Haploidentical Related Donor versus Matched Sibling Donor Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndrome Aged Over 50 Years: A Single-Center Retrospective Study.

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Abstract

BACKGROUND Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative therapeutic option for patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). Increasing data supports the utility of haploidentical related donor (HID) HSCT in fit older patients and resulting in improvement of outcomes. This study compared the outcomes of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) patients age ≥ 50 years underwent haploidentical related donor (HID) or matched sibling donor (MSD) allogeneic hematopoietic stem cell transplantation (allo-HSCT). **METHODS** We provided HID transplantation to 38 patients of AML/MDS age ≥ 50 years and compared their outcomes with 55 patients of the same ages who underwent matched sibling donor (MSD) transplantation. **RESULTS** The 100-day cumulative incidence of II-IV° acute graft-versus-host disease (GVHD) were $34.2 \pm 7.7\%$ and $23.6 \pm 5.7\%$, respectively, in HID and MSD groups ($P = 0.189$), and III-IV° acute GVHD were similar between two groups (5.3% and 7.3% , respectively, $P=0.700$). The 2-year cumulative incidence of limited and extensive chronic GVHD was not statistically different in HID and MSD groups ($22.8 \pm 10.8\%$ vs. $18.2 \pm 6.0\%$ and $18.3 \pm 10.4\%$ vs. $22.1 \pm 6.8\%$, $P = 0.890$ and $P=0.424$, respectively). The 2-year cumulative incidences of relapse ($29.5 \pm 10.3\%$ and $20.7 \pm 6.1\%$, $P=0.458$), 2-year overall survival ($58.5 \pm 9.7\%$ and $67.9 \pm 6.8\%$, $P=0.373$), 2-year transplant-related mortality ($17.3 \pm 6.4\%$ and $15.0 \pm 5.3\%$, $P=0.717$), 2-year progression free survival ($56.8 \pm 9.7\%$ and $64.6 \pm 7.4\%$, $P=0.312$) were similar in the two groups. **CONCLUSION** We conclude that HID allo-SCT is feasible and safe for elderly AML/MDS patients.

Background

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative therapy for patients with acute myeloid leukemia (AML) or myelodysplastic syndrome [MDS]. However, most of these patients are older adults aged ≥ 60 years(1). Historically, older adults were not taken into account in allo-HSCT given frequent comorbidities and higher transplant-related mortality. With technical advance in allo-HSCT, it has been broadened the application of older population, and its upper age limit has risen from 40 to 45 to 70 and to 75 years over the past 4 decades(2, 3). A growing number of studies has demonstrated that allo-HSCT results in improvement of outcomes and is not a contraindication for older AML and MDS(4-8).

Though HLA-identical sibling donor (MSD) is the best choice for allo-HSCT, it is difficult to older patients(9). In comparison, haploidentical donor (HID) is available to nearly all patients requiring allo-HSCT. Over the last decade, the efficacy and safety of HID transplants in hematologic malignancies have been confirmed. Some studies showed that HID might achieve comparable outcomes with HLA-matched sibling donor (MSD) in hematologic malignancies(10-13). However, these studies have mainly described younger population and lack data from older patients. In this report, we compared the transplant outcomes between HID and MSD transplants for AML and MDS aged ≥ 50 years. The results showed that HID transplant is feasible and safe for elderly AML/MDS patients.

Methods

Study Design and Data Collection

This is a retrospective study based on the transplantation database in our center. The inclusion criteria of this study were patients aged ≥ 50 years diagnosed with de novo AML or MDS who underwent HID transplant or MSD transplant between January 2013 to June 2018. This study was performed in accordance with the principles of the Declaration of Helsinki. Data was obtained from the patients' medical records. Variables collected for all patients included demographic features, pre-transplant-related parameters, transplant-related parameters and graft-versus-host disease (GVHD), relapse-related parameters, treatments-related parameters, survival, infections and so on. Written informed consent for submitting data to our database was routinely obtained when a patient was admitted to our center.

HLA typing

High-resolution DNA typing for HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 were performed for all patients and donors. MSDs were related sibling donors matching $\geq 9/10$ HLA and HIDs were related donors matching 5–8/10 HLA.

