**Title: Comparative analysis of the outcomes of allogeneic stem cell transplantation according to donor-type groups in adult severe aplastic anemia patients**

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**Running title:** Comparable outcomes of MSD-SCT and URD-SCT for SAA patients

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**ABSTRACT**

Recently improved survival of severe aplastic anemia (SAA) patients who received allogeneic stem cell transplantation (SCT) from unrelated donors suggests that its role can be further extended. To address this issue, the outcomes of adult SAA patients receiving SCT were compared according to the following three donor-type groups: 8/8-matched sibling (MSD), 8/8-matched unrelated (WM-URD), and 6–7/8-matched unrelated (PM-URD). Following a generally accepted therapeutic scheme, the proportion of patients experiencing immunosuppressive treatment failures was significantly higher in the URD groups (*P* < 0.01) than in the MSD group. Graft failure incidences, transplant-related mortality incidences, and graft-versus-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%, 13.8%, 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 significantly 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. The analysis of propensity score matching sub-cohort showed not significantly different OS rates between the MSD and URD groups (96.3% vs. 88.9%; *P* = 0.24). Our study showed comparable OS rates between the MSD and WM-URD groups, with the clinically acceptable rate of PM-URD group, which suggests the extending role of URD-SCT as a first-line treatment option for SAA patients.

**Keywords;** allogeneic stem cell transplantation; severe aplastic anemia; matched sibling donor; unrelated donor

**INTRODUCTION**

Aplastic anemia 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](#_ENREF_1) Patients with a severe form of the disease (severe aplastic anemia [SAA]) are significantly at higher risk of death due to its severe complications, such as fatal infection and/or hemorrhage, if they do not receive optimal therapeutic interventions. 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 first-line therapeutic modalities for younger (≤ 50 years old) and older (> 50 years old) adult SAA patients, respectively.[2](#_ENREF_2), [3](#_ENREF_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 to that of MSD-SCT.[4-6](#_ENREF_4) However, although patients who received IST as a first-line therapeutic modality can achieve excellent 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, disease relapse, and clonal evolution.[7](#_ENREF_7) Additionally, because of a frequently observed partial response after IST, achieving complete recovery of the quality of life seems to be difficult, followed by restrictions to daily activities due to subnormal hemoglobin and/or platelet counts or increased risk of infections due to subnormal neutrophil count and long-standing cyclosporin (CsA) exposure.[8](#_ENREF_8)

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.[9](#_ENREF_9), [10](#_ENREF_10) Recent studies showed that the outcomes of children and adolescent patients who received URD-SCT as a first-line treatment were insignificantly different to those of patients who received MSD-SCT.[11](#_ENREF_11), [12](#_ENREF_12) Reflecting these results, an updated guideline recommends that URD-SCT may be considered as a first-line therapeutic modality for pediatric patients without appropriate MSD.[3](#_ENREF_3) However, comparative studies regarding the outcomes of adult SAA patients who received MSD-SCT and URD-SCT are very rare. To address this issue, major long-term transplant-related outcomes of consecutive adult SAA patients who received MSD-SCT and URD-SCT at our institution were comparatively analyzed.

**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 to May 2018 at the Catholic Blood and Marrow Transplantation Center. According to conventional therapeutic schemes,[2](#_ENREF_2), [3](#_ENREF_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 CsA, as a first-line therapeutic modality. However, patients who immediately required treatment, per physicians’ discretion, received URD-SCT as a first-line treatment.[7](#_ENREF_7) On the contrary, patients experiencing IST failures received URD-SCT as a second-line therapeutic modality. 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. All patients were ≤ 65 years old with adequate organ function and performance status at the time of transplantation. Our current 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/m2 intravenously [IV] for 6 days) and cyclophosphamide (Cy, 50–60 mg/kg IV for 2 days) plus rabbit ATG (2.5 mg/kg IV for 4 days) for MSD-SCT or fractionated total body irradiation (TBI, 400 cGy for 2 days) plus Cy (50–60 mg/kg IV for 2 days) for URD-SCT. If potential candidates of MSD-SCT experienced severe concurrent infections, 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). Although we have requested BM harvest to all potential donors, the choice of BM and PB stem cells were determined according to their preferences. After the infusion of BM stem cells or granulocyte-colony stimulating factor-mobilized PB stem cells, the prophylaxis for graft-versus-host disease (GVHD) was as follows: short-course methotrexate (10 mg/m2 for MSD-SCT or 5 mg/m2 for URD-SCT at day 1, 3, 6, and 11) plus CsA (target through level of 200–250 ng/mL until patients achieved engraftment, thereafter 150–200 ng/mL) for MSD-SCT or FK506 (target through level of 15–20 ng/mL until patients achieved engraftment, thereafter 10–15 ng/mL) for URD-SCT. Since August 2009, low-dose rabbit ATG (1.25 mg/kg IV for 2 days) has been administered to all patients who received URD-SCT from HLA-mismatched donor and/or used PB stem cells.[13](#_ENREF_13) Other detailed transplant-related procedures, including supportive care strategies, were described in our previous reports.[13](#_ENREF_13), [14](#_ENREF_14)

