Table 1. Impact of patient and transplant characteristics on bronchiolitis obliterans syndrome.

	BOS		Control		Univariate		Multivariate	
	N	%	*N*	%	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Total	196	100	1960	100				
Sex								
Male	96	49	1119	57	1		1	
Female	100	51	841	43	1.38 (1.03–1.85)	0.031	1.47 (1.06–2.04)	0.019
Age (years)								
16–49	141	72	1378	70	1		NA	
50 and more	55	28	582	30	0.92 (0.65–1.29)	0.62	NA	
Disease								
Leukemia	165	84	1604	82	1		–	
Lymphoma	21	11	188	10	1.09 (0.68–1.77)	0.72	–	
Plasma cell neoplasm	2	1	35	2	0.56 (0.13–2.34)	0.43	–	
Marrow failure	3	2	108	6	0.27 (0.08–0.86)	0.026	–	
Others	5	3	25	1	1.92 (0.73–5.07)	0.19	–	
Disease risk								
Standard	149	76	1474	75	1		NA	
High	43	22	477	24	0.89 (0.63–1.27)	0.53	NA	
Missing	4	2	9	0				
CMV sero-status								
Negative	26	13	297	15	1		NA	
Positive	133	68	1356	69	1.14 (0.73–1.77)	0.56	NA	
Missing	37	19	307	16				
Sex match								
Match	86	44	1008	51	1		NA	
Male to female	49	25	417	21	1.34 (0.93–1.94)	0.12	NA	
Female to male	41	21	441	23	1.10 (0.74–1.63)	0.64	NA	
Missing	20	10	94	5				
ABO-mismatch								
Match	80	41	1013	52	1		1	
Minor mismatch	40	20	386	20	1.29 (0.87–1.92)	0.21	1.67 (1.10–2.51)	0.015
Major mismatch	39	20	339	17	1.46 (0.97–2.18)	0.069	1.73 (1.13–2.64)	0.012
Bidirectional mismatch	19	10	171	9	1.37 (0.80–2.33)	0.25	1.96 (1.12–3.43)	0.018
Missing	18	9	51	3				
Types of transplant								
MRD-BMT	43	22	445	23	1		1	
MMRD-BMT	7	4	78	4	0.89 (0.38–2.06)	0.78	0.64 (0.24–1.72)	0.38
MRD-PBSCT	40	20	318	16	1.21 (0.74–1.98)	0.44	1.28 (0.76–2.16)	0.35
MMRD-PBSCT	10	5	77	4	1.31 (0.62–2.81)	0.48	1.45 (0.65–3.22)	0.36
MUD-BMT	69	35	612	31	1.09 (0.71–1.68)	0.68	1.09 (0.69–1.72)	0.71
MMUD-BMT	6	3	85	4	0.69 (0.28–1.72)	0.42	0.58 (0.23–1.49)	0.26
CBT	8	4	307	16	0.26 (0.12–0.57)	<0.001	0.26 (0.11–0.58)	0.0011
Missing	13	7	38	2				
Conditioning								
CYTBI	83	42	843	43	1		1	
BUCY	43	22	274	14	1.68 (1.12–2.52)	0.011	1.74 (1.11–2.72)	0.016
Other MAC	26	13	219	11	1.25 (0.78–1.99)	0.36	1.40 (0.84–2.32)	0.19
Flu-based RIC	35	18	481	25	0.72 (0.48–1.09)	0.12	0.73 (0.47–1.14)	0.17
Other RIC	9	5	135	7	0.68 (0.34–1.39)	0.29	0.68 (0.31–1.46)	0.32
Missing	0	0	8	0				
In vivo T cell depletion								
None	193	98	1845	94	1		–	
Presence	3	2	115	6	0.25 (0.079–0.80)	0.019	–	
GVHD prophylaxis								
CsA-based	123	63	1167	60	1		NA	
Tac-based	67	34	751	38	0.83 (0.60–1.15)	0.25	NA	

