Older Matched Sibling Donors Remain a Favorable Option in Allogeneic Hematopoietic Stem Cell Transplantation for Aplastic Anemia: Impact of Donor Age Across Donor Types

So Yeon Park[1], Daehun Kwag[1], Gi June Min[1], Sung-Soo Park[1], Jae-Ho Yoon[1], Sung-Eun Lee[1], Byung-Sik Cho[1], Ki-Seong Eom[1], Yoo-Jin Kim[1], Hee-Je Kim[1], Chang-Ki Min[1], Seok-Goo Cho[1], and Silvia Park[1*]

1. Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea

Introduction

Donor age has emerged as an important determinant of allogeneic hematopoietic stem cell transplantation (allo-HSCT) outcomes, with evidence from hematologic malignancies suggesting that younger alternative donors may achieve results comparable or superior to older matched sibling donors (MSDs). Whether this applies to aplastic anemia (AA)—a non-malignant marrow failure disorder in which graft failure is a concern alongside graft-versus-host disease (GVHD)—remains unclear. We evaluated the impact of donor type and donor age on long-term outcomes in AA.

Method

We retrospectively analyzed 321 patients with severe or very severe AA who underwent a first allo-HSCT at a single center between 2009 and 2023. Donors were classified as MSD (n=145), matched unrelated donor (MUD, 8/8; n=65), mismatched unrelated donor (MMUD, ≤7/8; n=29), or haploidentical family donor (Haplo, 4–6/8; n=82); one-antigen–mismatched related donors were excluded. Conditioning regimens varied by donor type and era: fludarabine–cyclophosphamide–antithymocyte globulin (ATG) or total nodal irradiation for MSD; total body irradiation (TBI) 400–800 cGy with cyclophosphamide for MUD/MMUD; and TBI 600–800 cGy with fludarabine for Haplo. GVHD-free, failure-free survival (GFFS) was defined as the proportion of patients who were alive without specific events, including grade III to IV acute GVHD, chronic GVHD requiring systemic treatment, primary or secondary graft failure, or death from any cause after SCT (whichever came first) Cumulative incidences were estimated with death (and graft failure for chronic GVHD) treated as competing events.

Result

Baseline characteristics are shown in Table 1. Both recipient age and median donor age were higher in the MSD group than in the other groups, and bone marrow was used more frequently as the stem cell source in MSD recipients. Neutrophil and platelet engraftment occurred at a median of 12 and 14 days, respectively. Primary graft failure occurred in 1 patient and secondary graft failure in 29.

With a median follow-up of 10.1 years (IQR, 6.6–14.2), 5-year overall survival (OS), failure-free survival (FFS), and GFFS were 92.1%, 84.2%, and 68.4% for the entire cohort (Figure 1). Outcomes differed markedly across the four donor types: 5-year OS was 95.8%, 98.5%, 71.3%, and 87.6% for MSD, MUD, MMUD, and Haplo (P<.001); FFS was 80.1%, 96.9%, 67.4%, and 87.5% (p=.001); and GFFS was 74.6%, 69.6%, 43.5%, and 65.1% (p=.001). MMUD recipients had significantly poorer outcomes across all endpoints than MSD, MUD, and Haplo recipients, whereas MSD, MUD, and Haplo were comparable. When unrelated donors were analyzed as a single group, these differences were obscured (all p>.05).These divergent outcomes reflected distinct patterns of failure by donor type. MSD transplantation conferred the lowest GVHD burden—cumulative incidence of grade II–IV acute GVHD 6.2% (vs 27.7%, 37.9%, and 29.3%) and moderate-to-severe chronic GVHD 4.9% (vs 18.5%, 17.4%, and 14.9%)—but the highest incidence of graft failure (16.3% vs 1.5%, 3.4%, and 2.4%; P<.001), which was largely survivable and accounted for the lower FFS of MSD despite its excellent OS.

Finally, we examined whether older donor age was detrimental. When donors were dichotomized at 50 years, older donor age (>50 years) was associated with inferior OS in the overall cohort (85.0% vs 93.7%; p=.01), but not with FFS or GFFS (p=.32 and .62). Because all MUD and MMUD donors were ≤50 years, the effect of donor age was further assessed within the MSD and Haplo groups (Figure 2). Recipients of older MSDs had 5-year OS and GFFS of 90.6% and 78.1%, comparable to younger MSD recipients (97.3% and 74.5%; p=.10 and .58). In contrast, recipients of older Haplo donors had significantly lower OS (78.6% vs 92.4%; p=.03) and GFFS than younger Haplo recipients.

