Table 4. Multivariate analyses of grade 2 to 4/grade 3 to 4 acute graft-*versus*-host disease, and chronic/extensive-type chronic graft-*versus*-host disease.

	Grade 2 to 4 acute GVHD				Grade 3 to 4 acute GVHD				Chronic GVHD				Extensive-type chronic GVHD			
Outcome	N.	RR	95%CI	P	RR	95%CI	P	N.	RR	95%CI	P	RR	95%CI	P		
Children 15 years or younger																
HLA disparity																
Matched (6/6)	72	1.00			1.00			67	1.00			1.00				
5/6	196	2.13	(1.28-3.58)	0.004	1.75	(0.73-4.24)	0.212	186	1.79	(0.85-3.75)	0.123	4.15	(0.54-31.81)	0.17		
4/6	136	2.65	(1.55-4.52)	<0.001	2.25	(0.94-5.41)	0.07	114	2.99	(1.42-6.30)	0.004	7.62	(1.03-56.63)	0.047		
3/6	28	2.39	(1.18-4.84)	0.015	2.60	(0.82-8.26)	0.105	23	2.61	(0.96-7.11)	0.061	7.49	(0.81-69.63)	0.077		
Adults 16 years or older																
HLA disparity																
Matched (6/6)	56	1.00			1.00			49	1.00			1.00				
5/6	227	1.03	(0.64-1.65)	0.916	0.95	(0.38-2.37)	0.919	193	1.58	(0.83-3.02)	0.161	1.15	(0.47-2.80)	0.758		
4/6	765	1.27	(0.82-1.97)	0.276	1.27	(0.55-2.94)	0.573	650	1.90	(1.03-3.51)	0.04	1.62	(0.71-3.72)	0.253		
3/6	341	1.72	(1.10-2.70)	0.017	1.13	(0.47-2.68)	0.788	288	1.81	(0.96-3.38)	0.065	1.28	(0.54-3.02)	0.574		

For grade 2 to 4 acute GVHD, other predictive variables were total nucleated cell dose (>10x10^7/kg as the reference, RR=1.94 P=0.009 for 5.0-9.9x10^7/kg, RR=1.73 P=0.028 for 2.5-4.9x10^7/kg, and R=1.68 P=0.094 for <2.5x10^7/kg) in children, and cyclosporine-based GVHD prophylaxis (vs. tacrolimus-based) in adults. For grade 3 to 4 acute GVHD, male sex and advanced disease status in children, and male sex and male to female donor-recipient sex mismatch and reduced-intensity conditioning in adults. For chronic GVHD, no other predictive variables in children, and other predictive variable for adults was ABO major mismatch, and male to female sex mismatch and advanced risk disease status for decreased risk. For extensive-type chronic GVHD, no other predictive variables in children, and other predictive variable for adults was ABO major mismatch.

number of adult recipients. Our findings in children were similar to those in previous reports.[9,17,18,31,32] An increase in the number of HLA mismatches resulted in an increased risk of acute and chronic GVHD, which led to an increased risk of overall and transplant-related mortality. In contrast to the results in children, the probability of overall or relapse-free survival did not decrease with the number of mismatched antigens in adults. An increase in the number of HLA mismatches in UCB increased the incidence of cGVHD in 4/6 CB recipients; however, there was no increase in the risk of grade 2 to 4 or severe acute GVHD, or extensive-type chronic GVHD. These differences may have contributed to the decreased incidence of relapse without affecting TRM after HLA-mismatched UCBT in adults.

A major potential contributor to the different findings in children and adults is the difference in the nucleated cell dose. There was a dramatic difference in the nucleated cell dose between children and adults. TNC dose in adults is highly concentrated in a very small, low-dose area that is quite different from the doses used in children in our study and from the doses in previous reports, mainly in pediatric recipients.[9,18,32] A positive effect on the transplant outcome with a decreased incidence of acute GVHD and lower mortality with HLA matching might only be seen in the setting of pediatric recipients who receive cord blood with a larger cell dose compared to adults. A report from Eurocord of 171 adult recipients of single-unit CBT did not see a decrease in the probability of overall or relapse-free survival with the number of mismatched antigens.[33] A more recent collaborative study by the Center for International Blood and Marrow Transplant Research, the New York Blood Center National Cord Blood Program, and the Eurocord-Netcord registry with 514 adult recipients did not observe an increase in mortality after HLA-mismatched UCBT.[34]

Another potential cause of different findings in children and adults is differences in diagnosis. Adult recipients had a significantly greater proportion of patients with myeloid malignancy. The incidence of a graft-*versus*-leukemia effect is reportedly higher in myeloid malignancy.[35-37] The decreased risk of relapse with a significant graft-*versus*-leukemia effect in HLA-mismatched UCB recipients was also more prominent in adult recipients with acute myeloid leukemia in our study. Furthermore, there were differences in disease risk between children and adults. Only 36% of adults were in a standard-risk disease status at transplant, while this value was 50% in children. Although we had adjusted for the disease status at transplant, we cannot rule out the possibility that these differences influenced the results.

An increase in the total nucleated cell dose increased the neutrophil recovery rate in both children and adults, consistent with other reports.[18,31-35] A lower total nucleated cell dose was not associated with increased transplant-related or overall mortality in our cohort, thus, we did not see a combined effect of HLA disparity and total nucleated cell dose. This differs from the findings of a recent report from New York Cord Blood Bank.[19] In our cohort, a lower cell dose was associated with a slower recovery; however, the differences in the overall incidences of neutrophil recovery between cell dose groups were small, especially in the adult cohort. This may explain our finding that a lower total nucleated cell dose was not associated with increased mortality. Another probable reason for the different findings is that for our analyses we separated children and adults. A small percentage of older adults who received lower cell dose CB included in the subjects of previous studies may have affected increased mortality with lower cell doses. Lastly, TNC dose in adults is highly concentrated in a very small, low-dose area (nearly 70% lie in the range of 2.0-3.0 x 10^7/kg) which is a unique finding for adult recipients of single-unit cord blood in Japan. Therefore, differences in cell doses between the TNC dose groups is quite small, which is suspected to be one of the reasons for these findings. The results of our study support the current recommended cut-off TNC dose for cord blood search in Japan, which is 2.0 x 10^7/kg.

Although information is still limited because of the limited number of 6/6 and 5/6 CB adult recipients, the large number of adult recipients of 4/6 CB enabled us to analyze the association of outcomes with the type of HLA mismatches in this population. There was no effect of HLA mismatch type on overall mortality; therefore, there is no

preference recommendation for HLA mismatch types from our study. The increase in the number of HLA-DRB1 mismatch was associated with decreased mortality; however, it is important to note that HLA-DRB1 double mismatch was associated with increased transplant-related mortality.

This study included a large number of HLA-A, HLA-B, low-resolution and HLA-DRB1 high-resolution typed CB recipients, but there are limitations. UCB selection is mainly influenced by the availability of an acceptable cell dose, but is also influenced by many unmeasured factors that can affect the outcome. Although we adjusted for known risk factors and disparities between groups, we cannot rule out the influence of a potential selection bias. Another limitation involves the results for 3/6. Since, in current practice in Japan, HLA-DR typing for UCB unit selection is performed at low resolution, with a preference of up to two HLAantigen-mismatched UCB units, most (97%) of the HLA-A, HLA-B, low-resolution and HLA-DRB1 high-resolution 3/6 UCB in the present study were selected as one- or two-antigen-mismatched for theHLA-A, HLA-B, and HLA-DR low-resolution level. If we consider the effect of the current practice for UCB unit selection regarding 3/6 UCB, our conclusions should only apply to HLA-A, HLA-B, and HLA-DRB1 or HLA-A, HLA-B, and HLA-DR zero- to two-mismatched UCBT. Furthermore, we may have underestimated the impact of HLA-matching, since we did not have enough data to include low- or high-resolution information on HLA-C matching, which was recently reported to affect mortality.[36]

In conclusion, we found that the effects of HLA disparity on transplant outcome differed between children and adults. In children, an increased number of mismatched HLA loci correlated with an increased risk of mortality. These findings support the selection of a UCB unit with HLA 6/6 followed by 5/6, consistent with the recommendations from the US and Europe. In adults, there was no increase in mortality with an increase in the number of mismatched HLA loci. In this case, a UCB unit with up to 4/6 can be selected if transplant is urgently needed.

Acknowledgments

The authors are grateful for the assistance and co-operation of the staff members of the collaborating institutes of the Japan Society for Hematopoietic Cell Transplantation and the Japan Cord Blood Bank Network.

Funding

This work was supported by a Research Grant for Allergic Disease and Immunology (H23-013), and a Research Grant for Cancer (H23-010) from the Japanese Ministry of Health, Labor, and Welfare.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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Impact of the Direction of HLA Mismatch on Transplantation Outcomes in Single Unrelated Cord Blood Transplantation

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Article history:
Received 22 August 2012
Accepted 22 September 2012

Key Words:
HLA incompatibility
Graft-versus-host direction
Host-versus-graft direction
Overall survival
Nonrelapse mortality

A B S T R A C T

The impact of the direction of HLA mismatch (MM) on outcome in unrelated cord blood (UCB) transplantation has not yet been clarified. We conducted a retrospective study using national registry data on 2977 patients who underwent transplantation using a single UCB for leukemia or myelodysplastic syndrome. HLA matching was assessed by serologic data for HLA-A, -B, and -DR loci. The median age of the recipients at transplantation was 41 years (range, 0-82 years), and 2300 recipients (77%) were age ≥16 years. The 2-year overall survival rate was 0.46. The presence of MM only in the graft-versus-host direction or only in the host-versus-graft direction was not associated with overall mortality (hazard ratio [HR], 0.88; $P = .317$ and HR, 0.95; $P = .670$, respectively) compared with 1 bidirectional MM. This finding was consistent in both the child and adult cohorts. The presence of MM only in the graft-versus-host direction was associated with a lower incidence of nonrelapse mortality (HR, 0.65; $P = .040$), significant only in the child cohort. No MM category was associated with relapse. Our findings suggest that the direction of HLA MM does not have a significant impact on overall survival after UCB transplantation.

INTRODUCTION

Unrelated cord blood (UCB) has emerged as a promising alternative source of hematopoietic stem cells for adult and pediatric allogeneic hematopoietic cell transplantation [1-4], and the use of UCB transplantation (UCBT) has been rapidly increasing, particularly in the United States, Europe, and Japan. One advantage of using UCB as a hematopoietic stem cell source is that UCBT requires less stringent HLA matching compared with bone marrow or peripheral blood stem cell transplantation, making it easier to find candidate UCB units in UCB banks. One or 2 antigen/allele mismatches (MMs) in the HLA-A, -B, and -DR loci between a UCB unit and recipient are acceptable without ex vivo T cell depletion methods, and the clinical outcome of transplantation using a 0-2 antigen/allele-mismatched UCB unit was almost comparable to that from an HLA allele-matched unrelated donor [1-3].

Although the number of HLA MMs between a UCB unit and a recipient is usually counted without considering the MM direction, the effect of the immune reaction caused by HLA MM differs according to whether the MM is in the graft-versus-host (GVH) or host-versus-graft (HVG) direction. A mismatched antigen in the GVH direction can be a major target for donor T cells and can cause graft-versus-host disease (GVHD), whereas a mismatched antigen in the HVG direction can be a major target for the remaining recipient T cells and can lead to graft rejection. In related transplantation, the presence of HLA MMs in the GVH direction is associated with a higher incidence of GVHD, whereas the

Financial disclosure: See Acknowledgments on page 254.
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1083-8791/$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2012.09.017

presence of HLA MMs in the HVG direction is associated with a higher incidence of rejection [5-7]. Therefore, from a biological perspective, the impact of HLA MM should be discussed separately according to the direction of MM. However, because most patients have an equal number of MMs in the GVH and HVG directions (bidirectional MM), studying an adequate number of patients to evaluate an MM imbalance in the GVH and HVG directions has proven difficult.