Table 1. continued

	BOS		Control		Univariate		Multivariate	
	N	%	*N*	%	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Others	5	3	41	2	1.20 (0.46–3.12)	0.72	NA	
Missing	1	1	1	0				
Grade of acute GVHD								
0–1	107	55	1243	63	1		–	
2–4	88	45	714	36	1.44 (1.07–1.94)	0.017	–	
Missing	1	1	3	0				
Target of acute GVHD								
Skin								
No	73	37	867	44	1		1	
Present	122	62	1056	54	1.38 (1.02–1.87)	0.04	1.55 (1.11–2.18)	0.011
Missing	1	1	37	2				
Gut								
No	145	74	1502	77	1		NA	
Present	47	24	411	21	1.19 (0.84–1.69)	0.32		
Missing	4	2	47	2				
Liver								
No	183	93	1787	91	0.99 (0.54–1.83)	0.98	NA	
Present	12	6	120	6				
Missing	1	1	53	3				

BOS, bronchiolitis obliterans syndrome; CI, confidence interval; CMV, cytomegalovirus; MRD, HLA-matched related donor; MMRD, HLA-mismatched related donor; MUD, HLA-matched unrelated donor; MMUD, HLA-mismatched unrelated donor; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; CBT, cord blood transplantation; CY, cyclophosphamide; TBI, total body irradiation; BU, busulfan; MAC, myeloablative conditioning; Flu, fludarabine; RIC, reduced intensity conditioning; GVHD, graft-versus-host disease; CsA, cyclosporine; Tac, tacrolimus; NA, not assessed. "Marrow failure" includes aplastic anemia, pure red cell aplasia, and paroxysmal nocturnal hemoglobinuria. The "Other diseases" group includes EB virus-associated diseases, solid tumor, hemophagocytic syndrome, primary immunodeficiency, congenital metabolic disorders, and others.

involvement in 8% (7 of 92), organ failure other than respiratory failure in 7% (6 of 92), thrombotic microangiopathy in 1% (1 of 92), hemorrhage in 1% (1 of 92), and other unknown causes in 7% (6 of 92). The estimated 4-year NRM in the BOS group was 38% (95% CI 30–45%) (Fig. 2).

Discussion

A case–control study that included the largest number of recipients with BOS reported so far was performed, and the risk factors for the development of BOS were identified retrospectively. The risk for the development of BOS was significantly higher in female recipients, ABO-mismatch HSCT, recipients receiving BU+CY-based MAC, and those who experienced aGVHD involving the skin. On the other hand, the risk was significantly lower in patients receiving CBT. As the factors included in the analysis were pretransplant or supposed as events before the onset of BOS, the association was thought to be predictive factors.

To the best of our knowledge, this analysis is the first to reveal the adverse impact of ABO-mismatch on the development of BOS in the HSCT setting. It is well known that ABO-mismatch is critically associated with graft rejection in solid organ transplants [18,19]. Not only major but also minor ABO-mismatch organ transplant is supposed to have an increased risk for graft rejection, severe hemolysis, and lower survival rates, although it is controversial [18–26]. Similarly, both of the major and minor ABO-mismatches in HSCT were also reported to have an adverse impact on the incidence of GVHD and NRM [27]. BOS following HSCT is one manifestation of lung cGVHD and resembles chronic graft rejection after lung transplant. Taking all of these into consideration, it is plausible that ABO-mismatch has a potential to induce lung injuries in the HSCT setting [3,5]. The possible mechanism might be a direct capture on lung epithelial cells of anti-recipient-A/B antibodies produced by donor B cells in the minor ABO-mismatch HSCT setting [28,29]. Another possible mechanism might be through inflammation and activation of adhesion molecules induced by the destruction of donor-derived red blood cells and complexes with the allo-/auto-reactive antibodies produced by recipient remnant B cells in the major ABO-mismatch HSCT setting [30–32]. These inflammatory conditions are well observed in intravascular hemolysis, resulting in thrombosis and platelet activation [33,34]. Recently, rituximab has been reported to be a promising strategy in ABO-mismatch organ transplant to prevent graft rejection [35]. Therefore, rituximab might also affect the development of BOS in the ABO-mismatch HSCT setting.

