

## 研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yazaki M, Atsuta Y, Kato K, Kato S, <u>Taniguchi S</u> , Takahashi S, Ogawa H, Kouzai Y, Kobayashi T, Inoue M, Kobayashi R, Nagamura-Inoue T, Azuma H, Takanashi M, Kai S, Nakabayashi M, Saito H.	Incidence and risk factors of early bacterial infections after unrelated cord blood transplantation.	Biol Blood Marrow Transplant	15	439-446	2009
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#### IV. 研究成果の刊行物・別刷

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

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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-UCBT was 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.

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**KEY WORDS:** Early bacterial infection, Cord blood transplantation, The Japan Cord Blood Bank Network, Risk factor for infection, Unrelated 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].

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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 nucleated 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  $2 \times 10^7$ /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  $\geq$ 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 myelodysplastic syndrome/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 myeloablative conditioning 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  $5.10 \times 10^7$ . 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 myeloablative conditioning 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  $2.53 \times 10^7$ .

**Incidence and Timing of Early Bacterial Infection**

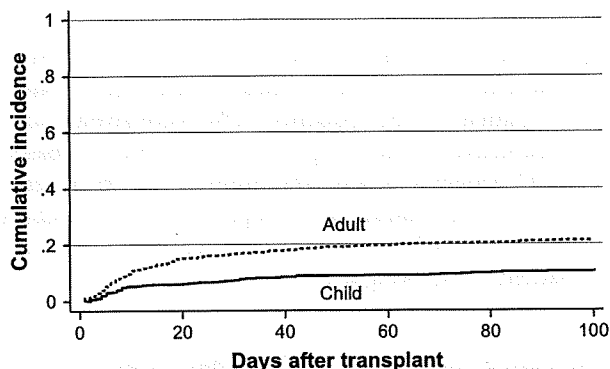
In the child cohort, 77 patients (12%) developed early bacterial infection with a cumulative incidence of 9% (95% confidence interval [CI] 7%-11%) at 50

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	
<b>Gram-positives</b>	234	(74)
<i>Staphylococcus</i> spp.	147	(47)
<i>Enterococcus</i> spp.	56	(18)
<i>Streptococcus</i> spp.	19	(6)
<i>Bacillus</i> spp.	8	(3)
<i>Corynebacterium</i> spp.	2	
<i>Clostridium</i> spp.	1	
<i>Mycobacterium tuberculosis</i>	1	
<b>Gram-negatives</b>	81	(26)
<i>Pseudomonas aeruginosa</i>	34	(11)
<i>Acinetobacter</i> spp.	7	
<i>Enterobacter cloacae</i>	7	
<i>E. coli</i>	5	
<i>Stenotrophomonas maltophilia</i>	5	
<i>Burkholderia cepacia</i>	4	
<i>Klebsiella pneumoniae</i>	3	
<i>Chryseobacterium</i> spp.	3	
<i>Alcaligenes xylosoxidans</i>	2	
<i>Salmonella</i> spp.	2	
<i>Serratia</i> spp.	1	
<i>Morganella morganii</i>	1	
<i>Leuconostoc</i> spp.	1	
<i>Micrococcus</i> spp.	1	
<i>Aeromonas hydrophila</i>	1	
<i>Capnocytophaga</i> spp.	1	
<i>Bacteroides fragilis</i>	1	
<i>Prevotella oralis</i>	1	
<i>Fusobacterium necrophorum</i>	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 microorganisms, *Pseudomonas aeruginosa* was found in 34 cases, accounting for 11% of all bacteremia cases, and *Stenotrophomonas maltophilia* in 5 cases. Anaerobic Gram-negative organisms, such as *Bacteroides fragilis* (n = 1), *Prevotella 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 maltophilia* 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 aeruginosa* 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 aeruginosa* 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 hematopoietic 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 <sup>+</sup> cell <1.42 × 10 <sup>5</sup> /kg	244/487	1.21	0.70-2.09	.494
Nucleated cell <5.10 × 10 <sup>7</sup> /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				
GVHD prophylaxis	75/664	1.58	0.83-3.01	.164
GVHD prophylaxis				
Cyclosporine based	401	1.00		
Tacrolimus based	199	1.23	0.72-2.08	.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 disease; CI, confidence interval; HR, hazard ratio.

\*Number of cells at freezing.

†Standard disease means first complete remission or first chronic phase of malignant disease.

