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Ⅷ. 研究成果の刊行物・別刷

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ORIGINAL ARTICLE

Impact of sex incompatibility on the outcome of single-unit cord blood transplantation for adult patients with hematological malignancies

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Donor–recipient sex incompatibility has been associated with transplant outcomes in allogeneic hematopoietic SCT. Such outcomes might be because mHA encoded by Y chromosome genes could be immunological targets for allogeneic T cells and B cells to induce GVHD, GVL effect and graft failure. However, its effect on the outcome of cord blood transplantation (CBT) is yet to be clarified. We retrospectively analyzed 191 adult patients who received single-unit CBT after myeloablative conditioning for malignant disease in our institute. In multivariate analysis, male recipients with female donors had a higher incidence of extensive chronic GVHD (hazard ratio (HR) 2.97, $P=0.02$), and female recipients with male donors had a lower incidence of platelet engraftment (HR 0.56, $P=0.02$) compared with female recipients with female donors as the reference. Nevertheless, there was no increase in mortality following sex-incompatible CBT. These data suggested that donor–recipient sex compatibility does not have a significant impact on survival after myeloablative CBT for hematological malignancies.

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Keywords: cord blood transplantation; sex incompatibility; H-Y antigens; minor histocompatibility antigens; graft-versus-host disease

INTRODUCTION

Several studies have reported associations between donor–recipient sex incompatibility and outcomes following allogeneic hematopoietic SCT (allo-HSCT).[1,2] In the setting of sex-mismatched allo-HSCT, male-specific mHA (H-Y) encoded by Y chromosome genes could be immunological targets for allogeneic female T cells and B cells to induce GVHD, GVL effect and graft failure. However, most of these studies analyzed patients receiving HLA-compatible transplants using BM or mobilized peripheral blood as a stem cell source for allo-HSCT.[3–8]

Cord blood transplantation (CBT) from an unrelated donor has recently been utilized as an alternative transplant method for adult patients without HLA-compatible, related or unrelated donors.[9–13] As the majority of patients receive an HLA-mismatched cord blood unit, the impact of HLA mismatch on the outcome in CBT has been analyzed extensively.[14–19] However, there have been no reports detailing the effect of sex incompatibility on the outcomes after CBT. In this study, we retrospectively analyzed whether donor–recipient sex incompatibility affects the outcomes of myeloablative CBT in 191 adult patients with hematological malignancies in our institute.

PATIENTS AND METHODS

Patients and transplant procedures

This retrospective study included data from 191 adult patients who underwent unrelated first allogeneic transplantation using single-unit CBT at The Institute of Medical Science, The University of Tokyo, between August 1998 and February 2013. Donor–recipient sex compatibility was categorized as follows: CBT from female donor to female recipient (F→F), CBT from female donor to male recipient (F→M), CBT from male donor to female recipient (M→F) and CBT from male donor to male recipient (M→M). All patients received 12 Gy TBI-based myeloablative conditioning regimens and cyclosporin (3 mg/kg/day) with or without short-term MTX (15 mg/m^2 on day 1 and 10 mg/m^2 on days 3 and 6) as a GVHD prophylaxis, and cord blood units were selected as previously reported.[12,13] The institutional review board of the Institute of Medical Science, The University of Tokyo approved this study. This study was conducted in accordance with the declaration of Helsinki.

End points and statistical analysis

The primary study end point was GVHD. Both acute GVHD (aGVHD) and chronic GVHD (cGVHD) were graded according to the previously published criteria.[20,21] The incidence of aGVHD was evaluated in all engrafted patients, whereas the incidence of cGVHD was evaluated in engrafted patients surviving for >100 days. Secondary end points were OS, relapse, TRM, and neutrophil and platelet engraftment. OS was defined as the time from the date of transplantation to the date of death or last contact. Relapse was defined by morphologic evidence of disease in peripheral blood, BM or extramedullary sites. TRM was defined as death during a remission. Neutrophil engraftment was defined as the first of three consecutive days during which the absolute neutrophil count was at least 0.5×10^9/L. Platelet engraftment was defined as the first of seven consecutive days with a platelet count of 20×10^9/L or higher without platelet transfusion.

Baseline patient and transplant characteristics were compared using the chi-square test for categorical variables and the Kruskal–Wallis test for

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continuous variables. The probability of OS was estimated according to the Kaplan–Meier method, and the groups were compared using the log-rank test. The probabilities of the others were estimated on the basis of a cumulative incidence method to accommodate competing risks.[22] Multivariate analysis was performed with a Cox proportional hazard model adjusted for OS, and a Fine and Gray proportional hazards model for the others.[23] The following variables were considered: age (<45 vs ⩾45 years), CMV serostatus (negative vs positive), disease status at CBT (standard risk vs high risk), cord blood $CD34^+$ cell count ($<1\times10^5$ vs $\geqslant1\times10^5$/kg), cord blood nucleated cell count ($<2.5\times10^7$ vs $\geqslant2.5\times10^7$/kg), HLA disparities (⩽2 vs ⩾3) and donor–recipient sex compatibility (F→F vs F→M vs M→F vs M→M). In this study, the F→F group was considered the reference group in the multivariate analyses, because this group is not influenced by H-Y Ags. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria).[24] $P<0.05$ was considered significant. Analysis of data was performed in August 2013.

RESULTS

Patients

The characteristics of patients and cord blood units are shown in Table 1. There were no significant differences among the four sex combination groups, except for cord blood nucleated cell counts (Table 1). The median period of follow-up for survivors after CBT was 92 months (range, 5–181 months).

GVHD

CBT in the F→M group had a theoretical increased risk of both aGVHD and cGVHD, because H-Y Ags can be targets for donor T cells and B cells. In univariate analysis, there was no significant difference in the cumulative incidence of grade II–IV aGVHD among the four groups (Figure 1a). In multivariate analysis, a lower cord blood $CD34^+$ cell count (hazard ratio (HR), 0.66; 95% confidence interval (CI), 0.46–0.94; $P=0.02$) and high risk of disease status at CBT (HR, 0.69; 95% CI, 0.48–0.98; $P=0.04$) were associated with a lower incidence of grade II–IV aGVHD. Nevertheless, the incidence of grade II–IV aGVHD was similar for the F→M group, M→F group and M→M group compared with the F→F group (Table 2). In addition, there was no significant difference in the cumulative incidence of grade III–IV aGVHD among the four groups ($P=0.34$) (Table 2). In univariate analysis, there was no significant difference in the cumulative incidence of extensive cGVHD among the four groups ($P=0.11$) (Figure 1b). Multivariate analysis indicated that the F→M group was a significant risk factor for extensive cGVHD compared with the F→F group (HR, 2.97; 95% CI, 1.14–7.69; $P=0.02$) (Table 2).

OS, relapse and TRM

The probability of OS at 7 years did not differ significantly among the four groups in univariate analysis ($P=0.32$) (Figure 1c) and

Table 1. Characteristics of patients, cord blood units and transplantation

	Total	*F→F*	*F→M*	*M→F*	*M→M*	P-*value*
Number (%)	191	37 (19)	59 (30)	39 (20)	56 (29)	
Age (years), median (range)	40 (16–55)	40 (18–53)	41 (16–52)	43 (16–55)	38 (16–55)	0.91
Disease type, number (%)						0.10
AML	101 (52)	17 (45)	28 (47)	28 (71)	28 (50)	
ALL	45 (23)	14 (37)	10 (16)	6 (15)	15 (26)	
MDS	25 (13)	4 (10)	11 (18)	1 (2)	9 (16)	
CML	11 (5)	1 (2)	6 (10)	2 (5)	2 (3)	
NHL	9 (4)	1 (2)	4 (6)	2 (5)	2 (3)	
Disease status at CBT, number (%)[a]						0.95
Standard risk	79 (41)	15 (40)	26 (44)	15 (38)	23 (41)	
High risk	112 (58)	22 (59)	33 (55)	24 (61)	33 (58)	
CMV serostatus, number (%)						0.60
Positive	166 (86)	34 (91)	52 (88)	34 (87)	46 (82)	
Negative	25 (13)	3 (8)	7 (11)	5 (12)	10 (17)	
Conditioning regimen, number (%)						0.07
TBI 12 Gy + Ara-C/G-CSF + CY	131 (68)	21 (56)	44 (74)	28 (71)	38 (67)	
TBI 12 Gy + Ara-C + CY	31 (16)	10 (27)	10 (6)	2 (5)	9 (16)	
TBI 12 Gy + CY	16 (8)	5 (13)	2 (3)	3 (7)	6 (10)	
TBI 12 Gy + others	13 (6)	1 (2)	3 (5)	6 (15)	3 (5)	
GVHD prophylaxis, number (%)						0.83
CsA + MTX	188 (98)	37 (100)	58 (98)	38 (97)	55 (98)	
CsA	3 (1)	0 (0)	1 (1)	1 (2)	1 (1)	
Number of nucleated cells, $\times10^7$/kg, median (range)	2.43 (1.32–5.69)	2.66 (1.92–5.50)	2.38 (1.51–5.07)	2.58 (1.72–5.69)	2.28 (1.32–4.09)	<0.01
Number of $CD34^+$ cells, $\times10^5$/kg, median (range)	0.92 (0.17–7.75)	0.89 (0.34–2.81)	0.93 (0.32–7.75)	1.07 (0.17–2.64)	0.92 (0.28–3.15)	0.77
HLA disparities, number (%)[b]						0.21
⩽2	129 (67)	30 (81)	37 (62)	27 (69)	35 (62)	
⩾3	62 (32)	7 (18)	22 (37)	12 (30)	21 (37)	

