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ORIGINAL ARTICLE

Increased opportunity for prolonged survival after allogeneic hematopoietic stem cell transplantation in patients aged 60–69 years with myelodysplastic syndrome

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Abstract

We conducted a nationwide retrospective study to evaluate the outcomes of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in 651 patients aged 60–69 years with de novo myelodysplastic syndrome (MDS). We divided patients into two groups: 152 and 499 patients with an early and advanced disease status, respectively. The 3-year overall survival (OS) rate of patients with an early disease status was 45.9% (95% confidence interval [CI], 37.0 to 54.2%). A multivariate analysis revealed five adverse factors for OS: performance status (PS) 2–4 (hazard ratio [HR] 4.48; $P < .001$), poor cytogenetic risk group (HR 1.83; $P = .041$), male recipient (HR 2.58; $P = .003$), use of HLA-mismatched related grafts (HR 4.75; P = .003), and unrelated cord blood (HR 2.47; $P = .023$). The 3-year OS rate of patients with an advanced disease status was 37.2% (95% CI 32.4 to 41.9%). Five factors correlated with worse OS: PS 2–4 (HR 1.72; P = .003), poor cytogenetic risk group (HR 1.49; P = .003), use of HLA-mismatched related grafts (HR 1.96; $P = .015$), unrelated cord blood (HR 2.05; $P < .001$), and the high number of red blood cell transfusions before transplantation (HR 1.85; $P = .018$). The present results revealed the more frequent utilization of allo-HSCT for MDS patients aged 60–69 years, which increases the curative potential.

Keywords Myelodysplastic syndrome · Allogeneic hematopoietic stem cell transplantation · Elderly · GVHD-free and relapse-free survival

Introduction

Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders with ineffective hematopoiesis, marrow dysplasia, and a high propensity to transform into acute myeloid leukemia (AML) [1]. The overall incidence of MDS increases with age; median age at the time of diagnosis was previously reported to be 65–71 years [2–6]. In many industrialized countries, including Japan, optimizing the management of elderly patients with MDS is becoming an increasingly important issue in the background of a progressively aging society.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) offers the only curative potential for patients with MDS [7–9]; however, early registry studies demonstrated the negative effects of an older age on transplant-related toxicity [10–12]. Nevertheless, the utilization of allo-HSCT has markedly increased in elderly patients with MDS in recent years due to improvements in conditioning regimens, donor selection, and supportive care [13]. Since approximately 75% of patients with MDS are 60 years or older, the number of these transplantation candidates considered for allo-HSCT by community may continue to increase.

Previous studies reported the feasibility of allo-HSCT for the elderly with myeloid neoplasms, including mainly AML [14–18]. In terms of therapeutic strategies before allo-HSCT

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(e.g., watch-and-wait approach and treatment with DNA hypomethylating agents) [19–24], the distribution of cytogenetic abnormalities [25], and an indolent clinical course [1, 2], the clinical features of MDS differ from those of AML. A recent literature review showed the survival benefits of reduced-intensity transplantation using human leukocyte antigen (HLA)-matched donors for MDS patients aged 60 to 70 years [26]. However, few studies have focused on identifying prognostic factors for post-transplant outcomes in more detailed analyses on a larger number of patients with various transplantation strategies. We previously analyzed post-transplant outcomes in older patients who underwent allo-HSCT between January 2001 and December 2010, in which the cohort mainly included patients with an advanced disease status who were younger than 60 years: 50–59 years ($n = 299$) and 60–69 years ($n = 149$) [27]. To more accurately assess post-transplant outcomes and prognostic factors in patients aged 60–69 years with MDS, we herein conducted a nationwide retrospective study in larger cohort ($n = 651$). Our study included the previous cohort with updated clinical information as well as data on patients who underwent allo-HSCT after December 2010.

Patients and methods

Data sources

Clinical data on de novo MDS patients aged 16 years and older who underwent their first allo-HSCT were collected by the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and the Japanese Data Center for Hematopoietic Cell Transplantation (JDCHCT) using the Transplantation Registry Unified Management Program (TRUMP), as described previously [28–30]. This study was approved by the TRUMP Committee (approval no. 8-13), and by the Ethics Committee of Nagasaki University Hospital (approval no. 12052896) at which this study was organized.

Patient population

The original dataset consisted of 3103 adults who were diagnosed with de novo MDS, as defined by the French-American-British (FAB) classification [31]. Patients with chronic myelomonocytic leukemia and secondary- and therapy-related MDS were excluded from this study. Since the absolute number of elderly patients who received allo-HSCT increased after 2002, data on 656 patients aged 60–69 years at transplantation between January 1, 2002 and December 31, 2013 were included in the present study. Five patients with missing data on transplant procedures were excluded from the survival analysis. A total of 651 patients were included in the survival analysis. Data on these patients were collected and updated as of December 31, 2014.

Definitions

Clinical data collected for analyses included patient age at allo-HSCT, patient sex, disease subtype according to the FAB classification, cytogenetic risk classification according to International Prognostic Scoring System (IPSS) [32], year of allo-HSCT, time from the MDS diagnosis to allo-HSCT, performance status (PS) according to the Eastern Cooperative Oncology Group criteria at allo-HSCT, the number of red blood cell (RBC) transfusion before allo-HSCT, the type of donor source according to the previous studies [27, 33–36], date alive at the last follow-up, and date and cause of death. Conditioning regimens were classified as myeloablative (MAC), reduced-intensity (RIC), and non-myeloablative conditioning (NMAC) according to established criteria [37, 38]. Graft-versus-host disease (GVHD) prophylaxis was either a cyclosporine (CsA)- or tacrolimus (Tac)-based regimen. HLA-A, -B, and -DRB1 were identified by serological or molecular typing in related donors by molecular typing in unrelated bone marrow donors and by serological typing in unrelated cord blood donors [29, 33]. To reflect current practices in Japan, the number of HLA mismatches was assessed with respect to serological data in related donors and unrelated cord blood donors and by allele data in unrelated bone marrow donors. The diagnosis and clinical grading of acute GVHD and chronic GVHD were performed according to standard criteria [39, 40].