Table 2. The association between bronchiolitis obliterans syndrome and target organs of chronic GVHD.

	BOS *N*	Control *N*	Univariate Odds ratio (95% CI)	*P*-value	Multivariate Odds ratio (95% CI)
Target organs of cGVHD	113	834			
Eye					
None	62	603	1	<0.0001	2.53 (1.62–3.95)
Present	51	231	2.53 (1.62–3.95)		
Mouth					
None	50	463	1	0.051	–
Present	63	371	1.52 (1.00–2.33)		
Skin					
None	35	309	1	0.21	NA
Present	78	525	1.32 (0.85–2.06)		
Liver					
None	66	463	1	0.83	NA
Present	47	371	0.96 (0.62–1.46)		
Mucosa/gut					
None	82	659	1	0.25	NA
Present	38	204	1.33 (0.82–2.15)		
Joint/muscle					
None	105	798	1	0.13	NA
Present	8	36	1.67 (0.67–4.18)		
Hair					
None	110	811	1	0.7	NA
Present	3	23	0.78 (0.23–2.71)		
Serositis					
None	111	820	1	0.75	NA
Present	2	14	0.78 (0.17–3.56)		
Other involvement					
None	107	789	1	0.54	NA
Present	6	45	0.75 (0.29–1.89)		

BOS, bronchiolitis obliterans syndrome; cGVHD, chronic graft-versus-host disease; NA, not assessed; "Other involvement" includes nephropathy, neuropathy, weight loss, thrombocytopenia, and other involvement.

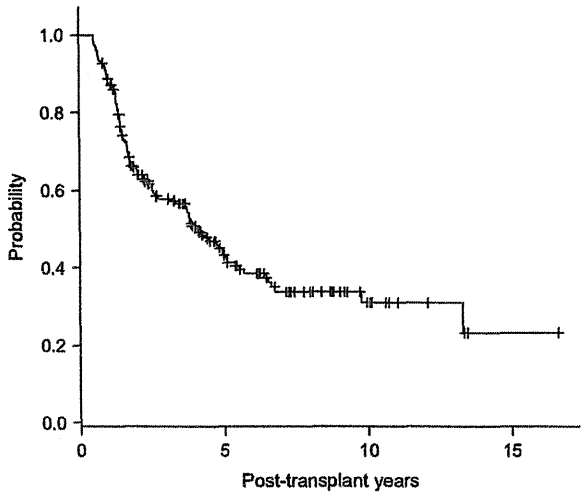

Figure 1 Overall survival of recipients with bronchiolitis obliterans syndrome from time of transplant.

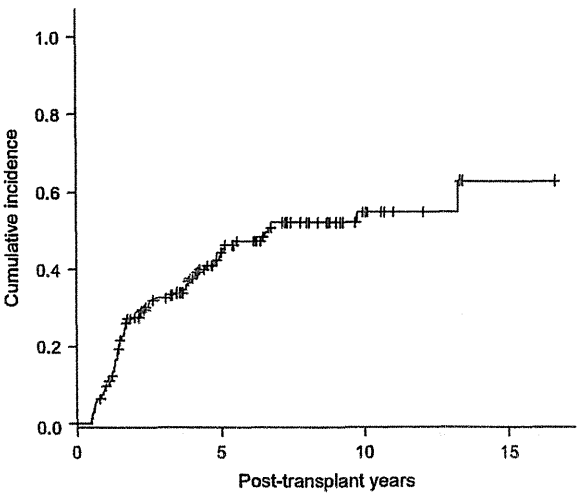

Figure 2 Nonrelapse mortality of recipients with bronchiolitis obliterans syndrome from time of transplant.

Lung injury as a result of conditioning toxicity is also one of the proposed mechanisms for the development of BOS [9,10,12,36]. Of the various conditioning regimens, BU-CY-based MAC was identified as a significant risk factor for the development of BOS in this study, which was consistent with the results of previous reports [9,10,36]. High concentrations of BU might contribute to lung injuries and the development of BOS, as well as liver injuries, inducing veno-occlusive disease [37].