Abbreviations: Ara-C = cytosine arabinoside; MDS = myelodysplastic syndrome; NHL = non-Hodgkin's lymphoma. [a]Disease status at CBT was classified as standard risk or high risk; CR1 or CR2 without poor prognostic karyotype for AML and ALL, refractory anemia for MDS, chronic phase for CML, and CR1 or CR2 for NHL were classified as standard risk, whereas patients in all other situations were classified as high risk. [b]The number of HLA disparities defined as low resolution for HLA-A and -B and high resolution for HLA-DRB1.

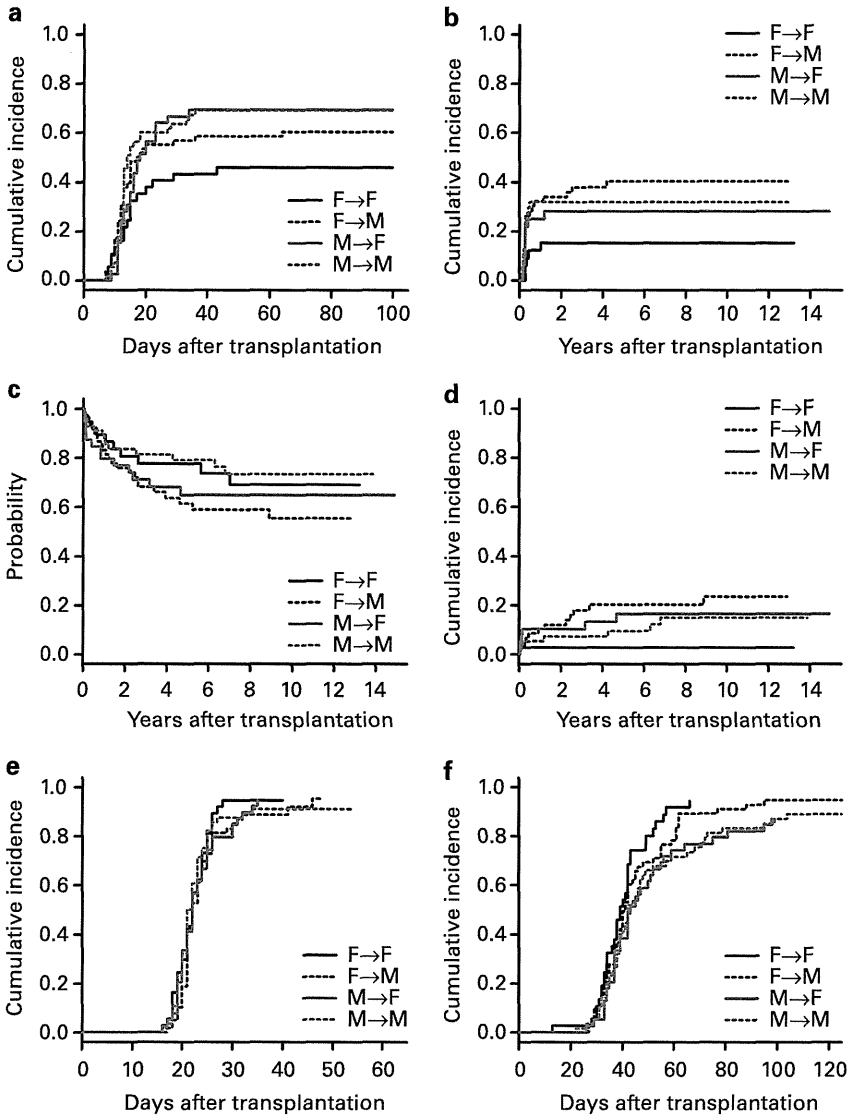

Figure 1. Cumulative incidence of grade II–IV aGVHD (**a**), extensive cGVHD (**b**), probability of OS (**c**), cumulative incidence of TRM (**d**), neutrophil engraftment (**e**) and platelet engraftment (**f**) according to donor–recipient sex combination after CBT.

multivariate analysis (Table 2). We also analyzed a subgroup of patients with standard risk or high risk of disease status at CBT. However, we were unable to find any impact of sex incompatibility on survival relating to disease risk at CBT (data not shown). Sex incompatibility was not associated with cumulative incidence of relapse (Table 2). A trend toward a higher incidence of TRM was observed in the F→M group compared with the F→F group, but this was not significant in univariate analysis ($P=0.09$) (Figure 1d) or multivariate analysis ($P=0.07$) (Table 2).

Engraftment

Female recipients with male donors have a theoretical increased risk of graft rejection, because the H-Y Ags can be a target for recipient T cells and B cells. In univariate analysis, there was no significant difference in the cumulative incidence of neutrophil engraftment among the four groups (Figure 1e). In multivariate analysis, a lower cord blood $CD34^+$ cell count (HR, 0.51; 95% CI, 0.37–0.70; $P<0.001$) and high risk of disease status at CBT (HR, 0.68; 95% CI, 0.51–0.93; $P=0.01$) were associated with a lower incidence of neutrophil engraftment, but sex incompatibility was not associated with neutrophil engraftment (Table 2). In univariate analysis, the cumulative incidence of platelet recovery was not significantly different among the four groups (Figure 1f). In multivariate analysis, the M→F group showed a significantly lower incidence of platelet engraftment when compared with the F→F group (HR, 0.56; 95% CI, 0.34–0.091; $P=0.02$) (Table 2). In addition, a lower cord blood $CD34^+$ cell count (HR, 0.58; 95% CI, 0.42–0.80; $P<0.01$), positive CMV serostatus (HR, 0.48; 95% CI, 0.32–0.74; $P<0.001$) and high risk of disease status at CBT (HR, 0.57; 95% CI, 0.41–0.78; $P<0.001$) were associated with a lower incidence of platelet engraftment.

DISCUSSION

We examined the effects of donor–recipient sex incompatibility on the outcome of CBT in our institute. The effect of sex incompatibility on transplant outcome might differ depending on the kinds of stem cell sources in allo-HSCT. Gallardo *et al.*[6] demonstrated the association of a sex-mismatch and grade III–IV aGVHD, higher TRM and lower OS in HLA-compatible BMT, but not HLA-compatible PBSC transplantation. In addition, Sterm *et al.*[25] reported the largest retrospective study for evaluating the effect of sex incompatibility in 53 988 allogeneic transplants using

Table 2. Univariate and multivariate analyses of sex compatibility for the outcomes of CBT

