F	ATLL	PR	3.99	0.20	MM	4/6	BD MM	F125/B8/TBI4	TAC
208	52/M	NHL	PD	2.41	0.52	MM	4/6	Minor MM	F125/M80/TBI4	TAC
209	52/M	AML/MDS	CR1	2.52	0.58	Match	4/6	Major MM	F125/M80/TBI4	TAC
212	57/M	AML/MDS	NT	2.08	0.57	MM	4/6	Minor MM	F125/M80/TBI4	TAC
215	47/F	NHL	PD	3.16	0.45	MM	4/6	Major MM	F180/B8	TAC
239	50/F	AML/MDS	PIF	2.34	0.31	MM	6/6	Match	F180/M140/TBI4	TAC
240	39/M	AML	RL1	2.62	0.29	MM	4/6	Minor MM	F125/M140/TBI4	TAC
242	33/F	AML	RL1	2.57	0.39	MM	4/6	Minor MM	F125/M160/TBI4	TAC
246	66/M	AML/MDS	PIF	2.37	0.65	MM	4/6	Major MM	F125/M80/TBI4	TAC
274	31/F	NHL	RL pASCT	2.72	0.22	MM	4/6	Match	F180/M140	TAC
278	59/M	AML/MDS	PIF	1.98	0.50	MM	4/6	Major MM	F125/M80/TBI4	TAC
280	40/F	NHL	RL1	2.35	0.90	Match	4/6	Minor MM	F125/M80/TBI4	TAC
282	62/M	AML	CR2	2.05	0.70	Match	4/6	Minor MM	F125/M80/TBI4	TAC/MMF

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; AML/MDS, acute myeloid leukaemia with multilineage dysplasia; ATLL, adult T-cell leukaemia/lymphoma; B, oral busulfan, mg/kg; BC, blastic crisis; BD, bidirectional; CML, chronic myeloid leukaemia; CR, complete response; F, fludarabine; GVHD, graft-versus-host disease; HLA, human leucocyte antigen; M, melphalan, mg/m²; MDS, myelodysplastic syndrome; MM, mismatch; MMF, mycophenolate mofetil; NHL, non-Hodgkin lymphoma; NT, not treated; pASCT, post autologous stem-cell transplantation; PD, progressive disease; PIF, primary induction failure; PR, partial response; RL, relapse; TAC, tacrolimus; TBI, total body irradiation; TNC, total nucleated cell count; TSP, tespamine.

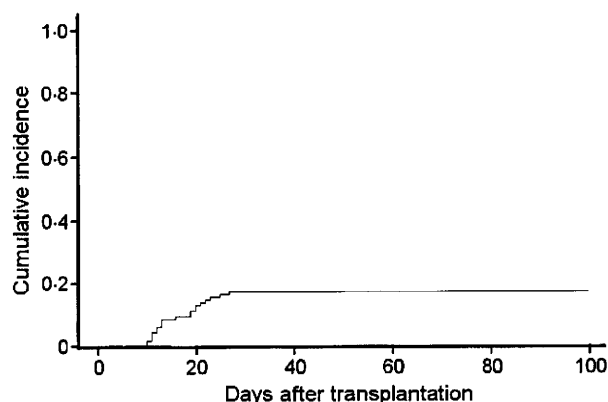


Fig 1. Cumulative incidence of HPS following CBT.

donor–recipient pairs had serological mismatches at two HLA loci, a gender mismatch and an ABO blood type mismatch in 17, 15 and 17 patients, respectively.

Clinical features of HSCT–HPS patients

Table III shows the clinical features and outcome of HSCT–HPS patients. All patients, except for one, presented with high grade fever. Hepatosplenomegaly was found in four patients and 11 had clinical manifestations of PIR. Serum aminotransferases

(predominantly aspartate, rather than alanine aminotransferase) and bilirubin were elevated in 12 patients each. None of them had acute hepatic failure. Serum LDH and ferritin levels were elevated in 16 and 19 patients respectively [median value (range) of highest LDH, 340 (65–2444) i/u per litre and ferritin, 9397 (1423–568500) µg/l]. The highest values of serum ferritin by day 30 after CBT significantly differed between patients with and without HPS ($P < 0.0094$) (Fig 2). The diagnosis of HPS was confirmed by cytological or pathological assessment of all patients, except for one with extremely elevated serum ferritin who rapidly developed secondary engraftment failure, which was strongly indicative for HSCT–HPS. Bone marrow aspirates from 18 of 19 patients exhibited haemophagocytosis (the remaining one was diagnosed by a bone marrow biopsy post-mortem). This test was performed between day 10 and 27 d after transplantation to determine the cause of delayed neutrophil recovery or to predict the development of HPS. Bone marrow aspiration smear showed very hypocellular marrow with a prominent increase of activated macrophages phagocytosing red cells and myeloid precursors.

Engraftment and chimaerism of HSCT–HPS patients

Of 14 patients with HPS who failed to engraft (primary engraftment failure), eight died within 28 d of CBT. Three patients achieved engraftment after day 29 of CBT (delayed

Table III. Clinical features and outcome of HSCT–HPS patients.

Patient	Engraftment (d)	M in BM (%)	Day of Dx	Chimaerism (% donor)	PIR	Fever	HSM	LDH (i/u per litre)	Ferritin (µg/l)	Intervention	Response
117	Not engrafted	29.0	19	NA	No	Yes	No	65	NA	None	Not engrafted
157	Not engrafted	66.0	19	98.4	Yes	Yes	Yes	1255	1423	CS/CsA	Not engrafted
161	Day 19, sEF	NA*	NA*	NA*	Yes	Yes	No	1372	9397	CS	Not engrafted
164	Day 13, sEF	1.0	25	96.2	No	Yes	Yes	2444	568500	CS/CsA	Engrafted
171	Not engrafted	43.0	27	0.2	No	Yes	No	166	6434	CS	Not engrafted
181	Not engrafted	53.0	12	94.0	No	Yes	Yes	587	18150	CS	Not engrafted
194	Not engrafted	24.0	13	98.8	Yes	Yes	No	664	34200	CS	Not engrafted
198	Not engrafted	17.0	20	94.6	Yes	Yes	No	208	2719	CS	Not engrafted
208	Not engrafted	21.5	13	99.6	Yes	Yes	No	994	18640	CS/VP16	Not engrafted
209	Not engrafted	51.0	12	64.0	No	Yes	No	174	1946	IVIG/second CBT	Engrafted
212	Day 30	30.5	11	63.6	Yes	Yes	NE	261	9339	IVIG	Engrafted
215	Day 33	18.5	21	99.8	Yes	Yes	No	216	9808	CS	Engrafted
239	Day 30	25.0	22	96.4	Yes	Yes	NE	313	5212	CS	Engrafted
240	Not engrafted	15.0	11	99.0	Yes	Yes	NE	268	58824	CS	Not engrafted
242	Not engrafted	10.0	10	96.4	Yes	Yes	No	143	3439	IVIG/second CBT	Engrafted
246	Not engrafted	15.0	21	18.2	No	Yes	No	800	7740	Second CBT	Engrafted
274	Not engrafted	90.0	11	68.4	Yes	Yes	NE	367	20304	Second CBT	Engrafted
278	Not engrafted	34.0	10	99.4	Yes	Yes	No	891	111800	None	Not engrafted
280	Not engrafted	11.5	13	100	No	Yes	Yes	1634	67600	CS/VP16	Not engrafted
282	Day 24, sEF	58.0	20	92.6	No	No	No	276	2464	CS	Not engrafted

BM, bone marrow; CBT, cord blood transplantation; CS, corticosteroid; CsA, ciclosporin; Dx, diagnosis; HSM, hepatosplenomegaly; IVIG, intravenous immunoglobulin; M, macrophage; NA, not available; NE, not evaluated; PIR, pre-engraftment immune reactions; sEF, secondary engraftment failure.

*Haemophagocytosis confirmed by post-mortem bone marrow biopsy.

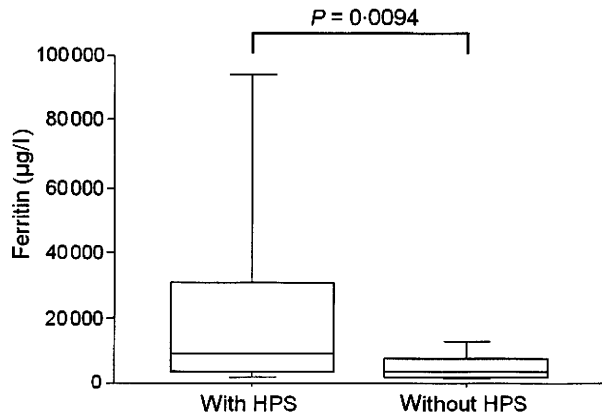


Fig 2. Comparison of highest value of serum ferritin by day 30 of CBT (with *versus* without HPS).

engraftment). Secondary engraftment failure occurred in three patients. Chimaerism data were obtained from 18 out of 20 patients. Donor chimaerism was complete at the time of HPS diagnosis in 13 patients. Three and two patients had donor- and recipient-dominant chimaerism, respectively. An examination of bone marrow clot specimens using XY-FISH method (Ishida *et al*, 2007) confirmed that the activated macrophages in two patients with HPS who achieved complete donor chimaerism (patients 157 and 181; Table II) were donor-derived.

Concomitant clinical conditions of HSCT-HPS patients

Concomitant clinical conditions might be relevant to the development of HPS. Twelve of 20 patients had extant infections, most of which were bacteraemia ($n = 10$). The pathogens in eight patients were Gram-positive cocci, namely coagulase-negative *Staphylococcus* ($n = 5$), *Enterococcus faecalis* ($n = 2$) and *Enterococcus faecium* ($n = 1$), and Gram-negative rods, *Stenotrophomonas maltophilia* ($n = 1$) and *Pseudomonas aeruginosa* ($n = 1$) in two. Three patients were infected with CMV. Two had simultaneous bacteraemia and HHV-6 infection was found in one patient who developed limbic encephalitis. Among eight patients who had no documented infections, five developed transient atypical lymphocytosis soon after transplantation, two had PIR, and the remaining patient developed HPS without any concomitant clinical conditions.

Therapeutic interventions for HSCT-HPS and outcome

Corticosteroid (CS) was administered in 13 of 20 patients to reduce macrophage activation, CsA was administered in addition to CS in two patients and etoposide (VP-16) was also administered in addition to CS in two others. Four patients underwent a second rescue CBT, two of which were after the administration of high-dose intravenous immunoglobulin (IVIg). One patient was treated with IVIg alone.

