Table 9 Intraclass Correlation Coefficients between child self-reports and parent proxy-reports in PedsQL Cancer Module

Children					Parents				
	P	N	PA	TA	W	CP	A	C	Total
Pain and hurt (P)	0.69**	0.35**	0.06	0.19**	0.35**	0.21**	0.25**	0.22**	0.44**
Nausea (N)	0.38**	0.79**	0.21**	0.27**	0.50**	0.21**	0.34**	0.30**	0.53**
Procedural anxiety (PA)	0.09	0.21**	0.73**	0.29**	0.03	0.04	0.10	0.17**	0.31**
Treatment anxiety (TA)	0.09	0.19**	0.26**	0.50**	0.21**	0.08	0.17**	0.21**	0.33**
Worry (W)	0.27**	0.48**	0.17**	0.28**	0.57**	0.23**	0.35**	0.37**	0.46**
Cognitive problems (CP)	0.18**	0.14*	0.04	0.12*	0.16*	0.60**	0.24**	0.30**	0.31**
Perceived physical appearance (A)	0.21**	0.24**	0.16*	0.25**	0.32**	0.25**	0.57**	0.29**	0.37**
Communication (C)	0.14*	0.31**	0.25**	0.29**	0.30**	0.36**	0.33**	0.60**	0.44**
Total	0.35**	0.47**	0.32**	0.43**	0.43**	0.35**	0.41**	0.44**	0.68**

*P = < 0.05, **P = < 0.01 (2-tailed)

doctor' and 'getting anxious about going to the hospital' might be difficult to explain to young children. Test-retest reliability coefficients for the 'pain and hurt' subscale and 'treatment anxiety' subscale in children aged 5 to 7 years were also low in the validation study of the Chinese version [17]. The German and the Brazilian versions of the PedsQL Cancer Module did not report the analysis for separate age groups. However, the total scales for each age group had moderate to high ICC values for both children and parents (> 0.70).

Second, the 'treatment anxiety' subscale for 13- to 18-year-olds also demonstrated a low ICC value because many children who had been off treatment for more than 12 months gave a different answer on the retest. However, scores on both the first test and retest were very high (first test: mean, 94.79 [SD, 8.84], range 75-100]; retest: mean, 94.05 [SD, 10.45], range 75-100) and not significantly different. We considered that the low ICC value in this age group might be due to minor differences in answers. Third, the 'worry' subscale in 8- to 12-year-olds also had a low ICC value. It may be because all the children except 1 who completed the retest were off treatment for over 12 months, so that they might have had trouble answering responses such

Table 10 Spearman's Correlation Coefficients between the PedsQL Cancer Module and the PedsQL Generic Core Scales

	PedsQL Generic Core Scales				
PedsQL Cancer Module	Physical health	Emotional functioning	Social functioning	School functioning	Total
Child self-report					
Pain and hurt	0.51**	0.45**	0.30**	0.31**	0.52**
Nausea	0.57**	0.48**	0.38**	0.36**	0.54**
Procedural anxiety	0.37**	0.30**	0.36**	0.14	0.35**
Treatment anxiety	0.17*	0.17*	0.30**	0.12	0.24**
Worry	0.52**	0.53**	0.33**	0.37**	0.58**
Cognitive problems	0.49**	0.53**	0.49**	0.59**	0.63**
Perceived physical appearance	0.51**	0.58**	0.44**	0.33**	0.58**
Communication	0.43**	0.42**	0.49**	0.38**	0.54**
Total	0.67**	0.66**	0.58**	0.48**	0.76**
Parent proxy-report					
Pain and hurt	0.49**	0.44**	0.25**	0.25**	0.47**
Nausea	0.62**	0.56**	0.26**	0.33**	0.50**
Procedural anxiety	0.37**	0.45**	0.30**	0.16*	0.36**
Treatment anxiety	0.29**	0.43**	0.30**	0.20**	0.38**
Worry	0.39**	0.45**	0.21**	0.32**	0.47**
Cognitive problems	0.32**	0.43**	0.39**	0.43**	0.51**
Perceived physical appearance	0.42**	0.50**	0.28**	0.22**	0.52**
Communication	0.39**	0.47**	0.31**	0.23**	0.44**
Total	0.65**	0.71**	0.44**	0.38**	0.70**

*P = < 0.05, **P = < 0.01 (2-tailed)

