ASBMT
American Society for Blood and Marrow Transplantation

Incidence and Risk Factors of Early Bacterial Infections after Unrelated Cord Blood Transplantation

Makoto Yazaki,[1] Yoshiko Atsuta,[2] Koji Kato,[3] Shunichi Kato,[4] Shuichi Taniguchi,[5] Satoshi Takahashi,[6] Hiroyasu Ogawa,[7] Yasuji Kouzai,[8] Takeshi Kobayashi,[9] Masami Inoue,[10] Ryoji Kobayashi,[11] Tokiko Nagamura-Inoue,[12] Hiroshi Azuma,[13] Minoko Takanashi,[14] Shunro Kai,[15] Masao Nakabayashi,[16] Hidehiko Saito[17] for the Japan Cord Blood Bank Network

Incidence and characteristics of early bacterial infection within 100 days after unrelated cord blood transplantation (UCBT) were assessed for 664 pediatric and 1208 adult recipients in Japan. Cumulative incidence of early bacterial infection at day 100 post-UCBTwas 11% (95% confidence interval [CI], 8%-13%) for children and 21% (CI, 19%-24%) for adults ($P < .0001$). Early bacterial infection in adults had a significant impact on mortality (hazard ratio [HR] = 2.1, CI, 1.7-2.6; $P < .0001$), although no significant risk factors were identified. Multivariate analysis identified older age group (6-10, and 11-15 years versus 0-5 years of age) at transplant (HR = 2.0 and 2.7, CI, 1.1-3.5 and 1.4-4.9; $P = .020$ and .002, respectively) as an independent risk factor of early bacterial infection for children. Early bacterial infection in children did not have a significant impact on mortality when adjusted. Of 315 bacteremia, 74% were caused by Gram-positive microorganisms. Pneumonia occurred in 39 patients including 13 cases of *Stenotrophomonas maltophilia* pneumonia. Early bacterial infection had a negative effect on survival for adults and the median day of development was 10 days after transplant, suggesting that the prevention of bacterial infection in the very early post-UCBT phase is important.

Biol Blood Marrow Transplant 15: 439-446 (2009) © *2009 American Society for Blood and Marrow Transplantation*

KEY WORDS: Early bacterial infection, Cord blood transplantation, The Japan Cord Blood Bank Network, Risk factor for infection, Urelated donor

INTRODUCTION

Infection is 1 of the major causes of morbidity and mortality for patients undergoing bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT) [1,2]. Recently, use of cord blood transplantation (CBT) from unrelated donors has increased for patients who do not have suitable donors for BMT or PBSCT, yielding promising results [3-7]. However, neutrophil recovery has been significantly delayed in unrelated CBT patients compared to unrelated BMT patients. Bacterial infection remains 1 of the most common problems after unrelated cord blood transplantation (UCBT) [5,8-10].

From the [1]Department of Pediatrics, Nagoya City East Medical Center, Nagoya, Japan; [2]Department of HSCT Data Management, Nagoya University School of Medicine, Nagoya, Japan; [3]Division of Hematology/Oncology, Children's Medical Center, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan; [4]Department of Cell Transplantation & Regenerative Medicine, Tokai University School of Medicine, Isehara, Japan; [5]Department of Hematology, Toranomon Hospital, Tokyo, Japan; [6]Division of Molecular Therapy, The Advanced Clinical Research Center, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan; [7]Division of Hematology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan; [8]Department of Transfusion Medicine, Tokyo Metropolitan Fuchu Hospital, Fuchu, Japan; [9]Division of Hematology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan; [10]Department of Hematology/Oncology, Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Japan; [11]Department of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo, Japan; [12]Division of Cell Processing and Transfusion, Research Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan; [13]Hokkaido Red Cross Blood Center, Sapporo, Japan; [14]Blood Preparation Department, The Japanese Red Cross Tokyo Blood Center, Tokyo, Japan; [15]Department of Blood Transfusion, Hyogo College of Medicine, Nishinomiya, Japan; [16]Department of Obstetrics/Gynecology, Maternal and Child Health Center Aiiku Hospital, Tokyo, Japan; and [17]Nagoya Central Hospital, Nagoya, Japan.

Financial disclosure: See Acknowledgments on page 446.

Correspondence and reprint requests: Makoto Yazaki, MD, Department of Pediatrics, Nagaya City East Medical Center, 1-2-23 Wakamizu, Chikusa-ku, Nagoya, Aichi 464-8547 Japan (e-mail: mhyazaki@sb.starcat.ne.jp).

Received August 11, 2008; accepted December 23, 2008

1083-8791/08/154-0001$36.00/0
doi:10.1016/j.bbmt.2008.12.508

In this paper, we report the results of our analysis of early bacterial infections before day 100 following UCBT in 1872 Japanese patients. We conducted this analysis to investigate the incidence and timing of infections, causative micro organisms, potential risk factors of infections, and the influence of infection on outcome.

PATIENTS AND METHODS

Patients

Between September 1997 and September 2005, 2362 UCBT procedures were performed using a single cord blood (CB) in 175 transplantation centers with 221 transplantation units supported by 11 CB banks affiliated with the Japan Cord Blood Bank Network (JCBBN) in Japan. The subjects analyzed were 1872 patients whose initial clinical report forms (CRFs), completed 100 days after UCBT, were submitted to the JCBBN. The clinical protocols for UCBT were approved by the institutional review board of the respective institutions. Patients underwent UCBT if they had no human leukocyte antigen (HLA)-identical, 1 locus mismatched relative or an HLA-matched unrelated BM donor could not be identified within 6 to 8 weeks [11]. The patients or their parents gave their consent for UCBT after being informed of the potential risks and benefits of the procedure. All patients received conditioning chemotherapy in the sterile unit with high-efficiency particulate air filtration. The conditioning regimen, acute graft-versus-host disease (aGVHD) prophylaxis and prevention of bacterial infections varied according to the institute's policy and type of disease, although most of the institutions used oral polymyxin B or fluoroquinolone with intravenous antibiotics to prevent bacterial infections.

Selection of Grafts

Searches for unrelated CB units were processed through the JCBBN, where 25,803 CB units were available in August 2006. Suitable CB in JCBBN was selected by cell count of nucleared cell before freezing and HLA compatibility between CB and patients. Preferred unrelated CB units were those that matched at least 4 of 6 HLA antigens, based on serologic typing for class I HLA-A and HLA-B, antigens and low-resolution DNA typing for class II HLA-DR and contained a minimum cell count of 2×10^7/kg nucleated cells of the recipient's body weight before freezing.

Bacterial Infections

We analyzed bacterial infections reported in the JCBBN 100-day CRF with clinical symptoms and pathogenic micro-organisms were discovered, because it is not easy to distinguish bacteremia or pneumonia without microbiologically documented infection from preengraftment fever or capillary leak syndrome in the early post-UCBT phase.

Early bacterial infections were defined as those occurring within the first 100 days after graft infusion. If a second episode with the same organism occurred within 7 days, it was counted as a single infection episode [10].

Collection of Data

Detailed patient and clinical variables were collected by the JCBBN CRF. Its 100-day CRFs were submitted by transplantation centers or units to the 11 CB banks and checked by a data manager of each bank for missing data and inconsistent data. After the data cleaning, all CRFs were submitted from CB banks to the data center of JCBBN. Annual follow-up for each transplant case is performed to update the data on engraftment, relapse, survival, and complications. The final data set used for the analyses was fixed in March 2006.

Statistical Analysis

Because preliminary study of all patients revealed that 16 years of age and older was the sole significant variable in multivariate analysis, separate analyses were performed for children (younger than 16 years of age) and adults (16 years of age and older) to find the risk factors and to investigate the impact of infection on survival. All episodes of infection were included in the analyses to identify causative micro-organisms of infections. Various clinical factors were evaluated as potential risk factors for early bacterial infection in univariate and multivariate analyses combined with the Cox proportional-hazards regression model. Factors found to be significant ($P < .05$) or marginally significant ($P < .1$) in univariate analysis were included in the multivariate analysis using a forward stepwise method. The categorization for the analyses of risk factors was based on the rule that the smaller group of variable needed to contain at least 10% of the patients. The proportional hazards regression model with early bacterial infection as a time-dependent covariate was used to determine the effect of early bacterial infection on survival. Survival distributions were estimated with the method of Kaplan and Meier. Probabilities of early bacterial infection were calculated by means of cumulative incidence curves treating death without early bacterial infection as competing risks. Statistical analyses were performed with Stata software version 9.0 (Stata Corp., College Station, TX).

RESULTS

Characteristics of Patients

Table 1 shows the characteristics of 664 pediatric (age <16 years) and 1208 adult (age ≥16 years) patients who underwent UCBT in Japan. In the child cohort,

Table 1. Characteristics of Pediatric and Adult Patients Who Received Unrelated Cord Blood Transplantation

Variable	Child (Age <16) No. Eval (n = 664)			Adult (age ≥16) No. Eval (n = 1208)		
Sex—no. (%)						
Male	664	403	(61)*	1208	662	(55)
Female		261	(39)		546	(45)
Age group—no. (%)						
0-15	664	664		1208		
16-30					270	(22)
31-45					338	(28)
≥46					600	(50)
Disease—no. (%)						
Acute lymphoblastic leukemia	664	279	(42)	1207	211	(17)
Acute myelogenous leukemia		151	(23)		490	(41)
Adult T cell leukemia		0			65	(5)
Chronic myelogenous leukemia		8	(1)		69	(6)
Chronic lymphocytic leukemia		0			3	
Myelodysplastic syndrome		15	(2)		103	(9)
MDS/MPD		20	(3)		7	(1)
Lymphoma		28	(4)		188	(16)
Myeloma		0			32	(3)
Solid tumor		27	(4)		6	
Aplastic anemia		14	(2)		24	(2)
Immunodeficiency		47	(7)		1	
Metabolic disease		25	(4)		0	
Others		50	(8)		8	(1)
History of previous transplantation—no. (%)						
No	664	556	(84)	1208	914	(76)
Yes		108	(16)		294	(24)
Conditioning regimen—no. (%)						
Myeloablative	664	545	(82)	1208	579	(48)
Nonmyeloablative		99	(15)		621	(51)
Unknown		20	(3)		8	(1)
Total-body irradiation	664	350	(53)	1208	928	(77)
ATG/ALG	664	75	(11)	1208	38	(3)
Prophylaxis against GVHD						
Cyclosporine based	630	401	(64)	1172	846	(72)
Tacrolimus based		199	(32)		312	(27)
Others		30	(5)		14	(1)
Methotrexate used	630	362	(57)	1172	582	(50)
Prednisolone used	630	161	(26)	1172	47	(4)
Mycophenolate mofetil used	630	2		1172	78	(7)
Nucleated cell dose/kg body weight—$\times 10^{-7}$						
Median	664	5.10		1208	2.53	
Range		1.18-24.91			1.02-6.42	
HLA compatibility(GVHD direction)—no./total no. (%)						
Matched	656	162	(25)	1187	129	(11)
One-antigen mismatch		380	(58)		457	(39)
Two-antigen mismatch		106	(16)		577	(49)
Three-antigen or more mismatch		8	(1)		24	(2)

MDS/MPD indicates myelodyplasticsyndrome/myeloproliferative disease; ATG, antithymocyte globulin; ALG, antilymphocyte globulin; GVHD, graft-versus-host disease; HLA, human leukocyte antigen.
*Figures in parentheses show percentages.

108 patients (16%) had a history of previous transplantation. Myeloablative conditioning regimen was administered to 545 patients (82%). Total body irradiation (TBI) was administered to 350 of 664 patients (53%) and 311 of 545 patients (57%) who received a myeloabalative condition regimen. For GVHD prophylaxis, cyclosporine (CsA)-based prophylaxis was administered to 401 patients (64%), and tacrolimus-based prophylaxis to 199 (32%). Methotrexate (MTX) was used for GVHD prophylaxis for 362 patients (57%), and prednisolone for 161 (26%). The median dose of nucleated cells per kilogram of patient's body weight was 5.10×10^7. In the adult cohort, 600 patients (50%) were 46 years old or older, and 294 patients (24%) had a history of previous transplantation. TBI was administered to 998 of 1208 patients (77%) and 504 of 579 patients (87%) who received a myeloabalative condition regimen, and 621 patients (51%) were given a nonmyeloablative conditioning regimen [12-15]. CsA-based GVHD prophylaxis was administered to 846 patients (72%), and tacrolimus-based prophylaxis to 312 patients (27%). The median dose of nucleated cells per kilogram of patient's body weight was 2.53×10^7.

