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ARTICLE

Comparison of HLA-matched sibling and unrelated donor transplantation in adult patients with acquired severe aplastic anemia

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Abstract

The recent improvements in the outcomes of severe aplastic anemia (SAA) patients who received allogeneic stem cell transplantation (SCT) from unrelated donors (URD) suggest the possibility of its alternative first-line treatment. To address this issue, results of adult SAA patients receiving allogeneic SCT were compared between the following three donor-type groups: 8/8–matched sibling (MSD; $n = 153$), 8/8 well-matched unrelated (WM-URD; $n = 72$), and 6–7/8 partially matched unrelated (PM-URD; $n = 33$). Proportion of patients who experienced immunosuppressive treatment failures was significantly higher in the URD groups than in the MSD group ($P < 0.01$). The incidences of graft failure and transplant-related mortality, and graft-vs.-host disease-free, failure-free survival rates of the MSD, WM-URD, and PM-URD groups were 14.6, 0, and 0% ($P < 0.01$); 6.1, 10.3, and 21.7% ($P = 0.03$); and 76.7, 55.5, and 51.5% ($P < 0.01$), respectively. The overall survival (OS) rate of the MSD group (93.9%) was higher than that of the PM-URD (78.3%; $P < 0.01$) group, but not to that of the WM-URD (86.2%; $P = 0.18$) group. Our study showed comparable OS between the MSD group and WM-URD group, which suggest that the URD-SCT can be used as a first-line treatment for adult SAA patients with WM-URD.

Introduction

Severe aplastic anemia (SAA) is a rare disease characterized by pancytopenia in the peripheral blood (PB) followed by bone marrow (BM) hypoplasia due to an immune-mediated destruction of hematopoietic precursors [1]. According to several guidelines, allogeneic stem cell transplantation (SCT) from human leukocyte antigen (HLA)-matched sibling donors (MSD-SCT) and immunosuppressive treatment (IST) have been considered as a first-line treatment for younger (≤40–50 years old) and older (>40–50 years old) adult SAA patients, respectively [2, 3]. Allogeneic SCT from HLA-matched unrelated donors (URD-SCT) has been considered as a second-line treatment option for patients who experienced IST failures, according to previous studies showing relatively poorer outcomes compared with those of MSD-SCT [4–6]. However, although patients who received IST as a first-line treatment can achieve long-term overall survival (OS) of 80–90%, a significant proportion of those patients suffer from a high treatment failure rate, including lack of response with transfusion-dependency, disease relapse, and clonal evolution [7].

Over the last two decades, high-resolution HLA typing with more optimized transplant-related techniques and better supportive care have improved the outcomes of URD-SCT for pediatric and adult SAA patients [8, 9]. Recent studies showed that the outcomes of children and adolescent patients who received URD-SCT as a first-line treatment were not significantly different to those of patients who received MSD-SCT [10, 11]. Reflecting these results, an

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updated guideline recommends that URD-SCT may be considered as a first-line treatment for pediatric patients without suitable MSD [3, 12]. However, comparative studies regarding the outcomes of adult SAA patients who received MSD-SCT and URD-SCT are rare, except the two recently published retrospective studies [13, 14]. To address this issue, major long-term outcomes of consecutive adult SAA patients who received MSD-SCT and URD-SCT at our institution were comparatively analyzed including propensity score matching analysis.

Patients and methods

Patients and treatment strategies

We analyzed the outcomes of 257 consecutive adult (≥18 years old) SAA patients who received MSD-SCT or URD-SCT between March 2002 and May 2018 at the Seoul St. Mary's Hospital, Seoul, Korea. According to conventional therapeutic schemes [2, 3], younger (≤40–50 years old) patients with appropriate MSD received MSD-SCT as a first-line treatment. Patients who were not considered as candidates of MSD-SCT received IST, consisting of horse or rabbit anti-thymocyte globulin (ATG) plus cyclosporin (CsA), as a first-line treatment. However, patients who immediately required treatment, per physicians' discretion, received URD-SCT as a first-line treatment [7]. Patients experiencing IST failures received URD-SCT as a second-line treatment. In searching for the appropriate MSD (8 of 8 allele-matched) and/or URD (≥6 of 8 allele-matched) by screening for HLA–A, HLA–B, HLA–C, and HLA–DRB1 alleles, the high-resolution (DNA sequencing) molecular typing method was performed. This study was approved by the institutional review board of the Seoul St. Mary's Hospital.

Transplant-related procedures

Patients received a conditioning of fludarabine (Flu, 30 mg/m^2 intravenously [IV] for 6 days) and cyclophosphamide (Cy, 50 mg/kg IV for 2 days) plus rabbit ATG (Thymoglobulin®, 2.5 mg/kg IV for 4 days) for MSD-SCT or fractionated total body irradiation (TBI, 400–800 cGy) plus Cy (50–60 mg/kg IV for 2 days) for URD-SCT. If potential candidates for MSD-SCT experienced severe infectious complications with/without significant comorbidities, they received a conditioning of total nodal irradiation (750 cGy for 1 day) plus rabbit ATG (1.25 mg IV for 3 days or 2.5 mg IV for 2 days). Since August 2009, low-dose rabbit ATG (1.25 mg/kg IV for 2 days) has been administered to patients who received URD-SCT from HLA-mismatched donor and/or PB stem cells [15]. Thereafter, the protocol was amended so that all patients, who have received URD-SCT since December 2016, received rabbit ATG (2.5 mg/kg IV for 2 days). Although we had requested BM harvest to all potential donors, the choice regarding the source of stem cells was determined according to their preferences. Other detailed transplant-related procedures, including graft-vs.-host disease (GVHD) prophylaxis and supportive care strategies, were described in our previous reports [15, 16].