Conditioning and Transplants

All patients received myeloablation conditioning regimens including BuCy (busulfan 3.2 mg/kg/day, days -7 to -4, cyclophosphamide 60mg/kg/day, days -3 and -2 and simustine 250mg/m², day -3) or BF (busulfan 3.2 mg/kg/day, days -6 to -3, fludarabine 30 mg/ m²/day, days -7 and -3 and simustine 250mg/m², day -3) or total body irradiation (TBI; 4.5 Gy/day, days -5 and -4) plus Cy(60 mg/kg/day, days -3 and -2). In HID group, 21 patients received BuCy, 11 patients received BF and 6 patients received TBI+Cy regimens. In the MSD group, 31 patients received BuCy, 19 patients received BF and 5 patients received TBI+Cy regimens. All HID patients were transplanted with a combination of bone marrow (BM) and peripheral blood stem cell (PBSC) grafts, whereas all MSD patients received PBSC grafts. Ciclosporin A (CsA), methotrexate (MTX) (on days +1, +3, and +6) and mycophenolate (MMF) were administered to patients undergoing MSD transplant for GVHD prophylaxis. CsA + MTX + MMF+ ATG was administered to patients undergoing HID transplant for GVHD prophylaxis(14, 15).

Evaluation points and definitions

This study mainly focused on engraftment, GVHD, relapse, transplant-related mortality (TRM), overall survival (OS), progression-free survival (PFS). TRM was estimated as death without evidence of leukemia recurrence. PFS was defined as survival in continuous complete remission without haematological relapse. aGVHD and cGVHD were graded according to the literature(16).

Statistical analysis

Our study data was analyzed on June 30, 2019. Comparisons of categorical variables were made by means of chi-squared and Fisher exact tests for small numbers. Differences between numerical variables were calculated by means of 2-sample t test. Incidence of time-dependent variables was estimated by the

method of Kaplan-Meier. The Cox' regression model was used for analyzing prognostic factors for relapse, PFS, TRM and OS. Numerical variables were analyzed as categories based on their values being below or above the median of the entire cohort. All statistical tests were two-sided, and P-value less than 0.05 was considered significant. A multivariate analysis was performed using Cox proportional hazards model. Variables were included in the multivariate model if they were conceptually important or if they approached or attained statistical significance by univariate analysis. All data analysis was performed on the SPSS 24.0(SPSS, IBM, USA).

Results

Patient clinical and Transplants Characteristics

A total of 93 AML or MDS patients aged ≥ 50 years after allo-HSCT were enrolled in this study, including 38 HID and 55 MSD. The median age of the patients was 58 (range, 50.4 to 69) years in HID group and 57.5 (range, 50.5 to 68) in MSD group ($P=0.762$). The median follow-up was 13.1 m (range, 0.4-67.8 m) in the HID group and 17.2 m (range, 2.1–68.8 m) in the MSD group ($P=0.350$). Thirty-four patients in the HID group were diagnosed as AML (29 CR and 5 no-CR) and 4 were MDS. In MSD group, 46 patients were AML (38 CR and 8 no-CR) and 9 were MDS, respectively. The proportion of patients with refractory AML of the two groups were similar ($p=0.999$). Characteristics of patients, donors and transplants are summarized in *Table 1*. Significant differences were noted in the donors' age, stem cell source and the family relationship of recipients and donors between both groups. There were no significant differences in patients' age, gender, gender match, disease status, conditioning regimen, hematopoietic cell transplantation comorbidity index (HCT-CI), time of follow-up, doses of nucleated cells between the two groups. Patients' clinical and transplant characteristics are shown in *Table 1*.

Engraftment

All patients achieved hematopoietic reconstitution except one patient in the HID group who died of graft failure. Neutrophils reconstruction occurred in the HID group at a median of 12 d (range, 9–18) and in the MSD group at a median of 12 d (range, 8–22), respectively ($P=0.458$). Platelet reconstruction in the HID and MSD groups occurred at a median of 13 d (range, 10–53) and 13 d (range, 8–91), respectively ($P=0.333$).

GVHD

The 100 days cumulative incidence of II-IV° aGVHD were $34.2 \pm 7.7\%$ and $23.6 \pm 5.7\%$, respectively, in HID and MSD groups ($P = 0.189$). Incidence of III-IV° aGVHD were $5.3 \pm 3.6\%$ and $7.3 \pm 3.5\%$, respectively, in HID and MSD groups ($P = 0.700$). One patient died of IV° gut aGVHD in MSD group, while no patients died of aGVHD in HID group. The 2-year cumulative incidence of limited and extensive cGVHD were $7.3 \pm 5.0\%$ and $9.2 \pm 6.4\%$, and $14.8 \pm 5.2\%$ and $18.0 \pm 5.8\%$, respectively, in HID and MSD groups ($P = 0.890$ and $P=0.424$, respectively). One patient died of cGVHD in HID group, three died of cGVHD in MSD group (2.63% vs 5.45%, $P=0.642$). Incidence of aGVHD and cGVHD are shown in Figure 1 and Figure 2. Sex

mismatch were significantly associated with higher risk of II-IV^aGVHD and cGVHD (HR 2.424 CI 1.067-5.506 P=0.034 and HR 2.264 CI 1.024-5.004 P=0.044) in multivariate analysis (*Table 3*).