Incidence and Timing of Early Bacterial Infection

In the child cohort, 77 patients (12%) developed early bacterial infection with a cumulative incidence of 9% (95% confidence interval [CI] 7%-11%) at 50

days and 11% (CI 8%-13%) at 100 days posttransplant (Figure 1). The median day of bacterial infection development was 8 days (range: 0-100) posttransplant. Seventy-five percent of early infection in children occurred within 31 days post-UCBT. In the adult cohort, the cumulative incidence of early bacterial infection was 19% (CI 17%-21%) at 50 days and 21% (CI 19%-24%) at 100 days after UCBT. Early bacterial infection on median day 10 (0-97) posttransplant occurred in the 260 adult recipients (22%) with 75% of the events occurring within 25 days. Statistical analysis demonstrated that the cumulative incidence of early bacterial infection in adults was significantly higher than that in children ($P < .0001$).

The majority of early bacterial infections developed during neutropenia (in 80% of children and 80% of adults). The median day of early bacterial infection development during neutropenia was 7 days (range: 0-80 days) for children and 8 days (0-80 days) for adults respectively, whereas the corresponding figures for early bacterial infections after neutrophil recovery were 55 days (20-100 days) and 46 days (14-97 days), respectively.

Types of Infections

Of the total of 1872 patients, 337 (18%) suffered from bacterial infections between day 0 and day 100 after UCBT, with 12% of children and 22% of adults suffering from early bacterial infections. As shown in Table 2, bacteremia was the most common infection within the first 100 days. In the child cohort, 68 cases of bacteremia, 2 of pneumonia, and 4 of colitis (2 of *Clostridium difficile* colitis) developed, and in the adult cohort, 247 cases of bacteremia, 38 of pneumonia, 2 of colitis (one of *Clostridium difficile* colitis), 2 each of urinary infection and sinusitis, and 1 each of *Bacillus cereus* meningitis and catheter infection. Of the 218

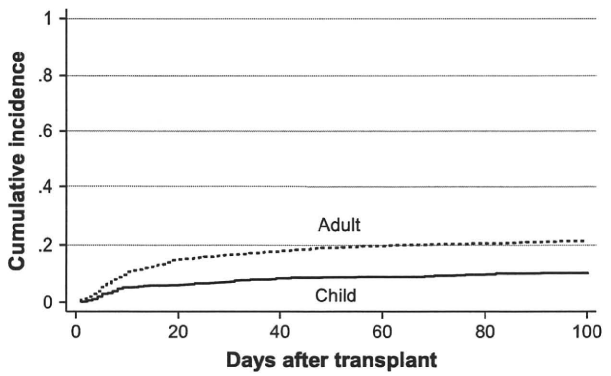

Figure 1. Cumulative incidence of early bacterial infection within 100 days following unrelated cord blood transplantation was 9% (95% CI 7%-11%) at 50 days and 11% (CI 8%-13%) at 100 days posttransplant for children. The corresponding values were 19% (CI 17%-21%) and 21% (CI 19%-24%) for adults.

Table 2. Patients with Early Bacterial Infections Who Received Cord Blood Transplantation

	Child (Age <16)		Adult (Age ≥16)	
	Patients	Episodes	Patients	Episodes
Bacteremia	65	68	218	247
Pneumonia	2	2	37*	38
Colitis	4	4	2	2
Urinary infection	0	0	2	2
Sinusitis	0	0	2	2
Meningitis	0	0	1	1
Catheter infection	0	0	1	1
Others	6	6	7	7

Total patients with infection in children and in adults were 77 and 260, respectively.
Number *Clostridium difficile* colitis 3.
*Ten patients with bacteremia developed pneumonia as the second bacterial infection.

adults with early bacteremia, 192 patients had 1 infection episode, 23 had 2, and 3 had 3 infection episodes.

Causative Micro organisms of Bacteremia

Of the 315 episodes of bacteremia, Gram-positive micro organisms accounted for 234 (74%), and Gram-negative micro organisms for 81 (26%) of the cases (Table 3). *Staphylococcus* species (spp) were the most common Gram-positive pathogens responsible for 147 of the bacteremia cases (47%), with coagulase-negative *Staphylococcus* (CNS) detected in 111 of these cases (76%). *Staphylococcus epidermidis* was the most

Table 3. Causative Micro organisms of the Early Bacteremia following Cord Blood Transplantation

	No. episodes		(%)
Bacteremia	315		
Gram-positives	234		(74)
Staphylococcus spp.		147	(47)
Enterococcus spp.		56	(18)
Sreptococcus spp.		19	(6)
Bacillius spp.		8	(3)
Corynebacterium spp.		2	
Clostridium spp.		1	
Mycobacterium tuberculosis		1	
Gram-negatives	81		(26)
Pseudomonas aeruginosa		34	(11)
Acinetobacter spp.		7	
Enterobacter cloacae		7	
E. coli		5	
Stenotrophomonas maltophilia		5	
Burkholderia cepacia		4	
Klebsiella pneumoniae		3	
Chyseobacterium spp.		3	
Alcaligenes xylosoxidans		2	
Salmonella spp.		2	
Serratia spp.		1	
Morganella morganii		1	
Leuconostoc spp.		1	
Micrococcus spp.		1	
Aeromonas hyrophila		1	
Capnocytophaga spp.		1	
Bacteroides fragilis		1	
Provotella oralis		1	
Fusobacterium necrophorum		1	

common CNS micro organism and was isolated in 94 cases. *Staphylococcus aureus* was isolated in 32 of the 147 cases, and was reported as methicillin-resistant *Staphylococcus aureus* (MRSA) in 25 of 32 (78%). *Enterococcus* spp was found in 56 cases (18% of all bacteremia cases), with 23 cases of *Enterococcus faecalis*, 21 cases of *Enterococcus faecium*, 1 case of *Enterococcus gallinarum*, and 11 unidentified cases. *Streptococcus* spp was the third most common Gram-positive pathogen (19 cases), with 15 cases of alpha-*Streptococcus*, 3 of *Streptococcus agalaciae*, and 1 unidentified case. *Streptococcus mitis* was found in 9 of the 15 alpha-*Streptococci* cases (60%). Of the 81 cases with Gram-negative micro-organisms, *Pseudomonas aeroginosa* was found in 34 cases, accounting for 11% of all bacteremia cases, and *Stenotrophomonas maltophillia* in 5 cases. Anaerobic Gram-negative organisms, such as *Bacteroides fragilis* (n = 1), *Provotella oralis* (n = 1), and *Fusobacterium necrophorum* (n = 1), were also isolated.

We also investigated causative micro organisms of early bacteremia that developed in children and adults either during neutropenia or after neutrophil recovery. The distribution of these micro organisms in all groups was similar except for that of *Stenotrophomonas maltophillia* and *Enterococcus* spp, with all 5 *Stenotrophomonas maltophilia* bacteremias that had developed in adults during neutropenia, the percentage of *Enterococcus* spp. bacteremia having developed in adults during neutropenia being 3.8 times higher than in children.

Causative Micro organisms of Pneumonia

Thirty-seven adults and 2 children developed bacterial pneumonia within the first 100 days after UCBT. Bacterial pneumonia developed as the first infection in 29 of these patients and 10 developed bacterial pneumonia following bacteremia, 4 of them because of the same micro organism that caused bacteremia and 6 because of a different micro organism. One patient developed secondary pneumonia of *Stenotrophomonas maltophilia* following MRSA pneumonia, which accounted for a total of 40 episodes of early bacterial pneumonia. Gram-positive and Gram-negative micro organisms accounted for 50% each of the cases of bacterial pneumonia. The causative micro organisms of pneumonia in adults were identified as *Staphylococcus aureus* (n = 6), CNS (n = 8), *Enterococcus* spp. (n = 3), *Corynebacterium* spp (n = 1), *Pseudomonas aeruginosa* (n = 5), *Burkholderia cepacia* (n = 2), and *Stenotrophomonas maltophilia* (n = 13). Eleven of the *Stenotrophomonas maltophilia* pneumonias developed during neutropenia.

Outcome of Patients with Early Bacterial Infection

Of the 43 patients who developed bacteremia with shock, 32 (74%) died as did 143 of 240 (60%) of those who developed bacteremia without shock. For patients who developed early bacteremia, bacterial infection was the main cause of death for 20 (47%) of the patients with bacteremia with shock, and 55 (23%) of the patients with bacteremia without shock. *Pseudomonas aeroginosa* bacteremia caused a higher mortality, because 73% of the patients with this type of bacteremia died. Bacterial infection was the main cause of death for 53% patients who developed *Pseudomonas aeroginosa* bacteremia. Twenty-six (70%) of the 37 adults who developed bacterial pneumonia died, as did 18 (49%) of the 37 adults who developed early bacterial pneumonia because of bacterial infection.

Risk Factors for Early Bacterial Infection after UCBT

Among the factors assessed as risk factors for early bacterial infection for children, older age group (6-10 years, and 11-15 years versus 0-5 years of age) at transplant (hazard ratio [HR] = 1.9 and 2.8, CI 1.1-3.3 and 1.6-5.1; $P = .024$ and $P < .0001$, respectively), presence of prior hematopoetic stem cell transplantation (HR = 1.8, CI 1.1-3.1; $P = .032$), infusion of $<5.10 \times 10^7$ nucleated cells per kilogram of patient's body weight (HR = 1.6, CI 1.0-2.6, $P = .049$), and use of nonmyeloablative conditioning regimen (HR = 1.8, CI 1.0-3.2; $P = .039$) were identified as significant in univariate analysis (Table 4). Use of prednisolone for GVHD prophylaxis was identified as a marginal risk factor (HR = 1.6, CI, 1.0-2.7; $P = .070$) in univariate analysis. Multivariate analysis identified older age group (6-10 years, and 11-15 years versus 0-5 years of age) at transplant (HR = 1.96 and 2.66, CI, 1.11-3.47 and 1.44-4.91; $P = .020$ and .002, respectively) as an independent risk factor of early bacterial infection for children. Use of prednisolone for GVHD prophylaxis was also identified as a marginal risk factor (HR = 1.63, CI 0.98-2.71; $P = .062$).

In the adult cohort, use of nonmyeloablative conditioning regimen was not significant. Univariate analysis results identified the use of tacrolimus for GVHD prophylaxis as a marginal risk factor (HR = 1.31, CI 1.0-1.7; $P = .055$) compared to the use of CsA for GVHD prophylaxis (Table 5). The cumulative incidence of early bacterial infection tended to be higher for patients in the adult cohort who received tacrolimus-based GVHD prophylaxis compared to those who received nontacrolimus GVHD prophylaxis (25%, 95% CI, 20%-30% versus 20%, 95% CI, 17%-24% at 100 days posttransplant, $P = .088$). No significant risk factor for early bacterial infection was identified in univariate analysis, so that multivariate analysis was not performed. The risk of early bacterial infection did not increase with age in the adult cohort (Table 5).

Effect of Early Bacterial Infections on Survival

The probability of survival of children 6 months and 2 years after UCBT was 70% (CI 66%-73%)

Table 4. Univariate Analysis for Risk of Early Bacterial Infection in Children

Factor	n	HR	95% CI	P value
Age at transplant (Years)				
0-5	392	1.00		
6-10	164	1.90	1.09-3.33	.024
11-15	107	2.84	1.60-5.05	<.0001
Prior HSCT				
≥1 prior HSCT	108/664	1.82	1.05-3.14	.032
Disease				
Acute myelogenous leukemia	151	1.00		
Acute lymphoblastic leukemia	279	0.89	0.49-1.62	.701
HLA disparity				
≥Two-antigens mismatch for GVHD direction	114/656	0.82	0.42-1.61	.574
≥Two-antigens mismatch for rejection direction	121/655	0.76	0.39-1.48	.415
Number of cells infused*				
$CD34^+$ cell $<1.42 \times 10^5$/kg	244/487	1.21	0.70-2.09	.494
Nucleated cell $<5.10 \times 10^7$/kg	332/664	1.62	1.00-2.63	.049
Conditioning regimen				
Myeloablative	545/664	1.00		
Nonmyeloablative	99/664	1.82	1.03-3.23	.039
Myeloablative condition with total body irradiation	331/664	1.24	0.78-1.99	0.368
Antithymocyte globulin/antilymphocyte globulin	75/664	1.58	0.83-3.01	.164
GVHD prophylaxis				
Cyclosporine based	401	1.00		
Tacrolimus based	199	1.23	0.72-7.08	.451
Prednisolone not used	469	1.00		
Prednisolone used	161	1.60	0.96-2.66	.070
Methotrexate not used	268	1.00		
Methotrexate used	362	0.87	0.53-1.42	.580
Disease status of malignant disease				
Standard disease†	215	1.00		
Advanced disease‡	308	1.03	0.61-1.76	.907

HSCT indicates hematopoietic stem cell transplantation; GVHD, graft-versus-host diseasel; CI, confidence interval; HR, hazard ratio.
*Number of cells at freezing.
†Standard disease means first complete remission or first chronic phase of maliganant disease.
‡Advanced disease means all others except standard disease.

