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ORIGINAL ARTICLE

Low incidences of acute and chronic graft-versus-host disease after unrelated bone marrow transplantation with low-dose anti-T lymphocyte globulin

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Abstract Anti-T lymphocyte globulin (ATG) is commonly used as prophylaxis for graft-versus-host disease (GVHD), especially in patients who are at high risk of GVHD. The appropriate dosage of ATG in Japan has not yet been assessed. We therefore conducted a nationwide survey of patients who received ATG-Fresenius as GVHD prophylaxis for unrelated bone marrow transplantation (uBMT). A total of 86 patients were identified (median age 31 years, range 1–68). The median total dose of ATG was 10 mg/kg. The cumulative incidence of neutrophil engraftment was 90 %. The probability of 2-year overall survival (OS) was 67 %. The cumulative incidence of 2-year non-relapse mortality was 25 %. The incidences of grade II–IV and grade III–IV acute GVHD were 20 and 8 %, respectively. The incidences of chronic and extensive chronic GVHD were 19 and 8 %, respectively. In adult patients, there was a reduction of acute GVHD with high-dose ATG (>10 mg/kg), which did not reach statistical significance. In conclusion, the addition of low-dose ATG to GVHD prophylaxis in Japanese patients who received uBMT resulted in decreased incidences of both acute and chronic GVHD without compromising OS. The effects of low-dose ATG should be assessed in a prospective clinical trial.

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Introduction

Over the past several decades, significant advances have been made in the field of allogeneic hematopoietic stem cell transplantation (HSCT), and allogeneic HSCT has become an integral part of treatment for a variety of hematological malignancies and some non-malignant diseases [1, 2]. However, acute and chronic graft-versus-host diseases (GVHD) are still major morbidities after allogeneic HSCT, especially in patients who receive stem cells from an unrelated donor. Finke et al. [3] conducted a large randomized-control trial which showed that anti-T lymphocyte globulin Fresenius (ATG-F) has a beneficial effect as GVHD prophylaxis in patients who have undergone unrelated HSCT. Furthermore, a long-term follow-up of this study demonstrated that the use of ATG-F significantly reduced the incidence of chronic GVHD, which should reduce late non-relapse mortality (NRM) and improve the quality of life (QOL) after unrelated HSCT [4].

Different preparations of ATG including Thymoglobulin and ATG-F have been tested as part of conditioning regimens to achieve in vivo T cell depletion. These two ATG preparations can differ substantially in their potency due to differences in production methods, i.e., in the cells used for immunization [5]. In addition, the intensity of GVHD prophylaxis may depend on the patient's ethnicity, since the risk of GVHD might differ among races [6, 7]. For example, regarding Thymoglobulin, 6.0–7.5 mg/kg is the usual dose for preventing GVHD, and 4 mg/kg was shown to be insufficient in Caucasian patients [5]. In contrast, in Korea, Kim et al. reported that the use of a very low dose of Thymoglobulin (total 2.5 mg/kg) was still associated with lower incidences of acute GVHD and NRM [8, 9]. Furthermore, ATG has multiple immunomodulatory effects, including the expansion of regulatory T cells [10]. Therefore, the effectiveness of ATG as GVHD prophylaxis cannot be assessed simply in terms of the degree of lymphodepletion. Profound immunosuppression could lead to an inferior outcome due to a high rate of infections or possibly to an increase in relapse caused by a loss of graft-versus-leukemia (GVL) effects.

Therefore, we assessed the clinical outcomes of patients who underwent unrelated HSCT using ATG-F as GVHD prophylaxis to identify a candidate dose of ATG-F for testing in a prospective clinical trial.

Patients and methods

Study design

This was a retrospective study that surveyed the use of ATG-F as GVHD prophylaxis in Japan. Patients who received ATG-F as GVHD prophylaxis for bone marrow transplant from an unrelated donor (uBMT) from April 2001 to December 2006 were included. In the era of this study, only BMT could be collected as a stem cell source from an unrelated volunteer donor. We performed a nationwide questionnaire survey at institutions in Japan that performed allogeneic HSCT. For patients who received ATG-F as GVHD prophylaxis, we also collected data regarding the dose and duration of ATG-F along with data from the national registry system of the Japan Society of Hematopoietic Cell Transplantation [11]. We identified 581 cases who received ATG for related or unrelated HSCT, and questionnaires were obtained for 509 (87.6 %). Among these 509 cases, 182 (35.8 %) received ATG-F. We only included patients who received ATG-F for an unrelated BMT, because most of the patients who received ATG for a related HSCT underwent a haploidentical HSCT. In terms of HLA typing, allele typing of 6 loci including HLA A, B and DRB1 was available, while information regarding HLA-C was unavailable. This study was approved by the Institutional Review Board of the Japan Society of Hematopoietic Cell Transplantation and Rinku General Medical Center, Osaka, Japan.

Clinical outcomes

Endpoints included neutrophil recovery, overall survival (OS), NRM, acute GVHD and chronic GVHD. Neutrophil

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recovery was defined as an absolute neutrophil count of $\geq 0.5 \times 10^9$/L for 3 consecutive days. The incidences of grade II–IV or III–IV acute and chronic or extensive chronic GVHD were based on standard criteria [12, 13].

