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# Graft-versus-Host Disease–Free, Relapse-Free Survival after Allogeneic Stem Cell Transplantation for Myelodysplastic Syndrome

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Graft-versus-host disease–free, relapse-free survival (GRFS) is a composite endpoint that measures survival free of relapse or significant morbidity after allogeneic hematopoietic stem cell transplantation (HSCT). Consecutive adult patients (N = 324) who received HSCT with fludarabine and busulfan–based conditioning for myelodysplastic syndrome (MDS) or secondary acute myeloid leukemia evolved from MDS were retrospectively analyzed. One-year and 3-year GRFS rates were 47.8% and 34.5%, respectively. Three fixed factors (circulating blast > 3%, high cytogenetic risk, and high comorbidity index) and 2 factors (which are) modifiable by clinicians (myeloablative conditioning [MAC] and low-dose [<7.5 mg/kg] antithymocyte globulin [ATG]) were independent factors for poor GRFS. Based on these 5 factors, 3 groups (3-year GRFS: 64.9% in low risk, 33.6% in intermediate risk, and 6.6% in high risk; $P < .001$) were identified. Fixed factor–adjusted GRFS in patients receiving reduced-intensity conditioning (RIC) plus high-dose ATG (≥7.5 mg/kg) was superior ($P < .001$) to those receiving MAC and/or low-dose ATG. Favorable influences of RIC plus ATG ≥ 7.5 mg/kg were evident in the low-risk group defined by fixed factors (3-year GRFS, 38.9% versus 4.4%; $P < .001$) but were not evident in the high-risk group (3-year GRFS, .0% versus 5.3%; $P = .678$). Conclusively, this study suggests that risk-adapted selection of conditioning intensity and ATG could improve qualified HSCT outcomes.



## INTRODUCTION

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal stem cell disorders with dismal prognosis [1], especially in patients with higher-risk MDS or those with lower-risk MDS having poor prognostic features [2]. Despite recent advances in knowledges of genetic and molecular pathogenesis [3], therapies for MDS currently are nonspecific approaches with unsatisfactory results. Among variable therapeutic options, allogeneic hematopoietic stem cell transplantation (HSCT) is peculiar in that it is the only considered option to cure MDS [4]. Advances in transplant technologies over time, such as high-resolution HLA typing, better supportive care, and development of reduced-intensity conditioning (RIC) regimens, have resulted in reduced transplant-related toxicities and enabled increasing use of HSCT in older or less fit patients [5,6]. More recent success in HSCT using alternative donors has also extended the use of allogeneic HSCT to a wider number of patients with MDS [7,8].

Long-term survival rate in HSCT for MDS patients ranges from 25% to 70%, indicating that a substantial portion of patients still experience treatment failure because of relapse or treatment-related mortality (TRM) [9,10]. Among various factors associated with those events, graft-versus-host disease (GVHD) is a key event because it can counterbalance the 2 components of transplant failure. GVHD itself and concomitant infections often related to treatment for GVHD are leading causes of TRM [11,12]. On the contrary, efforts to minimize GVHD can abrogate graft-versus-leukemia effects and increase relapse risk in MDS [13]. In addition to influences of GVHD on mortality, late morbidity caused by chronic GVHD also limits qualified success of HSCT [14,15]. All these findings suggest that successful achievement of both the graft-versus-leukemia effect and GVHD control with low immunosuppressive burden is fundamental for better relapse-free survival with good quality of life [11,16,17]. Such a qualified success of HSCT could be

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assessed by incorporating events of clinically significant GVHD into traditional transplant outcome measures. Composite endpoint of GVHD-free, relapse-free survival (GRFS) has been developed [18]. GRFS is being actively analyzed in various transplant settings or diseases. However, it has never been assessed solely in patients with MDS.

Therefore, the objective of this study was to retrospectively analyze overall GRFS in a large cohort of MDS patients receiving uniform conditioning regimens. We also tried to identify independent factors of GRFS for the development of a risk-stratified approach to improve GRFS, focusing on modifiability of influencing factors.

## METHODS

### *Patient Selection*

A total of 348 consecutive adult patients with MDS or secondary acute myeloid leukemia (AML) arising from MDS who received allogeneic HSCT between May 2004 and March 2016 at our center were enrolled as our initial cohort. With the intention to have at least a 1-year follow-up period, data were observed on March 2017. All patients received allogeneic HSCT after conditioning consisting of fludarabine and busulfan with or without total body irradiation. Excluded patients were as follows: 4 patients without marrow examination at the time of HSCT, 19 patients who enrolled in a previous phase I trial designed to administer post-HSCT preemptive chemotherapy [19], and 1 patient who received different GVHD prophylaxis consisting of alemtuzumab. After that, the final study cohort included 324 patients with MDS or secondary AML arising from MDS. This retrospective study was approved by the Institutional Review Board of the Seoul St. Mary's Hospital.

### *Definitions*

For hemogram at HSCT, hemoglobin level and platelet count independent of transfusion for at least 7 days and absolute neutrophil count without granulocyte colony-stimulating factor just before conditioning were documented. MDS, secondary AML arising from MDS, and related disease were diagnosed and categorized by the World Health Organization 2016 criteria [20]. Response at the time of HSCT after bridge therapy including pre-HSCT hypomethylating therapy or intensive chemotherapy was assessed according to the International Working Group 2006 criteria [21]. Refractoriness to bridge therapy included both primary and secondary treatment failure. Primary treatment failure was defined as stable disease without hematologic improvement or disease progression. Secondary treatment failure included failure after a complete response, partial response, marrow complete response, or stable disease with hematologic improvement [22]. Cytogenetics was classified according to the MDS Comprehensive Cytogenetic Scoring System [23]. Hematopoietic cell transplantation–specific comorbidity index (HCT-CI) was assessed according to Sorror et al. [24]. Acute and chronic GVHD were diagnosed and graded according to recent consensus criteria [25,26].

### *Transplantation Procedure, GVHD Prophylaxis, and Supportive Care*

Patients received either a RIC or myeloablative conditioning (MAC) regimen according to the treating physician's decision mainly based on disease status and comorbidities. Fludarabine (30 mg/m$^2$ per day for 5 days on days −6, −5, −4, −3, and −2) and busulfan (3.2 mg/kg per day for 2 days on days −5 and −4) were used for RIC, whereas fludarabine (30 mg/m$^2$ per day for 5 days on days −6, −5, −4, −3, and −2) and busulfan (3.2 mg/kg per day for 4 days on days −5, −4, −3, and −2) were administered for MAC. For GVHD prophylaxis a calcineurin inhibitor (tacrolimus for unrelated or haploidentical related donors and cyclosporine for sibling donors) was administered from day −1 in combination with a short-term course of methotrexate (5 mg/m$^2$ i.v. bolus on days +1, +3, +6, and +11). Total body irradiation was given for all transplants using haploidentical related donors and a subset of transplants of matched sibling or unrelated donors with a dose ≤ 800 cGy according to the treating physician's discretion. During conditioning antithymocyte globulin (ATG, Thymoglobulin; Sanofi Genzyme, Lyon, France) at various doses was infused i.v. into all patients who received stem cells from haploidentical related donors and a subset of patients who received HSCT from sibling or unrelated donors. Use of ATG and its dose were selected according to the treating physician's discretion. During transplantation procedures all patients were treated in a designated room with laminar airflow isolation. Other general supportive care, including administration of granulocyte colony-stimulating factor, prophylaxis of veno-occlusive disease, and administration of prophylactic antibiotics, was performed as described in our previous reports [8,27].