Table 5. Univariate Analysis for Risk of Early of Early Bacterial Infection Adults

Factor	n	HR	95% CI	P Value
Age at transplant (years)				
16-30	270	1.00		
31-45	338	0.85	0.59-1.21	.355
46-60	445	1.04	0.75-1.43	.834
≥61	155	1.05	0.69-1.59	.838
Prior HSCT				
≥1 prior HSCT	294/1208	1.02	0.76-1.37	.881
Disease				
Acute myelologenous leukemia	490	1.00		
Aute lymphoblastic leukemia	211	0.90	0.63-1.29	.572
Lymphoma	188	1.23	0.87-1.77	.233
HLA disparity				
≥Two-antigens mismatch for GVHD direction	601/1187	0.99	0.77-1.27	.937
≥Two-antigens mismatch for rejection direction	623/1187	0.92	0.71-1.17	.485
Number of cell infused *				
$CD34^+$ cell $<0.80 \times 10^5$/kg	560/1130	1.18	0.90-1.51	.240
Nucleated cell $<2.53 \times 10^7$/kg	608/1208	1.17	0.91-1.49	.224
Conditioing regiman				
Myeloablative	579/1208	1.00		
Nonmyeloablative	621/1208	1.21	0.95-1.55	.125
Myeloablative condition with total body irradiation	504/1208	1.21	094-1.55	0.145
GVHD prophylaxis				
Cyclosporine based	846	1.00		
Tacrolimus based	312	1.31	0.99-1.72	.055
Methotrexate not used	590	1.00		
Methotrexate used	582	0.84	0.66-1.08	.182
Disease status malignant disease				
Standard disease†	427	1.00		
Advanced disease‡	739	1.10	0.58-1.44	.469

HSCT indicates hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; CI, confidence interval; HR, hazard ratio.
*Number of cell at freezing.
†Standard disease means first complete remission or first chronic phase of maliganant disase.
‡Advanced disease means all other except standard disease.

and 52% (CI 48%-56%), respectively. The median follow-up of survivors was 2.1 years (range: 0.07-7.5). Bacterial infection was the main cause of death in 12 of the 77 pediatric recipients (16%) with early bacterial infection. Evaluation of early bacterial infection as a time-dependent covariate for patient's survival showed statistical significance (HR = 1.6, CI 1.2-2.2; $P = .005$) in univariate analysis. When adjusted for patient age, sex, disease status, presence of previous transplant, transplanted cell dose, HLA disparity, conditioning regimen, and GVHD prophylaxis, this factor showed no significance (HR = 1.5, CI 0.9-2.4; $P = .111$) for children.

In the adult cohort, the probability of survival 6 months and 1 year posttransplant was 50% (CI 47%-53%) and 41% (CI 38%-44%), respectively. The median follow-up of survivors was 1.0 year (range: 0.05-6.2). Bacterial infection was the main cause of death in 79 of the 260 adult recipients (30%) with early bacterial infection. The analysis of the effects of early bacterial infection showed statistical significance in univariate analysis (HR = 2.1, CI 1.7-2.5; $P < .0001$) as well as in multivariate analysis (HR = 2.1, CI 1.7-2.6; $P < .0001$) adjusted for the same variables as for the child cohort.

Overall survival (OS) rates of children who developed bacterial infection during neutropenia 100 and 365 days after infection were 58% (95% CI 44%-70%), and 40% (95% CI 27%-53%), respectively. The corresponding rates for children who developed bacterial infection after neutrophil recovery were 67% (95% CI,38%-85%) and 67% (95% CI 38%-85%), respectively. In the adult cohort, the corresponding rates were 40% (95% CI 33%-47%) and 27% (95% CI 20%-34%), for bacterial infection having developed during neutropenia and 49% (95% CI 34%-63%) and 38% (95% CI 23%-52%) for after neutrophil recovery.

Because early bacterial infection, neutrophil recovery, and aGVHD occur during the early phase after transplant, we performed multivariate analyses by treating these variables as time-dependent variables for the analysis of early bacterial infection in terms of status of neutrophil recovery and status of aGVHD.

Multivariate analyses revealed that early bacterial infection remained a significant risk factor for overall mortality of adults (HR = 2.05, CI 1.68-2.49; $P < .0001$). However, early bacterial infection did not affect child mortality (HR = 1.32, CI 0.81-2.15; $P = .27$). Neutrophil recovery was a significant risk factor for overall child mortality (HR = 0.43, CI 0.28-0.67; $P < .0001$) and adults (HR = 0.47, CI 0.38-0.59; $P < .0001$) after adjustment for patient and transplant characteristics. However, grade ii to iv aGVHD did not have an effect on child mortality (HR = 1.00, CI 0.72-1.38; $P = .98$) and adults (HR = 1.08, CI 0.89-1.32; $P = .43$). These findings suggest that early bacterial infection is an independent risk factor for overall mortality of adults.

DISCUSSION

Bacterial infections remain a major complication following UCBT. To the best of our knowledge, this study of 664 pediatric and 1208 adult patients represents the largest study reported to date for the examination of early bacterial infection following UCBT. The incidence of early bacterial infection for adult patients was significantly higher than that for pediatric patients. The median day of bacterial infection development was 8 days in children and 10 days in adults posttransplant, respectively.

Gram-positive organisms were predominant (74%) in the cases of early bacteremia examined in our study. Previous studies also reported that Gram-positive organisms were prominent in bacteremia following UCBT [8,12]. In our large-scale study, *Staphylococcus epidermidis* was the most common organism isolated in 94 of the 147 *Staphylococcus* spp. cases, whereas *Staphylococcus aureus* was isolated in 32 cases. Among patients with bacteremia of *Staphylococcus aureus*, MRSA was found in 78% of the patients. *Enterococcus* spp. was the second most common Gram-positive pathogen, with 23 cases of *Enterococcus faecalis* and 21 of *Enterococcus faecium*. The percentage of *Enterococcus* spp. bacteremia in adults was 3.8 times higher than that in children during neutropenia. Because carbapenems or vancomycin has been used in the past, vancomycin-resistant *Enterococcus faecalis* or *Enterococcus faecium* was found in some patients. *Streptococcus* spp. was the third most common Gram-positive pathogen (19 cases), 79% of which were accounted for by alpha-*Streptococcus*, with *Streptococcus mitis* being the most common pathogen. *Pseudomonas aeruginosa* was the most frequently occurring bacterium in Gram-negative organisms.

Stenotrophomonas maltophilia was found in 13 of 37 (35%) adults who developed early bacterial pneumonia, and the condition of 75% of these patients deteriorated in spite of intensive therapy. Eleven of 13 *Stenotrophomonas maltophillia* adult pneumonias developed during neutropenia. *Stenotrophomonas maltophilia* is naturally resistant to penicillins, cephems except ceftazidim and cefpiramide, aminoglycosides, and carbapenems, therefore, antibiotics must be carefully selected for the treatment of patients with bacteremia or pneumonia caused by this bacterium.

For children, use of nonmyeloablative conditioning regimen was identified to be significant in univariate analysis. It was somewhat surprising that the use of nonmyeloablative conditioning in children was associated with a higher frequency of infections than in the myeloablative treated patients. Because the standardized JCBBN 100-day CRF do not include items for identifying information on comorbidity such as the recently introduced comorbidity index by Sorror et al [16], we could not make adjustments for patients' comorbidity status at transplant. We therefore cannot rule out the possibility that high-risk patients with organ failure and poor infectious defense were more likely to have been treated with nonmyeloablative conditioning, increasing risk of bacterial infections.

Multivariate analysis identified older age (6-10 years, and 11-15 years versus 0-5 years of age) at transplant as an independent risk factor for early bacterial infection in children, whereas univariate analysis revealed that older age at transplant and infusion of $<5.10 \times 10^7$ nucleated cells per kilogram of patient's body weight were identified as significant. These findings suggest that older age of children was a stronger risk factor than the number of infused nucleated cells per kilogram of patient's body weight. Higher activity of cell reproduction in younger children may be associated with a low incidence of mucosal toxicity, thus contributing to a lower risk of bacterial infection.

In adults, the incidence of early bacterial infection was almost twice as high, 21% at 100 days posttransplant compared to 11% for children. Although no specific risk factor was identified in adults, the prognostic significance of early bacterial infection was clearly identified in our analysis, thus indicating the importance of the prevention of early bacterial infection. No tendency for risk to increase with age was observed in individuals 16 years or older.

In conclusion, we analyzed the incidence of early post-UCBT bacterial infection in pediatric and adult patients. The incidence of early bacterial infection for adult patients was significantly higher than that for pediatric patients. The risk of early bacterial infection increased with age for individuals younger than 16 years, but not for those 16 years or older. Early bacterial infection had a negative effect on survival, especially in adults for whom the incidence of early bacterial infection was 21% and the median day of development was 10 days post transplant. These findings suggest that the prevention of bacterial infection during conditioning and the very early post-UCBT phase is especially important. Prospective clinical

studies are needed to establish the better prophylaxis against early bacterial infection.

ACKNOWLEDGMENTS

The authors thank Dr. Toshitada Takahashi for his advice on this manuscript. We would like to thank the JCBBN and 11 cord blood banks in Japan for supplying the data for this study.

Financial disclosure: This work was supported in part by a research grant for Tissue Engineering (H17-014) and a research grant on Allergic Disease and Immunology (H20-015) from the Japanese Ministry of Health, Labor & Welfare.

REFERENCES

1. Engels EA, Ellis CA, Supran SE, et al. Early infection in bone marrow transplantation: quantitative study of clinical factors that affect risk. *Clin Infect Dis.* 1999;28:256-266.
2. Ketterer N, Espinouse D, Chomarat M, et al. Infections following peripheral blood progenitor cell transplantation for lymphoproliferative malignancies: etiology and potential risk factors. *Am J Med.* 1999;106:191-197.
3. Kurtzberg J, Laughlin M, Graham ML, et al. Placental blood as a source of hematopoetic stem cells for transplantation into unrelated recipients. *N Eng J Med.* 1996;335:157-166.
4. Gluckman E, Rocha V, Boyer-Chammard A, et al. Outcome of cord-blood transplantation from related and unrelated donors. *N Eng J Med.* 1997;337:373-381.
5. Rubinstein P, Carrier C, Scaradavou A, et al. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. *N Eng J Med.* 1998;339:1565-1577.
6. Laughlin MJ, Eapen M, Rubinstein P, et al. Outcomes after transplantation of cord blood or bone marrow from unrelataed donors in adults with leukemia. *N Eng J Med.* 2004;351:2265-2275.
7. 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 Eng J Med.* 2004;351:2276-2285.
8. Saavedra S, Sanz GF, Jarque I, et al. Early infections in adult patients undergoing unrelated donor cord blood transplantation. *Bone Marrow Transplant.* 2002;30:937-943.
9. Hamza NS, Lisgaris M, Yadavalli G, et al. Kinetics of myeloid and lymphocyte recovery and infectious complications after unrelated umbilical cord blood versus HLA-matched unrelated donor allogeneic transplantation in adults. *Br J Haematol.* 2004;124:488-498.
10. Barker JN, Hough RE, van Burik F, et al. Serious infections after unrelated donor transplantation in 136 children: impact of stem cell source. *Biol Blood Marrow.* 2005;11:362-370.
11. Nishihira H, Kato K, Isoyama K, et al. The Japanese cord blood bank network experience with cord blood transplantation from unrelated donors for haematologic malignancies: an evaluation of graft-versus-host disease prophylaxis. *Br J Haematol.* 2003; 120:516-522.
12. Narimatsu H, Matsumura T, Kami M, et al. Bloodstream infection after umbilical cord blood transplantation using reduced-intensity stem cell transplantation for adult patients. *Biol Blood Marrow Transplant.* 2005;11:429-436.
13. Giralt S, Estey E, Albitar M, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. *Blood.* 1997;89:4531-4536.
14. 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 maliganant and nonmaliganant hematologic diseases. *Blood.* 1998;91:756-763.
15. Childs R, Clave E, Contentin N, et al. Engraftment kinetics after nonmyeloablative allogeneic peripheral blood stem cell transplantation: full donor T-cell chimerism precedes alloimmune responses. *Blood.* 1999;94:3234-3241.
16. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HST)-specific comorbidity index: a new tool for risk assessment before allogeneic HST. *Blood.* 2005;106: 2912-2919.

blood

2009 113: 1631-1638
Prepublished online Dec 22, 2008;
doi:10.1182/blood-2008-03-147041

Disease-specific analyses of unrelated cord blood transplantation compared with unrelated bone marrow transplantation in adult patients with acute leukemia

Yoshiko Atsuta, Ritsuro Suzuki, Tokiko Nagamura-Inoue, Shuichi Taniguchi, Satoshi Takahashi, Shunro Kai, Hisashi Sakamaki, Yasushi Kouzai, Masaharu Kasai, Takahiro Fukuda, Hiroshi Azuma, Minoko Takanashi, Shinichiro Okamoto, Masahiro Tsuchida, Keisei Kawa, Yasuo Morishima, Yoshihisa Kodera, Shunichi Kato and for the Japan Marrow Donor Program and the Japan Cord Blood Bank Network

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published semimonthly by the American Society of Hematology, 1900 M St, NW, Suite 200, Washington DC 20036.