Another possible mechanism for the development of BOS is probably caused by allo-reactive immune responses. Allo-reactive donor T cells might target lung epithelial cells, inducing BOS as one of the manifestations of cGVHD in the lungs. In fact, GVHD and the possible risk factors for GVHD have been reported to be associated with the development of BOS in several studies [4,9,13,36]. In this study, it was also found that recipients who experienced grade 2–4 aGVHD and skin involvement of aGVHD had a significantly higher risk for the development of BOS on univariate analyses, although grade 2–4 aGVHD was not significant on multivariate analysis. The close relation between skin and lung complication might exist in HSCT setting as well as in connective tissue disease [38]. In addition, the development of BOS was associated with ocular involvement of cGVHD when focusing on recipients with cGVHD. However, it should be noted that the association between BOS and each target organ of cGVHD was assessed separately, and it was not known whether the ocular involvement of cGHVD developed earlier than BOS. This 20-year database included many recipients before NIH consensus 2005 [7]. Therefore, specific-organ involvements might be under diagnosed.

This is the first study to suggest that CBT was significantly associated with a lower risk for the development of BOS, although there was no association between PBSCT and the development of BOS. It is known that the incidences of acute and cGVHD in the CBT group are significantly lower than in the unrelated BMT group [39]. Therefore, the low incidence of GVHD might be attributable to the low incidence of BOS in the CBT group. A prospective study is needed to verify the favorable impact of CBT on the development of BOS. On the other hand, HLA mismatch and sex-mismatch, which are also reported as important risk factors for acute and cGVHD, had little impact on the development of BOS in the current analysis.

This analysis had several limitations as a result of its retrospective nature, and all information was based on the reports by attending physicians, not on a central review. First, the severity of BOS could not be assessed because the data of pulmonary function test were not available from the registry data. Second, it was not possible to assess the time-dependent impact of BOS on relapse and survival rates because the dates of BOS development were also not available. Third, because the study period was so long that the details mentioned above could not be fully collected although we realize the importance. Truly, only prospective cohort studies adhering to strict diagnostic criteria and other clinical data will be able to shed the light into the factors associated with the incidence and outcomes of BOS. However, the strength of this study is that it involved the largest number of recipients with BOS of all studies to date. Therefore, the detailed impact of conditioning regimens, stem cell sources, and ABO-mismatches could be analyzed. In addition, we obtained similar results even when we re-analyzed the risk factors for the development of BOS among the eligible entire cohort or a selected cohort between 2005 and 2009 for which few information were missing (data not shown).

In summary, the risk factors for the development of BOS included: female recipients, ABO-mismatch transplantation, BU+CY-based MAC, and skin involvement of aGVHD. On the other hand, the risk of BOS was significantly lower in recipients receiving CBT. Prospective studies are required to elucidate the risk factors for the development of BOS, and future investigations should focus on the development of a prophylactic approach against BOS based on these findings.

Authorship

HN: designed the study, analyzed data, and wrote the manuscript. JK, SY, YA and TM: advised on methods, analyzed data, and wrote the manuscript. HA, TF, KK, TA, TY, ST and JT: collected data. YM, TN and HS: collected data and were responsible for the data management of JMDP, JCBBN and JSHCT, respectively. MM: analyzed data, wrote the manuscript, and was responsible for the study and GVHD-WG of the JSHCT.

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ORIGINAL ARTICLE

Feasibility of reduced-intensity conditioning followed by unrelated cord blood transplantation for primary hemophagocytic lymphohistiocytosis: a nationwide retrospective analysis in Japan

Akihisa Sawada · Shouichi Ohga · Eiichi Ishii · Masami Inoue · Keiko Okada · Jiro Inagaki · Hiroaki Goto · Nobuhiro Suzuki · Kazutoshi Koike · Yoshiko Atsuta · Ritsuro Suzuki · Hiromasa Yabe · Keisei Kawa · Koji Kato · Koji Yasutomo