Table 11 Spearman's Correlation of the PedsQL child self-report with DSRS-C and with CES-D

	Depression scale	
	DSRS-C score > = 16	CES-D score > = 16
PedsQL Generic Core Scales		
Physical health	-0.636	-0.290
Emotional functioning	-0.815*	-0.883*
Social functioning	-0.849**	-0.202
School functioning	-0.617	-0.138
Total	-0.704	-0.775*
PedsQL Cancer Module		
Pain and hurt	-0.208	0.200
Nausea	-0.598	-0.257
Procedural anxiety	-0.811*	0.274
Treatment anxiety	-0.185	-0.397
Worry	-0.916**	-0.373
Cognitive problems	-0.556	-0.378
Perceived physical appearance	-0.849*	-0.294
Communication	-0.729	-0.486
Total	-0.889**	-0.371

*P = < 0.05, **P = < 0.01 (2-tailed)

CES-D: Center for Epidemiologic Studies Depression scale DSRS-C: Depression Self-Rating Scale for Children

as 'worrying about side effects from medical treatments' and 'worrying about whether or not his/her medical treatments are working.' ICC values among the parents were almost good to excellent.

For validity, exploratory factor analysis identified 7 factors for both child self-reports and parent proxy-reports in our study, even though the original English version has an 8-factor structure [11]. For children, the first item of 'worry' (worrying about side effects from medical treatments) loaded on the 'nausea' factor. This suggests that patients' worries about side effects increase when the children actually feel nauseated. The second and third items of 'worry' (worrying about whether or not his/her medical treatments are working, worrying that the cancer will reoccur or relapse) loaded on the 'communication' factor, This suggests that patients have a difficult time communicating with medical staff when they worry about treatment efficacy and/or relapse. In parent proxy-reports, the first and the second items of 'worry' loaded on the 'nausea' factor. In clinical practice in Japan, we feel many parents who have a child with cancer believe that the most effective chemotherapy should cause the worst side effects (such as nausea, stomatitis, and bone marrow suppression), so that their worry about treatment efficacy may link to the 'nausea' factor.

Spearman's correlation coefficients between the child self-reports and parent-proxy reports showed strong correlation between the same subscales ($P = < 0.01$), especially in physical health scales. We think the reason for this is that objective evaluation of physical symptoms are generally easier than emotional symptoms.

Comparing the Spearman's correlation coefficients between the PedsQL 3.0 Cancer Module and the PedsQL 4.0 Generic Core Scales, all subscales and the total score of the Cancer Module were significantly correlated with all the subscales and total score of the generic core scales for both children and their parents except between 'procedural anxiety,' 'treatment anxiety,' and 'school functioning.' Specifically, the 'physical health' subscale of the generic core scale demonstrated a strong correlation with physical, emotional, and social subscales of the Cancer Module. The scores of 'emotional functioning' were good if the children did not have much pain, nausea, or worry and did not have cognitive problems at school. A good self-image about their physical appearance correlated with good emotional and social functioning. Naturally, the 'cognitive problems' subscale of the Cancer Module showed a strong correlation with the 'school functioning' subscale of the generic core scale. For parents, a similar tendency was shown. These results suggests that physical, psychological, and social factors are related to each other. We therefore need to take a multidisciplinary approach to alleviating these types of pain in children with cancer [23].

To assess concurrent validity, we also examined the correlations between the PedsQL child self-report scores and child self-rating depression scale scores (DSRS-C: 8-15 y; CES-D: 16-18 y) among children who were considered to be depressed. It is reasonable that both the DSRS-C and CES-D scores were strongly correlated with the 'emotional functioning' score of the Generic

Table 12 Clinical validity of the PedsQL Cancer Module: Comparison of scores by treatment status