Disease-specific analyses of unrelated cord blood transplantation compared with unrelated bone marrow transplantation in adult patients with acute leukemia

Yoshiko Atsuta,[1] Ritsuro Suzuki,[1] Tokiko Nagamura-Inoue,[2] Shuichi Taniguchi,[3] Satoshi Takahashi,[4] Shunro Kai,[5] Hisashi Sakamaki,[6] Yasushi Kouzai,[7] Masaharu Kasai,[8] Takahiro Fukuda,[9] Hiroshi Azuma,[10] Minoko Takanashi,[11] Shinichiro Okamoto,[12] Masahiro Tsuchida,[13] Keisei Kawa,[14] Yasuo Morishima,[15] Yoshihisa Kodera,[16] and Shunichi Kato,[17] for the Japan Marrow Donor Program and the Japan Cord Blood Bank Network

[1]Department of Hematopoietic Stem Cell Transplantation Data Management, Nagoya University School of Medicine, Nagoya; [2]Department of Cell Processing & Transfusion, Research Hospital, Institute of Medical Science, University of Tokyo, and Tokyo Cord Blood Bank, Tokyo; [3]Department of Hematology, Toranomon Hospital, Tokyo; [4]Department of Molecular Therapy, Institute of Medical Science, University of Tokyo, Tokyo; [5]Department of Transfusion Medicine, Hyogo College of Medicine, Nishinomiya; [6]Division of Hematology, Tokyo Metropolitan Komagome Hospital, Tokyo; [7]Department of Transfusion Medicine, Tokyo Metropolitan Fuchu Hospital, Tokyo; [8]Department of Hematology, Sapporo Hokuyu Hospital, Sapporo; [9]Hematopoietic Stem Cell Transplantation Unit, National Cancer Center Hospital, Tokyo; [10]Hokkaido Red Cross Blood Center, Sapporo; [11]Japanese Red Cross Tokyo Blood Center, Tokyo; [12]Division of Hematology, Department of Medicine, Keio University School of Medicine, Tokyo; [13]Ibaraki Children's Hospital, Mito; [14]Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi; [15]Aichi Cancer Center Hospital, Nagoya; [16]BMT Center, Japanese Red Cross Nagoya First Hospital, Nagoya; and [17]Department of Cell Transplantation & Regenerative Medicine, Tokai University School of Medicine, Isehara, Japan

We made a disease-specific comparison of unrelated cord blood (CB) recipients and human leukocyte antigen allele–matched unrelated bone marrow (BM) recipients among 484 patients with acute myeloid leukemia (AML; 173 CB and 311 BM) and 336 patients with acute lymphoblastic leukemia (ALL; 114 CB and 222 BM) who received myeloablative transplantations. In multivariate analyses, among AML cases, lower overall survival (hazard ratio [HR] = 1.5; 95% confidence interval [CI], 1.0-2.0, $P = .028$) and leukemia-free survival (HR = 1.5; 95% CI, 1.1-2.0, $P = .012$) were observed in CB recipients. The relapse rate did not differ between the 2 groups of AML (HR = 1.2; 95% CI, 0.8-1.9, $P = .38$); however, the treatment-related mortality rate showed higher trend in CB recipients (HR = 1.5; 95% CI, 1.0-2.3, $P = .085$). In ALL, there was no significant difference between the groups for relapse (HR = 1.4, 95% CI, 0.8-2.4, $P = .19$) and treatment-related mortality (HR = 1.0; 95% CI, 0.6-1.7, $P = .98$), which contributed to similar overall survival (HR = 1.1; 95% CI, 0.7-1.6, $P = .78$) and leukemia-free survival (HR = 1.2; 95% CI, 0.9-1.8, $P = .28$). Matched or mismatched single-unit CB is a favorable alternative stem cell source for patients without a human leukocyte antigen–matched related or unrelated donor. For patients with AML, decreasing mortality, especially in the early phase of transplantation, is required to improve the outcome for CB recipients. (Blood. 2009;113:1631-1638)

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) with bone marrow (BM) or peripheral blood, the curative treatment of choice for acute leukemia, is limited by the inadequate supply of human leukocyte antigen (HLA)–identical related donors. Bone marrow from HLA-matched unrelated donors has been a major alternative graft source.[1-3] Umbilical cord blood (CB), an alternative stem cell source to BM or peripheral blood stem cells, has been used primarily in children,[4-10] but its use in adults is increasing.[11,12]

Clinical comparison studies of cord blood transplantation (CBT) and bone marrow transplantation (BMT) for leukemia from unrelated donors in adult recipients showed comparable outcomes.[11-13] Recipients of CBT showed delayed neutrophil recovery and lower incidence of acute graft-versus-host disease (GVHD).[11-13] Overall treatment-related mortality (TRM) was reported to be similar[12] or higher[11] compared with HLA-matched BM. Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) are different disease entities that require different chemotherapy regimens for treatment. However, previous comparison studies have included both diseases because of limitation in the number of CBTs given to adults.

In addition, the study periods of previous studies encompass the pioneering period of CBT, when the general practice was to use these grafts in patients in whom there were no other curative options and when the relevance of cell dose and HLA matching had not yet been recognized.[6,7,14]

Accumulation of a larger number of CBT results enabled us to make a controlled comparison with unrelated BMTs. To avoid the inclusion of the pioneering period of CBT, the subjects were limited to those who received transplantations in and after 2000.

Methods

Collection of data and data source

The recipients' clinical data were provided by the Japan Cord Blood Bank Network (JCBBN) and the Japan Marrow Donor Program (JMDP).[15]

Submitted March 21, 2008; accepted November 14, 2008. Prepublished online as *Blood* First Edition paper, December 22, 2008; DOI 10.1182/blood-2008-03-147041.

The online version of this article contains a data supplement.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

Peripheral blood stem cell donation from unrelated donors is not permitted in Japan. All 11 CB banks in Japan are affiliated to JCBBN. Both JCBBN and JMDP collect recipients' clinical information at 100 days after transplantation. Patients' information on survival, disease status, and long-term complications, including chronic GVHD and second malignancies, are renewed annually by follow-up forms. This study was approved by the data management committees of JMDP and JCBBN.

Patients

Between January 2000 and December 2005, a total of 1690 adult patients at least 16 years of age with acute leukemia (999 AML, 261 CB and 738 BM; and 691 ALL, 178 CB and 513 BM) received first HSCT with myeloablative conditioning either CB or BM from unrelated donors. Of these, patients who received a single CB unit with 0 to 2 HLA mismatches, or HLA-A, -B, -C, and DRB1 allele-matched BM from unrelated donors were analyzed. HLA matching of CB was performed using low-resolution molecular typing methods for HLA-A and -B, and high-resolution molecular typing for HLA-DRB1. Of 1023 BM recipients with complete HLA high-resolution data, the following recipients with HLA HLA-A, -B, -C, and DRB1 allele mismatches were excluded: 306 recipients with 1 of 8 mismatches (39 for HLA-A, 6 for HLA-B, 137 for HLA-C, and 124 for HLA-DRB1), 150 recipients with 2 of 8 mismatches (36 for 2 class I antigens, and 114 for class I and class II antigens), 33 recipients with 3 of 8 mismatches, and 1 recipient with 4 of 8 mismatches. Of 390 recipients of CB with complete HLA data, 95 recipients with 3 mismatches and 8 patients with 4 mismatches were excluded. A total of 484 patients with AML (173 CBTs and 311 BMTs) and 336 patients with ALL (114 CBTs and 222 BMTs) were the subjects for the analyses. Eighty-five centers performed 287 CBTs analyzed in this study, and 114 centers performed 533 BMTs.

Definitions

Neutrophil recovery was defined by an absolute neutrophil count of at least 500 cells/mm^3 for 3 consecutive points; platelet recovery was defined by a count of at least 50 000 platelets/mm^3 without transfusion support. Diagnosis and clinical grading of acute GVHD were performed according to the established criteria.[16] Relapse was defined as a recurrence of underlying hematologic malignant diseases. Treatment-related death was defined as death during a continuous remission. Leukemia-free survival (LFS) was defined as survival in a state of continuous remission.

Statistical analysis

Separate analyses were performed for AML and ALL. Descriptive statistical analysis was performed to assess patient baseline characteristics, diagnosis, disease classification, disease status at conditioning, donor-patient ABO mismatches, preparative regimen, and GVHD prophylaxis. The 2-sided χ^2 test was used for categorical variables, and the 2-sided Wilcoxon rank sum test was used for continuous variables. Cumulative incidence curves were used in a competing-risks setting to calculate the probability of neutrophil and platelet recovery, acute and chronic GVHD, relapse, and TRM.[17] For neutrophil and platelet recovery, death before neutrophil or platelet recovery was the competing event; for GVHD, death without GVHD and relapse were the competing events; for relapse, death without relapse was the competing event; and, for TRM, relapse was the competing event. Gray test was used for group comparison of cumulative incidence.[18] Overall survival (OS) and LFS were calculated using the Kaplan-Meier method. The log-rank test was used for group comparisons. Adjusted comparison of the stem cell source on OS and LFS was performed with the use of the Cox proportional-hazards regression model. For other outcomes, the Fine and Gray proportional-hazards model for subdistribution of a competing risk was used.[19] Adjusted probabilities of OS and DFS were estimated using the Cox proportional-hazards regression model, with consideration of other significant clinical variables in the final multivariate models. The variables considered were the patient's age at transplantation, patient's sex, donor-patient sex mismatch, donor-patient ABO mismatch, disease status at conditioning, and t(9;22) chromosome abnormality or others for ALL, cytogenetic information and French-American-British (FAB) classification of M5/M6/M7 or others for AML, the conditioning regimen, and the type of prophylaxis against GVHD. Factors differing in distribution between CB and BM recipients ($P < .10$) and factors known to influence outcomes (such as patient age at transplantation and chromosome abnormalities and FAB classification of leukemia) were included in the final models. Variables with more than 2 categories were dichotomized for the final multivariate model. The cutoff points of the variables were chosen to make optimal use of the information, with the proviso that smaller groups contain at least 20% of the patients. Variables were dichotomized as follows: patient age greater or younger than 45 years at transplantation, female donor to male recipient donor-recipient sex mismatch versus others for donor-recipient sex matching, donor-recipient ABO major mismatch versus others for ABO matching, M5/M6/M7 FAB classification versus others for classification of AML, chromosome abnormality other than favorable abnormalities for cytogenetics of AML, cyclophosphamide and total body irradiation (TBI) or busulfan and cyclophosphamide or others for conditioning regimen of AML, cyclophospohamide and TBI, or others for conditioning regimen of ALL, and cyclosporine-based versus tacrolimus-based prophylaxis against GVHD. Disease status at transplantation was categorized as first complete remission (1CR), second or later complete remission (2CR), or more advanced disease; which was included in the final model using dichotomized dummy variables. All P values were 2-sided.