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Abstract A nationwide retrospective analysis was performed on patients who received allogeneic hematopoietic stem cell transplantation for primary or familial hemophagocytic lymphohistiocytosis (HLH) in Japan. The present analysis investigated whether reduced-intensity conditioning (RIC) followed by cord blood transplantation (CBT) (RIC–CBT) is feasible, compared to the outcomes of myeloablative conditioning and bone marrow transplantation. Based on the JSHCT data, 53 patients were analyzed. The overall survival rate (OS) was 65.4 ± 6.6 %. RIC–CBT ($n = 13$) was not inferior to other methods. Patients with a performance status of PS 4 (ECOG scale) with HLH-associated severe organ dysfunction during the initiation of conditioning had extremely poor outcomes. The OS rate in the RIC–CBT patients, excluding those with a performance status 4, was 80.0 ± 12.6 %. RIC may reduce treatment-related mortality; in addition, patients with engraftment failure, which is the main adverse event following RIC–CBT, were successfully rescued with secondary CBT. Unrelated cord blood may represent an alternative source if a patient has no related donor. As a RIC regimen for CBT, 140 mg/m^2 melphalan with fludarabine and anti-lymphocyte globulin or anti-thymocyte globulin may be feasible, but further dosage optimization should be performed in controlled clinical trials.

A. Sawada (✉) · M. Inoue · K. Kawa
Department of Hematology/Oncology, Osaka Medical Center and Research Institute for Maternal and Child Health, 840 Murodo, Izumi, Osaka 594-1101, Japan
e-mail: asawada@mch.pref.osaka.jp

S. Ohga
Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

E. Ishii
Department of Pediatrics, Ehime University Graduate School of Medicine, Toon, Japan

K. Okada
Department of Pediatric Hematology/Oncology, Osaka City General Hospital, Osaka, Japan

J. Inagaki
Section of Pediatrics, National Kyusyu Cancer Center, Fukuoka, Japan

H. Goto
Department of Pediatrics, Yokohama City University School of Medicine, Yokohama, Japan

N. Suzuki
Department of Pediatrics, Sapporo Medical University School of Medicine, Sapporo, Japan

K. Koike
Division of Pediatric Hematology and Oncology, Ibaraki Children's Hospital, Mito, Japan

Y. Atsuta · R. Suzuki
Department of Hematopoietic Stem Cell Transplantation Data Management, Nagoya University School of Medicine, Nagoya, Japan

H. Yabe
Department of Cell Transplantation, Tokai University School of Medicine, Isehara, Japan

K. Kato
Division of Pediatric Hematology/Oncology, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan

K. Yasutomo
Department of Immunology and Parasitology, Institute of Health Biosciences, University of Tokushima, Tokushima, Japan

Keywords Primary HLH · FHL · Reduced-intensity conditioning · Cord blood transplantation

Introduction

Primary hemophagocytic lymphohistiocytosis (HLH), also known as familial HLH (FHL), is a distinct disease entity of congenital immunodeficiencies. Primary HLH involves genetically impaired production, transfer or release of cytotoxic granules of T or NK cells [1, 2]. Patients with primary HLH exhibit complete mortality due to hypercytokinemia, hemophagocytic syndrome (HPS) or organ failure including that of the brain and liver. Further, allogeneic hematopoietic stem cell transplantation (HSCT) is the only cure [1, 3].

Reduced-intensity conditioning (RIC) and umbilical cord blood transplantation (CBT) were developed in the 2000s. Comparing to myeloablative conditioning (MAC) [4], RIC is particularly desirable in children because it is less toxic and may reduce late complications such as short stature, hypogonadism, and infertility. Cord blood (CB) has immediate availability before disease progression if there is no family donor. One of the most severe adverse events after CBT following RIC (RIC–CBT) is engraftment failure and the subsequent infection. Although results regarding bone marrow transplantation (BMT) following RIC (RIC–BMT) for primary HLH were recently reported to be encouraging [5], these included few cases of CBT following RIC (RIC–CBT). A previous study on HSCT for FHL in Japan revealed that neither RIC nor CBT was inferior. However, this was a questionnaire-based study and not a nationwide study; additionally, it included few RIC–CBT cases [6].