### *Statistical Methods*

Overall survival (OS) was defined as the time from transplant to death from any cause or date of the last follow-up. Events for disease-free survival (DFS) were relapse or death. TRM was defined as death from any cause during continuous remission. Probabilities of relapse and TRM rates were calculated by cumulative incidence estimation treating nonrelapse deaths and relapse as competing risks, respectively. Cumulative incidence of GVHD was estimated considering competing risks including treating deaths, relapse, donor lymphocyte infusion, and graft failure. GRFS events were defined as the first event among grades III to IV acute GVHD, chronic GVHD requiring systemic treatment, cytogenetic or hematologic relapse, and death from any cause after HSCT. In analysis of frequencies of GRFS events, censoring data included patients who did not experience GRFS events or those who did not reach the specific time point.

OS, DFS, and GRFS rates were calculated using the Kaplan-Meier method and compared using the log-rank test. Investigating the association of factors with GRFS and an estimation of adjusted probabilities for GRFS was carried out using the Cox proportional hazard regression model. Variables with $P < .1$ in univariate analyses were entered into multivariate models with an exception for factor of donor type (sibling, unrelated, and haploidentical related). Finally, variables with $P < .1$ and factor of donor type regardless of $P$ value were included in multivariate models using a backward stepwise model selection. Scoring systems for predicting GRFS were developed using significant parameters with $P < .05$ in the multivariate analysis. Risk score was assigned for each parameter with a respective $\beta$-coefficient that was standardized to give the lowest score a value of 1. With gradation of .5 (ie, 1.0, 1.5, 2.0, and so on), other values were rounded to the nearest gradation according to their standardized $\beta$-coefficient values. All statistical analyses were conducted using R.3.1.1 statistical software (http://cran.r-progect.org/) and SPSS (SPSS Inc., Chicago, IL).

## RESULTS

### *Patient Characteristics*

The median age of patients at HSCT was 49.0 years (range, 18 to 69). Of all study patients (N = 324), 130 patients (40.1%) underwent upfront transplantation, whereas 194 (59.9%) patients initially received bridge therapy, including hypomethylating therapy (n = 149) and intensive chemotherapy (n = 45). Refractoriness to bridge therapy was shown in 110 of 194 patients (56.7%) who received bridge therapy. Cytogenetic status at HSCT was composed of 4 very low (1.2%), 167 low (51.5%), 94 intermediate (29.0%), 29 poor (9.0%), 12 very poor (3.7%), and 18 monosomal (5.6%) karyotypes. Risk groups were assessed by the Revised International Prognostic Scoring System at the time of HSCT and included 22 very low (6.8%), 37 low (11.4%), 95 intermediate (29.3%), 90 high (27.8%), and 80 very high (24.7%). Eighty-three patients (25.6%) had HCT-CI scores ≥ 3. Stem cells were collected from 144 matched sibling (44.4%), 109 unrelated (33.6%), and 71 haploidentical related (21.9%) donors. RIC was used for 219 patients (67.6%), whereas MAC was administered in 105 patients (32.4%). ATG was administered in 257 patients (79.3%) with a median dose of 10.0 mg/kg (range, 2.5 to 10). Other characteristics are summarized in Table 1.

### *Conventional Outcomes and GVHD*

After a median follow-up of 47.2 months (range, 12.4 to 181.2) for survivors, estimated OS and DFS rates at 3 years were 62.4% (95% confidence interval [CI], 56.7 to 67.6) and 58.8% (95% CI, 53.1 to 64.1), respectively. Three-year cumulative incidences of relapse and TRM were 21.1% (95% CI, 16.7 to 25.8) and 19.7% (95% CI, 15.5 to 24.3), respectively (Supplementary Figure 1), whereas 180-day cumulative incidences of grades II to IV and III to IV acute GVHD were 34.0% (95% CI, 28.8 to 39.1) and 11.7% (95% CI, 8.5 to 15.5), respectively. Three-year cumulative incidence of mild to severe chronic GVHD was 45.9% (95% CI, 40.3 to 51.4), whereas that of chronic GVHD requiring systemic treatment was 29.5% (95% CI, 24.4 to 34.6) (Supplementary Figure 2).

**Table 1**
Patient Clinical Characteristics (N = 324)

| Variables | Value |
|---|---|
| Median age of patient at HSCT, yr (range) | 49.0 (18-69) |
| Median age of donor at HSCT, yr (range) | 37.0 (12-71) |
| Gender | |
| Male | 218 (67.3) |
| Female | 106 (32.7) |
| Sex mismatch | |
| Female → male | 87 (26.9) |
| Others | 237 (73.1) |
| ABO match | |
| Identical | 190 (58.6) |
| Minor mismatch | 51 (15.7) |
| Major mismatch | 83 (25.6) |
| Transplant period | |
| 2004-2008 | 55 (17.0) |
| 2009-2016 | 269 (83.0) |
| Median interval from diagnosis to transplant, mo (range) | 8.7 (1.3-267.2) |
| Pre-HSCT chemotherapy | |
| Upfront HSCT | 130 (40.1) |
| Hypomethylating therapy | 149 (46.0) |
| Intensive chemotherapy | 45 (13.9) |
| Refractoriness to bridge therapy at HSCT | |
| No | 214 (66.0) |
| Yes | 110 (34.0) |
| Worst WHO classification before HSCT | |
| MDS with single lineage dysplasia, ring sideroblast, or isolated del(5q) | 10 (3.1) |
| MDS with multilineage dysplasia | 72 (22.2) |
| MDS with excess blasts-1 | 77 (23.8) |
| MDS with excess blasts-2 | 98 (30.2) |
| Chronic myelomonocytic leukemia | 12 (3.7) |
| MDS-u or MDS/MPN-u | 8 (2.5) |
| Secondary AML | 47 (14.5) |
| Median hemoglobin at HSCT, g/dL (range) | 7.9 (3.1-15.1) |
| Median absolute neutrophil count at HSCT, $\times 10^9$/L (range) | .65 (.0-26.86) |
| Median platelet count at HSCT, $\times 10^9$/L (range) | 48.0 (5.0-1010.0) |
| Median circulating blast at HSCT, % (range) | .0 (.0-92.0) |
| Median marrow blast at HSCT, % (range) | 4.0 (.0-90.0) |
| Cytogenetic status at HSCT | |
| Very low | 4 (1.2) |
| Low | 167 (51.5) |
| Intermediate | 94 (29.0) |
| High | 29 (9.0) |
| Very high | 12 (3.7) |
| Monosomal karyotype | 18 (5.6) |
| Revised International Prognostic Scoring System risk at HSCT (just before conditioning) | |
| Very low | 22 (6.8) |
| Low | 37 (11.4) |
| Intermediate | 95 (29.3) |
| High | 90 (27.8) |
| Very high | 80 (24.7) |
| HCT-CI | |
| Low to intermediate (score $< 3$) | 241 (74.4) |
| High (score $\geq 3$) | 83 (25.6) |
| Stem cell source | |
| Bone marrow | 12 (3.7) |
| Peripheral blood | 312 (96.3) |
| Donor type | |
| Matched sibling | 144 (44.4) |
| Unrelated | 109 (33.6) |
| Well matched (8/8) | 81 (25.0) |
| Partial matched | 14 (4.3) |
| Mismatched | 14 (4.3) |
| Haploidentical related | 71 (21.9) |
| Conditioning regimens | |
| Fludarabine (150 mg/m$^2$) and busulfan (6.4 mg/kg) | 219 (67.6) |
| Fludarabine (150 mg/m$^2$) and busulfan (12.8 mg/kg) | 105 (32.4) |
| Total body irradiation | |
| Yes (400 or 800 cGy) | 110 (34.0) |
| No | 214 (66.0) |
| ATG use | |
| Yes | 257 (79.3) |
| No | 67 (20.7) |