The few studies that have evaluated the impact of the HLA MM direction on UCBT outcome have reported inconsistent results [8-10]. Matsuno et al. [8] reported that an HLA MM in the GVH direction was associated with lower incidence of neutrophil engraftment. In contrast, Stevens et al. [9] showed that UCBT with an MM only in the GVH direction was associated with a lower incidence of nonrelapse mortality (NRM) and overall mortality compared with UCBT with an 1 bidirectional MM, whereas UCBT with an MM only in the HVG direction was associated with a lower incidence of neutrophil engraftment and a higher incidence of relapse.

To clarify the significance of the direction of HLA MM on transplantation outcomes, we conducted a retrospective study using national registry data in 2977 patients who underwent a single UCBT.

METHODS

Data Collection

Data for 2987 patients with acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), and chronic myelogenous leukemia (CML) who underwent a first transplantation using a single UCB unit between January 1, 1998, and December 31, 2009, were obtained from the Transplant Registry Unified Management Program (TRUMP) [11], in which all UCBTs are registered through the Japan Cord Blood Bank Network (JCBBN), a national network of all 11 cord blood banks in Japan. Ten patients lacking data on survival status or survival date were excluded. A total of 2977 patients met the criteria for study inclusion. The study design was approved by the TRUMP Data Management Committee and the Institutional Review Board of Saitama Medical Center, Jichi Medical University, where this study was organized.

Histocompatibility

Histocompatibility data for the HLA-A, -B, and -DR loci were obtained from reports collected from the institution at which the transplantation was performed or cord blood banks. HLA typing methods have been described previously [12]. To reflect current practice in Japan, HLA matching was assessed by serologic data for HLA-A, -B, and -DR loci. A secondary analysis using antigen level data for HLA-A, -B and available allele level data for HLA-DRB1 was also performed to compare our data with previously published data from the United States and Europe. HLA-DRB1 allele information was available in 84% of patients (2498 of 2977). Among these patients, 62% had the same number of MMs at HLA-DRB1 loci at either the antigen or allele level. An HLA MM in the GVH direction was defined as when the recipient's antigens or alleles were not shared by the donor, and an MM in the HVG direction was defined as when the donor's antigens or alleles were not shared by the recipient.

Endpoints

The primary study endpoint was overall survival (OS). Other endpoints assessed were relapse, NRM, neutrophil and platelet engraftment, grade II-IV or III-IV acute GVHD, and chronic GVHD. Neutrophil recovery was defined as an absolute neutrophil count exceeding 0.5×10^9/L for 3 consecutive days after UCBT. Platelet recovery was defined as an absolute platelet count exceeding 50×10^9/L without platelet transfusion. The physicians who performed transplantation at each center diagnosed and graded acute and chronic GVHD according to traditional criteria [13,14]. The incidence of acute GVHD was evaluated in patients who engrafted, and that of chronic GVHD was evaluated in patients who engrafted and survived for more than 100 days.

Statistical Analysis

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 relapse, NRM, neutrophil and platelet engraftment, and acute and chronic GVHD were estimated based on cumulative incidence curves [15]. Competing events were death without relapse for relapse, relapse for NRM, death without engraftment for neutrophil and platelet engraftment, and death or relapse without GVHD for acute and chronic GVHD. The groups were compared using Gray's test [16]. The Cox proportional hazards model was used to evaluate the effect of confounding variables on OS, and the Fine and Gray proportional hazards model was used for the other endpoints [17]. Based on the report by the Center for International Blood and Marrow Transplant Research, we classified the conditioning regimens as myeloablative if total body irradiation >8 Gy, oral busulfan ≥9 mg/kg, i.v. busulfan ≥7.2 mg/kg, or melphalan >140 mg/m^2 was used in the conditioning regimen; otherwise, the conditioning regimen was classified as reduced intensity [18]. For patients with insufficient data regarding dosages of the agents used in the conditioning regimen, we used the information on conditioning intensity (myeloablative or reduced intensity) reported by the treating clinicians. We defined AML and ALL in first or second remission, CML in first or second chronic phase or accelerated phase, and MDS with refractory anemia or refractory anemia with ringed sideroblasts as standard risk, and all other conditions as high risk.

The following possible confounding variables were considered: recipient age group (0-5 years, 6-15 years, 16-49 years, or ≥50 years at transplantation), matching of ABO blood type between the recipient and UCB (match or major, minor, or bidirectional MM), recipient sex, sex MM between recipient and UCB (match, male donor–female recipient, or female donor–male recipient), disease (AML, ALL, CML, or MDS), disease status before transplantation (standard or high risk), type of conditioning regimen (myeloablative or reduced intensity), type of GVHD prophylaxis (calcineurin inhibitor plus methotrexate, calcineurin inhibitor only, others), and year of transplantation (1998-2004 or 2005-2009). Factors other than HLA MM and total nucleated cell (TNC) dose category were selected in a stepwise manner from the model with a variable retention criterion of $P < .05$. HLA MM and TNC dose category (≥10.0, 5.0-9.9, 2.5-4.9, 2.0-2.4, and $<2.0 \times 10^7$/kg) were then added to the final model. All tests were 2-sided, and a P value <.05 was considered statistically significant. All statistical analyses were performed with Stata version 12 (StataCorp, College Station, TX) and 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) [19]. More precisely, EZR is a modified version of R commander (version 1.6-3) designed to add statistical functions used frequently used in biostatistics.

RESULTS

Patient Characteristics

Table 1 summarizes patient and transplant characteristics. The median age of the recipients at transplantation was 41 years (range, 0-82 years), and 2300 patients (77%) were age ≥16 years. Diagnoses for transplantation were AML in 1606 patients, ALL in 893, CML in 135, and MDS in 343. Half of the patients had standard-risk disease. UCBT was performed between 1998 and 2004 in 1153 patients (39%) and between 2005 and 2009 in 1824 patients (61%). The combination of a calcineurin inhibitor (tacrolimus or cyclosporine) and methotrexate was used in 62% of patients, whereas a calcineurin inhibitor alone was used in 22% of patients.

Some 40% of patients received a UCB unit containing $<2.5 \times 10^7$/kg TNCs, and 45% received a UCB unit containing $2.5\text{-}4.9 \times 10^7$/kg TNCs. Roughly 12% of patients received $\geq 5.0 \times 10^7$/kg TNCs, but 93% of these patients were age <16 years. Median body weight was 17 kg (range, 4-68 kg) for the children and 55 kg (range, 24-165 kg) for the adults. HLA MM was categorized as follows: HLA match in both the GVH and HVG directions (GVH 0/HVG 0 MM group; n = 273 [9%]), 1-2 antigen MMs in the GVH direction but 0 MMs in the HVG direction (GVH 1-2/HVG 0 MM group; n = 150 [5%]), 1-2 antigen MMs in the HVG direction but 0 MM in the GVH direction (GVH 0/HVG 1-2 MM group; n = 136 [5%]), 1 antigen MM in both the GVH and HVG directions at the same locus (GVH 1/HVG 1 MM group; n = 716 [24%]), 2 antigen MMs in both the GVH and HVG directions (GVH 2/HVG 2 MM group; n = 1170 [39%]), 2 antigen MMs in the GVH direction and 1 antigen MM in the HVG direction (GVH 2/HVG 1 MM group; n = 231 [8%]), 1 antigen MM in the GVH direction and

Table 1
Patient Characteristics

Characteristic	Total	Children (0-15 Years)	Adults (16+ Years)
Recipient age at UCBT, years, median (range)	41 (0-82)	5 (0-15)	49 (16-82)
Recipient age at UCBT, years, n (%)			
0-9	511 (17)	511 (75)	0 (0)
10-19	272 (9)	166 (25)	106 (5)
20-29	287 (10)	0 (0)	287 (12)
30-39	371 (12)	0 (0)	371 (16)
40-49	422 (14)	0 (0)	422 (18)
50-59	625 (21)	0 (0)	625 (27)
≥60	489 (16)	0 (0)	489 (21)
ABO matching, n (%)			
Match	994 (33)	248 (37)	746 (32)
Minor	815 (27)	174 (26)	641 (28)
Major	704 (24)	149 (22)	555 (24)
Bidirectional	458 (15)	104 (15)	354 (15)
Missing	6 (0)	2 (0)	4 (0)
Recipient sex, n (%)			
Female	1316 (44)	305 (45)	1011 (44)
Male	1661 (56)	372 (55)	1289 (56)
Donor–recipient sex match, n (%)			
Match	1157 (39)	290 (43)	867 (38)
Male donor and female recipient	635 (21)	153 (23)	482 (21)
Female donor and male recipient	768 (26)	172 (25)	596 (26)
Missing	417 (14)	62 (9)	355 (15)
Diagnosis, n (%)			
AML	1606 (54)	234 (35)	1372 (60)
ALL	893 (30)	391 (58)	502 (22)
CML	135 (5)	11 (2)	124 (5)
MDS	343 (12)	41 (6)	302 (13)
Disease risk at UCBT, n (%)			
Standard risk	1385 (47)	423 (62)	962 (42)
High risk	1450 (49)	226 (33)	1224 (53)
Missing	142 (5)	28 (4)	114 (5)
Conditioning regimen, n (%)			
Myeloablative	1980 (67)	585 (86)	1395 (61)
Reduced intensity	986 (33)	86 (13)	900 (39)
Missing	11 (0)	6 (1)	5 (0)
In vivo T cell depletion (ATG or alemtuzumab), n (%)			
No	2935 (99)	665 (98)	2270 (99)
Yes	42 (1)	12 (2)	30 (1)
GVHD prophylaxis, n (%)			
CSA only	250 (8)	59 (9)	191 (8)
TAC only	407 (14)	27 (4)	380 (17)
CSA + MTX	1105 (37)	209 (31)	896 (39)
TAC + MTX	755 (25)	241 (36)	514 (22)
CSA + MMF	104 (3)	0 (0)	104 (5)
TAC + MMF	148 (5)	6 (1)	142 (6)
CSA + corticosteroid	87 (3)	67 (10)	20 (1)
TAC + corticosteroid	34 (1)	26 (4)	8 (0)
Other	66 (2)	33 (5)	33 (1)
Missing	21 (1)	9 (1)	12 (1)
Year of UCBT, n (%)			
1998-2004	1153 (39)	389 (57)	764 (33)
2005-2009	1824 (61)	288 (43)	1536 (67)
TNC dose when frozen, n (%)			
$\geq 10.0 \times 10^7$/kg	99 (3)	99 (15)	0 (0)
$5.0\text{-}9.9 \times 10^7$/kg	259 (9)	234 (35)	25 (1)
$2.5\text{-}4.9 \times 10^7$/kg	1344 (45)	268 (40)	1076 (47)
$2.0\text{-}2.4 \times 10^7$/kg	924 (31)	44 (6)	880 (38)
$<2.0 \times 10^7$/kg	275 (9)	21 (3)	254 (11)
Missing	76 (3)	11 (2)	65 (3)
Weight, kg, median (range)	52 (4-165)	17 (4-68)	55 (24-165)
HLA MM			
0 MM	273 (9)	144 (21)	129 (6)
1-2 MM/GVH only	150 (5)	45 (7)	105 (5)
1-2 MM/rejection only	136 (5)	39 (6)	97 (4)
1 bidirectional MM	716 (24)	314 (46)	402 (17)
2 bidirectional MM	1170 (39)	98 (14)	1072 (47)
2 MM: bidirectional + GVHD	231 (8)	16 (2)	215 (9)
2 MM: bidirectional + rejection	264 (9)	19 (3)	245 (11)
2 MM: GVHD + rejection	37 (1)	2 (0)	35 (2)

ATG indicates antithymocyte globulin; CSA, cyclosporine; MMF, mycophenolate mofetil; MTX, methotrexate; TAC, tacrolimus; 0 MM, HLA match in both the GVH and HVG directions; 1-2 MM/GVH only, antigen MMs in the GVH direction and 0 MMs in the HVG direction; 1-2 MM/rejection only, 1 or 2 antigen MMs in the HVG direction and no MMs in the GVH direction; 1 bidirectional MM, 1 antigen MM in both the GVH and HVG directions at the same locus; 2 bidirectional MM, 2 antigen MMs in both the GVH and HVG directions; 2 MM: bidirectional + GVHD, 2 antigen MMs in the GVH direction and 1 antigen MM in the HVG direction; 2 MM: bidirectional + rejection, 1 antigen MM in the GVH direction and 2 antigen MMs in the HVG direction; 2 MM: GVHD + rejection, 1 antigen MM in the GVH direction at one locus and 1 antigen MM in the HVG direction at another locus.