Due to missing data on IPSS components at allo-HSCT in TRUMP, the disease risk was stratified according to the FAB classification as previously reported [27, 34, 41]; early disease status group contained patients whose subtype had remained as refractory anemia (RA) or RA with ring sideroblasts (RARS) from diagnosis to transplantation. Patients diagnosed as RA with excess blasts (RAEB) or RAEB in transformation (RAEB-t) at any time between diagnosis and transplantation were considered to be an advanced disease status.

Study end points

The primary outcome studied was overall survival (OS). Patients were considered to have an event at the time of death from any cause; survivors were censored at the last follow-up. Transplantation-related death was defined as any death from any cause other than the relapse or progression of MDS. GVHD-free and relapse-free survival (GRFS) was defined as the time from the date of transplantation to the date of grade III to IV acute GVHD, chronic GVHD requiring systemic immunosuppressive treatment, relapse, or death due to any cause [42, 43].

Statistical analysis

Continuous variables were compared using the Wilcoxon rank-sum test or Mann-Whitney *U* test. Categorical variables were compared between groups using the chi-squared test. The probabilities of OS and GRFS were estimated by the Kaplan-Meier method and group comparisons were performed by the Log-rank test. The cumulative incidence of relapse (CIR) and transplantation-related mortality (TRM) were estimated in the competing risks setting, and group comparisons were performed by Gray's test. Death before relapse was the competing event for relapse, while death after relapse was the competing event for TRM [44, 45]. Death before neutrophil engraftment was the competing event for neutrophil engraftment, while death without GVHD and relapse were the competing events for GVHD. In order to assess variables potentially affecting post-transplant outcomes, OS and GRFS were evaluated using Cox's proportional hazards regression models, whereas CIR and TRM were evaluated using the Fine and Gray proportional hazards model for the subdistribution of competing risks [45].

Factors associated with at least borderline significance ($P \leq .10$) in the univariate analysis and patient age at allo-HSCT were subjected to a multivariate analysis using a backward stepwise covariate selection. Potential interactions were examined. Effect estimates were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). A two-sided *P* value $\leq .05$ was considered to be significant. All statistical analyses were performed using Stata software, version 12 (Stata, College Station, TX, USA), and graphical presentations were performed using EZR software, version 1.24 (Saitama Medical Center, Jichi Medical University) [46].

Results

Utilization of allo-HSCT for adults aged 16 years and older

The total number per 4 years of MDS patients who received allo-HSCT over time was shown in Fig. 1. Among patients aged 60–69 years, the absolute number of allo-HSCT markedly increased over time: from 16 patients in 1998–2001 years to 378 in 2010–2013. The continuously increasing utilization of allo-HSCT for all patients with MDS was mainly attributed to the proportion of patients aged 60–69 years. The present study did not include patients aged 70 years or older due to a small number of patients ($n = 32$).

Patient and transplantation characteristics

The baseline demographic and transplantation characteristics of 651 patients for the survival analysis are shown in Table 1. In all patients, the type of donor source shifted from HLA-matched related donors at 42.1% in 2002–2005 to unrelated bone marrow and unrelated cord blood donors at 45.0 and 36.0%, respectively, in 2010–2013. Regarding the intensity of the conditioning regimen, the RIC regimen was mostly used for more than 72% in the 2002–2005 and 2006–2009 periods, and for 53.2% in 2010–2013. The number of applications of the MAC regimen continuously increased from 7.9% in 2002–2005 to 39.9% in 2010–2013. Fludarabine with melphalan (≤ 140 mg/m^2; Flu/Mel)- or busulfan (6.4 mg/kg intravenously or 8 mg/kg orally; Flu/Bu2)-based regimens were mainly used as the RIC regimen, and fludarabine with busulfan (12.8 mg/kg intravenously or 16 mg/kg orally; Flu/Bu4) was mostly used as the MAC regimen over time. The proportion of the NMAC regimen slightly decreased from 15.8% in 2002–2005 to 6.9% in 2010–2013. In contrast, the utilization of Flu/Bu4-based MAC regimen was markedly increased after 2010: 1, 18, and 130 patients in 2002–2005, 2006–2009, and 2010–2013, respectively. The use of prior-to-transplantation azacitidine markedly increased in 2010–2013 because azacitidine became available for use in clinical practice after March 2011 in Japan. In the present study, no patients received T cell-replete HLA-haploidentical HSCT using post-transplant cyclophosphamide. Transplantation procedures in each period are shown in supplemental Table 1.

We analyzed post-transplant outcomes by the disease status, and patients were divided into two groups: 152 (23.3%) and 499 patients (76.7%) with an early and advanced disease status, respectively. Median ages at the time of allo-HSCT were 63 years (range, 60–69 years) and 63 years (range, 60–69 years) in the early and advanced disease status groups, respectively. Comparing with patients in early disease status, those in advanced disease status group had significantly different clinical features such as more male recipient ($P = .033$), and shorter interval from diagnosis and allo-HSCT ($P = .009$). There were also significant differences in the distribution of cytogenetic risk group ($P = .013$), treatment prior to allo-HSCT ($P < .001$), and the number of RBC transfusion before allo-HSCT ($P = .008$).