The present study is a nationwide retrospective analysis on the outcome of allogeneic HSCT for primary HLH in Japan. This analysis aims to clarify whether RIC–CBT is inferior to MAC or BMT. Furthermore, if RIC–CBT is feasible, this study aims to provide insights into the timing, eligibility, optimized regimen, and dosage for RIC–CBT. This study was approved by the Research Ethics Committee of Osaka Medical Center and Research Institute for Maternal and Child Health.

Patients and methods

Data collection

The Japan Society for Hematopoietic Cell Transplantation (JSHCT) annually collects data on HSCT in Japan using a standardized reporting form, the Transplant Registry Unified Management Program (TRUMP) system. A total of 72

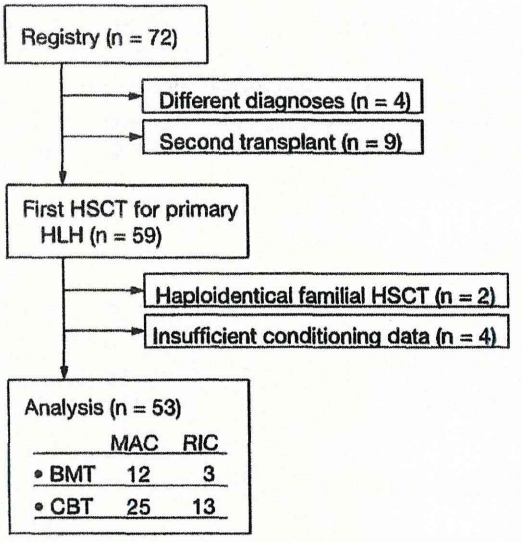

Fig. 1 Analyzed patients selected from the registry. Different diagnoses ($n = 4$) were as follows: one patient with acute myeloid leukemia, one with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)-like disease, one with chronic inflammatory neurological cutaneous articular (CINCA)-like disease and a patient of extreme age (36 years old) for primary/familial HLH. The analysis focuses on 1st HSCT for primary HLH in non-haploidentical setting

HSCT cases were registered as primary/familial HLH between January 1990 and December 2009 (Fig. 1). There is no information in the registry on the affected genes. Furthermore, no autologous HSCTs were recorded, and 13 allogeneic HSCTs were excluded at data clearance including 4 due to different diagnoses and 9 due to second HSCT. We initially extracted 59 patients who underwent the first allogeneic HSCT for primary/familial HLH (Fig. 1). Subsequently, 2 patients who underwent peripheral blood (PB) stem cell transplantation were excluded because the donors were haploidentical. Further, 4 patients were excluded because of insufficient conditioning data that may represent unestablished RIC regimen other than fludarabine (Flu) and melphalan (LPAM). Therefore, 53 patients were included in the following analysis.

End points

The primary end point was the overall survival (OS), which was defined as the time from HSCT until death due to any cause. Second HSCTs were not censored in the OS. Patients alive at the last follow-up were censored. The causes of death were categorized as progression of disease (i.e., fulminant HLH) or treatment-related mortality (TRM); in turn, TRM was subcategorized into infection, graft-versus-host disease (GVHD), and organ failure as a post-HSCT adverse event or progression of pre-HSCT

morbidity due to primary disease (i.e., without fulminant HLH after HSCT). Event-free survival (EFS) was defined as the time from HSCT until any of the following events: recurrence/progression of disease, TRM, or second HSCT (due to engraftment failure or loss of donor chimerism with or without primary disease).

Definitions

MAC and RIC were defined according to the consensus report on the intensity of conditioning regimens by Bacigalupo et al. [7]. Representative regimens were shown in Table 1. The date of neutrophil recovery was regarded as the first day of 3 consecutive days in which the absolute neutrophil count exceeded 500/μL. Engraftment failure was defined as an absolute neutrophil count <500/μL or donor chimerism <5 % in the white blood cells (WBCs) from PB on day 30 after HSCT or later. Continuous complete donor chimerism was defined as neutrophil count >500/μL and donor-type WBC >95 % in PB; mixed chimerism was defined as neutrophil count >500/μL and donor-type WBC of 5–95 % in PB on day 30 or later. The performance status (PS) of each patient was scaled at the initiation of conditioning based on the Eastern Cooperative Oncology Group (ECOG) PS scale [8].