PedsQL Subscales	Children				Parents			
	Mean n Rank	Difference	Kruskal Wallis Test	*P* value	Mean n Rank	Difference	Kruskal Wallis Test	*P* value
Pain and hurt		a,c**	10.392	0.006		a,c***, b,c*	21.296	0.000
On $Tx_{(a)}$	63 85.63				87 97.70			
Off Tx = < $12_{(b)}$	27 91.06				33 113.92			
Off Tx > $12_{(c)}$	110 111.33				120 138.84			
Nausea		a,c***, b, c***	66.648	0.000		a,b*, b,c***, a, c***	88.814	0.000
On $Tx_{(a)}$	64 61.97				82 68.57			
Off Tx = < $12_{(b)}$	26 74.13				32 99.81			
Off Tx > $12_{(c)}$	107 127.19				117 153.67			
Procedural anxiety		a,c**	8.225	0.016		a,c***, b,c*	12.438	0.002
On $Tx_{(a)}$	65 86.58				85 103.49			
Off Tx = < $12_{(b)}$	27 94.31				33 107.65			
Off Tx > $12_{(c)}$	109 111.25				122 135.82			
Treatment anxiety			3.279	0.194		a,b*, a,c***	12.013	0.002
On $Tx_{(a)}$	64 99.73				84 100.32			
Off Tx = < $12_{(b)}$	27 88.19				33 127.80			
Off Tx > $12_{(c)}$	110 104.88				122 131.44			
Worry		a,c***, b,c*	26.914	0.000		a,c***	14.792	0.001
On $Tx_{(a)}$	63 73.54				85 100.80			
Off Tx = < $12_{(b)}$	27 89.44				33 112.21			
Off Tx > $12_{(c)}$	110 118.65				122 136.47			
Cognitive problems			1.367	0.505			3.323	0.190
On $Tx_{(a)}$	63 93.13				86 110.42			
Off Tx = < $12_{(b)}$	27 101.78				33 131.41			
Off Tx > $12_{(c)}$	109 103.53				122 125.64			
Perceived physical appearance			1.287	0.525		a,c*	4.944	0.084
On $Tx_{(a)}$	65 96.07				86 109.20			
Off Tx = < $12_{(b)}$	27 97.52				33 117.06			
Off Tx > $12_{(c)}$	110 105.69				122 130.38			
Communication		a,c*	6.392	0.041		a,c***	11.325	0.003
On $Tx_{(a)}$	65 90.70				84 102.44			
Off Tx = < $12_{(b)}$	27 89.17				33 111.58			
Off Tx > $12_{(c)}$	110 110.91				122 134.37			

On Tx: on treatment sample; Off Tx = < 12: off treatment = < 12 months sample; Off Tx > 12: off treatment > 12 months sample.
* P < 0.05, **P = < 0.01, ***P = < 0.001 by Mann-Whitney U test.

Core Scales because direct emotional expressions were used in this subscale, such as 'I feel afraid or scared,' 'I feel sad or blue,' and 'I feel angry.' These strong correlations were compatible with the results of a previous validation study to develop a Japanese version of the PedsQL generic core scales even though the participants were healthy children [14].

For the PedsQL Cancer Module, DSRS-C scores were strongly correlated with emotional domains and the total score, but not with CES-D scores. In 2010, Kamibeppu et al [28] reported that no significant differences in depression and anxiety were seen between healthy children and childhood cancer survivors who were over 16 years old. They evaluated the children's mental

status with the Japanese version of the K10 [29] (10-item self-report screening instrument for mood and anxiety disorders based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition [DSM-IV]) [30]. They also demonstrated that childhood cancer survivors had remarkably greater posttraumatic growth compared to healthy children and concluded that the cancer experience itself does not cause depression even though they had significantly more posttraumatic stress syndrome. This would be a probable explanation for why CES-D scores of children who were considered depressed did not correlate with any subscale of the PedsQL Cancer Module. Other factors were suspicious for depression.

Kruskal-Wallis and Mann-Whitney U tests demonstrated that physical and emotional quality of life scores associated with anti-cancer treatment were significantly improved among children who had been off treatment over 12 months. However, social and school functioning, such as 'cognitive problems' and 'perceived physical appearance' did not improve. Moreover, 'communication' scores took more than 12 months to improve. We should remember that childhood cancer survivors need continuous social support.

The percentage of missing values was 0.68% for child self-reports and 0.98% for parent proxy-reports in our study. This is similar to the original English version (0.50% for child self-reports and 1.00% for parent proxy-reports) [11]. The time required to complete the questionnaires was 5 to 10 minutes (median, 8 min) for the child self-reports and 2 to 5 minutes (median, 3 min) for the parent proxy-reports.

Although 'Treatment anxiety' subscale that showed high negative skewness and ceiling effect could be improved in the future, our Japanese version of the PedsQL Cancer Module would be feasible to use in clinical practice.