Values are n (%) unless otherwise defined. WHO indicates World Health Organization; MDS-u, myelodysplastic syndrome, unclassifiable; MDS/MPN-u, myelodysplastic/myeloproliferative neoplasms, unclassifiable.

### GRFS and Its Events

After a median duration of 41.1 months (range, 12.1 to 148.9) for patients who did not experience GRFS events (n = 113), estimated GRFS rates at 1 and 3 years were 47.8% (95% CI, 42.3 to 53.2) and 34.5% (95% CI, 29.2 to 39.9), respectively (Figure 1A). At 1 and 3 years of HSCT the order of GRFS events frequencies was similar. The most frequent GRFS event was chronic GVHD requiring systemic treatment, followed by relapse, grades III to IV acute GVHD, and death from any cause. Each frequency of GRFS event is shown in Figure 1B.

### Analyses of Factors Affecting GRFS

Using potential variables for GRFS derived from univariate analysis (Supplementary Table 1), multivariate analysis was done to identify significant factors affecting poor GRFS: circulating blast > 3% at HSCT, monosomal karyotype or very poor cytogenetic risk, high HCT-CI, MAC, and HSCT with ATG at a dose of 2.5 to 5.0 mg/kg or without ATG (Table 2). Donor type was intentionally included in the multivariate analysis regardless of *P* value in the univariate analysis. It did not affect GRFS rate.

Effect of independent factors of GRFS on conventional transplant outcomes and GVHD incidence was also assessed (Table 3). Circulating blast, cytogenetic status, and HCT-CI affected OS and DFS with statistical significance (all $P < .001$). Circulating blast was significantly associated with both relapse and TRM, whereas cytogenetic status and HCT-CI were only associated with relapse and TRM, respectively. ATG dose significantly affected the incidence of both grades III to IV acute GVHD ($P = .040$) and chronic GVHD requiring systemic treatment ($P < .001$). However, conditioning intensity had no significant impact on overall outcome or GVHD.

### Scoring System and Development of a Model for GRFS

Risk score for each patient was obtained by summing each score of 5 parameters (Table 4). Based on GRFS rates according to risk scores (Supplementary Figure 3A), 3 risk groups for GRFS were developed. GRFS rate at 3 years was 64.9% (95% CI, 50.2 to 76.3), 33.6% (95% CI, 27.1 to 40.1), and 6.6% (95% CI, 1.8 to 15.8) in the low-risk group (score, 0), intermediate-risk group (score, 1.0 to 3.5), and high-risk group (score ≥ 4), respectively (Figure 2A; all $P < .001$). Figure 2B shows frequencies of GRFS events at 3 years according to risk groups. Frequencies of relapse, death from any cause, and grades III to IV acute GVHD showed increasing trends with advancing risk, whereas those of chronic GVHD requiring systemic treatment did not show such trends according to increasing risk.

### Differential Impact of Modifiable Factors on GRFS

Because conditioning intensity and ATG dose can be chosen at the time of HSCT, these modifiable factors could affect GRFS outcomes. To determine their influences we analyzed fixed factor–adjusted GRFS rate according to their combinations. The group receiving RIC plus ATG ≥ 7.5 mg/kg showed superior GRFS rate in comparison with other combinations (Figure 3). To investigate the interaction between modifiable and fixed factors (circulating blast, cytogenetic status, and HCT-CI) on GRFS, we reconstructed another model only based on scores of fixed factors (f-GRFS model) in the same manner (Table 4 and Supplementary Figure 3B). As shown in Figure 4A, the f-GRFS scoring system discriminatively divided patients into 2 groups (low risk [score < 2.5], 38.9% [95% CI, 33.0 to 44.8] at 3 years versus high risk [score ≥ 2.5], 4.4% [95% CI, .4 to 16.3] at 3 years; $P < .001$). Regarding GRFS events, higher frequencies of relapse, death from any cause, and grades III to IV acute GVHD were observed in the high-risk group compared with those in the low-risk group (Figure 4B). When GRFS rate was separately analyzed in low-risk and high-risk groups of the f-GRFS model, there were significant differences in GRFS rate between patients receiving RIC plus ATG ≥ 7.5 mg/kg and others in the low-risk group (56.8% [95% CI, 43.3 to 68.2] versus 32.7% [95% CI, 26.3 to 39.2], $P < .001$) (Figure 4C) but not in the high-risk group (Figure 4D). These results suggest that modifiable factors have differential impacts on GRFS according to risk levels derived from fixed factors.