Transplantation outcomes by disease-risk stratification

In the entire cohort, the 3-year probability of OS and GRFS after transplantation were 39.2% (95% CI 35.0 to 43.4%) and 21.6% (95% CI 18.3 to 25.2%), respectively. The 3-year CIR and TRM were 34.5% (95% CI 30.7 to 38.4%) and 31.7% (95% CI 28.0 to 35.6%), respectively. The cumulative incidence of neutrophil engraftment was 86.2% (95% CI 83.3 to 88.7%). In the univariate analysis, the advanced disease status was associated with increased CIR ($P < .001$), but there was no significant difference of OS, GRFS, neutrophil

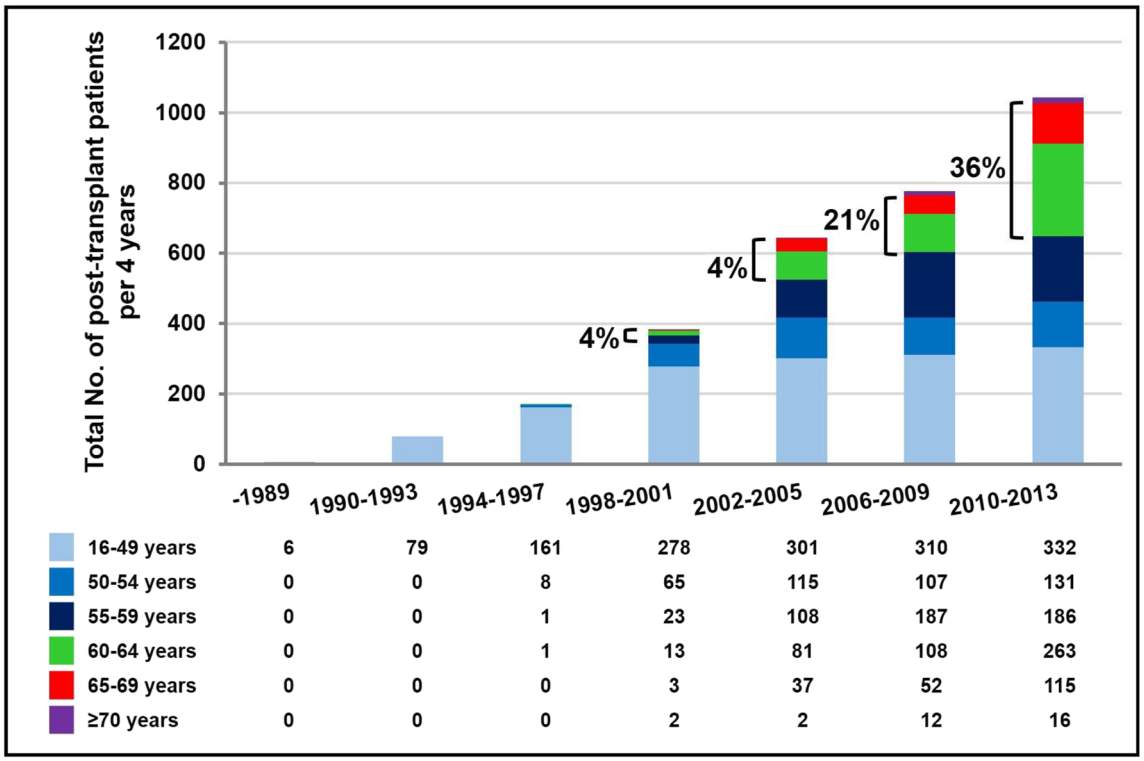

Fig. 1 Number of MDS patients who received allo-HSCT in Japan. Among 3103 adults with MDS who received allo-HSCT over time, 656 were 60–69 years old and 32 were 70 years or older. The proportion of patients aged 60–69 years was given on the left side of each bar. *MDS* myelodysplastic syndrome, *allo-HSCT* allogeneic hematopoietic stem cell transplantation

engraftment, CIR, and TRM between early and advanced disease status (Supplemental Fig. 1).

Post-transplant outcomes in patients with an early disease status

In all patients with an early disease status, OS, GRFS, CIR, and TRM rates 3 years after allo-HSCT were 45.9% (95% CI 37.0 to 54.2%), 29.1% (95% CI 21.8 to 36.7%), 21.8% (95% CI 15.4 to 28.9%), and 35.5% (95% CI 27.4 to 43.7%), respectively (Fig. 2a, b). The 100-day cumulative incidence of neutrophil engraftment was 84.8% (95% CI 77.9 to 89.6%). The cumulative incidence rate of acute GVHD on day 100 was 49.4% (95% CI 41.2 to 57.0%). The cumulative incidence rates of chronic GVHD at 1 and 3 years were 40.3% (95% CI 31.0 to 49.3%) and 43.8% (95% CI 34.1 to 53.1%), respectively. Factors related to the cumulative incidence of neutrophil engraftment, acute GVHD, and chronic GVHD were shown in supplemental Table 2. The most frequent cause of death was the relapse or progression of MDS, accounting for 34.9% of all deaths, followed by infection at 30.3% (Table 2).

Prognostic factors for mortality in patients with an early disease status

The results of univariate and multivariate analyses were shown in supplemental Table 3. Table 3 showed variables that correlated with OS, GRFS, TRM, and CIR in patients with an early disease status. Significant prognostic factors for inferior survival were male recipient (HR, 2.58; 95% CI 1.40 to 4.79; $P = .003$), PS 2–4 (HR, 4.48; 95% CI 2.28 to 8.81; $P < .001$), poor cytogenetic risk group (HR, 1.83; 95% CI 1.02 to 3.28; $P = .041$), use of HLA-mismatched related donors (HR, 4.75; 95% CI 1.80 to 12.53; $P = .003$), and unrelated cord blood (HR, 2.47; 95% CI 1.13 to 5.38; $P = .023$). Two factors negatively correlated with a worse GRFS: male recipient (HR, 1.97; 95% CI 1.24 to 3.12; $P = .004$) and poor cytogenetic risk group (HR, 2.18; 95% CI 1.39 to 3.42; $P = .001$). Four factors correlated with increased TRM: the use of HLA-mismatched related donors (HR, 5.22; 95% CI 1.19 to 22.90; $P = .028$), unrelated cord blood donors (HR, 3.08; 95% CI 1.05 to 9.06; $P = .041$), the high number of RBC transfusions before transplantation (i.e., ≥20 times) (HR, 7.90; 95% CI 1.01 to 61.47; $P = .048$), and the missing data on the