Table 1 Patient characteristics

	Graft source and conditioning type				MAC vs. RIC (*p*)
	BMT		CBT		
	MAC ($n = 12$)	RIC ($n = 3$)	MAC ($n = 25$)	RIC ($n = 13$)	
Age at HSCT (years)					
0	4 (33 %)	2 (67 %)	7 (28 %)	6 (46 %)	
1–4	6 (50)	0 (–)	12 (48)	4 (31)	>0.1
>5	2 (17)	1 (33)	6 (24)	3 (23)	
Sex					
Male	3 (25)	1 (33)	12 (48)	9 (69)	>0.1
Female	9 (75)	2 (67)	13 (52)	4 (31)	
Conditioning regimen					
MAC					
BU + CY + Etp-based	10 (83)	–	13 (52)	–	
TBI + CY-based	1 (8)	–	7 (28)	–	–
Others	1 (8)	–	5 (20)	–	
RIC					
Flu + LPAM-based	–	3 (100)	–	13 (100)	
GVHD prophylaxis					
CsA-based	7 (58)	2 (67)	16 (64)	3 (23)	
Tac-based	4 (33)	1 (33)	6 (24)	10 (77)	–
Others	1 (8)	0 (–)	3 (12)	0 (–)	
HLA mm for GVH direction					
Related donor					
HLA 6/6	5 (42)	2 (67)	–	–	
HLA 5/6	1 (8)	0 (–)	–	–	
Unrelated donor					
HLA 6/6	6 (50)	0 (–)	6 (24)	8 (62)	–
HLA 5/6	0 (-)	1 (33)	13 (52)	4 (31)	
HLA ≤ 4/6	–	–	6 (24)	1 (8)	
Year of HSCT					
1990–1994	1 (8)	0 (–)	0 (–)	0 (–)	
1995–1999	5 (42)	0 (–)	8 (32)	0 (–)	0.002
2000–2004	3 (25)	2 (67)	13 (52)	3 (23)	
2005–2009	3 (25)	1 (33)	4 (16)	10 (77)	

HLA mm serological mismatch in HLA-A, B and DR for graft-versus-host (GVH) direction, *HSCT* hematopoietic stem cell transplantation, *BMT* bone marrow transplantation, *CBT* cord blood transplantation, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *BU* busulfan, *CY* cyclophosphamide, *Etp* etoposide, *Flu* fludarabine, *GVHD* GVH disease, *CsA* cyclosporin A, *Tac* tacrolimus

Statistics

Statistical analyses were performed using SPSS version 14 (SPSS Inc., Chicago, IL, USA). Survival rate was estimated by the Kaplan–Meier method and assessed with the log-rank test. The χ^2 test was used for univariate analysis.

Results

The characteristics of the 53 patients are shown in Table 1. Remarkably, more than half of the patients were treated with RIC–CBT since 2005. The 2-year EFS (median ± standard error) and OS rates were 57.6 ± 6.9 % and 65.4 ± 6.6 %, respectively. The EFS and OS rates with respect to the conditioning regimen and graft source are shown in Fig. 2. The number of patients after RIC–BMT was very small for statistical analysis ($n = 3$). The EFS rates of the patients after MAC–BMT, MAC–CBT, and RIC–CBT were 65.6 ± 14.0 % ($n = 12$), 59.1 ± 10.0 % ($n = 25$), and 46.2 ± 13.8 % ($n = 13$), respectively, and there was no statistical difference ($p = 0.35$). The OS rates of the patients after MAC–BMT, MAC–CBT, and RIC–CBT were 74.1 ± 12.9 %, 63.1 ± 9.8 %, and 61.5 ± 13.5 %, respectively, and there was no statistical difference ($p = 0.66$).

Causes of death

Out of 53 patients, 2 died of disease progression, and 16 patients experienced TRM: 6 deaths were attributed to bacterial infection, 2 to viral infection [1 cytomegalovirus (CMV) pneumonitis, 1 post-transplant lymphoproliferative disease (PTLD)], 1 to chronic GVHD, and 7 to organ failure.