Conclusions

This study confirmed the reliability, validity, and feasibility of the Japanese version of the PedsQL 3.0 Cancer Module. This is expected to help improve the quality of life of Japanese children with cancer because until now there has been no instrument to measure pediatric cancer-specific HRQOL. The results are comparable to those of the original version and translated versions in other countries. Therefore, this module can be used for international cooperative research to measure HRQOL in pediatric cancer patients.

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Authors' contributions

NT, NK, KK,** and YI conceptualized the rationale and design of the study. KK advised NT about data management for SPSS. NT, YT, WO, YY, TK, KA, KT, HN, TI, MM, JO, TK**, AM, and YI coordinated participants and settings in each hospital. After approval of each Institutional Review Board, they administered questionnaires to children with cancer and their parents and collected data. NT and EM conducted statistical analyses and drafted the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Cord Blood Transplantation from Unrelated Donors for Children with Acute Lymphoblastic Leukemia in Japan: The Impact of Methotrexate on Clinical Outcomes

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Cord blood transplantation (CBT) from an unrelated donor is recognized as one of the major treatment modalities in allogeneic stem cell transplantation (SCT) for children with hematologic malignancies. We analyzed the clinical outcomes of CBT for children with acute lymphoblastic leukemia (ALL) in Japan and identified the risk factors for the transplant outcomes. From 1997 to 2006, 332 children with ALL underwent CBT from unrelated donors, 270 of which had no prior transplant. Their disease statuses at transplant were first complete remission (CR) (n = 120), second CR (n = 71), and more advanced stages (n = 75). As preconditioning for SCT, total body irradiation (TBI) was given to 194 patients and, for the prophylaxis of graft-versus-host disease (GVHD), methotrexate (MTX) was given to 159 patients. The cumulative incidents of neutrophil and platelet recovery (>20 K) were 88.5% and 78.4%, respectively. The incidents of grade II-IV, III-IV acute GVHD (aGVHD), and chronic GVHD (cGVHD) were 45.6%, 20.4%, and 19.2%, respectively, and treatment-related mortality was 22.6%. The 5-year event-free survival (EFS) and overall survival (OS) at CR1, CR2, and advanced status were 47.4%, 45.5%, 15.0%, and 63.7%, 59.7%, and 20.7%, respectively. Multivariate analysis revealed that MTX with calcineurin inhibitor (CNI) was associated with decreased incidence of grade II-IV GVHD (CNI alone: hazard ratio [HR] = 1.74, 95% confidence interval [CI] = 1.06-2.83, $P = .027$; CNI + prednisolone (PSL), HR = 1.61, 95% CI = 1.03-2.50, $P = .036$), III-IV aGVHD (CNI alone: HR = 3.02, 95% CI = 1.55-5.91, $P = 0.001$; CNI + PSL, HR = 1.89, 95% CI = 0.93-3.83, $P = .078$), or cGVHD (CNI alone: HR = 1.78, 95% CI = 0.83-3.82, $P = .143$; CNI + PSL, HR = 2.44, 95% CI = 1.24-4.82, $P = .01$), compared with CNI alone or CNI + PSL. At an advanced stage of disease, GVHD prophylaxis with MTX + CNI is associated with improved OS compared with CNI alone (CNI alone: HR = 3.20, 95% CI = 1.43-7.15, $P = .005$; CNI + PSL, HR = 1.47, CI = 0.67-3.20, $P = .332$). Our retrospective study showed that CBT for children with ALL is feasible and GVHD prophylaxis with MTX + CNI is associated with significant favorable outcomes in prevention of aGVHD and cGVHD as well as survival advantage in advanced cases.

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KEY WORDS: Cord blood transplantation, Acute lymphoblastic leukemia, HLA, Methotrexate

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INTRODUCTION

Multiagent chemotherapy for children with acute lymphoblastic leukemia (ALL) has achieved excellent clinical outcomes in recent years [1,2]. However, those patients who relapsed during or after chemotherapy or those with very high-risk features, such as Philadelphia chromosome-positive ALL (Ph+ALL) or infant ALL with mixed lineage leukemia (MLL) gene rearrangement, are proposed as candidates for allogeneic stem cell transplantation (SCT) [3-6] at their first remission. Patients and donors are required to be compatible in terms of human leukocyte antigen (HLA) for better transplant outcome and, if they lack an HLA-identical related donor, they have options of alternative donors, such as bone marrow transplantation (BMT), peripheral blood stem cell transplantation (PBSCT), cord blood transplantation (CBT) from an unrelated donor, or transplantation from an HLA-haploidentical family donor [7-9]. Out of these four treatment modalities, CBT has advantages such as immediate availability of a CB unit for an urgent transplant, lower risks of severe acute and chronic graft-versus-host disease (aGVHD, cGVHD), and a less stringent requirement of HLA compatibility than unrelated or haploidentical BMT. In Japan, the Japan Cord Blood Bank Network (JCBBN) was established in 1999, and 11 local cord blood banks are affiliated to JCBBN where more than 7000 CBT were performed by the end of 2010. Here, we report the clinical outcomes and risk factors of children with ALL who underwent CBT in Japan.

