Bone Marrow Transplantation (2020) 55:1784–1795
https://doi.org/10.1038/s41409-020-0821-9

ARTICLE

Comparison of the outcomes after haploidentical and cord blood salvage transplantations for graft failure following allogeneic hematopoietic stem cell transplantation

Kaito Harada[1] · Shigeo Fuji[2] · Sachiko Seo[3] · Junya Kanda[4] · Toshimitsu Ueki[5] · Fumihiko Kimura[6] · Koji Kato[7] · Naoyuki Uchida[8] · Kazuhiro Ikegame[9] · Makoto Onizuka[1] · Ken-ichi Matsuoka[10] · Noriko Doki[11] · Toshiro Kawakita[12] · Yasushi Onishi[13] · Shingo Yano[14] · Takahiro Fukuda[15] · Minoko Takanashi[16] · Yoshinobu Kanda[17] · Yoshiko Atsuta[18,19] · Masao Ogata[20] · on behalf of the transplant complications working group of the Japan Society for Hematopoietic Cell Transplantation

Received: 7 October 2019 / Revised: 27 January 2020 / Accepted: 28 January 2020 / Published online: 12 February 2020

Abstract

Graft failure (GF) is a life-threatening complication after allogeneic stem cell transplantation (SCT). Although salvage SCTs can be performed with haploidentical donor (HID) or cord blood (CB), no study has compared the performances of these two sources. Using nationwide registration data, we compared the transplant outcomes of patients who developed GF and underwent salvage transplantation from HID ($n = 129$) and CB ($n = 570$) from 2007 to 2016. The HID group demonstrated better neutrophil recovery (79.7 vs. 52.5% at 30 days, $P < 0.001$). With a median follow-up of 3 years, both groups demonstrated similar overall survival (OS) and nonrelapse mortality (NRM; 1-year OS, 33.1 vs. 34.6% and 1-year NRM, 45.1 vs. 49.8% for the HID and CB groups). After adjustments for other covariates, OS did not differ in both groups. However, HID was associated with a lower NRM (hazard ratio, 0.71; $P = 0.038$) than CB. The incidence of acute graft-versus-host disease (GVHD)-related deaths was significantly higher in the HID group, although infection-related deaths were observed more frequently in the CB group. HID may be a promising salvage SCT option after GF due to its faster engraftment and low NRM.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-SCT) is a potentially curative therapy and has become a standard of care for various hematologic diseases [1, 2]. The outcomes of patients undergoing allo-SCT have improved over the last decades [3, 4]. However, graft failure (GF) is still a life-threatening complication of the procedure due to the prevailing use of cord blood (CB) or human leukocyte antigen (HLA) mismatched donors as stem cell sources, and reduced-intensity conditioning [5–9]. Studies have shed light on the mechanism of GF [10, 11], which includes rejection by residual recipient T lymphocytes [12], absence of facilitating donor T [13] or natural killer cells [14], donor-specific antibody reactions [15, 16], low counts of infused donor cells [6, 7], stromal cell damage [17], inflammatory cytokinemia [18, 19], and concomitant severe infections [20]. GF occurs in as many as 4.0–7.3% of allo-SCTs, with a higher incidence in the setting of CB transplantations [5–9].

The survival rate of patients who developed GF is dismal, at only 11–58% [6, 7, 21–25]. This can be attributed to severe infections caused by prolonged neutropenic periods, organ failure due to conditioning [26], acute graft-versus-host disease (GVHD) after salvage transplantation [27], and disease relapse or progression. CB is favored for urgent salvage transplantations due to its availability [22–25]. During the last decade, haploidentical donors (HIDs) have emerged as alternative donors due to the promising survival outcomes reported [28–30]. HIDs are also considered for salvage transplantations because of their availability and the fast engraftment they afford [22, 31–36]. A Japanese study

Supplementary information The online version of this article (https://doi.org/10.1038/s41409-020-0821-9) contains supplementary material, which is available to authorized users.

✉ Kaito Harada
k.harada@fuji.tokai-u.jp

Extended author information available on the last page of the article

showed the superiority of bone marrow (BM) or peripheral blood (PB) to CB, but they included HLA-matched and -mismatched donors, and their BM and PB populations were small due to GF rarity [22]. To date, no large-scale studies have directly compared CB and HID as stem cell sources in the setting of salvage transplantation after allo-SCT, and the optimal donor selection strategy for GF remains unclear.

To address this question, we analyzed transplant outcomes for patients who developed GF after first allo-SCT and underwent salvage transplantation from HID or CB stem cells from data on a nationwide registry of the Japan Society for Hematopoietic Cell Transplantation.

Methods

The Transplant Registry Unified Management Program 2 of the Japanese Data Center for Hematopoietic Cell Transplantation provided the clinical data for this study [37, 38]. We included data from patients over 16 years who were suspected or diagnosed with GF and underwent a second allo-SCT using CB or HID between 2007 and 2016 ($n = 744$). Because of the registration data-based retrospective study, we could not distinguish primary and secondary GF and therefore included both. We excluded data from patients who underwent a second allo-SCT without antecedent conditioning regimens ($n = 21$), and from those who developed GF concomitantly with a relapse diagnosis ($n = 11$). In addition, we excluded records from patients lacking data on clinical outcomes ($n = 1$, data for survival) and infused cell dose ($n = 12$). Finally, 699 patients were included. Our study protocol adhered to the principles of the Declaration of Helsinki, and the Institutional Review Board of Tokai University School of Medicine approved this retrospective study.

Overall survival (OS) was defined as the time between transplantation and death or the time of last visit. Progression-free survival (PFS) was defined as the time between transplantation and the first event (relapse or death). Nonrelapse mortality (NRM) was defined as death without relapse or disease progression. Neutrophil recovery required an absolute neutrophil count of at least 0.5×10^9/L for 3 consecutive days. The first day was considered the recovery day; platelet recovery required a platelet count of at least 20×10^9/L without transfusions for 3 consecutive days. We defined HID as a related donor with HLA disparity of at least two serological levels. We classified the conditioning intensity [39] and disease risk index [40] in line with the published criteria. Acute and chronic GVHD was diagnosed and graded at each center according to published criteria [41, 42]. Finally, we defined acute GVHD-related death as that caused primarily or secondarily by GVHD; and infection-related death as that due to GF or infection, but not to acute GVHD.

We compared distributions of patient characteristics using Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. We estimated OS probabilities using the Kaplan–Meier method, and analyzed differences between groups using the log-rank test. We used a cumulative incidence method to determine the incidences of NRM, engraftment, acute and chronic GVHD, and Gray's test to analyze differences between the groups. We considered relapse and disease progression as competing risks in the NRM analysis and NRM as competing risk in the relapse analysis. Relapse and NRM were considered to be competing risks in the analysis of engraftment, whereas relapse, NRM, and GF after salvage transplantation were considered in the analysis of acute and chronic GVHD. We performed multivariate analyses with the Cox proportional hazard regression model for OS and PFS or the Fine–Gray proportional hazards model for NRM, relapse, engraftment, and the incidence of acute and chronic GVHD. We included factors demonstrating significance at P values < 0.05 in the univariate analysis into the multivariate analyses, and calculated hazard ratios (HR) with 95% confidence intervals (CIs). We considered the following covariates in the univariate models for each analysis: stem cell source (HID vs. CB), age (<55 vs. ≥55 years), sex (male vs. female), donor source at first SCT (CB vs. BM/PB), disease risk index (DRI) (low/intermediate vs. high/very high), presence of anti-HLA antibody (absence vs. presence), presence of donor-specific anti-HLA antibody (absence vs. presence), conditioning intensity (myeloablative, reduced-intensity, or nonmyeloablative conditionings), alkylating agents use (no vs. yes), total body irradiation (TBI) (no vs. yes), GVHD prophylaxis (calcineurin inhibitors [CNI] plus methotrexate [MTX], CNI plus mycophenolate mofetil [MMF], CNI plus prednisolone [PSL], CNI alone, or another combination), ABO incompatibility (match vs. mismatch), transplantation year (2007–2011 vs. 2012–2016), and days from first SCT to salvage SCT (<42 days vs. ≥42 days). All P values were two-sided, and we performed all statistical analyses using EZR, a graphical user interface for R software (The R Foundation for Statistical Computing, version 2.13.0, Vienna, Austria) [43].