	Univariate analysis			*Multivariate analysis*		
	Number	*% (95% CI)*	P-*value*	*Hazard Ratio*	*95% CI*	P-*value*
Grade II–IV aGVHD at 100 days			0.17			
F→F	37	45.9 (29.2–61.2)		1.00		Reference
F→M	58	60.3 (46.4–71.7)		1.42	0.75–2.69	0.27
M→F	39	69.2 (51.7–81.5)		1.57	0.84–2.90	0.15
M→M	55	69.1 (54.8–79.7)		1.83	0.99–3.38	0.05
Grade III–IV acute GVHD at 100 days			0.34			
F→F	37	2.7 (0.2–12.3)		1.00		Reference
F→M	58	12.1 (5.3–21.9)		4.19	0.55–32.00	0.17
M→F	39	12.8 (4.6–25.4)		4.07	0.48–33.90	0.19
M→M	55	7.3 (2.3–16.2)		2.36	0.30–18.24	0.41
Extensive cGVHD at 3 years			0.11			
F→F	32	15.3 (5.4–29.7)		1.00		Reference
F→M	53	38.0 (24.9–51.0)		2.97	1.14–7.69	0.02
M→F	31	28.3 (13.9–44.6)		1.62	0.54–4.80	0.38
M→M	47	32.0 (19.2–45.5)		2.43	0.86–6.83	0.09
OS at 7 years[a]			0.32			
F→F	37	69.1 (49.3–82.4)		1.00		Reference
F→M	59	58.9 (44.2–71.0)		1.91	0.85–4.28	0.11
M→F	39	64.9 (47.2–78.0)		1.58	0.66–3.76	0.29
M→M	56	73.4 (58.2–83.9)		0.99	0.40–2.46	0.98
Relapse at 7 years			0.29			
F→F	37	31.5 (16.7–47.5)		1.00		Reference
F→M	59	21.6 (11.8–33.4)		0.80	0.32–1.97	0.63
M→F	39	23.4 (11.4–37.8)		0.89	0.34–2.32	0.82
M→M	56	13.1 (5.7–23.7)		0.52	0.17–1.55	0.25
TRM at 7 years			0.10			
F→F	37	2.7 (0.2–12.3)		1.00		Reference
F→M	59	20.1 (10.6–31.8)		7.96	0.82–77.19	0.07
M→F	39	16.4 (6.5–30.4)		5.62	0.58–53.67	0.13
M→M	56	15.0 (6.4–27.1)		3.95	0.38–40.64	0.25
Neutrophil engraftment at 60 days			0.76			
F→F	37	94.6 (75.8–98.9)		1.00		Reference
F→M	59	95.1 (75.9–99.1)		0.79	0.51–1.21	0.28
M→F	39	94.9 (73.5–99.1)		0.85	0.53–1.34	0.49
M→M	56	91.1 (78.8–96.4)		1.01	0.64–1.60	0.95
Platelet engraftment at 100 days			0.05			
F→F	37	94.6 (72.1–99.1)		1.00		Reference
F→M	59	94.7 (82.3–98.5)		0.80	0.51–1.24	0.33
M→F	39	87.2 (69.0–95.0)		0.56	0.34–0.91	0.02
M→M	56	87.0 (73.6–93.9)		0.63	0.38–1.03	0.06

Abbreviation: CI = confidence interval. [a]Hazards ratio for overall mortality.

various hematopoietic stem cell sources. As only 734 (1.3%) patients received CBT among the 53 988 patients, the details of CBT outcomes were not described. In the CBT setting, the sex of recipients has become a confounding factor for outcome.[26,27] Although sex incompatibility was considered as a factor influencing the outcome in several CBT studies,[14–16,28,29] there have been no reports detailing the effect of sex incompatibility on outcomes after CBT. Our results showed a higher risk of extensive cGVHD in the F→M group and a lower incidence of platelet engraftment in the M→F group compared with the F→F group in the multivariate analysis. These effects might be associated with allogeneic immune responses against H-Y Ags. However, there were no differences in OS, TRM and relapse among all four groups.

Male recipients with female donors had an increased incidence of GVHD, particularly cGVHD,[3–7,30] which led to a higher TRM and lower OS in the setting of HLA-compatible allo-HSCT. Recently, Newell *et al.*[31] demonstrated a shorter duration and a higher response of cGVHD to systemic immunosuppressive treatment in CBT recipients than in BMT or PBSC transplantation recipients, which might have contributed to extensive cGVHD not being shown to increase TRM in our study. It has been reported that a decreased risk of relapse is associated with aGVHD and cGVHD in leukemia patients after BMT.[32] In fact, several studies demonstrated that male recipients with female donors had a lower risk of relapse in leukemia and myeloma,[3–5] suggesting that sex incompatibility may contribute to the GVL effects. However, we were unable to find any impact of sex incompatibility on relapse in the entire cohort and in subgroup analysis on the basis of disease risk at CBT (data not shown). On the other hand, it has been reported that female recipients with male donors had a higher risk of graft failure in aplastic anemia following allo-HSCT.[8] Moreover, the role of H-Y Ags in graft rejection of solid organ transplantations has also been reported extensively, particularly in kidney transplantations.[33,34] In our study, female recipients with

male donors were significantly associated with a lower incidence of platelet engraftment, but not neutrophil engraftment. Our data showed that the most important factor in neutrophil and platelet engraftment was the cord blood $CD34^+$ cell count, indicating that this is more important than sex incompatibility in engraftment after CBT.

In HLA-compatible allo-HSCT, GVHD and GVL effects might be induced by allogeneic immune responses against mHA, which can be presented by HLA in normal or leukemia cells. mHA are HLA-restricted polymorphic peptides derived from intracellular proteins encoded by polymorphic genes. H-Y Ags can be recognized by female donor or recipient T cells in the setting of sex-mismatched allo-HSCT. Several H-Y Ags, such as SMCY, DFFRY, UTY, DBY, RPS4Y and TMSB4Y, have been identified and were recognized by either $CD4^+$ or $CD8^+$ T cells.[35,36] It has been reported that male recipients with female donors have a greater risk of cGVHD than aGVHD in allo-HSCT.[3–7,30] In addition, the detection of alloantibody and alloantibody-producing B cells against H-Y Ags was associated with cGVHD in sex-mismatched allo-HSCT.[37,38] In fact, our data also showed that male recipients with female donors were significantly associated with a higher incidence of extensive cGVHD, but not aGVHD. Although the existence of alloantibodies against H-Y Ags was not clarified in our study, specific alloantibodies against H-Y Ags should be investigated in future studies.

In conclusion, our data showed that donor–recipient sex combination affects the incidences of extensive cGVHD and platelet engraftment, but does not have a significant effect on the OS after CBT. However, these results should be interpreted with caution because this retrospective study included a relatively small number of Japanese patients who received single-unit CBT following 12 Gy TBI-based myeloablative conditioning regimens for hematological malignancies. Although these findings should be confirmed in prospective studies, donor–recipient sex combination does not appear to have a significant impact on survival after CBT.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Comparable Long-Term Outcome of Unrelated Cord Blood Transplantation with Related Bone Marrow or Peripheral Blood Stem Cell Transplantation in Patients Aged 45 Years or Older with Hematologic Malignancies after Myeloablative Conditioning

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A B S T R A C T

We investigated whether bone marrow or peripheral blood stem cells from older sibling donors or cord blood from unrelated donors provided a better outcome in allogeneic hematopoietic stem cell transplantation for relatively older patients who were candidates for myeloablative conditioning. Clinical outcomes of 97 patients aged 45 years or older with hematologic malignancies who received unrelated cord blood transplantation (CBT) (n = 66) or bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT) from related donors (n = 31) were compared. The cumulative incidences of grades III to IV acute and extensive chronic graft-versus-host diseases were similar between both groups. Although transplant-related mortality was significantly lower after CBT compared with BMT/PBSCT from related donors (hazard ratio [HR], .29, $P = .04$), overall mortality (HR, .72, $P = .47$) and relapse (HR, 2.02, $P = .23$) were not significantly different after CBT and BMT/PBSCT from related donors. These data suggest that CBT could be as safe and effective as BMT/PBSCT from older related donors for relatively older patients when it is used as a primary unrelated stem cell source.

INTRODUCTION

Donor age has been associated with transplant outcomes in allogeneic hematopoietic stem cell transplantation (allo-HSCT) after myeloablative conditioning or reduced-intensity conditioning (RIC) [1-5]. Older donor age resulted in an increased incidence of severe graft-versus-host disease (GVHD), which led to higher transplant-related mortality (TRM) or overall mortality after allo-HSCT from unrelated adult donors [1,2]. In contrast, it is difficult to determine the exact effect of the age of related donors, because increasing recipient age is frequently accompanied by increased donor age after allo-HSCT from related donors. However, older donor age of related donors may also be associated with adverse outcomes [3-5].