Definitions

The diagnosis of the disease and categorization of the severity were performed according to the criteria proposed by Camitta et al. [17]. Patients' pretransplant comorbidities were assessed according to the Hematopoietic Cell Transplantation-Specific Comorbidity index [18]. The neutrophil and platelet engraftments were defined as an absolute neutrophil (ANC) count $\geq 0.5 \times 10^9$/L for at least three consecutive days and a platelet count $\geq 20 \times 10^9$/L for at least seven consecutive days without transfusion support. Primary and secondary graft failure (GF) were characterized by a failure of neutrophil engraftment at days 28 with either irreversible ANC $< 0.5 \times 10^9$/L or platelet count $< 20 \times 10^9$/L, with and without previous donor engraftment, respectively. Posttransplant complications were evaluated according to the previous published criteria [19–24]. We defined a composite end-point of GVHD-free, failure-free survival (GFFS) based on the following: being alive without experiencing primary or secondary GF, grade III–IV acute GVHD, and chronic GVHD requiring systemic therapy [16, 25]. In our current study, allogeneic SCT as a first-line treatment indicates transplantation without previously receiving IST including ATG plus CsA and CsA monotherapy.

Statistical analysis

This study aimed to compare the major outcomes, including GF incidence, transplant-related mortality (TRM) incidence, GFFS rate, and OS rate, of adult SAA patients who received allogeneic SCT from the following donor-type groups: MSD (the MSD group), well-matched URD (8/8 allele-matched; the WM-URD group), and partially matched URD (6–7/8 allele-matched; the PM-URD group).

Continuous and categorical variables were described by median with ranges and count with relative frequency, respectively. Comparisons between the baseline and transplant-related factors according to donor-type groups were suitably performed by using the independent two-sample *t*-test, the χ^2 test and the Fisher's exact test. All time-dependent parameters were measured from the first day of

Table 1 Patients' baseline and transplant-related characteristics according to donor group.

Characteristics	MSD	WM-URD	PM-URD	*P*
Number of patients	153 (59.3%)	72 (27.9%)	33 (12.79%)	NA
Age				
≤40 yrs/>40 yrs[a,b]	84 (54.9%)/69 (45.1%)	54 (75.0%)/18 (25.0%)	29 (87.9%)/4 (12.1%)	<0.01
Sex				
Male/female[a]	87 (56.9%)/66 (43.1%)	54 (75.0%)/18 (25.0%)	24 (72.7%)/9 (27.3%)	0.02
Disease severity				
SAA/VSAA	103 (67.3%)/50 (32.7%)	50 (69.4%)/22 (30.6%)	26 (78.8%)/7 (21.2%)	0.43
Presence of PNH clone				
Yes/No	18 (11.8%)/135 (88.2%)	4 (5.6%)/68 (94.4%)	4 (12.1%)/29 (87.9%)	0.32
Serum ferritin level[c]				
≤1000 ng/mL/>1000 ng/mL	70 (47.9%)/76 (52.1%)	27 (40.3%)/40 (59.7%)	12 (37.5%)/20 (62.5%)	0.40
Preceding IST history				
Yes/No[a,b]	46 (30.1%)/107 (69.9%)	57 (79.2%)/15 (20.8%)	30 (90.9%)/3 (9.1%)	<0.01
Heavily transfusion history (>100 units)				
Yes/No[a]	118 (77.1%)/35 (22.9%)	66 (91.7%)/6 (8.3%)	31 (93.9%)/2 (6.1%)	0.01
Interval from diagnosis to transplant				
≤12 month/>12 month[a,b]	60 (39.2%)/93 (60.8%)	10 (13.9%)/62 (86.1%)	5 (15.2%)/28 (84.8%)	<0.01
HCT-CI				
<3/≥3	93 (60.8%)/60 (39.2%)	44 (61.1%)/28 (38.9%)	18 (54.5%)/15 (45.5%)	0.79
HLA mismatch				
1 allele/2 allele	NA	NA	25 (75.8%)/8 (24.2%)	NA
ABO blood type mismatch				
Yes/No	59 (38.6%)/94 (61.4%)	42 (58.3%)/30 (41.7%)	26 (78.8%)/7 (21.2%)	<0.01
Donor-recipient sex mismatch				
Female to male/others	28 (18.3%)/125 (81.7%)	11 (15.3%)/61 (84.7%)	3 (9.1%)/30 (90.9%)	0.41
Stem cell source				
BM/PBSC[a]	101 (66.0%)/52 (34.0%)	34 (47.2%)/38 (52.8%)	16 (48.5%)/17 (51.5%)	0.01

MSD matched sibling donor, *WM-URD* well-matched unrelated donor, *PM-URD* partially matched unrelated donor, *NA* not available, *SAA* severe aplastic anemia, *VSAA* very severe aplastic anemia, *PNH* paroxysmal nocturnal hemoglobinuria, *IST* immunosuppressive treatment, *HCT-CI* hematopoietic cell transplantation-specific comorbidity index, *HLA* human leukocyte antigen, *BM* bone marrow, *PBSC* peripheral blood stem cells.

[a]Indicates $P < 0.05$ between the MSD and the WM-URD groups.

[b]Indicates $P < 0.05$ between the MSD and the PM-URD groups.

[c]Pretransplant serum ferritin level were available in 245 (95.0%) patients.

stem cell infusion. GFFS and OS rates were calculated using Kaplan–Meier estimates and compared using the log-rank test. The neutrophil and platelet engraftment, primary and secondary GF, acute GVHD and chronic GVHD, and TRM were described as the cumulative incidence estimate and compared using the Gray's test. The prognostic significance of covariates was determined suitably using the Cox proportional hazards model for GFFS and OS and the proportional hazards model for the sub-distribution of a competing risk for acute and chronic GVHD, primary and secondary GF, and TRM.