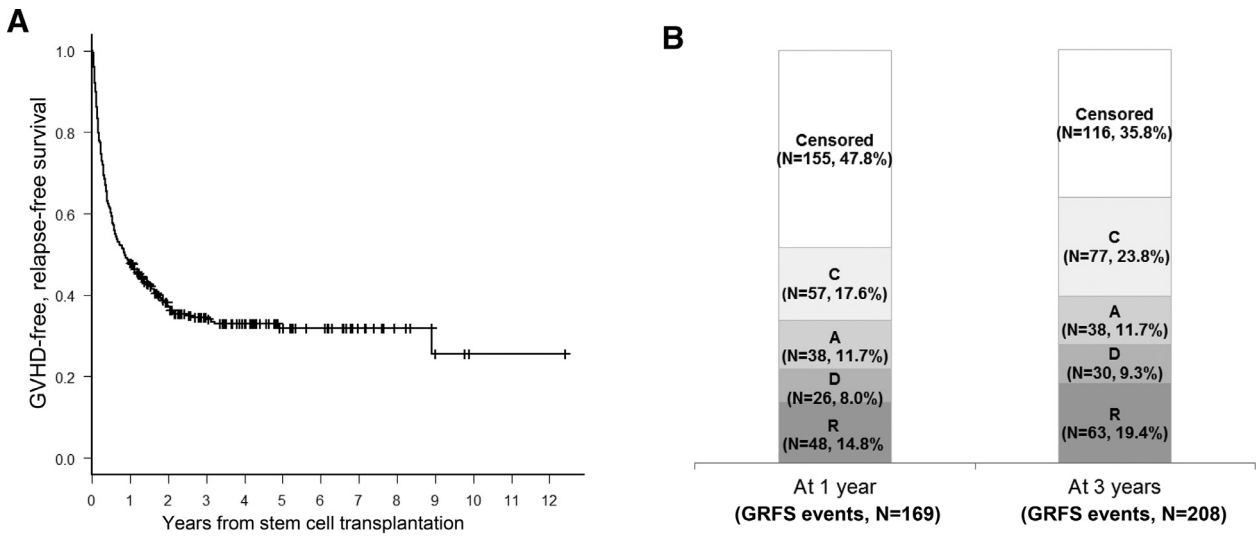


**Figure 1.** (A) Estimated GRFS in total patients. (B) Distribution of GRFS events at 1 and 3 years. R indicates relapse; D, death from any cause; A, grades III to IV acute GVHD; C, chronic GVHD requiring systemic treatment.

**Table 2**
Multivariate Analysis of Factors Affecting GRFS

| | Univariate | | | Multivariate | |
|---|---|---|---|---|---|
| Variable | No. of Patients | GRFS at 3 Years (%) (95% CI) | *P* | HR (95% CI) | *P* |
| Donor age | | | .025 | | .070 |
| Age ≤ 37 yr | 154 | 40.8 (32.8-48.6) | | 1 | |
| Age > 37 yr | 170 | 28.7 (21.8-36.0) | | 1.301 (.979-1.730) | |
| Sex mismatch | | | .051 | | .104 |
| Other | 237 | 37.8 (31.4-44.1) | | 1 | |
| Female → male | 87 | 25.5 (16.5-35.5) | | 1.293 (.949-1.761) | |
| Refractoriness to bridge therapy at HSCT | | | .009 | | .052 |
| No | 214 | 38.4 (31.6-45.1) | | 1 | |
| Yes | 110 | 27.1 (18.8-36.0) | | 1.329 (.997-1.772) | |
| History of AML before HSCT | | | <.001 | | .165 |
| No progression to AML | 277 | 37.6 (31.7-43.5) | | 1 | |
| Progression to AML | 47 | 16.2 (7.2-28.4) | | 1.331 (.889-1.994) | |
| Circulating blast at HSCT | | | <.001 | | .001 |
| ≤3% | 289 | 36.6 (30.8-42.3) | | 1 | |
| >3% | 35 | 17.1 (7.0-31.1) | | 1.984 (1.320-2.982) | |
| Bone marrow blast at HSCT | | | .001 | | .925 |
| <10% | 264 | 37.5 (31.5-43.5) | | 1 | |
| ≥10% | 60 | 19.5 (9.3-32.5) | | .981 (.651-1.477) | |
| Cytogenetic status | | | <.001 | | <.001 |
| Very good to poor | 294 | 37.5 (31.8-43.3) | | 1 | |
| Monosomal karyotype or very poor | 30 | 4.4 (.4-17.9) | | 2.329 (1.534-3.536) | |
| HCT-CI | | | .001 | | .009 |
| Low/intermediate risk (score < 3) | 241 | 38.4 (32.0-44.6) | | 1 | |
| High risk (score ≥ 3) | 83 | 22.9 (13.8-33.3) | | 1.516 (1.111-2.069) | |
| Conditioning intensity | | | .039 | | .001 |
| RIC with FB2 | 219 | 37.0 (30.3-43.7) | | 1 | |
| MAC with FB4 | 105 | 29.3 (20.9-38.2) | | 1.700 (1.241-2.330) | |
| ATG dose | | | <.001 | | <.001 |
| 7.5-10.0 mg/kg | 154 | 43.2 (34.8-51.3) | | 1 | |
| 2.5-5.0 mg/kg | 103 | 33.0 (23.9-42.3) | | 1.378 (.969-1.960) | .074 |
| None | 67 | 17.1 (9.2-27.2) | | 2.296 (1.596-3.303) | <.001 |
| Donor source | | | .204 | | .285 |
| Matched sibling | 144 | 28.3 (20.8-36.2) | | 1 | |
| Unrelated | 109 | 39.9 (30.3-49.3) | | .999 (.680-1.466) | .994 |
| Haploidentical related | 71 | 38.3 (26.8-49.7) | | .642 (.359-1.146) | .134 |

HR indicates hazard ratio; FB2, B2, fludarabine 30 mg/m2/day for 5 days plus busulfan 3.2 mg/kg/day for 2 days; FB4, fludarabine 30 mg/m2/day for 5 days plus busulfan 3.2 mg/kg/day for 4 days.

## DISCUSSION

In this study we observed that 47.8% and 34.5% of MDS patients survived up to 1 year and 3 years, respectively, without GRFS events. Independent factors for GRFS were percentages of circulating blast, risk groups of cytogenetics, HCT-CI, conditioning intensity, and use of ATG. Models comprising these factors were helpful for predicting GRFS rate. Intensity of conditioning regimens and ATG use affected GRFS rate. However, favorable impacts of RIC and ATG were limited to a subset of patients having lower risks stratified by fixed factors.

GRFS is believed to be a better proposal for qualified transplant outcomes. Prior studies have shown that the probability of GRFS in patients with heterogeneous hematologic malignancies is 25.0% to 50.0% at the first year after HSCT [18,28–30]. By analyzing transplant recipients of MDS only, our results showed relatively high GRFS rates. To the best of our knowledge, this is the first report on GRFS of the disease. Our study extended evaluation of GRFS rates up to 3 years to reflect more valid healthy recovery after HSCT. Frequencies of GRFS events were in the order of chronic GVHD requiring systemic treatment, relapse, grades III to IV acute GVHD, and death. This order was similar to that of previous study that included patients with myeloid malignancies [28].

Unlike other studies, the homogeneity of the disease entity and conditioning regimen of our study were found to be appropriate for identifying influencing factors. Thus, we modeled a scoring system for the anticipation of GRFS that would be helpful in designing HSCT. Among identified factors, fixed variables of percentages of circulating blast, risk groups of cytogenetics, or HCT-CI could not be modified at the time of HSCT by treating physicians. However, conditioning intensity and use of ATG could be chosen to enhance GRFS rate. Regarding fixed factors, their well-known influences on relapse or TRM were also reflected in GRFS prediction. Shaffer et al. [31] recently showed that circulating blasts > 3% and high cytogenetic risk are predictors of survival. For cytogenetics and HCT-CI, their impacts on relapse or TRM were also validated by studies analyzing factors for HSCT in MDS [3,32].