Results

Patient and transplant characteristics

We included data from 129 eligible patients in the HID group, and 570 in the CB group. Table 1 shows the characteristics of patients and transplants. We found significant

Table 1 Characteristics of patients and transplants.

	Haploidentical donor ($n = 129$)	Cord blood ($n = 570$)	*P* value
Age, median [range]	51 [16–76]	52 [16–74]	0.21
<55	80 (62.0)	324 (56.8)	0.32
≥55	49 (38.0)	246 (43.2)	
Sex (%)			
Male	81 (62.8)	366 (64.2)	0.76
Female	48 (37.2)	204 (35.8)	
Body weight at SCT [range]	58.0 [37.5–93.0]	56.0 [36.8–92.7]	0.12
Stem cell source			
BM/PB	1/128		
Donor source at first SCT (%)			
Cord blood	65 (50.4)	425 (74.6)	<0.001
BM/PB	64 (49.6)	145 (25.4)	
Matched related BM/PB	0 (0.0)	7 (1.2)	
Unrelated BM/PB	36 (27.9)	120 (21.1)	
Haploidentical BM/PB	28 (21.7)	18 (3.2)	
$CD34^+$ cell count (10^5/kg), median [range]	25.0 [6.90–97.0]	0.78 [0.08–4.86]	
TNC count (10^7/kg), median [range]	–	2.59 [0.31–7.54]	
Disease risk index (%)			
Low/intermediate	62 (48.1)	333 (58.4)	0.039
High/very high	67 (51.9)	237 (41.6)	
Disease (%)			
Acute myeloid leukemia	61 (47.3)	269 (47.4)	0.72
Myelodysplastic syndrome	29 (22.5)	122 (21.5)	
Acute lymphoblastic leukemia	18 (14.0)	68 (12.0)	
Lymphoma	12 (9.3)	59 (10.4)	
Chronic myeloid leukemia	2 (1.6)	21 (3.7)	
Nonmalignant disease	5 (3.9)	26 (4.6)	
Other	2 (1.6)	3 (0.5)	
Anti-HLA antibody (%)			
Absence	62 (48.1)	330 (57.9)	0.012
Presence	21 (16.3)	110 (19.3)	
Unknown	46 (35.7)	130 (22.8)	
Donor specific anti-HLA antibody (%)			
Absence	76 (58.9)	431 (75.6)	<0.001
Presence	7 (5.4)	9 (1.6)	
Unknown	46 (35.7)	130 (22.8)	
Conditioning intensity (%)			
MAC	7 (5.4)	9 (1.6)	0.012
CyTBI	3 (2.3)	2 (0.4)	
BuCy	1 (0.8)	1 (0.2)	
Other MAC	3 (2.3)	6 (1.1)	
RIC	88 (68.2)	440 (77.2)	
FluCyTBI	26 (20.2)	213 (37.4)	
FluMel-based	37 (28.7)	174 (30.5)	
FluBu-based	13 (10.1)	28 (4.9)	
Other RIC	12 (9.3)	25 (4.4)	
NMA	34 (26.4)	121 (21.2)	
FluCy	17 (13.2)	64 (11.2)	
FluTBI	3 (2.3)	17 (3.0)	
Flu-based other combination	12 (9.3)	37 (6.5)	
Other NMA	2 (1.6)	3 (0.5)	
Use of alkylating agents as a part of conditioning (%)	101 (78.3)	492 (86.3)	0.029
Use of TBI as a part of conditioning (%)	59 (45.7)	338 (59.3)	0.006
GVHD prophylaxis (%)			
CI + MTX	40 (31.0)	173 (30.4)	<0.001
CI + MMF	21 (16.3)	176 (30.9)	
CI + PSL	42 (32.6)	13 (2.3)	
CI alone	19 (14.7)	191 (33.5)	
Other combination	7 (5.4)	17 (3.0)	
Use of ATG (%)	87 (67.4)	61 (10.7)	<0.001
Use of PT-Cy (%)	10 (7.8)		
ABO incompatibility (%)			
Match	80 (62.0)	205 (36.0)	<0.001
Mismatch	49 (38.0)	364 (64.0)	
Year of transplantation (%)			
2007–2011	57 (44.2)	255 (44.7)	0.92
2012–2016	72 (55.8)	315 (55.3)	
Days from first SCT to salvage SCT, median [range]	42 [17–757]	42 [19–2250]	0.57
Follow-up period for survivors, median [range]	1015 [210–3644]	1153 [33–3828]	0.99

SCT stem cell transplantation, *BM* bone marrow, *PB* peripheral blood, *TNC* total nucleated cell, *HLA* human leukocyte antigen, *MAC* myeloablative conditioning, *Cy* cyclophosphamide, *TBI* total body irradiation, *Bu* busulfan, *RIC* reduced-intensity conditioning, *Flu* fludarabine, *Mel* melphalan, *NMA* nonmyeloablative conditioning, *GVHD* graft-versus-host disease, *CNI* calcineurin inhibitor, *MTX* methotrexate, *MMF* mycophenolate mofetil, *PSL* prednisolone, *TBI* total body irradiation, *ATG* antithymocyte globulin, *PT-Cy* post-transplant cyclophosphamide.

differences between the groups in terms of donor source during the first SCT, DRI, presence of anti-HLA antibody, and donor-specific anti-HLA antibody, conditioning intensity, use of alkylating agents and TBI, GVHD prophylaxis, use of antithymocyte globulin (ATG), and ABO incompatibility. The median CD34+ cell counts were 25.0×10^5/kg (range, 6.90–97.0) in the HID group and 0.78×10^5/kg (range, 0.08–4.86) in the CB group. In the HID group, ten patients (7.8%) received posttransplant cyclophosphamide (PT-Cy) as GVHD prophylaxis. Other characteristics were similar between the groups. All but one in the HID group received PB, rather than BM, as a stem cell source. No patient received donor cell with ex vivo T-cell depletion in the HID group. In the CB group, all patients received single CB. The median time from first SCT to salvage SCT was 42 days in both groups (ranges: HID, 17–757; CB, 19–2250). The median follow-up period for survivors was 1111 days.