Several studies, including ours, comparing both cord blood transplantation (CBT) and bone marrow transplantation (BMT)/peripheral blood stem cell transplantation (PBSCT) from unrelated donors after myeloablative conditioning in adult patients demonstrated that the incidence of severe GVHD was significantly lower after CBT than after unrelated BMT/PBSCT. The survival rate and relapse incidence in CBT recipients were comparable with those in unrelated BMT/PBSCT recipients [6-9]. Moreover, we also demonstrated similar survival, relapse, and TRM between unrelated CBT and related BMT/PBSCT (rBMT/PBSCT) recipients [10]. The incidences of grades III to IV acute GVHD (aGVHD) and extensive chronic GVHD (cGVHD) among CBT recipients were also significantly lower than those among rBMT/PBSCT recipients. Because the lower risk of severe GVHD is one of the most attractive advantages of CBT, the use of cord blood instead of bone marrow or mobilized peripheral blood as a stem cell source might offer the possibility of decreasing severe GVHD in older patients. However, there has been no comparative study between CBT and BMT/PBSCT from older related donors after myeloablative conditioning in relatively older patients.

We previously reported that unrelated CBT after myeloablative conditioning is feasible in patients over the age of 45 years [11,12]. In this retrospective study, we report on a clinical comparison of CBT from unrelated donors and BMT/PBSCT from older related donors in patients older than 45 years of age with hematologic malignancies who were candidates for a myeloablative conditioning.

METHODS

Patients and Transplant Procedures

This retrospective study included 97 consecutive patients, 45 years of age or older, who received CBT (n = 66) from unrelated donors or BMT (n = 26) or PBSCT (n = 5) from related donors for acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), and non-Hodgkin lymphoma (NHL) at the Institute of Medical Science, University of Tokyo between May 1992 and July 2013. Nineteen patients who received rBMT/PBSCT and 32 patients who received CBT were included from our previous study with extended

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Table 1
Characteristics of Patients, Grafts, and Transplantation

Characteristic	rBMT/PBSCT	CBT	*P*
Number of patients	31	66	
Recipient age, yr, median (range)	48 (45-58)	49 (45-55)	.60
Recipient sex, n (%)			.51
Male	20 (64)	37 (56)	
Female	11 (35)	29 (43)	
Recipient CMV serostatus, n (%)			.18
Positive	28 (90)	64 (96)	
Negative	0 (0)	2 (3)	
Unknown	3 (9)	0 (0)	
Disease type, n (%)			.08
AML	16 (51)	44 (66)	
MDS	2 (6)	8 (12)	
CML	6 (19)	3 (4)	
ALL	3 (9)	8 (12)	
NHL	4 (12)	3 (4)	
Disease status at transplantation,* n (%)			.48
Standard	8 (25)	23 (34)	
High	23 (74)	43 (65)	
Conditioning regimen, n (%)			<.01
TBI12Gy+Ara-C/G-CSF	21 (64)	0 (0)	
TBI12Gy+Ara-C/G-CSF+CY	2 (6)	52 (78)	
TBI12Gy+Ara-C/G-CSF+Flu	0 (0)	3 (4)	
TBI12Gy+CY	3 (9)	3 (4)	
TBI12Gy+Ara-C+CY	1 (3)	8 (12)	
TBI12Gy+VP16	4 (12)	0 (0)	
GVHD prophylaxis, n (%)			.23
Cyclosporine A+methotrexate	29 (93)	65 (98)	
Cyclosporine A	2 (6)	1 (1)	
Number of nucleated cells, $\times 10^7$/kg, median (range)	26.6 (3.13-50.0)‡	2.39 (1.72-5.07)	<.01
Number of CD34$^+$ cells, $\times 10^5$/kg, median (range)	40.5 (20.6-75.0)§	1.04 (.17-3.15)	<.01
Donor age, yr, median (range)	46.5 (38-58)	—	—
Sex compatibility, n (%)			.81
Female donor to male recipient	8 (25)	20 (30)	
Other	23 (74)	46 (69)	
HLA disparities,† n (%)			<.01
0	28 (90)	1 (1)	
1	2 (6)	13 (19)	
2	1 (3)	52 (78)	
ABO incompatibility, n (%)			.04
Match	19 (61)	20 (30)	
Major mismatch	4 (12)	17 (25)	
Minor mismatch	5 (16)	18 (27)	
Bidirectional mismatch	3 (9)	11 (16)	
Time from diagnosis to transplantation, days, median (range)	521 (59-2501)	390.5 (55-6783)	.84
<365 d, n (%)	12 (38)	31 (46)	.51
≥365 d, n (%)	19 (61)	35 (53)	
Year of transplantation, n (%)			<.01
1992-2002	27 (87)	17 (25)	
2003-2013	4 (12)	49 (74)	
Follow-up for survivors, mo, median (range)	185 (32-258)	87 (4-175)	<.01

CMV indicates cytomegalovirus; CY, cyclophosphamide; Flu, fludarabine; VP-16, etoposide.

* Disease status at transplantation was classified as standard risk or high risk; CR1 or CR2 without poor prognostic karyotype for AML and ALL, refractory anemia for MDS, chronic phase for CML, and CR1 or CR2 for NHL were classified as standard risk, whereas patients in all other situations were classified as high risk.

† Number of HLA disparities defined as low resolution for HLA-A, -B, and -DR.

‡ Number of nucleated cells was only for BMT recipients.

§ Number of CD34$^+$ cells was only for PBSCT recipients.

follow-up [10]. For disease status at transplantation, patients in first complete remission (CR1) or second complete remission (CR2) without poor prognostic karyotype for AML and ALL, refractory anemia for MDS, chronic phase for CML, and CR1 or CR2 for NHL were classified as standard risk, whereas patients in all other situations were classified as high risk.

Although bone marrow or mobilized peripheral blood from HLA-compatible related donors within immediate families is a frontline graft source, patients without a suitable closely HLA-compatible related donor were eligible for CBT as an alternative first treatment option, unless they had any type of anti-HLA antibody. Cord blood units were obtained from the Japan Cord Blood Bank Network and were selected as reported previously [9,10]. All patients received 12 Gy total body irradiation (TBI)-based myeloablative conditioning regimens, and cyclosporine-based GVHD prophylaxis regimens, as previously reported [9,10]. For myeloid disease, granulocyte colony-stimulating factor (G-CSF) was added to the conditioning regimen to increase the susceptibility to cytosine arabinoside (Ara-C) through induction of cell cycle entry of dormant leukemia cells, as previously reported [10]. Almost all patients received some supportive care, such as antibacterial, antifungal and antiviral agents, as previously reported [9,10]. The institutional review board of the Institute of Medical Science, University of Tokyo approved this study, which was conducted in accordance with the Declaration of Helsinki.

End Points and Definitions

The primary study end point was overall survival (OS), which was defined as the time from the date of transplantation to the date of death or last contact. Secondary end points were relapse, TRM, GVHD, and neutrophil and platelet recovery. Relapse was defined by morphologic evidence of disease in peripheral blood, bone marrow, or extramedullary sites. TRM was defined as death during a remission. Both aGVHD and cGVHD were graded according to previously published criteria [13,14]. The incidence of aGVHD

was evaluated in all engrafted patients, whereas the incidence of cGVHD was evaluated in engrafted patients surviving more than 100 days. Neutrophil engraftment was defined as the first of 3 consecutive days during which the absolute neutrophil count was at least .5 × 10^9/L. Platelet engraftment was defined as the first of 7 consecutive days with a platelet count of 20 × 10^9/L or higher without platelet transfusion.

Statistical Analysis

Baseline patient and transplant characteristics were compared using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. The probability of OS was estimated according to the Kaplan-Meier method, and groups were compared using Cox regression models or the log-rank test. The probabilities of relapse, TRM, aGVHD and cGVHD, and neutrophil and platelet engraftment were estimated based on a cumulative incidence method to accommodate competing risks. Multivariate analysis was performed with a Cox proportional hazard model adjusted for OS and a Fine and Gray proportional hazards model for the others. In addition to the stem cell source (CBT versus rBMT/PBSCT), the following variables were considered: disease type (myeloid [AML, MDS, CML] versus lymphoid [ALL, NHL] disease), disease status at transplantation (standard risk versus high risk), time from diagnosis to transplantation (<365 days versus ≥365 days), sex compatibility between donor and recipient (female donor to male recipient versus other), ABO compatibility between donor and recipient (match versus mismatch), and year of transplantation (1992 to 2002 versus 2003 to 2013).

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphic user interface for R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) [15]. $P < .05$ was considered significant. Analysis of data was performed in December 2013.