Furthermore, we compared the major outcomes between the MSD and the URD (WM-URD and PM-URD) groups for the propensity score matching sub-cohort of patients receiving allogeneic SCT as a first-line treatment. It was established by propensity score calculated by using a logistic regression model [26], fitted for a donor-type group according to the following variables: age, interval from diagnosis to transplant, and stem cell source, which significantly affected transplant-related outcomes in a previous study [27]. Subsequently, one-to-three matched groups were created by nearest neighbor matching without replacement. Factors were considered significant if they had an associated $P < 0.05$ as determined by the likelihood ratio test, using two-tailed significance testing. Data were analyzed in December 2018 using R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Table 2 The cumulative incidences of neutrophil engraftment, platelet engraftment, acute GVHD, and chronic GVHD according to donor groups.

Engraftment and GVHD	Cumulative incidence (95% CI)			*P*
	MSD	WM-URD	PM-URD	
Neutrophil engraftment at day 28	99.3% (95.4–99.9)	100%	97.0% (59.8–99.8)	0.79
Median (range)	12 (5–21)	11 (8–26)	11 (10–21)	
Platelet engraftment at day 28	88.0% (81.5–92.3)	81.9% (70.7–89.2)	75.8% (56.4–87.4)	0.48
Median days (range)	16 (7–99)	17 (7–433)	18 (7–49)	
Acute GVHD at day 100				
Grade II–IV[a,b,c]	8.5% (4.8–13.6)	36.1% (25.1–47.2)	57.6% (38.6–72.6)	<0.01
Grade III–IV[a,b]	7% (0.1–3.3)	9.8% (4.3–18.1)	18.2% (7.2–33.1)	<0.01
Chronic GVHD at 6 years				
Mild-to-severe[a,b]	8.6% (4.8–13.8)	43.4% (31.6–54.6)	36.6% (18.0–77.5)	<0.01
Moderate-to-severe[a,b]	2.6% (0.9–6.2)	30.6% (20.3–41.4)	27.3% (13.4–43.2)	<0.01
Severe[a,b]	0.7% (0.1–3.6)	12.5% (6.1–21.3)	12.1% (3.7–25.8)	<0.01

GVHD graft-versus-host disease, *MSD* matched sibling donor, *WM-URD* well-matched unrelated donor, *PM-URD* partially matched unrelated donor, *CI* confidence interval.

[a]Indicates $P < 0.01$ between the MSD and the WM-URD groups.

[b]Indicates $P < 0.01$ between the MSD and the PM-URD groups.

[c]Indicates $P < 0.01$ between the WM-URD and the PM-URD groups.

Results

Baseline and transplant-related characteristics

The median age of our patients was 34 (range, 15–64) years at transplantation, with 167 (64.7%) aged ≤40 years. At the transplantation, 133 (51.6%) patients experienced failures for one or more courses of IST, with the proportions significantly higher in the WM-URD ($P < 0.01$) and the PM-URD ($P < 0.01$) groups compared with that of the MSD group, which contributed to relatively higher proportions of patients who had longer (>12 months) interval from diagnosis to transplantation ($P < 0.01$ and $P = 0.02$, respectively) and heavily (>100 units) transfusion history ($P = 0.01$ and $P = 0.05$, respectively) of the WM-URD and the PM-URD groups compared with that of the MSD group. In addition, the MSD group had relatively higher proportions of patients who were older (>40 years) ($P < 0.01$ in both), using BM stem cells ($P = 0.01$ and $P = 0.09$, respectively), compared with those of the WM-URD and PM-URD groups. More detailed baseline and transplant-related characteristics according to donor-type groups are described in Table 1. Infused CD34+ and CD3+ cell doses of patients who received BM and PB stem cells were 3.01×10^6/kg (range, 0.25–14.37) and 4.92×10^6/kg (range, 1.81–17.03), and 38.79×10^6/kg (range, 1.70–463.68) and 329.64×10^6/kg (range, 1.34–1234.70), respectively.

Engraftment

Except two (0.8%) patients who died of infectious complication at day 7 (in the PM-URD group) and cerebrovascular event at day 10 (in the MSD group), all patients achieved neutrophil engraftment at a median 12 (range, 5–26) days. Excluding three (1.2%) patients who did not experience platelet count nadir (in the MSD group), 230 (95.0%) patients achieved platelet engraftment at a median 17 (range, 7–433) days. More detailed incidences of neutrophil and platelet engraftments are described in Table 2.

GVHD and other posttransplant complications

At a median 29 (range, 9–162) days, 68 (26.4%) patients experienced grades II–IV acute GVHD, including grade II in 53 (20.5%), grade III in 10 (3.9%), and grade IV in five (1.9%) patients. Grades II–IV acute GVHD incidences of the MSD, the WM-URD, and the PM-URD groups were 8.5% (95% CI, 4.8–13.6), 36.1% (95% CI, 25.1–47.2), and 57.6% (95% CI, 38.6–72.6) at day 100, respectively ($P < 0.01$). At a median 7.3 (range, 0.9–131.9) months, 57 (22.1%) patients developed mild-to-severe chronic GVHD, including mild in 23 (8.9%), moderate in 21 (8.1%), severe in 15 (5.8%) patients. Mild-to-severe chronic GVHD incidences of the MSD, the WM-URD, and the PM-URD groups were 8.6% (95% CI, 4.8–13.8), 43.4% (95% CI, 31.6–54.6), and 36.6% (95% CI, 20.3–53.0) at 6 years, respectively ($P < 0.01$). More detailed incidences of acute and chronic GVHD according to donor-type groups are presented in Table 2.

At a median 2.1 (range, 0.2–114.4) months, 86 (33.3%) patients experienced grade ≥3 infectious complications. Grade ≥3 infectious complications incidences of the MSD, the WM-URD, and the PM-URD groups were 26.1% (95%

Table 3 The cumulative incidences of posttransplant complications according to donor-type groups.