PATIENTS AND METHODS

Patient and Donor Characteristics

From 1997 to 2006, 332 unrelated CBT were performed for children with ALL and 270 transplantations were undertaken as the first SCT in Japan. Because the overall survival (OS) of patients who underwent transplantation as the first SCT was significantly better than that of those with prior SCT (50.3% vs 12.7%, $P < .001$), we restricted this analysis to only patients with no prior SCT in order to interpret the exact risk factors of CBT. The patient and donor characteristics are shown in Table 1. Patients transplanted at first complete remission (CR1) (n = 120) include 41 infant ALL and 17 patients with Ph +ALL.

The HLA typing of cord blood units was performed in each CB bank by low-resolution molecular typing of HLA-A and B, combined with high-resolution molecular typing of DRB1. The high-resolution molecular typing for 3 loci of HLA-A, B, and DRB1 was performed in 187 patients.

In JCBBN, CB units of 0 to 2 HLA antigen mismatches with the patient were allowed for transplantation, and the minimum number of nucleated cells recommended for transplantation was 2×10^7/kg of patient body weight at cryopreservation.

Transplantation

All CB units were provided from the 11 local CB banks affiliated to JCBBN, and all transplant institutions were required to meet the minimum requirements of JCBBN in terms of experience of allogeneic SCT. The numbers of transplanted cells, preconditioning, as well as GVHD prophylaxis are shown in Table 1. Supportive care after transplantation, such as gut decontamination, empirical administration of antibiotics, prophylaxis or treatment of cytomegalovirus (CMV) infection, was performed according to each institutional protocol. Grading of GVHD was performed according to the standard criteria [10].

Definition and Statistics

The median duration of follow-up was 438 days (range: 10-3293 days). In this study, rates of neutrophil and platelet engraftment, incidents of aGVHD and cGVHD, leukemic relapse, nonrelapse mortality (NRM), and probabilities of event-free survival (EFS) and OS were analyzed. The variables evaluated included recipient age, sex, sex mismatch, disease status at transplants (CR1/CR2 vs advanced disease), ABO compatibility, HLA matching by low- and high-resolution typing, number of nucleated cells, colony-forming unit-granulocyte-macrophage (CFU-GM) and CD34-positive cells of the cord blood units at cryopreservation conditioning regimens with total body irradiation (TBI), administration of granulocyte-colony stimulating factor (G-CSF), GVHD prophylaxis (calcineurin inhibitor [CNI] alone, CNI + methotrexate [MTX] versus CNI + prednisolone [PSL]), mixed lineage leukemia (MLL) gene rearrangement, t(4;11), and transplantation year. Because the information of high-resolution DNA typing was only available for a limited number of patients, it was not included in the multivariate analysis. The day of neutrophil engraftment was defined as the first day of 3 consecutive days with absolute neutrophil count (ANC) $\geq 500/mm^3$, and that of platelet engraftment was the first day of platelet count over $20,000/mm^3$ without transfusion. The treatment-related mortality was defined as all causes of nonleukemic deaths after transplantation. The EFS was defined as patients who are alive in CR with engraftment. The probabilities of OS and EFS were calculated by the method of Kaplan and Meier. The log-rank test was used for group comparisons. Time-to-event outcomes for neutrophil and platelet engraftment, treatment-related mortality, relapse,