RESULTS

Characteristics of Patients and Grafts

The characteristics of patients, grafts, and transplant procedures are summarized in Table 1. Recipients' age, sex, cytomegalovirus serostatus, disease type, disease status at transplantation, GVHD prophylaxis, sex incompatibility between donors and recipients, and time from diagnosis to transplantation were almost the same between the CBT and rBMT/PBSCT recipients. On the other hand, there were significant differences in the following variables (Table 1). The conditioning regimen significantly differed between the CBT and rBMT/PBSCT recipients ($P < .01$). The most common conditioning regimen was TBI12Gy+Ara-C/G-CSF+cyclophosphamide (78%) for CBT and TBI12Gy+Ara-C/G-CSF (64%) for rBMT/PBSCT. The number of nucleated cells or $CD34^+$ cells for CBT recipients was 1 log lower than in rBMT or rPBSCT recipients, respectively. The proportion of HLA disparity and ABO incompatibility was higher among CBT recipients than rBMT/PBSCT recipients. CBT was more frequently performed in recent years, resulting in the significantly shorter follow-up period for CBT compared with that for rBMT/PBSCT. Median follow-up was 185 months (range, 32 to 258 months) for rBMT/PBSCT recipients and 87 months (range, 4 to 175 months) for CBT recipients ($P < .01$).

Table 2
Univariate and Multivariate Analysis of Transplant Outcomes after rBMT/PBSCT and CBT in Patients Aged 45 Years or Older

	Univariate Analysis		Multivariate Analysis*	
	HR (95% CI)	P	HR (95% CI)	P
Neutrophil engraftment rBMT/PBSCT vs. CBT	.69 (.38-1.04)	.07	.46 (.26-.81)	<.01
Platelet engraftment rBMT/PBSCT vs. CBT	.30 (.14-.61)	<.01	.24 (.12-.50)	<.01
Grades III-IV aGVHD rBMT/PBSCT vs. CBT	.57 (.18-1.85)	.36	.53 (.15-1.90)	.34
Extensive cGVHD rBMT/PBSCT vs. CBT	1.01 (.53-1.91)	.97	1.08 (.49-2.35)	.84
Overall mortality rBMT/PBSCT vs. CBT	.69 (.36-1.32)	.26	.72 (.30-1.73)	.47
Relapse rBMT/PBSCT vs. CBT	1.42 (.52-3.87)	.49	2.02 (.63-6.42)	.23
TRM rBMT/PBSCT vs. CBT	.38 (.16-.93)	.03	.29 (.08-.99)	.04

* For neutrophil engraftment, lymphoid disease was also a significant variable (HR, 2.40; 95% CI, 1.52 to 3.79; $P < .01$). For platelet engraftment, lymphoid disease was also a significant variable (HR, 1.74; 95% CI, 1.17 to 2.59; $P < .01$). For grades III-IV aGVHD, ABO incompatibility was a significant variable (HR, 4.41; 95% CI, 1.06 to 18.24; $P = .04$). For extensive cGVHD, high risk of disease status at transplantation was a significant variable (HR, 3.14; 95% CI, 1.39 to 7.09; $P < .01$). For overall mortality, high risk of disease status at transplantation (HR, 3.33; 95% CI, 1.36 to 8.11; $P < .01$) and ABO incompatibility (HR, 3.14; 95% CI, 1.44 to 6.87; $P < .01$) were significant variables. For relapse, high risk of disease status at transplantation was a significant variable (HR, 4.55; 95% CI, 1.08 to 19.23; $P = .03$). For TRM, female donor to male recipient (HR, 2.89; 95% CI, 1.11 to 7.52; $P = .02$) and ABO incompatibility (HR, 5.20; 95% CI, 1.56 to 17.33; $P < .01$) were also significant variables.

Neutrophil and Platelet Engraftment

One patient in the CBT group died on day 21 due to encephalitis, and 1 patient in the rBMT/PBSCT group died on day 7 due to organ failure. Primary graft failure occurred in 3 of the surviving 65 patients in the CBT group, but there was no primary graft failure in the rBMT/PBSCT group. As expected, neutrophil recovery was significantly delayed after CBT as compared with rBMT/PBSCT. Median times to neutrophil recovery were 22 days (range, 18 to 34 days) after CBT, as compared with 18 days (range, 11 to 40 days) after rBMT/PBSCT ($P < .01$). The cumulative incidence of neutrophil recovery on day 60 was slightly lower after CBT (93.9%; 95% confidence interval [CI], 83.5% to 97.9%) compared with rBMT/PBSCT (96.8%; 95% CI, 57.8% to 99.8%) ($P = .07$). In the multivariate analysis, the hazard risk of neutrophil engraftment was significantly lower after CBT as compared with rBMT/PBSCT (hazard ratio [HR], .46; 95% CI, .26 to .81; $P < .01$, Table 2).

Platelet recovery was also significantly delayed after CBT as compared with rBMT/PBSCT. Median times to platelet recovery were 42 days (range, 13 to 104 days) after CBT, as compared with 24 days (range, 15 to 300 days) after rBMT/PBSCT ($P < .01$). The cumulative incidence of platelet recovery on day 100 was significantly lower after CBT (90.8%; 95% CI, 80.0% to 95.9%) compared with rBMT/PBSCT (93.5%; 95% CI, 71.5% to 98.7%) in the univariate analysis ($P < .01$); the difference was also significant in multivariate analyses (HR, .24; 95% CI, .12 to .50; $P < .01$, Table 2).

Acute and Chronic GVHD

The cumulative incidences of grades II to IV (HR, .90; 95% CI, .49 to 1.64; $P = .76$) and grades III to IV aGVHD (HR, .53; 95% CI, .15 to 1.90; $P = .34$) were similar between CBT and rBMT/PBSCT recipients in multivariate analyses (Table 2). The unadjusted cumulative incidence of grades III to IV aGVHD at 100 days was 9.2% (95% CI, 3.7% to 17.8%) in CBT recipients and 16.1% (95% CI, 5.7% to 31.2%) in rBMT/PBSCT recipients ($P = .35$). Extensive cGVHD developed in 27 of 58 CBT recipients and in 13 of 27 rBMT/PBSCT recipients surviving more than 100 days. In a multivariate analysis, the cumulative incidences of cGVHD (HR, .94; 95% CI, .55 to 1.62; $P = .84$) and extensive cGVHD (HR, 1.08; 95% CI, .49 to 2.35; $P = .84$) were similar between CBT and rBMT/PBSCT recipients in multivariate analysis (Table 2).

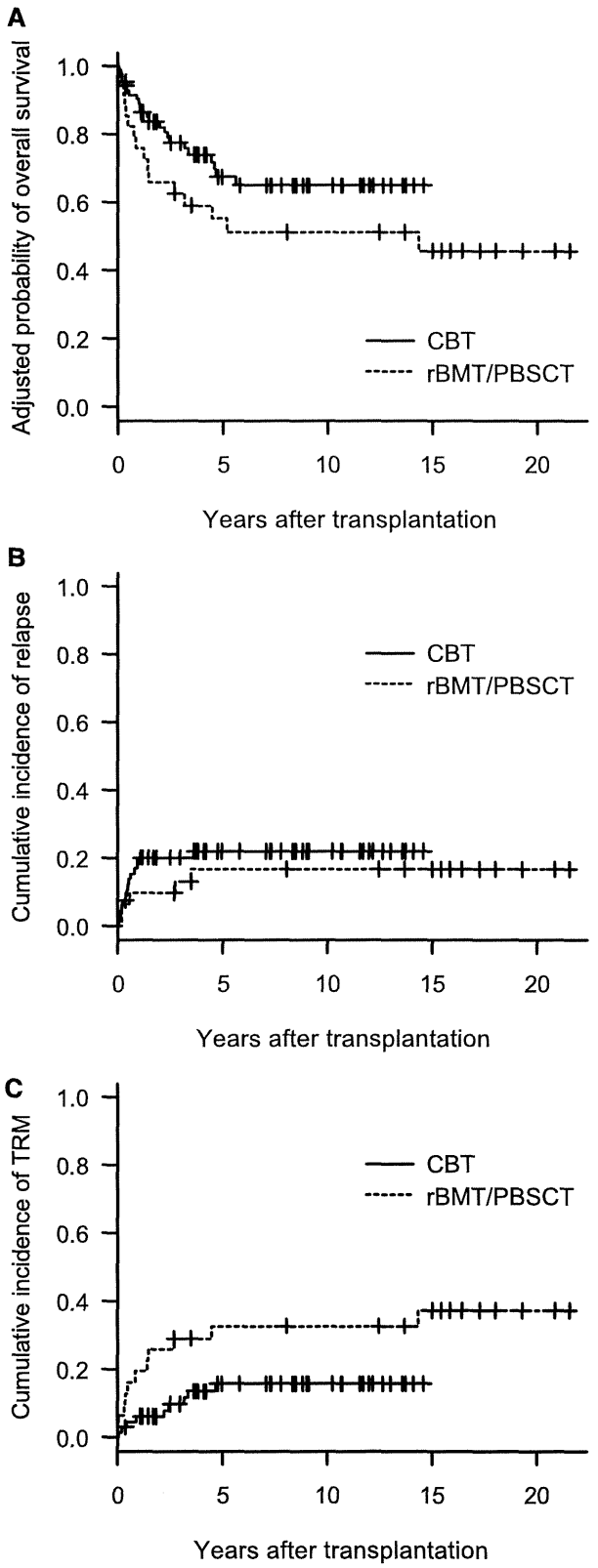

Figure 1. Outcomes after CBT or BMT/PBSCT from related donors in patients aged 45 years or older with hematologic malignancies after a myeloablative conditioning regimen. Adjusted probability of OS (A), unadjusted cumulative incidence of relapse (B), and TRM (C).