Complications	MSD	WM-URD	PM-URD	*P*
	Cumulative incidence at 6 yrs (95% CI)			
Infectious complication (grade ≥3)[a]	26.1% (19.3–33.5)	35.2% (24.2–46.4)	57.6% (38.6–72.6)	<0.01
CMV reactivation requiring preemptive therapy	43.8% (35.8–51.5)	36.1% (25.1–47.2)	51.5% (33.1–67.2)	0.21
CMV disease	4.6% (2.0–8.7)	8.3% (3.4–16.2)	6.2% (1.1–18.2)	0.53
Herpes zoster	30.8% (23.4–38.4)	28.4% (18.3–39.4)	45.5% (27.7–61.6)	0.12
Hemorrhagic cystitis (grade ≥2)	7.3% (3.8–12.1)	6.9% (2.5–14.4)	15.2% (5.4–29.5)	0.31
Sinusoidal obstruction syndrome	0.7% (0.1–3.3)	4.2% (1.1–10.7)	0%	0.11

CI confidence interval, *MSD* matched sibling donor, *WM-URD* well-matched unrelated donor, *PM-URD* partially matched unrelated donor, *CMV* cytomegalovirus.

[a]Indicates $P = 0.04$ between the MSD and the WM-URD groups and $P < 0.01$ between the MSD and the PM-URD groups.

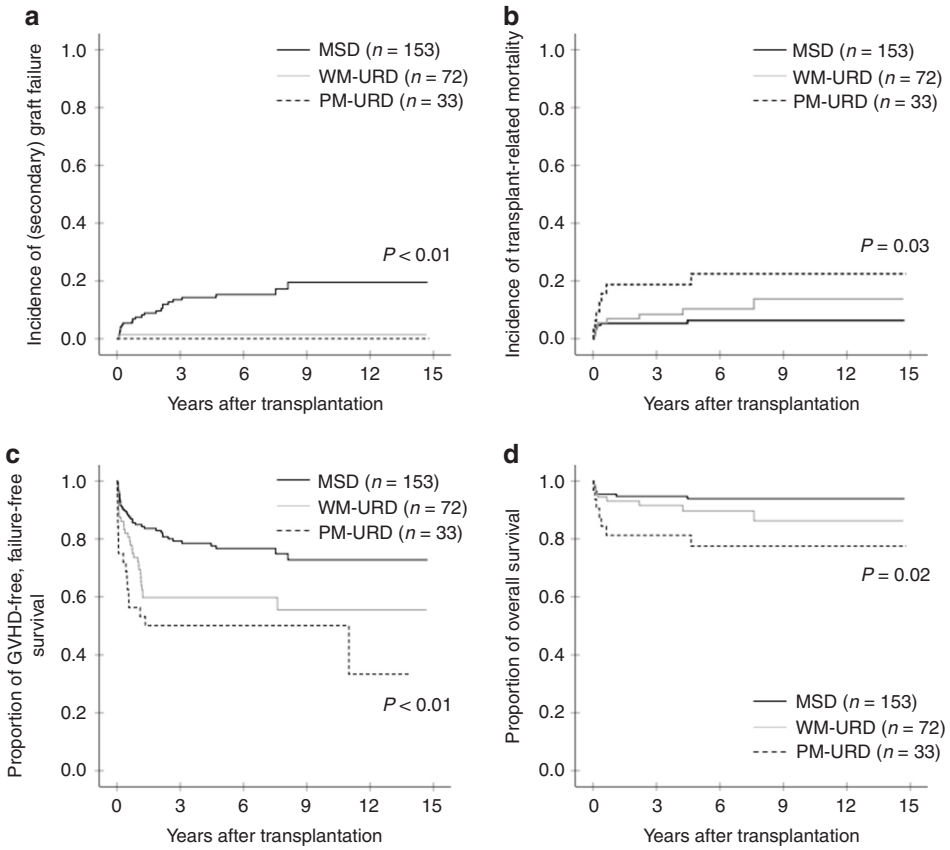

Fig. 1 Transplant outcomes according to donor-type groups. a graft failure, **b** transplant-related mortality, **c** GFFS rate, and **d** OS rate.

CI, 19.3–33.5), 35.2% (95% CI, 24.2–46.4), and 57.6% (95% CI, 38.6–72.6) at 6 years, respectively ($P < 0.01$). More detailed posttransplant complications incidences according to donor-type groups are described in Table 3.

Graft failure and transplant-related mortality

Although primary GF was not observed in any patient, 23 (8.9%) patients (only in the MSD group) experienced secondary GF at a median 14.1 (range, 0.9–97.2) months. Secondary GF incidences of the MSD, the WM-URD, and the PM-URD groups were 14.6% (95% CI, 9.3–20.9), 0, and 0% at 6 years, respectively ($P < 0.01$). The secondary GF incidence of the MSD group was significantly higher compared with that of the WM-URD ($P < 0.01$) and the PM-URD ($P < 0.01$) groups (Fig. 1a).

At a median 2.1 (range, 0.2–9) months, 23 (8.9%) patients died without experiencing GF due to the following causes: acute GVHD in 8 (3.1%), infectious complications in 8 (3.1%), secondary malignancies in 4 (1.6%), chronic GVHD in 2 (0.8%), and cerebrovascular hemorrhage in 1 (0.4%). TRM incidences of the MSD, the WM-URD, and

Table 4 Univariate and multivariate analysis of factors affecting GFFS and OS.