Two patients could not undergo specific treatments due to severe infections and/or severe organ damage. These efforts finally resolved the failed engraftment in eight patients. The prognosis was poor; 17 of 20 patients died (85%) and eight had died by 28 d after CBT. The causes of death were sepsis ($n = 7$), relapse of primary disease ($n = 3$), haemorrhage ($n = 2$), TMA ($n = 2$), GVHD ($n = 2$) and central nervous system complication ($n = 1$). As of December 2007, the median follow-up after CBT for surviving patients was 598 d (range, 26–1426 d). The Kaplan–Meier probability of overall survival at 4 years was 31.4% (95% confidence interval, 20.0–42.8%). The overall survival was significantly poorer for patients with HPS than without HPS (15.0% vs. 35.4%; $P = 0.0002$, Fig 3).

Risk factors for HSCT-HPS

Univariate and multivariate analysis identified having fewer infused CD34⁺ cells as a significant risk factor for the development of HPS ($P = 0.01$ and 0.006 respectively, Table IV). Patients were subdivided into two groups according to the intensity of preparative regimen; those who received 16 mg/kg of BU or 8 Gy of TBI were categorized as 'myeloablative' ($n = 18$), and the others who received less intensive regimens were classified as 'reduced-intensity' ($n = 10$). The incidence of HPS was higher in the 'reduced-intensity' group, although it did not reach statistical significance ($P = 0.17$).

Discussion

This study of clinical manifestations, therapeutic management, outcome and risk factors for HPS after CBT is the largest to date. Our results demonstrated that HPS is an aggressive and devastating complication after CBT that closely correlates with delayed engraftment or failure, resulting in a poor OS. As far as we understand from the English medical literature (Table V), only 23 patients in 16 case reports appear to have developed HPS after autologous ($n = 5$) and allogeneic ($n = 18$) HSCT

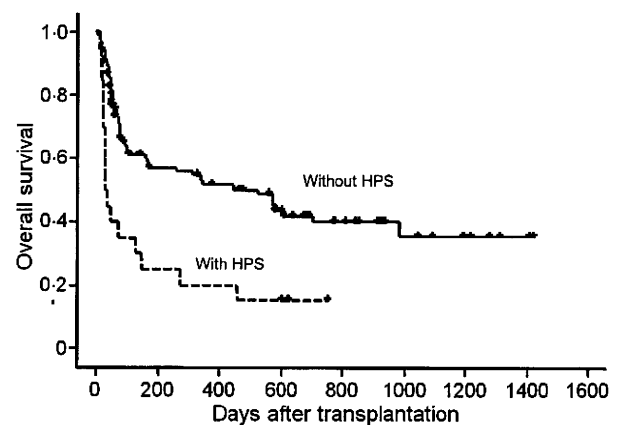


Fig 3. Comparison of overall survival (with *versus* without HPS).

Table IV. Risk factors of HPS development.

Univariate factors	Cumulative incidence	P value
Age (<55 vs. ≥55 years)	19.3% vs. 14.5%	0.50
Gender (mismatch <i>versus</i> match)	18.3% vs. 11.5%	0.41
Blood type (mismatch <i>versus</i> match)	20.8% vs. 8.1%	0.09
Underlying disease (non-lymphoma <i>versus</i> lymphoma)	17.1% vs. 16.3%	0.85
Risk of underlying disease (standard <i>versus</i> high)	18.8% vs. 16.5%	0.80
Preparative regimen (reduced-intensity <i>versus</i> myeloablative)	19.4% vs. 5.6%	0.17
GVHD prophylaxis (TAC alone <i>versus</i> others)	18.4% vs. 7.7%	0.35
Disparity of HLA-A, -B, -DR antigen (1 or 0 vs. 2-antigen mismatch)	18.8% vs. 16.5%	0.89
GVH vector (2 vs. 1 or 0-mismatch)	18.4% vs. 12.5%	0.41
HVG vector (1 or 0 vs. 2-antigen mismatch)	21.1% vs. 15.1%	0.53
Number of infused total nucleated cells (<2.52 vs. ≥2.52 × 10 ⁷ /kg)	18.6% vs. 15.0%	0.60
Number of infused CD34 ⁺ cells (<0.766 vs. ≥0.766 × 10 ⁵ /kg)	27.1% vs. 6.8%	0.01

Multivariate factors	Hazard ratio	95% Confidence interval	P value
Blood type (mismatch <i>versus</i> match)	2.80	0.79–9.86	0.11
Preparative regimen (reduced-intensity <i>versus</i> myeloablative)	2.76	0.43–17.8	0.29
GVHD prophylaxis (TAC alone <i>versus</i> others)	2.71	0.41–17.9	0.30
Number of infused CD34 ⁺ cells (<0.766 vs. ≥0.766 × 10 ⁵ /kg)	4.48	1.54–13.1	0.006
GVH vector (1 or 0 vs. 2-antigen mismatch)	1.48	0.52–4.21	0.46

GVH, graft-*versus*-host; HVG, host-*versus*-graft.

(Sokal *et al*, 1987; Levy *et al*, 1990; Reardon *et al*, 1991; Nagafuji *et al*, 1998; Sato *et al*, 1998; Takahashi *et al*, 1998; Ishikawa *et al*, 2000; Fukuno *et al*, 2001; Abe *et al*, 2002; Tanaka *et al*, 2004, 2007; Kishi *et al*, 2005a; Boelens *et al*, 2006; Ostronoff *et al*, 2006; Ishida *et al*, 2007; Koyama *et al*, 2007). Among 18 patients who received allogeneic HSCT, reduced-intensity preparative regimens were employed in nine patients and three underwent CBT. Thus, HPS has been considered a rare event after HSCT. The incidence of HPS following CBT in our study, however, was strikingly higher than previous reports have indicated.

Multivariate analyses identified the dose of CD34⁺ cells as the only statistically significant risk factor. Given that a low dose of CD34⁺ cells can negatively affect the rate of engraftment and duration to neutrophil recovery, more infectious complications accompanying low CD34⁺ cell counts might be directly related to the onset of HPS. In our study cohort, the incidence of infectious complications arising during the early phase after transplant (by day 28) was higher in those with HPS than those without HPS (12/20 vs. 37/99; $P = 0.027$), suggesting that infections are associated with the likelihood of developing HPS. The high prevalence of elderly patients and of those with high-risk disease status might explain this high incidence of infections. Consequently, the poor outcome following development of HPS was mainly due to the engraftment failure and following exacerbation of infections.

The intriguing finding of our chimaerism analysis of patients with HPS was that of donor-dominancy in 16 of 18 patients. XY-FISH determined that the phagocytosing macrophages were also of the donor type in the two evaluated

patients. These findings indicated that HPS after CBT might be mediated by donor-derived macrophages rather than host-derived, and that engraftment failure is not due to a simple rejection mechanism, but to factors and events that activates donor-derived macrophages and leads to the cascade of HPS. The incidence of HPS may have been underestimated in previous reports, as the reason for graft failure after transplantation had often not been described, especially for graft failure with donor-dominant chimaerism.

The postulated pathophysiology of HPS is that excessive cytokine production from T cells activate macrophages, leading to a substantial loss of haematopoietic cells. Although of great interest, the role of cytokine levels in the precise mechanism of HPS needs further study in the future. We previously described unique early immune reactions after CBT and termed them PIR (pre-engraftment immune reactions), i.e. non-infectious high-grade fever concomitant with eruption, diarrhoea and weight gain, starting on a median of day 9 after CBT (Kishi *et al*, 2005b). In the present study, 61% of the patients developed this syndrome, suggesting that immune cells became activated soon after transplantation. We regarded this syndrome as early onset of acute GVHD, where activated donor T cell secreted various cytokines (Reddy & Ferrara, 2003).

We also recently reported that the degree of HLA mismatch in the graft-*versus*-host direction was inversely associated with engraftment kinetics after RI-CBT (Matsuno *et al*, 2009). Paradoxically to the former notion of graft failure, the degree of HLA mismatch in the host-*versus*-graft direction had no impact on the engraftment kinetics. These findings propose a novel mechanism responsible for

Table V. Occurrence of haemophagocytic syndrome among autologous and allogeneic haematopoietic stem cell transplantation reported in English medical literature.

Ref.	Age (years)/gender	Disease	Stem cell HLA match	Preparative regimen	GVHD prophylaxis	Day of Dx	Principal cause	Intervention	Response
(A) After autologous haematopoietic stem cell transplantation									
Levy et al (1990)	6/F	Wilms tumour	Auto BM	Local RT/Mel/ADM	-	28	ADV-11	IVIG	Not engrafted
Nagafuji et al (1998)	52/F	AML	Auto PBSC	BU/VP16/Ara-C	-	25	CMV	CS/IVIG	Not resolved
Takahashi et al (1998)	43/F	NHL	Auto PBSC	CY/VP16/MCNU/CBDCA	-	130	Lymphoma	CS/IVIG	Not resolved
Fukuno et al (2001)	67/F	NHL	Auto PBSC	CY/VP16/MCNU	-	12	MRSA	CS/CsA	Not engrafted
Ostromoff et al (2006)	54/F	MM	Auto PBSC	Mel	-	16	ND	CS/IVIG	Engrafted
(B) After allogeneic haematopoietic stem cell transplantation									
Sokal et al (1987)	8/M	FA	ur-BM, 6/6	CY/TBI 4	CsA	300	HSV-1	-	Resolved
Reardon et al (1991)	8/F	ALL	r-BM, 6/6	BU/CY	CsA/Cs	38	ADV	-	Not resolved
Sato et al (1998)	40/F	AML	ur-BM, 6/6	VP16/TBI 12	CsA/sMTX	59	CMV	IVIG/VP16	Not resolved
Ishikawa et al (2000)	40/M	AML	r-BM, 6/6	CY/TBI 12	CsA/sMTX	16 (D)	ND	CS	Engrafted
Abe et al (2002)	39/M	NHL	r-PBSC, 6/6	TBI 2	CsA/MMF	15 (D)	ND	CS/VP16	Not engrafted
Abe et al (2002)	50/F	NHL	r-PBSC, 5/6	TBI 2	CsA/MMF	56 (D)	ND	CS	Not engrafted
Tanaka et al (2004)	7/F	AML/MDS	ur-CB, 5/6	CY/TBI 12/Ara-C	CsA/sMTX	20 (D)	MRCNS	CS/second PBSC	Engrafted
Kishi et al (2005a)	30/M	AML	r-PBSC, 5/6	BU/CY	TAC	11	ND	CS	Not resolved
Boelens et al (2006)	2/F	HS	r-BM/PBSC, 3/6	Flu/Mel/TSP/ATG	NR	35, sEF (D)	EBV-LPD	CS	Resolved
Ishida et al (2007)	2/M	JMML	ur-BM, 6/6	Flu/Mel/BU	TAC/sMTX	39, sEF (R)	NR	IVIG/second CBT	Engrafted
Ishida et al (2007)	2/M	JMML	ur-CB, -	Flu/Mel/VP16	TAC	11 (R)	NR	IVIG/VP16	Engrafted
Tanaka et al (2007)	54/M	AML	ur-CB, 5/6	CY/TBI 12/Ara-C	CsA/sMTX	33, sEF	NR	CS/second CBT	Engrafted
Koyama et al (2007)	9/-	ID	ur-BM, 4/6	Mel/TBI 6/ATG	TAC/sMTX	10	NR	CS/IVIG/VP16	Engrafted
Koyama et al (2007)	3/-	AML	r-BM, 4/6	Flu/TBI 12/Ara-C/VP16	TAC/sMTX	10	NR	CS/IVIG	Engrafted
Koyama et al (2007)	2/-	ALL	r-PBSC, -	TBI 10/TSP	TAC	8	NR	IVIG/VP16	Not engrafted
Koyama et al (2007)	16/-	EBV-LPD	r-PBSC, -	Flu/Mel/ATG	TAC	7	NR	CS/VP16	Not engrafted
Koyama et al (2007)	9/-	AML	ur-BM, 6/6	CY/TBI 12/TSP	TAC/sMTX	12	NR	CS/VP16	Engrafted
Koyama et al (2007)	3/-	NHL	r-BM, 3/6	TBI 12/VP16/TSP	TAC/sMTX/CS	5	NR	CS/VP16	Engrafted