Table 1 Patient characteristics and transplant procedures

No. of patients	Early disease status	Advanced disease status	*P* value
Total	152	499	
Median age at allo-HSCT (range), years	63 (60–69)	63 (60–69)	0.598
60–64 years	102 (67.1%)	347 (69.5%)	0.617
65–69 years	50 (32.9%)	152 (30.5%)	
Patient's sex			0.033
Male	97 (63.8%)	364 (72.9%)	
Female	55 (36.2%)	135 (27.1%)	
Sex match			0.439
Match	74 (48.7%)	259 (51.9%)	
Mismatch	67 (44.1%)	200 (40.1%)	
Missing	11 (7.2%)	40 (8.0%)	
Cytogenetic risk			0.013
Good risk	80 (52.6%)	209 (41.9%)	
Intermediate risk	16 (10.5%)	84 (16.8%)	
Poor risk	43 (28.3%)	187 (37.5%)	
Unknown	13 (8.6%)	19 (3.8%)	
FAB at diagnosis			< 0.001
RA	142 (93.4%)	63 (12.6%)	
RARS	10 (6.6%)	5 (1.0%)	
RAEB	–	350 (70.2%)	
RAEB-t	–	81 (16.2%)	
IPSS at diagnosis			0.615
Low	12 (7.9%)	11 (2.2%)	
Intermediate-1	62 (40.8%)	86 (17.2%)	
Intermediate-2	22 (14.5%)	187 (37.6%)	
High	4 (2.6%)	101 (20.2%)	
Missing	52 (34.2%)	114 (22.8%)	
PS at allo-HSCT			0.925
0–1	132 (86.8%)	453 (87.2%)	
2–4	15 (9.9%)	48 (9.6%)	
Missing	5 (3.3%)	16 (3.2%)	
HCT-CI			0.101
0–2	90 (59.2%)	304 (60.9%)	
≥ 3	18 (11.8%)	86 (17.2%)	
Missing	44 (29.0%)	109 (21.9%)	
Chemotherapy before allo-HSCT			< 0.001
No chemotherapy	94 (61.8%)	204 (40.9%)	
Azacitidine alone	15 (9.9%)	88 (17.6%)	
Chemotherapy[a]	29 (19.1%)	186 (37.3%)	
Unknown	14 (9.2%)	21 (4.2%)	
Conditioning regimen intensity			0.694
MAC	44 (29.0%)	151 (30.3%)	
RIC	98 (64.5%)	305 (61.1%)	
NMAC	10 (6.6%)	43 (8.6%)	
Donor source			0.558
HLA-matched related	34 (22.4%)	95 (19.0%)	
HLA-mismatched related	12 (7.9%)	31 (6.2%)	
Unrelated bone marrow	61 (40.1%)	201 (40.3%)	
Unrelated cord blood	45 (29.6%)	172 (34.5%)	

Table 1 (continued)

No. of patients	Early disease status	Advanced disease status	*P* value
GVHD prophylaxis			0.261
CsA-based	47 (30.9%)	165 (33.1%)	
Tac-based	102 (67.1%)	331 (66.3%)	
Other	3 (2.0%)	3 (0.6%)	
The use of ATG as conditioning regimen			0.347
No	134 (88.2%)	454 (91.0%)	
Yes	18 (11.8%)	45 (9.0%)	
Year of allo-HSCT			0.281
2002–2005	29 (19.1%)	85 (17.0%)	
2006–2009	43 (28.3%)	116 (23.3%)	
2010–2013	80 (52.6%)	298 (47.7%)	
Interval between diagnosis and allo-HSCT, mo	11.7 (0.6–155.7)	7.7 (1.4–92.0)	0.009
< 8 months	59 (38.8%)	257 (51.5%)	
≥ 8 months	90 (59.2%)	238 (47.7%)	
RBC transfusion from diagnosis to allo-HSCT			0.008
None	14 (9.2%)	46 (9.2%)	
1–19 times	44 (28.9%)	214 (42.9%)	
≥ 20 times	57 (37.5%)	128 (25.7%)	
Missing	37 (24.4%)	111 (22.2%)	
Median follow-up of survivors, years	2.4 (0.2–12.0)	2.2 (0.1–11.2)	
Final status			
Alive	66 (43.4%)	198 (39.7%)	
Death after relapse (disease-associated death)	30 (19.7%)	152 (30.5%)	
Death without relapse (treatment-related death)	56 (36.8%)	149 (29.9%)	

FAB classification French-American-British classification, *RA* refractory anemia, *RARS* refractory anemia with ringed sideroblasts, *RAEB* refractory anemia with excess of blasts, *RAEB-t* refractory anemia in transformation, *IPSS* international prognostic scoring system, *PS* performance status, *HCT-CI* hematopoietic cell transplantation–specific comorbidity index, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *NMAC* non-myeloablative conditioning, *HLA* human leukocyte antigen, *GVHD* graft-versus-host disease, *CsA* cyclosporine, *Tac* tacrolimus, *ATG* anti-thymocyte globulin, *RBC* red blood cell

[a] Chemotherapy included cytotoxic agents alone, cytotoxic agents followed by azacitidine, and cytotoxic agents preceded by azacitidine

history of RBC transfusions (HR, 9.17; 95% CI 1.10 to 76.22; $P = .040$). The history of chemotherapy before transplantation was associated with increased CIR (HR, 3.61; 95% CI 1.39 to 9.32; $P = .008$). The patient age at allo-HSCT (60–64 vs. 65–69 years) was not an independent risk factor for any post-transplant outcome.

In the univariate analysis regarding donor-recipient sex combination, there was no significant difference of OS, GRFS, CIR, and TRM by sex match between donor and recipient for both male and female recipient. For the patients who underwent allo-HSCT from HLA-matched related, the use of other than sibling graft ($n = 3$) was associated with worse OS ($P = .008$) and TRM ($P < .001$) than that of sibling graft ($n = 31$). Due to the small number of these patients, we failed to evaluate the prognostic value of other than sibling graft in the multivariate analysis.