Statistical analysis

The probability of OS was calculated by the Kaplan–Meier method. The cumulative incidences of engraftment, NRM and GVHD were evaluated using Gray's method. In the competing risk models for engraftment and GVHD, relapse and death before these events were defined as competing risks. In the competing risk models for NRM, relapse was defined as a competing risk. A two-sided P value of <0.05 was considered statistically significant. Standard risk was defined as the first complete remission of acute leukemia, the first chronic phase of chronic myeloid leukemia, or non-malignant diseases. High risk was defined as other hematological malignancies. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0) [14]. More precisely, it is a modified version of R commander (version 1.6-3) that was designed to add statistical functions that are frequently used in biostatistics.

Results

Patients' characteristics

The details of the patients' characteristics are shown in Table 1. The median age was 31 years (range 1–68). The underlying disease was non-malignant and hematologically malignant in 51 and 35 patients, respectively. Among hematological malignancies, 27 patients (84 %) had a high-risk disease. In pediatric patients (age < 18), 31 of 34 patients had non-malignant disease. Among the 85 patients for whom data on HLA typing were available, 41 received bone marrow from a donor with an HLA mismatch (one antigen mismatch $n = 13$, one allele mismatch $n = 24$, 2–3 allele mismatch $n = 4$). As GVHD prophylaxis, tacrolimus was used in 67 patients (78 %). Most patients received a reduced-intensity conditioning regimen (RIC $n = 33$) or a non-myeloablative conditioning regimen (NMA $n = 46$) [15, 16]. NMA was only used in patients with a non-malignant disease.

Regarding the total dose of ATG-F, 10 and 20 mg/kg were used in 35 and 20 patients, respectively. ATG-F was administered on 2 and 4 days in 28 patients and 44 patients, respectively.

Table 1 Patients' characteristics

	N (%)
No. of patients	86
Age, median (range), year	31 (1–68)
Pediatrics	34 (40)
Adults	52 (60)
Sex (Male/Female)	54/32
Diagnosis	
SAA	45 (52.5)
AML/MDS	21 (24.5)
NHL	9 (10)
MM	1 (1)
CML/MPD	4 (5)
Primary immunodeficiency	3 (3.5)
Inherited metabolic diseases	3 (3.5)
HLA mismatch	
None	44 (51)
HLA antigen mismatch	13 (15)
B	3
DR	10
HLA allele mismatch	28 (29)[a]
A	7
B	7
DRB1	15
Unknown	1
GVHD prophylaxis	
CSP ± MTX	17 (20)
TAC ± MTX	59 (69)
TAC + MTX + PSL	8 (9)
Others	2 (2)
Conditioning	
Myeloablative	
MEL + TBI	3 (3)
BU + CY	2 (2)
CY + TBI	2 (2)
Reduced-intensity	
Flu + BU-based	28 (33)
Flu + MEL-based	5 (6)
Non-myeloablative	
Flu + CY-based	25 (29)
CY + TBI/TLI	20 (23)
CY alone	1 (1)

SAA severe aplastic anemia, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndrome, *NHL* non-Hodgkin's lymphoma, *MM* multiple myeloma, *CML* chronic myeloid leukemia, *MPD* myeloproliferative disorder, *CSP* cyclosporin, *MTX* methotrexate, *TAC* tacrolimus, *PSL* prednisolone, *Flu* fludarabine, *BU* busulfan, *CY* cyclophosphamide, *TBI* total body irradiation, *TLI* total lymphoid irradiation, *MEL* melphalan