Factors	GFFS				OS			
	Univariate Rate at 6 yrs (%)	*P*	Multivariate HR (95% CI)	*P*	Univariate Rate at 6 yrs (%)	*P*	Multivariate HR (95% CI)	*P*
Donor-type group		<0.01[a]		<0.01[a]		0.02[a]		0.04[a]
WM-URD vs. MSD	55.5% vs. 76.7%	<0.01	1.78 (1.02–3.13)	0.04	86.2% vs. 93.9%	0.18	1.69 (0.65–4.40)	0.28
PM-URD vs. MSD	51.5% vs. 76.7%	<0.01	2.44 (1.25–4.76)	<0.01	78.3% vs. 93.9%	<0.01	3.27 (1.21–8.85)	0.02
Age (≤40 yrs vs. >40 yrs)	76.8% vs. 64.3%	0.06	0.79 (0.48–1.32)	0.37	91.8% vs. 88.7%	0.46		
Sex (Male vs. female)	70.1% vs. 66.1%	0.60			90.5% vs. 91.1%	0.86		
Disease severity (SAA vs. VSAA)	70.8% vs. 63.9%	0.32			91.8% vs. 88.1%	0.40		
Presence of PNH clone (Yes vs. No)	68.2% vs. 68.8%	0.90			88.5% vs. 91.0%	0.56		
Serum ferritin level[b] (≤1000 ng/mL/>1000 ng/mL)	72.2% vs. 65.9%	0.35			92.6% vs. 88.1%	0.43		
Preceding IST history (Yes vs. No)	61.3% vs. 76.7%	0.01	1.16 (0.68–1.98)	0.58	88.1% vs. 93.6%	0.15		
Heavily transfusion history (>100 units) (Yes vs. No)	66.2% vs. 81.1%	0.13			89.3% vs. 97.7%	0.09	3.76 (0.50–28.34)	0.02
Interval from diagnosis to transplant (≤12 month/>12 month)	73.1% vs. 66.9%	0.28			93.3% vs. 89.6%	0.35		
HCT-CI (<3 /≥3)	69.5% vs. 67.6%	0.71			92.0% vs. 88.9%	0.57		
ABO blood type mismatch (Yes vs. No)	68.0% vs. 69.5%	0.80			90.2% vs. 91.2%	0.87		
Donor-recipient sex mismatch (Female to male/Others)	65.3% vs. 69.1%	0.90			89.1% vs. 90.9%	0.89		
Stem cell source (BM/PBSC)	71.7% vs. 64.5%	0.20			90.6% vs. 90.2%	0.78		

GFFS graft-versus-host disease-free, failure-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *WM-URD* well-matched unrelated donor, *MSD* matched sibling donor, *PM-URD* partially matched unrelated donor, *SAA* severe aplastic anemia, *VSAA* very severe aplastic anemia, *PNH* paroxysmal nocturnal hemoglobinuria, *IST* immunosuppressive treatment, *HCT-CI* hematopoietic cell transplantation-specific comorbidity index, *BM* bone marrow, *PBSC* peripheral blood stem cell.

[a]Indicate the result of Wald test for overall *p* value.

[b]Pretransplant serum ferritin level were available in 245 (95.0%) patients.

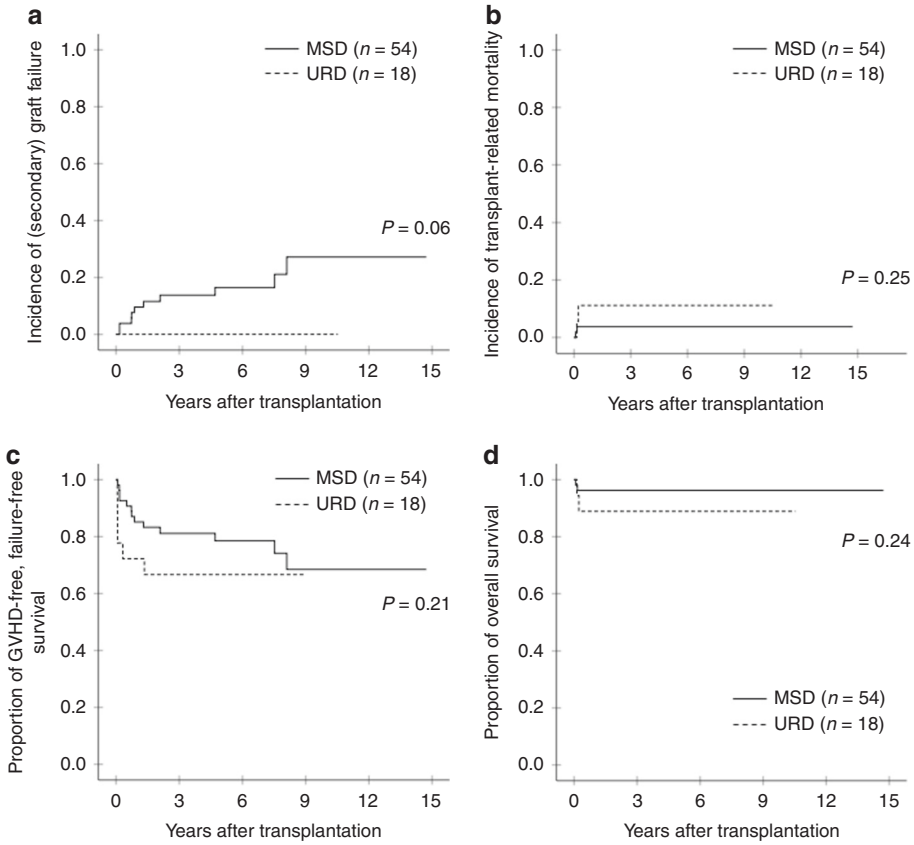

Fig. 2 Transplant outcomes according to donor-type groups for the propensity-score matching cohort of patients receiving SCT as a first-line treatment. a graft failure, **b** transplant-related mortality, **c** GFFS rate, and **d** OS rate.

the PM-URD groups were 6.1% (95% CI, 3.0–10.8), 10.3% (95% CI, 4.4–19.0), and 21.7% (95% CI, 9.4–37.4) at 6 years, respectively ($P = 0.03$). The TRM incidence of the PM-URD group was significantly higher than that of the MSD group ($P = 0.01$). There were no significant differences of TRM incidences between the MSD and the WM-URD groups ($P = 0.21$), and the WM-URD and the PM-URD groups ($P = 0.19$) (Fig. 1b). Other baseline and transplant-related characteristics did not affect the TRM incidence ($P > 0.20$).