Regarding modifiable factors, our study showed that RIC was an independent factor for better GRFS despite inconclusive association between RIC and GRFS in prior studies. Two recent retrospective analyses for patients with AML have shown similar GRFS rates between RIC and MAC [33,34]. Holtan et al. [18] also reported that RIC does not improve GRFS in a cohort with various hematologic disease. On the other hand, results of prospective studies comparing RIC and MAC [35,36] seem to support our observation. Despite the absence of direct relationship between GRFS and RIC, RIC resulted in lower incidence of both acute and chronic GVHD with better quality of life compared with MAC without compromising either OS or DFS in a subgroup consisting of MDS. Although included cases of MDS were relatively small in that study, better GRFS could depend on RIC considering that GRFS reflects an ideal heathy recovery including quality of life [37]. Considering another

**Table 3**
Overall Outcomes According to Factors Affecting GRFS

| Variables | OS at 3 Years (95% CI) | *P* | DFS at 3 Years (95% CI) | *P* | Cumulative Incidence of Relapse at 3 Years (95% CI) | *P* | Cumulative Incidence of TRM at 3 Years (95% CI) | *P* | Cumulative Incidence of Acute GVHD Grades III-IV at 180 Days (95% CI) | *P* | Cumulative Incidence of Chronic GVHD Requiring Systemic Treatment at 3 Years (95% CI) | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Circulating blast at HSCT | | <.001 | | <.001 | | .026 | | <.001 | | .149 | | .054 |
| ≤3% | 66.6 (60.6-71.9) | | 62.5 (56.4-67.9) | | 19.5 (15.1-24.5) | | 17.6 (13.3-22.3) | | 11.1 (7.8-15.0) | | 31.3 (25.9-36.9) | |
| >3% | 28.6 (14.9-43.8) | | 28.6 (14.9-43.8) | | 34.3 (19.0-50.2) | | 37.1 (21.3-53.0) | | 17.1 (6.8-31.4) | | 14.3 (5.0-28.2) | |
| Cytogenetic status | | <.001 | | <.001 | | <.001 | | .130 | | .444 | | .056 |
| Very good to poor | 66.9 (60.9-72.1) | | 63.2 (57.2-68.6) | | 17.7 (13.5-22.5) | | 18.6 (14.3-23.4) | | 11.2 (7.9-15.1) | | 31.1 (25.7-36.6) | |
| Monosomal karyotype or very poor | 19.0 (7.3-35.0) | | 16.0 (5.5-31.4) | | 54.0 (33.7-70.5) | | 30.0 (14.6-47.1) | | 16.7 (5.9-32.1) | | 14.0 (4.0-30.1) | |
| HCT-CI | | <.001 | | <.001 | | .240 | | .001 | | .147 | | .121 |
| Low/intermediate risk (score < 3) | 67.2 (60.7-72.9) | | 64.1 (57.5-69.9) | | 20.0 (15.2-25.4) | | 15.4 (11.1-20.3) | | 10.4 (6.9-14.6) | | 31.6 (25.7-37.7) | |
| High risk (score ≥ 3) | 48.4 (36.7-59.2) | | 43.3 (31.8-54.2) | | 24.6 (15.4-34.9) | | 32.1 (22.1-42.6) | | 15.7 (8.8-24.3) | | 23.5 (14.5-33.7) | |
| Conditioning intensity | | .058 | | .065 | | .256 | | .404 | | .476 | | .343 |
| RIC with FB2 | 65.0 (57.9-71.2) | | 60.4 (53.2-66.8) | | 20.4 (15.1-26.3) | | 19.2 (14.1-24.8) | | 11.0 (7.3-15.5) | | 27.8 (21.8-34.1) | |
| MAC with FB4 | 57.0 (46.9-65.8) | | 55.1 (45.1-64.0) | | 22.9 (15.3-31.3) | | 21.0 (13.7-29.2) | | 13.3 (7.7-20.6) | | 32.7 (23.8-41.8) | |
| ATG dose | | .155 | | .203 | | .713 | | .103 | | .040 | | <.001 |
| 7.5-10.0 mg/kg | 69.3 (61.2-76.1) | | 66.6 (58.3-73.6) | | 19.5 (13.5-26.3) | | 14.0 (9.0-20.1) | | 8.4 (4.7-13.5) | | 23.7 (17.0-31.1) | |
| 2.5-5.0 mg/kg | 57.0 (46.4-66.3) | | 53.4 (42.9-62.8) | | 20.6 (13.1-29.3) | | 25.9 (17.7-34.9) | | 12.6 (7.1-19.8) | | 25.2 (17.3-34.0) | |
| None | 56.3 (43.5-67.2) | | 40.4 (37.8-61.6) | | 25.5 (15.7-36.5) | | 22.5 (13.3-33.3) | | 17.9 (9.8-28.0) | | 48.4 (35.7-59.9) | |

Values are percents.

**Table 4**
Prognostic Scoring System According to GRFS

| Variables | β-Coefficients | P | HR (95% CI) | Score | Modifiability |
|---|---|---|---|---|---|
| Circulating blast at HSCT | | | | | |
| ≤3% | 0 (reference) | | 1 | 0 | |
| >3% | .685 | .001 | 1.984 (1.320-2.982) | 2.0 | No |
| Cytogenetic status | | | | | |
| Very good to poor | 0 (reference) | | 1 | 0 | |
| Monosomal karyotype or very poor | .846 | <.001 | 2.329 (1.534-3.536) | 2.5 | No |
| HCT-CI | | | | | |
| Low/intermediate risk (score < 3) | 0 (reference) | | 1 | 0 | |
| High risk (score ≥ 3) | .416 | .009 | 1.516 (1.111-2.069) | 1.5 | No |
| Conditioning intensity | | | | | |
| RIC with FB2 | 0 (reference) | | 1 | 0 | |
| MAC with FB4 | .531 | .001 | 1.700 (1.241-2.330) | 1.5 | Yes |
| ATG dose | | | | | |
| 7.5-10.0 mg/kg | 0 (reference) | | 1 | 0 | |
| 2.5-5.0 mg/kg | .321 | .074 | 1.378 (.969-1.960) | 1 | |
| None | .831 | <.001 | 2.296 (1.596-3.303) | 2.5 | Yes |

recent prospective study showing similar OS and DFS rates regardless of conditioning intensity [35], the role of RIC should be redefined in the context of GRFS rather than traditional transplant outcome measures. Contrary to scarce data about conditioning intensity, many studies have suggested favorable influences of ATG on GRFS via its impact on GVHD [38–42]. Although optimal dose and schedule of ATG remain to be validated, our data suggest that a higher dose of ATG (≥7.5 mg/kg) might be more beneficial than a lower dose of ATG (≤5 mg/kg) in terms of GRFS, at least in patients receiving peripheral blood stem cells after fludarabine/busulfan-based conditioning for MDS.