Engraftment

The median days of neutrophil recovery were 13 and 28.5 days, in the HID and CB groups, respectively. The cumulative incidence of neutrophil recovery after 30 days from transplantation was significantly higher in the HID group (79.7%) than the CB group (52.5%; $P < 0.001$; Fig. 1a). In the multivariate analysis, the HID group was significantly associated with neutrophil recovery (HR, 2.94; 95% CI, 2.11–4.10; $P < 0.001$; Table 2). Other significantly favorable factors for neutrophil recovery were GVHD prophylaxis other than CNI + MTX and use of TBI and alkylating agents. Among patients who survived longer than

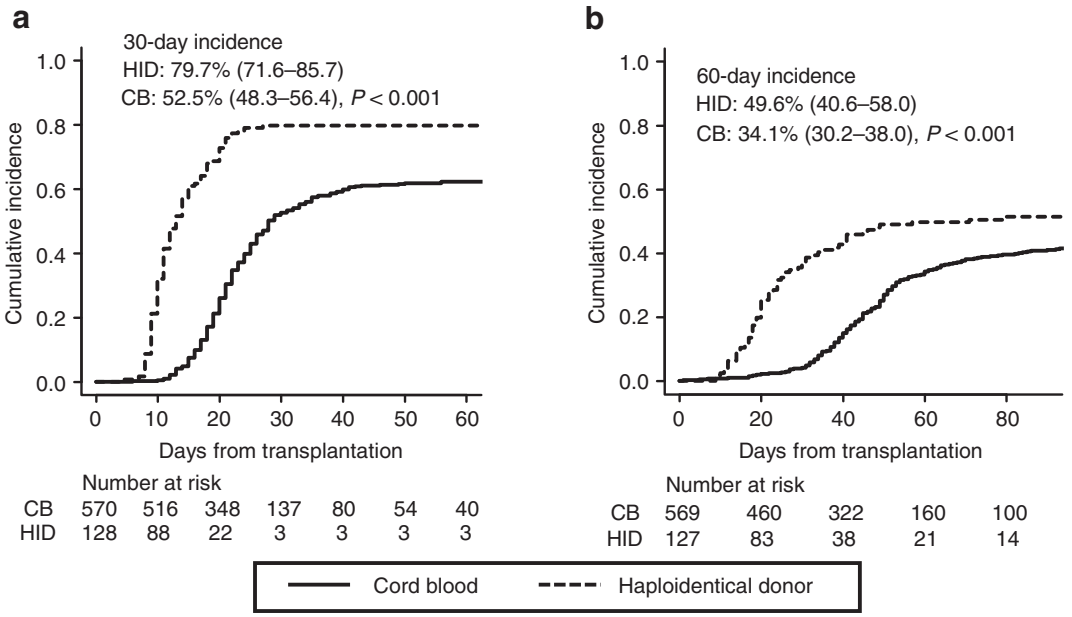

Fig. 1 Engraftment rate after salvage transplantation. Cumulative incidence of neutrophil (**a**) and platelet recoveries (**b**) after salvage transplantation according to the stem cell source were shown. Relapse and NRM are competing risks in each analysis.

28 days after salvage SCT, 2.9% (3/102) in the HID and 19.5% (86/440) in the CB groups again developed GF ($P < 0.001$). CB was also a significant risk factor for GF after salvage transplantation. The cumulative incidence of platelet recovery after 60 days was also significantly higher in the HID group (49.6%) than in the CB group (34.1%; $P < 0.001$; Fig. 1b).

OS, PFS, NRM, and relapse rate

Both groups demonstrated similar OS (33.1% in the HID group vs. 34.6% in the CB group at 1 year; $P = 0.40$; Fig. 2a). After adjustments for the other covariates, the HID group tended to give better OS, but the difference did not reach a statistical significance (HR, 0.83, 95% CI, 0.64–1.07, $P = 0.16$). The significant risk factors for OS included old age, poor DRI, GVHD prophylaxis with other combination, nonuse of TBI, and myeloablative conditioning. GVHD prophylaxis with CNI + MMF was a significant favorable factor for OS, whereas time from first SCT to salvage SCT (<42 vs. ≥42 days) did not affect OS. Regarding PFS, there was no significant difference between the groups (28.3% in the HID group vs. 30.3% in the CB group at 1 year; $P = 0.38$; Fig. 2b). In multivariate analysis, stem cell source was not a significant risk factor for PFS (Supplementary Table 1). Both groups had similar NRMs (45.1% in the HID group vs. 49.8% in the CB group at 1 year; $P = 0.48$; Fig. 2c). However, after adjustments for the other covariates, the HID group was associated with a lower NRM than the CB group (HR, 0.71, 95% CI, 0.52–0.98, $P = 0.038$). GVHD prophylaxis with CNI + MMF and use of TBI were also associated with lower NRMs. On the other hand, old age and GVHD prophylaxis with other combination were significant risk factors for NRM. In the HID group, the use of ATG or PT-Cy did not result in a significant decrease in NRM after 180 days (44.6% in patients administered ATG ($n = 87$), 30.0% in those administered PT-Cy ($n = 10$), and 36.1% in those administered neither ATG nor PT-Cy ($n = 32$); $P = 0.52$ by univariate Gray's test). In the CB group, the use of ATG was associated with higher NRM in the univariate analysis (63.5% in patients who received ATG vs. 48.2% in those who did not receive ATG at 1 year; $P = 0.029$); however, the difference was not significant in the multivariate analysis (HR, 1.16; 95% CI, 0.84–1.61; $P = 0.37$). Regarding relapses, the cumulative incidence in the HID group was significantly higher than that in the CB group (26.6 vs. 19.9% at 1 year; $P = 0.046$), although the difference was not significant in the multivariate analysis (Supplementary Table 1).

GVHD and infections

Given that the faster engraftment did not translate into significantly better OS in the HID group, we focused on acute GVHD development. The cumulative incidence of acute GVHD after 100 days was significantly higher in the HID group than in the CB group, regardless of the severity (grade II–IV, 34.1% in the HID group vs. 16.4% in the CB group, $P < 0.001$; and grade III–IV, 19.4% in the HID group vs. 4.0% in the CB group, $P < 0.001$; Fig. 3a, b). After

Table 2 Multivariate analysis for neutrophil recovery, OS, and NRM.

	Hazard ratio (95% CI)	*P* value
Neutrophil recovery		
Stem cell source		
Cord blood	Reference	
Haploidentical donor	2.94 (2.11–4.10)	<0.001
Disease risk index		
Low/intermediate	Reference	
High/very high	0.87 (0.71–1.06)	0.17
GVHD prophylaxis		
CNI + MTX	Reference	
CNI + MMF	1.63 (1.29–2.05)	<0.001
CNI + PSL	2.51 (1.50–4.18)	<0.001
CNI alone	1.38 (1.06–1.79)	0.016
Other combination	0.45 (0.18–1.09)	0.078
Conditioning intensity		
RIC	Reference	
MAC	0.72 (0.35–1.49)	0.38
NMA	1.07 (0.75–1.53)	0.72
Use of TBI		
No	Reference	
Yes	1.35 (1.06–1.71)	0.016
Use of alkylating agents		
No	Reference	
Yes	1.73 (1.14–2.63)	0.009
ABO incompatibility		
Match	Reference	
Mismatch	0.90 (0.73–1.11)	0.31
OS		
Stem cell source		
Cord blood	Reference	
Haploidentical donor	0.83 (0.64–1.07)	0.16
Age		
<55	Reference	
≥55	1.47 (1.22–1.76)	<0.001
Disease risk index		
Low/intermediate	Reference	
High/very high	1.50 (1.25–1.79)	<0.001
GVHD prophylaxis		
CNI + MTX	Reference	
CNI + MMF	0.77 (0.61–0.98)	0.037
CNI + PSL	1.38 (0.95–1.98)	0.087
CNI alone	1.11 (0.89–1.39)	0.36
Other combination	3.12 (1.98–4.92)	<0.001
Use of alkylating agents		
No	Reference	
Yes	0.77 (0.59–1.01)	0.055
Use of TBI		
No	Reference	
Yes	0.70 (0.58–0.86)	<0.001
Conditioning intensity		
RIC	Reference	
MAC	1.94 (1.15–3.30)	0.014
NMA	1.00 (0.77–1.29)	0.98
NRM		
Stem cell source		
Cord blood	Reference	
Haploidentical donor	0.71 (0.52–0.98)	0.038
Age		
<55	Reference	
≥55	1.32 (1.07–1.63)	0.009
GVHD prophylaxis		
CNI + MTX	Reference	
CNI + MMF	0.61 (0.45–0.82)	<0.001
CNI + PSL	1.33 (0.88–2.00)	0.18
CNI alone	1.05 (0.81–1.36)	0.71
Other combination	3.31 (1.98–5.54)	<0.001
Conditioning intensity		
RIC	Reference	
MAC	0.84 (0.35–2.03)	0.71
NMA	1.01 (0.74–1.36)	0.97
Use of alkylating agents		
No	Reference	
Yes	0.81 (0.60–1.10)	0.19
Use of TBI		
No	Reference	
Yes	0.72 (0.57–0.91)	0.007