The statistical power to detect hazard ratios (HRs) of 2.0 and 1.5 (a regression coefficient equal to 0.6931 and 0.4055, respectively) on Cox regression of the log hazard ratio at a .05 significance level adjusted for event rate were 99% and 78%, respectively, for 484 patients with AML and 97% and 60%, respectively, for 336 patients with ALL. The levels of statistical power for subgroup analyses were as follows: 54% and 22% for 1CR, 51% and 21% for 2CR, 96% and 58% for more advanced in AML patients, 62% and 26% for 1CR, 47% and 20% for 2CR, and 67% and 29% for more advanced in ALL patients.[20]

Results

Patient characteristics

The characteristics of the patients are shown in Table 1. There was no significant difference in recipients' age at transplantation in AML (median age, CB vs BM = 38 vs 38 years, $P = .61$) and in ALL (median age, CB vs BM = 34 vs 32 years, $P = .29$). The female/male ratio was higher (CB vs BM = 54% vs 38% in AML patients, and CB vs BM = 54% vs 38% in ALL patients, $P < .001$ and $P = .005$, respectively) in CB recipients, resulting in the lower donor-patient sex match rate (CB vs BM = 48% vs 69% in AML patients, and CB vs BM = 46% vs 65% in ALL patients, $P < .001$ and $P = .002$, respectively) in CB recipients. The proportion of ALL patients with Philadelphia chromosome abnormality was higher (CB vs BM = 38% vs 23%) in CB recipients. CB recipients were likely to have more advanced disease status at transplantation (relapse or induction failure, CB vs BM = 47% vs 31% in AML patients, and CB vs BM = 26% vs 19% in ALL patients), and the difference was significant in AML ($P = .003$). HLA-A, -B (low-resolution typing), and -DRB1 (high-resolution typing) was mismatched in 93% of both AML and ALL among CB recipients, whereas HLA -A, -B, -C, and -DRB1 were all genotypically matched for BM recipients. The ABO-matched donor-patient pair proportion was consistently lower for CB (CB vs BM = 34% vs 59% in AML patients and CB vs BM = 32% vs 58% in ALL patients).

A preparative regimen with TBI and cyclophosphamide was used in almost all patients, and cytosine arabinoside was supplemented for CB recipients with AML (36%) in addition to TBI and cyclophosphamide. For GVHD prophylaxis, tacrolimus (CB vs BM = 29% vs 56% in AML patients, and CB vs BM = 37% vs 53% in ALL patients) and

Table 1. Characteristics of recipients of cord blood or bone marrow from unrelated donors in 484 patients with acute myeloid leukemia and 336 patients with acute lymphoblastic leukemia

	Acute myeloid leukemia			Acute lymphoblastic leukemia		
Characteristic	**U-CBT**	**U-BMT**	***P***	**U-CBT**	**U-BMT**	***P***
No. of transplantations	173	311		114	222	
Median patient age at transplantation, y (range)	38 (16-69)	38 (16-60)	.61	34 (16-58)	32 (16-59)	.29
Patient sex, n (%)						
Male	80 (46)	194 (62)	< .001	52 (46)	137 (62)	.005
Female	93 (54)	117 (38)		62 (54)	85 (38)	
Sex matching, n (%)			< .001			.002
Matched	83 (48)	216 (69)		52 (46)	145 (65)	
Male to female	44 (25)	57 (18)		35 (31)	42 (19)	
Female to male	46 (27)	37 (12)		27 (24)	35 (16)	
Unknown	0 (0)	1 (0)		0 (0)	0 (0)	
Disease classification						
AML (French-American-British)			.045			
M0	17 (10)	26 (8)				
M1	30 (17)	38 (12)				
M2	52 (30)	88 (28)				
M3	4 (2)	25 (8)				
M4	27 (16)	55 (18)				
M5	23 (13)	41 (13)				
M6	3 (2)	18 (6)				
M7	2 (1)	5 (2)				
Others/unknown	15 (9)	15 (5)				
Cytogenetics			.042			
Favorable*	19 (11)	66 (21)				
Normal	74 (43)	116 (37)				
Other	57 (33)	95 (31)				
Unknown	23 (13)	34 (11)				
ALL cytogenetics						.022
t(9;22)				43 (38)	52 (23)	
t(4;11)				2 (2)	3 (1)	
Others				22 (19)	51 (23)	
Normal				27 (24)	85 (38)	
Unknown				20 (18)	31 (14)	
Disease status			.003			.33
First CR	50 (29)	130 (42)		63 (55)	130 (59)	
Second or after CR	39 (23)	82 (26)		21 (18)	48 (22)	
Relapse/induction failure	81 (47)	95 (31)		30 (26)	42 (19)	
Unknown	3 (2)	4 (1)		0 (0)	2 (1)	
HLA matching†						
0 mismatched loci	12 (7)			8 (7)		
1 mismatched locus	35 (20)			25 (22)		
2 mismatched loci	126 (73)			81 (71)		
ABO matching			< .001			< .001
Matched	59 (34)	185 (59)		37 (32)	128 (58)	
Minor mismatch	48 (28)	57 (18)		30 (26)	48 (22)	
Major mismatch	37 (21)	59 (19)		24 (21)	41 (18)	
Bidirectional	28 (16)	8 (3)		23 (20)	3 (1)	
Unknown	1 (1)	2 (1)		0 (0)	2 (1)	
Nucleated cells infused per 10^7/kg, median (range)	2.44 (1.65-5.49)	26.3 (2.10-58.8)	< .001	2.48 (1.51-4.06)	28.2 (2.30-79.0)	< .001
Preparative regimen			< .001			.38
CY + TBI	43 (25)	142 (46)		42 (37)	92 (41)	
CY + CA + TBI	62 (36)	41 (13)		31 (27)	53 (24)	
CY + BU + TBI	7 (4)	36 (12)		3 (3)	5 (2)	
Other TBI regimen	42 (24)	33 (11)		34 (30)	54 (24)	
BU + CY	18 (10)	55 (18)		4 (4)	12 (5)	
Other non-TBI regimen	1 (1)	4 (1)		0 (0)	6 (3)	
GVHD prophylaxis			< .001			< .001
Cyclosporine A + sMTX	103 (60)	131 (42)		65 (57)	100 (45)	
Cyclosporine A ± other	20 (12)	4 (1)		6 (5)	3 (1)	
Tacrolimus + sMTX	34 (20)	168 (54)		26 (23)	106 (48)	
Tacrolimus ± other	15 (9)	5 (2)		16 (14)	11 (5)	
Others	1 (1)	3 (1)		1 (1)	2 (1)	

U-CBT, indicates unrelated cord blood transplantation; U-BMT, unrelated bone marrow transplantation; CR, complete remission; HLA, human leukocyte antigen; CY, cyclophosphamide; CA, cytarabine; BU, oral busulfan; TBI, total body irradiation; and sMTX, short-term methotrexate.

*Favorable abnormal karyotypes are defined as t(8;21), inv16,or t(15;17).

†Number of mismatches was counted among HLA-A, -B (low-resolution typing), and DRB1 (high-resolution typing).

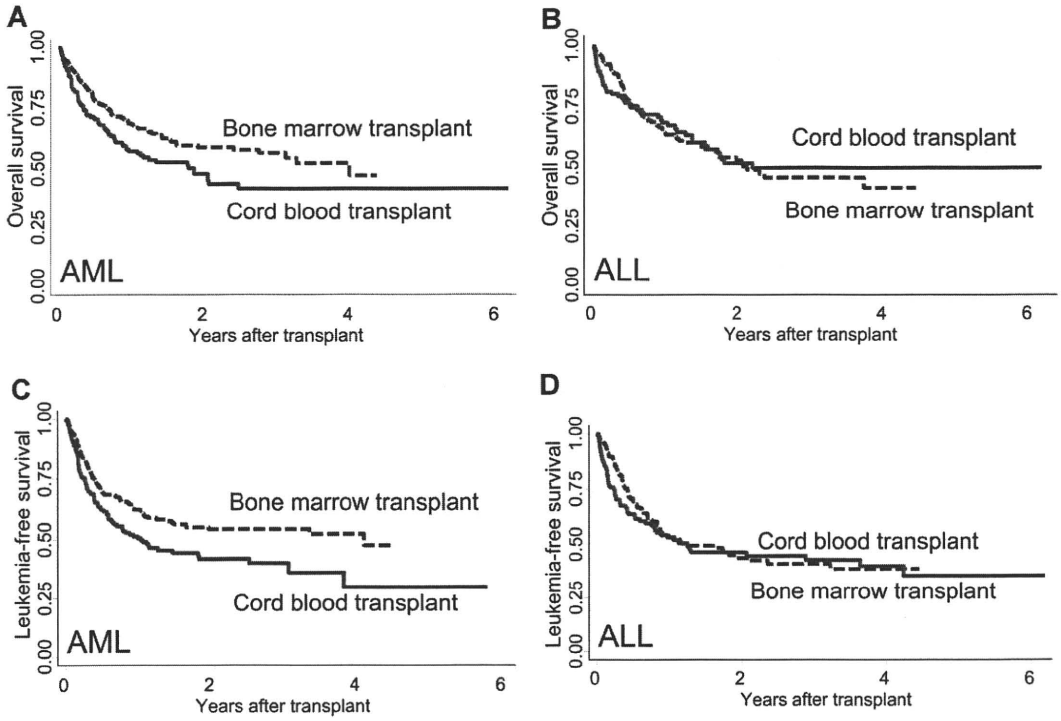

Figure 1. Adjusted OS and LFS of recipients with AML or ALL of CB or BM from unrelated donors. For patients with AML, adjusted probabilities of (A) OS (CB vs BM = 48% vs 59% at 2 years, $P = .010$) and (C) LFS (CB vs BM = 42% vs 54% at 2 years, $P = .004$) were both lower in CB recipients. For patients with ALL, the adjusted probabilities of (B) OS (CB vs BM = 52% vs 53% at 2 years, $P = .99$) and (D) LFS (CB vs BM = 46% vs 44% at 2 years, $P = .41$) were similar between CB recipients and BM recipients.

short-term methotrexate (CB vs BM = 80% vs 96% in AML patients, and CB vs BM = 80% vs 93% in ALL patients) were used preferentially in BM recipients. The median follow-up period for survivors was 1.9 years (range, 0.1-6.2 years) for CB recipients and 1.4 years (range, 0.3-4.5 years) for BM recipients.

Outcome

OS. For patients with AML, the unadjusted probabilities of OS were lower for CB recipients at 1 year (51% vs 69%) and 2 years (43% vs 60%) compared with BM recipients ($P < .001$). For patients with ALL, there were no significant differences between the 2 groups (CB vs BM = 66% vs 66% at 1 year, 49% vs 57% at 2 years, $P = .40$).

Among patients with AML, the use of CB remained a significant risk factor for overall mortality after adjustment for other factors (HR = 1.5; 95% confidence interval [CI], 1.0-2.0; $P = .028$; Table 2). However, in patients with ALL, the use of CB was not a significant factor for overall mortality on multivariate analysis (HR = 1.1; 95% CI, 0.7-1.6; $P = .78$). The adjusted probability of OS was significantly lower for CB recipients (57% vs 69% at 1 year, and 48% vs 59% at 2 years, $P = .010$; Figure 1A) compared with BM recipients for patients with AML, whereas the adjusted probability of OS was similar (69% vs 64% at 1 year, and 52% vs 53% at 2 years, $P = .99$; Figure 1B) between the groups for patients with ALL.

Results of the subgroup analyses showed that the difference in survival among AML patients was prominent in patients demonstrating 1CR at transplantation (RR = 2.9, 95% CI = 1.4-6.2, $P = .005$; Table 3).

LFS. For patients with AML, the unadjusted probabilities of LFS were significantly lower for CB recipients at 1 year (43% vs 62%) and 2 years (36% vs 54%) compared with BM recipients ($P < .001$). For patients with ALL, the unadjusted probabilities of LFS were lower with marginal significance for CB recipients at 1 year (52% vs 58%) and 2 years (45% vs 51%) compared with BM recipients ($P = .06$).

Among patients with AML, the use of CB remained as a significant risk factor for treatment failure (ie, relapse or death) after adjustment for other factors (HR = 1.5; 95% CI, 1.1-2.0; $P = .012$; Table 2). However, in patients with ALL, the use of CB was not a significant factor for treatment failure by multivariate analysis (HR = 1.2; 95% CI, 0.9-1.8; $P = .28$). The adjusted probability of LFS was significantly lower for CB recipients (51% vs 62% at 1 year, and 42% vs 54% at 2 years, $P = .004$; Figure 1C) compared with BM recipients for patients with AML, whereas the adjusted probability of LFS was similar (53% vs 53% at 1 year, and 46% vs 44% at 2 years, $P = .41$; Figure 1D) between the groups for patients with ALL.