ADM, adriamycin; ADV, adenovirus; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; AML/MDS, acute myeloid leukaemia with multilineage dysplasia; Ara-C, cytosine arabinoside; ATG, anti-thymoglobulin; Auto, autologous; BM, bone marrow; BU, busulfan; CB, cord blood; CBDCA, carboplatin; CMV, cytomegalovirus; CS, corticosteroid; CsA, ciclosporin; CY, cyclophosphamide; Dx, diagnosis; (D), donor-derived; EBV-LPD, Epstein-Barr virus associated lymphoproliferative disorder; F, female; FA, Fanconi anaemia; Flu, fludarabine; HS, Hurler syndrome; HSV, herpes virus; ID, immunodeficiency; IVIG, intravenous immunoglobulin; JMML, juvenile myelomonocytic leukaemia; M, male; MCNU, ranimustine; Mel, melphalan; MM, multiple myeloma; MME, mycophenolate mofetil; MRCNS, methicillin-resistant coagulase negative *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; ND, not detected; NHL, non-Hodgkin lymphoma; NR, not referred; PBSC, peripheral blood stem cell; r, related; (R), recipient-derived; Ref, reference; RT, radiation therapy; ur, unrelated; sEF, secondary engraftment failure; sMTX, short-term methotrexate; TAC, tacrolimus; TBI, total body irradiation; TSP, tespamine; VP16, etoposide.

engraftment failure after CBT and HPS might be one of the relevant mechanisms. HLA disparity in the graft-versus-host direction may augment allo-immune reactions, which evoke hypercytokinaemia, macrophage activation, and occasionally result in establishment of HPS. Indeed, most of our patients received cord blood units with an HLA mismatch due to the limited availability of cord blood units with a sufficient cell dose, and received relatively less intensive GVHD prophylaxis using calcineurin inhibitor alone. Thus, the donor T cells in the grafts were more susceptible to stimuli of cytokines triggered by infections and tissue damage from preparative regimens. In most of the other reported series, methotrexate (MTX), anti-thymocyte globulin (ATG), steroid, or MMF was used along with calcineurin inhibitor for GVHD prophylaxis and there are little reports about HPS. More intensive immunosuppression may have a positive effect on preventing post-transplant immune reactions (Narimatsu *et al*, 2007b) and the development of HPS.

An optimal strategy has not been established to treat HPS, especially after HSCT. Although CS was administered at the discretion of the primary physician to 13 HPS patients to reduce macrophage activation, HPS was resolved in only three patients and all four who could tolerate a second rescue CBT achieved durable engraftment.

In conclusion, HPS is a significant complication associated with engraftment delay and failure following CBT. The development of HPS increased mortality rates after CBT, worsening the prognosis. The precise mechanism of HPS development after HSCT remains unknown, although several lines of evidence suggest that donor immune cells are critically involved and therefore a key. The identification of high risk patients, more intensified GVHD prophylaxis, close and careful follow-up and prompt differential diagnosis are important for managing HSCT-HPS and avoiding engraftment failure. More detailed data from patients who have undergone CBT as well as other types of transplantation are warranted to further understand the mechanisms behind the development of HSCT-HPS and to develop more effective prophylaxis and treatment for this complication.

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Authors' contribution

S. Takagi and K.M. performed research and extracted data; Y.O., K.O. and A.Y. reviewed histopathological findings; N.M. and S. Takagi performed statistical analysis; N.U. and

S. Taniguchi reviewed study design and methods; K.I., A.H., M.T., H.Y., D.K., Y.M., E.K., S.S., T.M., S. Miyakoshi and S. Makino contributed to writing the paper.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

References

- Abe, Y., Choi, I., Hara, K., Matsushima, T., Nishimura, J., Inaba, S., Nawata, H. & Muta, K. (2002) Hemophagocytic syndrome: a rare complication of allogeneic nonmyeloablative hematopoietic stem cell transplantation. *Bone Marrow Transplantation*, **29**, 799–801.
- Ballen, K.K., Spitzer, T.R., Yeap, B.Y., McAfee, S., Dey, B.R., Attar, E., Haspel, R., Kao, G., Liney, D., Aleya, E., Lee, S., Cutler, C., Ho, V., Soiffer, R. & Antin, J.H. (2007) Double unrelated reduced-intensity umbilical cord blood transplantation in adults. *Biology of Blood and Marrow Transplantation*, **13**, 82–89.
- Barker, J.N., Weisdorf, D.J., DeFor, T.E., Blazar, B.R., Miller, J.S. & Wagner, J.E. (2003) Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced-intensity conditioning. *Blood*, **102**, 1915–1919.
- Barker, J.N., Weisdorf, D.J., DeFor, T.E., Blazar, B.R., McGlave, P.B., Miller, J.S., Verfaillie, C.M. & Wagner, J.E. (2005) Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. *Blood*, **105**, 1343–1347.
- Boelens, J.J., Lazo, G., Gaiser, J.F. & Wulffraat, N.M. (2006) Epstein-Barr virus-associated haemophagocytic lympho-histiocytosis after stem cell transplantation. *Bone Marrow Transplantation*, **38**, 709–710.
- Brunstein, C.G., Barker, J.N., Weisdorf, D.J., DeFor, T.E., Miller, J.S., Blazar, B.R., McGlave, P.B. & Wagner, J.E. (2007) Umbilical cord blood transplantation after nonmyeloablative conditioning: impact on transplantation outcomes in 110 adults with hematologic disease. *Blood*, **110**, 3064–3070.
- Chao, N.J., Koh, L.P., Long, G.D., Gasparetto, C., Horwitz, M., Morris, A., Lassiter, M., Sullivan, K.M. & Rizzieri, D.A. (2004) Adult recipients of umbilical cord blood transplants after nonmyeloablative preparative regimens. *Biology of Blood and Marrow Transplantation*, **10**, 569–575.
- Fernandez, M.N., Regidor, C., Cabrera, R., Garcia-Marco, J.A., Fores, R., Sanjuan, I., Gayoso, J., Gil, S., Ruiz, E., Little, A.M., McWhinnie, A. & Madrigal, A. (2003) Unrelated umbilical cord blood transplants in adults: early recovery of neutrophils by supportive co-transplantation of a low number of highly purified peripheral blood CD34+ cells from an HLA-haploidentical donor. *Experimental Hematology*, **31**, 535–544.
- Fukuno, K., Tsurumi, H., Yamada, T., Oyama, M. & Moriwaki, H. (2001) Graft failure due to hemophagocytic syndrome after autologous peripheral blood stem cell transplantation. *International Journal of Hematology*, **73**, 262–265.
- Gooley, T.A., Leisenring, W., Crowley, J. & Storer, B.E. (1999) Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Statistics in Medicine*, **18**, 695–706.
- Henter, J.I., Elinder, G. & Ost, A. (1991) Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. *Seminars in Oncology*, **18**, 29–33.