2 antigen MMs in the HVG direction (GVH 1/HVG 2 MM group; n = 264 [9%]), and 1 antigen MM in the GVH direction at 1 locus and 1 antigen MM in the HVG direction at another locus (GVH 1/HVG 1 2-antigen MM group; n = 37 [1%]).

OS, Relapse, and NRM

The median follow-up period in survivors was 2.2 years (range, 0.0-11.1 years). The 2-year OS rate was 0.46 (95% confidence interval [CI], 0.44-0.48) (Figure 1). To clarify the impact of HLA MM in each vector, the GVH 1/HVG 1 MM group was considered the reference group in the multivariate analyses, in accordance with the approach of Stevens et al. [9], and the following hazard ratios (HRs) were adjusted for the other significant variables, including TNC dose category. The GVH 1-2/HVG 0 MM (HR, 0.88; 95% CI, 0.69-1.13; $P = .317$), the GVH 0/HVG 1-2 MM (HR, 0.95; 95% CI, 0.74-1.22; $P = .670$), and other groups were not associated with overall mortality compared with the GVH 1/HVG 1 MM group (Table 2 and Figure 1). The GVH 0/HVG 0 MM group

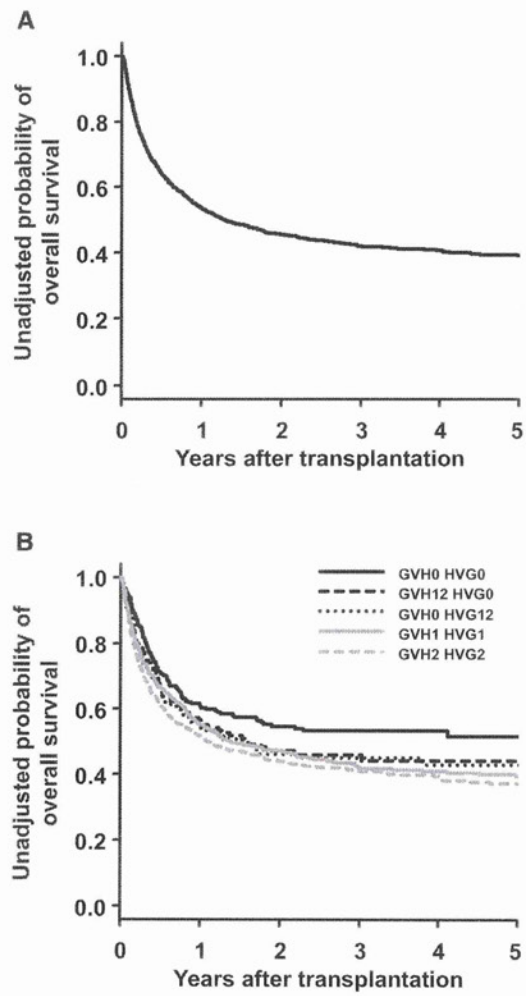

Figure 1. OS of total patients (A) and patients grouped according to HLA MM category (B). GVH0 HVG0, HLA match in both the GVH and HVG directions; GVH12 HVG0, antigen MMs in the GVH direction and 0 MMs in the HVG direction; GVH0 HVG12, 1 or 2 antigen MMs in the HVG direction and 0 MM in the GVH direction; GVH1 HVG1, 1 antigen MM in both the GVH and HVG directions at the same locus; GVH2 HVG2, 2 antigen MMs in both the GVH and HVG directions.

Table 2
Overall Mortality

HLA MM Category	Total*			Child			Adult		
	Number	HR 95% CI	*P* Value	Number	HR 95% CI	*P* Value	Number	HR 95% CI	*P* Value
0 MM	273	0.79 (0.64-0.97)	.025	144	0.74 (0.53-1.04)	.079	129	0.82 (0.63-1.06)	.134
1-2 MM/GVH only	150	0.88 (0.69-1.13)	.317	45	0.73 (0.44-1.20)	.208	105	0.92 (0.69-1.22)	.560
1-2 MM/rejection only	136	0.95 (0.74-1.22)	.670	39	0.85 (0.49-1.46)	.557	97	0.96 (0.72-1.29)	.796
1 bidirectional MM	716	1.00	Reference	314	1.00	Reference	402	1.00	Reference
2 bidirectional MM	1170	0.90 (0.79-1.03)	.122	98	0.88 (0.61-1.26)	.480	1072	0.89 (0.76-1.03)	.118
2 MM: bidirectional + GVHD	231	0.97 (0.79-1.18)	.737	16	1.10 (0.55-2.20)	.785	215	0.94 (0.76-1.17)	.594
2 MM: bidirectional + rejection	264	0.93 (0.77-1.13)	.481	19	2.08 (1.19-3.63)	.011	245	0.87 (0.71-1.08)	.208
2 MM: GVHD + rejection	37	0.55 (0.35-0.87)	.012	2			35	0.54 (0.33-0.87)	.012

* Other significant variables were recipient age group, 0-5 years (reference, 1.00), 6-15 years (HR, 0.93; 95% CI, 0.69-1.24; $P = .603$), 16-49 years (HR, 1.32; 95% CI, 1.00-1.75; $P = .053$), ≥50 years (HR, 1.96; 95% CI, 1.48-2.60; $P < .001$); recipient sex, female (reference, 1.00), male (HR, 1.16; 95% CI, 1.05-1.28; $P = .005$); disease risk, standard risk (reference, 1.00), high risk (HR, 2.42; 95% CI, 2.16-2.71; $P < .001$); GVHD prophylaxis, CSA/TAC + MTX (reference, 1.00), CSA/TAC only (HR, 1.30; 95% CI, 1.15-1.46; $P < .001$), others (HR, 1.13; 95% CI, 0.98-1.31; $P = .091$), year of transplantation, 1998-2004 (reference, 1.00), 2005-2009 (HR, 0.83; 95% CI, 0.75-0.93; $P = .001$).

was associated with lower overall mortality compared with the GVH 1/HVG 1 MM group (HR, 0.79; 95% CI, 0.64-0.97; $P = .025$); however, in both the child and adult cohorts, the association was not significant, owing in part to a lack of statistical power. The GVH 1/HVG 1 2-antigen MM group, which was represented mostly in the adult cohort, was associated with lower overall mortality compared with the GVH 1/HVG 1 MM group (HR, 0.55; 95% CI, 0.35-0.87; $P = .012$).

We performed an additional analysis according to the HLA matching criteria used in the United States and Europe (HLA-A and -B for antigen level and -DRB1 for allele level) (Supplemental Table 1). Consistent with the result obtained using our criteria (HLA-A, -B, and -DR for antigen level), there were no differences in the impact of the MM direction (GVH or HVG) on OS. The difference in OS between the GVH 0/HVG 0 MM and GVH 1/HVG 1 MM groups was not significant in this analysis.

The cumulative incidence rates of relapse and NRM at 2 years were 0.34 (95% CI, 0.32-0.36) and 0.26 (95% CI, 0.24-0.27), respectively. There was no difference in the incidence of relapse between the GVH 1/HVG 1 MM and any other MM group (Table 3 and Figure 2). The GVH 1-2/HVG 0 MM group was significantly associated with lower NRM compared with the GVH 1/HVG 1 MM group (HR, 0.65; 95% CI, 0.44-0.98; $P = .040$) (Table 3 and Figure 2), but only in the child cohort (child, $P = .048$; adult, $P = .215$).

Because our cohorts were mainly adults, and most adults received a TNC dose of 2.0-4.9 $\times$ 10^7/kg, we performed an additional analysis in the subset of adults who received a TNC dose of 2.0-2.4 $\times$ 10^7/kg or 2.5-4.9 $\times$ 10^7/kg (Supplemental Table 2). In the subset of adults who received a TNC dose of 2.0-2.4 $\times$ 10^7/kg, compared with the GVH 1/HVG 1 MM group, the GVH 0/HVG 0 MM group was associated with lower overall mortality ($P = .027$) and NRM ($P = .007$) and a higher incidence of relapse ($P = .028$), and the GVH 2/HVG 2 MM group was associated with lower overall mortality ($P = .001$) and NRM ($P = .008$). The GVH 1-2/HVG 0 MM group was significantly associated with lower NRM compared with the GVH 1/HVG 1 MM group ($P = .033$). In the subset of adults who received a TNC dose of 2.5-4.9 $\times$ 10^7/kg, no HLA MM group was associated with overall mortality, relapse, or NRM, except for lower overall mortality in the GVH 1/HVG 1 2-antigen MM group compared with the GVH 1/HVG 1 MM group ($P = .046$).

Neutrophil and Platelet Engraftment

The cumulative incidence rates of neutrophil and platelet engraftment in our study cohort were 0.76 (95% CI, 0.74-0.77) and 0.57 (95% CI, 0.55-0.59), respectively. The GVH 1-2/HVG 0 MM group was marginally associated with better neutrophil and platelet engraftment kinetics compared with the GVH 1/HVG 1 MM group (neutrophil engraftment: HR, 1.18; 95% CI, 0.98-1.42; $P = .081$; platelet engraftment: HR, 1.23; 95% CI, 1.00-1.51; $P = .053$) (Table 4 and Figure 3). The impact on neutrophil engraftment was significant only in the adult cohort (child, $P = .496$; adult, $P = .045$).

Acute and Chronic GVHD

In all engrafted patients, the cumulative incidence rates of grade II-IV and III-IV acute GVHD were 0.45 (95% CI, 0.43-0.47) and 0.15 (95% CI, 0.14-0.17), respectively. The GVH 0/HVG 0 MM group was significantly associated with a lower incidence of grade II-IV acute GVHD compared with the GVH 1/HVG 1 MM group (HR, 0.70; 95% CI, 0.54-0.90; $P = .006$) (Supplemental Table 3 and Figure 4), but only in the child cohort (child, $P = .002$; adult, $P = .506$). The GVH 0/HVG 0 MM group was marginally associated with a lower incidence of chronic GVHD compared with the GVH 1/HVG 1 MM group (HR, 0.72; 95% CI, 0.51-1.00; $P = .050$).

DISCUSSION

This nationwide retrospective study that included a large number of both pediatric and adult patients allowed us to consider an adequate number of patients who underwent UCBT with an HLA MM only in the GVH direction or only in the HVG direction, and to analyze the impact of an MM in the GVH or HVG direction on clinical outcomes after a single UCBT. Neither the GVH 1-2/HVG 0 MM group nor the GVH 0/HVG 1-2 MM group was associated with overall mortality compared with the GVH 1/HVG 1 MM group. The point estimates of HRs of the GVH 1-2/HVG 0 MM and GVH 0/HVG 1-2 MM groups compared with the GVH 1/HVG 1 MM group were similar and both <1 (HR, 0.88 and 0.95, respectively), suggesting that HLA MMs in the GVH and HVG directions post-UCBT do not have different effects on OS. This finding does not support the conclusion of Stevens et al. [9], who recommended using UCB units with an HLA MM only in the GVH direction and avoiding units with an HLA MM only in the HVG direction.