**Definitions**

The diagnosis of the disease and categorization of the severity were performed according to the criteria proposed by Camitta et al.[15](#_ENREF_15) Patients’ pre-transplant comorbidities were assessed according to the Hematopoietic Cell Transplantation-Specific Comorbidity index.[16](#_ENREF_16) Neutrophil and platelet engraft-ment were defined as an absolute neutrophil (ANC) count ≥ 0.5 × 109/L for at least 3 consecutive days and a platelet count ≥ 20 × 109/L for at least 7 consecutive days without transfusional support. Primary and secondary graft failure (GF) were characterized by a failure of neutrophil engraftment at days 28 with either irreversible ANC < 0.5 × 109/L or platelet count < 20 × 109/L, with or without evidence of previous donor engraftment, respectively. Post-transplant complications of acute and chronic GVHD, grade ≥ 3 infectious complications, sinusoidal obstruction syndrome, and hemorrhagic cystitis were evaluated according to the previous published criteria.[17](#_ENREF_17) Additionally, we defined a composite end-point of GVHD-free, failure-free survival (GFFS) based on the following: being alive without experiencing grade III-IV acute GVHD, chronic GVHD requiring systemic therapy and primary or secondary GF.[14](#_ENREF_14), [18](#_ENREF_18)

**Statistical analysis**

This study aimed to compare the major outcomes, including GF incidence, 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), 8/8 allele-matched URD (the WM-URD group), and 6–7/8 allele-matched URD (the PM-URD group). All time-dependent parameters were measured from the first day of stem cell infusion. Continuous and categorical variable were described by median with ranges and count with relative frequency, respectively. Comparisons between the baseline and transplant-related characteristics according to donor-type groups were performed by using the independent two-sample t-test, the χ2 test, and Fisher’s exact test. 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 and chronic GVHD, and TRM were described as the cumulative incidence estimate and compared using the Grey’s test. The prognostic significance of covariates was determined 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 plus PM-URD) groups for the propensity score-matching sub-cohort of patients receiving allogeneic SCT as a first-line treatment, considering the limited number of patients of the URD group. The propensity score-matching sub-cohort was established by propensity score calculated by using a logistic regression model for each individual patient, 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.[19](#_ENREF_19) 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).

**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. The etiologies of the disease were categorized as follows: idiopathic in 234 (90.7%), pregnancy-associated in 9 (3.5%), hepatitis-related in 7 (2.7%), drug-induced in 5 (1.9%), and others in 3 (1.2%) patients. 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 to 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 massive (> 100 units) transfusion history (*P* = 0.01 and *P* = 0.05, respectively) of the WM-URD and the PM-URD groups compared to that of the MSD group. With the discriminable transplantation processes according to donor-type groups, 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), and using ABO blood type-matched donor (*P* = 0.01 and *P* < 0.01, respectively) compared to that 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 × 106/kg (range, 0.25–14.37) and 4.92 × 106/kg (range, 1.81–17.03), and 38.79 × 106/kg (range, 1.70–463.68) and 329.64 × 106/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. Neutrophil engraftment incidences of the MSD, the WM-URD, and the PM-URD groups were 99.3% (95% confidence interval [CI], 95.4–99.9), 100%, and 97.0% (95% CI, 59.8–99.8) at day 28, respectively (*P* = 0.79). Excluding three (1.2%) patients who did not experience platelet count nadir (in the MSD group), 230 (95.0%) patients achieved platelet engraft-ment at a median 17 (range, 7–433) days. Platelet engraftment incidences in the MSD, the WM-URD, and the PM-URD groups were 88.0% (95% CI, 81.5–92.3), 81.9% (95% CI, 70.7–89.2), and 75.8% (95% CI, 56.4–87.4) at day 28, respectively (*P* = 0.48). More detailed incidences of neutrophil and platelet engraftments are described in Table 2.