Post-transplant outcomes in patients with an advanced disease status

In all patients with an advanced disease status, OS, GRFS, CIR, and TRM rates 3 years after allo-HSCT were 37.2% (95% CI 32.4 to 41.9%), 19.3% (95% CI 15.6 to 23.3%), 38.4% (95% CI 33.9 to 43.0%), and 30.5% (95% CI 26.3 to 34.8%), respectively (Fig. 2c, d). The 100-day cumulative incidence of neutrophil engraftment was 86.7% (95%CI, 83.4 to 89.4%). The cumulative incidence rate of acute GVHD on day 100 was 48.0% (95% CI 43.6 to 52.3%). The cumulative incidence rates of chronic GVHD at 1 and 3 years were 32.8% (95% CI 28.0 to 37.6%) and 36.4% (95% CI 31.3 to 41.4%), respectively. Risk factors for neutrophil engraftment, acute GVHD, and chronic GVHD were shown in supplemental Table 4. The most frequent cause of death was the

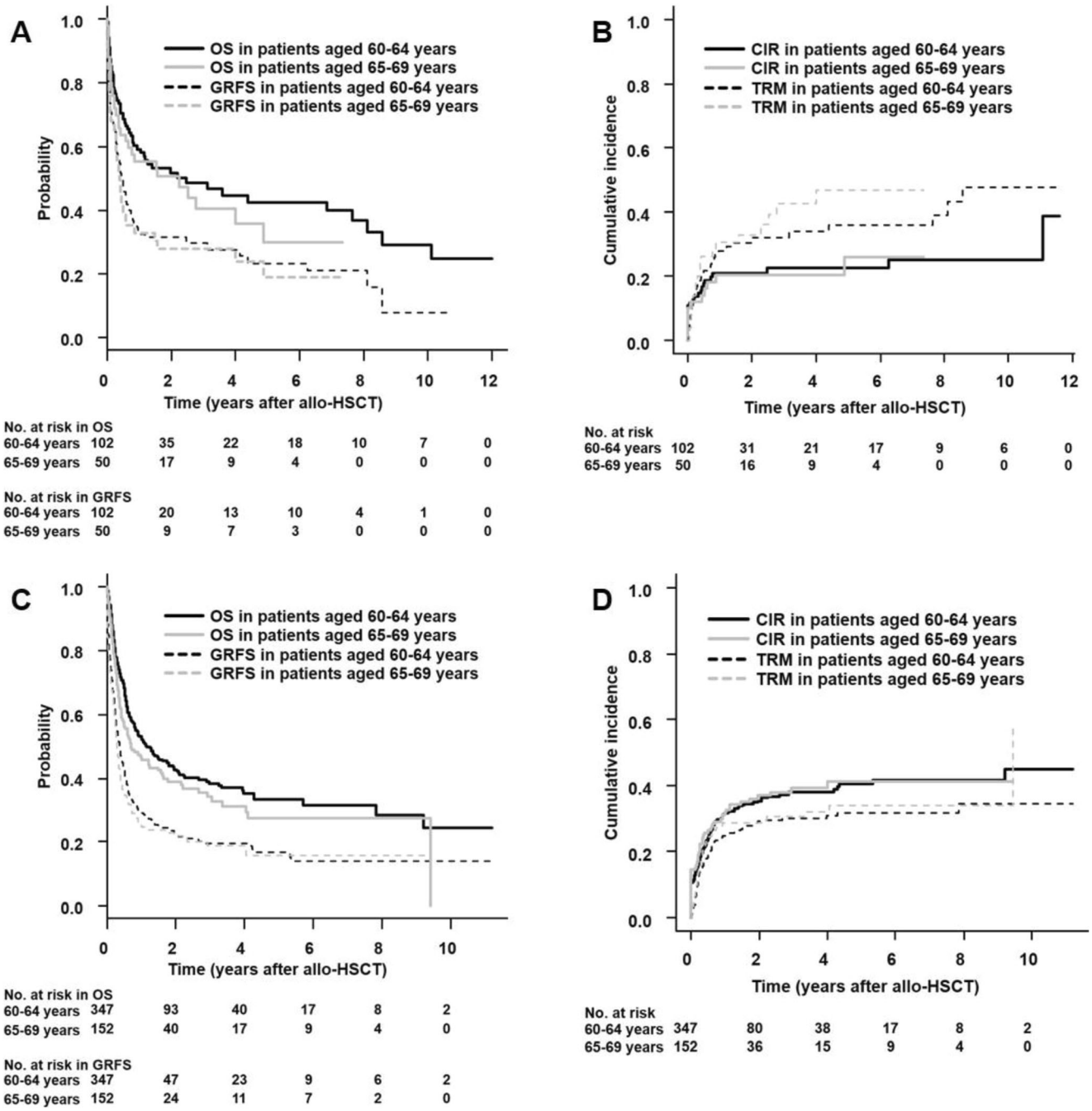

Fig. 2 Post-transplant outcomes in MDS patients aged 60 years and older. Among patients with an early disease status, overall survival (OS) (60–64 years vs 65–69 years, 48.5% [95% CI 37.7 to 58.4%] vs 40.4% [95% CI 25.1 to 55.1%]; $P = .439$); GVHD-free and relapse-free survival (GRFS) (60–64 years vs 65–69 years, 29.7% [95% CI 20.7 to 39.1%] vs 27.7% [95% CI 15.8 to 41.0%]; $P = .713$) (**a**); the cumulative incidence of relapse (CIR) (60–64 years vs 65–69 years, 22.6% [95% CI 14.7 to 31.6%] vs 20.4% [95% CI 10.4 to 32.8%]; $P = .958$), and transplantation-related mortality (TRM) (60–64 years vs 65–69 years, 31.8% [95% CI 22.7 to 41.3%] vs 43.1% [95% CI 27.2 to 58.1%]; $P = .405$) (**b**). Among patients with an advanced disease status, OS (60–64 years vs 65–69 years, 38.4% [95% CI 32.7 to 44.1%] vs 34.2% [95% CI 26.0 to 42.6%]; $P = .149$) and GRFS (60–64 years vs 65–69 years, 19.4% [95% CI 14.9 to 24.3%] vs 19.0% [95% CI 12.8 to 26.1%]; $P = .378$) (**c**); CIR (60–64 years vs 65–69 years, 38.0% [95% CI 32.6 to 43.5%] vs 39.3% [95% CI 31.0 to 47.5%]; $P = .875$), and TRM (60–64 years vs 65–69 years, 30.4% [95% CI 25.4 to 35.6%] vs 30.8% [95% CI 23.3 to 38.5%]; $P = .570$) (**d**). *OS* overall survival, *GRFS* GVHD-free and relapse-free survival, *CIR* cumulative incidence of relapse, *TRM* transplantation-related mortality