CI confidence interval, *OS* overall survival, *NRM* nonrelapse mortality, *GVHD* graft-versus-host disease, *CNI* calcineurin inhibitor, *MTX* methotrexate, *MMF* mycophenolate mofetil, *PSL* prednisolone, *RIC* reduced-intensity conditioning, *MAC* myeloablative conditioning, *NMA* nonmyeloablative conditioning, *TBI* total body irradiation.

adjustments for other covariates, the HID group was significantly associated with a higher incidence of grade II–IV (HR, 2.76; 95% CI, 1.81–4.21; $P < 0.001$) and III–IV acute GVHD (HR, 4.46; 95% CI, 2.22–8.97; $P < 0.001$). In comparison with CNI + MTX, GVHD prophylaxis with CNI + MMF and CNI alone were associated with development of grade II–IV acute GVHD, whereas the latter was also associated with grade III–IV acute GVHD (Table 3). Figure 4 shows the cumulative incidence of acute GVHD-related or infection-related deaths. The HID group demonstrated a lower incidence of infection-related deaths than the CB group (18.7% in the HID group vs. 33.0% in the CB group at 1 year, $P = 0.003$; Fig. 4a). Conversely, the cumulative incidence of acute GVHD-related deaths was significantly higher in the HID group than in the CB group (12.4% in the HID group vs. 1.6% in the CB group at 1 year, $P < 0.001$; Fig. 4b). The list of primary causes of deaths is shown in Supplementary Table 2.

Patients with donor-specific anti-HLA antibody

As shown in Table 1, 21 (16.3%) in the HID and 110 (19.3%) in the CB groups had anti-HLA antibody, of which seven (5.4%) and nine (1.6%) were donor specific. For patients with donor-specific anti-HLA antibody, the cumulative incidence of neutrophil recovery at 30 days after salvage SCT was higher in the HID group than in the CB

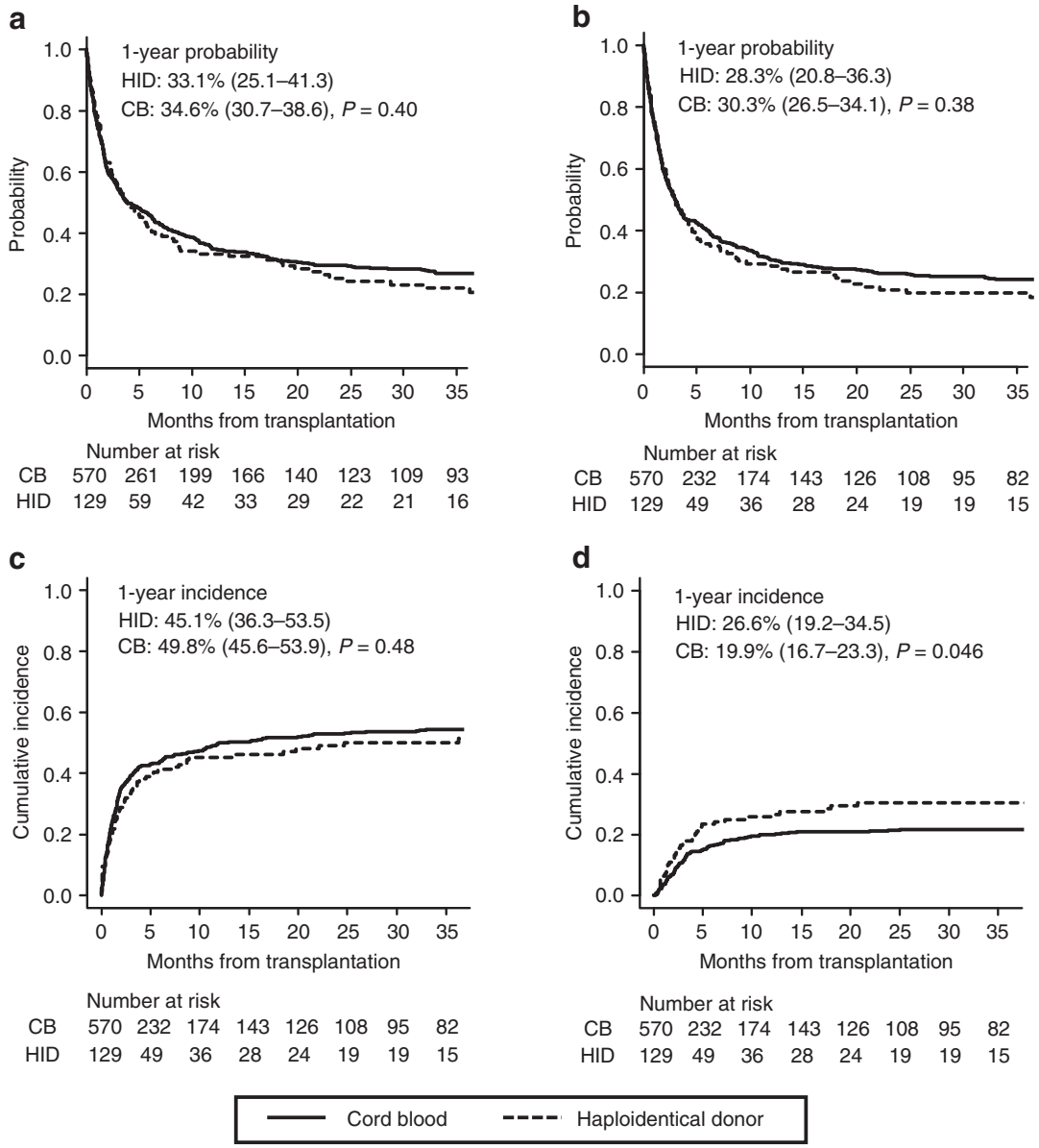

Fig. 2 Overall survival (**a**), progression-free survival (**b**), nonrelapse mortality (**c**), and relapse rate (**d**) after salvage transplantations according to the stem cell source.

group, although the difference was not significant (71.4 vs. 22.2%; $P = 0.18$). The 1-year OS was 28.6% in the HID and 0% in the CB groups ($P = 0.203$). Figure 5 shows the forest plot for OS stratified by patient characteristics, including the presence of donor-specific antibodies.