**Graft-versus-host disease and other post-transplant 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 5 (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 experienced 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 (including grades III-IV) and chronic (including moderate-to-severe and severe) GVHD according to donor-type groups are described 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% 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). There were no significant differences of other post-transplant complications incidences according to donor-type groups (*P* > 0.10). More detailed post-transplant 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 to that of the WM-URD (*P* < 0.01) and the PM-URD (*P* < 0.01) groups. There was no significant difference of secondary GF incidences between the WM-URD and the PM-URD groups (*P* = 0.32) (Figure 2A). Other baseline and transplant-related characteristics did not affect the secondary GF incidence (*P* > 0.20). Of those who experienced secondary GF, 19 (86.4%) patients received secondary allogeneic SCT, followed by achieving sustained engraftment without mortality. Three (13.6%) who only received supportive care patients remained alive at the last follow-up.

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 one (0.4%) patients. TRM incidences of the MSD, the WM-URD, and the PM-URD groups were 6.1% (95% CI, 3.0–10.8), 13.8% (95% CI, 5.8–25.0), 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) (Figure 2B). Other baseline and transplant-related characteristics did not affect the TRM incidence (*P* > 0.20).

**Graft-versus-host disease-free, failure-free survival and overall survival**

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 and grades III-IV acute, 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 to 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) (Figure 2C). Patients’ age (≤ 40 years vs. > 40 years, 64.3% vs. 76.8% 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] 2.08, 95% CI 0.69–6.24; *P* = 0.19 and PM-URD vs. MSD, HR 4.54, 95% CI 1.35–15.28; *P* = 0.01) was the only significant factor affecting GFFS rate in multivariate analysis (*P* = 0.05).

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 (Figure 2D). There was no significant difference in OS rates between the WM-URD and the PM-URD groups (*P* = 0.18). Massive transfusion history (≤ 100 units vs. > 100 units, 97.7% vs. 89.3%; *P* = 0.09) was another potential candidate affecting OS rate. However, donor 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 1.12–8.85; *P* = 0.02) was only significant factor affecting OS rate in multivariate analysis (*P* = 0.04).

**Subgroup analysis for the propensity-score matching cohort of patients receiving allogeneic stem cell transplant as a first-line treatment**

We compared the major post-transplant 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. The patients’ baseline and transplant-related characteristics were not significantly different between the MSD and the URD groups (*P* > 0.05), except significantly higher proportion of patients who had male sex (*P* = 0.03) 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 (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 to that 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. (Figure 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 to that of the MSD group, although it was acceptable to be used in the clinical practice. 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. Nevertheless, there are several considerations that should be taken with caution.

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 to that of URD groups. Conversely, the proportions of those who had longer interval from diagnosis to transplant (> 12 months) and massive transfusion history (> 100 units) were significantly higher in the URD groups, since most patients in the URD groups experienced previous IST failures, compared to that of the MSD group. Additionally, 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 these factors were associated with poor post-transplant outcomes,[19-22](#_ENREF_19) except a significantly higher proportion of patients having older age (> 40 years) that was more frequently observed in the MSD group than in the URD groups. It might more negatively attribute post-transplant outcomes of the URD groups than the MSD group. Consequently, an unbalanced distribution of the clinical and transplant-related characteristics of the donor-type groups cannot significantly affect our major conclusion of the comparable OS rates between the MSD and the WM-URD groups. Certainly, this observed limitation of this study should be validated by further well-designed prospective cohorts with well-balanced groups.

A substantially high secondary GF incidence only in the MSD group may be an additional limitation in our study. GF incidences of the previously published studies analyzing post-transplant outcomes of SAA patients who received allogeneic SCT using Flu-based conditioning were commonly low (from 0% to 13.9%),[23-25](#_ENREF_23) supporting the hypothesis that a high secondary GF incidence of the MSD group was not only due to the low intensity of conditioning regimen. When we compared the clinical and transplant-related characteristics of the current study and other previous studies’ cohorts, the proportion of the MSD group patients who had massive transfusion history was relatively higher in our cohort than that in the previous studies’ cohort. Consequently, it suggests that a Flu-based conditioning might be insufficient to overcome the possible occurrence of GF in these high-risk patients of the MSD-SCT group. In contrast, despite the fact that a substantial proportion of patients in the URD groups also had a massive transfusion history and some of them with 1–2 allele mismatched donor, secondary GF was not observed in any of them. Previous studies investigating the factors affecting GF incidence for SAA patients who received allogeneic SCT showed that irradiation-based conditioning might facilitate sustained engraftment.[26](#_ENREF_26), [27](#_ENREF_27) Therefore, a very low GF incidence of the URD groups might be due to the potent immunosuppression of the TBI-based conditioning sufficient to overcome a possible occurrence in high-risk patients of the URD groups. Furthermore, whether this limitation of Flu-based conditioning can be solved by the intensification of conditioning should be investigated by further studies.