In the current study 2 modifiable factors on GRFS did not show clinical impacts on conventional survival outcomes such as OS, DFS, cumulative incidences of relapse, or TRM. However, we questioned whether the impact of modifiable factors might differ according to the degree of negative influences of fixed factors on relapse or TRM. For that purpose, risk groups based only on fixed unmodifiable factors (f-GRFS model) were reconstructed, and effects of modifiable factors in low-risk and high-risk groups of f-GRFS model were analyzed as the main interest of our study. Interestingly, combination of RIC and ATG ≥ 7.5 mg/kg led to significantly better GRFS in the low-risk group but not in the high-risk group. These results suggest that a differential approach is needed to select modifiable factors according to the level of risks derived from fixed factors (f-GRFS model). For this risk-adapted strategy, separation of modifiable and fixed factors and development of a prediction model should be essential for better GRFS. Regarding high-risk linking most frequent GRFS event as the relapse, unmet needs for an approach to minimize relapse risk appeared in cases having that risk. Novel therapeutic strategies that can enhance anti-MDS activity without increasing toxicity should be developed. Those that can induce graft-versus-leukemia effects are under development [43]. Until their introduction into real clinical practice, currently available cellular therapy for the induction of GVHD aiming to evoke graft-versus-leukemia effects could be considered even at the expense of morbidities related to GVHD [44]. For disease that outpaces the development of GVHD, pretransplant debulking treatment or post-transplant maintenance chemotherapy could be an option [19,45,46].

Contrary to the expectation for the impact of donor type identified as an independent factor affecting GRFS in previous data [18,47,48], donor type did not have a significant effect on GRFS in our study. In line with our result, large retrospective data including 3568 patients with acute leukemia also have

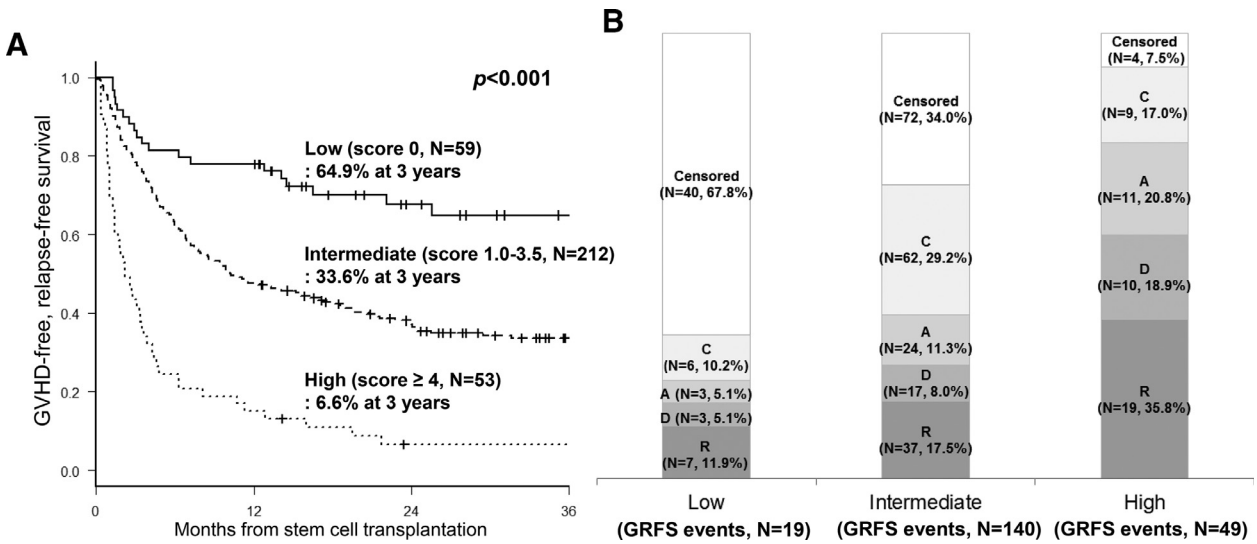


**Figure 2.** (A) GRFS according to a scoring system constructed by using all factors affecting GRFS. (B) Distribution of GRFS events according to the scoring system.