Table 1. Patient and Donor Characteristics

Total Number of Patients			270
Age (year)	median (range)		5 (0-15)
Body weight (kg)	median (range)		18 (4-60)
Sex	male/female		156/114
Duration from diagnosis to transplantation (days)	median (range)		249 (94-3670)
Disease status at transplantation (patients)	CR1		120
	CR2		71
	advanced		75
	unknown		4
Cytogenetics (patients)	Philadelphia chromosome		31
	MLL gene rearrangement		73
	t(4;11)		40
Preparative regimen (patients)	TBI regimen		194
		TBI + CY + VP16	68
		TBI + CY ± others	67
		TBI + L-PAM ± others	56
		Others	3
	non-TBI regimen		76
		BU + CY ± others	55
		Others	21
G-CSF (patients)	+		249
	−		21
GVHD prophylaxis (pts)	CNI only	cyclosporine	29
		tacrolimus	12
	CNI + MTX	cyclosporine + MTX	83
		tacrolimus + MTX	66
	CNI + PSL	cyclosporine + PSL	36
		tacrolimus + PSL	11
	ATG + CNI ± MTX		7
	others		15
	none		11
Number of cells at cryopreservation, median (range)	Nucleated cell ($\times 10^7$/kg)	(n = 270)	5.00 (1.35-24.91)
	CFU-GM ($\times 10^3$/kg)	(n = 258)	34 (0.87-473.2)
	CD34 ($\times 10^5$/kg)	(n = 207)	1.49 (0.17-15.02)
Blood type of donor and recipient (pts)	match		89
	minor		77
	major		103
	unknown		1
Sex of donor and recipient (pts)	M to M		78
	F to F		64
	M to F		50
	F to M		78
HLA disparity in low resolution (patients)	No. of disparities	GVHD direction	Rejection direction
	0	54	57
	1	168	167
	2	47	45
	unknown	1	1
HLA disparity in high resolution (patients)	No. of disparities	GVHD direction	Rejection direction
	0	21	23
	1	56	58
	2	77	72
	3	28	29
	4	4	4
	5	1	1
	unknown	83	83

G-CSF indicates granulocyte-colony stimulating factor; GVHD, graft-versus-host disease; TBI, total body irradiation; CNI, calcineurin inhibitor; MTX, methotrexate; PSL, prednisolone; CY, cyclophosphamide.

and GVHD were estimated using cumulative incidence curves. The competing risk of engraftment is death before engraftment, that of GVHD is death without GVHD or relapse, and that of relapse is death without relapse. The Cox proportional-hazards regression model was used for multivariate analysis of clinical variables. P values <.05 were considered statistically significant. Risk factors with a P value <.1 in each univariate analysis were included in the multivariate analysis. STATA version 10 (Stata Corporation, College Station, TX) and NCSS 2004 (Number Cruncher Statistical Systems, Kaysville, UT) were used for the statistical analysis of data.

RESULTS

Neutrophil Engraftment

Neutrophil engraftment was obtained in 239 patients. The probability of neutrophil engraftment

was 88.5% (95% confidence interval [CI], 84.8%-92.4%) by day 90, and the median number of days to reach ANC over 500/mm^3 was 22. In univariate analysis, younger versus older than 1 year old (92.3% vs 87.6%, $P = .001$), higher versus lower than 3 $\times$ 10^7/kg of nucleated cells (89.5% vs 84.6%, $P = .003$), higher versus lower than the median number of CFU-GM (90.8% vs 86.8%, $P < .001$), higher versus lower than the median number of CD34$^+$ cells (1.5 $\times$ 10^5/kg, 89.7% vs 85.1%, $P < .001$), 0-1 versus 2 Ag HLA mismatches in either GVHD (89.2% vs 85.1%, $P = .008$) or rejection (90.2% vs 80.0%, $P = .004$) direction, allelic 0-1 versus 2 or more HLA mismatches in either GVHD (92.2% vs 87.3%, $P = .009$) or rejection (92.6% vs 86.8%, $P = .006$) direction by high-resolution typing, CR1 or CR2 versus advanced status at transplantation (89.5% vs 85.3%, $P = .022$), and presence versus absence of G-CSF (91.2% vs 57.1%, $P < .001$) were significantly associated with higher neutrophil engraftment rate. The presence or absence of MTX did not affect the neutrophil engraftment (data not shown). In multivariate analysis, favorable predictive factors of neutrophil engraftment were higher number of CD34$^+$ cells, administration of G-CSF, and HLA disparity of 0-1 antigen for rejection direction (Table 2).