GFFS and OS

With a median survivor's follow-up duration of 79.1 (range, 6.1–177.6) months, 175 (67.8%) patients were alive without experiencing GF, grades III–IV acute GVHD, and chronic GVHD requiring systemic therapy. The GFFS rates of the MSD, the WM-URD, and the PM-URD groups were 76.7% (95% CI, 63.2–80.2), 55.5% (95% CI, 41.3–67.5), and 51.5% (95% CI, 33.5–66.9) at 6 years, respectively ($P < 0.01$). The GFFS rate of the MSD group was significantly higher compared with that of the WM-URD ($P < 0.01$) and the PM-URD ($P < 0.01$) groups. There was no significant difference of the GFFS rates between the WM-URD and the PM-URD groups ($P = 0.22$) (Fig. 1c). Patients' age (≤40 years vs. >40 years; 76.8 vs. 64.3% at 6 years, $P = 0.06$) and preceding IST history (yes vs. no; 61.3 vs. 76.7% at 6 years, $P = 0.01$) were also potential candidates affecting GFFS rate. However, donor-type group (WM-URD vs. MSD; hazard ratio [HR] 1.78, 95% CI, 1.02–3.13, $P = 0.04$ and PM-URD vs. MSD; HR 2.44, 95% CI, 1.25–4.76, $P < 0.01$) was the only significant factor affecting GFFS rate in multivariate analysis ($P < 0.01$) (Table 4).

At the time of analysis, 234 (90.7%) patients were alive. The OS rates of the MSD, the WM-URD, and PM-URD groups were 93.9% (95% CI, 88.6–96.8), 86.2% (95% CI, 72.9–93.3), and 78.3% (95% CI, 59.6–89.0) at 6 years, respectively ($P = 0.02$). The OS rate of the MSD group was significantly higher than that of the PM-URD ($P < 0.01$), but not to that of the WM-URD ($P = 0.18$) group (Fig. 1d). There was no significant difference in OS rates between the WM-URD and the PM-URD groups ($P = 0.18$). Donor-type group (WM-URD vs. MSD, HR 1.69, 95% CI, 0.65–4.40; $P = 0.28$ and PM-URD vs. MSD; HR 3.27, 95% CI, 1.21–8.85; $P = 0.02$) and heavily transfusion history (HR 3.76, 95% CI, 0.50–28.34; $P = 0.02$) were independent significant factors affecting OS rate in multivariate analysis (Table 4).

Subgroup analysis for the propensity-score matching cohort of patients receiving SCT as a first-line treatment

We compared the major posttransplant outcomes between the MSD and the URD groups for the propensity score matching cohort of patients who received allogeneic SCT as a first-line treatment (54 and 18 patients of the MSD and URD groups, respectively). The patients' baseline and transplant-related characteristics were not significantly different between the MSD and the URD groups, except significantly higher proportion of patients who had male sex ($P = 0.03$), longer interval from diagnosis to transplant ($P < 0.01$), and used PB stem cells ($P < 0.01$) in the URD group (Table S1). Grades II–IV acute (5.6 vs. 50.0% at day 100; $P < 0.01$) and grades III–IV acute GVHD (0 vs. 16.7% at day 100; $P < 0.01$), and mild-to-severe chronic (12.0 vs. 38.7% at 6 years; $P < 0.01$), moderate-to-severe chronic (19 vs. 22.2% at 6 years; $P < 0.01$) and severe chronic (0 vs. 16.7% at 6 years; $P < 0.01$) GVHD incidences were significantly higher in the URD group compared with those of the MSD group. There were no significant differences of GF incidence (15.9 vs. 0%; $P = 0.06$), TRM incidence (3.7 vs. 11.8% at 6 years; $P = 0.25$), GFFS rate (78.5 vs. 66.7% at 6 years; $P = 0.21$), and OS rate (96.3 vs. 88.9% at 6 years; $P = 0.24$) between the MDS and the URD groups (Fig. 2).

Discussion

In our current study, which compared the long-term outcomes of adult SAA patients who received allogeneic SCT according to donor-type groups, there was no significant difference of the OS rates between the MSD and the WM-URD groups. However, the OS rate of the PM-URD group was significantly lower compared with that of the MSD group. These results suggest the possibility of URD-SCT, especially using WM-URD, as a first-line treatment option for adult SAA patients, at least in terms of OS rate.

The most evident limitation of this study is the unbalanced distribution of the clinical and transplant-related characteristics of the donor-type groups. According to our therapeutic scheme, the proportion of older (>40 years) patients was significantly higher in the MSD group compared with that of URD groups. Conversely, the proportions of those who had longer interval from diagnosis to transplant (>12 months) and heavily transfusion history (>100 units) were significantly higher in the URD groups since most patients in the URD groups experienced previous IST failures compared with that of the MSD group. In addition, PB stem cells were more frequently used in the URD groups due to donors' preferences than in the MSD group. The unequally distributed characteristics might suggest that most of the results from our current study can be depreciated. However, most of unequally distributed factors that are associated with poor posttransplant outcomes [27–30], except a significantly higher proportion of patients having older age (>40 years), were more frequently observed in the URD group than in the MSD groups. Consequently, an unbalanced distribution of the clinical and transplant-related characteristics of the donor-type groups cannot significantly affect our major conclusion of at least not inferior OS rate of the WM-URD group compared with that of the MSD groups.