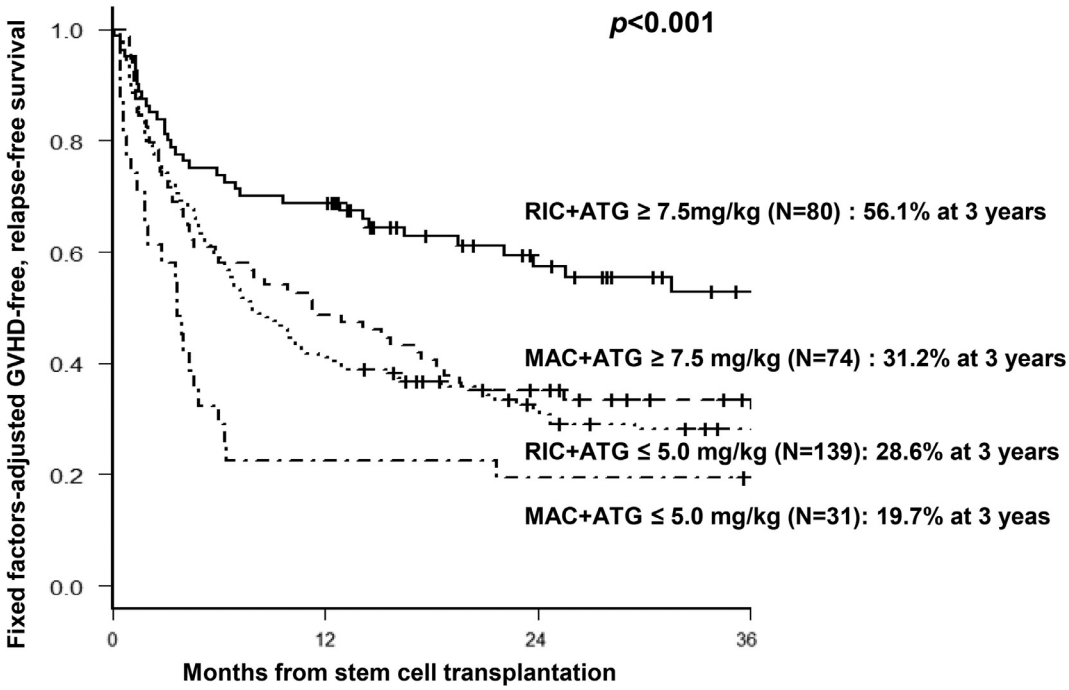


**Figure 3.** Fixed factor–adjusted GRFS according to the combination of conditioning intensity and ATG dose.

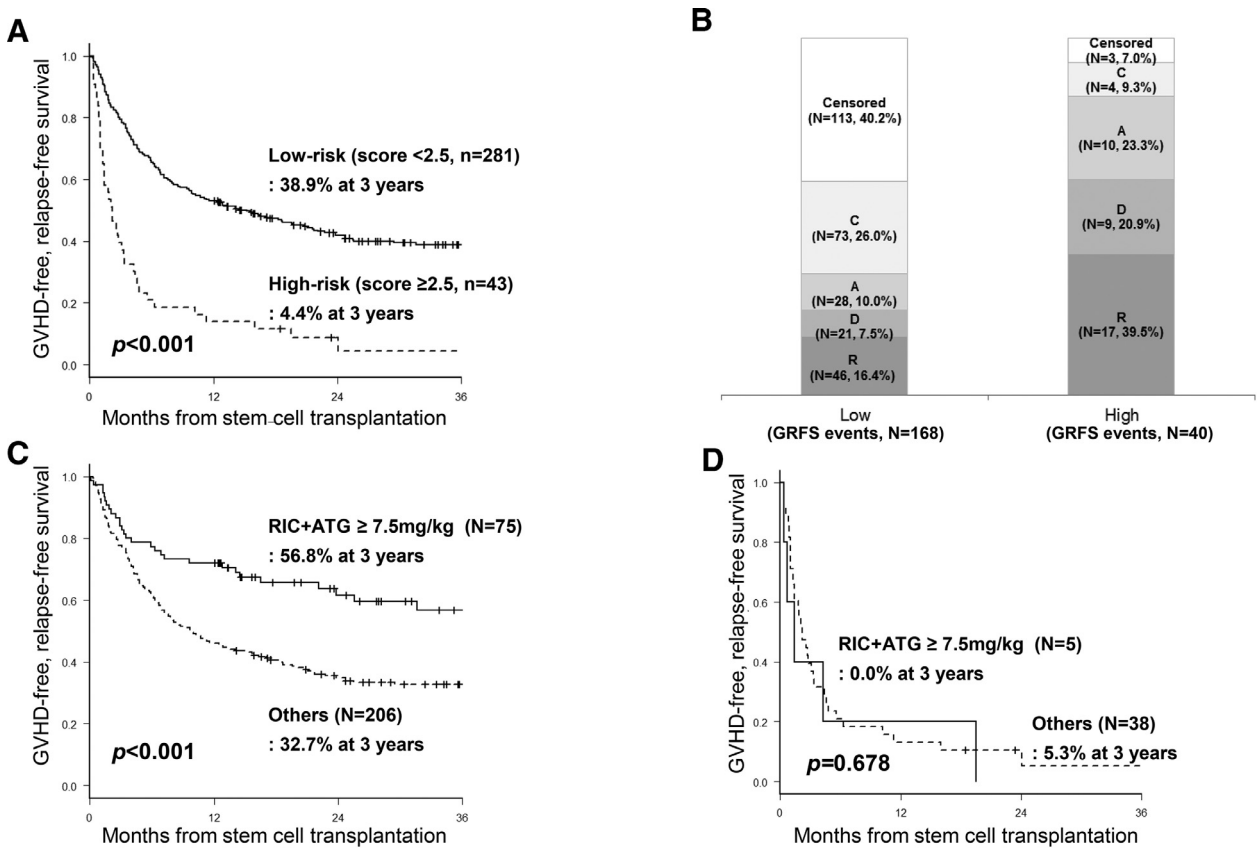


**Figure 4.** (A) GRFS according to risk group of the f-GRFS model. (B) Distribution of GRFS events according to the scoring system for risk group of the f-GRFS model. (C) Discriminative GRFS by combination of RIC plus ATG ≥ 7.5 mg/kg in the low-risk group of the f-GRFS model. (D) Similar GRFS regardless of combination of RIC plus ATG ≥ 7.5 mg/kg in the high-risk group of the f-GRFS model.

shown similar GRFS when comparing donor type between unrelated and haploidentical related donors [49]. Such discrepancy might be due to heterogeneity in disease type, disease status, and different transplant procedures among different studies.

This study contains a number of limitations. Two important shortcomings are an absence of the verification for our scoring system by use of a separate cohort and the relatively small sample size of high-risk groups in the f-GRFS model. Therefore, the current model for GRFS and impact of ATG and RIC on GRFS might need to be validated in a future cohort.

In conclusion, this study identified 3 fixed unmodifiable factors (circulating blast > 3%, high cytogenetic risk, and high HCT-CI) and 2 modifiable factors (RIC and ATG dose) that affected GRFS after HSCT for MDS. Using risks of these independent factors, a model predicting GRFS was developed. Further analysis by separating modifiable and fixed factors suggested that HSCT should include RIC and ATG $\geq$ 7.5 mg/kg if a case is categorized into the low-risk group of the f-GRFS model. However, alternative approaches that can suppress relapse should be pursed for patients who are categorized into high-risk group of the f-GRFS model.

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## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.bbmt.2018.08.004.

## REFERENCES

1. Ades L, Itzykson R, Fenaux P. Myelodysplastic syndromes. *Lancet*. 2014;383:2239–2252.
2. Mittelman M, Oster HS, Hoffman M, Neumann D. The lower risk MDS patient at risk of rapid progression. *Leuk Res*. 2010;34:1551–1555.
3. Yoshizato T, Nannya Y, Atsuta Y, et al. Genetic abnormalities in myelodysplasia and secondary acute myeloid leukemia: impact on outcome of stem cell transplantation. *Blood*. 2017;129:2347–2358.
4. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. *Blood*. 2017;129:1753–1762.
5. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2010;363:2091–2101.
6. Hahn T, McCarthy Jr. PL, Hassebroek A, et al. Significant improvement in survival after allogeneic hematopoietic cell transplantation during a period of significantly increased use, older recipient age, and use of unrelated donors. *J Clin Oncol*. 2013;31:2437–2449.
7. Kroger N. From nuclear to a global family: more donors for MDS. *Blood*. 2013;122:1848–1850.
8. Shin SH, Kim JH, Jeon YW, et al. Feasible outcomes of T cell-replete haploidentical stem cell transplantation with reduced-intensity conditioning in patients with myelodysplastic syndrome. *Biol Blood Marrow Transplant*. 2015;21:342–349.
9. Zeidan AM, Linhares Y, Gore SD. Current therapy of myelodysplastic syndromes. *Blood Rev*. 2013;27:243–259.
10. Parmar S, de Lima M, Deeg HJ, Champlin R. Hematopoietic stem cell transplantation for myelodysplastic syndrome: a review. *Semin Oncol*. 2011;38:693–704.
11. Bhatia S, Francisco L, Carter A, et al. Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study. *Blood*. 2007;110:3784–3792.
12. Martin PJ, Lee SJ, Przepiorka D, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: VI. The 2014 Clinical Trial Design Working Group report. *Biol Blood Marrow Transplant*. 2015;21:1343–1359.
13. Valcarcel D, Martino R, Caballero D, et al. Sustained remissions of high-risk acute myeloid leukemia and myelodysplastic syndrome after reduced-intensity conditioning allogeneic hematopoietic transplantation: chronic graft-versus-host disease is the strongest factor improving survival. *J Clin Oncol*. 2008;26:577–584.
14. Pidala J, Kurland B, Chai X, et al. Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD Consortium. *Blood*. 2011;117:4651–4657.
15. Fraser CJ, Bhatia S, Ness K, et al. Impact of chronic graft-versus-host disease on the health status of hematopoietic cell transplantation survivors: a report from the Bone Marrow Transplant Survivor Study. *Blood*. 2006;108:2867–2873.
16. Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2003;9:215–233.
17. Martin PJ. Study design and endpoints in graft-versus-host disease. *Best Pract Res Clin Haematol*. 2008;21:357–372.
18. Holtan SG, DeFor TE, Lazaryan A, et al. Composite end point of graft-versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation. *Blood*. 2015;125:1333–1338.
19. Han S, Kim YJ, Lee J, et al. Model-based adaptive phase I trial design of post-transplant decitabine maintenance in myelodysplastic syndrome. *J Hematol Oncol*. 2015;8:118.
20. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127:2391–2405.
21. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108:419–425.
22. Prebet T, Gore SD, Esterni B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. *J Clin Oncol*. 2011;29:3322–3327.
23. Schanz J, Tuchler H, Sole F, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. *J Clin Oncol*. 2012;30:820–829.
24. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106:2912–2919.
25. Harris AC, Young R, Devine S, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant*. 2016;22:4–10.
26. Pavletic SZ, Vogelsang GB, Lee SJ. 2014 National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: preface to the series. *Biol Blood Marrow Transplant*. 2015;21:387–388.
27. Lee SE, Kim YJ, Yahng SA, et al. Survival benefits from reduced-intensity conditioning in allogeneic stem cell transplantation for young lower-risk MDS patients without significant comorbidities. *Eur J Haematol*. 2011;87:510–520.
28. Nazha A, Rybicki L, Abounader D, et al. GvHD-free, relapse-free survival after reduced-intensity allogeneic hematopoietic cell transplantation in older patients with myeloid malignancies. *Bone Marrow Transplant*. 2016;51:1642–1643.
29. Ruggeri A, Labopin M, Ciceri F, Mohty M, Nagler A. Definition of GvHD-free, relapse-free survival for registry-based studies: an ALWP-EBMT analysis on patients with AML in remission. *Bone Marrow Transplant*. 2016;51:610–611.
30. Shimoni A, Labopin M, Savani B, et al. Intravenous busulfan compared with treosulfan-based conditioning for allogeneic stem cell transplantation in acute myeloid leukemia: a study on behalf of the Acute Leukemia Working Party of European Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2018;24:751–757.
31. Shaffer BC, Ahn KW, Hu ZH, et al. Scoring system prognostic of outcome in patients undergoing allogeneic hematopoietic cell transplantation for myelodysplastic syndrome. *J Clin Oncol*. 2016;34:1864–1871.