Platelet Engraftment

Platelet engraftment over 20,000/mm^3 was obtained in 202 patients, and the probability of platelet engraftment by day 180 was 78.4%. In univariate analysis, younger versus older than 1 year old (82.8% vs 77.1%, $P = .004$), higher versus lower than the median number of nucleated cells (78.8% vs 76.6%, $P = .008$), higher versus lower than the median number of CFU-GM (82.8% vs 73.7%, $P = .004$), higher versus lower than the median number of CD34$^+$ cells (84.9% vs 71.8%, $P < .001$), disease status of CR1 or CR2 versus advanced (83.8% vs 63.3%, $P < .001$), and presence versus absence of G-CSF (80.1% vs 57.8%, $P = .017$) were significantly associated with higher platelet engraftment rate. Multivariate analysis revealed that a higher number of CD34$^+$ cells and CR1 or CR2 at transplantation were favorable prognostic factors for platelet engraftment (Table 2).

GVHD

The cumulative incidents of grade II-IV and III-IV aGVHD were 45.6% (95% CI, 40.0%-51.9%) and 20.4% (95% CI, 16.1%-25.8%), respectively. In univariate analysis, HLA-mismatched donor versus matched donor in GVHD direction by low resolution (49.3% vs 31.5%, $P = .023$) and high resolution (51.2% vs 14.3%, $P = .003$), and presence versus absence of TBI (51.6% vs 30.3%, $P = .003$) were significantly associated with the development of grade II-IV aGVHD, and MTX + CNI showed a trend of impact on the development of grade II-IV aGVHD (40.3% in MTX + CNI, 53.7% in CNI alone, and 63.8% in CNI + PSL, $P = .096$). GVHD prophylaxis with MTX + CNI was the only significant predictive factor for decreased incidence of grade III-IV GVHD (14.1% in MTX + CNI, 27.7% in CNI + PSL and 36.7% in CNI alone, $P = .011$) (Figure 1). Multivariate analysis revealed that TBI was significantly associated with increased incidence of grade II-IV aGVHD, and GVHD prophylaxis with MTX + CNI was significantly associated with decreased incidence of grade II-IV and III-IV aGVHD (Table 2).

The cumulative incidence of the development of cGVHD was 19.2% (95% CI, 15.0%-24.6%), and the incidence of cGVHD was significantly reduced in HLA-matched donor in low resolution for rejection direction compared with that in the GVHD direction (12.2% vs 22.6%, $P = .002$), as well as GVHD prophylaxis with MTX + CNI compared with that with CNI alone or CNI + PSL (16.1% vs 22.5%, or 29.3%, respectively, $P = .03$) (Figure 1). In multivariate analysis, HLA mismatch for rejection direction in low resolution and GVHD prophylaxis with CNI + PSL were the significant risk factors for the development of cGVHD (Table 2). In our study population, only 7 patients were given anti-T cell globulin (ATG) for GVHD prophylaxis. The cumulative incidence of grade II-IV aGVHD and cGVHD in this population was 14.7%, respectively, and 5 patients died of either relapse or transplantation-related complications.

Transplant-Related Mortality (TRM)

The cumulative incidence of TRM after CBT was 22.6% (95% CI, 17.7%-27.8%). Univariate analysis showed that HLA mismatch of 2 or more loci versus 0-1 in high-resolution typing for either GVHD direction (23.2% vs 10.4%, $P = .03$) or rejection direction (23.1% vs 11.2%, $P = .03$), advanced disease status versus CR1 or CR2 (35.3% versus 17.4%, $P < .001$), and GVHD prophylaxis other than MTX + CNI (15.1% in MTX + CNI, 29.3% in CNI alone, and 31.4% in CNI + PSL, $P = .01$) were significantly associated with a higher incidence of TRM. Multivariate analysis revealed that advanced disease status at transplantation was a risk factor for TRM (Table 2).

Leukemic Relapse

Eighty-six patients relapsed between 8 and 976 days (median 182) after CBT. The cumulative incidence of leukemic relapse at 3 years was 35.2% (95% CI, 29.8%-42.1%). Advanced disease versus CR1 or CR2 (48.8% vs 30.6%, $P < .001$) and presence