Discussion

The utility of haploidentical salvage transplantations for GF has been reported only in studies with small patient populations [22, 34–36]; no large-scale studies have directly compared the outcomes of salvage transplantation from HID and CB in adult patients. In this study, we demonstrated the faster engraftment and the lower NRM after salvage transplantation for the HID group patients compared with the CB group patients. However, these HID advantages did not translate into significantly better OS. Fuji et al. reported HID's superiority using nationwide registry data [22]; but their BM/PB donors included HLA-matched or HLA-partially mismatched donors, and the number of patients in the BM/PB group was small. These differences may contribute to the discrepancy in the outcomes between our studies. Another explanation for the

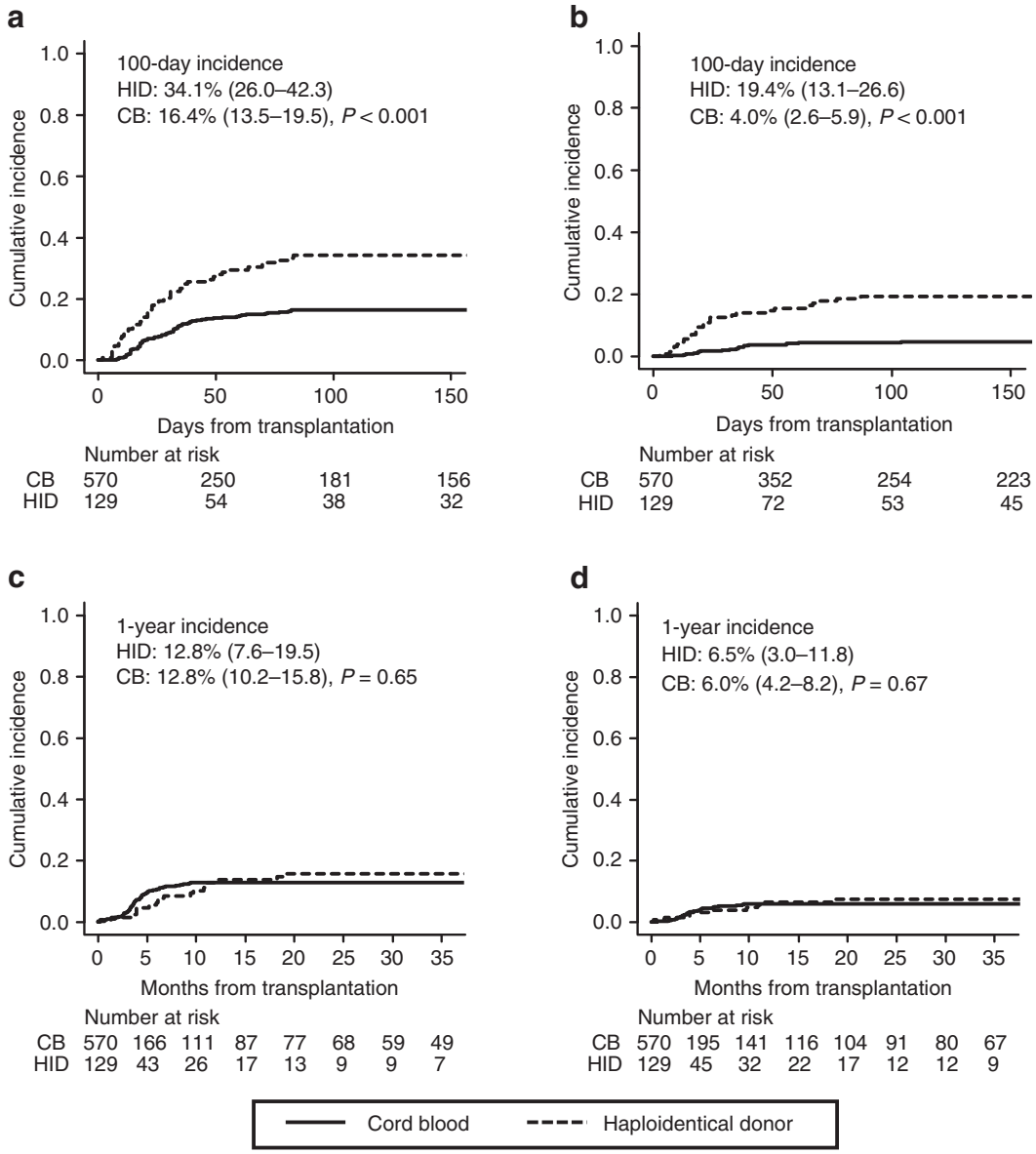

Fig. 3 Cumulative incidences of grade II–IV (**a**) and III–IV (**b**) acute graft-versus-host disease, and all-grade (**c**) and extensive chronic graft-versus-host disease (**d**) after salvage transplantations according to the stem cell source. Relapse, NRM, and graft failure after salvage transplantation are competing risks in each analysis.

similar survival outcomes of HID and CB groups is that, in our study, the relapse rate after salvage transplantation was significantly higher in the HID group than in the CB group. In fact, the poor DRI was observed in the HID group. The difference between the groups could hamper the definitive conclusion. Similar survival outcomes for HID and CB transplants have also been reported in a pediatric cohort in Japan [44]. Although the results should be interpreted with caution, owing to the rapid availability of CB, which does not need a waiting period for the HLA test results, both CB and HID can be reasonable choices in the GF setting.

The stem cell source had significant effects on the cause of death in our study. Acute GVHD-related mortality was higher after HID transplants than after CB transplants, while infection-related mortality was lower after HID transplants than it was after CB transplants. Although the faster neutrophil recovery in the HID group could prevent infection-related deaths to a certain extent, severe GVHD development was a major problem after haploidentical salvage transplantation. The advantages in the HID group were partly negated by acute GVHD development, which also may have contributed to the similar OS rates after both transplantations. A higher incidence of acute GVHD after

Table 3 Multivariate analysis for the development of acute GVHD.

	Hazard ratio (95% CI)	*P* value
Grade II–IV acute GVHD		
Stem cell source		
Cord blood	Reference	
Haploidentical donor	2.76 (1.81–4.21)	<0.001
GVHD prophylaxis		
CNI + MTX	Reference	
CNI + MMF	1.63 (1.03–2.58)	0.038
CNI + PSL	1.47 (0.76–2.82)	0.25
CNI alone	1.74 (1.11–2.74)	0.016
Other combination	0.49 (0.13–1.88)	0.3
Use of ATG		
No	Reference	
Yes	0.83 (0.55–1.26)	0.38
Grade III–IV acute GVHD		
Stem cell source		
Cord blood	Reference	
Haploidentical donor	4.46 (2.22–8.97)	<0.001
Age		
<55	Reference	
≥55	0.56 (0.30–1.04)	0.068
GVHD prophylaxis		
CNI + MTX	Reference	
CNI + MMF	2.02 (0.88–4.68)	0.099
CNI + PSL	2.07 (0.84–5.10)	0.12
CNI alone	2.30 (1.01–5.20)	0.046
Other combination	0.79 (0.12–5.34)	0.8
Use of ATG		
No	Reference	
Yes	1.13 (0.60–2.11)	0.71

GVHD graft-versus-host disease, *CI* confidence interval, *CNI* calcineurin inhibitor, *MTX* methotrexate, *MMF* mycophenolate mofetil, *PSL* prednisolone, *ATG* antithymocyte globulin.

haploidentical salvage transplantation was also reported in other studies [22, 33]. PT-Cy was introduced in the last decade as an effective GVHD prophylaxis during haploidentical transplantations with fewer episodes of acute GVHD and lower NRM than ATG-based prophylaxis [45]. Unfortunately, our study included only ten patients transplanted with PT-Cy in the HID group, and our study lacked statistical power for analyzing the effects of PT-Cy in the HID group. Future studies should compare GVHD incidences after haploidentical salvage transplantation with PT-Cy to those with other GVHD prophylaxes.