- Hughes, W.T., Armstrong, D., Bodey, G.P., Bow, E.J., Brown, A.E., Calandra, T., Feld, R., Pizzo, P.A., Rolston, K.V., Shenep, J.L. & Young, L.S. (2002) 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clinical Infectious Diseases*, **34**, 730–751.
- Imashuku, S. (1997) Differential diagnosis of hemophagocytic syndrome: underlying disorders and selection of the most effective treatment. *International Journal of Hematology*, **66**, 135–151.
- Ishida, H., Yoshida, H., Yoshihara, T., Ito, M. & Morimoto, A. (2007) Origin of macrophages involved in the development of allogeneic hematopoietic stem cell transplantation-associated hemophagocytic syndrome: observations on a patient with juvenile myelomonocytic leukemia. *Bone Marrow Transplantation*, **40**, 701–703.
- Ishikawa, J., Maeda, T., Miyazaki, T., Manabe, N., Honda, S., Nishiura, T., Tomiyama, Y. & Matsuzawa, Y. (2000) Early onset of hemophagocytic syndrome following allogeneic bone marrow transplantation. *International Journal of Hematology*, **72**, 243–246.
- Jacobsohn, D.A., Duerst, R., Tse, W. & Kletzel, M. (2004) Reduced intensity haemopoietic stem-cell transplantation for treatment of non-malignant diseases in children. *Lancet*, **364**, 156–162.
- Kishi, Y., Kami, M., Murashige, N., Tanaka, Y., Haraguchi, K., Fujisaki, G., Kusumoto, S., Mori, S.I., Takaue, Y. & Tanosaki, R. (2005a) Hyperacute GVHD and emergence of peripheral CD3+ CD56+ T cells and activated natural killer cells are useful markers for early diagnosis of post-transplant hemophagocytic syndrome. *Bone Marrow Transplantation*, **35**, 415–417.
- Kishi, Y., Kami, M., Miyakoshi, S., Kanda, Y., Murashige, N., Teshima, T., Kusumi, E., Hara, S., Matsumura, T., Yuji, K., Masuoka, K., Wake, A., Morinaga, S., Kanemaru, M., Hayashi, T., Tanaka, Y. & Taniguchi, S. (2005b) Early immune reaction after reduced-intensity cord-blood transplantation for adult patients. *Transplantation*, **80**, 34–40.
- Komatsu, T., Narimatsu, H., Yoshimi, A., Kurita, N., Kusakabe, M., Hori, A., Murashige, N., Matsumura, T., Kobayashi, K., Yuji, K., Tanaka, Y. & Kami, M. (2007) Successful engraftment of mismatched unrelated cord blood transplantation following reduced intensity preparative regimen using fludarabine and busulfan. *Annals of Hematology*, **86**, 49–54.
- Koyama, M., Sawada, A., Yasui, M., Inoue, M. & Kawa, K. (2007) Encouraging results of low-dose etoposide in the treatment of early-onset hemophagocytic syndrome following allogeneic hematopoietic stem cell transplantation. *International Journal of Hematology*, **86**, 466–467.
- Laughlin, M.J., Eapen, M., Rubinstein, P., Wagner, J.E., Zhang, M.J., Champlin, R.E., Stevens, C., Barker, J.N., Gale, R.P., Lazarus, H.M., Marks, D.I., van Rood, J.J., Scaradavou, A. & Horowitz, M.M. (2004) Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. *New England Journal of Medicine*, **351**, 2265–2275.
- Levy, J., Wodell, R.A., August, C.S. & Bayever, E. (1990) Adenovirus-related hemophagocytic syndrome after bone marrow transplantation. *Bone Marrow Transplantation*, **6**, 349–352.
- Matsumura, T., Narimatsu, H., Kami, M., Yuji, K., Kusumi, E., Hori, A., Murashige, N., Tanaka, Y., Masuoka, K., Wake, A., Miyakoshi, S., Kanda, Y. & Taniguchi, S. (2007) Cytomegalovirus infections following umbilical cord blood transplantation using reduced intensity conditioning regimens for adult patients. *Biology of Blood and Marrow Transplantation*, **13**, 577–583.
- Matsuno, N., Wake, A., Uchida, N., Ishiwata, K., Araoka, H., Takagi, S., Tsuji, M., Yamamoto, H., Kato, D., Matsuhashi, Y., Seo, S., Masuoka, K., Miyakoshi, S., Makino, S., Yoneyama, A., Kanda, Y. & Taniguchi, S. (2009) Impact of HLA disparity in the graft-versus-host direction on engraftment in adult patients receiving reduced-intensity cord blood transplantation. *Blood*, doi:10.1182/blood-2008-12-194696.
- Misawa, M., Kai, S., Okada, M., Nakajima, T., Nomura, K., Wakae, T., Toda, A., Itoi, H., Takatsuka, H., Itsukuma, T., Nishioka, K., Fujimori, Y., Ogawa, H. & Hara, H. (2006) Reduced-intensity conditioning followed by unrelated umbilical cord blood transplantation for advanced hematologic malignancies: rapid engraftment in bone marrow. *International Journal of Hematology*, **83**, 74–79.
- Miyakoshi, S., Yuji, K., Kami, M., Kusumi, E., Kishi, Y., Kobayashi, K., Murashige, N., Hamaki, T., Kim, S.W., Ueyama, J., Mori, S., Morinaga, S., Muto, Y., Masuo, S., Kanemaru, M., Hayashi, T., Takaue, Y. & Taniguchi, S. (2004) Successful engraftment after reduced-intensity umbilical cord blood transplantation for adult patients with advanced hematological diseases. *Clinical Cancer Research*, **10**, 3586–3592.
- Miyakoshi, S., Kami, M., Tanimoto, T., Yamaguchi, T., Narimatsu, H., Kusumi, E., Matsumura, T., Takagi, S., Kato, D., Kishi, Y., Murashige, N., Yuji, K., Uchida, N., Masuoka, K., Wake, A. & Taniguchi, S. (2007) Tacrolimus as prophylaxis for acute graft-versus-host disease in reduced intensity cord blood transplantation for adult patients with advanced hematologic diseases. *Transplantation*, **84**, 316–322.
- Nagafuji, K., Eto, T., Hayashi, S., Tokunaga, Y., Gondo, H. & Niho, Y. (1998) Fatal cytomegalovirus interstitial pneumonia following autologous peripheral blood stem cell transplantation. Fukuoka Bone Marrow Transplantation Group. *Bone Marrow Transplantation*, **21**, 301–303.
- Narimatsu, H., Kami, M., Kato, D., Matsumura, T., Murashige, N., Kusumi, E., Yuji, K., Hori, A., Shibata, T., Masuoka, K., Wake, A., Miyakoshi, S., Morinaga, S. & Taniguchi, S. (2007a) Reduced dose of foscarnet as preemptive therapy for cytomegalovirus infection following reduced-intensity cord blood transplantation. *Transplant Infectious Disease*, **9**, 11–15.
- Narimatsu, H., Terakura, S., Matsuo, K., Oba, T., Uchida, T., Iida, H., Hamaguchi, M., Watanabe, M., Kohno, A., Murata, M., Sawa, M., Miyamura, K. & Morishita, Y. (2007b) Short-term methotrexate could reduce early immune reactions and improve outcomes in umbilical cord blood transplantation for adults. *Bone Marrow Transplantation*, **39**, 31–39.
- Nishihira, H., Kato, K., Isoyama, K., Takahashi, T.A., Kai, S., Kato, S., Takanashi, M., Sato, N., Sato, H., Kitajima, K., Naoe, T. & Saito, H. (2003) The Japanese cord blood bank network experience with cord blood transplantation from unrelated donors for hematological malignancies: an evaluation of graft-versus-host disease prophylaxis. *British Journal of Haematology*, **120**, 516–522.
- Ostronoff, M., Ostronoff, F., Coutinho, M., Calixto, R., Souto Maior, A.P., Sucupira, A., Florencio, R. & Tagliari, C. (2006) Hemophagocytic syndrome after autologous peripheral blood stem cell transplantation for multiple myeloma; successful treatment with high-dose intravenous immunoglobulin. *Bone Marrow Transplantation*, **37**, 797–798.
- Reardon, D.A., Roskos, R., Hanson, C.A. & Castle, V. (1991) Virus-associated hemophagocytic syndrome following bone marrow transplantation. *The American Journal of Pediatric Hematology/Oncology*, **13**, 305–309.
- Reddy, P. & Ferrara, J.L. (2003) Immunobiology of acute graft-versus-host disease. *Blood Reviews*, **17**, 187–194.

- Rocha, V., Labopin, M., Sanz, G., Arcese, W., Schwerdtfeger, R., Bosi, A., Jacobsen, N., Ruutu, T., de Lima, M., Finke, J., Frasson, F. & Gluckman, E. (2004) Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *New England Journal of Medicine*, **351**, 2276–2285.
- Sato, M., Matsushima, T., Takada, S., Hatsumi, N., Kim, K., Sakuraya, M., Saito, T., Tamura, J., Karasawa, M., Murakami, H. & Naruse, T. (1998) Fulminant, CMV-associated, haemophagocytic syndrome following unrelated bone marrow transplantation. *Bone Marrow Transplantation*, **22**, 1219–1222.
- Shpall, E.J., Quinones, R., Giller, R., Zeng, C., Baron, A.E., Jones, R.B., Bearman, S.I., Nieto, Y., Freed, B., Madinger, N., Hogan, C.J., Slat-Vasquez, V., Russell, P., Blunk, B., Schissel, D., Hild, E., Malcolm, J., Ward, W. & McNiece, I.K. (2002) Transplantation of ex vivo expanded cord blood. *Biology of Blood and Marrow Transplantation*, **8**, 368–376.
- Sokal, E., Michel, M., Ninane, J., Latinne, D., de Bruyere, M. & Cornu, G. (1987) Bone marrow transplantation from an unrelated donor for Fanconi's anaemia: two unusual complications. *Bone Marrow Transplantation*, **2**, 99–102.
- Takahashi, T., Kanda, Y., Mori, M., Saito, T., Chiba, S., Mitani, K., Hirai, H. & Yazaki, Y. (1998) B cell lymphoma-associated hemophagocytic syndrome after PBSCT. *Bone Marrow Transplantation*, **21**, 623–625.
- Takahashi, S., Iseki, T., Ooi, J., Tomonari, A., Takasugi, K., Shimohakamada, Y., Yamada, T., Uchimar, K., Tojo, A., Shirafuji, N., Kodo, H., Tani, K., Takahashi, T., Yamaguchi, T. & Asano, S. (2004) Single-institute comparative analysis of unrelated bone marrow transplantation and cord blood transplantation for adult patients with hematologic malignancies. *Blood*, **104**, 3813–3820.
- Tanaka, T., Matsubara, H., Adachi, S., Chang, H., Fujino, H., Higashi, Y., Yasumi, T., Kobayashi, M., Watanabe, K., Takahashi, M., Kobayashi, Y., Maruya, E., Saji, H. & Nakahata, T. (2004) Second transplantation from HLA 2-loci-mismatched mother for graft failure due to hemophagocytic syndrome after cord blood transplantation. *International Journal of Hematology*, **80**, 467–469.
- Tanaka, H., Ohwada, C., Sakaida, E., Takeda, Y., Abe, D., Oda, K., Ozawa, S., Shimizu, N., Masuda, S., Cho, R., Nishimura, M., Saito, Y. & Nakaseko, C. (2007) Successful engraftment by second cord blood transplantation with reduced-intensity conditioning after graft rejection due to hemophagocytic syndrome following initial CBT. *Bone Marrow Transplantation*, **40**, 995–996.
- Thiede, C., Florek, M., Bornhauser, M., Ritter, M., Mohr, B., Brendel, C., Ehninger, G. & Neubauer, A. (1999) Rapid quantification of mixed chimerism using multiplex amplification of short tandem repeat markers and fluorescence detection. *Bone Marrow Transplantation*, **23**, 1055–1060.
- Tsuda, H. (1997) Hemophagocytic syndrome (HPS) in children and adults. *International Journal of Hematology*, **65**, 215–226.
- Uchida, N., Wake, A., Takagi, S., Yamamoto, H., Kato, D., Matsuhashi, Y., Matsumura, T., Seo, S., Matsuno, N., Masuoka, K., Kusumi, E., Yuji, K., Miyakoshi, S., Matsuzaki, M., Yoneyama, A. & Taniguchi, S. (2008) Umbilical cord blood transplantation after reduced-intensity conditioning for elderly patients with hematologic diseases. *Biology of Blood and Marrow Transplantation*, **14**, 583–590.
- Yuji, K., Miyakoshi, S., Kato, D., Miura, Y., Myojo, T., Murashige, N., Kishi, Y., Kobayashi, K., Kusumi, E., Narimatsu, H., Hamaki, T., Matsumura, T., Kami, M., Fukuda, T., Masuo, S., Masuoka, K., Wake, A., Ueyama, J., Yoneyama, A., Miyamoto, K., Nagoshi, H., Matsuzaki, M., Morinaga, S., Muto, Y., Takeue, Y. & Taniguchi, S. (2005) Reduced-intensity unrelated cord blood transplantation for patients with advanced malignant lymphoma. *Biology of Blood and Marrow Transplantation*, **11**, 314–318.