[a] Four patients had a 2–3 allele mismatch

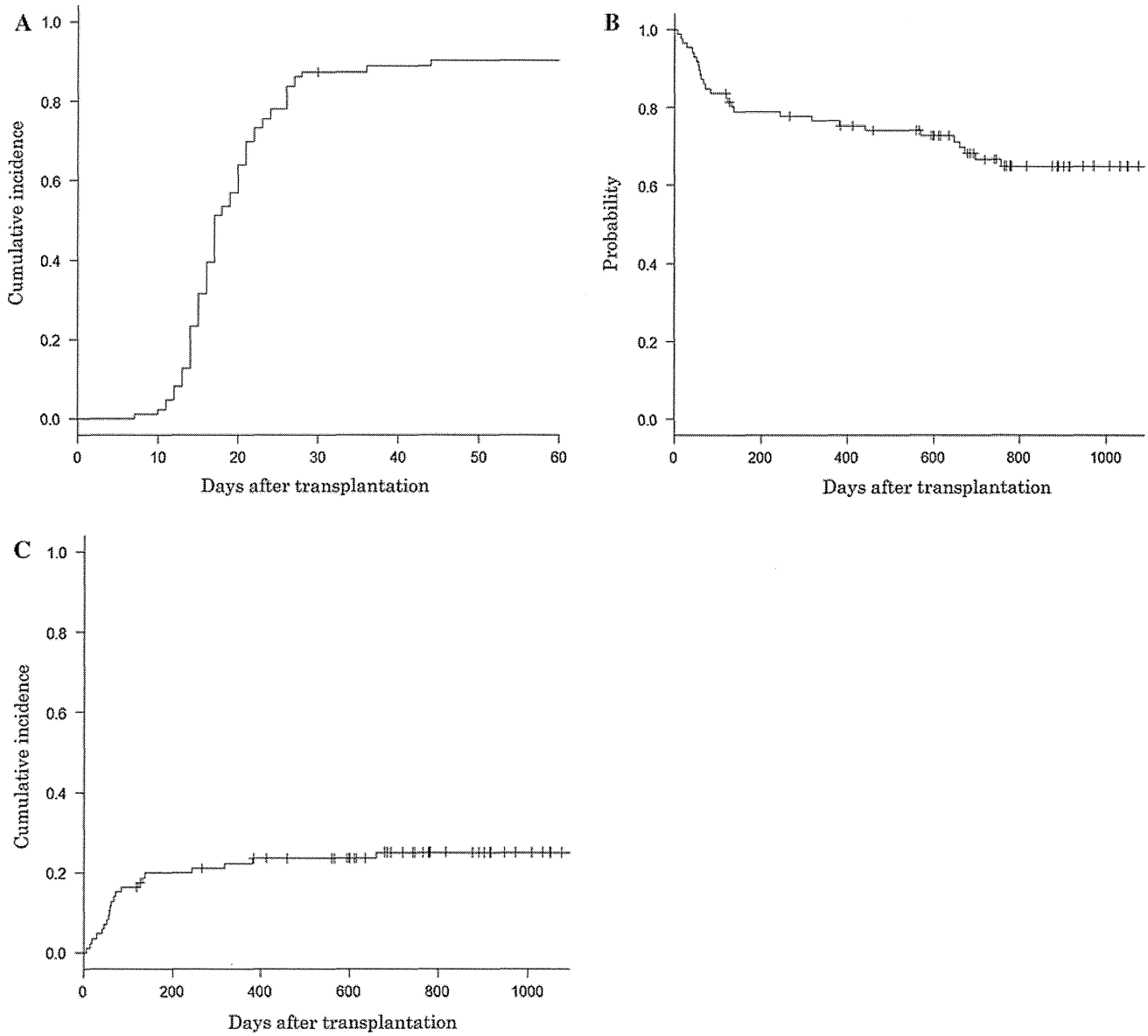

Fig. 1 Engraftment (**a**), overall survival (**b**) and non-relapse mortality (**c**)

Clinical outcomes

The median follow-up of surviving patients was 888 days after uBMT (range 118–2122 days). The cumulative incidence of neutrophil engraftment was 90 % (Fig. 1a). The probability of 2-year OS was 67 % (Fig. 1b). The cumulative incidence of 2-year NRM was 25 % (Fig. 1c).

Patients with a non-malignant disease had a significantly better 2-year OS than those with a malignant disease (81 vs. 44 %, $P = 0.0004$; Fig. 2a), but there was no significant difference in the incidence of NRM between the 2 groups (19 vs. 35 %, $P = 0.16$, Fig. 2b). UBMT from an HLA antigen-mismatched donor had a significantly inferior OS compared to uBMT from an HLA-matched donor (37 vs. 69 %, $P = 0.008$), but there was no significant difference between uBMT from an HLA allele-mismatched donor and that from an HLA-matched donor (78 vs. 69 %, $P = 0.50$). Patients who received an uBMT from an HLA antigen-mismatched donor tended to have a higher incidence of NRM than those who received uBMT from an HLA-matched donor (46 vs. 21 %, $P = 0.051$). However, there was no significant difference between uBMT from an HLA allele-mismatched donor and that from an HLA-matched donor (22 vs. 21 %, $P = 0.91$).

GVHD and post-transplant lymphoproliferative disease (PTLD)

The cumulative incidences of grade II–IV and grade III–IV acute GVHD were 20 and 8 %, respectively (Fig. 3a).

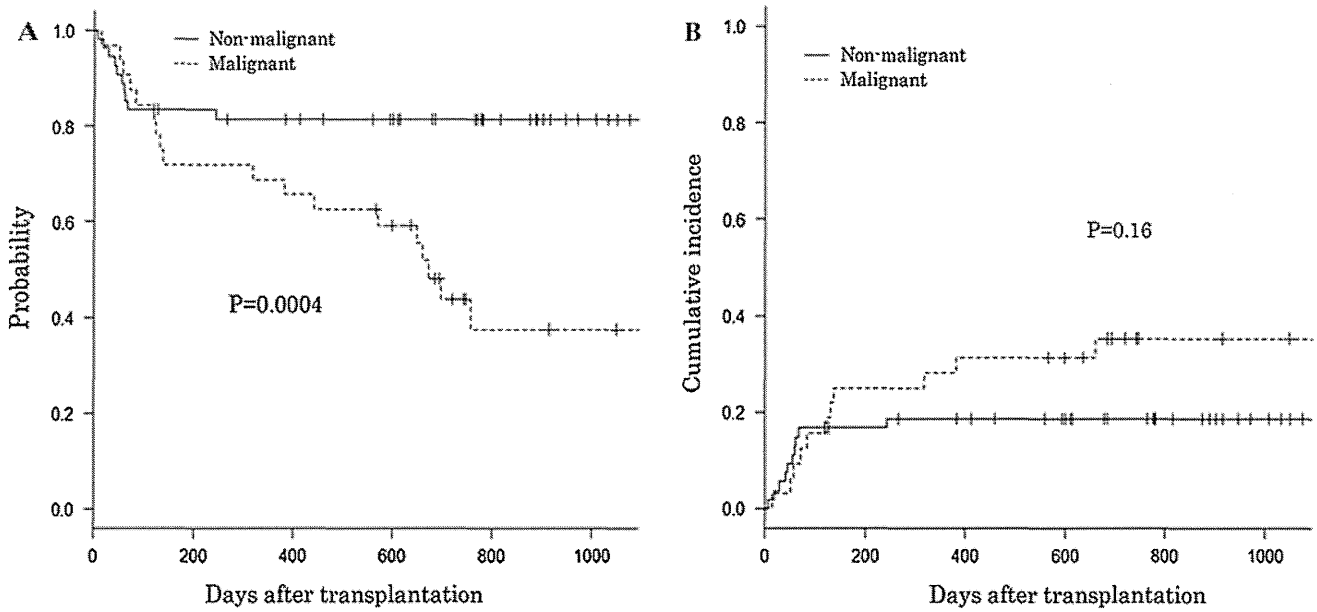

Fig. 2 Overall survival (**a**) and non-relapse mortality (**b**) according to the underlying disease