Table 2 Causes of death after transplantation

	Early disease status	Advanced disease status	All
Total	86	301	387
Relapse or progression of MDS	30 (34.9%)	152 (50.5%)	182 (47.0%)
Infection			
Bacteria	12 (14.0%)	31 (10.3%)	43 (11.1%)
Fungus	7 (8.1%)	10 (3.3%)	17 (4.4%)
Virus	3 (3.5%)	10 (3.3%)	13 (3.4%)
Other	4 (4.7%)	7 (2.3%)	11 (2.8%)
Organ failure with or without infection	5 (5.8%)	24 (8.0%)	29 (7.5%)
GVHD with or without infection	6 (7.0%)	14 (4.7%)	20 (5.2%)
Idiopathic pulmonary syndrome	2 (2.3%)	9 (3.0%)	11 (2.8%)
Bleeding	0 (0.0%)	9 (3.0%)	9 (2.3%)
SOS	3 (3.5%)	5 (1.7%)	8 (2.1%)
Rejection	1 (1.2%)	7 (2.3%)	8 (2.1%)
TMA	2 (2.3%)	5 (1.7%)	7 (1.8%)
Secondary malignancy	0 (0.0%)	2 (0.7%)	2 (0.5%)
Other	11 (12.8%)	16 (5.3%)	27 (7.0%)

MDS myelodysplastic syndrome, *SOS* sinusoidal obstructive syndrome, *TMA* thrombotic microangiopathy

relapse or progression of MDS, which accounted for 50.5% of all deaths, followed by infection at 19.2% (see Table 2).

Prognostic factors for mortality in patients with an advanced disease status

The results of univariate and multivariate analyses were shown in supplemental Table 5. Significant factors associated with OS, GRFS, TRM, and CIR were summarized in Table 3. Five factors correlated with worse OS: PS 2–4 (HR, 1.72; 95% CI 1.20 to 2.46; $P = .003$), poor cytogenetic risk group (HR, 1.49; 95% CI 1.14 to 1.94; $P = .003$), the use of HLA-mismatched related donors (HR, 1.96; 95% CI 1.14 to 3.39; $P = .015$), unrelated cord blood donors (HR, 2.05; 95% CI 1.43 to 2.95; $P < .001$), and the high number of RBC transfusions before transplantation (i.e., ≥ 20 times) (HR, 1.85; 95% CI 1.11 to 3.09; $P = .018$). The following factors correlated with reduced GRFS: PS 2–4 (HR, 1.83; 95% CI 1.32 to 2.53; $P < .001$), poor cytogenetic risk group (HR, 1.34; 95% CI 1.06 to 1.69; $P = .013$), and HCT-CI ≥ 3 (HR, 1.31; 95% CI 1.00 to 1.72; $P = .047$). Two factors correlated with TRM: the application of azacitidine treatment before allo-HSCT (HR, 0.59; 95% CI 0.35 to 0.99; $P = .047$) and the use of unrelated cord blood donors (HR, 1.65; 95% CI 1.02 to 2.68; $P = .041$). The following factors significantly affected CIR: poor cytogenetic risk group (HR, 1.62; 95% CI 1.10 to 2.37; $P = .014$), 8 months or longer from the initial diagnosis to transplantation (HR, 0.66; 95% CI 0.46 to 0.96; $P = .029$), the number of RBC transfusion before transplantation (i.e., 1–19 times) (HR, 3.01; 95% CI 1.05 to 8.61; $P = .040$), and missing data on the history of RBC transfusion (HR, 3.81; 95% CI 1.29 to 11.27; $P = .016$). The high number of RBC transfusion (i.e., ≥ 20 times) correlated with increased CIR, but the P value for this association was at the borderline of statistical significance (HR, 2.85; 95% CI 0.95 to 8.58; $P = .062$). The patient age at allo-HSCT (60–64 vs. 65–69 years) had no significant impact on any post-transplant outcome.

In the univariate analysis among both male and female recipient, donor-recipient sex combination between donor and recipient had no significant impact on any post-transplant outcomes. Among the patients who underwent allo-HSCT using HLA-matched related donor, no significant difference was identified in OS, GRFS, CIR, and TRM between sibling ($n = 88$) and other than sibling donors ($n = 7$).

Discussion

The aim of this nationwide registry-based study was to reveal outcomes after allo-HSCT and identify prognostic factors in MDS patients aged 60–69 years. This cohort more closely reflects the real-world situation in Japan over the last 12 years because the TRUMP database was introduced to > 99% of approximately 250 adult transplant centers in Japan. In order to better understand transplant success in MDS patients aged 60–69 years, we assessed not only OS but also overall GRFS in a large cohort.