Table 3
Relapse and NRM

HLA MM category	Relapse*			NRM†		
	Number	HR 95% CI	*P* Value	Number	HR 95% CI	*P* Value
0 MM	258	1.07 (0.84-1.37)	.560	258	0.74 (0.53-1.02)	.063
1-2 MM/GVH only	147	1.20 (0.90-1.59)	.215	147	0.65 (0.44-0.98)	.040
1-2 MM/rejection only	131	1.18 (0.84-1.64)	.338	131	0.81 (0.55-1.19)	.292
1 bidirectional MM	667	1.00	Reference	667	1.00	Reference
2 bidirectional MM	1106	0.99 (0.83-1.19)	.930	1106	0.88 (0.72-1.07)	.191
2 MM: bidirectional + GVHD	217	1.00 (0.76-1.33)	.979	217	0.81 (0.60-1.10)	.184
2 MM: bidirectional + rejection	243	1.27 (0.99-1.63)	.060	243	0.66 (0.49-0.91)	.010
2 MM: GVHD + rejection	36	0.64 (0.32-1.24)	.184	36	0.61 (0.32-1.16)	.131

* Other significant variables were recipient age group, 0-5 years (reference, 1.00), 6-15 years (HR, 0.61; 95% CI, 0.44-0.84; $P = .002$), 16-49 years (HR, 0.71; 95% CI, 0.52-0.97; $P = .030$), ≥50 years (HR, 0.72; 95% CI, 0.52-0.98; $P = .040$); diagnosis, AML (reference, 1.00), ALL (HR, 1.11, 95% CI, 0.94-1.30, $P = .210$), CML (HR, 1.33, 95% CI, 0.99-1.79, $P = .059$), MDS (HR, 0.67, 95% CI, 0.51-0.87, $P = .003$); disease risk, standard risk (reference, 1.00), high risk (HR, 2.93; 95% CI, 2.54-3.39; $P < .001$); GVHD prophylaxis, CSA/TAC + MTX (reference, 1.00), CSA/TAC only (HR, 0.72; 95% CI, 0.61-0.86; $P < .001$), others (HR, 0.87; 95% CI, 0.71-1.05; $P = .145$).

† Other significant variables were recipient age group, 0-5 years (reference, 1.00), 6-15 years (HR, 1.44; 95% CI, 0.90-2.30; $P = .128$), 16-49 years (HR, 2.04; 95% CI, 1.29-3.22; $P = .002$), ≥50 years (HR, 3.52; 95% CI, 2.24-5.52; $P < .001$); GVHD prophylaxis, CSA/TAC + MTX (reference, 1.00), CSA/TAC only (HR, 1.90; 95% CI, 1.60-2.26; $P < .001$), others (HR, 1.42; 95% CI, 1.14-1.75; $P = .001$), year of transplantation, 1998–2004 (reference, 1.00), 2005-2009 (HR, 0.71; 95% CI, 0.61-0.83; $P < .001$).

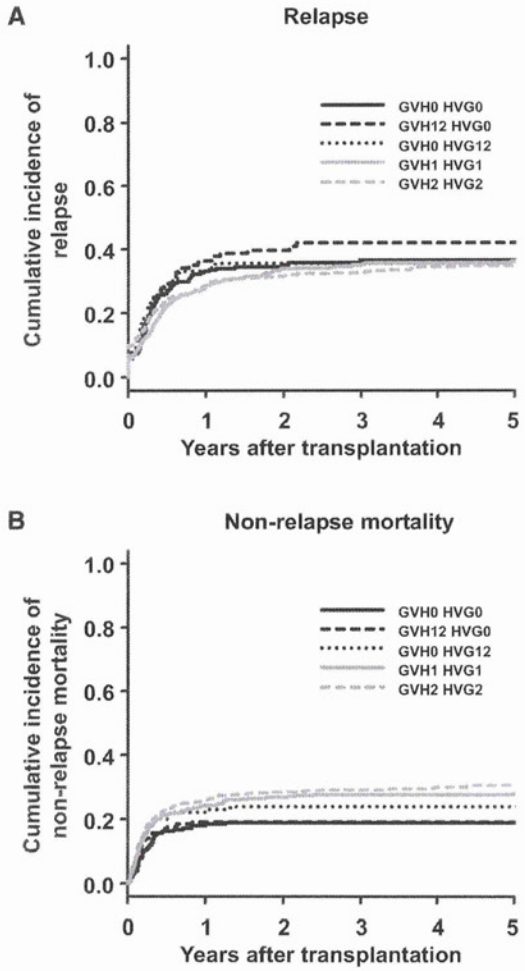

Figure 2. Relapse and NRM.

Several differences in patient background between the study of Stevens et al. [9] and the present study warrant clarification. The first difference is in the age distribution of patients. Stevens et al.'s series included 907 pediatric patients age <16 years and 295 adult patients; in contrast, our series included 677 pediatric patients and 2300 adult patients, which can provide useful information for both pediatric and adult transplant physicians. Since the cell doses of UCB units in child and adult cohorts are significantly different, which may affect the impact of HLA MM, we performed stratified analyses in the child and adult cohorts. Our results consistently showed that the direction of MM had no apparent impact on overall mortality in either cohort. Consistent with the results of Stevens et al. [9], the GVH 1-2/HVG 0 MM group was associated with lower NRM in the child cohort, but this advantage was offset by a higher incidence of relapse in this cohort. A second difference between the 2 studies is in conditioning regimens. A myeloablative regimen was used in 92% of the patients in the Stevens et al. study, compared with 67% in our study. Consequently, we performed a separate analysis in the patients who received a myeloablative regimen and confirmed that the direction of MM had no apparent impact on overall mortality (data not shown).

The third difference between the 2 studies relates to GVHD prophylaxis. Cyclosporine and steroids were used as GVHD prophylaxis in 62% of the patients in the Stevens et al. study, but in only 3% of the patients (10% of the child cohort) in our study, which might have affected outcomes. The fourth difference is in the number of patients with an HLA MM only in the GVH direction or only in the HVG direction. The Stevens et al. study included 35 patients with a GVH 1-2/HVG 0 MM and 22 patients with a GVH 0/HVG 1-2 MM in the overall mortality analysis, compared with 150 and 136 patients, respectively, in our study. Finally, the level of HLA typing used to determine the number of HLA MMs differed between the 2 studies. In the present study, MMs in HLA-DR loci were counted at the antigen level in accordance with current practice in Japan, whereas Stevens et al. counted HLA-DRB1 MMs at the allele level. Consequently, we performed an additional analysis using the same HLA matching criteria as in previous studies from the United States and Europe (HLA-A and -B for antigen level and -DRB1 for allele level), and reached a similar conclusion that an MM only in the GVH or only in the HVG direction had no impact on overall mortality.

Table 4
Neutrophil and Platelet Engraftment

HLA MM Category	Neutrophil Engraftment*			Platelet Engraftment†		
	Number	HR 95% CI	*P* Value	Number	HR 95% CI	*P* Value
0 MM	272	1.03 (0.88-1.20)	.718	272	1.06 (0.88-1.27)	.559
1-2 MM/GVH only	149	1.18 (0.98-1.42)	.081	149	1.23 (1.00-1.51)	.053
1-2 MM/rejection only	136	1.01 (0.82-1.26)	.899	136	0.84 (0.66-1.07)	.164
1 bidirectional MM	716	1.00	Reference	714	1.00	Reference
2 bidirectional MM	1167	0.98 (0.87-1.09)	.672	1166	0.96 (0.85-1.10)	.590
2 MM: bidirectional + GVHD	231	0.91 (0.76-1.08)	.278	230	0.91 (0.74-1.13)	.406
2 MM: bidirectional + rejection	264	0.86 (0.72-1.02)	.089	264	0.98 (0.80-1.19)	.816
2 MM: GVHD + rejection	37	1.40 (1.03-1.89)	.030	37	2.21 (1.46-3.33)	<.001

* Other significant variables were TNC category, 2.5-4.9 × 10^7/kg (reference, 1.00), ≥10.0 × 10^7/kg (HR, 1.76; 95% CI, 1.33-2.33; $P < .001$), 5.0-9.9 × 10^7/kg (HR, 1.26; 95% CI, 1.05-1.52; $P = .015$), 2.0-2.4 × 10^7/kg (HR, 0.87; 95% CI, 0.79-0.95; $P = .003$), <2.0 × 10^7/kg (HR, 0.82; 95% CI, 0.71-0.95; $P = .007$); diagnosis, AML (reference, 1.00), ALL (HR, 1.11, 95% CI, 1.00-1.22, $P = .040$), CML (HR, 0.87, 95% CI, 0.73-1.04, $P = .124$), MDS (HR, 0.88, 95% CI, 0.75-1.04, $P = .129$); disease risk, standard risk (reference, 1.00), high risk (HR, 0.74; 95% CI, 0.67-0.80; $P < .001$); GVHD prophylaxis, CSA/TAC + MTX (reference, 1.00), CSA/TAC only (HR, 1.16; 95% CI, 1.04-1.30; $P = .010$), others (HR, 1.09; 95% CI, 0.96-1.23; $P = .169$), year of transplantation, 1998-2004 (reference, 1.00), 2005-2009 (HR, 1.21; 95% CI, 1.11-1.33; $P < .001$).

† Other significant variables were TNC category, 2.5-4.9 × 10^7/kg (reference, 1.00), ≥10.0 × 10^7/kg (HR, 1.49; 95% CI, 1.09-2.03; $P = .013$), 5.0-9.9 × 10^7/kg (HR, 1.26; 95% CI, 1.01-1.57; $P = .040$), 2.0-2.4 × 10^7/kg (HR, 0.95; 95% CI, 0.84-1.06; $P = .365$), <2.0 × 10^7/kg (HR, 0.81; 95% CI, 0.67-0.97; $P = .022$); recipient age group, 0-5 years (reference, 1.00), 6-15 years (HR, 1.00; 95% CI, 0.79-1.25; $P = .971$), 16-49 years (HR, 0.99; 95% CI, 0.77-1.26; $P = .909$), ≥50 years (HR, 0.70; 95% CI, 0.55-0.90; $P = .006$); recipient sex, female (reference, 1.00), male (HR, 0.90; 95% CI, 0.82-0.99; $P = .034$); disease risk, standard risk (reference, 1.00), high risk (HR, 0.58; 95% CI, 0.53-0.64; $P < .001$); GVHD prophylaxis, CSA/TAC + MTX (reference, 1.00), CSA/TAC only (HR, 0.81; 95% CI, 0.71-0.91; $P = .001$), others (HR, 0.88; 95% CI, 0.76-1.01; $P = .074$), and year of transplantation, 1998-2004 (reference, 1.00), 2005-2009 (HR, 1.26; 95% CI, 1.14-1.40; $P < .001$).

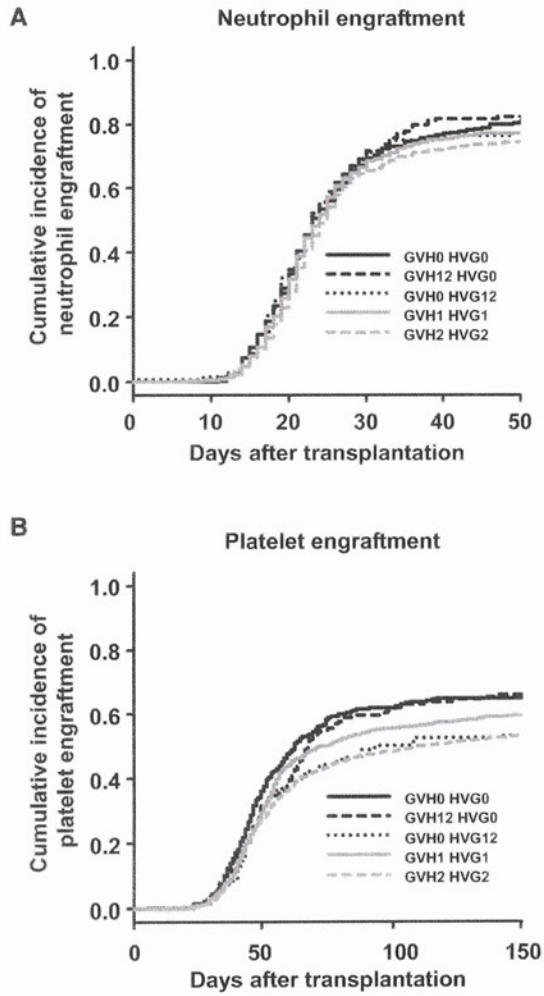

Figure 3. Neutrophil and platelet engraftment.