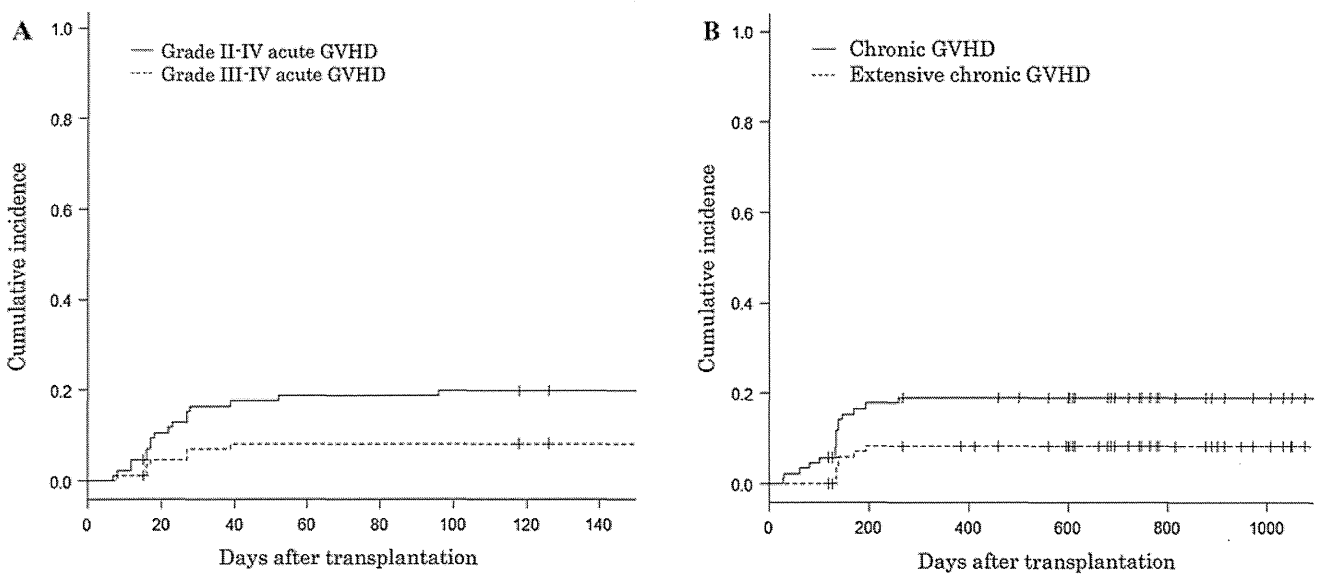

Fig. 3 Grade II–IV and grade III–IV acute GVHD (**a**) and chronic and extensive chronic GVHD (**b**)

The cumulative incidences of chronic GVHD and extensive chronic GVHD were 19 and 8 %, respectively (Fig. 3b). There was no significant difference in the incidence of acute GVHD between patients with a non-malignant disease and those with a malignant disease (19 vs. 22 %, $P = 0.79$). In terms of the incidences of grade II–IV and grade III–IV acute GVHD, there was no significant difference regardless of the presence of an HLA mismatch (grade II–IV 31, 18, 16 % and grade III–IV 23, 4, 7 % in patients with an HLA antigen-mismatched donor, HLA allele-mismatched donor, and HLA-matched donor, respectively). There were no reported cases of PTLD.

Dose of ATG-F

For a comparison of the effect of the ATG-F dose, we included only adult patients (≥18 years old). The median dose of ATG-F was 10 mg/kg. We divided patients into 2 groups: those who received more than 10 mg/kg of ATG-F ($n = 21$, high ATG group) and those who received 10 mg/kg or less of ATG-F ($n = 31$, low ATG group). The characteristics of the 2 groups are shown in Supplementary Table 1. The high-ATG group included significantly more patients with a non-malignant disease (76 vs. 23 %, $P < 0.001$) and more younger patients compared to the