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Impact of HLA disparity in the graft-versus-host direction on engraftment in adult patients receiving reduced-intensity cord blood transplantation

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Delayed engraftment or graft failure is one of the major complications after cord blood transplantation (CBT). To investigate factors impacting engraftment, we conducted a retrospective analysis of adult patients who underwent reduced-intensity CBT at our institute, in which preparative regimens mainly consisted of fludarabine, melphalan, and total body irradiation with graft-versus-host (GVH) disease prophylaxis using single calcineurin inhibitors. Among 152 evaluable

patients, the cumulative incidence of neutrophil engraftment was 89%. High total nucleated cell and CD34⁺ cell dose were associated with the faster speed and higher probability of engraftment. In addition, the degree of human leukocyte antigen (HLA) mismatch in the GVH direction was inversely associated with engraftment kinetics, whereas no statistically significant association was observed with the degree of HLA mismatch in the host-versus-graft direction. Similarly, the num-

ber of HLA class I antigens mismatched in the GVH direction, but not in the host-versus-graft direction, showed a negative correlation with engraftment kinetics. HLA disparity did not have significant impact on the development of GVH disease or survival. This result indicates the significant role of HLA disparity in the GVH direction in the successful engraftment, raising the novel mechanism responsible for graft failure in CBT. (Blood. 2009;114:1689-1695)

Introduction

Recent studies have demonstrated cord blood transplantation (CBT) as a safe and feasible alternative to bone marrow (BM) or peripheral blood (PB) stem cell transplantation (SCT) in adults when no suitable related donor is available.¹⁻⁴ The incidence and severity of acute graft-versus-host disease (GVHD) after CBT have been low compared with those after unrelated donor BM transplantation,¹⁻⁴ permitting use of a mismatched unit as a graft. The use of CBT has also been increasing because of the potential advantage of rapid availability and the lower risk to donors. The development of reduced-intensity (RI) conditioning regimens for transplantation, which results in less toxicity and depends largely on graft-versus-tumor effects rather than high-dose therapy to eliminate malignant cells, has been shown to allow elderly patients to undergo allogeneic transplantation.^{5,6} We and other groups have reported the feasibility of RI-CBT for adult patients with advanced hematologic diseases.⁷⁻¹²

Despite the obvious advantage of CBT, high treatment-related toxicity has been observed, which precludes the application of CBT as a primary graft source. One of the major complications of CBT is delayed engraftment or graft failure. Thus far, several factors have been found to impact engraftment, including total nucleated cell (TNC) dose, CD34⁺ cell dose, and human leukocyte antigen (HLA) disparity.¹³⁻¹⁵ Here, we report the results of a retrospective analysis of 163 adult patients who underwent RI-CBT at our institute, which revealed, for the first time, the importance of HLA disparity in the graft-versus-host (GVH) direction, adding a new viable factor in choosing cord blood (CB) units as transplantable grafts.

Methods

Study patients

This study included adult patients with hematologic malignancies who underwent RI-CBT as their first allogeneic SCT at Toranomon Hospital between January 2002 and December 2006 consecutively. Twenty-nine patients who had active serious infection or showed an Eastern Cooperative Oncology Group performance status of 3 or 4 before transplantation were not eligible for this study because of differences in transplantation procedures or supportive care resulting from serious organ dysfunction and active infection. Then, the remaining 163 consecutive patients were reviewed. All patients had diseases that were incurable with conventional treatments, lacked suitable sibling or unrelated donors, and were considered inappropriate for conventional allo-SCT as they were older than 50 years and/or had organ dysfunction (often attributable to previous intense chemotherapy and/or radiotherapy). Characteristics of the 163 patients are summarized in Table 1.

For disease status, those with hematologic malignancies in the first or second complete remission at the time of transplantation, those in the chronic phase or accelerated phase of chronic myeloid leukemia, and those with refractory anemia of myelodysplastic syndrome were defined as being at standard risk (n = 32), whereas those in other situations were defined as being at high risk (n = 131). All patients received a single CB unit. All patients provided written informed consent in accordance with the Declaration of Helsinki, and the study was conducted in accordance with the requirements of the Institutional Review Board of Toranomon Hospital.

Donor selection

CB units were obtained from the Japanese Cord Blood Bank Network. All CB samples, as well as the patient's blood samples, were serologically typed for HLA-A, -B and -DR antigens before transplantation. Alleles at the HLA-A, -B,

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Table 1. Patient and cord blood characteristics

Variable	Value
No. of patients	163
Median age, y (range)	55 (17-79)
Sex: male/female, no. of patients	98/65
Primary diseases, no. of patients	
Acute lymphoblastic leukemia	20
Acute myeloid leukemia	63
Chronic myelogenous leukemia	5
Myelodysplastic syndrome	12
Malignant lymphoma	39
Adult T-cell leukemia/lymphoma	18
Multiple myeloma	2
Others	4
Risk of underlying disease, no. of patients: standard/high	32/131
Preparative regimens, no. of patients	
Flu + Mel + TBI 2-8 Gy	135
Flu + BU + TBI 4-8 Gy	18
Flu + Mel	6
Flu + BU	4
Median no. of infused nucleated cells, 10^7 /kg (range)	2.68 (1.82-4.83)
Median no. of infused CD34 ⁺ cells, 10^5 /kg (range)	0.76 (0.05-4.40)
Blood-type mismatch, no. of patients: match/mismatch	47/116
HLA antigen mismatch, no. of patients	
0	3
1	24
2	136
GVHD prophylaxis, no. of patients	
Cyclosporine A alone	73
Tacrolimus alone	90

Flu indicates fludarabine; Mel, melphalan; TBI, total body irradiation; and BU, busulfan.

and -DRB1 loci were identified by high-resolution DNA typing in 107 pairs because HLA typing of alleles was not routinely performed in Japanese CB banks. In 127 pairs, HLA-A and -B antigens were identified by serologic typing and HLA-DRB1 alleles were determined by high-resolution DNA typing. CB grafts had at most 2 mismatches for HLA-A, -B, and -DR antigens and had a cryopreserved cell dose of at least 1.8×10^7 nucleated cells per kg of recipient body weight. Mismatch was counted separately in the GVH and host-versus-graft (HVG) direction, respectively. HLA mismatch in the GVH direction was defined when the recipient's antigens or alleles were not shared by the donor, whereas HLA mismatch in the HVG direction was defined when the donor's antigens or alleles were not shared by the recipient.

Transplantation procedures

Pretransplantation conditioning regimens varied and were determined by each attending physician according to the patient's disease, disease status, and history of prior therapy. All patients received purine analog-based preparative regimens. The majority of patients ($n = 119$) received preparative regimens consisting of

fludarabine 125 mg/m^2 , melphalan 80 mg/m^2 , and 4 Gy total body irradiation (TBI). Patients in relatively poor performance status were conditioned with busulfan to avoid severe gastrointestinal tract toxicity induced by the use of melphalan. GVHD prophylaxis was carried out using a continuous infusion of cyclosporine A 3 mg/kg or tacrolimus 0.03 mg/kg from day -1 until the patients could tolerate oral administration.

Supportive care

All patients were treated in reverse isolation in laminar airflow-equipped rooms and received trimethoprim/sulfamethoxazole for *Pneumocystis jirovecii* prophylaxis. Fluoroquinolone, azole, and acyclovir were administered to prevent bacterial, fungal, and herpes virus infection, respectively. Cytomegalovirus pp65 antigenemia was monitored weekly. Hemoglobin and platelet counts were maintained at more than 7 g/dL and at $10 \times 10^9/\text{L}$, respectively. Granulocyte colony-stimulating factor was administered intravenously from day 1 until neutrophil recovery became durable.

Definition of engraftment, GVHD, and survival

Date of engraftment was defined as the first of 3 consecutive days when the neutrophil counts exceeded $0.5 \times 10^9/\text{L}$. Patients who did not achieve this criterion at any time after transplantation were considered as primary graft failure. Chimerism was assessed using fluorescent in situ hybridization in sex-mismatched donor-recipient pairs. In sex-matched pairs, polymerase chain reaction for variable numbers of tandem repeats was used with donor cells detected at a sensitivity of 10%. Acute and chronic GVHD was diagnosed and graded according to standard criteria.^{16,17} Overall survival was calculated from the day of transplantation until death from any cause or last follow-up. Event-free survival was defined as the duration of survival after transplantation without disease progression, relapse, graft failure, or death. Final follow-up was conducted in December 2007, with a median follow-up of surviving patients being 29.0 months (range, 3.7-58.9 months).

Statistical methods

Cumulative incidence of neutrophil engraftment was calculated using the Gray method, treating death before engraftment or second transplantation as competing events.¹⁸ Similarly, in the analysis of GVHD, death resulting from other causes or relapse leading to early withdrawal of immune suppression was considered competing risk. The probabilities of survival were estimated using the Kaplan-Meier method. Multivariate analysis was performed using the proportional hazards model. P values $< .05$ were considered statistically significant.