In general, there were no significant differences between the MAC–BMT, MAC–UCB, and RIC–CBT groups with respect to cause of death (Table 2). However, the ratio of organ failure was high in the CBT groups. In the MAC–CBT group, organ failure occurred after HSCT in 4 cases, i.e., 2 cases of interstitial pneumonitis, 1 case of acute respiratory distress syndrome, and 1 case of thrombotic microangiopathy. However, in the RIC–CBT group, 3 patients had a PS of 4 during the initiation of conditioning; all of them suffered from HLH-associated severe organ dysfunction [the lungs, 2 patients; the liver and central nervous system (CNS), 1 patient] and died due to progression of organ failure without fulminant HLH after HSCT. Therefore, the EFS and OS rates of the RIC–CBT group, excluding those with PS of 4, were 60.0 ± 15.5 % and 80.0 ± 12.6 %, respectively.

Conditioning regimen and engraftment in the RIC–CBT group

In the patients who lived 30 days or more after HSCT, 5/6, 2/2, 15/22, and 4/10 patients in the MAC–BMT, RIC–BMT, MAC–CBT, and RIC–CBT groups, respectively, achieved complete donor chimerism. In the RIC–CBT and MAC–CBT groups who did not achieve neutrophil recovery, 4 out of 5 patients underwent a second HSCT (Table 2); 3 achieved complete donor chimerism, while the others did not achieve neutrophil recovery and died of a bacterial infection. Conversely, a low ratio of donor chimerism might be able to control the primary disease [9].

We analyzed the conditioning regimens and engraftment in patients who lived 30 days or more after RIC–CBT ($n = 10$) in further detail (Table 3). Higher doses of LPAM (>120 mg/m^2 in total) with Flu and anti-lymphocyte globulin or anti-thymocyte globulin (ALG/ATG)

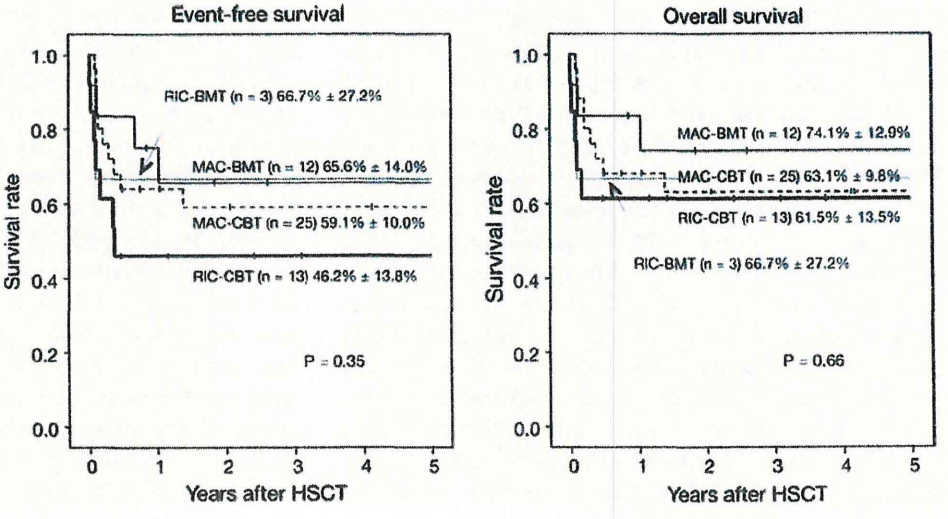

Fig. 2 Survival rates after HSCT. In total ($n = 53$), the 2-year event-free survival (EFS) and overall survival (OS) rates (median ± standard error %) were 57.6 ± 6.9 % and 65.4 ± 6.6 %, respectively. The EFS and OS according to the conditioning regimen and graft source are shown. The number of RIC–BMT was too small ($n = 3$) for further statistical analysis. There were no statistical differences in EFS and OS between MAC–BMT, MAC–CBT and RIC–CBT. *Solid line* MAC–BMT, *dotted line* RIC–BMT, *broken line* MAC–CBT, *bold line* RIC–CBT