Table 3
Cause of Death

	Death before 100 Days		Death after 100 Days	
	rBMT/PBSCT (n = 2)	CBT (n = 4)	rBMT/PBSCT (n = 14)	CBT (n = 19)
Primary disease	0	2	5	12
GVHD	0	0	5	5
Infection	1	2	4	2
Organ failure	1	0	0	0

Survival, Relapse, and TRM

The adjusted probabilities of OS at 5 years were 67.4% (95% CI, 55.7% to 81.6%) for recipients of CBT and 55.2% (95% CI, 39.4% to 77.4%) for recipients of rBMT/PBSCT (Figure 1A). In multivariate analysis, the hazard risk of overall mortality was similar between CBT and rBMT/PBSCT recipients (HR, .72; 95% CI, .30 to 1.73; $P = .47$; Table 2). We also compared OS of both groups for each disease risk. However, OS of both recipient groups was also equivalent in standard-risk patients (n = 31) and high-risk patients (n = 66) (data not shown). The unadjusted cumulative incidence of relapse at 5 years was 22.0% (95% CI, 12.7% to 33.0%) in CBT recipients and 16.7% (95% CI, 5.9% to 32.3%) in rBMT/PBSCT recipients ($P = .48$) (Figure 1B). In multivariate analysis, the hazard risk for relapse was similar between CBT and rBMT/PBSCT recipients (HR, 2.02; 95% CI, .63 to 6.42; $P = .23$; Table 2). The unadjusted cumulative incidence of TRM was significantly lower after CBT at 100 days (3.0%; 95% CI, .6% to 9.4%) and 5 years (15.8%; 95% CI, 7.6% to 26.6%) compared with rBMT/PBSCT at 100 days (6.5%; 95% CI, 1.1% to 18.9%) and 5 years (32.7%; 95% CI, 16.8% to 49.6%) ($P = .04$) (Figure 1C). In multivariate analysis, the hazard risk of TRM was significantly lower after CBT as compared with rBMT/PBSCT (HR, .29; 95% CI, .08 to .99; $P = .04$; Table 2).

We also analyzed a subgroup of patients aged 50 years or older after CBT (n = 29) and rBMT/PBSCT (n = 11). In multivariate analysis, the hazard risk of overall mortality (HR, .36, $P = .10$) and relapse (HR, 2.73, $P = .41$) after CBT was comparable with that after rBMT/PBSCT, respectively. However, the hazard risk of TRM was lower after CBT than after rBMT/PBSCT (HR, .16; 95% CI, .04 to .56; $P < .01$).

The causes of death before and after 100 days after transplantation by donor type are summarized in Table 3. The major cause of death in both recipient groups was primary disease. However, GVHD and infection as a primary cause of late mortality were more common after rBMT/PBSCT compared with CBT.

DISCUSSION

The objective of this study was to compare the transplant outcomes after CBT and rBMT/PBSCT in relatively older patients who were candidates for myeloablative conditioning. Unexpectedly, there were no significant differences in aGVHD and cGVHD between CBT and rBMT/PBSCT recipients. However, TRM was higher after rBMT/PBSCT compared with CBT. The reduced TRM in CBT might be in part due to improved supportive care, because CBT was more frequently performed in recent years. However, year of transplantation did not affect any clinical results in our multivariate analysis. On the other hand, we used almost the same 12-Gy TBI-based myeloablative conditioning and cyclosporine-based GVHD prophylaxis regimens during the period for both recipients of CBT and rBMT/PBSCT. Among relatively older

patients who were candidates for such myeloablative conditioning, survival and relapse were not significantly different after CBT and rBMT/PBSCT.

Whether an older sibling donor or unrelated donor should be chosen as an optimal donor is an important question in allo-HSCT for older patients. There have been some clinical comparisons of allo-HSCT from older sibling donors and unrelated donors in older patients [16-18]. A European Group for Blood and Marrow Transplantation analysis by Kröger et al. [16] reported on comparisons of allo-HSCT from older sibling donors and young unrelated donors in 719 patients older than 50 years with MDS. They showed that recipients from young unrelated donors had improved survival compared with those from older sibling donors among older patients with MDS. A single-institute analysis by Ayuk et al. [17] showed similar outcomes from older sibling donors compared with young unrelated donors among older patients with AML in CR. On the other hand, Alousi et al. [18] of the Center for International Blood and Marrow Transplantation also performed a similar study in 2172 patients older than 50 years with leukemia or lymphoma. In contrast, their data showed that the risks of overall mortality, relapse, and TRM were lower after allo-HSCT from older sibling donors compared with those from young unrelated donors. However, comparative clinical outcomes of CBT and BMT/PBSCT from older related donors after myeloablative conditioning have yet to be clarified. Our data showed comparable outcomes for CBT and BMT/PBSCT from older related donors after myeloablative conditioning in relatively older patients when cord blood was selected as a primary unrelated donor source.

In comparison with other sources of allo-HSCT, the lower risk of GVHD without compromised graft-versus-leukemia effects is one of the most important advantages of CBT. In our study, the incidences of severe aGVHD and cGVHD were not significantly different after CBT and rBMT/PBSCT. Relapse was also similar between CBT and rBMT/PBSCT recipients. However, TRM was significantly lower after CBT compared with that after rBMT/PBSCT. GVHD-associated mortality was a common cause of late death after rBMT/PBSCT compared with CBT. Newell et al. [19] reported a shorter duration and a higher response of cGVHD to systemic immunosuppressive treatment in CBT recipients than in BMT/PBSCT recipients, suggesting that a longer duration of systemic immunosuppressive treatment for cGVHD might have contributed to higher infection-related late mortality after rBMT/PBSCT compared with CBT. In fact, we previously reported that the termination of immunosuppressive treatment for rBMT/PBSCT recipients was slower than those for CBT recipients [10]. These effects might have contributed to higher TRM after rBMT/PBSCT compared with CBT in our study. In addition, the absence of risk for donors may also be one of the most attractive advantages of CBT for older patients. Older patients generally have older donors as well when they have an HLA-compatible sibling. Because older donors are more likely to have organ dysfunction or comorbidity, older patients hardly ever find healthy sibling donors. These problems could be overcome with the advantages of CBT, especially in older patients.

Myeloablative conditioning regimens for allo-HSCT have been restricted to younger patients and those without comorbidities, because TRM occurs more frequently among older patients and those with serious comorbidities. RIC regimens have recently been expanded for use with graft sources not only from bone marrow or mobilized peripheral blood but also from cord blood. Although the risk of graft failure after CBT has been reported to be higher after RIC compared with myeloablative conditioning [20], several reports showed similar survival with acceptable engraftment between CBT and other graft sources from related and unrelated adult donors after RIC [21,22]. Further studies are warranted to establish optimal RIC regimens for CBT.

In conclusion, our data showed that CBT had almost equivalent results compared with rBMT/PBSCT after myeloablative conditioning for relatively older patients. However, these results should be interpreted with caution because this study was a retrospective single-institute analysis that included a heterogeneous population and a relatively small number of patients. In addition, although our study was performed in patients older than 45 years of age, it should be noted that most patients were younger than 55 years of age. This is because the patients in our cohort received myeloablative conditioning, which often excludes even older patients. As such, our results cannot be extended to patients older than 60 years of age until another similar study is performed using RIC in those older than 55 years. Although these findings should be confirmed in larger prospective studies, CBT could be as safe and effective as BMT/PBSCT from older related donors after myeloablative conditioning for relatively older patients when it is used as a primary unrelated stem cell source.

