secondary cancer and to promote patient education and preventive practices, since there has been a dramatic increase in the number of transplant recipients who are more than 50 years of age at transplant over the past decade. In comparison with the general population, younger patients were at a higher risk of developing a solid tumor. Several high-risk cancer sites (esophagus, liver, and bronchus/lung) in younger group did have only one observed cases, therefore, these results should not be emphasized and need to be confirmed in other studies. These sites were found to be significant because the expected numbers in general population for these sites were extremely small.

Although this study included a large number of recipients and a large number of person-years of follow-up, there are limitations. The follow-up years for older recipients were still limited, and therefore we may find a higher incidence of and risk of secondary solid cancers among recipients who are 50 years of age or older at transplant in the future. Second limitation involves possible under-reporting by recipients to transplant centers or by transplant centers to the registry. Until recently, transplant recipients have received only limited information regarding screening or the prevention of secondary solid cancers. Another limitation of this analysis was lack of central pathology review for secondary solid tumors. JSHCT data collection does not include the submission of specimen or pathology report. Since this study included transplants from 1990, central pathology review was difficult to perform at the time of analyses. In addition, limiting secondary tumors to centrally diagnosed tumors would decrease the number of identified secondary tumors; therefore, secondary solid tumors were identified as reported from transplant centers.

In conclusion, recipients of allogeneic hematopoietic stem cell transplant had a significantly higher risk of developing secondary solid cancers than the general population. Older recipients are at higher risk of developing secondary solid tumors, as in the general population. Lifelong screening is important for high-risk organ sites, especially for oral, pharynx, and esophageal cancers in recipients with active, or a history of, chronic GVHD.

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disclosure

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Age influences non-relapse mortality in adults with acute GVHD of varying severity following allogeneic hematopoietic cell transplantation

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Age influences non-relapse mortality in adults with acute GVHD of varying severity following allogeneic hematopoietic cell transplantation

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Abstract

We retrospectively analyzed 2682 patients who developed grade II–IV acute graft-versus-host disease (GVHD). On analysis with stratification into five age groups (20–29, 30–39, 40–49, 50–59, and ≥60), two-year non-relapse mortality rates (NRM) after the onset of GVHD were 20.7, 26.2, 26.6, 37.0 and 40.4% respectively ($p<0.001$). We found a significant interaction between the patient's age and GVHD severity with respect to NRM ($p=0.004$). On multivariate analyses stratified by GVHD severity, the hazard ratio (HR) for NRM in the groups aged 50 years or more (reference: age group of 20-29) was about twice as great in patients with grade II acute GVHD when compared with grade III–IV disease (HR in those aged 50–59 years: 2.9 for grade II and 1.5 for grades III–IV; HR if ≥60 years: 3.3 for grade II and 1.5 for grades III–IV).

Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is one of the curative therapies for hematologic malignancy. Although several studies reported a recent decrease in non-relapse mortality (NRM) [1, 2], NRM continues to be a major problem that decreases overall survival (OS) after allo-HCT. Acute graft-versus-host disease (GVHD) is a major cause of NRM and several studies have also reported that older age too results in increased NRM [3-5]. However relatively few reports describe the effect of age on NRM in patients who develop acute GVHD. Three recent reports show a significant increase in NRM in older patients who developed acute GVHD [6-8], whereas other reports show no such association [9-11]. Of these six reports, five studies [6-9, 11] included children, and two studies [9, 10] did not include patients aged over 55 years. Four of six reports included patients with grade I acute GVHD [6, 9-11]. No report investigated the influence of age on NRM in adult patients, including those over 55 years old, who developed grade II to IV acute GVHD, although it is reasonable to expect that older age might negatively influence transplant outcomes even if we limit our investigation to this population. We therefore embarked on a plan to explore this point more clearly, using a larger cohort. In addition, we suspected that the influence of a patient's age on NRM might differ depending on the severity of their acute GVHD, something that has not been reported. We hypothesized that the negative impact of older

age on NRM might be additively or synergistically greater in patients with grade III–IV acute GVHD than in those with grade II disease. In order to clarify this hypothesis, we planned to perform additional analyses stratified by the severity of acute GVHD.