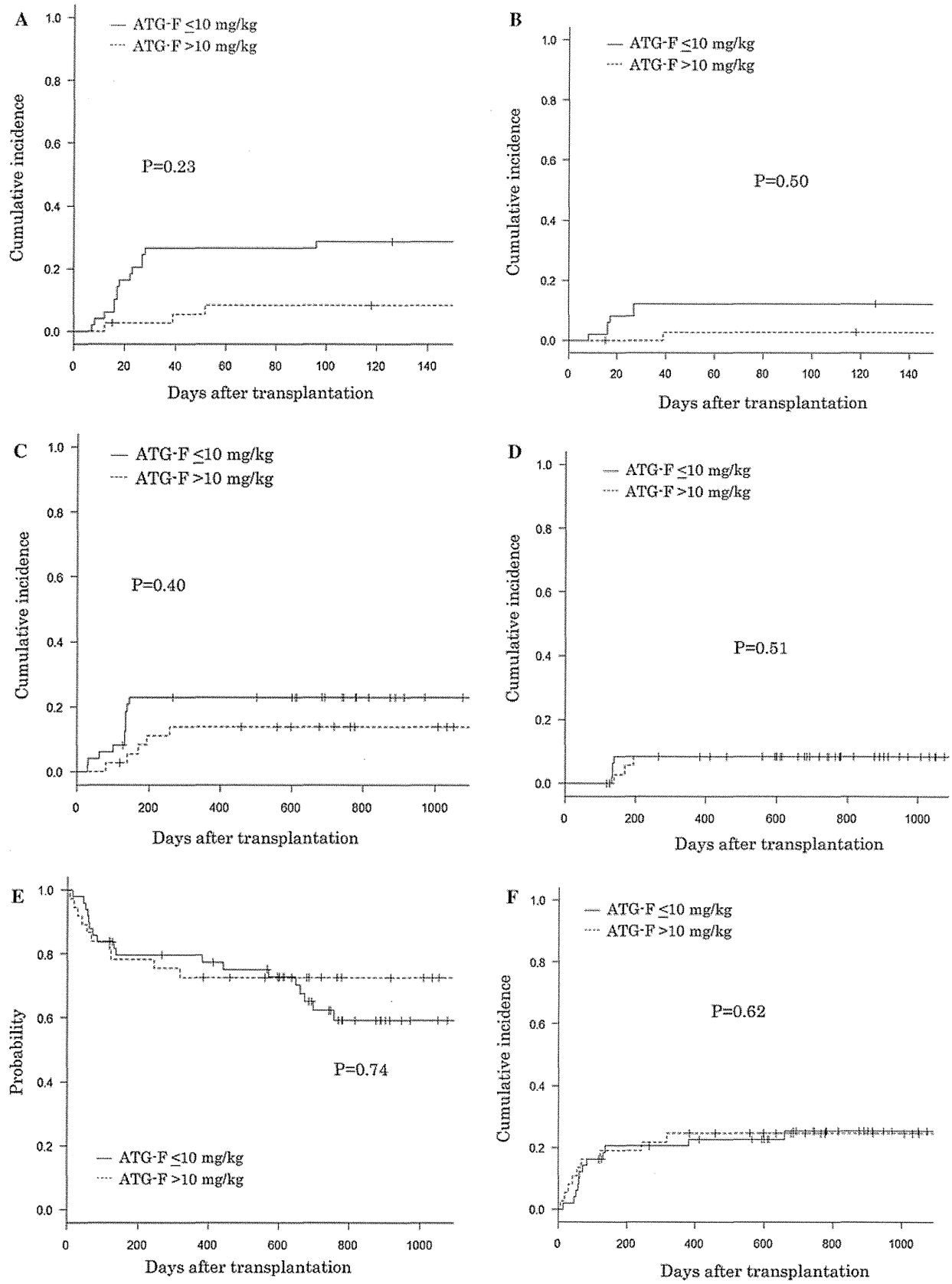

Fig. 4 Grade II–IV acute GVHD (**a**), grade III–IV acute GVHD (**b**), chronic GVHD (**c**), extensive chronic GVHD (**d**), overall survival (**e**) and non-relapse mortality (**f**) according to the dose of ATG-F in adult patients

low-ATG group. The high-ATG group included more patients with an HLA mismatch, but this difference was not statistically significant. The cumulative incidences of grade II–IV acute GVHD in the low- and high-ATG groups were 23 and 10 %, respectively ($P = 0.23$; Fig. 4a). The incidence of grade II–IV acute GVHD in the low-ATG group tended to be higher than that in the high-ATG group, but this difference was not statistically significant. The cumulative incidences of grade III–IV acute GVHD in the low- and high-ATG groups were 10 and 5 %, respectively ($P = 0.50$; Fig. 4b). The cumulative incidences of chronic GVHD in the low- and high-ATG groups were 19 and 10 %, respectively ($P = 0.40$; Fig. 4c). The cumulative incidences of extensive chronic GVHD in the low- and high-ATG groups were 10 and 5 %, respectively ($P = 0.51$; Fig. 4d). The probabilities of 2-year OS in the low- and high-ATG groups were 39 and 57 %, respectively ($P = 0.74$; Fig. 4e). The cumulative incidences of 2-year NRM in the low- and high-ATG groups were 34 and 38 %, respectively ($P = 0.62$; Fig. 4f).

Discussion

We determined the clinical outcomes of Japanese patients who received ATG-F as GVHD prophylaxis for an uBMT. We found low incidences of both acute and chronic GVHD with the use of low-dose ATG-F, considering that all patients received BMT from an unrelated donor and about half received BMT from a donor with an HLA mismatch.

A previous large Japanese retrospective study reported that the incidences of grade II–IV and grade III–IV acute GVHD in patients who received uBMT from an HLA-matched donor were 34.5 and 11.8 %, respectively [17]. In addition, that study reported that the incidence of grade III–IV acute GVHD in patients who received an unrelated BMT from an HLA one allele-mismatched donor was 16.1–27.8 %, depending on the locus of mismatch [17]. In that study, only 176 of 1282 patients (14 %) received ATG. Therefore, it seems that the incidence of acute GVHD in patients who received low-dose ATG-F (grade II–IV 20 %, grade III–IV 8 %) was lower than that for all of the registered patients in Japan.

Our study also showed low incidences of chronic GVHD and extensive chronic GVHD (19 and 8 %, respectively). A previous report that focused on chronic GVHD showed that the incidences of chronic GVHD and extensive chronic GVHD after uBMT in Japan were 45.8 and 28.2 %, respectively [18]. In that study, only 203 of 2937 patients (7 %) received ATG [18]. In patients with an HLA-mismatched donor, the incidence of chronic GVHD was significantly higher than that in patients with an HLA-matched donor in previous studies [12, 13]. Compared to a previous report from Japan, the incidence of chronic GVHD in patients with ATG-F in our study seems to be promising, and the reduction of chronic GVHD was consistent with previous reports [4, 18].