Relapse

On univariate analyses, the cumulative incidence of relapse was higher for CB recipients with marginal significance in both AML (27% vs 20% at 1 year, and 31% vs 24% at 2 years) and ALL (27% vs 19% at 1 year, and 31% vs 24% at 2 years) ($P = .067$, and .085, respectively; Figure 2A,B).

On multivariate analyses adjusted by other factors, there was no significantly higher risk of relapse for CB recipients with either AML (RR = 1.2, 95% CI = 0.8-1.9, $P = .38$) or ALL (RR = 1.4, 95% CI = 0.8-2.4, $P = .19$; Table 2).

TRM

For patients with AML, the unadjusted cumulative incidence of TRM was significantly higher for CB recipients at 1 year (30% vs 19%) and 2 years (33% vs 22%) compared with those for BM recipients ($P = .004$; Figure 2C). For patients with ALL, the

Table 2. Results of multivariate analysis of outcomes in 173 recipients of cord blood and 311 recipients of bone marrow with acute myeloid leukemia, and 114 recipients of cord blood and 222 recipients of bone marrow with acute lymphoblastic leukemia

	Acute myeloid leukemia		Acute lymphoblastic leukemia	
Outcome	**RR (95% CI)**	***P***	**RR (95% CI)**	***P***
Overall survival*				
BM	1.00		1.00	
CB	1.45 (1.04-2.01)	.028	1.06 (0.71-1.57)	.78
Leukemia-free survival†				
BM	1.00		1.00	
CB	1.48 (1.09-2.01)	.012	1.22 (0.85-1.76)	.28
Relapse‡				
BM	1.00		1.00	
CB	1.21 (0.79-1.87)	.38	1.42 (0.84-2.41)	.19
TRM§				
BM	1.00		1.00	
CB	1.47 (0.95-2.28)	.085	1.01 (0.59-1.73)	.98
Neutrophil recovery‖				
BM	1.00		1.00	
CB	0.41 (0.33-0.51)	< .001	0.37 (0.29-0.48)	< .001
Platelet recovery¶				
BM	1.00		1.00	
CB	0.34 (0.27-0.44)	< .001	0.43 (0.33-0.56)	< .001
Acute GVHD#				
BM	1.00		1.00	
CB	0.80 (0.56-1.15)	.23	0.61 (0.39-0.95)	.028
Chronic GVHD**				
BM	1.00		1.00	
CB	0.94 (0.63-1.42)	.79	1.08 (0.66-1.77)	.77
Chronic GVHD, extensive type††				
BM	1.00		1.00	
CB	0.36 (0.18-0.72)	.004	0.58 (0.28-1.20)	.14

RR indicates relative risk; CI, confidence interval; BM, bone marrow; CB, cord blood; and GVHD, graft-versus-host disease.

*For overall survival, other significant variables for AML were patient age more than 45 years at transplantation, more advanced disease status at conditioning, M5/M6/M7 French-American-British classification, and female donor to male recipient donor-recipient sex mismatch; other significant variables for ALL were second or after complete remission disease status, more advanced disease status, and Philadelphia chromosome abnormality.

†For leukemia-free survival, other significant variables for AML were patient age more than 45 years at transplantation, more advanced disease status at conditioning, M5/M6/M7 French-American-British classification, and female donor to male recipient donor-recipient sex mismatch; other significant variables for ALL were second or after complete remission disease status, more advanced disease status, and Philadelphia chromosome abnormality.

‡For relapse, other significant variables for AML were more advanced disease status at conditioning, donor-recipient ABO major mismatch, chromosome abnormality other than favorable abnormalities, and cyclophosphamide and total body irradiation or busulfan and cyclophosphamide conditioning regimen; other significant variables for ALL were second or after complete remission disease status, more advanced disease status, and cyclophosphamide and total body irradiation conditioning.

§For TRM, other significant variables for AML were patient age more than 45 years at transplantation, second or after complete remission disease status, more advanced disease status, and chromosome abnormality other than favorable abnormalities; other significant variables for ALL were patient age more than 45 years at transplantation, more advanced disease status at conditioning, and conditioning other than cyclophosphamide and total body irradiation.

‖For neutrophil recovery, other significant variables for AML were second or after complete remission disease status and more advanced disease status; other significant variables for ALL were more advanced disease status at conditioning and cyclosporine-based GVHD prophylaxis.

¶For platelet recovery; other significant variables for AML were second or after complete remission disease status, more advanced disease status, female donor to male recipient donor-recipient sex mismatch, and tacrolimus-based GVHD prophylaxis; other significant variables for ALL were more advanced disease status at conditioning and conditioning other than cyclophosphamide and total body irradiation.

#For acute GVHD, no other significant variables were identified for both AML and ALL.

**For chronic GVHD, other significant variables for AML were more advanced disease status and conditioning other than cyclophosphamide and total body irradiation or busulfan and cyclophosphamide; there were no other significant variables identified for ALL.

††For extensive chronic GVHD, there were no other significant variables identified for AML; another significant variable for ALL was patient male sex.

cumulative incidence of TRM was similar between the 2 groups (CB vs BM = 21% vs 23% at 1 year, 24% vs 25% at 2 years, $P = .83$; Figure 2D).

On multivariate analyses adjusted by other factors, the risk for TRM was higher for CB recipients compared with that for BM recipients among patients with AML (RR = 1.5, 95% CI = 1.0-2.3, $P = .085$; Table 2) with marginal significance. For patients with ALL, the risk for TRM was similar between CB and BM recipients (RR = 1.0, 95% CI = 0.6-1.7, $P = .98$).

Cause of death

Recurrence of the primary disease was the leading cause of death in each group (CB vs BM = 37% vs 33% in patients with AML and 36% vs 41% in patients with ALL). The following causes were infection and organ failure in all groups (Table 4).

Other outcomes of transplantation

Neutrophil and platelet recovery. The unadjusted cumulative incidence of neutrophil recovery or platelet recovery at day 100 was significantly lower in CB recipients for both AML (77% vs 94%) and ALL (80% vs 97%) compared with that among BM recipients ($P < .001$ for both). On multivariate analyses, neutrophil recovery was significantly lower among CB recipients for both AML (RR = 0.4, 95% CI = 0.3-0.5, $P < .001$) and ALL (RR = 0.4, 95% CI = 0.3-0.5, $P < .001$; Table 2).

Table 3. Results of multivariate analysis of overall survival according to disease status at transplantation

	First complete remission			Second or after complete remission			More advanced		
Overall survival	n	RR (95% CI)	P	n	RR (95% CI)	P	n	RR (95% CI)	P
AML									
UBMT	130	1.00		82	1.00		95	1.00	
UCBT	50	2.92 (1.38-6.18)	.005	39	1.24 (0.51-3.04)	.63	81	1.29 (0.84-1.98)	.25
ALL									
UBMT	130	1.00		48	1.00		42	1.00	
UCBT	63	1.60 (0.84-3.05)	.16	21	0.62 (0.22-1.74)	.36	30	0.80 (0.38-1.69)	.57

RR indicates relative risk; CI, confidence interval; UBMT, unrelated bone marrow transplantation; and UCBT, unrelated cord blood transplantation.

The unadjusted cumulative incidence of platelet recovery greater than 50 000/μL at 4 months was significantly lower among CB recipients for both AML (59% vs 85%) and ALL (61% vs 83%) compared with that of BM recipients ($P < .001$ for both). The difference was also significant on multivariate analyses for both AML (RR = 0.3, 95% CI = 0.3-0.4, $P < .001$) and ALL (RR = 0.4, 95% CI = 0.3-0.6, $P < .001$; Table 2).

Acute GVHD. The unadjusted cumulative incidence of grade 2 to 4 acute GVHD was lower among CB recipients compared with that among BM recipients (32% vs 35% in AML, 28% vs 42% in ALL); the difference was significant in patients with ALL ($P = .39$ in AML, $P = .008$ in ALL). The difference was also significant on multivariate analyses in ALL (RR = 0.6, 95% CI = 0.4-1.0, $P = .028$). There was no significant difference in patients with AML (RR = 0.8, 95% CI = 0.6-1.2, $P = .23$; Table 2).

Chronic GVHD. The unadjusted cumulative incidence of chronic GVHD at 1 year after transplantation did not significantly differ between CB recipients and BM recipients in both AML (28% vs 32%, $P = .46$) and ALL (27% vs 30%, $P = .50$). The cumulative incidence of extensive-type chronic GVHD was significantly lower among CB recipients compared with that among BM recipients in both AML (8% vs 20%, $P < .001$) and ALL (10% vs 17%, $P = .034$). On multivariate analyses, the risk of developing chronic GVHD was similar in CB recipients and BM recipients in both AML (RR = 0.9, 95% CI = 0.6-1.4, $P = .79$) and ALL (RR = 1.1, 95% CI = 0.7-1.8, $P = .77$). The risk of developing extensive chronic GVHD was lower in CB recipients compared with BM recipients (RR = 0.4, 95% CI = 0.2-0.7, $P = .004$ in AML, and RR = 0.6, 95% CI, 0.3-1.2, $P = .14$ in ALL) and was significantly different in patients with AML (Table 2).

Discussion

The objective of our study was to investigate the outcomes of HLA-A, -B, low-resolution, and -DRB1 high-resolution 0 to 2 mismatched single-unit unrelated CBT in adult patients with acute leukemia compared with those of HLA-A, -B, -C, and -DRB1 (8 of 8) allele-matched unrelated BMT. Although AML and ALL are different diseases, previous comparisons of unrelated BMT and

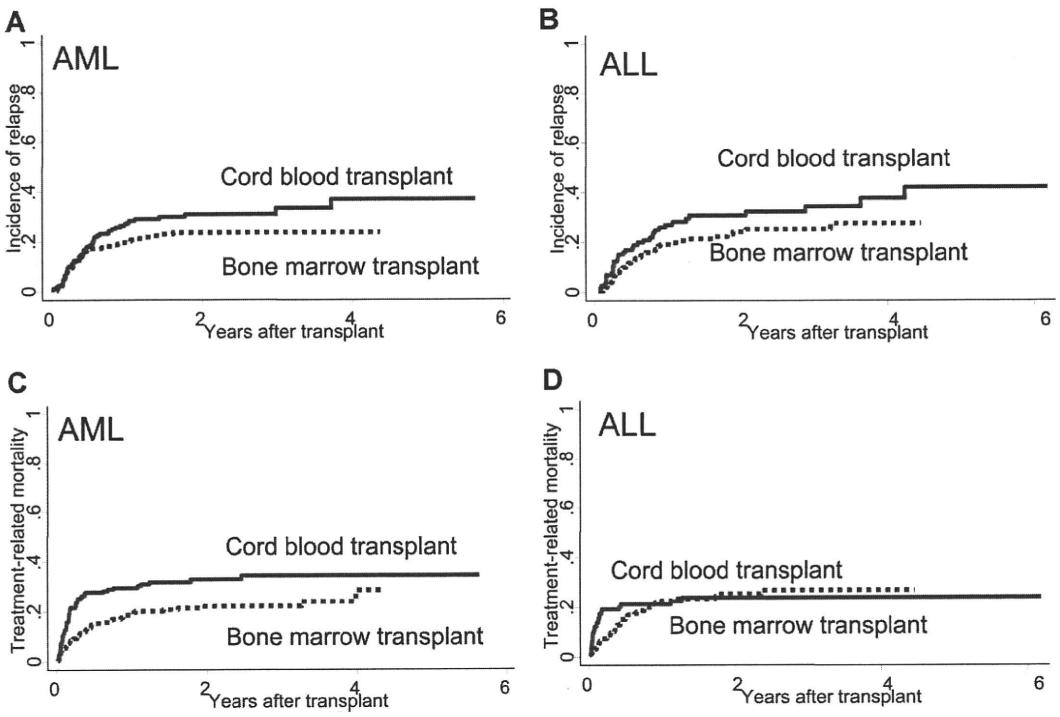

Figure 2. Cumulative incidence of relapse or TRM of recipients of CB or BM among patients with AML or ALL. For patients with AML, the cumulative incidence of (A) relapse (CB vs BM = 31% vs 24% at 2 years, $P = .068$) and (C) TRM (CB vs BM = 33% vs 22% at 2 years, $P = .004$) was higher in CB recipients. For patients with ALL, the cumulative incidence of relapse (B) was higher in CB recipients with marginal significance (CB vs BM = 31% vs 24% at 2 years, $P = .085$), but the incidence of TRM (D) was similar in CB and BM recipients (CB vs BM = 24% vs 25% at 2 years, $P = .83$).