The present study showed the most pronounced increase in the utilization of allo-HSCT for MDS was in patients aged 60–69 years. The majority of this increase was attributed to the widespread use of Flu/Bu2- or Flu/Mel-based RIC and Flu/Bu4-based MAC regimens. Of note, the practical use of Flu/

Table 3 Multivariate models for mortality after allo-HSCT in MDS patients aged 60–69 years

Variables	Overall mortality			Failure for GRFS			Transplantation-related mortality			Relapse		
	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
Early disease status												
Patient sex												
Female	1.00			1.00			1.00			–		
Male	2.58	(1.40–4.79)	0.003	1.97	(1.24–3.12)	0.004	1.67	(0.78–3.58)	0.185	–		
PS at allo-HSCT												
0–1	1.00			1.00			–			–		
2–4	4.48	(2.28–8.81)	< 0.001	1.51	(0.85–2.71)	0.159	–			–		
Disease-altering therapy before allo-HSCT												
No disease-altering therapy										1.00		
Azacitidine alone										2.21	(0.46–10.65)	0.324
Chemotherapy[a]										3.61	(1.39–9.34)	0.008
Cytogenetic risk group												
Good	1.00			1.00			1.00			–		
Intermediate	1.43	(0.66–3.12)	0.367	1.03	(0.54–1.95)	0.933	1.51	(0.58–3.98)	0.400	–		
Poor	1.83	(1.02–3.28)	0.041	2.18	(1.39–3.42)	0.001	1.74	(0.79–3.87)	0.172	–		
Type of donor source												
HLA-matched related	1.00			–			1.00			–		
HLA-mismatched related	4.75	(1.80–12.53)	0.003	–			5.22	(1.19–22.90)	0.028	–		
Unrelated bone marrow	1.74	(0.85–3.55)	0.129	–			2.59	(0.92–7.34)	0.072	–		
Unrelated cord blood	2.47	(1.13–5.38)	0.023	–			3.08	(1.05–9.06)	0.041	–		
RBC transfusion from diagnosis to HSCT												
None	–			–			1.00			Not selected		
1–19 times	–			–			5.55	(0.69–44.8)	0.107	Not selected		
≥ 20 times	–			–			7.90	(1.01–61.47)	0.048	Not selected		
Missing	–			–			9.17	(1.10–76.22)	0.040	Not selected		
Advanced disease status												
PS at allo-HSCT												
0–1	1.00			1.00			–			–		
2–4	1.72	(1.20–2.46)	0.003	1.86	(1.34–2.57)	< 0.001	–			–		
HCT-CI												
0–2	Not selected			1.00			Not selected			–		
≥ 3	Not selected			1.31	(1.00–1.72)	0.047	Not selected			–		
Missing	Not selected			1.15	(0.86–1.53)	0.353	Not selected			–		
Disease-altering therapy before allo-HSCT												
No disease-altering therapy	–			1.00			1.00			1.00		
Azacitidine alone	–			0.85	(0.63–1.15)	0.289	0.59	(0.35–0.99)	0.047	1.49	(0.92–2.40)	0.103
Chemotherapy[a]	–			0.97	(0.77–1.23)	0.828	0.90	(0.63–1.30)	0.586	1.07	(0.72–1.59)	0.751
Cytogenetic risk group												
Good	1.00			1.00			–			1.00		
Intermediate	0.92	(0.64–1.33)	0.648	1.06	(0.79–1.44)	0.692	–			0.69	(0.37–1.28)	0.244
Poor	1.49	(1.14–1.94)	0.003	1.36	(1.08–1.72)	0.008	–			1.62	(1.10–2.37)	0.014
Type of donor source												
HLA-matched related	1.00			–			1.00			–		
HLA-mismatched related	1.96	(1.14–3.39)	0.015	–			1.52	(0.70–3.34)	0.293	–		
Unrelated bone marrow	1.13	(0.77–1.68)	0.530	–			1.03	(0.63–1.69)	0.916	–		
Unrelated cord blood	2.05	(1.43–2.95)	< 0.001	–			1.65	(1.02–2.68)	0.041	–		

Table 3 (continued)

Variables	Overall mortality			Failure for GRFS			Transplantation-related mortality			Relapse		
	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
Interval from diagnosis to allo-HSCT												
< 8 months	–			–			–			1.00		
≥ 8 months	–			–			–			0.66	(0.46–0.96)	0.029
GVHD prophylaxis												
CsA-based	1.00			–			–			–		
Tac-based	0.74	(0.55–0.99)	0.039	–			–			–		
Other	0.61	(0.15–2.50)	0.490	–			–			–		
RBC transfusion from diagnosis to allo-HSCT												
None	1.00			Not selected			–			1.00		
1–19 times	1.26	(0.76–2.07)	0.366	Not selected			–			3.01	(1.05–8.61)	0.040
≥ 20 times	1.85	(1.11–3.09)	0.018	Not selected			–			2.85	(0.95–8.58)	0.062
Missing	1.48	(0.87–2.51)	0.151	Not selected			–			3.81	(1.29–11.27)	0.016

HR hazard ratio, *CI* confidential incidence

[a] Chemotherapy included cytotoxic agents alone, cytotoxic agents followed by azacitidine, and cytotoxic agents preceded by azacitidine

Bu4-based regimen resulted in the increased number of MAC for the elderly who received allo-HSCT after 2010. Moreover, the introduction of azacitidine treatments may prompt MDS patients aged 60–69 years to undergo allo-HSCT. This result indicated the efficacy with less toxicity of prior-to-transplantation azacitidine treatments for the elderly, which was consistent with previous findings [21, 22, 24]. Additionally, from a societal perspective, changes in physician and patient willingness to consider the indication of allo-HSCT for the elderly may promote transplant growth, similar to autologous HSCT and solid organ transplantation [47–49]; however, this is difficult to measure.

The most important results of this study were that allo-HSCT offers a curative potential for MDS patients aged 60–69 years; to the best of our knowledge, this is the largest study on allo-HSCT among the elderly (≥ 60 years) having de novo MDS with both an early and advanced disease status. Moreover, in the present study, 1-year GRFS rates after allo-HSCT were 33.3 and 27.7% in patients with an early and advanced disease status, respectively, which are similar to previously published data on hematological malignancies, including mainly younger patients (< 60 years) [33, 42, 43]. Although patient age was the most significant indicator to decide a patient's eligibility for allo-HSCT, patient age (60–64 vs. 65–69 years) did not have any prognostic impact in the present study. Our results supported patient age alone not being precluded for allo-HSCT [14–16]. Considering that the patient-related factors, such as PS at transplantation, patient sex, and HCT-CI, were identified as independent risks in the present study, we need to consider the indication of allo-HSCT with careful attention to individualized patient-related risks in all potential older candidates.