In Western countries, the total dose of ATG-F for GVHD prophylaxis is usually 30–60 mg/kg [3, 4]. In Asian countries, as shown in the current study, a smaller dose of ATG is commonly used, since the incidence of GVHD itself is lower in Asian patients than in Caucasian patients [6, 7]. Kim et al. [8] reported that the use of low-dose ATG (Thymoglobulin 2.5 mg/kg) was associated with a low incidence of acute GVHD in patients who received an HLA-mismatched unrelated HSCT. In our study with a low dose of ATG-F (median 10 mg/kg), the incidences of both acute and chronic GVHD were relatively low. In a subset analysis, the use of a lower dose of ATG-F ($\leq$10 mg/kg) did not significantly increase the incidence of GVHD compared to ATG-F at a higher dose, albeit the size of the study was limited. A reduction of chronic GVHD should lead to not only a reduction of morbidity and mortality associated with chronic GVHD but also an improvement of QOL which is an important clinical outcome in long-term survivors [4, 19]. Such low dosages of ATG-F should be good candidates for testing in a prospective clinical trial.

Another concern with the use of ATG is a possible increase in infectious diseases [20]. The CIBMTR study showed that the incidence of EBV-related PTLD in patients with ATG was significantly higher than that in those without T cell depletion (2 vs. 0.1 %, $P = 0.005$) [20]. Although the number of patients was limited, there were no cases of PTLD in this study, which suggested that the immunosuppression with low-dose ATG-F was not very intense. However, the incidence of PTLD should be confirmed in a larger study.

This study has several limitations. Even though we included all patients in the registry who received ATG-F as GVHD prophylaxis for uBMT, the number of patients was still quite small. This must be because of the use of ATG-F as GVHD prophylaxis was not covered by insurance in Japan in the era of this study. Furthermore, the patients had heterogeneous characteristics. Especially, the underlying disease and the conditioning regimen varied significantly. As recently reported by Soiffer et al. [20], the benefit of ATG could differ depending on the intensity of the conditioning regimen. Therefore, based on the results of the current study, the impact of low-dose ATG-F with a uniform conditioning regimen and GVHD prophylaxis should be assessed.

In conclusion, the use of low-dose ATG-F in Japanese patients who underwent an uBMT was associated with promisingly low incidences of both acute and chronic GVHD, with a low incidence of late NRM. The role of low-dose ATG-F as prophylaxis for GVHD should be further assessed in a prospective clinical trial.

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Conflict of interest None.

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ERRATUM

Erratum to: Low incidences of acute and chronic graft-versus-host disease after unrelated bone marrow transplantation with low-dose anti-T lymphocyte globulin

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A published-ahead-of-print version of this article was made available online on 7 November 2012. Subsequently an error was discovered in Fig. 4. The corrected version of Fig. 4 is shown here. The major findings and conclusions of this paper are not affected by these changes.

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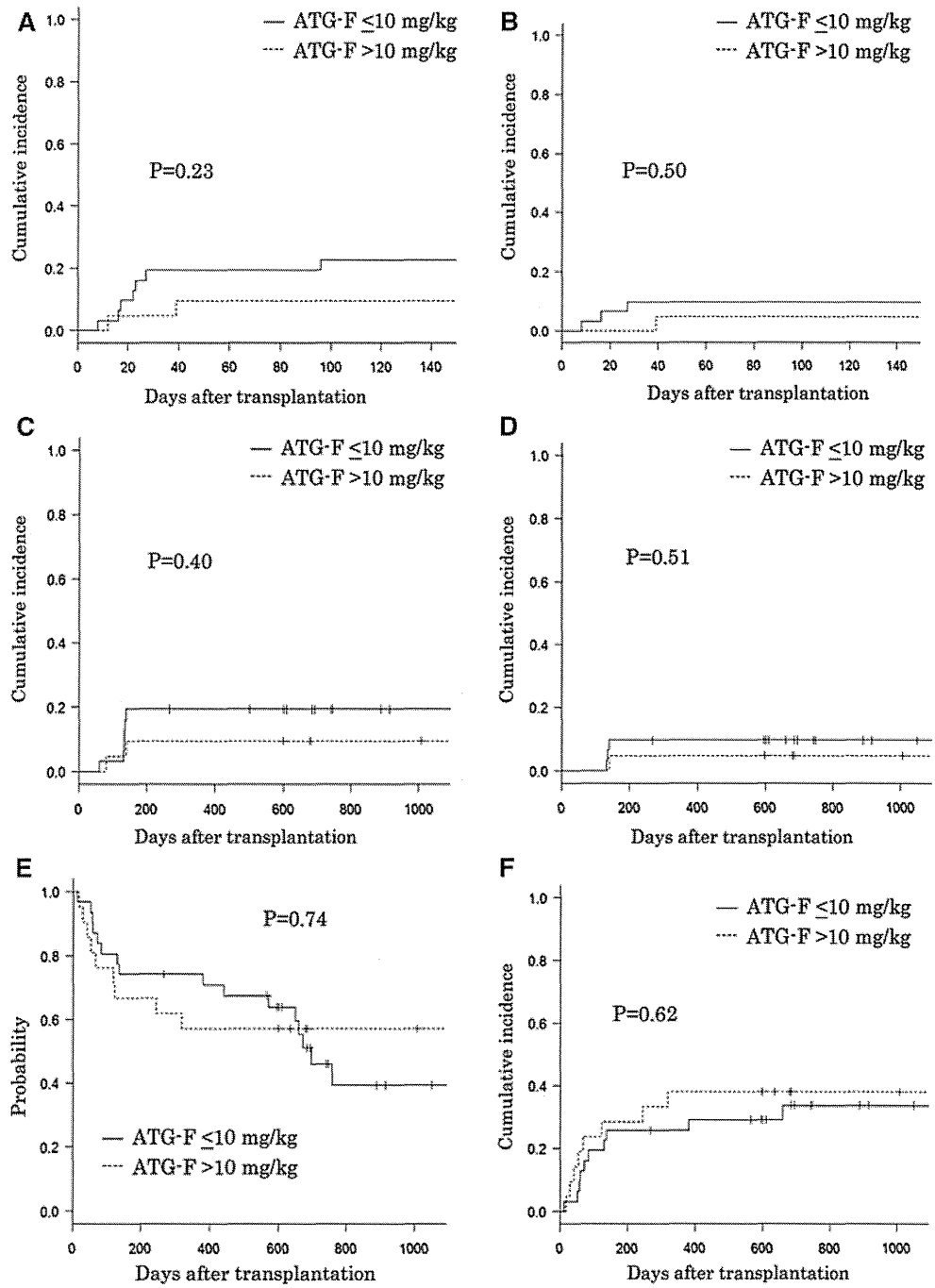