Table 4. Causes of death after transplantation of unrelated cord blood or unrelated bone marrow among patients with acute myeloid leukemia or acute lymphoblastic leukemia

	Acute myeloid leukemia		Acute lymphoblastic leukemia	
Cause of death	UCBT	UBMT	UCBT	UBMT
Recurrence of disease	35 (37)	34 (33)	18 (36)	34 (41)
Graft failure/rejection	3 (3)	4 (4)	0 (0)	3 (4)
Graft-versus-host disease	6 (6)	7 (7)	3 (6)	5 (6)
Infection	22 (23)	19 (18)	13 (26)	11 (13)
Idiopathic pneumonia	4 (4)	4 (4)	2 (4)	6 (7)
Organ failure	17 (18)	17 (16)	8 (16)	10 (12)
Secondary cancer	0 (0)	1 (1)	0 (0)	0 (0)
Other causes	5 (5)	5 (5)	2 (4)	4 (5)
Unknown/data missing	2 (2)	13 (13)	4 (8)	10 (12)
Total	94 (100)	104 (100)	50 (100)	83 (100)

Data are presented as n (%).

UCBT indicates unrelated cord blood transplantation; and UBMT, unrelated bone marrow transplantation.

unrelated CBT did not separate these 2 diseases. Our report is the first to show the result of disease-specific analyses with a sufficient number of patients.

For AML patients, the recipients of CB were more likely to have advanced leukemia at the time of transplantation, as reported previously, suggesting that CB was used as an alternative stem cell source in the later phase of unrelated donor searches, especially in adults.[11,12,14] A larger proportion of CB recipients with ALL had the Philadelphia chromosome abnormality, which correlates with highly aggressive ALL and usually requires urgent transplantation, in which CB has an advantage over BM.[21]

Different outcomes of mortality were found between AML and ALL in a controlled comparison using multivariate analyses. Whereas significantly lower OS and LFS rates were observed in CB recipients with AML, rates of overall mortality and treatment failure were similar between CB and BM recipients with ALL. The relapse rate was not different between CBT and BMT in patients with both AML and ALL, which was consistent with previous reports.[11-13] In adult patients with ALL, a previous report showed no difference in the outcome of related compared with unrelated BM or peripheral blood transplantation in 1CR.[22] Favorable disease status at transplantation could be a more important factor affecting outcome rather than the type of stem cell source or donor type in patients with ALL. It is notable that TRM in HLA allele-matched unrelated BM recipients with AML was quite low in our study. This is probably associated with the low incidence of acute and chronic GVHD in the Japanese population, which is thought to be the result of genetic homogeneity.[23-26] Among patients with AML, although the difference was not statistically significant, a higher trend of TRM observed in CB recipients might be associated with higher overall and TRM rates in CB recipients. Reasons for higher TRM could include the graft source and delayed neutrophil recovery. Better supportive care is required after CBT for patients going through a prolonged neutropenic period. Development of better graft engineering or better conditioning regimens would help to decrease the TRM rate in CB recipients. Because relapse was the major cause of death in all groups, any attempt to decrease TRM should preserve the antileukemia effect to improve OS and LFS. Another reason for the higher TRM could be a higher risk patient population, higher risk for both disease status and comorbid conditions, requiring rapid transplantation. Searching for unrelated donors earlier and providing transplantation earlier in the disease course could help to decrease TRM in CB recipients.

Neutrophil and platelet recovery was slower in CB recipients with either AML or ALL, consistent with the results of previous reports.[11,12,27] Multiple studies have reported lower incidence of acute GVHD in CB recipients.[8-10,12,13] In our study, particularly in patients with ALL, the risk of developing grade 2 to 4 acute GVHD in CB recipients was lower compared with BM recipients, which was reported to be lower compared with the incidence reported from Western countries.[23-25] The risk of developing chronic GVHD was similar between CB and BM recipient with either disease, but the risk of developing extensive-type chronic GVHD was lower in CB recipients; the difference was significant in patients with AML. It is notable that there was no increase in the incidence of acute or chronic GVHD in CB recipients among patients with either AML or ALL, despite HLA disparity.

For differences in outcomes between AML and ALL, one possibility is a difference of treatment before conditioning therapy. Most AML patients received a more intense treatment for induction and consolidation therapy compared with that for ALL. There was no adjustment made for previous treatment, and this could be the reason for higher mortality in CBT, which requires a longer time for neutrophil recovery. Another possible cause of the difference in outcomes is the difference in conditioning regimens. Preparative regimens were similar between CB and BM recipients among ALL patients. However, in patients with AML, the proportion of standard regimens, such as cyclophosphamide and TBI or busulfan and cyclophosphamide, was smaller among CB recipients. These differences in the distribution of preparative regimens were also seen in a previous report.[11] Although the final model was adjusted for conditioning regimens, we cannot rule out the possibility of an effect that larger CB recipients received additional or different chemotherapeutic agents compared with BM recipients among patients with AML. Although the difference was small, the median age of CB recipients with AML was 4 years older than CB recipients with ALL (median age, 38 vs 34 years, $P = .021$), which might have affected the higher mortality rate among CB recipients with AML. It is also possible that some unknown biologic aspects have contributed to these differences, and this would require further evaluation in future studies.

Further subgroup analyses indicated that the superiority of HLA allele-matched BM versus CB for OS was mostly found in patients with AML showing 1CR at conditioning. However, because of the limited numbers of patients in these subgroup analyses and the possibility of an unidentified bias in stem cell source selection, our findings should be verified by further analysis in a larger population.

In conclusion, we found different outcomes between patients with AML and ALL, indicating the importance of disease-specific analyses in alternative donor studies. HLA-A, -B low-resolution, and -DRB1 high-resolution 0 to 2 mismatched single-unit CB is a favorable alternative stem cell source for patients without a suitable related or 8 of 8 matched unrelated BM donor. In the absence of a suitable donor, unrelated CBT should be planned promptly to transplant the patient while in a better disease status and better clinical condition. For patients with AML, decreasing mortality, especially in the early phase of transplantation, is required to improve the outcome for CB recipients.

Acknowledgments

The authors thank all the staff members of the collaborating institutes of the Japan Cord Blood Bank Network and Japan Marrow Donor Program for their assistance and cooperation and

Dr Takakazu Kawase for validating human leukocyte antigen data of the Japan Marrow Donor Program.

This work was supported by a Research Grant for Tissue Engineering (H17-014), a Research Grant for Allergic Disease and Immunology (H20-015), and a Research Grant for Cancer (H19-1) from the Japanese Ministry of Health, Labor, and Welfare.

Authorship

Contribution: Y.A. and R.S. designed the study and wrote the paper; Y.A. analyzed results and made the figures; S. Kato and Y.M. designed the research; T.-N.I., H.A., and M. Takanashi reviewed and cleaned the Japan Cord Blood Bank Network data and reviewed the results; S. Taniguchi, S. Takahashi, S. Kai, H.S., Y. Kouzai, M.K., and T.F. submitted and cleaned the data; and S.O., M. Tsuchida, K.K., Y.M., and Y. Kodera reviewed and cleaned the Japan Marrow Donor Program data and reviewed the results.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

A complete list of members from the Japan Marrow Donor Program and the Japan Cord Blood Bank Network can be found in the Supplemental Appendix (available on the *Blood* website; see the Supplemental Materials link at the top of the online article).

Correspondence: Yoshiko Atsuta, Department of Hematopoietic Stem Cell Transplantation Data Management, Nagoya University School of Medicine, 1-1-20 Daiko-Minami, Higashi-ku Nagoya, 461-0047 Japan; e-mail: y-atsuta@med.nagoya-u.ac.jp.

References

1. Szydlo R, Goldman JM, Klein JP, et al. Results of allogeneic bone marrow transplants for leukemia using donors other than HLA-identical siblings. J Clin Oncol. 1997;15:1767-1777.
2. Petersdorf EW, Gooley TA, Anasetti C, et al. Optimizing outcome after unrelated marrow transplantation by comprehensive matching of HLA class I and II alleles in the donor and recipient. Blood. 1998;92:3515-3520.
3. Hansen JA, Gooley TA, Martin PJ, et al. Bone marrow transplants from unrelated donors for patients with chronic myeloid leukemia. N Engl J Med. 1998;338:962-968.
4. Wagner JE, Rosenthal J, Sweetman R, et al. Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: analysis of engraftment and acute graft-versus-host disease. Blood. 1996;88:795-802.
5. Kurtzberg J, Laughlin M, Graham ML, et al. Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. N Engl J Med. 1996;335:157-166.
6. Gluckman E, Rocha V, Boyer-Chammard A, et al. Outcome of cord-blood transplantation from related and unrelated donors: Eurocord Transplant Group and the European Blood and Marrow Transplantation Group. N Engl J Med. 1997;337:373-381.
7. Rubinstein P, Carrier C, Scaradavou A, et al. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. N Engl J Med. 1998;339:1565-1577.
8. Rocha V, Wagner JE Jr, Sobocinski KA, et al. Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA-identical sibling: Eurocord and International Bone Marrow Transplant Registry Working Committee on Alternative Donor and Stem Cell Sources. N Engl J Med. 2000;342:1846-1854.
9. Rocha V, Cornish J, Sievers EL, et al. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. Blood. 2001;97:2962-2971.
10. Eapen M, Rubinstein P, Zhang MJ, et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. Lancet. 2007;369:1947-1954.
11. 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.
12. 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.
13. 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.
14. Sanz MA. Cord-blood transplantation in patients with leukemia: a real alternative for adults. N Engl J Med. 2004;351:2328-2330.
15. Kodera Y, Morishima Y, Kato S, et al. Analysis of 500 bone marrow transplants from unrelated donors (UR-BMT) facilitated by the Japan Marrow Donor Program: confirmation of UR-BMT as a standard therapy for patients with leukemia and aplastic anemia. Bone Marrow Transplant. 1999;24:995-1003.
16. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15:825-828.
17. 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.
18. Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988;16:1141-1154.
19. Fine JP, Gray RJ. A proportional hazards model for subdistribution of a competing risk. J Am Stat Assoc. 1999;94:456-509.
20. Hsieh FY, Lavori PW. Sample-size calculations for the Cox proportional hazards regression model with nonbinary covariates. Control Clin Trials. 2000;21:552-560.
21. Barker JN, Krepski TP, DeFor TE, Davies SM, Wagner JE, Weisdorf DJ. Searching for unrelated donor hematopoietic stem cells: availability and speed of umbilical cord blood versus bone marrow. Biol Blood Marrow Transplant. 2002;8:257-260.
22. Kiehl MG, Kraut L, Schwerdtfeger R, et al. Outcome of allogeneic hematopoietic stem-cell transplantation in adult patients with acute lymphoblastic leukemia: no difference in related compared with unrelated transplant in first complete remission. J Clin Oncol. 2004;22:2816-2825.
23. Morishima Y, Morishita Y, Tanimoto M, et al. Low incidence of acute graft-versus-host disease by the administration of methotrexate and cyclosporine in Japanese leukemia patients after bone marrow transplantation from human leukocyte antigen compatible siblings; possible role of genetic homogeneity. The Nagoya Bone Marrow Transplantation Group. Blood. 1989;74:2252-2256.
24. Sasazuki T, Juji T, Morishima Y, et al. Effect of matching of class I HLA alleles on clinical outcome after transplantation of hematopoietic stem cells from an unrelated donor: Japan Marrow Donor Program. N Engl J Med. 1998;339:1177-1185.
25. 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.
26. Atsuta Y, Suzuki R, Yamamoto K, et al. Risk and prognostic factors for Japanese patients with chronic graft-versus-host disease after bone marrow transplantation. Bone Marrow Transplant. 2006;37:289-296.
27. 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.

Bone Marrow Transplantation (2009), 1–3

www.nature.com/bmt

LETTER TO THE EDITOR

T-cell post-transplant lymphoproliferative disorder in a patient with chronic idiopathic myelofibrosis following allogeneic PBSC transplantation

Bone Marrow Transplantation advance online publication, 14 December 2009; doi:10.1038/bmt.2009.347

Post-transplant lymphoproliferative disorder (PTLD) is a well-recognized complication after solid organ and hematopoietic SCTs (HSCTs). The majority are of B-cell origin and EBV related.[1] Most of the T-cell PTLD cases have been described as occurring after solid organ transplantations;[2] T-cell PTLD cases following HSCT are exceedingly rare. There are only three reported cases of T-cell PTLD following allogeneic HSCT[3] and four cases following autologous HSCT.[4–7] Here we report a case of T-cell PTLD after allogeneic-PBSC transplantation (allo-PBSCT) in a patient with chronic idiopathic myelofibrosis (CIMF).