‡Advanced disease means all others 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

**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 myelogenous leukemia	490	1.00		
Acute 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 <sup>+</sup> cell <0.80 × 10 <sup>5</sup> /kg	560/1130	1.18	0.90-1.51	.240
Nucleated cell <2.53 × 10 <sup>7</sup> /kg	608/1208	1.17	0.91-1.49	.224
Conditioning regimen				
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	0.94-1.55	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 malignant disease.

‡Advanced disease means all other except standard disease.

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 maltophilia* adult pneumonias

developed during neutropenia. *Stenotrophomonas maltophilia* is naturally resistant to penicillins, cepheems 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.

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

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

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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.<sup>1-3</sup> Umbilical cord blood (CB), an alternative stem cell source to BM or peripheral blood stem cells, has been used primarily in children,<sup>4-10</sup> but its use in adults is increasing.<sup>11,12</sup>

Clinical comparison studies of cord blood transplantation (CBT) and bone marrow transplantation (BMT) for leukemia from unrelated donors in adult recipients showed comparable outcomes.<sup>11-13</sup> Recipients of CBT showed delayed neutrophil recovery and lower incidence of acute graft-versus-host disease (GVHD).<sup>11-13</sup> Overall treatment-related mortality (TRM) was reported to be similar<sup>12</sup> or higher<sup>11</sup> 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.<sup>6,7,14</sup>

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 (JMDF).<sup>15</sup>

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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<sup>3</sup> for 3 consecutive points; platelet recovery was defined by a count of at least 50 000 platelets/mm<sup>3</sup> without transfusion support. Diagnosis and clinical grading of acute GVHD were performed according to the established criteria.<sup>16</sup> 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  $\chi^2$  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.<sup>17</sup> 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.<sup>18</sup> 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.<sup>19</sup> 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, cyclophosphamide 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.<sup>20</sup>

## 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

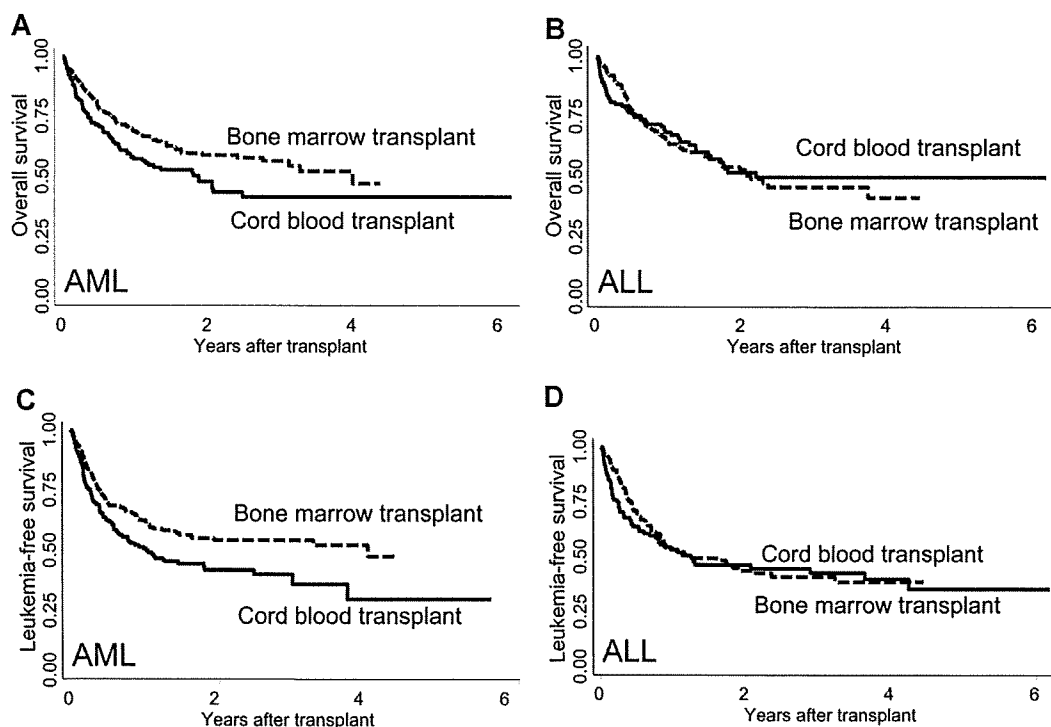
**Table 1. Characteristics of recipients of cord blood or bone marrow from unrelated donors in 484 patients with acute myeloid leukemia and 336 patients with acute lymphoblastic leukemia**

Characteristic	Acute myeloid leukemia			Acute lymphoblastic leukemia		
	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 <sup>7</sup> /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**

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