Fig. 4 Grade II–IV acute GVHD (**a**), grade III–IV acute GVHD (**b**), chronic GVHD (**c**), extensive chronic GVHD (**d**), overall survival (**e**) and non-relapse mortality (**f**) according to the dose of ATG-F in adult patients

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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.

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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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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, $P=0.001$).

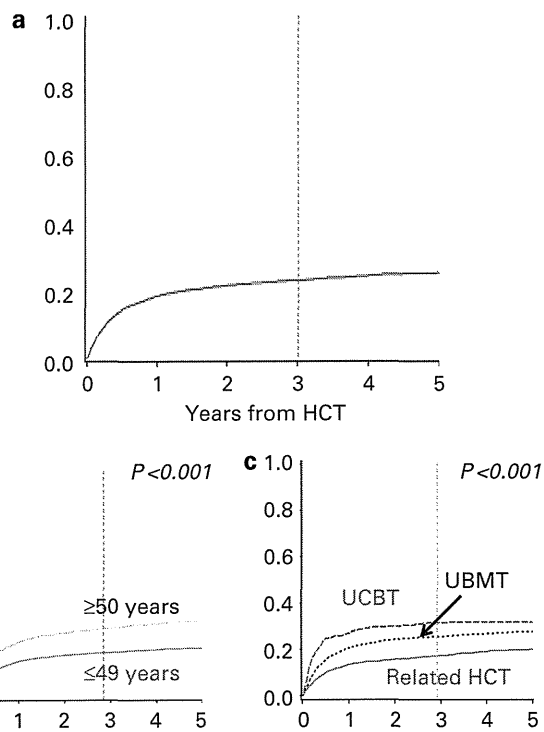

Figure 1. NRM over the past 12 years among 6501 patients who received allo-HCT in remission is shown in (**a**). NRM according to age (**b**) and donor source (**c**) are also shown.

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,

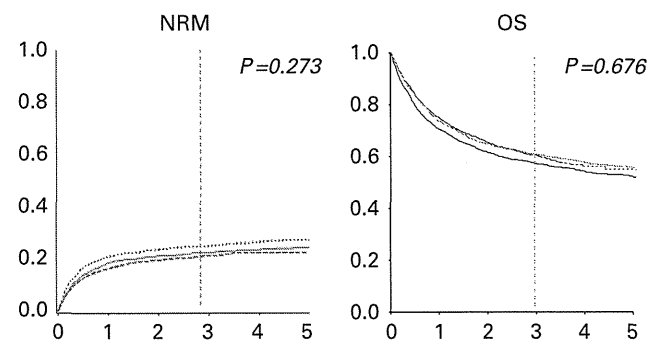

Figure 2. NRM and OS at 4-year periods (1997–2000, solid line; 2001–2004, dotted line; 2005–2008, dashed line) in the overall patients.

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.