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ORIGINAL ARTICLE

Myeloablative unrelated cord blood transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia: comparison with other graft sources from related and unrelated donors

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Abstract Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL) is a distinct clinical entity among ALL and is associated with adverse outcomes and higher rates of relapse when conventional chemotherapy is used alone. Although allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative therapy for patients with Ph+ALL, the impact of graft sources, particularly cord blood transplantation (CBT), on allo-HSCT for patients with Ph+ ALL has yet to be clarified. We retrospectively compared clinical outcomes after unrelated CBT (n=20), unrelated bone marrow transplantation (n=7), and related bone marrow and peripheral blood stem cell transplantations (n=13) following myeloablative conditioning in 40 patients with Ph+ALL. Although graft source had no significant impact on survival or relapse, disease status at transplantation did significantly affect outcomes. These data suggest that unrelated CBT is feasible and should be considered early in the course of patients with Ph+ALL when HLA-compatible related and unrelated donors are not available.

Keywords Philadelphia chromosome · Acute lymphoblastic leukemia · Cord blood transplantation · Bone marrow transplantation · Peripheral blood stem cell transplantation · Myeloablative conditioning

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Introduction

Philadelphia (Ph) chromosome presents in approximately 3 % of children and 25 % of adults with acute lymphoblastic leukemia (ALL) and has been associated with adverse outcomes and higher rates of relapse when conventional chemotherapy is used alone [1]. Although tyrosine kinase inhibitors (TKI) have shown higher rates of complete remission (CR) in combination with conventional induction chemotherapy, several studies showed a beneficial effect of allogeneic hematopoietic stem cell transplantation (allo-HSCT) over conventional chemotherapy in patients with Ph+ALL [2–4]. Therefore, graft search should be initiated as soon as possible after diagnosis of Ph+ALL.

Several registration-based studies, as well as our single-institute study, comparing both cord blood transplantation (CBT) and bone marrow transplantation (BMT) / peripheral blood stem cell transplantation (PBSCT) from unrelated donors after myeloablative conditioning in adult patients demonstrated that the survival rate and relapse incidence in CBT recipients were comparable to those in BMT/PBSCT recipients [5–8]. Moreover, we demonstrated similar survival rates and relapse incidences between unrelated CBT and related BMT/PBSCT recipients [9]. These studies indicated that CBT should be considered an option as a graft source for patients lacking human leukocyte antigen (HLA)-compatible related and unrelated donors. However, reports of disease-specific outcomes for patients with Ph+ALL after CBT are still limited. Furthermore, a comparison of transplant outcomes of Ph+ALL according to graft source has yet to be clarified.

In this retrospective study, we report on clinical comparative outcomes after unrelated CBT, unrelated BMT (uBMT),

and related BMT/PBSCT (rBMT/PBSCT) following myeloablative conditioning for patients with Ph+ALL, and identify variables influencing long-term outcomes.

Methods

Patients

This retrospective study included 40 consecutive patients who received CBT from unrelated donors (n=20), BMT from unrelated donors (n=7), or BMT (n=12) or PBSCT (n=1) from related donors for Ph+ALL at the Institute of Medical Science, The University of Tokyo between May 1990 and August 2012. Five patients were children younger than 15 years at allo-HSCT, and 35 were adults. Nine patients in CBT, two patients in uBMT, and eight patients in rBMT/PBSCT were included from our previous studies with extended follow-up [8–10].

Transplant procedures

Although bone marrow (BM) or mobilized peripheral blood (PB) from HLA-compatible related donors within immediate families is a frontline graft source, patients without a suitable closely HLA-compatible related donor have been eligible for BMT or CBT from an unrelated donor as an alternative treatment option. If patients had any type of anti-HLA antibody, HLA-compatible BMT from an unrelated donor was preferable. If there was insufficient time for an unrelated BM donor search due to disease status or if the preliminary search indicated a low likelihood of obtaining an HLA-compatible unrelated BM donor, cord blood (CB) was selected as a primary graft source. All unrelated BM donor searches were processed through the Japan Marrow Donor Program. CB units were obtained from the Japan Cord Blood Bank Network, and CB units were selected as reported previously [8, 9]. All CBT recipients received single-unit CBT. All patients received 12 Gy total body irradiation (TBI) or busulfan-based myeloablative conditioning regimens, cyclosporine or tacrolimus-based graft-versus-host disease (GVHD) prophylaxis regimens, and similar supportive care, as reported previously [8, 9]. The institutional review board of the Institute of Medical Science, The University of Tokyo approved this study. This study was conducted in accordance with the Declaration of Helsinki.

End points and statistical analysis

The primary study end point was overall survival (OS), which was defined as the time from the date of transplantation to the date of death or last contact. Secondary end points were relapse, which was defined by morphologic evidence of disease in PB, BM, or extramedullary sites.

Baseline patient and transplant characteristics were compared using the chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables. The probability of OS was estimated according to the Kaplan–Meier method, and the groups were compared using Cox regression models or the log-rank test. The probability of relapse was estimated based on a cumulative incidence method to accommodate competing risks. Multivariate analysis was performed with a Cox proportional hazard model adjusted for OS, and a Fine and Gray proportional hazards model for relapse. In addition to the graft source (rBMT/PBSCT vs. uBMT vs. CBT), the following variables were considered: age at transplantation (<30 years vs. ≥30 years), white blood cell counts at diagnosis ($<30\times10^9$/L vs. $\geq30\times10^9$/L), use of TKI before transplantation (yes vs. no), disease status at transplantation (CR1 vs. beyond CR1), and year of transplantation (1990 to 2000 vs. 2001 to 2012). All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) [11]. P<0.05 was considered significant. Analysis of data was performed in December 2013.

Results

Characteristics of patients and grafts

The characteristics of patients, grafts, and transplantation procedures are summarized in Table 1. There were no significant differences between the three groups of recipients, except for the following variables. Recipients of uBMT were younger than recipients of CBT or rBMT/PBSCT (P=0.03). Since imatinib became commercially available from December 2001 in Japan, 20 patients received induction chemotherapy with TKI. CBT was more frequently performed in recent years (P<0.01), resulting in the more frequent use of TKI before transplantation (P<0.01), and the significantly shorter follow-up period of CBT compared with rBMT/PBSCT (P=0.02). The conditioning regimen (P<0.01) and GVHD prophylaxis (P=0.03) significantly differed between the three groups of recipients. The most common conditioning regimen for CBT was TBI12Gy+cytosine arabinoside (Ara-C)+cyclophosphamide (CY) (55 %), for uBMT, TBI12Gy+CY (42 %), and for rBMT/PBSCT, TBI12Gy+etoposide (VP-16) (53 %). Tacrolimus+methotrexate were more frequently used in uBMT as a GVHD prophylaxis. The number of nucleated cells for CBT recipients was 1 log lower than in uBMT or rBMT/rPBSCT recipients (P<0.01). Since all CBT recipients received an HLA-mismatched CB unit, the proportion of HLA disparity was higher among CBT recipients than uBMT or rBMT/PBSCT recipients (P<0.01).