TRM

The causes of death included relapse (n = 15) and TRM (n = 16). Of the 16 patients who died of TRM, infections (n = 9) were the main cause, including 4 infectious diseases for HID recipients, 5 for MSD recipients. Other causes included aGVHD (n = 1), cGVHD (n = 3), thrombotic microangiopathy (n = 1), cerebral infarction (n = 1), graft rejection (n = 1). The 2-year cumulative incidences of TRM in the HID and MSD groups were 17.3 ± 6.4% vs. 15.0 ± 5.3%, (P = 0.717, Figure 3A). Patient's age and sex mismatch were significantly associated with higher risk of TRM (HR 3.718 CI 1.242-11.133 P=0.019 and HR 4.931 CI 1.713-14.190 P=0.003) in multivariate analysis (Table 3).

Infections

Patients in the HID group has significantly higher rates of CMV DNAemia (p = 0.0005). The incidence of other major infectious complications, including sepsis, CMV disease, EBV DNAemia and Invasive fungal infection, were similar between the 2 groups (Table 2).

Relapse and Survival

The median follow-up was 13.1 m (range, 0.4-67.8 m) in the HID group and 17.2 m (range, 2.1–68.8 m) in the MSD group(P=0.350). No difference was observed in the cumulative incidence of relapse, PFS and OS according to donor type. Leukemia relapse occurred in 7 and 9 patients, respectively, in HID and MSD group (P = 0.559). The 2-year cumulative incidence of relapse (29.5 ± 10.3% and 20.7 ± 6.1%, P = 0.458), 2-year PFS (56.8±9.7% and 64.6±7.4%, P=0.312) and 2-year OS (58.5±9.7% and 67.9±6.8%, P=0.373) were similar in the HID and MSD groups (Figure 3B, Figure 4). Disease status at transplants was significantly associated with higher risk of relapse (HR 6.746 CI 2.340-19.446 P<0.001) in multivariate analysis (*Table 3*). Patient's age (older than 60), disease status at transplants and sex mismatch were independent risk factors for OS (HR 2.438 CI 1.028-5.782 P=0.043, HR 3.474 CI 1.532-7.878 P=0.003 and HR 3.468 CI 1.643-7.317 P=0.001) and PFS (HR 2.398 CI 1.013-5.675 P=0.047, HR 3.759 CI 1.658-8.520 P=0.002 and HR 3.541 CI 1.642-7.256 P=0.001).

Discussion

Here, we report the outcomes of HID versus MSD allo-HSCT for patients with AML/MDS aged ≥50 years. The results showed that the two cohorts had comparable outcomes including TRM, GVHD, relapse and survival.

Traditionally, allo-HSCT in the elderly has a higher TRM because of the patient's frequent comorbidities and poor performance status. Reports from main transplant centers for older patients have shown 2-year TRM rates ranging from 7% to 35%(2, 7, 17-19). Some studied reported that myeloablative conditioning regimen (MAC) was associated with higher TRM rates compared to those who underwent

nonmyeloablative conditioning (NMAC) or reduced-intensity (RIC) conditioning regimen(20-23). In the present study, the 2-year cumulative incidences of TRM in the HID and MSD groups ranging from 15% to 17.3%. The report from Seattle of 1055 patients undergoing allo-HSCT showed that the 2-year TRM was 14%, 21%, and 41% for the patients with HCT-CI scores 0, 1 to 2 and 3 or more, respectively(24). A reasonable interpretation of the relatively lower TRM is that our patients have relatively lower HCT-CI. In this report, only 18.4% of the patients in HID group and 16.3% of the patients in MSD group has HCT-CI scores ≥ 3 . Besides, 11 patients (28.9%) in HID group and 19 patients (34.5%) in MSD group received BuF MAC. This may also be one of the reasons for the lower TRM. Other researchers and we have shown that patients received BuF MAC has a lower TRM incidence than that of received BuCy(25, 26). Whether HID transplants have a higher TRM than MSD is currently under discussion. A growing number of studies show that there is no difference between HID and MSD in TRM, including the elderly(17-19, 27, 28). Similar results were obtained in this study.