Results

Engraftment

Eleven of the 163 patients reviewed were not evaluable for the analyses of donor engraftment resulting from early death (before 28 days after

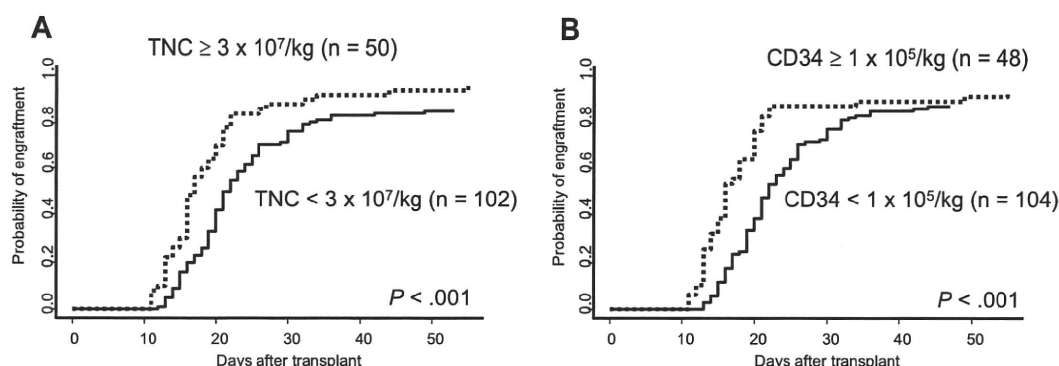


Figure 1. Cumulative incidence of neutrophil engraftment. (A) Effect of TNC dose. (B) Effect of CD34⁺ cell dose.

transplantation) from disease progression ($n = 1$), infection ($n = 6$), and multiple organ failure ($n = 4$). Of 152 evaluable patients, 135 patients achieved neutrophil engraftment. The cumulative incidence of engraftment at day 60 was 89%, and the median time to engraftment was 20 days (range, 11-55 days). Chimerism analyses were performed in 125 of 135 patients who achieved engraftment using either PB or BM samples at the time of neutrophil recovery. All patients except for one who had residual leukemic cells in PB at the time of engraftment showed complete donor chimerism ($> 90\%$). The median length of time required to donor chimerism was 22 days (range, 11-55 days).

Age, recipient sex, risk of underlying disease, blood type mismatch, and GVHD prophylaxis did not affect engraftment kinetics (data not shown). TNC more than or equal to $3 \times 10^7/\text{kg}$ was associated with a significantly higher probability of engraftment ($P < .001$), with the median time to engraftment of 16.5 days (range, 11-55 days) compared with 21 days (range, 12-49 days) for those who received less than $3 \times 10^7/\text{kg}$ (Figure 1A). Similarly, $\text{CD}34^+$ cell dose more than or equal to $10^5/\text{kg}$ was associated with a significantly faster engraftment ($P < .001$) than those who received less than $10^5/\text{kg}$ (Figure 1B).

The cumulative incidence of engraftment and the time to engraftment according to the degree of HLA mismatch are shown in Table 2. Patients who had 0 and 1 antigen mismatch with the grafts were combined, considering the small number of patients in 0 mismatch group and comparable rate of engraftment and time to neutrophil recovery between 0 and 1 antigen-mismatched group (Figure 2A-B), and were compared with those of 2 antigens mismatched. Although patients with 0 or 1 antigen mismatch showed a trend toward superior engraftment kinetics compared with patients with 2 antigens mismatched, the differences did not reach statistical significance (Figure 2A; Table 2). We further analyzed the influence of HLA disparity on engraftment in both the HVG and GVH direction. In the HVG direction, the cumulative incidence of engraftment at day 60 was 93% in 0 or 1 antigen mismatch and 87% in 2 antigens mismatched ($P = .4$, Table 2). In the GVH direction, however, the cumulative incidence of engraftment was 96% in 0 or 1 antigen mismatch and 85% in 2 antigens mismatched ($P < .001$, Figure 2B; Table 2), demonstrating that HLA antigen disparity in the GVH direction was significantly associated with engraftment kinetics. As shown in Figure 2C, HLA antigen disparity in the HVG direction did not contribute to engraftment kinetics in patients with 0 or 1 antigen mismatch in the GVH direction, as was also observed in those with 2 antigens mismatched in the GVH direction. Although the number of patients in each group was small, patients with 0 or 1 mismatch in the GVH direction but 2 mismatches in the HVG direction ($n = 28$) showed a trend toward superior engraftment kinetics compared with patients with 0 or 1 mismatch in the HVG direction but 2 mismatches in the GVH direction ($n = 18$; $P = .07$). This finding may indicate that HLA disparity in the GVH direction plays a greater role in engraftment than that in the HVG direction.

In addition to the degree of mismatch, we analyzed the significance of class I (HLA-A, -B) or class II (HLA-DR) mismatch (Table 2). The number of class I antigens mismatched in the GVH direction showed a negative correlation with the probability and the speed of engraftment ($P = .006$, Figure 2D), but not in the HVG or both directions. More specifically, the presence of HLA-B antigens mismatched in the GVH direction was significantly associated with inferior engraftment kinetics ($P = .04$). To the contrary, HLA-DR antigen mismatch did not influence engraftment kinetics in either the HVG or the GVH direction.

The cumulative incidence of engraftment was also assessed using 120 pairs who had HLA-A, -B antigens and -DRB1 allele information available (Table 2). Patients with 0 or 1 mismatch

showed better engraftment kinetics compared with those with 2, 3, or 4 mismatches in the GVH direction, which was about to be significant statistically ($P = .05$), whereas HLA mismatch in the HVG direction did not show significant impact on engraftment.

HLA allele mismatch at the HLA-A, -B, and -DR was examined in 102 pairs. In the GVH direction, the cumulative incidence of engraftment was 94% in 0 or 1 allele mismatch, 88% in 2 alleles mismatched, and 80% in 3 to 5 alleles mismatched ($P = .05$), showing that alleles mismatched in the GVH direction could be inversely associated with engraftment kinetics (Table 2). In contrast, allele disparity in the HVG direction did not affect engraftment (Table 2). When HLA-A, -B, and -DR alleles were analyzed independently, no statistically significant differences were observed in any allele tested in either the GVH or HVG direction (data not shown).

Multivariate analyses revealed that low TNC dose ($< 3 \times 10^7/\text{kg}$) and HLA antigens mismatched in the GVH direction (0 or 1 vs 2 antigens mismatched) were significantly associated with inferior engraftment kinetics, when age, recipient sex, risk of underlying disease, GVHD prophylaxis, and blood type mismatch were included as covariates ($P = .002$ and $P = .004$, respectively).

Clinical features of graft failure

There were 17 patients who failed to achieve engraftment: 8 males and 9 females, median age of 55 years (range, 17-68 years), high-risk diseases in 12 patients. Median TNC dose of CB grafts was $2.36 \times 10^7/\text{kg}$ (range, 2.01 - $3.40 \times 10^7/\text{kg}$), and median $\text{CD}34^+$ cell dose was $0.59 \times 10^5/\text{kg}$ (range, 0.30 - $1.38 \times 10^5/\text{kg}$). Nine of them died before engraftment because of disease progression ($n = 2$), infection ($n = 5$), multiple organ failure ($n = 1$), and idiopathic pneumonia syndrome ($n = 1$). The remaining 8 patients received a second RI-CBT at a median of 34 days (range, 28-49 days) after first RI-CBT, and 3 of them were alive in remission.

Among those who did not achieve engraftment, chimerism analyses in the BM early after transplantation were performed on 8 patients (median, 12 days; range, 10-17 days). Of those, 4 achieved complete donor chimerism, one had mixed chimerism (60% donor type), and 3 patients showed recipient chimerism. Four of 5 patients with donor dominant chimerism showed hemophagocytosis in the BM. On the other hand, all 3 patients with recipient chimerism did not show hemophagocytosis.

GVHD and survival

Among 134 evaluable patients, the cumulative incidence of acute GVHD of grade II to IV was 43%. The incidence of acute GVHD according to HLA disparity in the GVH direction was summarized in Table 3. Patients with 2 antigens mismatched showed a trend toward higher incidence of acute GVHD II-IV ($P = .08$). The number of class I or class II antigens mismatched had no correlation with the incidence of acute GVHD. Similarly, HLA disparity in the allele level was not significantly associated with the incidence of acute GVHD. Among 66 evaluable patients, the cumulative incidence of chronic GVHD was 51%. The degree of HLA mismatch was not significantly associated with the incidence of chronic GVHD (data not shown). Other pretransplantation factors, including age, infused cells, and GVHD prophylaxis, did not affect the incidence of GVHD. Overall survival and event-free survival at 2 years were 35% and 30%, respectively. HLA disparity in the GVH direction, as well as in the HVG direction, did not influence overall survival and event-free survival (Table 3; and data not shown).

Table 2. Univariate analyses of engraftment kinetics according to HLA disparity

No. of HLA mismatches	n	Neutrophil engraftment			P
		Cumulative incidence, %	Median day	Range	
HLA-A, -B, -DR (antigen)					.09
0 + 1	23	91	17	11-30	
2	129	89	20	11-55	
HLA-A, -B, -DR (antigen, HVG)					.4
0 + 1	43	93	19	11-55	
2	109	87	20	11-49	
HLA-A, -B, -DR (antigen, GVH)					< .001
0 + 1	53	96	19	11-36	
2	99	85	20	11-55	
HLA-A, -B (class I antigen)					.1
0	13	92	17	12-30	
1	86	91	20	11-44	
2	53	85	20	11-55	
HLA-A, -B (class I antigen, HVG)					.4
0	22	96	18	12-36	
1	86	89	20	11-55	
2	44	84	20	11-49	
HLA-A, -B (class I antigen, GVH)					.006
0	23	95	17.5	11-36	
1	88	91	20.5	11-44	
2	41	81	20	12-55	
HLA-A (antigen)					.7
0	87	89	19	11-44	
1 + 2	65	89	20	11-55	
HLA-A (antigen, HVG)					.8
0	96	89	20	11-55	
1 + 2	56	89	20	11-49	
HLA-A (antigen, GVH)					.2
0	103	90	19	11-44	
1 + 2	49	86	20	13-55	
HLA-B (antigen)					.07
0	36	94	19	12-34	
1 + 2	116	87	20	11-55	
HLA-B (antigen, HVG)					.06
0	45	95	19	12-36	
1 + 2	107	86	20	11-55	
HLA-B (antigen, GVH)					.04
0	42	95	18.5	11-36	
1 + 2	110	86	20	11-55	
HLA-DR (antigen)					.4
0	70	87	20	11-55	
1 + 2	82	90	19.5	11-44	
HLA-DR (antigen, HVG)					.7
0	76	88	20	11-55	
1 + 2	76	89	20	11-44	
HLA-DR (antigen, GVH)					.8
0	83	88	20	11-55	
1 + 2	69	90	20	11-44	
HLA-A, -B (antigen), -DR (allele)					.5
0 + 1	13	92	18	14-30	
2	63	84	20	11-47	
3 + 4	44	86	20	11-49	
HLA-A, -B (antigen, HVG), -DR (allele, HVG)					.2
0 + 1	25	96	18	11-32	
2	54	80	20	11-44	
3 + 4	41	90	20	11-49	
HLA-A, -B (antigen, GVH), -DR (allele, GVH)					.05
0 + 1	26	96	18	11-36	
2	57	84	19.5	11-49	
3 + 4	37	84	20	11-34	

Table 2. Univariate analyses of engraftment kinetics according to HLA disparity (Continued)

No. of HLA mismatches	Neutrophil engraftment				P
	n	Cumulative incidence, %	Median day	Range	
HLA-A, -B, -DR (allele)					
0 + 1	10	90	18	14-30	.4
2	36	86	20	11-44	
3 + 4 + 5	56	84	19	11-49	
HLA-A, -B, -DR (allele, HVG)					
0 + 1	19	94	19	11-32	.3
2	34	79	20	13-44	
3 + 4 + 5	49	86	21	11-49	
HLA-A, -B, -DR (allele, GVH)					
0 + 1	16	94	17	11-30	.05
2	40	88	20	11-44	
3 + 4 + 5	46	80	20	11-49	

Discussion

Delayed hematopoietic recovery and graft failure are significant concerns in adult CBT. In the present study, median time to engraftment was 20 days, which was comparable with that reported in previous studies.^{1,4,7,19} These data indicate that our pretransplantation conditioning regimens, consisting mainly of fludarabine, melphalan, and 4 Gy TBI, along with single calcineurin inhibitors for GVHD prophylaxis, can exert reasonable immunosuppressive effects that allow rapid hematopoietic recovery after CBT. The engraftment was durable except for disease progression.