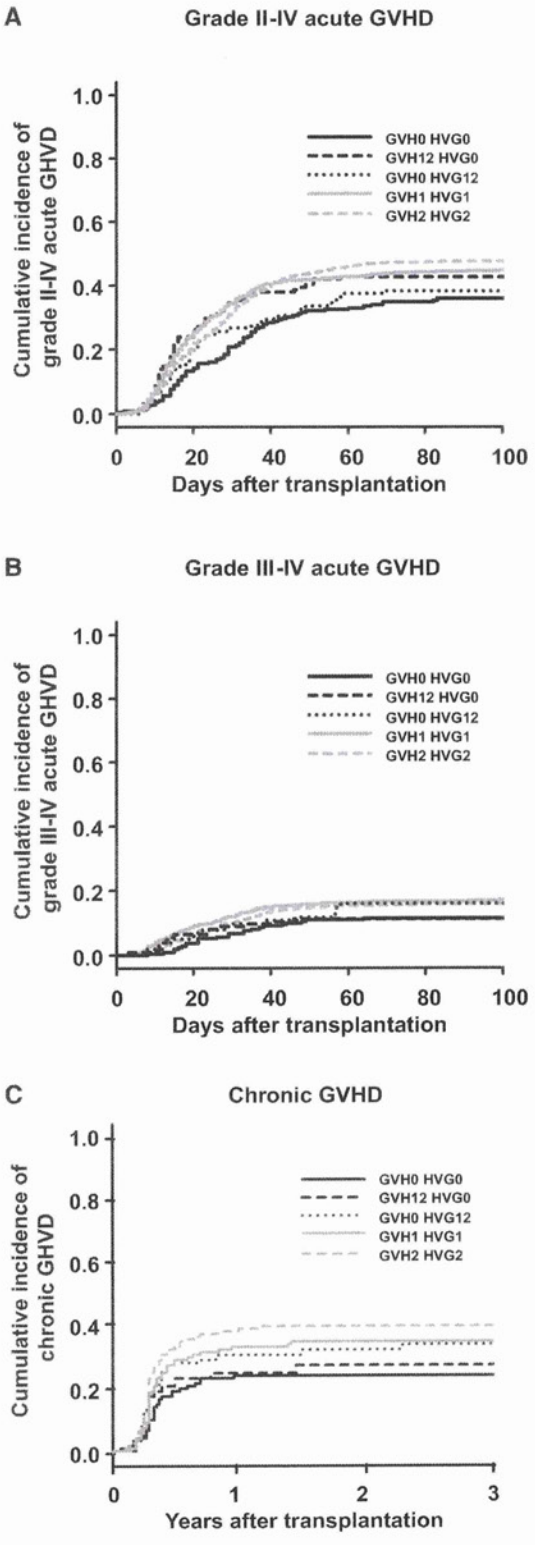

Figure 4. Acute and chronic GVHD.

Similar to Stevens et al. [9], we found a tendency for better neutrophil and platelet engraftment kinetics in the GVH 1-2/HVG 0 MM group. This finding suggests that an HLA MM in the GVH direction enhances engraftment by eradicating or suppressing the host residual immune cells responsible for the rejection or inhibition of donor cell engraftment. In contrast to our findings, Matsuno et al. [8] analyzed the impact of GVH/HVG MM on 152 patients who underwent a single UCBT in a single center, and found that the presence of a 2-antigen MM in the GVH direction was associated with slower and lower neutrophil engraftment compared with a 0- or 1-antigen MM in the GVH direction. Because Matsuno et al. used only a calcineurin inhibitor for GVHD prophylaxis in all of the patients in their cohort, we recategorized the HLA MM group according to HLA category (GVH 0-1/HVG 0-1 MM, GVH 0–1/HVG 2 MM, GVH 2/HVG 0-1 MM, and GVH 2/HVG 2 MM) and performed additional analyses in which patients were stratified according to GVHD prophylaxis (calcineurin inhibitor plus methotrexate, calcineurin inhibitor only, or other). Similar to the findings of Matsuno et al., an MM in the GVH direction was significantly associated with a lower incidence of engraftment in patients who received only a calcineurin inhibitor (data not shown). In contrast, an MM in the GVH direction was associated with a higher incidence of engraftment in patients who received a calcineurin inhibitor plus methotrexate. These findings suggest that the impact of HLA MM differs according to GVHD prophylaxis. A possible explanation for the different

effects of GVHD prophylaxis on engraftment is the high incidence of hemophagocytic syndrome (HPS) and pre-engraftment immune reaction in patients who received only a calcineurin inhibitor as GVHD prophylaxis [20,21]. Takagi et al. [20] reported HPS in 20 of 119 patients who underwent UCBT with mostly tacrolimus alone as GVHD prophylaxis, resulting in a high incidence of graft failure. Less-intensive GVHD prophylaxis may enhance the immune reaction caused by donor T cells that recognize the HLA MM antigen in the GVH direction in the early phase after transplantation, which could lead to HPS or similar conditions and decrease the rate of neutrophil engraftment. These findings demonstrate the need for a prospective study using uniform GVHD prophylaxis to further evaluate the impact of HLA MM on neutrophil engraftment.

This study has several limitations. First, the patients' heterogeneous backgrounds might have produced statistical bias, although we attempted to reduce this bias by adjusting the impact in the multivariate analyses. Second, the number of subjects in each HLA MM group category was limited. Nevertheless, the number of subjects in the GVH 1-2/HVG 0 and GVH 0/HVG 1-2 MM groups was much greater than that in previous studies [8,9]. Third, we might have underestimated the degree of HLA MM, given our incomplete allelic and HLA-C antigen information; for example, the group that had only an HLA MM in the GVH direction might have included an allelic MM in the HVG direction. A potential HLA-C antigen MM or KIR ligand MM also might have affected outcomes, but we did not evaluate HLA-C in the present study. The foregoing issues might have weakened the power of this study to detect differences.

In conclusion, our findings do not support a strategy for selecting UCB donors based on the direction of the HLA MM, although GVH 1-2/HVG 0 MMs may be associated with better neutrophil engraftment, particularly when a calcineurin inhibitor plus other immunosuppressive agents, such as methotrexate, are used for GVHD prophylaxis. The impact of HLA MMs in only the GVH direction remains to be clarified further under a uniform GVHD prophylaxis regimen.

ACKNOWLEDGMENTS

We thank all of the physicians and data managers at the centers who contributed valuable data on transplantation to the JCBBN and TRUMP. We also thank the members of the Data Management Committees of JCBBN and TRUMP for their assistance. J.K. is a Research Fellow of the Japan Society for the Promotion of Science.

Financial disclosure: This work was supported in part by a Grant-in-Aid for JSPS Fellows (to J.K.).

Authorship statement: J.K. and Y.K. designed the research, organized the project, and wrote the manuscript. J.K., Y.A., and Y.K. performed the statistical analysis and analyzed the data; K.K. and T.N.-I. collected data from JCBBN; and all of the authors interpreted the data, and reviewed and approved the final manuscript.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.bbmt.2012.09.017.

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Bone Marrow Transplantation (2013) **48,** 529–536

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ORIGINAL ARTICLE

Changes in incidence and causes of non-relapse mortality after allogeneic hematopoietic cell transplantation in patients with acute leukemia/myelodysplastic syndrome: an analysis of the Japan Transplant Outcome Registry

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The outcomes for allogeneic hematopoietic cell transplantation (allo-HCT) are heavily influenced by non-relapse mortality (NRM). We retrospectively assessed the changes in the incidence and causes of NRM after allo-HCT over the past 12 years. NRM, relapse rate and OS were analyzed using the Japan transplant outcome database of 6501 adult patients with acute leukemia or myelodysplastic syndrome who received their first allo-HCT in remission from 1997 through 2008. In multivariate analysis in patients aged 16–49 years, the adjusted hazard ratios (HRs) for NRM for 2001–2004 and 2005–2008 were 0.78 (95% confidence interval, 0.65–0.93) and 0.64 (0.54–0.78), respectively, compared with 1997–2000. The HR for overall mortality in 2005–2008 was 0.81 (0.70–0.93) compared with 1997–2000. In patients aged 50–70 years, the HRs for NRM and overall mortality in 2005–2008 were 0.56 (0.46–0.68) and 0.66 (0.47–0.93), respectively, compared with those in 2001–2004. We found that causes of death that contributed to the changes in NRM varied among subgroups. In conclusion, our study indicated that the incidence of NRM after allo-HCT has significantly decreased over the past 12 years, which has led to an improvement of OS, and also showed reductions in NRM in subgroups consisting of older patients and those who received unrelated cord blood transplantation.

Bone Marrow Transplantation (2013) **48,** 529–536; doi:10.1038/bmt.2012.172; published online 10 September 2012

Keywords: leukemia; allogeneic hematopoietic cell transplantation; non-relapse mortality; GVHD; cord blood transplantation

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) has been recognized as a potent strategy for curing hematological malignancies. However, there have always been concerns about the risk of non-relapse mortality (NRM). As the risk of relapse is known to be significantly reduced after allo-HCT, the outcome of and indications for allo-HCT are heavily influenced by the risk for NRM.

Over the past few decades, many changes have been made to improve the outcome after allo-HCT, including improvements in the conditioning regimen, donor selection, and prophylaxis and treatment for organ complications, GVHD and infectious diseases, which have led to a reduction in NRM.[1–4]

Although an improvement in NRM has been reported in relatively younger patients who have received allo-HCT from a BM or peripheral blood (PB) donor, NRM has not been fully examined in other settings, such as in elderly patients, or in cord blood (CB) transplantation.

To evaluate the effects of these advances, we retrospectively assessed the changes in the incidence and causes of NRM over the past 12 years, using a nationwide registry database of more than 6000 patients who received various types of allo-HCT.

PATIENTS AND METHODS

Data source

The clinical data were extracted from a nationwide transplant outcome registry database provided by the Japan Society for Hematopoietic Cell Transplantation (JSHCT), the Japan Marrow Donor Program (JMDP) and the Japan Cord Blood Bank Network (JCBBN). The JSHCT collect clinical data through the Transplant Registry Unified Management Program, as described previously.[5] This study was approved by the data management committees of JSHCT, JMDP and JCBBN, and by the Institutional Review Board at the National Cancer Center Hospital.

Patients and definitions

We evaluated the data on patients aged between 16 and 70 years who had AML, acute lymphocytic leukemia (ALL) or myelodysplastic syndrome (MDS), and who received their first allo-HCT between 1997 and 2008. We compared the incidence of NRM after allo-HCT in three consecutive 4-year

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Received 15 June 2012; revised and accepted 6 August 2012; published online 10 September 2012

periods (1997–2000, 2001–2004 and 2005–2008) for younger patients (16–49 years), and in the latter two periods for older patients (50–70 years). NRM was defined as death without recurrent disease after allo-HCT. Analyses were performed for patients with acute leukemia/MDS in remission or low-risk MDS (refractory anemia with or without ringed sideroblast: RA/RARS). Analyses were performed on the basis of patients' age (16–49 years and 50–70 years) and donor source (HLA-6/6-serum-matched or 1-Ag-mismatched related, unrelated BM and unrelated CB). In the era considered by this study, only BM from unrelated volunteer donors was used in Japan. In 2003, JMDP nationally recommended DNA typing of HLA-A and B, as well as HLA-DRB1. Since 2005, JMDP required all the candidates of unrelated allo-HCT to examine high-resolution typing of HLA-A, B and DRB1, and also recommended high-resolution typing of the C-locus. Conditioning regimens were classified as indicated by Giralt *et al.*[6] The incidences of mortality associated with GVHD, infection and organ failure were analyzed. In patients who had multiple causes among GVHD, infection and organ failure, information regarding the main cause of death was prioritized.