Donor-specific anti-HLA antibody is a risk factor for GF. In our study, 16 patients underwent salvage SCT from the antibody-specific donor. For patients with donor-specific anti-HLA antibody, HID was numerically associated with neutrophil engraftment, although the difference was not significant. It was probably attributed to the small patient sample. However, no patients with donor-specific antibody in the CB group survived at 1 year after salvage SCT, which shows the dismal outcome after salvage SCT with donor-specific antibody. As shown in Fig. 5, no specific population had significantly benefited from each donor source in terms of OS. In the setting of salvage SCT with donor-specific antibody, it might be reasonable to choose a HID donor to ensure the engraftment, although a larger study is required.

Not only the stem cell source, but several transplant characteristics affected the transplant outcomes in our study. In terms of conditioning regimen and intensity, using alkylating agents and TBI were associated with neutrophil recovery, and the latter was also associated with better survival and lower NRM. Also, we identified myeloablative conditioning as an unfavorable factor for survival. Other studies have attributed a similar prognostic relevance to alkylating agents and TBI [22–24, 44]; thus, reduced-intensity conditioning using alkylating agents and TBI may become a first choice for salvage transplantations. Regarding GVHD prophylaxis, CNI + MTX was associated with poor engraftment, while it led to fewer episodes of acute GVHD than other prophylaxis methods. On the other hand, CNI + MMF offered better engraftment than CNI + MTX, probably due to the lower myelotoxic effect of MMF over that of MTX [46]. Although the advantage of CNI + MMF was partly counterbalanced by the higher incidence of acute GVHD, the OS and NRM were significantly better in patients who received CNI + MMF than in those who received CNI + MTX. In general, CNI + MMF seems to provide favorable GVHD prophylaxis for salvage transplantations [24], but the optimal GVHD prophylaxis should probably consider the stem cell source, the conditioning regimen, and the use of ATG or PT-Cy. Therefore, the impact of GVHD prophylaxis on salvage transplantation should be discussed under more specific settings.

We are aware of the limitations in our study. First, this was a registry-based retrospective study, and the patients' characteristics differed significantly between the groups. In fact, patients in the HID group exhibited poor DRI and were more likely to experience disease relapses after salvage transplantation, which would have affected the survival rate. In addition, patients included in this study were heterogeneous in terms of cause of GF (primary or secondary), underlying disease, conditioning regimen, and GVHD prophylaxis. Second, some data on patient characteristics were lacking, especially that on anti-HLA antibody that might have led to some biases. Third, as described above, few patients received PT-Cy, which prevented us from analyzing the effects of different GVHD prophylaxes for haploidentical transplantations. However,

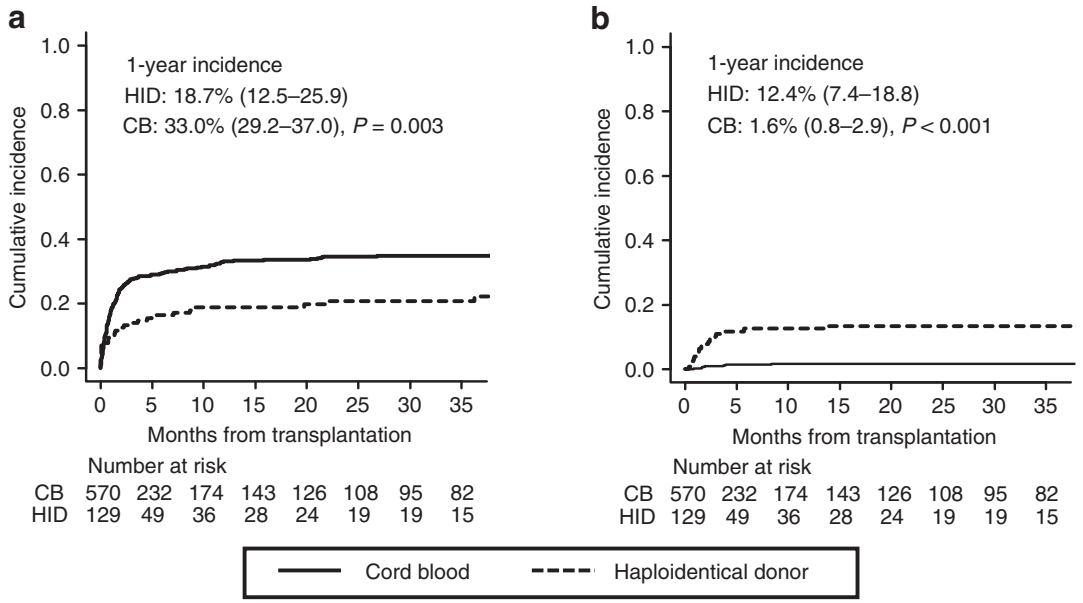

Fig. 4 Cumulative incidence of infection-related (**a**) and acute graft-versus-host disease-related deaths after salvage transplantations according to the stem cell source.

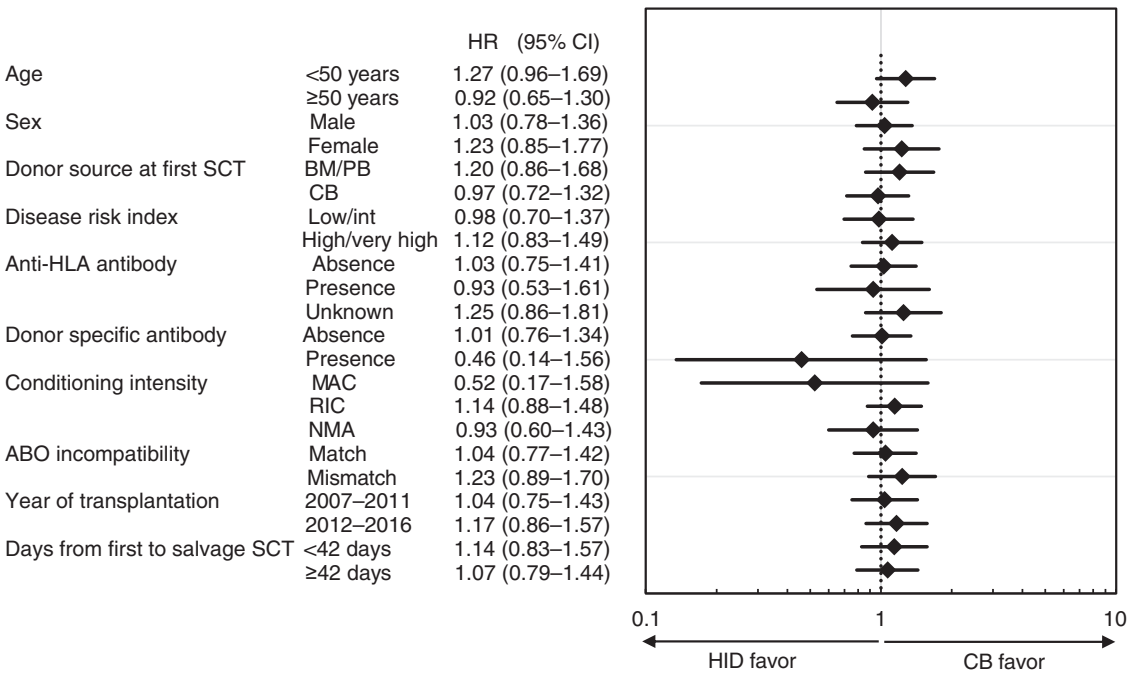

Fig. 5 Forest plot for overall survival stratified by patient characteristics.

to our knowledge, our study included the largest number of patients with GF after allo-SCT until now, and it should provide useful information about donor selection in the GF setting.