Conclusion

Although younger donors are increasingly preferred over older matched siblings in the transplantation of hematologic malignancies, this paradigm did not extend to aplastic anemia. Here, the prognostic impact of donor age was donor-type dependent: older matched sibling donors achieved outcomes comparable to younger siblings and remained a favorable option, whereas older donor age was detrimental in the haploidentical setting. MSD transplantation conferred a markedly lower GVHD burden, offset by a higher incidence of graft failure. These findings suggest that an older matched sibling should not be passed over in favor of a younger alternative donor in AA, and that the impact of donor age must be interpreted in the context of donor type. Confirmation in larger cohorts is warranted.

Table 1. Baseline characteristics

Table 1. Baseline Patient Characteristics

Characteristic	Overall (*n*=321)	MSD (*n*=145)	MUD (*n*=65)	MMUD (*n*=29)	Haplo (*n*=82)	*P* value
Patient characteristics						
Age at HSCT, y, median (IQR)	37.0 (29.0-47.0)	41.0 (29.0-49.0)	31.0 (26.0-47.0)	34.0 (29.0-45.0)	34.0 (27.2-44.0)	.06
Male sex, No. (%)	143 (44.5)	59 (40.7)	29 (44.6)	15 (51.7)	40 (48.8)	.56
Disease severity, No. (%)						.11
SAA	211 (65.7)	96 (66.2)	47 (72.3)	22 (75.9)	46 (56.1)	
VSAA	110 (34.3)	49 (33.8)	18 (27.7)	7 (24.1)	36 (43.9)	
Time from diagnosis to HSCT, mo, median (IQR)	34.2 (5.0-128.2)	10.8 (3.6-105.3)	68.2 (10.3-164.1)	81.2 (21.8-149.8)	54.0 (7.2-130.9)	<.001
PNH clone positive, No. (%)	54 (19.3)	28 (23.0)	9 (16.4)	5 (20.8)	12 (15.2)	.52
Missing	41	23	10	5	3	
Abnormal cytogenetics, No. (%)	24 (8.2)	9 (7.0)	10 (16.7)	0 (0.0)	5 (6.6)	.04
Missing	28	16	5	1	6	
Prior immunosuppressive therapy, No. (%)	204 (63.6)	53 (36.6)	52 (80.0)	25 (86.2)	74 (90.2)	<.001
Pre-transplant serum ferritin, ng/mL, median (IQR)	1,680 (993-2,816)	1,514 (923-2,812)	1,600 (817-2,530)	1,550 (905-3,020)	1,932 (1,331-2,791)	.11
HCT-CI, No. (%)						.02
0 (low)	87 (27.1)	30 (20.7)	16 (24.6)	11 (37.9)	30 (36.6)	
1-2 (intermediate)	123 (38.3)	60 (41.4)	28 (43.1)	6 (20.7)	29 (35.4)	
3 or higher (high)	111 (34.6)	55 (37.9)	21 (32.3)	12 (41.4)	23 (28.0)	

Continuous variables are summarized as median (IQR) and compared with the Kruskal-Wallis test; categorical variables as No. (%) and compared with the Pearson chi-square or Fisher exact test.

P values were calculated using the Kruskal-Wallis test, Pearson chi-square test, Monte Carlo exact test, and linear-by-linear trend test.

Abbreviations: HSCT, hematopoietic stem cell transplantation; MSD, matched sibling donor; MUD, matched unrelated donor; MMUD, mismatched unrelated donor; Haplo, haploidentical donor; IQR, interquartile range; SAA, severe aplastic anemia; VSAA, very severe aplastic anemia; PNH, paroxysmal nocturnal hemoglobinuria; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; BM, bone marrow; PBSC, peripheral blood stem cell.

Table 1 (continued). Transplant Characteristics

Characteristic	Overall (*n*=321)	MSD (*n*=145)	MUD (*n*=65)	MMUD (*n*=29)	Haplo (*n*=82)	*P* value
Transplant characteristics						
Donor age, y, median (IQR)	35.0 (27.0-46.0)	41.0 (32.0-49.0)	29.0 (25.0-33.0)	30.0 (26.0-34.0)	39.0 (26.2-54.0)	<.001
Female-to-male donor, No. (%)	55 (17.1)	31 (21.4)	8 (12.3)	3 (10.3)	13 (15.9)	.27
ABO matching, No. (%)						.002
Matched	156 (48.6)	84 (57.9)	22 (33.8)	10 (34.5)	40 (48.8)	
Major mismatch	79 (24.6)	35 (24.1)	17 (26.2)	8 (27.6)	19 (23.2)	
Minor mismatch	60 (18.7)	19 (13.1)	20 (30.8)	4 (13.8)	17 (20.7)	
Bidirectional mismatch	26 (8.1)	7 (4.8)	6 (9.2)	7 (24.1)	6 (7.3)	
Stem cell source, No. (%)						<.001
PBSC	228 (71.0)	70 (48.3)	52 (80.0)	24 (82.8)	82 (100.0)	
BM	90 (28.0)	72 (49.7)	13 (20.0)	5 (17.2)	0 (0.0)	
BM+PBSC	3 (0.9)	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	
CD34+ cell dose, x10^6/kg, median (IQR)	4.9 (3.0-7.4)	3.6 (2.3-5.3)	5.6 (4.3-7.5)	4.7 (3.1-7.2)	7.1 (4.6-10.4)	<.001
CD3+ cell dose, x10^6/kg, median (IQR)	294.3 (62.4-417.5)	70.5 (38.0-374.5)	293.1 (179.3-361.4)	334.3 (162.8-386.7)	408.0 (278.1-492.4)	<.001