Statistical analysis

Data were retrospectively reviewed and analyzed as of June 2011. Among the three time periods, patient characteristics were compared using the χ^2 test. The primary end point of the study was NRM after allo-HCT. Probabilities of NRM and relapse were estimated with the use of cumulative incidence curves, with relapse viewed as a competing risk of NRM, and with NRM viewed as a competing risk of relapse. The Pepe and Mori test was used to evaluate the differences between groups. For the 151 patients (2%) who were known to have relapsed but whose date of relapse was unavailable, mid-point imputation was performed by substituting the midpoint from HCT to date of last contact as the date of relapse. The probability of OS was estimated using the Kaplan-Meier product limit method, and 95% confidence intervals (CIs) were calculated using the Greenwood formula. To compare the OS between groups, the log-rank test was used. Incidences of NRM, relapse and OS were estimated as probabilities at 3 years from allo-HCT. Multivariate analyses for NRM and relapse were performed using competing risk regression by the method of Fine and Gray, and for OS using a Cox proportional hazard regression model. The multivariate analyses were performed separately among patients aged 16–49 years and patients aged 50–70 years, where the year of allo-HCT (1997–2000 vs 2001–2004 or 2005–2008 among younger patients, 2001–2004 vs 2005–2008 among older patients or those who received unrelated CB transplantation (UCBT)), disease type (AML vs ALL or MDS), patient age (16–29 years vs 30–39 or 40–49 among younger patients, 50–59 vs 60–70 among older patients), patient gender (male vs female), donor source (HLA-6/6-Ag-matched sibling vs other family donors, HLA-6/6-Ag-matched unrelated BM, mismatched unrelated BM or unrelated CB) and conditioning regimens (myeloablative vs reduced-intensity) were considered as covariates. Multivariate analyses were also performed separately for those receiving related allo-HCT, where HLA-6/6-Ag-matched sibling vs other family donors were considered as covariates for the donor source, those receiving unrelated BM transplantation (UBMT), where HLA-6/6-Ag-matched unrelated BM vs mismatched BM were considered as covariates, and those who received UCBT, where the covariates above were examined other than the donor source. We considered two-sided *P*-values of <0.05 to be statistically significant. Statistical analyses were performed with SAS version 9.1.3 (SAS, Cary, NC, USA) and the SPSS software version 11.0.1 (SPSS, Chicago, IL, USA).

RESULTS

Patients

A total of 6501 patients registered from 266 institutions across the country[5] were analyzed, with a median age of 40 years and a median follow-up of 39 months. Characteristics of the patients and

Table 1. Patients' characteristics according to the time period of transplant

Characteristics	*1997–2000,* N *(%)*	*2001–2004,* N *(%)*	*2005–2008,* N *(%)*	P
Total number of patients	1354	2292	2855	
Age at transplant (years)				<0.001
16–34	740 (55)	892 (39)	862 (30)	
35–49	491 (36)	783 (34)	939 (33)	
50–59	116 (9)	489 (21)	743 (26)	
60–70	7 (1)	128 (6)	311 (11)	
Donor source				<0.001
Related BM	511 (38)	367 (16)	504 (18)	
Related peripheral blood	158 (12)	546 (24)	456 (16)	
Unrelated BM	588 (43)	998 (44)	1312 (46)	
Unrelated cord blood	14 (1)	321 (14)	534 (19)	
Others	83 (6)	60 (3)	49 (2)	
Disease type				0.991
AML	699 (52)	1226 (53)	1516 (53)	
ALL	505 (37)	744 (32)	949 (33)	
MDS	150 (11)	322 (14)	390 (14)	
Disease status				0.001
CR1	811 (60)	1288 (56)	1802 (63)	
CR2	311 (23)	552 (24)	654 (63)	
CR3 or beyond	76 (6)	96 (4)	77 (3)	
MDS RA/RARS	83 (6)	202 (9)	267 (9)	
Other remission state/no detailed data	73 (5)	154 (7)	55 (2)	
Conditioning				<0.001
Myeloablative	1131 (84)	1585 (69)	1788 (63)	
Reduced-intensity	21 (2)	394 (17)	689 (24)	
Not categorized	202 (15)	313 (14)	378 (13)	
GVHD prophylaxis				<0.001
CYA-based	1041 (77)	1367 (60)	1354 (47)	
Tacrolimus-based	270 (20)	825 (36)	1373 (48)	
No data available	43 (3)	100 (4)	128 (4)	

Abbreviations: MDS = myelodysplastic syndrome; RA/RARS = refractory anemia with or without ringed sideroblast.

transplantation procedures according to the time period are shown in Table 1. The overall proportions of AML, ALL and MDS were 53%, 34% and 13%, respectively. A total of 1354, 2292 and 2855 allo-HCTs were performed in 1997–2000, 2001–2004 and 2005–2008, respectively. The number and proportion of patients aged 50–70 years (1997–2000, $n=123$, 9%; 2001–2004, $n=617$, 27%; 2005–2008, $n=1054$, 37%), allo-HCT from an unrelated CB donor ($n=14$, 1%; $n=321$, 14%; $n=534$, 19%), and the use of a reduced-intensity conditioning regimen ($n=21$, 2%; $n=394$, 17%; $n=689$, 24%) increased over the three periods. Most of the myeloablative conditioning regimens (96%) consisted of high-dose CY with TBI or BU. Tacrolimus-based GVHD prophylaxis increased, especially in allo-HCT from an unrelated BM and CB donor (BM: $n=218$, 37%; $n=579$, 58%; $n=945$, 72%; CB: $n=3$, 21%; $n=99$, 31%; $n=229$, 43%).

Outcomes of allo-HCT over the three periods

The incidence of NRM of the entire 6501 patients was 23% at 3 years after allo-HCT (Figure 1a). Overall, 265 patients died of acute or chronic GVHD (median OS: 143 days, range: 18–3360), 497 died of infection (median OS: 116 days, range: 0–3184) and 500 died of organ failure (median OS: 145 days, range: 0–4013).

Older patients had a significantly higher incidence of NRM than younger patients (31% vs 20%, $P<0.001$, Figure 1b). The donor source significantly affected the incidence of NRM, and unrelated CB had the highest risk of NRM (related, 17%; unrelated BM, 25%; unrelated CB, 31%, $P<0.001$, Figure 1c). In a comparison of the outcome after allo-HCT among the three time periods in the overall 6501 patients (Figure 2), there were no linear improvements in NRM and OS over the three periods (NRM: 23%, 25% and 21%; OS: 61%, 57% and 60% at 3 years after allo-HCT). By the multivariate analysis that adjusted for disease type, patient age, patient gender, donor source and conditioning regimens, in younger patients (Table 2), the hazard ratios (HRs) for NRM in 2001–2004 and 2005–2008 compared with 1997–2000 were 0.78 (95% CI 0.65–0.93, $P=0.005$) and 0.64 (95% CI 0.54–0.78, $P<0.001$), respectively. The HR for overall mortality in 2005–2008 was significantly lower than that in 1997–2000 (HR 0.81, 95% CI 0.70–0.93, $P=0.004$). The HRs for relapse did not differ significantly among the periods. In older patients, the HRs for NRM and overall mortality in 2005–2008 compared with 2001–2004 were 0.56 (95% CI 0.46–0.68, $P<0.001$) and 0.66 (95% CI 0.47–0.93, $P=0.017$), respectively. However, the HR for relapse in 2005–2008 significantly increased (HR 1.53, 95% CI 1.20–1.97, $P=0.001$).

Allo-HCT from an HLA-matched or 1-Ag-mismatched related donor

In younger patients who received allo-HCT from a related donor (Figure 3a), the incidence of NRM remained rather low throughout the 12 years. Although NRM and OS slightly improved in 2005–2008, the differences were not statistically significant.

In older patients who received allo-HCT from a related donor, NRM was significantly reduced in 2005–2008 compared with 2001–2004 (Figure 3b, HR 0.62, 95% CI 0.44–0.88, $P=0.007$, Table 2). The incidences of death associated with organ failure and GVHD were significantly reduced in 2005–2008 (organ failure, 11 and 6%, $P=0.007$; GVHD, 6 and 3%, $P=0.015$, Figure 4a). In contrast, a significant increase in relapse was observed in 2005–2008 compared with 2001–2004 (21 and 36%, $P<0.001$, data not shown), and the same result was also shown by a multivariate analysis (HR 1.97, 95% CI 1.38–2.81, $P<0.001$, Table 2). This result remained the same when the analyses were restricted to HCT using reduced-intensity regimens or myeloablative regimens. Consequently, the improvement in OS in 2005–2008 was not statistically significant (Figure 3b and Table 2).

Allo-HCT from an unrelated BM donor

A significant reduction in NRM was seen over the three periods among younger patients who received allo-HCT from an unrelated BM donor (Figure 3c), with the HRs of 0.69 (95% CI 0.55–0.88, $P=0.003$) and 0.61 (95% CI 0.47–0.78, $P<0.001$) in 2001–2004 and 2005–2008, respectively (Table 2). The incidences of death associated with GVHD and organ failure were significantly reduced over the three periods (GVHD, 7, 4 and 4%, $P=0.011$; organ failure, 12, 10 and 8%, $P=0.002$, Figure 4b). OS significantly improved in 2005–2008 (Figure 3c and Table 2).

In older patients who received allo-HCT from an unrelated BM donor, NRM and OS significantly improved in 2005–2008 compared with 2001–2004 (Figure 3d). The HR for NRM in 2005–2008 was 0.58 (95% CI 0.41–0.82, $P=0.002$). The incidences of death associated with infection and organ failure were reduced in 2005–2008 (infection, 14 and 10%, $P=0.054$; organ failure,

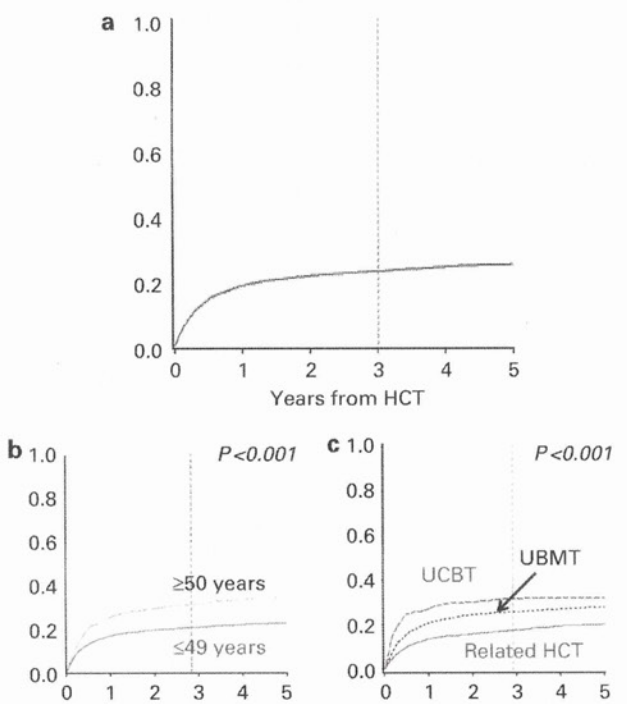

Figure 1. NRM over the past 12 years among 6501 patients who received allo-HCT in remission is shown in (**a**). NRM according to age (**b**) and donor source (**c**) are also shown.

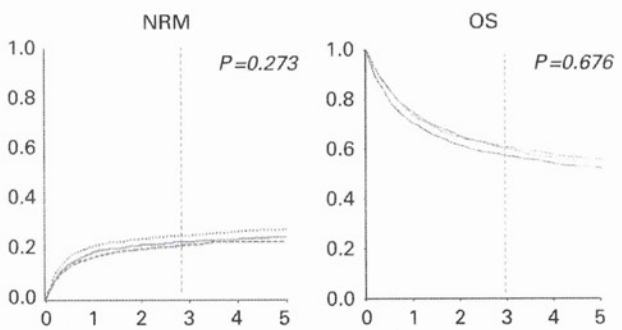

Figure 2. NRM and OS at 4-year periods (1997–2000, solid line; 2001–2004, dotted line; 2005–2008, dashed line) in the overall patients.