Table 1 Characteristics of patients, grafts, and transplantation

	Total	CBT	uBMT	rBMT/PBSCT	*P*
Number	40	20	7	13	
Age at transplantation, years, median (range)	35(8–55)	39.5(8–55)	21(8–47)	35(9–49)	0.03
Sex, number (%)					0.61
Male	18(45 %)	10(50 %)	2(28 %)	6(46 %)	
Female	22(55 %)	10(50 %)	5(71 %)	7(53 %)	
CMV serostatus, number (%)					0.81
Positive	35(77 %)	17(85 %)	6(85 %)	12(92 %)	
Negative	5(12 %)	3(15 %)	1(14 %)	1(7 %)	
WBC count at diagnosis, $\times 10^9$/L, median (range)	16.6(3.1–388.0)	12.0(3.5–388.0)	25.0(6.3–238.9)	19.8(3.1–189.9)	0.53
Cytogenetics at diagnosis, number (%)					0.28
Philadelphia only	19(47 %)	12(60 %)	2(28 %)	5(38 %)	
Additional chromosome abnormality	21(52 %)	8(40 %)	5(71 %)	8(61 %)	
TKI administration before transplantation, number (%)					<0.01
No	20(50 %)	3(15 %)	5(71 %)	12(92 %)	
Yes	20(50 %)	17(85 %)	2(28 %)	1(7 %)	
MRD status at transplantation*, number (%)					0.26
Negative	10(35 %)	8(44 %)	2(50 %)	0	
Positive	16(57 %)	10(55 %)	2(50 %)	4(66 %)	
Missing	2(7 %)	0	0	2(33 %)	
Disease status at transplantation, number (%)					0.08
CR1	23(46 %)	15(75 %)	3(42 %)	5(38 %)	
CR2, CR3	5(12 %)	3(15 %)	1(14 %)	1(7 %)	
Non CR	12(30 %)	2(10 %)	3(42 %)	7(53 %)	
Time from diagnosis to transplantation, months, median (range)	7.5(3–43)	8(3–29)	10(7–43)	6(3–15)	0.11
Year of transplantation, number (%)					<0.01
1990–2000	16(40 %)	2(10 %)	4(57 %)	10(76 %)	
2001–2012	24(60 %)	18(90 %)	3(42 %)	3(23 %)	
Conditioning regimen, number (%)					<0.01
TBI12Gy+Ara-C+CY	13(32 %)	11(55 %)	2(28 %)	0	
TBI12Gy+VP-16+CY	5(12 %)	2(10 %)	2(28 %)	1(7 %)	
TBI12Gy+CY	14(35 %)	7(35 %)	3(42 %)	4(30 %)	
TBI12Gy+VP-16	7(17 %)	0	0	7(53 %)	
Busulfan-based regimen	1(2 %)	0	0	1(7 %)	
GVHD prophylaxis, number (%)					0.03
CyclosporineA+Methotrexate	35(87 %)	18(90 %)	4(57 %)	13(100 %)	
CyclosporineA+Prednisone	1(2 %)	1(5 %)	0	0	
CyclosporineA	2(5 %)	1(5 %)	1(14 %)	0	
Tacrolimus+Methotrexate	2(5 %)	0	2(28 %)	0	
Number of nucleated cells,$\times 10^7$/kg, median (range)	-	2.96(1.74–5.69)	28.5(3.50–52.0)	36.7(3.25–57.0)¶	<0.01
Number of $CD34^+$cells,$\times 10^5$/kg, median (range)	-	1.05(0.32–3.15)	-	25.4¶	-
HLA disparities†, number (%)					<0.01
0	16(40 %)	0	7(100 %)	9(69 %)	
1	6(15 %)	4(20 %)	0	2(15 %)	
2	18(45 %)	16(80 %)	0	2(15 %)	
ABO incompatibility, number (%)					0.75
Match	21(52 %)	9(45 %)	5(71 %)	7(53 %)	
Major mismatch	9(22 %)	5(25 %)	0	4(30 %)	
Minor mismatch	5(12 %)	3(15 %)	1(14 %)	1(7 %)	
Bidirectional mismatch	5(12 %)	3(15 %)	1(14 %)	1(7 %)	

Table 1 (continued)

	Total	CBT	uBMT	rBMT/PBSCT	*P*
Follow-up for survivors, months, median (range)	69.5(15–213)	60.5 (15–121)	67(36–213)	179 (135–189)	0.04
Neutrophil engraftment ‡, days, median (range)	16.5(11–65)	21(17–65)	15(11–21)	16(11–18)	<0.01
Platelet engraftment §, days, median (range)	20.5(14–65)	41.5(29–65)	20.5(15–37)	20(14–35)	<0.01
Grades III–IV acute GVHD at 100 days	15(6–27)	5(0–21)	28(3–63)	23(5–48)	0.22
Extensive chronic GVHD at 3 years	26(12–42)	11(1–31)	28(2–64)	50(10–80)	0.07
TKI administration after transplantation, number (%)					0.06
No	28(70 %)	11(55 %)	7(100 %)	10(76 %)	
Yes	12(30 %)	9(45 %)	0	3(23 %)	

CMV indicates cytomegalovirus; WBC, white blood cell; TKI, tyrosine kinase inhibitor; MRD, minimum residual disease; CR, complete remission; TBI, total body irradiation; Ara-C, cytosine arabinoside; CY, cyclophosphamide; VP-16, etoposide; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; CBT, cord blood transplantation; uBMT, unrelated bone marrow transplantation; rBMT/PBSCT, related bone marrow transplantation/ peripheral blood stem cell transplantation.

*MRD status at transplantation was measured by qualitative or quantitative polymerase chain reaction of BCR-ABL transcripts in CR patients.

† The number of HLA disparities defined as low resolution for HLA-A, -B, and -DR.

‡ Neutrophil engraftment was defined as being achieved on the first of three consecutive days during which the absolute neutrophil count was at least 0.5×10^9/L.

§ Platelet engraftment was defined as being achieved on the first of three consecutive days when the platelet count was higher than 20×10^9/L without transfusion support.

¶ The median number of nucleated cells and CD34+ cells was for 12 BMT and 1 PBSCT recipients, respectively.

Engraftment and GVHD

Although primary graft failure occurred in 1 CBT recipient, the patient has been in CR following a second CBT after the confirmation of engraftment failure. As expected, neutrophil recovery was significantly delayed after CBT as compared with uBMT or rBMT/PBSCT. Median times to neutrophil recovery were 21 days (range, 17 to 65 days) after CBT, as compared with 15 days (range, 11 to 21 days) after uBMT (P=0.01) or 16 days (range, 11 to 18 days) after rBMT/PBSCT (P<0.01). Platelet recovery was also significantly delayed after CBT as compared with uBMT or rBMT/PBSCT. Median times to platelet recovery were 41.5 days (range, 29 to 65 days) after CBT, as compared with 20.5 days (range, 15 to 37 days) after uBMT (P<0.01) or 20 days (range, 14 to 35 days) after rBMT/ PBSCT (P<0.01). The cumulative incidences of grades III–IV acute GVHD and extensive chronic GVHD were lower after CBT, as compared with uBMT or rBMT/PBSCT, but the differences were not significant.

Survival and relapse

At a median follow-up for survivors of 69.5 months (range, 15 months to 213 months) in the entire cohort, the probability of OS at five years was 52.9 % (95 % confidence interval [CI], 35.7 % to 67.5 %). The cumulative incidence of relapse at five years was 43.2 % (95 % CI, 27.2 % to 58.2 %). The cumulative incidence of TRM at 100 days and at one year was 2.5 % (95 % CI, 0.2 % to 11.4 %) and 5.0 % (95 % CI, 0.9 % to 15.0 %), respectively. Advanced disease status at transplantation (hazard ratio [HR], 7.07; 95 % CI, 2.07–24.14; P<0.01) was the only significant factor associated with a higher overall mortality in multivariate analysis. Regarding graft source, multivariate analysis showed no significant difference of overall mortality between rBMT/PBSCT and uBMT (HR, 0.45; 95 % CI, 0.10 to 1.87; P=0.27), or CBT (HR, 2.23; 95 % CI, 0.55 to 9.09; P= 0.26) (Table 2). After adjusting for disease status at transplantation, the probabilities of overall survival at five years were 62.0 % (95 % CI, 41.2 % to 93.2 %) for recipients of CBT, 73.8 % (95 % CI, 50.4 to 100 %) for recipients of uBMT, and 48.5 % (95 % CI, 26.4 % to 88.9 %) for recipients of rBMT/PBSCT (Fig. 1). Non-use of TKI before transplantation (HR, 6.23; 95 % CI, 1.35 to 28.67; P=0.01) and advanced disease status at transplantation (HR, 3.83; 95 % CI, 1.01–14.49; P=0.04) were associated with a higher incidence of relapse in multivariate analysis. Regarding graft source, multivariate analysis showed no significant difference between rBMT/PBSCT and uBMT (HR, 0.82; 95 % CI, 0.20 to 3.27; P=0.79), or CBT (HR, 1.07; 95 % CI, 0.31 to 3.72; P=0.91) (Table 2).

TKI administration after transplantation

Twelve patients received TKI after transplantation because of hematological relapse (n=5), molecular detection of BCR-ABL transcripts by polymerase chain reaction (n=4), and maintenance therapy (n=3). The median time from transplantation to TKI administration was 124 days (range, 63 to 245 days). The median