Concerns have been expressed regarding increased TRM after allo-HSCT for the elderly. Difficulties are associated with directly comparing the impact of the donor source because of the strong influence of donor availability on graft selection. Nevertheless, we observed a lower incidence of neutrophil engraftment (see supplemental data) and higher TRM, mainly due to infectious complications, in patients with the use of unrelated cord blood, as previously reported [50, 51]. In order to reduce TRM after unrelated cord blood transplantation for the elderly with MDS, further efforts are needed to develop transplantation procedures to facilitate engraftment and minimize the risk of life-threating infections [52–54].

Another interesting result was that prior-to-transplantation azacitidine treatments alone were associated with reduced TRM in patients with an advanced disease status. While previous studies reported a slightly lower incidence of relapse in patients receiving prior-to-transplantation azacitidine treatments [23, 24], few have described the positive effects of prior-to-transplantation azacitidine treatments on TRM. This difference may be partly due to the present study including only patients aged 60 years or older who are more vulnerable to the toxicity of chemotherapies before allo-HSCT. Prior-to-transplantation azacitidine treatments may not interfere with post-transplant outcomes in the elderly with MDS. Since we did not collect detailed information on azacitidine treatments, the optimization of azacitidine treatments as bridging therapy will be of interest in future studies.

We are also interested in the post-transplant outcomes after 2014, given the recent development of transplant procedures, such as the use of unrelated peripheral blood stem cells and the conditioning regimen

containing post-transplantation cyclophosphamide, alemtuzumab, and low-dose antithymocyte globulin for allo-HSCT using HLA-haploidentical related donors [55–60]. In addition, the recent studies showed the increasing number of allo-HSCT for patients aged ≥ 70 years probably relating with the increased life expectancy in general and the improvement of transplant procedures [13, 61]. Further investigations are warranted to clarify the post-transplant outcomes among the elderly, including 70 years and older, with MDS.

This study has several limitations that are common among retrospective observational studies. The present study included patients with heterogenous baseline characteristics and transplant procedures, and the lack of some required data (i.e., HCT-CI and the history of RBC transfusion), which could potentially affect the result of our analysis. Furthermore, a selection bias for the older transplant cohort may influence post-transplant outcomes; a previous study indicated that candidates aged > 65 years were less likely to underutilize allo-HSCT [62]. Although several factors, such as gene mutational profile and serum ferritin level at allo-HSCT, potentially affect the post-transplant outcomes for MDS patients [63–67], the prognostic values of these factors were not fully evaluated in the present study because of the lack of data. Thus, prospective studies are needed to assess the benefits of allo-HSCT in older patients with each disease status.

In conclusion, the present study showed the increased utilization of allo-HSCT for elderly patients, which may offer an opportunity for long-term remission and a potential cure. Although an older age per se cannot be regarded as a contraindication to allo-HSCT, novel therapeutic strategies are required to reduce transplant-related toxicity while maximizing the benefits of allo-HSCT.

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Author's contribution H.I. and Y.M. designed the research, organized the project, analyzed the data, and wrote the manuscript. H.I., K. Ishiyama, K.A., J.A., T. Ishikawa, and Y.M. collected data from TRUMP. H.I., K. Ishiyama, K.A., J.A., T. Ishikawa, N.A., K.O., Y.U., T.F., T.S., Y.O., K. Iwato, H.O., T.K., T. Ichinohe, M.T., Y.A., and Y.M. interpreted data, and reviewed and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

The following institutions and hematologists contributed to this study: Nagasaki University: Dr. H. Itonaga and Dr. Y. Miyazaki; Kyoto University: Dr. A. Takeda and Dr. K. Aoki; Kanagawa Cancer Center: Dr. J. Aoki, Dr. M. Tanaka, and Dr. T Takahana; Kanazawa University Hospital: Dr. K. Ishiyama; Kobe City Medical General Hospital: Dr. Y. Shimomura and Dr. T. Ishikawa; Keio University School of Medicine: Drs. J. Kato and S. Okamoto; Japanese Red Cross Nagoya First Hospital: Dr. Y. Ozawa; Tokyo Metropolitan Cancer and Infectious Disease Centre Komagome Hospital: Drs. K. Kakizoe and N. Doki; JA Aichi Konan Kosei Hospital: Dr. A. Kohno; Toranomon Hospital: Dr. S. Takagi; Aichi Medical University: Dr. A. Takami; Hyogo College of Medicine: Dr. H. Tamaki; Akita University Hospital: Dr. M. Hirokawa; Mishuku Hospital: Dr. K. Masuoka; Niigata University: Dr. M. Masuko; Kinki University: Dr. K. Ashizawa and Dr. T. Ashida; NTT Medical Center Tokyo: Dr. R. Kida and Dr. K. Usuki; Hamanomachi Hospital: Dr. T. Eto; Sapporo Hokuyu Hospital: Dr. K. Minauchi and Dr. S. Ohta; Tohoku University Hospital: Dr. Y. Onishi; Kanazawa University Graduate School of Medical Sciences: Dr. S. Nakao; Shizuoka Cancer Center: Dr. T. Enami and Dr. T. Ikeda; Kansai Medical University Hirakata Hospital: Dr. K. Ishii; Tokyo Metropolitan Geriatric Hospital: Dr. S. Kobayashi; Tokai University School of Medicine: Dr. S. Machida; Osaka City University: Dr. H. Koh; National Cancer Center Hospital: Dr. T. Suzuki; The University of Tokyo: Dr. T. Konuma; Nagoya University Graduate School of Medicine: Dr. K. Miyao and Dr. T. Morishita; Tokyo Women's Medical University: Dr. K. Yoshinaga; Ishikawa Prefectural Central Hospital: Dr. Y. Mizumaki and Dr. C. Sugimori; Kokura Memorial Hospital: Dr. A. Yonezawa; Okawama University Hospital: Dr. S. Fujii.

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