Almost all reports on CBT have demonstrated the profound impact of infused cell dose on engraftment.^{13,14,20} We showed that both high numbers of TNCs and CD34⁺ cells were favorably

associated with time to engraftment and the probability of engraftment, confirming previous findings on the association of cell dose with neutrophil recovery. Considering that CD34⁺ cell dose reflects stem cell contents in the CB unit, stem cell dose is one of the major determinants of successful engraftment, as has been observed in the xenogeneic transplantation model.²¹⁻²³

Although our results, demonstrating that HLA disparity in the GVH direction affected engraftment kinetics more than HLA disparity in the HVG direction, may seem paradoxical to the former notion of graft failure that results from graft rejection in most cases, they suggest a novel mechanism of graft failure in CBT. Previously, we have reported that a high incidence of noninfectious high-grade fever often coexisted with eruption, diarrhea, and weight gain, starting on a median of day 9 in more than 50% of the patients receiving CBT.^{8,24} We regarded this reaction as early onset of acute

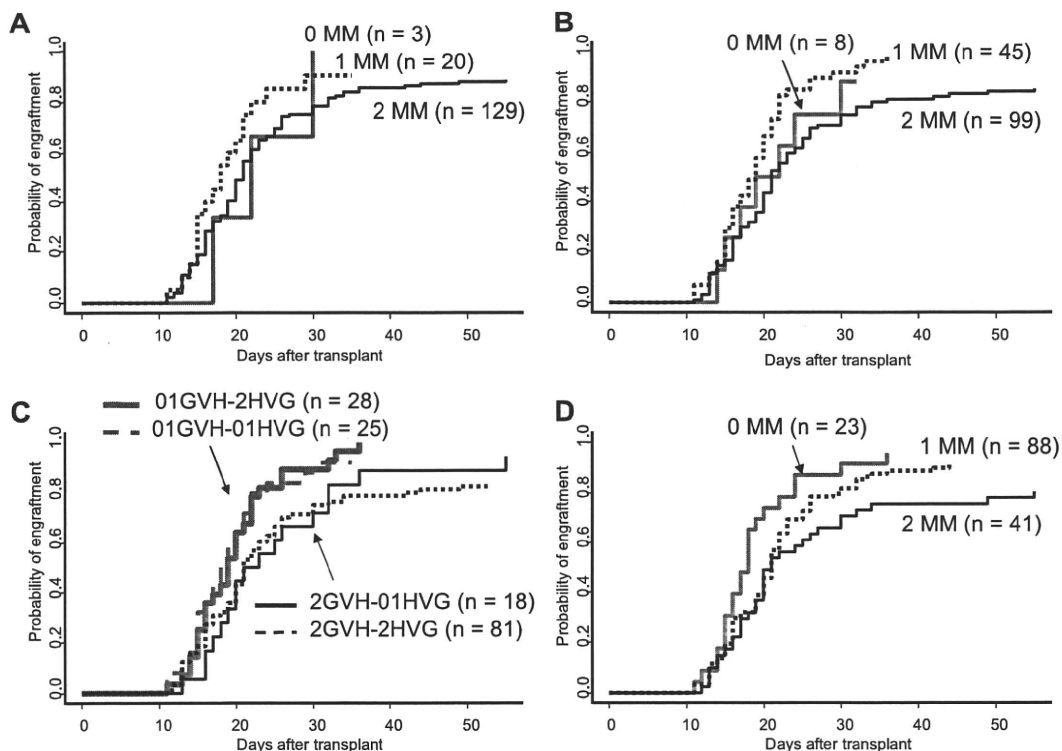


Figure 2. Cumulative incidence of neutrophil engraftment. MM indicates mismatch. (A) Effect of HLA antigen mismatch. (B) Effect of HLA antigen mismatch in the GVH direction. (C) Effect of HLA antigen mismatch according to mismatch both in the GVH and the HVG directions. 2GVH indicates 2 antigens mismatch in the GVH direction; 2HVG, 2 antigens mismatch in the HVG direction; 01GVH, 0 or 1 antigen mismatch in the GVH direction; 01HVG, 0 or 1 antigen mismatch in the HVG direction. (D) Effect of HLA class I antigen mismatch in the GVH direction.

Table 3. Univariate analyses of acute GVHD and survival according to HLA disparity in the GVH direction

No. of HLA mismatches in the GVH direction	Acute GVHD II-IV			2-year overall survival		
	n	Cumulative incidence, %	P	n	Survival rate, %	P
HLA-A, -B, -DR (antigen)			.08			.5
0 + 1	50	33		59	36	
2	84	48		104	35	
HLA-A, -B (class I antigen)			.5			.2
0	22	36		24	54	
1	80	42		96	32	
2	32	46		43	32	
HLA-DR (class II antigen)			.5			.9
0	71	38		91	32	
1 + 2	63	47		72	38	
HLA-A, -B (antigen), -DR (allele)			.4			1.0
0 + 1	25	32		29	38	
2	48	51		60	38	
3 + 4	30	44		38	39	
HLA-A, -B, -DR (allele)			.3			.4
0 + 1	15	27		16	56	
2	35	49		41	37	
3 + 4 + 5	36	51		50	35	

GVHD in which activated donor T cells secreted various cytokines.²⁵ HLA disparity in the GVH direction may augment alloimmune reactions, which evoke hypercytokinemia and macrophage activation and occasionally result in establishment of hemophagocytic syndrome, one of the major complications directly related to graft failure in recipients.²⁶⁻²⁸ Indeed, a considerable number of patients showed hemophagocytosis in the BM with donor dominancy, leading to graft failure, even though we cannot exclude the possibility of graft rejection caused by recipient lymphocytes in some cases. In addition, among those who achieved donor cell engraftment, delayed neutrophil recovery was prominent for those with more HLA mismatch in the GVH direction rather than in the HVG direction. Myelosuppression is commonly observed during acute or chronic GVHD, indicating that GVHD can negatively affect hematopoietic function of the graft, possibly because of an attack on the hematopoiesis-supporting recipient stromal cells²⁹ or production of cytokines from immune cells, such as transforming growth factor- β , known to regulate hematopoiesis negatively.³⁰ The delayed engraftment observed in our study may have been caused by similar mechanisms during the recovery of donor cells. Furthermore, our results demonstrated that HLA class I antigen mismatch in the GVH direction was associated with inferior engraftment. Higher impact of HLA class II disparity on the development of acute GVHD has been reported in National Marrow Donor Program data.³¹ On the contrary, the Japan Marrow Donor Program registry data showed that mismatch in class I had higher impact than that in class II.³² The discrepancy may be explained by unique ethnic background of the Japanese population. The observation shown here may further strengthen our hypothesis that GVH reactions play a crucial role in engraftment process. In the analysis using allele data, the statistical power of HLA disparity in the GVH direction on engraftment had decreased. This discrepancy probably results from the small sample size in each mismatched category but may be suggestive of more powerful immunogenicity of mismatch in antigen rather than allele level.

In the Eurocord registry data, which includes 550 CBTs, HLA disparity was shown to have a negative impact on engraftment, although the effect of direction of mismatch was not described.^{14,33} More specifically, it was reported from the Düsseldorf Cord Blood Bank and Eurocord-Netcord Registry that HLA-A locus high-resolution typing in the HVG direction was associated with reduced cumulative incidence of

engraftment in 122 patients receiving CBT.³⁴ Several reasons may explain this discrepancy from our observations. First, patients included in our study received relatively uniform pretransplantation conditioning regimens consisting mainly of fludarabine, melphalan, and TBI, whereas those in the Eurocord database had more variable pretransplantation conditioning regimens. Second, all of our patients had GVHD prophylaxis using single calcineurin inhibitors, whereas most of those in the Eurocord Registry received additional chemicals or anti-thymocyte globulin. Many institutes use methotrexate,^{35,36} mycophenolate mofetil,^{19,37} corticosteroids,¹³ or anti-thymocyte globulin^{38,39} in combination with a calcineurin inhibitor as GVHD prophylaxis in CBT. Narimatsu et al demonstrated that use of short-term methotrexate was associated with a lower rate of posttransplantation immune reactions without compromising engraftment.³⁶ Thus, more intensive immunosuppression may be beneficial for controlling early immune reactions and overcoming the issue of HLA mismatch. In addition, the unavoidable high incidence of gastrointestinal tract damage caused by TBI or melphalan in preparative regimens may have increased the chance of triggering GVH reactions.⁴⁰

In the present study, HLA disparity had little association with the development of GVHD and survival, despite its obvious impact on engraftment. According to the Eurocord Registry data, better HLA match was not associated with better outcome in hematologic malignancies receiving CBT.²⁰ Further analyses are required to determine whether this is the result of the unique immunologic immaturity of CB or to the heterogeneous patient population with the majority being in the high-risk disease status.

In conclusion, HLA disparity in the GVH direction, especially class I disparity, was found to have a significant impact on engraftment. These results shed light on a novel mechanism responsible for graft failure in CBT and add a valuable clue for choosing a better CB unit to avoid graft failure.

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Authorship

Contribution: N.M. and A.W. performed research and extracted data; A.Y. reviewed histopathologic methods; N.M. and Y.K.