Table 2. Multivariate analyses for NRM, relapse and overall mortality after allo-HCT among the three periods

	All patients N = *6501*			*Related HCT* N = *2542*			*UBMT* N = *2898*			*UCBT* N = *869*		
	HR	*95% CI*	P *value*	*HR*	*95% CI*	P *value*	*HR*	*95% CI*	P *value*	*HR*	*95% CI*	P *value*
		N = 4707			*N* = 1846			*N* = 2202			*N* = 518	
Patient age at transplant, 16–49 years												
NRM												
1997–2000	1.00			1.00			1.00					
2001–2004	0.78	(0.65–0.93)	0.005	1.00	(0.75–1.33)	0.980	0.69	(0.55–0.88)	0.003	1.00		
2005–2008	0.64	(0.54–0.78)	<0.001	0.62	(0.44–0.88)	0.007	0.61	(0.47–0.78)	<0.001	1.04	(0.72–1.51)	0.830
Relapse												
1997–2000	1.00			1.00			1.00					
2001–2004	1.16	(0.98–1.37)	0.094	0.95	(0.74–1.21)	0.650	1.39	(1.39–1.06)	0.019	1.00		
2005–2008	1.12	(0.94–1.34)	0.220	1.20	(0.94–1.52)	0.150	1.20	(0.89–1.61)	0.240	0.66	(0.43–1.00)	0.049
Overall mortality												
1997–2000	1.00			1.00			1.00					
2001–2004	0.94	(0.82–1.06)	0.310	1.00	(0.82–1.22)	0.990	0.88	(0.73–1.06)	0.188	1.00		
2005–2008	0.81	(0.70–0.93)	0.004	0.89	(0.71–1.11)	0.285	0.77	(0.62–0.94)	0.010	0.84	(0.57–1.23)	0.373
		N = 1794			*N* = 696			*N* = 696			*N* = 351	
Patient age at transplant, 50–70 years												
NRM												
2001–2004	1.00			1.00			1.00			1.00		
2005–2008	0.56	(0.46–0.68)	<0.001	0.49	(0.33–0.71)	<0.001	0.58	(0.41–0.82)	0.002	0.57	(0.40–0.83)	0.003
Relapse												
2001–2004	1.00			1.00			1.00			1.00		
2005–2008	1.53	(1.20–1.97)	0.001	1.97	(1.38–2.81)	<0.001	1.46	(0.93–2.28)	0.100	0.96	(0.59–1.58)	0.880
Overall mortality												
2001–2004	1.00			1.00			1.00			1.00		
2005–2008	0.66	(0.47–0.93)	0.017	0.87	(0.67–1.15)	0.334	0.82	(0.61–1.09)	0.169	0.67	(0.49–0.91)	0.010

Abbreviations: CI = confidence interval; HCT = hematopoietic cell transplantation; HR = hazard ratio; NRM = non-relapse mortality; UBMT = unrelated BM transplantation; UCBT = unrelated cord blood transplantation. Year of allo-HCT (1997–2000 vs 2001–2004 or 2005–2008 among younger patients, 2001–2004 vs 2005–2008 among older patients or those who received UCBT), disease type (AML vs ALL or MDS), patient age (16–29 years vs 30–39 or 40–49 among younger patients, 50–59 vs 60–70 among older patients), patient gender (male vs female), donor source (HLA-matched sibling vs other family donors, HLA-matched unrelated BM, mismatched unrelated BM or unrelated CB), and conditioning regimens (myeloablative vs reduced-intensity) were considered as covariates. In the analysis for related HCT, donor source (HLA-matched sibling vs other family donors), year of allo-HCT, disease type, patient age, patient gender and conditioning regimens were considered as covariates. In the analysis for UBMT, donor source (HLA-matched BM vs mismatched unrelated BM), year of allo-HCT, disease type, patient age, patient gender and conditioning regimens were considered as covariates. In the analysis for UCBT, year of allo-HCT, disease type, patient age, patient gender and conditioning regimens were considered.

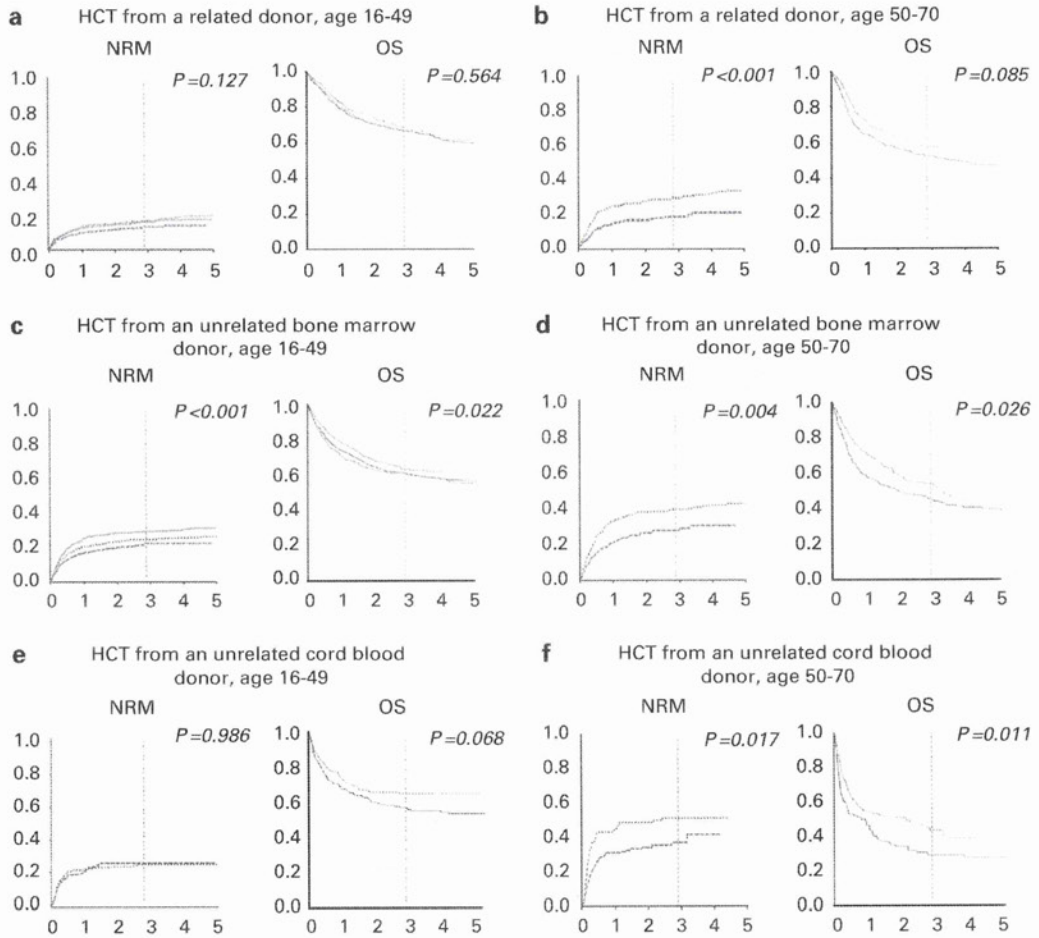

Figure 3. (**a**) NRM and OS at 3 years from HCT among younger patients (16–49 years) who received allo-HCT from a related donor were 15%, 16% and 12% ($P = 0.127$), and 67%, 66% and 68% ($P = 0.564$), respectively in the period of 1997–2000 ($n = 587$, solid line), 2001–2004 ($n = 620$, dotted line) and 2005-2008 ($n = 639$, dashed line). (**b**) NRM and OS among older patients (50–70 years) who received related donor transplantation were 28% and 17% ($P < 0.001$) and 52% and 57% ($P = 0.085$), respectively in the period of 2001–2004 ($n = 293$, dotted line) and 2005–2008 ($n = 321$, dashed line). (**c**) NRM and OS among younger patients who received allo-HCT from an unrelated BM donor were 28%, 24% and 22% ($P < 0.001$), and 60%, 60% and 63% ($P = 0.022$), respectively in the period of 1997–2000 ($n = 560$, solid line), 2001–2004 ($n = 803$, dotted line) and 2005-2008 ($n = 839$, dashed line). (**d**) NRM and OS among older patients who received allo-HCT from an unrelated BM donor were 39% and 27% ($P = 0.004$) and 45% and 54% ($P = 0.026$), respectively in the period of 2001–2004 ($n = 195$, dotted line) and 2005–2008 ($n = 473$, dashed line). (**e**) Non-relapse mortality and OS among younger patients who received allogeneic hematopoietic cell transplantation from an unrelated cord blood donor were 25% and 25% ($P = 0.986$), and 55% and 65% ($P = 0.068$), respectively in the period 2001–2004 ($n = 214$, dotted line) and 2005–2008 ($n = 292$, dashed line). (**f**) Non-relapse mortality and OS among older patients who received allogeneic hematopoietic cell transplantation from an unrelated cord blood donor were 51% and 37% ($P = 0.017$), and 29% and 44% ($P = 0.011$), respectively in the period of 2001–2004 ($n = 107$, dotted line) and 2005–2008 ($n = 242$, dashed line).

14 and 8%, $P = 0.049$, Figure 4c). We found a significant reduction in mortality rates associated with bacterial and fungal infection.

Allo-HCT from an unrelated CB donor

In younger patients who received allo-HCT from an unrelated CB donor, there was no significant difference in the incidence of NRM between the two periods (Figure 3e). In this group, there was a marked reduction in the relapse rate (25 and 18%, $P = 0.018$, data not shown; HR 0.66, 95% CI 0.43–1.00, $P = 0.049$, Table 2). OS was better in 2005–2008; however, the difference was not statistically significant.

Significant improvements in NRM and OS were observed in 2005–2008 among older patients who received UCBT (Figure 3f). The HRs for NRM and overall mortality in 2005–2008 were 0.57 (95% CI 0.40–0.83, $P = 0.003$) and 0.67 (95% CI 0.49–0.91, $P = 0.010$), respectively. Reductions in the incidences of death associated with GVHD and infection seemed to contribute to the improvements in NRM (GVHD, 7 and 3%, $P = 0.163$; infection, 23 and 13%, $P = 0.136$). The mortality rate due to bacterial infection was significantly reduced.

Incidence of and mortality after severe acute GVHD

In subgroups that showed a significant reduction in the incidence of NRM, younger patients who received UBMT, older patients who received related HCT and older patients who received UCBT showed significant reductions in the incidence of GVHD-related mortality. In younger patients who received UBMT, the incidence of severe acute GVHD was significantly reduced over the three