A 44-year-old Japanese woman with anemia and fever was diagnosed with CIMF in November 2006. At the time of her diagnosis, her WBC count was 900/μl, Hb 6.9 g/dl, plt count 39 000/μl with no morphologically abnormal cells in her peripheral blood, and an abdominal CT scan showed mild splenomegaly without hepatomegaly, lymphadenopathy or liver tumor. A specimen of her biopsied BM showed diffuse fibrosis and a decreased number of hematopoietic cells. No abnormal cell proliferation was observed. In December 2006, she underwent allo-PBSCT from an HLA-identical brother. Neutrophil engraftment was achieved on day 17 after transplant, and BM analysis showed full hematological recovery with 100% donor-type chimerism assessed by Y chromosome-based FISH analysis. As grade II acute GVHD involving the skin and subsequently an extensive type of chronic GVHD (cGVHD) developed; continued immunosuppressive therapy with cyclosporine and prednisolone was required for several months after the transplant. At 5 months after transplant, a liver tumor, 2 cm in diameter, was detected by an abdominal CT scan. Although PTLD was raised as a differential diagnosis, biopsied liver tissue was inadequate for pathological examination. Immunosuppressive therapy was reduced, resulting in a decrease in liver tumor size to 1.6 cm in 2 months. However, a subsequent flare-up of cGVHD required more intensive immunosuppressive therapy, and the liver tumor's diameter increased twice in size. A liver tumor biopsy performed at this time showed a diffuse proliferation of atypical lymphoid cells (Figure 1a). Immunohistochemically, these tumor cells were positive for LCA, CD3, CD7 and CD8, and negative for CD4, CD5, CD34, CD79a, MPO, CD30, CD56 and TdT (Figure 1b). These pathological findings are compatible with peripheral T-cell lymphoma-unspecified (Figure 1c). EBV infection was not detected by *in situ* hybridization. Y chromosome-based FISH analysis revealed the tumor cells were of recipient origin. She suffered from fever, pancytopenia and decreased liver function, and was hospitalized for further therapy in November 2007. BM examination showed infiltration of 4% abnormal lymphoid cells and the proliferation of macrophage with hemophagocytosis, with no sign of CIMF recurrence. Chromosome analysis of the BM cells showed 44, X, der(X)t(X;7)(q13;q11.2), add(2)(q21), add(4)(p11), add(4)(p16), der(9;17)(q10;q10), −10, −13, add(15)(p11), +mar [2/20]. An abdominal CT scan showed that the liver tumor grew rapidly to a size of $12 \times 6\,cm^2$ (Figure 1d). Serological tests for HIV, HBV, HCV and HTLV-1 were negative, and the EBV VCA IgG was positive but negative for IgM. Analyses by real-time PCR were negative for human herpesvirus-6, VZV, CMV and EBV in her peripheral blood. She was diagnosed with T-cell PTLD with lymphoma-associated hemophagocytic syndrome. CHOP therapy was started, but the disease progressed within 2 weeks after this. She underwent urgent unrelated cord blood transplantation (UCBT) from an HLA two antigen-mismatched donor. Her post-transplant course was complicated by sepsis, renal failure and respiratory failure. She died on day 6 after UCBT. An autopsy was not performed.

To our knowledge, there have been only four cases of T-cell PTLD following allo-SCT, including our case (Table 1). Time to T-cell PTLD diagnosis ranges from 2 to 43 months after a transplant. Although the type of PTLD was not consistent, ranging from precursor to peripheral T-cell neoplasms, none of them were associated with EBV infection. Our case was negative for EBV, and the type was peripheral T-cell lymphoma-unspecified.

There have been a few reports describing myelofibrosis in association with T-cell lymphoma.[8] In these cases, PDGF and tumor growth factor β, which may have been secreted by neoplastic T lymphocytes, had an important role in the development of myelofibrosis. In our case, there was no clinical evidence of T-cell lymphoma at the time of CIMF diagnosis, and no sign of myelofibrosis recurrence at the onset of T-cell lymphoma. Thus, the development of T-cell lymphoma in this case was considered to be independent of the CIMF.

All three patients reported as having T-cell PTLD following allo-SCT had severe GVHD and received a heavy dose of immunosuppressive agents, suggesting some viral agents in an immunosuppressed state may have an important role in the development of T-cell PTLD. However, we were unable to find any evidence of viral

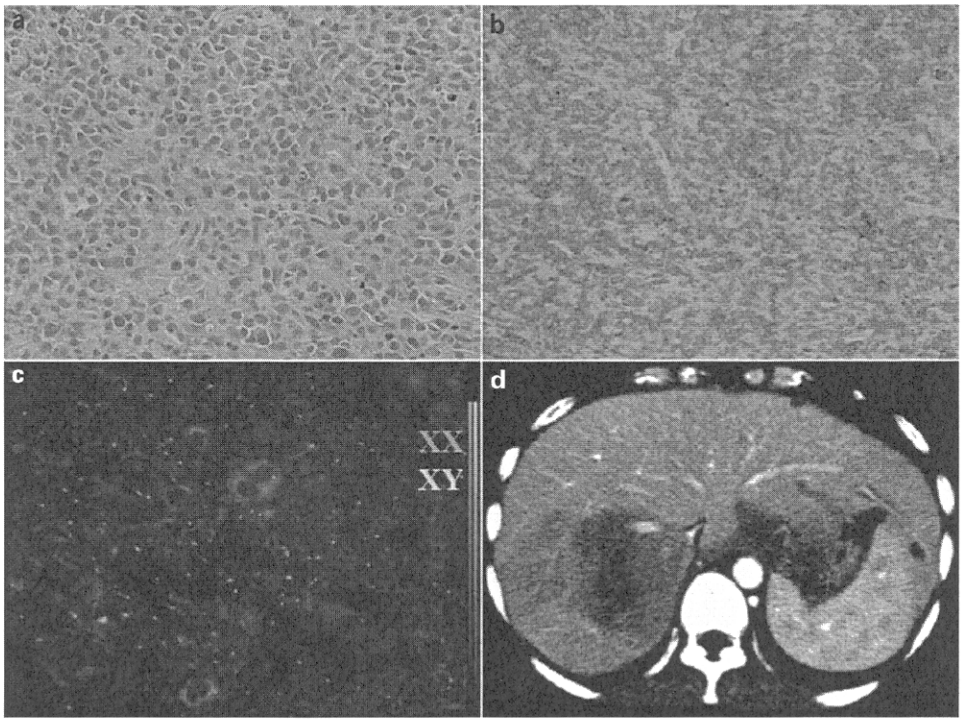

Figure 1 (**a**) Liver tumor biopsy shows monotonous infiltration of atypical lymphoid cells (H&E stain × 400). (**b**) Immunostaining for CD3 shows a large number of positive cells within the tumor. (**c**) Y chromosome-based FISH reveals the tumor cells are of recipient origin (XX signal). (**d**) Abdominal CT scan shows a low-density area with 12 cm diameter on the right side of the liver.

Table 1 T-cell post-transplant lymphoproliferative disorder after allogeneic stem cell transplantation

Authors	*Age/sex*	*Initial Dx*	*HSCT*	*Type of PTLD Dx (months after HSCT)*	*Origin*	*EBV*	*GVHD*	*Outcome (months after Dx)*
Zutter *et al.*[3]	14/M	AML	HLA-identical BM graft	T-lymphoblastic lymphoma (43)	Recipient	Neg	Mild aGVHD(S,L,Gut) Severe cGVHD(S,L,Gut)	Death (28)
	9/M	ALL	HLA-identical BM graft	T-lymphoblastic lymphoma (21)	Donor	Neg	Mild aGVHD(S) Severe cGVHD(S,L)	Death (6)
	2/F	ALL	HLA-2 mismatched BM graft	Polymorphic T-cell lymphoma (2)	Donor?	Neg	Severe aGVHD(S,L)	Death (0)
Present case	44/F	CIMF	HLA-identical allogeneic PBSC	PTCL-u (5)	Recipient	Neg	aGVHDII(S3,L0,Gut0) Extensive cGVHD(S,L)	Death (2)

Abbreviations: aGVHD = acute GVHD; cGVHD = chronic GVHD; CIMF = chronic idiopathic myelofibrosis; Dx = diagnosis; F = female; Gut = gastrointestinal tract; HSCT = hematopoietic stem cell transplantation; L = liver; M = male; neg = negative; PTCL-u = peripheral T-cell lymphoma-unspecified; PTLD = post-transplant lymphoproliferative disorder; S = skin.

infection and reactivation in our case and previously reported cases. It has been reported that only 15 of 76 cases of T-cell PTLD after solid organ transplantation were EBV positive,[9] and any other viral involvement has not been clearly demonstrated. These findings suggest that not only viral infection but also other factors, such as chronic antigenic stimulation, impaired immunoregulation and genetic factors, may be associated with the development of T-cell PTLD.[10]

The outcomes of reported T-cell PTLD so far are poor. All patients died because of the progression of the disease. In our patient, a transient response was observed by reducing immunosuppression, suggesting a graft-versus-lymphoma effect, which was necessitated to increase the immunosuppression. Standard cytotoxic chemotherapy led to a poor response in our patient, similar to the other cases previously described. More intensive chemotherapy, donor lymphocyte infusion or second HSCT should be considered at an early stage of the disease.

In conclusion, T-cell PTLD rarely occurs after allo-HSCT. Further research, however, is needed to fully characterize the clinicopathological features of this condition and to investigate the optimal therapy.

Conflict of interest

The authors declare no conflict of interest.

A Nishida[1], H Yamamoto[1], Y Ohta[2], M Karasawa[1], D Kato[1], N Uchida[1], A Wake[1] and S Taniguchi[1]
[1]*Department of Hematology, Toranomon Hospital, Tokyo, Japan and*
[2]*Department of Pathology, Toranomon Hospital, Tokyo, Japan*
E-mail: hhisa-sea@r7.dion.ne.jp

References

1 Loren AW, Porter DL, Stadtmauer EA, Tsai DE. Post-transplant lymphoproliferative disorder: a review. *Bone Marrow Transplant* 2003; **31**: 145–155.
2 Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. *Crit Rev Oncol Hematol* 2005; **56**: 155–167.
3 Zutter MM, Durnam DM, Hackman RC, Loughran Jr TP, Kidd PG, Ashley RL *et al.* Secondary T-cell lymphoproliferation after marrow transplantation. *Am J Clin Pathol* 1990; **94**: 714–721.
4 Awaya N, Adachi A, Mori T, Kamata H, Nakahara J, Yokoyama K *et al.* Fulminant Epstein-Barr virus (EBV)-associated T-cell lymphoproliferative disorder with hemophagocytosis following autologous peripheral blood stem cell transplantation for relapsed angioimmunoblastic T-cell lymphoma. *Leuk Res* 2006; **30**: 1059–1062.
5 Lau LG, Tan LK, Salto-Tellez M, Koay ES, Liu TC. T-cell post-transplant lymphoproliferative disorder after hematopoietic stem cell transplantation: another case and a review of the literature. *Bone Marrow Transplant* 2004; **34**: 821–822.
6 Narumi H, Kojima K, Matsuo Y, Shikata H, Sekiya K, Niiya T *et al.* T-cell large granular lymphocytic leukemia occurring after autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 2004; **33**: 99–101.
7 Yufu Y, Kimura M, Kawano R, Noguchi Y, Takatsuki H, Uike N *et al.* Epstein-Barr virus-associated T cell lymphoproliferative disorder following autologous blood stem cell transplantation for relapsed Hodgkin's disease. *Bone Marrow Transplant* 2000; **26**: 1339–1341.
8 Uehara E, Tasaka T, Matsuhashi Y, Fujita M, Tamura T, Shimoura Y *et al.* Peripheral T-cell lymphoma presenting with rapidly progressing myelofibrosis. *Leuk Lymphoma* 2003; **44**: 361–363.
9 Costes-Martineau V, Delfour C, Obled S, Lamant L, Pageaux GP, Baldet P *et al.* Anaplastic lymphoma kinase (ALK) protein expressing lymphoma after liver transplantation: case report and literature review. *J Clin Pathol* 2002; **55**: 868–871.
10 Penn I. The role of immunosuppression in lymphoma formation. *Springer Semin Immunopathol* 1998; **20**: 343–355.