Recently, 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).[11](#_ENREF_11) 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).[12](#_ENREF_12) They also compared the outcomes of those who received IST and URD-SCT as a first-line treatment, which showed a significantly higher event-free survival rate of the latter group than that of the former group (40% vs. 92% at 2 years; *P* < 0.01). These above-mentioned studies suggest an extending role of URD-SCT as a considerable first-line treatment option for children and adolescent SAA patients, which have changed the treatment scheme for these patients.[3](#_ENREF_3) However, comparative studies that analyzed the outcomes of adult SAA patients who received MSD-SCT and the URD-SCT are insufficient. A large European Group for Blood and Marrow Transplantation registry-based study by Bacigalupo et al. showed insignificantly different OS rates between the MSD and the URD groups (HR 1.20; 95% CI 0.93–1.55; *P* = 0.16).[19](#_ENREF_19) However, this study has difficulty in representing the comparable OS rates of adult SAA patients who received MSD-SCT and URD-SCT, considering the proportion of patients aged of ≤ 20 years approaching to approximately 50%. Our study showed insignificantly different OS rates between the MSD and WM-URD groups in 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 SAA patients who received MSD-SCT and URD-SCT as a first-line treatment might make our results more evident, although a very limited number of patients of this cohort result in a difficulty in drawing conclusive results.

The incidences of acute and chronic GVHD of the URD groups were significantly higher than those of the MSD group. Additionally, we showed the GFFS is a novel composite end point, which suggests post-transplant recovery without ongoing but non-lethal morbidity.[18](#_ENREF_18) It was significantly higher in the MSD group than that of the URD group. Considering relatively high morbidity and mortality of patients experiencing acute and chronic GVHD,[28](#_ENREF_28), [29](#_ENREF_29) 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 problem.[13](#_ENREF_13) It showed significantly lower acute grades 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) of patients who received additional low-dose ATG (2.5 mg/kg) compared to patients who did not receive additional low-dose ATG. Furthermore, emerging prophylactic approaches with an improved understanding of GVHD pathophysiology will lead us to overcome this challenging area of allogeneic SCT. Consequently, these may support the extended role of URD-SCT as a first-line treatment in the near future.

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 insignificantly 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 unique comparative analysis including only adult SAA patients who received allogeneic SCT between the MSD and the URD groups. However, because this is a retrospective study with a limited number of patients who received allogeneic SCT as a first-line treatment, future well-designed prospective studies to confirm our results are required.

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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 yrs1,2 | 84 (54.9%) / 69 (45.1%) | 54 (75.0%) / 18 (25.0%) | 29 (87.9%) / 4 (12.1%) | < 0.01 |
| Sex |  |  |  |  |
| Male / Female1 | 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† |  |  |  |  |
| ≤ 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 / No1,2 | 46 (30.1%) / 107 (69.9%) | 57 (79.2%) / 15 (20.8%) | 30 (90.9%) / 3 (9.1%) | < 0.01 |
| Massive transfusion history (> 100 units) |  |  |  |  |
| Yes / No1 | 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 mo / > 12 mo1,2 | 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 / PBSC1 | 101 (66.0%) / 52 (34.0%) | 34 (47.2%) / 38 (52.8%) | 16 (48.5%) / 17 (51.5%) | 0.01 |

Abbreviations: 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

1 indicates *P* < 0.05 between the MSD and the WM-URD groups and 2 indicates *P* < 0.05 between the MSD and the PM-URD groups.

† Pre-transplant serum ferritin level were available in 245 (95.0%) patients.

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Engraftment and GVHD | MSD | WM-URD | PM-URD | *P* |
| Cumulative incidence (95% CI) | | |
| 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-IV1,2,3 | 8.5% (4.8–13.6) | 36.1% (25.1–47.2) | 57.6% (38.6–72.6) | < 0.01 |
| Grade III-IV1,2 | 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-severe1,2 | 8.6% (4.8–13.8) | 43.4% (31.6–54.6) | 36.6% (18.0–77.5) | < 0.01 |
| Moderate-to-severe1,2 | 2.6% (0.9–6.2) | 30.6% (20.3–41.4) | 27.3% (13.4–43.2) | < 0.01 |
| Severe1,2 | 0.7% (0.1–3.6) | 12.5% (6.1–21.3) | 12.1% (3.7–25.8) | < 0.01 |

Abbreviations: GVHD = graft-versus-host disease; MSD = matched sibling donor; WM-URD = well-matched unrelated donor; PM-URD = partially matched unrelated donor; CI = confidence interval

1 indicates *P* < 0.01 between the MSD and the WM-URD groups, 2 indicates *P* < 0.01 between the MSD and the PM-URD groups, and 3 indicates *P* < 0.01 between the WM-URD and the PM-URD groups.