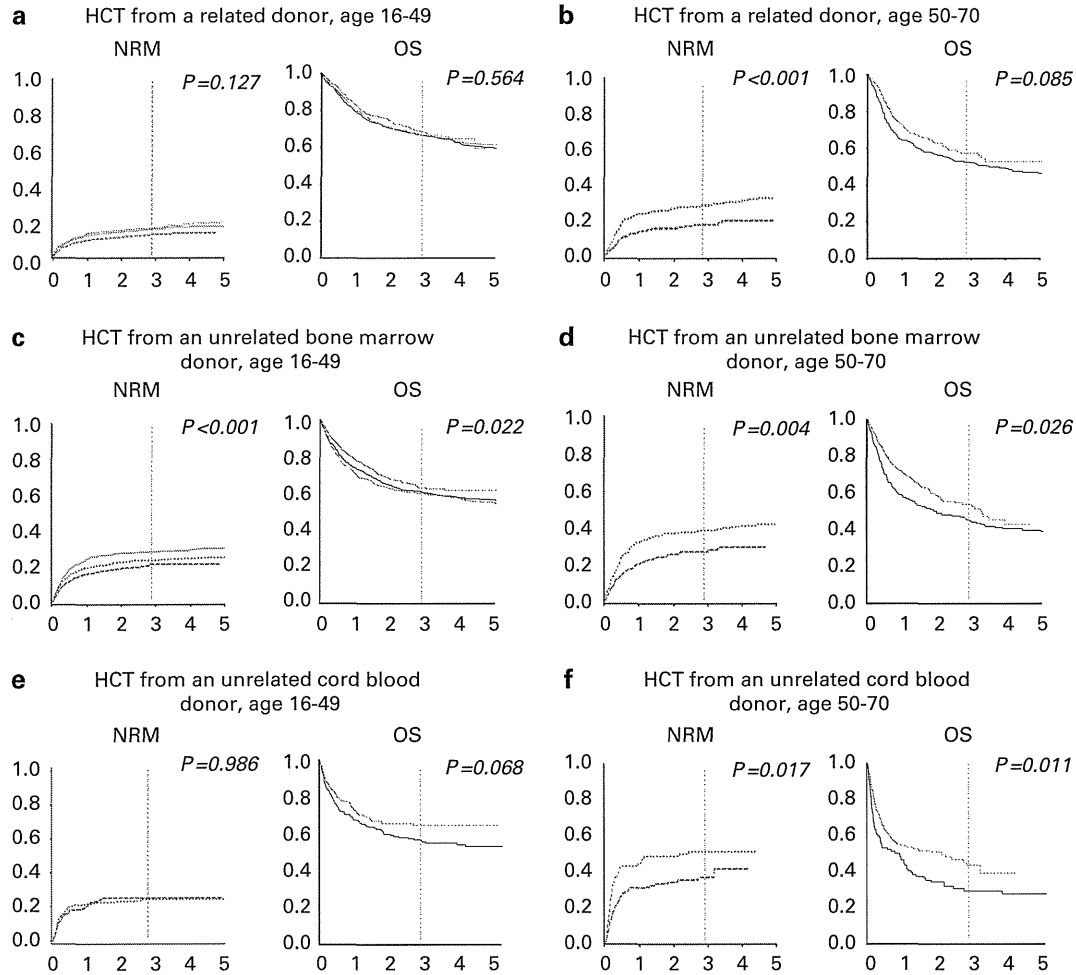

Figure 3. (**a**) NRM and OS at 3 years from HCT among younger patients (16–49 years) who received allo-HCT from a related donor were 15%, 16% and 12% ($P=0.127$), and 67%, 66% and 68% ($P=0.564$), respectively in the period of 1997–2000 ($n=587$, solid line), 2001–2004 ($n=620$, dotted line) and 2005-2008 ($n=639$, 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

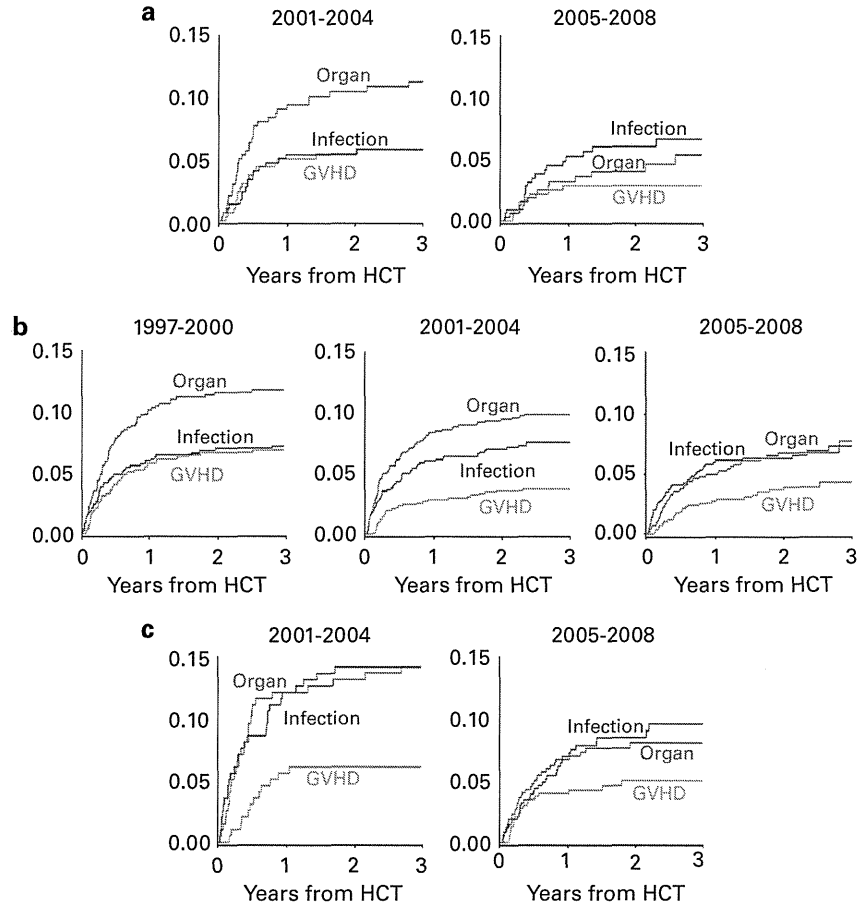

Figure 4. Change in the causes of NRM among different time periods is shown. Cumulative incidences of death due to GVHD, infection and organ failure are separately presented in each time period. (**a**) In older patients who received allo-HCT from a related donor, the incidences of death associated with 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.

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