Continuous variables are summarized as median (IQR) and compared with the Kruskal-Wallis test; categorical variables as No. (%) and compared with the Pearson chi-square or Fisher exact test.

P values were calculated using the Kruskal-Wallis test, and Monte Carlo exact test.

Abbreviations: HSCT, hematopoietic stem cell transplantation; MSD, matched sibling donor; MUD, matched unrelated donor; MMUD, mismatched unrelated donor; Haplo, haploidentical donor; IQR, interquartile range; SAA, severe aplastic anemia; VSAA, very severe aplastic anemia; PNH, paroxysmal nocturnal hemoglobinuria; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; BM, bone marrow; PBSC, peripheral blood stem cell.

Figure 1. Overall survival (OS), failure-free survival (FFS), and GVHD-free, failure-free survival (GFFS) of the entire cohort.

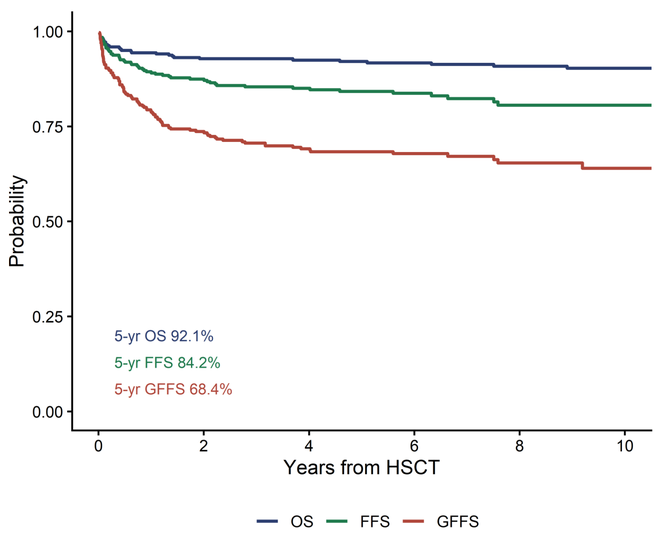
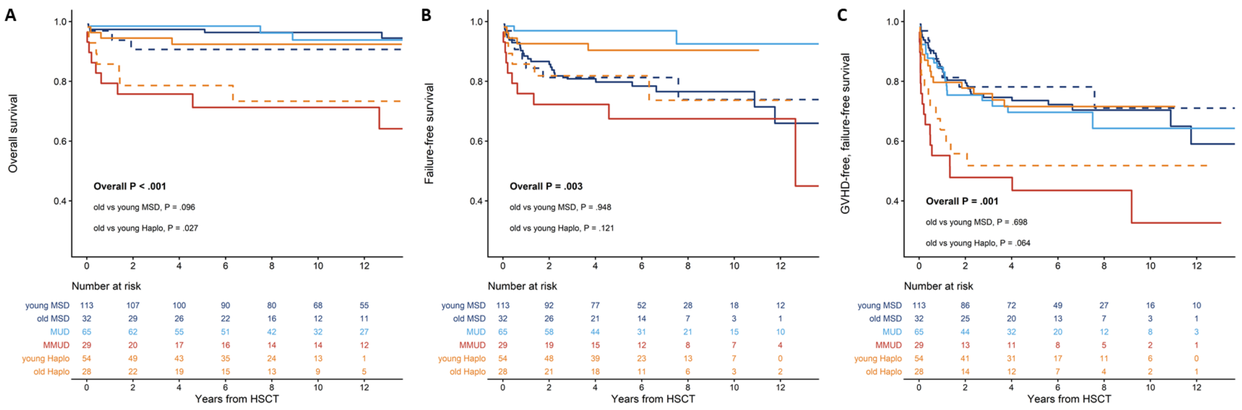


Figure 2. Overall survival (A), failure-free survival (B), and GVHD-free, failure-free survival (C) according to donor type and donor age.



Contact Information

Presenter : So Yeon Park (soyeonp20@catholic.ac.kr), Corresponder: Silvia Park (silvia.park@catholic.ac.kr)

www.iachlive.cme-congresses.com