References

- Barker JN, Davies SM, DeFor T, Ramsay NK, Weisdorf DJ, Wagner JE. Survival after transplantation of unrelated donor umbilical cord blood is comparable with that of human leukocyte antigen-matched unrelated donor bone marrow: results of a matched-pair analysis. *Blood*. 2001;97:2957-2961.
- Rocha V, Labopin M, Sanz G, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N Engl J Med*. 2004;351:2276-2285.
- Laughlin MJ, Eapen M, Rubinstein P, et al. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. *N Engl J Med*. 2004;351:2265-2275.
- Takahashi S, Iseki T, Ooi J, et al. Single-institute comparative analysis of unrelated bone marrow transplantation and cord blood transplantation for adult patients with hematologic malignancies. *Blood*. 2004;104:3813-3820.
- Giralt S, Thall PF, Khouri I, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. *Blood*. 2001;97:631-637.
- Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. *Blood*. 1998;91:756-763.
- Barker JN, Weisdorf DJ, DeFor TE, Blazar BR, Miller JS, Wagner JE. Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced-intensity conditioning. *Blood*. 2003;102:1915-1919.
- Miyakoshi S, Yuji K, Kami M, et al. Successful engraftment after reduced-intensity umbilical cord blood transplantation for adult patients with advanced hematologic diseases. *Clin Cancer Res*. 2004;10:3586-3592.
- Ballen KK, Spitzer TR, Yeap BY, et al. Double unrelated reduced-intensity umbilical cord blood transplantation in adults. *Biol Blood Marrow Transplant*. 2007;13:82-89.
- Miyakoshi S, Kami M, Tanimoto T, et al. Tacrolimus as prophylaxis for acute graft-versus-host disease in reduced intensity cord blood transplantation for adult patients with advanced hematologic diseases. *Transplantation*. 2007;84:316-322.
- Uchida N, Wake A, Takagi S, et al. Umbilical cord blood transplantation after reduced-intensity conditioning for elderly patients with hematologic diseases. *Biol Blood Marrow Transplant*. 2008;14:583-590.
- Majhail NS, Brunstein CG, Tomblyn M, et al. Reduced-intensity allogeneic transplant in patients older than 55 years: unrelated umbilical cord blood is safe and effective for patients without a matched related donor. *Biol Blood Marrow Transplant*. 2008;14:282-289.
- Wagner JE, Barker JN, DeFor TE, et al. Transplantation of unrelated donor umbilical cord blood in 102 patients with malignant and nonmalignant diseases: influence of CD34 cell dose and HLA disparity on treatment-related mortality and survival. *Blood*. 2002;100:1611-1618.
- Gluckman E, Rocha V, Arcese W, et al. Factors associated with outcomes of unrelated cord blood transplant: guidelines for donor choice. *Exp Hematol*. 2004;32:397-407.
- Terakura S, Azuma E, Murata M, et al. Hematopoietic engraftment in recipients of unrelated donor umbilical cord blood is affected by the CD34+ and CD8+ cell doses. *Biol Blood Marrow Transplant*. 2007;13:822-830.
- Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995;15:825-828.
- Sullivan KM, Agura E, Anasetti C, et al. Chronic graft-versus-host disease and other late complications of bone marrow transplantation. *Semin Hematol*. 1991;28:250-259.
- Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med*. 1999;18:695-706.
- Brunstein CG, Barker JN, Weisdorf DJ, et al. Umbilical cord blood transplantation after nonmyeloablative conditioning: impact on transplantation outcomes in 110 adults with hematologic disease. *Blood*. 2007;110:3064-3070.
- Gluckman E, Rocha V. Donor selection for unrelated cord blood transplants. *Curr Opin Immunol*. 2006;18:565-570.
- Larochelle A, Vormoor J, Hanenberg H, et al. Identification of primitive human hematopoietic cells capable of repopulating NOD/SCID mouse bone marrow: implications for gene therapy. *Nat Med*. 1996;2:1329-1337.
- Cashman JD, Lapidot T, Wang JC, et al. Kinetic evidence of the regeneration of multilineage hematopoiesis from primitive cells in normal human bone marrow transplanted into immunodeficient mice. *Blood*. 1997;89:4307-4316.
- Ishikawa F, Livingston AG, Wingard JR, Nishikawa S, Ogawa M. An assay for long-term engrafting human hematopoietic cells based on newborn NOD/SCID/beta2-microglobulin(null) mice. *Exp Hematol*. 2002;30:488-494.
- Kishi Y, Kami M, Miyakoshi S, et al. Early immune reaction after reduced-intensity cord-blood transplantation for adult patients. *Transplantation*. 2005;80:34-40.
- Reddy P, Ferrara JL. Immunobiology of acute graft-versus-host disease. *Blood Rev*. 2003;17:187-194.
- Abe Y, Choi I, Hara K, et al. Hemophagocytic syndrome: a rare complication of allogeneic nonmyeloablative hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2002;29:799-801.
- Kishi Y, Kami M, Murashige N, et al. Hyperacute GVHD and emergence of peripheral CD3+CD56+ T cells and activated natural killer cells are useful markers for early diagnosis of post-transplant hemophagocytic syndrome. *Bone Marrow Transplant*. 2005;35:415-417.
- Henter JL, Elinder G, Soder O, Hansson M, Andersson B, Andersson U. Hypercytokinemia in familial hemophagocytic lymphohistiocytosis. *Blood*. 1991;78:2918-2922.
- Hows JM. Mechanisms of graft failure after human marrow transplantation: a review. *Immunol Lett*. 1991;29:77-80.
- Banovic T, MacDonald KP, Morris ES, et al. TGF-beta in allogeneic stem cell transplantation: friend or foe? *Blood*. 2005;106:2206-2214.
- Petersdorf EW, Kollman C, Hurley CK, et al. Effect of HLA class II gene disparity on clinical outcome in unrelated donor hematopoietic cell transplantation for chronic myeloid leukemia: the US National Marrow Donor Program Experience. *Blood*. 2001;98:2922-2929.
- Morishima Y, Sasazuki T, Inoko H, et al. The clinical significance of human leukocyte antigen (HLA) allele compatibility in patients receiving a marrow transplant from serologically HLA-A, HLA-B, and HLA-DR matched unrelated donors. *Blood*. 2002;99:4200-4206.
- Gluckman E, Kogler G, Rocha V. Human leukocyte antigen matching in cord blood transplantation. *Semin Hematol*. 2005;42:85-90.
- Kogler G, Enczmann J, Rocha V, Gluckman E, Wernet P. High-resolution HLA typing by sequencing for HLA-A, -B, -C, -DR, -DQ in 122 unrelated cord blood/patient pair transplants hardly improves long-term clinical outcome. *Bone Marrow Transplant*. 2005;36:1033-1041.
- Takahashi S, Ooi J, Tomonari A, et al. Comparative single-institute analysis of cord blood transplantation from unrelated donors with bone marrow or peripheral blood stem-cell transplants from related donors in adult patients with hematologic malignancies after myeloablative conditioning regimen. *Blood*. 2007;109:1322-1330.
- Narimatsu H, Terakura S, Matsuo K, et al. Short-term methotrexate could reduce early immune reactions and improve outcomes in umbilical cord blood transplantation for adults. *Bone Marrow Transplant*. 2007;39:31-39.
- Osunkwo I, Bessmerly O, Harrison L, et al. A pilot study of tacrolimus and mycophenolate mofetil graft-versus-host disease prophylaxis in childhood and adolescent allogeneic stem cell transplant recipients. *Biol Blood Marrow Transplant*. 2004;10:246-258.
- Sanz GF, Saavedra S, Planelles D, et al. Standardized, unrelated donor cord blood transplantation in adults with hematologic malignancies. *Blood*. 2001;98:2332-2338.
- Lekakis L, Giralt S, Couriel D, et al. Phase II study of unrelated cord blood transplantation for adults with high-risk hematologic malignancies. *Bone Marrow Transplant*. 2006;38:421-426.
- Hill GR, Ferrara JL. The primacy of the gastrointestinal tract as a target organ of acute graft-versus-host disease: rationale for the use of cytokine shields in allogeneic bone marrow transplantation. *Blood*. 2000;95:2754-2759.

SPECIAL REPORT

Hematopoietic SCT activity in Asia: a report from the Asia-Pacific Blood and Marrow Transplantation Group

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The hematopoietic SCT (HSCT) activity in nine Asian countries/regions was surveyed to overview the current situation. Data of 58 113 HSCTs (allogeneic: 63% vs autologous: 37%) performed between 1986 and 2006 by 432 transplant teams were collected. The number of HSCTs has been increasing in the past two decades in most countries/regions. The increase in allogeneic HSCTs is greater than in autologous HSCTs. The proportion of unrelated donors among allogeneic HSCTs in 2006 varied widely from <1% (Iran and Vietnam) to 62% (Japan). The use of each stem cell source, that is, BM, PBSC, cord blood and others (including co-infusion of BM and PBSC), also varied widely (36, 58, 0.1 and 6% in HSCT from related donors, respectively, and 53, 11, 35 and 1% in HSCT from unrelated donors, respectively). HSCTs have been continuously increasing for all indications except for chronic myelogenous leukemia and solid tumors. Hemoglobinopathy is a common indication among non-malignant diseases in many Asian countries/regions except for China, Japan and Korea. This survey clearly shows the recent progress of HSCTs in Asia and also some differences in donor and stem cell selection and disease application among countries/regions.

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Keywords: hematopoietic SCT; registry; Asia

Introduction

Hematopoietic SCT (HSCT) is now an established treatment procedure for many patients suffering from various malignant and non-malignant diseases.^{1–3} Over the past two decades, its use has expanded rapidly, and many changes and progress have occurred in technology, stem cell sources and infrastructure. The activity and the trends of HSCTs are different among countries, reflecting the different disease prevalences, economic situations and availability of donor programs.⁴ HSCT is still a challenge for several countries with low incomes because of its high cost of establishment and maintenance of HSCT system. Recent reports on HSCT from Asian countries suggest the progress of HSCT in this region.^{5–21} However, no comprehensive picture of the current state of HSCT in Asia has been obtained. The Asia-Pacific region consists of countries with various ethnic, economical and social backgrounds. The Asia-Pacific Blood and Marrow Transplantation Group (APBMT) was established in 1990 to promote HSCT in Asia (<http://www.apbmt.org>). In 2006, its data center was established to develop the APBMT Registry to collect data on HSCT in this region. As a first step, we performed a retrospective transplant activity survey to provide an overview of the current state of HSCT in nine Asian countries.

Materials and methods

Data collection

The data on transplants performed between 1986 and 2006 in nine Asian countries/regions (mainland China, Hong Kong, Iran, Japan, Korea, Malaysia, Singapore, Taiwan

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