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Complications | MSD | WM-URD | PM-URD | *P* |
| Cumulative incidence at 6 yrs (95% CI) | | |
| Infectious complication (grade ≥ 3)1 | 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 |

Abbreviations: CI = confidence interval; MSD = matched sibling donor; WM-URD = well-matched unrelated donor; PM-URD = partially matched unrelated donor; CMV = cytomegalovirus; PTLD = post-transplant lymphoproliferative disease

1 indicates *P* = 0.04 between the MSD and the WM-URD groups and *P* < 0.01 between the MSD and the PM-URD groups.

**FIGURE LEGEND**

Figure 1. The graft-failure incidence, transplant-related mortality incidence, graft-versus-host disease-free survival rate, and overall survival rate according to donor-type groups.

Figure 2. The graft-failure incidence, transplant-related mortality incidence, graft-versus-host disease-free survival rate, and overall survival rate according to donor-type groups for the propensity-score matching cohort of patients receiving allogeneic stem cell transplant as first-line treatment.

Table S1. Patients’ baseline and transplant-related characteristics of the propensity score-matching first-line allogeneic SCT cohort according to donor-type group

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | MSD | URD | *P* |
| Number of patients | 54 | 18 | NA |
| Age |  |  |  |
| ≤ 40 yrs / > 40 yrs | 34 (63.0%) / 20 (37.0%) | 15 (83.3%) / 3 (16.7%) | 0.19 |
| Sex |  |  |  |
| Male / Female | 31 (57.4%) / 23 (42.6%) | 16 (88.9%) / 2 (11.1%) | 0.03 |
| Disease severity |  |  |  |
| SAA / VSAA | 36 (66.7%) / 18 (33.3%) | 14 (77.8%) / 4 (22.2%) | 0.56 |
| Presence of PNH clone |  |  |  |
| Yes / No | 46 (14.8%) / 8 (14.8%) | 16 (88.9%) / 2 (11.1%) | 1.00 |
| Serum ferritin level† |  |  |  |
| ≤ 1000 ng/mL / > 1000 ng/mL | 26 (49.1%) / 27 (50.9%) | 11 (61.1%) / 7 (38.9%) | 0.54 |
| Massive transfusion history (> 100 units) |  |  |  |
| Yes / No | 39 (72.2%) / 15 (27.8%) | 15 (83.3%) / 3 (16.7%) | 0.53 |
| Interval from diagnosis to transplant |  |  |  |
| ≤ 12 mo / > 12 mo | 29 (53.7%) / 25 (46.3%) | 3 (16.7%) / 15 (83.3%) | 0.01 |
| HCT-CI |  |  |  |
| < 3 / ≥ 3 | 28 (51.9%) / 26 (48.1%) | 10 (55.6%) / 8 (44.4%) | 1.00 |
| HLA mismatch |  |  |  |
| 1 allele / 2 allele | NA | 3 (16.7%) / 0 | NA |
| ABO blood type mismatch |  |  |  |
| Yes / No | 22 (40.7%) / 32 (59.3%) | 13 (72.2%) / 5 (27.8%) | 0.04 |
| Donor-recipient sex mismatch |  |  |  |
| Female to male / Others | 14 (25.9%) / 40 (74.1%) | 2 (11.1%) / 16 (88.9%) | 0.33 |
| Stem cell source |  |  |  |
| BM / PBSC | 34 (63.0%) / 20 (37.0%) | 4 (22.2%) / 14 (77.8%) | 0.01 |

Abbreviations: MSD = matched sibling donor; URD = unrelated donor; NA = not available; SAA = severe aplastic anemia; VSAA = very severe aplastic anemia; PNH = paroxysmal nocturnal hemoglobinuria; HCT-CI = hematopoietic cell transplantation-specific comorbidity index; HLA = human leukocyte antigen; BM = bone marrow; PBSC = peripheral blood stem cells

† 64 (88.9%) patients had available pre-transplant serum ferritin level were analyzed.