Relapse is a major cause of failure in patients undergoing allo-HSCT. Many factors influence relapse, such as donor resources, disease status at transplants, patient's age, conditioning and so on(29-31). For donor resources, some studies showed that HID had stronger GVL than MSD transplantation, making relapse lower(14, 32, 33). Other studies suggested that there was no difference in the relapse rate between two donor resources(13, 17, 18, 34, 35). In the present study, there was no difference in relapse between two groups. In multivariate analysis, we found disease status at transplants were independent risk factors for relapse, similar to other reports(36, 37).

GVHD is the most common transplant-related complication that affects the outcomes of transplants(38, 39). Traditionally, HID was associated with higher incidence of GVHD compared with MSD transplantation. Over the last decade, great improvements have been made in prophylaxis for GVHD in HID transplantation, especially the use of T-cell depletion in vivo by means of Cy or ATG(17, 32, 40). A growing number of evidences showed that the incidences of GVHD in HID were not different from that in MSD, especially cGVHD(14, 17, 27, 40-42). In the ATG protocol, our previous results showed that the incidences of grade II-IV aGVHD was higher for HID than MSD, but the incidences of severe aGVHD and cGVHD were comparable between two groups(14, 32, 42). In this study, HID was associated with a trend of higher incidences of grade II-IV aGVHD than MSD. In multivariate analysis, we found that sex mismatched donor (female donor/male recipient) was significantly associated with higher risk of aGVHD and cGVHD. Several other studies have also reported the same results(43-47).

As we know, ATG as GVHD prophylaxis was associated with higher incidences of infections, especially fatal viral infections(48-50). In the present study, although HID was associated with much higher incidences of CMV-anemia than MSD, the number of deaths caused by viral diseases and other infectious diseases did not differ between two groups. A possible explanation for these results might be attributed to the extensive experience at the study centers in effectively managing infectious diseases, resulting in many patients with CMV or other infections avoiding TRM.

The limitations of this study are the relatively small number of patients and the nature of this retrospective single-center study. We were not able to perform subgroup analyses that would have been informative in some specific setting such as advanced cytogenetics and/or older age. Sample size limitations of the oldest age group may mask smaller differences in outcomes. Selection bias may also have influenced inferences from the data. It is possible that the older patients included in these transplants were a highly selected group with a lower score of HCT-CI.

Conclusion

The present data showed similar outcomes in patients aged 50 years and older underwent HID compared to MSD at our institution. We conclude that HID transplant is feasible and safe for elderly AML/MDS patients. The lack of an HLA-identical donor in elderly patients with AML/MDS should not preclude allo-SCT.

Abbreviations

Allo-HSCT: allogeneic hematopoietic stem cell transplantation

AML: acute myeloid leukemia

ATG: anti-thymocyte globulin

BM: bone marrow

Bu: busulfan

CI: confidence intervals

CMV: cytomegalovirus

CsA: ciclosporin A

Cy: cyclophosphamide

CR: complete remission

EBV: Epstein-Barr Virus

GVHD: graft-versus-host disease

GVL: graft-versus leukemia

HCT-CI: hematopoietic cell transplantation comorbidity index

HID: haploidentical related donor

HLA: human leukocyte antigen

HR: hazard ratio

MAC: myeloablative conditioning

MDS: myelodysplastic syndrome

MMF: mycophenolate

MSD: matched sibling donor

MTX: methotrexate

NMAC: nonmyeloablative conditioning

OS: overall survival

PBSC: peripheral blood stem cell

PFS: progression-free survival

RIC: reduced-intensity

TBI: total body irradiation

TRM: transplant-related mortality

Declarations

Ethics approval and consent to participate: The study's protocol was approved by Southern Medical University Nanfang Hospital's Research Ethics Committee, and all the study's procedures were undertaken in accordance with the principles of the 1983 revision of the Declaration of Helsinki.

Consent for publication: Not applicable.

Availability of data and material: The datasets are available from the corresponding authors on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Qifa Liu generated the study idea. Fen Huang, Zhiping Fan, Na Xu, Li Xuan, Hui Liu, Pengcheng Shi, Ling Jiang, Yu Zhang and Jing Sun collected data, Jiafu Huang carried out statistical analysis and drafted the manuscript. Qifa Liu revised the manuscript. All authors read and approved the manuscript.

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Tables

Table 1. Patient clinical and Transplants Characteristics.