Patients and methods

Collection of data

The clinical data, which were confirmed in 2010 using the Transplant Registry Unified Management Program (TRUMP), provided by the Japan Society for Hematopoietic Cell Transplantation (JSHCT). We conducted this study as one of the investigations of the GVHD working group of the Japan Society for Hematopoietic Cell Transplantation. From the 54072 patients in this database, we selected 8406 adult patients (20 years or older) with hematological malignancies, all of whom received their first allo-HCT between January 1, 2005 and December 31, 2009. After selection of 2960 (35.2%) patients with grade II to IV acute GVHD between day 1 and 200 after transplantation and exclusion of 278 patients with missing or inadequate data on major outcomes, we finally used 2682 patients for this study. This retrospective study was approved by the Data Management Committee of JSHCT and the Institutional Review Board of the Graduate School of Medicine, Osaka City University.

Definitions

Diagnosis and clinical grading of acute GVHD were performed according to established criteria [12]. Initial organ involvement was defined based on evaluation performed during the first three days from the day of onset. We added this factor to the analysis because a previous study reported that initial liver involvement worsened NRM [10]. NRM was defined as death without relapse or progression of the original disease. We considered the following patients to be at standard disease risk: acute leukemia in the first or second complete remission (CR), chronic myeloid leukemia (CML) in the first or second chronic phase, myelodysplastic syndrome (MDS) in the absence of refractory anemia with excess blasts, and lymphoma in complete remission. All other diseases were considered to be at high risk. We used the definition of conditioning intensity from previous reports [13]. In summary, any conditioning regimen that included total body irradiation > 8 Gray, melphalan >140 mg/m^2, or oral busulfan $\geq$ 9 mg/kg (intravenous busulfan $\geq$7.2 mg/kg) was defined as myeloablative conditioning. 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. A serological HLA-A, B, and DR 6/6 matched related donor was defined as a "matched related donor (MRD)"; a related donor matched for 3–5/6 antigens was defined as a "mismatched related donor

(MMRD)"; 6/6 matched HLA-A, B, and DRB1 alleles from an unrelated volunteer donor was defined as a "matched unrelated donor (MURD)", and any other unrelated volunteer donor was defined as a "mismatched unrelated donor (MMURD)". Cord blood (CB) was treated as a single donor category. Where multiple etiologies were mentioned as non-relapse causes of the death, the cause that most strongly contributed to NRM was selected.

Endpoints

The study endpoints were intended to clarify whether older age of adult patients was related to transplant outcomes (OS, NRM, and relapse) after grade II–IV acute GVHD and to identify whether older age has a different effect on NRM when patients are stratified according to the severity of acute GVHD.

Statistical analysis

Comparisons between the groups were performed using the chi-square test or extended Fisher's exact test as appropriate for categorical variables and the Mann-Whitney U-test for continuous variables. Time to OS was defined as the interval between the onset of acute GVHD and the last day of follow up. The probability of OS was estimated according to the Kaplan–Meier method, and the groups were compared using the log-rank test. Time to NRM or relapse was defined as the interval between the

onset of acute GVHD and the day of death due to a non-relapse cause or disease relapse/progression. The cumulative incidences of NRM and relapse were analyzed under the assumption that risk factors represented competing risks, defining relapse as a competing event for NRM [14], and comparisons between the groups were performed using Gray's test [15]. The Cox proportional hazards model was used to test the statistical significance of patient age (20–29, 30–39, 40–49, 50–59, or ≥60 years of age at transplant) for NRM, relapse, and OS, adjusted by the following covariates that are shown in table 1; patient gender, performance status (PS) as defined by the Eastern Cooperative Oncology Group score at transplantation, disease, disease status, sex mismatch between recipient and donor, cytomegalovirus serostatus, donor source, conditioning regimen, GVHD prophylaxis (cyclosporine- or tacrolimus-based, use of methotrexate or not, and with or without *in vivo* T cell depletion such as the use of ATG or Campath), acute GVHD grade, day of onset of acute GVHD, and initial organ involvement ('yes' or 'no' for skin, gut and liver). We treated acute GVHD grade as one of the factors at the time of onset of acute GVHD because we could not precisely identify from the database the day on which the maximum grade was attained. We performed these analyses in which we set up another category for those patients with missing data.