In conclusion, we demonstrated a lower NRM after haploidentical transplantations than after CB transplantations, although that did not lead to better survival. The engraftment advantage of haploidentical transplantations was partly counterbalanced by a higher incidence of acute GVHD. A study focusing on the optimal GVHD prophylaxis in the setting of haploidentical transplantations is needed to improve outcomes in these patients.

Acknowledgements We thank all the physicians and staff at the transplant centers who provided the clinical data to the Transplant Registry Unified Management Program of the Japan Society of

Hematopoietic Cell Transplantation. This work was supported in part by the Practical Research Project for Allergic Diseases and Immunology (Research Technology of Medical Transplantation) from the Japan Agency for Medical Research and Development, AMED under Grant Number 18ek0510023h0002.

Compliance with ethical standards

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

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. nccn.org [internet]. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 3. 2019. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed 11 Aug.
2. Kumar R, Bonfim C, George B. Hematopoietic cell transplantation for aplastic anemia. Curr Opin Hematol. 2017;24:509–14.
3. Canaani J, Beohou E, Labopin M, Ghavamzadeh A, Beelen D, Hamladji RM, et al. Trends in patient outcome over the past two decades following allogeneic stem cell transplantation for acute myeloid leukaemia: an ALWP/EBMT analysis. J Intern Med. 2019;285:407–18.
4. Bacigalupo A, Sormani MP, Lamparelli T, Gualandi F, Occhini D, Bregante S, et al. Reducing transplant-related mortality after allogeneic hematopoietic stem cell transplantation. Haematologica. 2004;89:1238–47.
5. Narimatsu H, Kami M, Miyakoshi S, Murashige N, Yuji K, Hamaki T, et al. Graft failure following reduced-intensity cord blood transplantation for adult patients. Br J Haematol. 2006;132:36–41.
6. Olsson R, Remberger M, Schaffer M, Berggren DM, Svahn BM, Mattsson J, et al. Graft failure in the modern era of allogeneic hematopoietic SCT. Bone Marrow Transplant. 2013;48:537–43.
7. Olsson RF, Logan BR, Chaudhury S, Zhu X, Akpek G, Bolwell BJ, et al. Primary graft failure after myeloablative allogeneic hematopoietic cell transplantation for hematologic malignancies. Leukemia. 2015;29:1754–62.
8. Cluzeau T, Lambert J, Raus N, Dessaux K, Absi L, Delbos F, et al. Risk factors and outcome of graft failure after HLA matched and mismatched unrelated donor hematopoietic stem cell transplantation: a study on behalf of SFGM-TC and SFHI. Bone Marrow Transplant. 2016;51:687–91.
9. Sun YQ, He GL, Chang YJ, Xu LP, Zhang XH, Han W, et al. The incidence, risk factors, and outcomes of primary poor graft function after unmanipulated haploidentical stem cell transplantation. Ann Hematol. 2015;94:1699–705.
10. Masouridi-Levrat S, Simonetta F, Chalandon Y. Immunological basis of bone marrow failure after allogeneic hematopoietic stem cell transplantation. Front Immunol. 2016;7:362.
11. Ozdemir ZN, Civriz Bozdağ S. Graft failure after allogeneic hematopoietic stem cell transplantation. Transfus Apher Sci. 2018;57:163–7.
12. Kawashima N, Terakura S, Nishiwaki S, Koyama D, Ozawa Y, Ito M, et al. Increase of bone marrow macrophages and CD8+ T lymphocytes predict graft failure after allogeneic bone marrow or cord blood transplantation. Bone Marrow Transplant. 2017;52:1164–70.
13. Martin PJ. Prevention of allogeneic marrow graft rejection by donor T cells that do not recognize recipient alloantigens: potential role of a veto mechanism. Blood. 1996;88:962–9.
14. Murphy WJ, Bennett M, Kumar V, Longo DL. Donor-type activated natural killer cells promote marrow engraftment and B cell development during allogeneic bone marrow transplantation. J Immunol. 1992;148:2953–60.
15. Ciurea SO, Thall PF, Milton DR, Barnes TH, Kongtim P, Carmazzi Y, et al. Complement-binding donor-specific anti-HLA antibodies and risk of primary graft failure in hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2015;21:1392–8.
16. Kongtim P, Cao K, Ciurea SO. Donor specific Anti-HLA antibody and risk of graft failure in haploidentical stem cell transplantation. Adv Hematol. 2016;2016:4025073.
17. Kong Y, Wang YT, Hu Y, Han W, Chang YJ, Zhang XH, et al. The bone marrow microenvironment is similarly impaired in allogeneic hematopoietic stem cell transplantation patients with early and late poor graft function. Bone Marrow Transplant. 2016;51:249–55.
18. Selleri C, Sato T, Anderson S, Young NS, Maciejewski JP. Interferon-gamma and tumor necrosis factor-alpha suppress both early and late stages of hematopoiesis and induce programmed cell death. J Cell Physiol. 1995;165:538–46.
19. Merli P, Caruana I, De Vito R, Strocchio L, Weber G, Del Bufalo F, et al. Role of IFNγ in immune-mediated graft failure occurring after allogeneic hematopoietic stem cell transplantation. Haematologica. 2019. https://doi.org/10.3324/haematol.2019.216101.
20. Alcazer V, Conrad A, Valour F, Bachy E, Salles G, Huynh A, et al. Early-onset severe infections in allogeneic hematopoietic stem cell transplantation recipients with graft failure. Am J Hematol. 2019;94:E109–11.
21. Schriber J, Agovi MA, Ho V, Ballen KK, Bacigalupo A, Lazarus HM, et al. Second unrelated donor hematopoietic cell transplantation for primary graft failure. Biol Blood Marrow Transplant. 2010;16:1099–106.
22. Fuji S, Nakamura F, Hatanaka K, Taniguchi S, Sato M, Mori S, et al. Peripheral blood as a preferable source of stem cells for salvage transplantation in patients with graft failure after cord blood transplantation: a retrospective analysis of the registry data of the Japanese Society for Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. 2012;18:1407–14.
23. Waki F, Masuoka K, Fukuda T, Kanda Y, Nakamae M, Yakushijin K, et al. Feasibility of reduced-intensity cord blood transplantation as salvage therapy for graft failure: results of a nationwide survey of adult patients. Biol Blood Marrow Transplant. 2011;17:841–51.
24. Onishi Y, Mori T, Kako S, Koh H, Uchida N, Kondo T, et al. Outcome of second transplantation using umbilical cord blood for graft failure after allogeneic hematopoietic stem cell transplantation for aplastic anemia. Biol Blood Marrow Transplant. 2017;23:2137–42.
25. Lund TC, Liegel J, Bejanyan N, Orchard PJ, Cao Q, Tolar J, et al. Second allogeneic hematopoietic cell transplantation for graft failure: poor outcomes for neutropenic graft failure. Am J Hematol. 2015;90:892–6.
26. Shimada K, Narimatsu H, Morishita Y, Kohno A, Saito S, Kato Y. Severe regimen-related toxicity of second transplantation for graft failure following reduced-intensity cord blood transplantation in an adult patient. Bone Marrow Transplant. 2006;37:787–8.
27. Davies SM, Weisdorf DJ, Haake RJ, Kersey JH, McGlave PB, Ramsay NK, et al. Second infusion of bone marrow for treatment of graft failure after allogeneic bone marrow transplantation. Bone Marrow Transplant. 1994;14:73–7.
28. Rashidi A, Slade M, DiPersio JF, Westervelt P, Vij R, Romee R. Post-transplant high-dose cyclophosphamide after HLA-matched vs haploidentical hematopoietic cell transplantation for AML. Bone Marrow Transplant. 2016;51:1561–4.