Table 2. Multivariate Analysis of Risk Factors for Transplantation Outcomes

	Variable		Hazard Ratio	P Value	95% CI
Neutrophil engraftment	CD34 ($\times 10^5$/kg)	<1.5	1		
		≥1.5	1.7	.001	1.26-2.28
	G-CSF	no	1		
		yes	3.06	.001	1.60-5.83
	HLA disparity in low resolution (rejection direction)	0-1	1		
		2	0.62	.024	0.41-0.94
Platelet engraftment (≥20,000/mm^3)	CD34 ($\times 10^5$/kg)	<1.5	1		
		≥1.5	1.9	.001	1.35-2.66
	Disease status	CR1, CR2	1		
		advanced	0.58	.008	0.39-0.87
Acute GVHD (≥II)	TBI	no	1		
		Yes	1.859	.015	1.13-3.06
	GVHD prophyalxis	CNI + MTX	1		
		CNI only	1.74	.027	1.06-2.83
		CNI + PSL	1.61	.036	1.03-2.50
Acute GVHD (≥III)	GVHD prophylaxis	CNI + MTX	1		
		CNI only	3.02	.001	1.55-5.91
		CNI + PSL	1.89	.078	0.93-3.83
Chronic GVHD	HLA disparity in low resolution (GVHD direction)	0	1		
		1,2	2.73	.055	0.98-7.61
	GVHD prophylaxis	CNI + MTX	1	.029	
		CNI only	1.777	.143	0.83-3.82
		CNI + PSL	2.44	.01	1.24-4.82
Treatment-related mortality	Disease status	CR1, CR2	1		
		advanced	2.56	.005	1.33-4.92
Relapse	Disease status	CR1, CR2	1		
		advanced	3.16	<.001	2.04-4.89
	t(4;11)	no	1		
		yes	1.93	.014	1.14-3.26
Overall survival	Disease status	CR1, CR2	1		
		advanced	3.62	<.001	2.44-5.8
Event-free survival	Disease status	CR1, CR2	1		
		advanced	2.54	<.001	1.83-3.51

CI indicates confidence interval; G-CSF indicates granulocyte-colony stimulating factor; GVHD, graft-versus-host disease; TBI, total body irradiation; CNI, calcineurin inhibitor; MTX, methotrexate PSL, prednisolone.

versus absence of t(4;11) chromosomal abnormality (48.3% vs 33.1%, $P = .044$) were significantly associated with leukemic relapse in univariate analysis. Both of these factors were also significant in multivariate analyses (Table 2).

OS

One hundred fifty-two patients were alive after CBT, and their median number of days of survival was 961 (91-3293). The cause of death in 118 patients included relapse or progressive disease (n = 50), TRM (n = 66), and unknown reason (n = 2). The probability of projected 5-year OS for all patients was 50.3% (95% CI, 43.4%-56.8%), and it was 63.7% in CR1, 59.7% in CR2, and 20.7% at more advanced disease status (Figure 2). Univariate analysis revealed that HLA mismatch of ≥2 versus 0 or 1 for rejection direction (50.9% vs 66.0%, $P = .017$) in high-resolution typing, advanced disease versus CR1 or CR2 (20.7% vs 62.1%, $P < .001$), and GVHD prophylaxis of other than MTX + CNI (56.8% in MTX + CNI, 43.3% in CNI alone, and 40.6% in CNI + PSL, $P = .049$) were significantly associated with OS (Figure 3). In multivariate analysis, advanced disease status at transplantation was the only risk factor for OS. When multivariate analysis was restricted to the patients with advanced diseases, OS was significantly superior for patients with GVHD prophylaxis of MTX + CNI than CNI alone (CNI alone: HR = 3.20, 95% CI = 1.43-7.15, $P = .005$; CNI + PSL, HR = 1.47, CI = 0.67-3.20, $P = .332$).

EFS

The probability of projected 5-year EFS for all patients was 38.1% (95% CI, 31.8%-44.4%), and it was 47.4% in CR1, 45.5% in CR2, and 15.0% at more advanced disease status. Univariate analysis revealed that HLA mismatch of 1 or more versus 0 with high-resolution typing in either GVHD direction (33.9% vs 51.3%, $P = .047$) or rejection direction (31.5% vs 52.9%, $P = .010$), advanced disease status versus CR1 or CR2 (15.0% vs 46.6%, $P < .001$), and absence versus presence of G-CSF (22.0% vs 39.3%, $P = .028$) were significantly associated with EFS. The EFS rates of patients according to the HLA disparity in high-resolution typing in GVHD direction were 61.9% in 0 of 6 (n = 21), 47.0% in 1 of 6 (n = 56), 36.4% in 2 of 6 (n = 77), and 28.4% in 3 of 6 (n = 28) ($P = .127$). Although this was not significant, the more the HLA disparity increased, the lower the EFS became. In multivariate analysis, advanced disease