32. Yahng SA, Jeon YW, Yoon JH, et al. Dynamic prognostic value of the revised international prognostic scoring system following pretransplant hypomethylating treatment in myelodysplastic syndrome. *Bone Marrow Transplant*. 2017;52:522–531.
33. Baron F, Ruggeri A, Beohou E, et al. RIC versus MAC UCBT in adults with AML: a report from Eurocord, the ALWP and the CTIWP of the EBMT. *Oncotarget*. 2016;7:43027–43038.
34. Shimoni A, Labopin M, Savani B, et al. Long-term survival and late events after allogeneic stem cell transplantation from HLA-matched siblings for acute myeloid leukemia with myeloablative compared to reduced-intensity conditioning: a report on behalf of the Acute Leukemia Working Party of European Group for Blood and Marrow Transplantation. *J Hematol Oncol*. 2016;9:118.
35. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35:1154–1161.
36. Pasquini MC, Logan B, Wu J, et al. Results of a phase III randomized, multicenter study of allogeneic stem cell transplantation after high versus reduced intensity conditioning in patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML): Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0901. Blood 126, no. 23 (2015): LBA-8. Accessed September 13, 2018. http://www.bloodjournal.org/content/126/23/LBA-8.
37. Konuma T, Kato S, Oiwa-Monna M, Ishii H, Tojo A, Takahashi S. Comparison of graft-versus-host disease-free, relapse-free survival of transplantation using matched sibling donor, matched unrelated donor or unrelated cord blood after myeloablative conditioning for adult patients with hematological malignancies. *Leuk Lymph*. 2016;57:2126–2132.
38. Finke J, Schmoor C, Bethge WA, et al. Long-term outcomes after standard graft-versus-host disease prophylaxis with or without anti-human-T-lymphocyte immunoglobulin in haemopoietic cell transplantation from matched unrelated donors: final results of a randomised controlled trial. *Lancet Haematol*. 2017;4:e293–e301.
39. Ravinet A, Cabrespine A, Socie G, et al. Impact of thymoglobulin by stem cell source (peripheral blood stem cell or bone marrow) after myeloablative stem cell transplantation from HLA 10/10-matched unrelated donors: a report from the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. *Transplantation*. 2016;100:1732–1739.
40. Baron F, Labopin M, Blaise D, et al. Impact of in vivo T-cell depletion on outcome of AML patients in first CR given peripheral blood stem cells and reduced-intensity conditioning allo-SCT from a HLA-identical sibling donor: a report from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2014;49:389–396.
41. Kuriyama K, Fuji S, Inamoto Y, et al. Impact of low-dose rabbit anti-thymocyte globulin in unrelated hematopoietic stem cell transplantation. *Int J Hematol*. 2016;103:453–460.
42. Gauthier J, Poire X, Gac AC, et al. Better outcome with haploidentical over HLA-matched related donors in patients with Hodgkin's lymphoma undergoing allogeneic haematopoietic cell transplantation—a study by the Francophone Society of Bone Marrow Transplantation and Cellular Therapy. *Bone Marrow Transplant*. 2018;53:400–409.
43. Locatelli F, Moretta F, Brescia L, Merli P. Natural killer cells in the treatment of high-risk acute leukaemia. *Semin Immunol*. 2014;26:173–179.
44. Chang X, Zang X, Xia CQ. New strategies of DLI in the management of relapse of hematological malignancies after allogeneic hematopoietic SCT. *Bone Marrow Transplant*. 2016;51:324–332.
45. Yahng SA, Kim M, Kim TM, et al. Better transplant outcome with pre-transplant marrow response after hypomethylating treatment in higher-risk MDS with excess blasts. *Oncotarget*. 2017;8:12342–12354.
46. de Lima M, Giralt S, Thall PF, et al. Maintenance therapy with low-dose azacitidine after allogeneic hematopoietic stem cell transplantation for recurrent acute myelogenous leukemia or myelodysplastic syndrome: a dose and schedule finding study. *Cancer*. 2010;116:5420–5431.
47. Solh M, Zhang X, Connor K, et al. Factors predicting graft-versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation: multivariable analysis from a single center. *Biol Blood Marrow Transplant*. 2016;22:1403–1409.
48. Kongtim P, Adekola K, Milton DR, et al. Donor type, in addition to transplantation in chronic phase and myeloablative conditioning, influence transplant survival for patients with advanced chronic myeloid leukemia in the era of tyrosine kinase inhibitors. *Leukemia*. 2017;31:1654–1657.
49. Piemontese S, Ciceri F, Labopin M, et al. A comparison between allogeneic stem cell transplantation from unmanipulated haploidentical and unrelated donors in acute leukemia. *J Hematol Oncol*. 2017;10:24.