29. Bashey A, Zhang X, Jackson K, Brown S, Ridgeway M, Solh M, et al. Comparison of outcomes of hematopoietic cell transplants from T-replete haploidentical donors using post-transplantation cyclophosphamide with 10 of 10 HLA-A, -B, -C, -DRB1, and -DQB1 allele-matched unrelated donors and hla-identical sibling donors: a multivariable analysis including disease risk index. Biol Blood Marrow Transplant. 2016;22:125–33.
30. Wang Y, Liu QF, Xu LP, Liu KY, Zhang XH, Ma X, et al. Haploidentical vs identical-sibling transplant for AML in remission: a multicenter, prospective study. Blood. 2015;125:3956–62.
31. Singh H, Nikiforow S, Li S, Ballen KK, Spitzer TR, Soiffer R, et al. Outcomes and management strategies for graft failure after umbilical cord blood transplantation. Am J Hematol. 2014;89:1097–101.
32. Kliman D, Bilmon I, Kwan J, Blyth E, Micklethwaite K, Panicker S, et al. Rescue haploidentical peripheral blood stem cell transplantation for engraftment failure: a single-centre case series. Intern Med J. 2018;48:988–91.
33. Yoshihara S, Ikegame K, Taniguchi K, Kaida K, Kim EH, Nakata J, et al. Salvage haploidentical transplantation for graft failure using reduced-intensity conditioning. Bone Marrow Transplant. 2012;47:369–73.
34. Moscardó F, Romero S, Sanz J, Sanz MA, Montesinos P, Lorenzo I, et al. T cell-depleted related HLA-mismatched peripheral blood stem cell transplantation as salvage therapy for graft failure after single unit unrelated donor umbilical cord blood transplantation. Biol Blood Marrow Transplant. 2014;20:1060–3.
35. Tang BL, Zhu XY, Zheng CC, Liu HL, Geng LQ, Wang XB, et al. Successful early unmanipulated haploidentical transplantation with reduced-intensity conditioning for primary graft failure after cord blood transplantation in hematologic malignancy patients. Bone Marrow Transplant. 2015;50:248–52.
36. Prata PH, Resche-Rigon M, Blaise D, Socié G, Rohrlich PS, Milpied N, et al. Outcomes of salvage haploidentical transplant with post-transplant cyclophosphamide for rescuing graft failure patients: a report on behalf of the francophone society of bone marrow transplantation and cellular therapy. Biol Blood Marrow Transplant. 2019. https://doi.org/10.1016/j.bbmt.2019.05.013.
37. Atsuta Y. Introduction of Transplant Registry Unified Management Program 2 (TRUMP2): scripts for TRUMP data analyses, part I (variables other than HLA-related data). Int J Hematol. 2016;103:3–10.
38. Kanda J. Scripts for TRUMP data analyses. Part II (HLA-related data): statistical analyses specific for hematopoietic stem cell transplantation. Int J Hematol. 2016;103:11–9.
39. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant. 2009;15:1628–33.
40. Armand P, Gibson CJ, Cutler C, Ho VT, Koreth J, Alyea EP, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. Blood. 2012;120:905–13.
41. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15:825–8.
42. Sullivan KM, Agura E, Anasetti C, Appelbaum F, Badger C, Bearman S, et al. Chronic graft-versus-host disease and other late complications of bone marrow transplantation. Semin Hematol. 1991;28:250–9.
43. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452–8.
44. Kato M, Matsumoto K, Suzuki R, Yabe H, Inoue M, Kigasawa H, et al. Salvage allogeneic hematopoietic SCT for primary graft failure in children. Bone Marrow Transplant. 2013;48:1173–8.
45. Ruggeri A, Sun Y, Labopin M, Bacigalupo A, Lorentino F, Arcese W, et al. Post-transplant cyclophosphamide versus antithymocyte globulin as graft- versus-host disease prophylaxis in haploidentical transplant. Haematologica. 2017;102:401–10.
46. Terakura S, Kuwatsuka Y, Yamasaki S, Wake A, Kanda J, Inamoto Y, et al. GvHD prophylaxis after single-unit reduced intensity conditioning cord blood transplantation in adults with acute leukemia. Bone Marrow Transplant. 2017;52:1261–7.

Affiliations

Kaito Harada[1] · Shigeo Fuji[2] · Sachiko Seo[3] · Junya Kanda[4] · Toshimitsu Ueki[5] · Fumihiko Kimura[6] · Koji Kato[7] · Naoyuki Uchida[8] · Kazuhiro Ikegame[9] · Makoto Onizuka[1] · Ken-ichi Matsuoka[10] · Noriko Doki[11] · Toshiro Kawakita[12] · Yasushi Onishi[13] · Shingo Yano[14] · Takahiro Fukuda[15] · Minoko Takanashi[16] · Yoshinobu Kanda[17] · Yoshiko Atsuta[18,19] · Masao Ogata[20] · on behalf of the transplant complications working group of the Japan Society for Hematopoietic Cell Transplantation

1 Department of Hematology and Oncology, Tokai University School of Medicine, Isehara, Japan

2 Department of Hematology, Osaka International Cancer Institute, Osaka, Japan

3 Department of Hematology and Oncology, Dokkyo Medical University School of Medicine, Mibu, Japan

4 Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

5 Department of Hematology, Nagano Red Cross Hospital, Nagano, Japan

6 Division of Hematology, National Defense Medical College, Tokorozawa, Japan

7 Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan

8 Department of Hematology, Federation of National Public Service Personnel Mutual Aid Associations Toranomon Hospital, Tokyo, Japan

9 Division of Hematology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

10 Department of Hematology and Oncology, Okayama University Hospital, Okayama, Japan

11 Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan

12 Department of Hematology, National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan

[13] Department of Hematology and Rheumatology, Tohoku University Hospital, Sendai, Japan

[14] Clinical oncology and Hematology, The Jikei University School of Medicine, Tokyo, Japan

[15] Hematopoietic Stem Cell Transplantation Division, National Cancer Center Hospital, Tokyo, Japan

[16] Blood Service Headquarters, Japanese Red Cross Society, Tokyo, Japan

[17] Division of Hematology, Jichi Medical University Saitama Medical Center, Saitama, Japan

[18] Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan

[19] Department of Healthcare Administration, Nagoya University Graduate School of Medicine, Nagoya, Japan

[20] Department of Hematology, Oita University Hospital, Yufu, Japan