Yagasaki et al. analyzed the outcomes of children and adolescent SAA patients who received allogeneic SCT, which showed no significant difference of OS rates between the MSD and the URD groups (100 vs. 93.8% at 10 years; $P = 0.25$) [10]. Dufour et al. also showed comparable OS rates of pediatric SAA patients who received allogeneic SCT as a first-line treatment between the MSD and the URD groups (91 vs. 96% at 2 years; $P = 0.30$) [11]. These above-mentioned studies suggest an extending role of URD-SCT as a considerable first-line treatment option for children and adolescent patients, which have changed the treatment scheme for these patients [3]. However, comparative studies that analyzed the outcomes of adult SAA patients who received MSD-SCT and URD-SCT are insufficient. Only two recently published retrospective studies by Vaht et al. and Zhang et al. compared the OS rates of patients who received MSD-SCT and URD-SCT, which provided results similar to that of the current study (90.6 vs 83.3% at 5 years; $P = 0.41$ and 89.3 vs. 82.0% at 5 years; $P = 0.40$, respectively) [13, 14]. However, because these studies analyzed a small number of patients, they had substantial difficulty in drawing confirmatory results. Our study showed not significantly different OS rates between the MSD and WM-URD groups in a sufficient number of adult SAA patients, along with the clinically acceptable outcomes of the PM-URD group. This supports a considerable role of URD-SCT as a first-line treatment option in adult SAA patients. Furthermore, our additional propensity score matching sub-cohort analysis showing a comparable OS rate of patients who received MSD-SCT and URD-SCT as a first-line treatment makes our results more evident, although a very limited number of patients of URD cohort result in a difficulty in drawing definite conclusion.

The incidences of acute and chronic GVHD of the URD groups were significantly higher than those of the MSD group. In addition, we showed that the GFFS was significantly higher in the MSD group than that of the URD groups. Considering relatively high morbidity and mortality of patients experiencing acute and chronic GVHD [31, 32], these results should be a major consideration when

performing URD-SCT as a first-line treatment for adult SAA patients. Therefore, all possible efforts to ameliorate the incidences of acute and chronic GVHD for patients to achieve long-term survival with an adequate quality of life are essential. Our recently published report for adult SAA patients who received URD-SCT using PM-URD or PB stem cells may provide with a possible solution for this issue [15]. It showed significantly lower acute grade II–IV and chronic GVHD incidences (31.2 vs. 61.5% at day 100; $P < 0.01$ and 21.9 vs. 65.4% at 3 years; $P < 0.01$, respectively) in patients who received low-dose ATG (2.5 mg/kg) compared with patients who did not receive low-dose ATG. Furthermore, emerging prophylactic approaches of various action mechanisms, including T-cell depletion, functional inhibition of donor T-cell activation, inhibition of signals mediated by extracellular mediators, and B-cell depletion [33], with an improved understanding of GVHD pathophysiology will lead us to overcome this challenging area of allogeneic SCT.

In conclusion, our current study showed that OS rates between the MSD and the WM-URD groups of adult SAA patients who received allogeneic SCT, along with the clinically acceptable outcomes of PM-URD group, were not significantly different, which suggests the possibility for the role of URD-SCT as a first-line treatment option. The strength of our study is as follows: this is a large comparative analysis including only adult SAA patients who received allogeneic SCT between the MSD and the URD groups. However, this is a retrospective study with an unbalanced distribution of clinical and transplant-related characteristics of the donor-type groups, although it is an unavoidable feature of a real-world description. In addition, there was only a small number of patients who received allogeneic SCT as a first-line treatment, especially in the URD group, which should be an additional limitation. Until more clinical evidences by future well-designed prospective studies are available, URD-SCT as the first-line treatment for SAA should be recommended in younger patients (<40 years old).