Characteristics	HID group(N=38)	MSD group(N=55)	P value
Age, median (range)	58(50.4-69)	57.5(50.5-68)	0.762
Sex			0.823
Male	26(68.4%)	39(70.1%)	
Female	12(31.6%)	16(29.1%)	
Follow-up in months, median (range)	13.1(0.4-67.8)	17.2(2.1-68.8)	0.350
Disease, N (%)			0.264
AML	34(89.5%)	44(80.0%)	
MDS	4(10.5%)	11(20.0%)	
Stem cell source N (%)			<0.0001
BM+PBSC	38(100%)		
PBSC		55(100%)	
Disease status at SCT, N (%)			0.167
CR	30(78.9%)	35(63.6%)	
No CR	8(21.1%)	20(36.4%)	
Donor age, median (range)	26(14-48)	49(39-62)	<0.0001
Sex mismatch, N (%)			0.167
Female donor/Male recipient	8(21.1%)	20(36.4%)	
Others(M/M,F/F,M/F)	30(78.9%)	35(63.6%)	
Relationship between donor and recipient, N (%)			<0.0001
sibling	10(26.3%)	55 (100%)	
child	28(73.4%)	0	
HCT-CI score			
0-2	31(81.6%)	46(83.7%)	0.788
≥ 3	7(18.4%)	9(16.3%)	
Mononucleated cell count (range, 108/kg)	9.9(3.5-12.5)	10.0(6.05-38)	0.432

HID, haploidentical related donor;MSD, matched sibling donor; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; BM, bone marrow; PBSC, peripheral blood stem cell; CR, complete remission; HCT-CI, hematopoietic cell transplantation comorbidity index.

Table 2. Characteristics of infectious complications post-SCT

	HID group(N=38)	MSD group(N=55)	P
Sepsis	7(18.42%)	7(12.73%)	0.558
CMV DNAemia	23(60.53%)	13(23.64%)	0.001
CMV disease	1(2.63%)	1(1.82%)	0.999
EBV DNAemia	2(5.26%)	4(7.27%)	0.999
Invasive fungal infection	12(31.58%)	19(34.55%)	0.826
Urinary tract infection	3(7.89%)	1(1.82%)	0.301

HID, haploidentical related donor; MSD, matched sibling donor; CMV, cytomegalovirus; EBV, epstein-barr virus.

Table 3. Multivariate analysis of outcomes.

Outcome/variable	HR(95% CI)	P
OS		
Patients age		
≥60	2.438(1.028-5.782)	0.043
<60	1	
Disease status at SCT		
No CR	3.474(1.532-7.878)	0.003
CR	1	
Sex mismatch		
Female donor/male recipient	3.468(1.643-7.317)	0.001
Others(M/M,F/F,M/F)	1	
PFS		
Patients age		
≥60	2.398(1.013-5.675)	0.047
<60	1	
Disease status at SCT		
No CR	3.759(1.658-8.520)	0.002
CR	1	
Sex mismatch		
Female donor/male recipient	3.451(1.642-7.256)	0.001
Others(M/M,F/F,M/F)	1	
TRM		
Patients age		
≥60	3.718(1.242-11.133)	0.019
<60	1	
Disease status at SCT		
No CR	1.567(0.335-7.336)	0.568
CR	1	
Sex mismatch		
Female donor/male recipient	4.931(1.713-14.190)	0.003
Others(M/M,F/F,M/F)	1	
Relapse		
Patients age		
≥60	1.207(0.268-5.445)	0.807
<60	1	
Disease status at SCT		
No CR	6.746(2.340-19.446)	<0.001
CR	1	
Sex mismatch		
Female donor/male recipient	2.324(0.783-6.893)	0.129

Others(M/M,F/F,M/F)	1	
II-IV°aGVHD		
Patients age		
≥60	1.231(0.419-3.622)	0.705
<60	1	
Sex mismatch		
Female donor/male recipient	2.424(1.067-5.506)	0.034
Others(M/M,F/F,M/F)	1	
cGVHD		
Patients age		
≥60	1.193(0.408-3.489)	0.747
<60	1	
Sex mismatch		
Female donor/male recipient	2.264(1.024-5.004)	0.044
Others(M/M,F/F,M/F)	1	

OS, overall survival; PFS, progression free survival; TRM, transplant related mortality; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; CR, complete remission.

Figures

Fig 1

Figure 1

(A) Cumulative incidence of II-IV°aGVHD after HID or MSD transplants ($P = 0.189$); (B) cumulative incidence of III-IV°aGVHD ($P = 0.700$).

Fig 2

Figure 2

(A) cumulative incidence of limited cGVHD($P=0.890$) ;(B) cumulative incidence of extensive cGVHD($P=0.424$).

Fig 3

Figure 3

(A) cumulative incidence of TRM ($P = 0.717$); (B) cumulative incidence of relapse ($P = 0.458$).

Fig 4

Figure 4

(A) probability of survival (P=0.373); (B) probability of PFS (P=0.312).