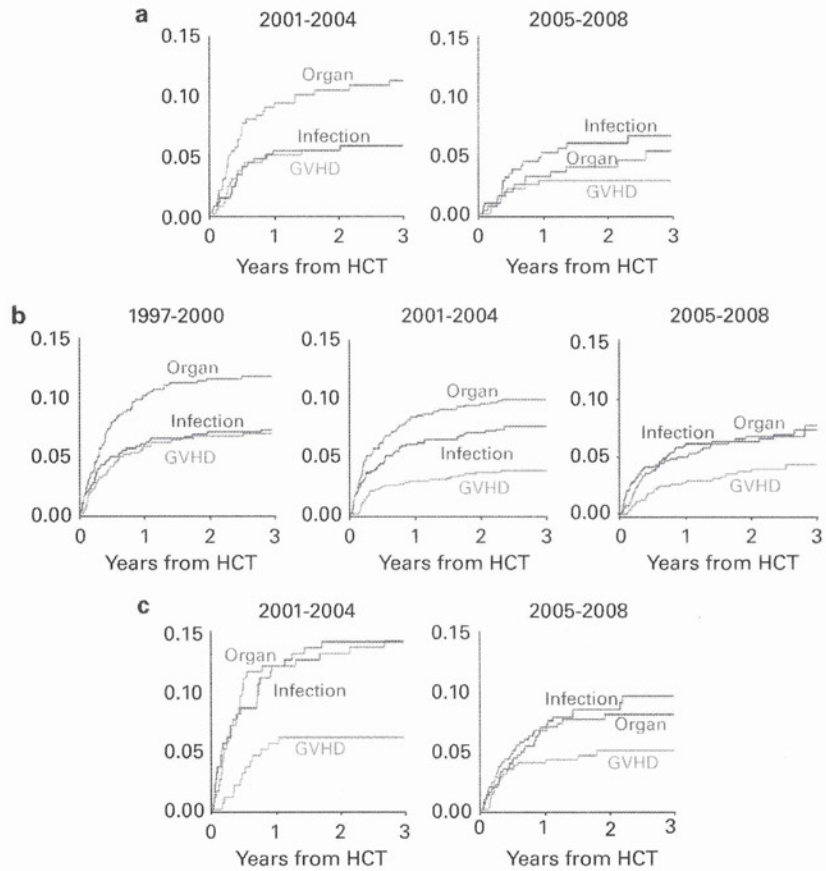

Figure 4. Change in the causes of NRM among different time periods is shown. Cumulative incidences of death due to GVHD, infection and organ failure are separately presented in each time period. (**a**) In older patients who received allo-HCT from a related donor, the incidences of death associated with organ failure and GVHD were significantly reduced in 2005–2008 (organ failure, 11 and 6%, $P = 0.007$; GVHD, 6 and 3%, $P = 0.015$). (**b**) In younger patients who received allo-HCT from an unrelated BM donor, the incidences of death associated with GVHD and organ failure were significantly reduced (GVHD, 7, 4 and 4%, $P = 0.011$; organ failure, 12, 10 and 8%, $P = 0.002$). (**c**) In older patients who received allo-HCT from an unrelated BM donor, the incidences of death associated with infection and organ failure were reduced in 2005–2008 (infection, 14 and 10%, $P = 0.054$; organ failure, 14 and 8%, $P = 0.049$).

periods (16, 15 and 12% at 100 days after allo-HCT, $P = 0.021$). In older patients who received related HCT, the incidence of severe acute GVHD was reduced in 2005–2008 relative to 2001–2004, but this difference was not statistically significant (14 and 10%, $P = 0.099$). In older patients who received UCBT, there was no remarkable reduction in the incidence of severe acute GVHD in the later period (18 and 16%, $P = 0.542$). However, the mortality rate was significantly reduced among older patients who suffered severe acute GVHD after UCBT (92 and 67% at 3 years after allo-HCT, $P = 0.022$).

DISCUSSION

In this study that used a large database of 6501 patients, we found that the incidence of NRM after allo-HCT for adult patients has significantly decreased over the past 12 years, which has led to an improvement of OS. As prior studies have primarily focused on the changes in NRM among younger patients who received allo-HCT with myeloablative conditioning,[2,4] this is the first study to show the changes in NRM in subgroups comprising older patients and UCBT.

We found that demographic, disease and transplantation characteristics have been changing, as previous studies reported.[1,2,4] The marked increase in the number of older patients, allo-HCT with reduced-intensity conditioning and UCBT might reflect an increase in allo-HCT for 'more vulnerable' patients. Gooley *et al.*[1] reported that the hematopoietic cell transplantation-specific comorbidity index (HCT-CI)[7] scores were higher in HCT recipients in more recent time periods. Unfortunately, we were not able to evaluate HCT-CI in the current study because of a lack of information.

Among patients who received related HCT, remarkable improvement in NRM was observed in older patients. Another distinguishing finding was an increase in relapse in overall older patients, especially among those who received related HCT in remission. There was no recent shift in the use of allo-HCT in a later remission state, and we obtained a similar result when the analyses were restricted to HCT using reduced-intensity regimens or myeloablative regimens. In addition, the proportional use of anti-thymocyte globulin has remained unchanged over the periods. Less use of PB donors and more aggressive selection of older patients as indicated for allo-HCT may have affected the result. Despite this increase in relapse, older patients who received HCT in remission showed, by multivariate analyses, a significant reduction in mortality with a remarkable reduction in HRs for NRM irrespective of donor sources.

In analyses based on the donor source, UBMT showed remarkable improvements in NRM and OS throughout the age subgroups. Along with high-resolution donor–recipient HLA

matching,[8,9] the lesser proportion of donor/patient pairs with allele mismatches may have reduced the incidence of GVHD-related mortality, and contributed to the improvement in outcomes after UBMT.

Among patients who received UCBT, we found a decreased risk of relapse in younger patients with no change in NRM. On the other hand, older patients had a decreased risk of NRM with no change in relapse. These outcomes may be explained by the changes in clinical practice in 2001–2004, 'learning phase' of UCBT, and that after 2005, including the indication of UCBT and the prophylaxis and treatment for GVHD/infection.

A recent reduction in the incidence of GVHD-related mortality was observed in younger patients receiving UBMT and older patients receiving related allo-HCT or UCBT. With the changes in prophylaxis and treatment against GVHD including high-resolution donor–recipient HLA matching,[8,9] the incidence of grade 3 to 4 severe acute GVHD has decreased in younger patients receiving UBMT and older patients receiving related HCT, which may have led to the reduction in GVHD-related mortality in these subgroups. Interestingly, in older patients receiving UCBT, there was no reduction in the incidence of severe acute GVHD; however, the mortality rate among those who developed severe acute GVHD was reduced. The prompt initiation of treatment after a more thorough examination to diagnose GVHD,[10] supportive care and nutritional management may have improved the prognosis of those who had severe GVHD. Alternatively, the unique HLA epidemiological genetics of Japanese patients may have affected the results.[11,12]

A recent reduction in the incidence of infection-related mortality was observed in older patients receiving UBMT or UCBT. New antifungal drugs, including mold-active azoles, micafungin or liposomal amphotericin B, are now more likely to be administered as empiric or preemptive strategies for patients who have a positive galactomannan Ag test or pulmonary nodules.[1,13,14] As GVHD and infection have been reported to be associated with each other's development and exacerbation,[13,15–18] an improved control of severe GVHD may have led to the reduction of the risk of infection-related mortality.[13,14]

We included all of the organ toxicities that were documented after allo-HCT as the cause of organ failure-related mortality, including conditioning regimen-related toxicity,[19,20] lung injury[15] and late effects on any organs.[21] We observed a reduction in the incidence of organ failure-related mortality in older patients receiving related HCT and those who received UBMT. In the future, more detailed analyses are warranted based on each specific organ toxicity.

As this analysis is based on a retrospectively collected multicenter database, our results may be susceptible to the disadvantages of any retrospective study, such as the heterogeneity in the treatment strategies chosen at the discretion of the physicians. Because of the nature of the multicenter registry, detailed data were not available regarding the incidences of infection and specific organ failure, and prophylactic treatment toward infection. Although we acknowledge this limitation, the results obtained from this large database that contains clinical data on over 6000 patients should provide valuable information. In addition, for the first time, we found reductions in NRM in subgroups consisting of older patients and those who received UCBT. We also showed the causes of death that contributed to the reduction of NRM in each donor/age subgroup. By further evaluating the risks of NRM and relapse in each demographic subgroup, we would be able to more clearly define the indications for allo-HCT, and tailor the strategy for individual patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by grants from the Japanese Ministry of Health, Labour and Welfare, and the National Cancer Research and Development Fund (23-A-28). The results were presented at the 52nd Annual Meeting of the American Society of Hematology in Orlando, FL, USA, 7 December 2010.

Author contributions: SK designed the study, prepared the data file, performed the analysis, interpreted the data and wrote the manuscript; KY contributed to the study design, data file preparation, data analysis and interpretation of the data; TY was primarily responsible for the study design, data analysis and interpretation of the data; YA reviewed and cleaned the data, interpreted the data and helped to write the manuscript; TNI reviewed, cleaned and interpreted the data, HA, ST, KM, ST, TE, HO and MK obtained and interpreted the data; JT, KK, KK, RS, YM and HS reviewed, cleaned and interpreted the data; TF designed the study, interpreted the data and helped to write the manuscript.

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ORIGINAL ARTICLE

Unrelated cord blood transplantation vs related transplantation with HLA 1-antigen mismatch in the graft-versus-host direction

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Little information is available regarding whether an unrelated cord blood (UCB) unit or a related donor with a 1-antigen mismatch at the HLA-A, HLA-B or HLA-DR locus in the graft-versus-host direction (RD/1AG-MM-GVH) should be selected as an alternative donor for patients without an HLA-matched related/unrelated donor. Therefore, we conducted a retrospective study using national registry data on patients with leukemia or myelodysplastic syndrome who received transplantation using a single UCB ($n = 2288$) unit or an RD/1AG-MM-GVH ($n = 525$). We found that the survival rate in the UCB group was comparable to that in the RD/1AG-MM-GVH group, although the RD/1AG-MM-GVH group with an HLA-B mismatch showed significantly higher overall and non-relapse mortality. Neutrophil and platelet engraftment were significantly faster, whereas the incidence of acute or chronic graft-versus-host disease (GVHD) was significantly higher in the RD/1AG-MM-GVH group. The incidence of acute or chronic GVHD in the RD/1AG-MM-GVH group with *in vivo* T-cell depletion was comparable to that in the UCB group, which translated into a trend toward better overall survival, regardless of the presence of an HLA-B mismatch. In conclusion, UCB and RD/1AG-MM-GVH are comparable for use as an alternative donor, except for RD/1AG-MM-GVH involving an HLA-B mismatch.

Leukemia (2013) **27,** 286–294; doi:10.1038/leu.2012.203

Keywords: cord blood transplantation; related transplantation; HLA mismatch; alternative donor

INTRODUCTION

For patients who lack an HLA-identical sibling, an HLA-matched unrelated donor (MUD) is considered to be the preferred alternative donor in allogeneic hematopoietic cell transplantation (HCT).[1–5] However, it is difficult to find an MUD for patients with rare HLA haplotypes. Furthermore, it takes at least a few months from the start of an unrelated donor search to actually receive a graft. Therefore, there is a large demand for an alternative source to an HLA-identical sibling or MUD, particularly for patients who have a rare haplotype or who need immediate transplantation.

Unrelated cord blood (UCB) has emerged as a promising alternative source for pediatric and adult patients.[6–17] In UCB transplantation, up to two antigen/allele mismatches between a recipient and cord blood unit are acceptable without an increased risk of acute graft-versus-host disease (GVHD). The clinical outcome in UCB transplantation is improving, and is almost comparable to that in HLA 8/8 allele MUD transplantation, although a high risk of graft failure and early treatment-related complications are still major issues.[15–17]

Another alternative source is an HLA-mismatched related donor, particularly when a related donor with a 1-antigen mismatch at the HLA-A, HLA-B, or HLA-DR locus in the graft-versus-host (GVH) direction (RD/1AG-MM-GVH) is available. HCT from an RD/1AG-MM-GVH results in a higher but acceptable incidence of acute GVHD.[18–20] In previous studies, HLA mismatches in the host-versus-graft (HVG) direction were associated with a higher incidence of graft failure and lower overall survival (OS).[18,19,21] However, the risk of graft failure might have been improved by the use of conditioning regimens that strongly suppress the recipient's immune system.[22] Therefore, in current clinical practice in Japan, stem cell transplantation from an RD/1AG-MM-GVH is being performed while accepting multiple antigen mismatches in the HVG direction without specific *ex vivo* stem cell manipulation.[18,19,23] We have recently reported that OS in transplantation from an RD/1AG-MM-GVH involving an HLA-B antigen mismatch was inferior, whereas that from an RD/1AG-MM-GVH involving an HLA-A or -DR antigen mismatch was comparable to that from an 8/8-MUD in standard-risk diseases.[23]

Unlike transplantation from an MUD, transplantation using a UCB unit or an RD/1AG-MM-GVH can be performed immediately when necessary. However, little information is available regarding the priority in selecting these alternative donors. Therefore, we conducted a retrospective study using national registry data on 2813 patients with leukemia or myelodysplastic syndrome (MDS)

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Received 15 June 2012; revised 5 July 2012; accepted 11 July 2012; accepted article preview online 18 July 2012; advance online publication, 10 August 2012