Compliance with ethical standards

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

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References

1. Shin SH, Lee SE, Lee JW. Recent advances in treatment of aplastic anemia. Korean J Intern Med. 2014;29:713–26.
2. Scheinberg P, Young NS. How I treat acquired aplastic anemia. Blood. 2012;120:1185–96.
3. Killick SB, Bown N, Cavenagh J, Dokal I, Foukaneli T, Hill A, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol. 2016;172:187–207.
4. Deeg HJ, O'Donnell M, Tolar J, Agarwal R, Harris RE, Feig SA, et al. Optimization of conditioning for marrow transplantation from unrelated donors for patients with aplastic anemia after failure of immunosuppressive therapy. Blood. 2006;108:1485–91.
5. Kojima S, Matsuyama T, Kato S, Kigasawa H, Kobayashi R, Kikuta A, et al. Outcome of 154 patients with severe aplastic anemia who received transplants from unrelated donors: the Japan Marrow Donor Program. Blood. 2002;100:799–803.
6. Passweg JR, Perez WS, Eapen M, Camitta BM, Gluckman E, Hinterberger W, et al. Bone marrow transplants from mismatched related and unrelated donors for severe aplastic anemia. Bone Marrow Transpl. 2006;37:641–9.
7. Shin SH, Lee JW. The optimal immunosuppressive therapy for aplastic anemia. Int J Hematol. 2013;97:564–72.
8. Maury S, Balere-Appert ML, Chir Z, Boiron JM, Galambrun C, Yakouben K, et al. Unrelated stem cell transplantation for severe acquired aplastic anemia: improved outcome in the era of high-resolution HLA matching between donor and recipient. Haematologica. 2007;92:589–96.
9. Viollier R, Socie G, Tichelli A, Bacigalupo A, Korthof ET, Marsh J, et al. Recent improvement in outcome of unrelated donor transplantation for aplastic anemia. Bone Marrow Transpl. 2008;41:45–50.
10. Yagasaki H, Takahashi Y, Hama A, Kudo K, Nishio N, Muramatsu H, et al. Comparison of matched-sibling donor BMT and unrelated donor BMT in children and adolescent with acquired severe aplastic anemia. Bone Marrow Transpl. 2010;45:1508–13.
11. Dufour C, Veys P, Carraro E, Bhatnagar N, Pillon M, Wynn R, et al. Similar outcome of upfront-unrelated and matched sibling stem cell transplantation in idiopathic paediatric aplastic anaemia. A study on behalf of the UK Paediatric BMT Working Party, Paediatric Diseases Working Party and Severe Aplastic Anaemia Working Party of EBMT. Br J Haematol. 2015;171:585–94.
12. Marsh JCW, Risitano AM, Mufti GJ. The case for upfront HLA-matched unrelated donor hematopoietic stem cell transplantation as a curative option for adult acquired severe aplastic anemia. Biol Blood Marrow Transpl. 2019;25:e277–84.
13. Zhang Y, Wu L, Mo W, Zhou M, Li Y, Chen X, et al. Comparable outcomes of first-line hematopoietic stem cell transplantation from unrelated and matched sibling donors in adult patients with aplastic anemia: a retrospective single-center study. Biol Blood Marrow Transpl. 2019;25:1567–75.
14. Vaht K, Goransson M, Carlson K, Isaksson C, Lenhoff S, Sandstedt A, et al. High graft-versus-host disease-free, relapse/rejection-free survival and similar outcome of related and unrelated allogeneic stem cell transplantation for aplastic anemia: a nationwide swedish cohort study. Biol Blood Marrow Transpl. 2019;25:1970–4.
15. Park SS, Kwak DH, Jeon YW, Yoon JH, Lee SE, Cho BS, et al. Beneficial role of low-dose antithymocyte globulin in unrelated stem cell transplantation for adult patients with acquired severe aplastic anemia: reduction of graft-versus-host disease and improvement of graft-versus-host disease-free, failure-free survival rate. Biol Blood Marrow Transpl. 2017;23:1498–508.
16. Shin SH, Jeon YW, Yoon JH, Yahng SA, Lee SE, Cho BS, et al. Comparable outcomes between younger (40 years) and older (>40 years) adult patients with severe aplastic anemia after HLA-matched sibling stem cell transplantation using fludarabine-based conditioning. Bone Marrow Transpl. 2016;51:1456–63.
17. Camitta BM, Storb R, Thomas ED. Aplastic anemia (first of two parts): pathogenesis, diagnosis, treatment, and prognosis. N. Engl J Med. 1982;306:645–52.

18. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106:2912–9.
19. Champlin RE, Perez WS, Passweg JR, Klein JP, Camitta BM, Gluckman E, et al. Bone marrow transplantation for severe aplastic anemia: a randomized controlled study of conditioning regimens. Blood. 2007;109:4582–5.
20. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 consensus conference on acute GVHD grading. Bone Marrow Transpl. 1995;15:825–8.
21. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transpl. 2005;11:945–56.
22. McDonald GB, Hinds MS, Fisher LD, Schoch HG, Wolford JL, Banaji M, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. Ann Intern Med. 1993;118:255–67.
23. Silva Lde P, Patah PA, Saliba RM, Szewczyk NA, Gilman L, Neumann J, et al. Hemorrhagic cystitis after allogeneic hematopoietic stem cell transplants is the complex result of BK virus infection, preparative regimen intensity and donor type. Haematologica. 2010;95:1183–90.
24. The National Cancer Institute Common Terminology Criteria for adverse events version 3.0. Available at: Common Terminology Criteria for Adverse Events v3.0. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed 17 January 2020.
25. Holtan SG, DeFor TE, Lazaryan A, Bejanyan N, Arora M, Brunstein CG, et al. Composite end point of graft-versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation. Blood. 2015;125:1333–8.
26. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res. 2011;46:399–424.
27. Bacigalupo A, Socie G, Hamladji RM, Aljurf M, Maschan A, Kyrcz-Krzemien S, et al. Current outcome of HLA identical sibling versus unrelated donor transplants in severe aplastic anemia: an EBMT analysis. Haematologica. 2015;100:696–702.
28. Bacigalupo A, Socie G, Schrezenmeier H, Tichelli A, Locasciulli A, Fuehrer M, et al. Bone marrow versus peripheral blood as the stem cell source for sibling transplants in acquired aplastic anemia: survival advantage for bone marrow in all age groups. Haematologica. 2012;97:1142–8.
29. Schrezenmeier H, Passweg JR, Marsh JC, Bacigalupo A, Bredeson CN, Bullorsky E, et al. Worse outcome and more chronic GVHD with peripheral blood progenitor cells than bone marrow in HLA-matched sibling donor transplants for young patients with severe acquired aplastic anemia. Blood. 2007;110:1397–400.
30. Eapen M, Le Rademacher J, Antin JH, Champlin RE, Carreras J, Fay J, et al. Effect of stem cell source on outcomes after unrelated donor transplantation in severe aplastic anemia. Blood. 2011;118:2618–21.
31. MacMillan ML, Robin M, Harris AC, DeFor TE, Martin PJ, Alousi A, et al. A refined risk score for acute graft-versus-host disease that predicts response to initial therapy, survival, and transplant-related mortality. Biol Blood Marrow Transpl. 2015;21:761–7.
32. Fiuza-Luces C, Simpson RJ, Ramirez M, Lucia A, Berger NA. Physical function and quality of life in patients with chronic GvHD: a summary of preclinical and clinical studies and a call for exercise intervention trials in patients. Bone Marrow Transpl. 2016;51:13–26.
33. Servais S, Beguin Y, Delens L, Ehx G, Fransolet G, Hannon M, et al. Novel approaches for preventing acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Expert Opin Investig Drugs. 2016;25:957–72.