In the stratified analysis of the influence of age on NRM by severity of acute GVHD (grade II and III–IV), we also performed the analysis with adjustment using all of the factors included in Table 1 except for acute GVHD grade. In the analysis of the cause of death, the chi-square test was used for overall comparison between the age groups (20–49 and ≥50) in patients with grade II or III–IV acute GVHD.

Statistical analyses were performed using EZR [16] (Saitama Medical Center, Jichi Medical University, version 1.24), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, version 2.13.0) and Stata statistical software (Version 12, StataCorp, TX).

Role of the funding source

The role of the funding source was in part for research data collection and analyses.

Results

Patient characteristics

Table I shows the characteristics of all 2682 patients included in this study. Median age at transplant was 48 years (range: 20–82 years); 1824 patients (68%) had acute leukemia and 1322 patients (49%) had high-risk disease. Among age groups (20–29, 30–39, 40–49, 50–59, and ≥60), the distribution of following factors was significantly different; PS, disease, disease status, sex mismatch, cytomegalovirus serostatus, donor

source, conditioning regimen, GVHD prophylaxis (cyclosporine- or tacrolimus-based and use of methotrexate or not), day of onset of acute GVHD and initial skin involvement (Table I). There was no significant difference in grade of acute GVHD between age groups (p=0.62). During the follow-up period, 1263 patients (47%) died and median follow-up in survivors was 766 days after acute GVHD onset (range: 14–2076 days).

NRM, Relapse, and OS of each age group

The two-year cumulative incidence of NRM and relapse after onset of acute GVHD in all 2682 patients with grade II-IV acute GVHD was 31.1% (95% confidence interval (CI): 29.2–32.9) and 20.7% (95% CI: 19.1–22.3), respectively. The two-year OS in all patients was 51.8% (95% CI: 49.8–53.8). On analysis following stratification into five age groups (20–29, 30–39, 40–49, 50–59, and ≥60), the two-year cumulative incidences of NRM after grade II–IV acute GVHD were significantly different (two-year NRM: 20.7%, 26.2%, 26.6%, 37.0%, and 40.4% respectively (p<0.001; Figure 1a). Two-year OS was also significantly different between age groups (p<0.001), while the incidence of relapse was almost the same among all age groups (p=0.727) (Figure 1c and 1b, respectively), suggesting that older patient age was related to lower OS due to higher NRM after acute GVHD onset.

Then we analyzed the influence of age on transplant outcomes (NRM, relapse and OS), adjusted for the other factors shown in Table I. When compared with the group aged 20–29 years, older age groups showed higher hazard ratios (HR) for OS and NRM, and there were also significant differences for OS and NRM in the groups aged more than 40 years and more than 50 years respectively; for all groups there was no significant difference regarding relapse (Table II).

Effect of age on transplant outcome stratified by acute GVHD severity

First, for outcome we checked the interaction between patient age and GVHD severity (grade II or III–IV) — there was a significant interaction for NRM (p=0.004), but not for OS (p=0.51) or relapse (p=0.49). We therefore undertook an additional analysis for NRM alone, stratified by severity of acute GVHD (grade II or III-IV). On multivariate analysis, for grade II disease there was a significantly higher HR for NRM in groups aged 50 years or older (reference: age group of 20–29 years; HR: 2.9 (range: 1.8-4.8) in the group aged 50–59 years and 3.3 (range: 1.9-5.7) in the group aged ≥60 years). On multivariate analysis of the grade III–IV group, there was also a significantly higher HR for NRM in age groups of 50 years or older (HR: 1.5 (range: 1.03–2.1) in the group aged 50–59 years and 1.5 (range: 1.02–2.3) in the group aged ≥60 years). These results indicated that the HR for NRM in patients of 50 years or older was about twice

as great in the grade II group than in the grade III–IV group (Table III).

Cause of NRM after grade II-IV acute GVHD

We analyzed the causes of NRM in order to examine the reason why older age had a stronger effect on NRM in patients with grade II disease than in those with grade III–IV disease. In all 873 cases with NRM, the most common primary cause of NRM was infection (n=276, 31.6%), followed by GVHD (n=184, 21.1%) and organ failure (n=117, 13.4%). As anticipated, the proportion of NRM by GVHD was higher in grade III–IV acute GVHD than grade II (28.3% (142/501) and 11.2% (42/372), respectively). On overall comparison between two age subgroups (20–49 and >50 years old) in each of the grade II or III-IV groups with acute GVHD; there was no significant difference between the groups with grade II and III–IV acute GVHD (p=0.43 and p=0.06, Table IV).

Discussion

This study revealed the following two observations. First, those patients aged 50 years or older who developed grade II–IV acute GVHD had a risk of NRM that was about twice as great as that of those aged 20–29 years; this decreased their OS with acute GVHD. Second, there was an interaction between older age and the severity of acute GVHD with respect to NRM — older age may have a greater effect on NRM in

patients with grade II acute GVHD than in those with grade III–IV. The latter observation has not been reported previously; our study concentrated on the effect of older age and contains the largest cohort yet reported.

Several recent studies report the effect of age on transplant outcome and the initial treatment response after acute GVHD [6-11]. Three studies report that older age influences the prognosis of acute GVHD [6-8], although the patients assessed in these studies differed from ours in that one study contained grade I acute GVHD [6] and all of the studies contained children. Several studies that included the PAM score and EBMT score suggest that older age worsens NRM in all patients who received allo-HCT [1-3]. Our study, which was limited to patients who developed grade II–IV acute GVHD, also showed the same tendency. On the other hand, *Leisenning et al.* reported that there was no significant improvement in the area under the receiver operating characteristic curve when they added age as a continuous variable to the optimal model for predicting NRM after acute GVHD [9]. Robin et al. also showed that older age was not significantly associated with NRM after acute GVHD, comparing patients 15 years or older with those younger than 15 years, all of whom underwent myeloablative conditioning [10]. These results may be due to the lack of patients over 55 years old. *Levine et al.* also reported that age did not influence the likelihood of response to initial treatment of

GVHD measured on day 28, and that these findings correlated with NRM, despite having patients in the age range of 8–70 years [11]. There is no clear explanation why our findings differ, however, the following points may be relevant: 1) their study included grade 0–I acute GVHD and children; 2) the age groups they used (<10, 10–17, 18–35, and >35) were different from our study.

Although we initially anticipated that more severe acute GVHD would additively or synergistically lead to worse NRM in older patients than in younger patients, our results unexpectedly showed that age had a greater effect on NRM with grade II acute GVHD than with grade III–IV. This result indicates the possibility that severe acute GVHD caused higher NRM regardless of age as shown by the elevation of NRM even in younger patients, and that the influence of age on NRM showed a relative decline. On examination of the causes of NRM in the group with grade II GVHD, infection made up a higher proportion in patients aged 50 years or older than in those aged 20–49 years (36.7% (80/218) and 29.2% (45/154), respectively). This result suggests that we may need to pay more attention to infectious complications in patients with grade II acute GVHD aged 50 years or older, as well as in all patients with grade III–IV acute GVHD.

This study has the following limitations. First, although our study includes the largest and most recently published cohort, information bias cannot be avoided in a

retrospective study. Second, heterogeneous background factors that include diseases, conditioning regimens and GVHD prophylaxis may also have resulted in bias, although we tried to adjust for possible confounders with the use of multivariate analyses. Third, in this retrospective study, we treated the maximum grade of acute GVHD as one of the factors at acute GVHD onset, not as a time-dependent covariate because the day on which the maximum grade was attained was not recorded in the database. Our results need to be carefully interpreted with respect to these points.

In conclusion, older age significantly increased NRM and worsened OS after grade II–IV acute GVHD, and for NRM there was an interaction between older age and acute GVHD severity. The influence of older age on NRM after acute GVHD might be greater in patients with grade II acute GVHD than in those with grade III–IV disease. These findings should be considered in future study of acute GVHD.

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Conflict of interest

The authors declare no conflict of interest.

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