Allogeneic hematopoietic stem cell transplantation from non-sibling 10/10 HLA-matched related donors: a single-center experience

Hematopoietic stem cell transplantation (HSCT) from an allogeneic donor (allo-HSCT) is a potentially curative treatment for hematologic malignancies and nonmalignant disorders. Although human leukocyte antigen (HLA) matching between donors and recipients is critical for transplant outcomes,[1] with the development of novel methods to overcome the alloreactivity caused by HLA disparity and improvements in the management of transplant-related complications, the use of HLA-haploidentical donors as an alternative source of stem cells has increased continuously over the past decade and grafts from such sources may have a superior graft-*versus*-leukemia effect compared to those from HLA-matched siblings.[2,3] Studies have suggested that various donor-related factors, such as age, sex, ABO compatibility, natural killer cell alloreactivity, donor-recipient cytomegalovirus serostatus and donor-specific anti-HLA antibodies are correlated with recipients' survival after haploidentical allogeneic HSCT (haplo-HSCT).[4] However, the degree of HLA mismatch between donors and recipients may not influence transplant outcomes, especially among patients being treated within the Beijing protocol.[5] Given the extreme polymorphism of HLA genes, without consanguineous marriage the probability of finding a non-sibling 10/10 HLA-matched related donor (NSMRD) is quite low. Since recipients and donors have one identical haplotype and one matched haplotype, the risk of graft-*versus*-host disease (GvHD), relapse and leukemia-free survival after transplantation from these unique donors may have some particularities that cannot simply be extrapolated from ordinary HLA-haploidentical donors, HLA-identical siblings or 10/10 matched unrelated donors. In this study, we describe our experience with allo-HSCT in 23 patients with hematologic malignancies transplanted from NSMRD and compare the outcomes to those of patients who underwent conventional haplo-HSCT. The relatively higher relapse rate and lower acute GvHD incidence show that NSMRD are less immunogenic than conventional haploidentical donors and that individualized treatment with adjustment of the dosage of antithymocyte globulin (ATG) is reasonable for recipients of grafts from such donors.

From December 2012 to December 2019, 2,726 HSCT from family members (HLA-matched sibling donors and HLA-haploidentical related donors) were performed in our hospital, and only 23 cases (15 males, 8 females) (0.8%) were transplanted from NSMRD. All patients received the same modified busulfan/cyclophosphamide/ATG-based myeloablative conditioning regimen recommended by Chinese guidelines, except the total dose of ATG was 10.0 mg/kg in patients undergoing conventional haplo-HSCT,[6] but it was reduced in NSMRD-HSCT patients at the discretion of each physician. Of these 23 patients transplanted from NSMRD, 13 were treated with ATG at doses ≤6.0 mg/kg, and ten were treated with ATG at doses >6.0 mg/kg. The median ATG dose was 5.0 mg/kg and the interquartile range was 5.0 to 8.4 mg/kg. GvHD prophylaxis consisted of continuous infusion of cyclosporine at 3.0 mg/kg/day starting on day -10 and a short course of methotrexate and mycophenolate mofetil at a dose of 1.0 g/day from days -10 to +30. The median follow-up time of living patients was 19 months (range, 2 to 93 months). The patients' characteristics are shown in Table 1. The study was approved by the Institutional Review Board of our hospital.

All patients achieved engraftment with full donor chimerism at day 30. The median time to neutrophil and platelet engraftment was 12 days (range, 11 to 12) and 12 days (range, 12 to 15), respectively. Eight patients developed acute GvHD, which reached grade I in one patient, grade II in six patients and grade III in one patient. The cumulative incidence of grade II-IV acute GvHD was 38.8% (95% confidence interval [95% CI]: 20.4% to 61.2%) for the whole cohort. This was the same in patients who were treated with ATG at doses ≤6.0 mg/kg as in those who were treated with ATG at doses >6.0 mg/kg. The only patient who experienced grade III acute GvHD was in the ATG high-dose group. In patients who survived and were in remission beyond day 100, chronic

Table 1. Characteristics of the study participants at enrollment (total patients N 22).

Variables	
Age (years), median (IQR)	37 (27, 51)
Gender, n (%)	
Female	8 (35)
Male	15 (65)
Diagnosis, n (%)	
Acute lymphocytic leukemia	7 (30)
Acute myeloid leukemia	9 (39)
Myelodysplastic syndrome	7 (31)
CR/CRi at transplant, n (%)	
Yes	18 (78)
No	5 (22)
Donor-recipient relationship, n (%)	
Daughter	3 (13)
Son	8 (35)
Mother	4 (17)
Father	8 (35)
Donor-recipient ABO group match, n (%)	
Matched	14 (61)
Major mismatched	5 (21)
Minor mismatched	4 (18)
Stem cell source, n (%)	
Bone marrow	1 (4)
Bone marrow + peripheral blood	14 (61)
Peripheral blood	8 (35)
Mononuclear cells, mean±SD	10.96 ± 4.5
CD34, mean±SD	3.56 ± 1.48
Antithymocyte globulin dose, n (%)	
≤6.0 mg/kg	13 (57)
>6.0 mg/kg	10 (43)
Time to granulocyte recovery (days), median (IQR)	12 (11, 12)
Time to platelet recovery (days), median (IQR)	12 (12, 15)
Acute GvHD grade, n (%)	
Grade 0	15 (65)
Grade 1	1 (4)
Grade 2	6 (26)
Grade 3-4	1 (4)

IQR: interquartile range; CR: complete remission; Cri: CR with incomplete count recovery; SD: standard deviation; GvHD: graft-*versus*-host disease.

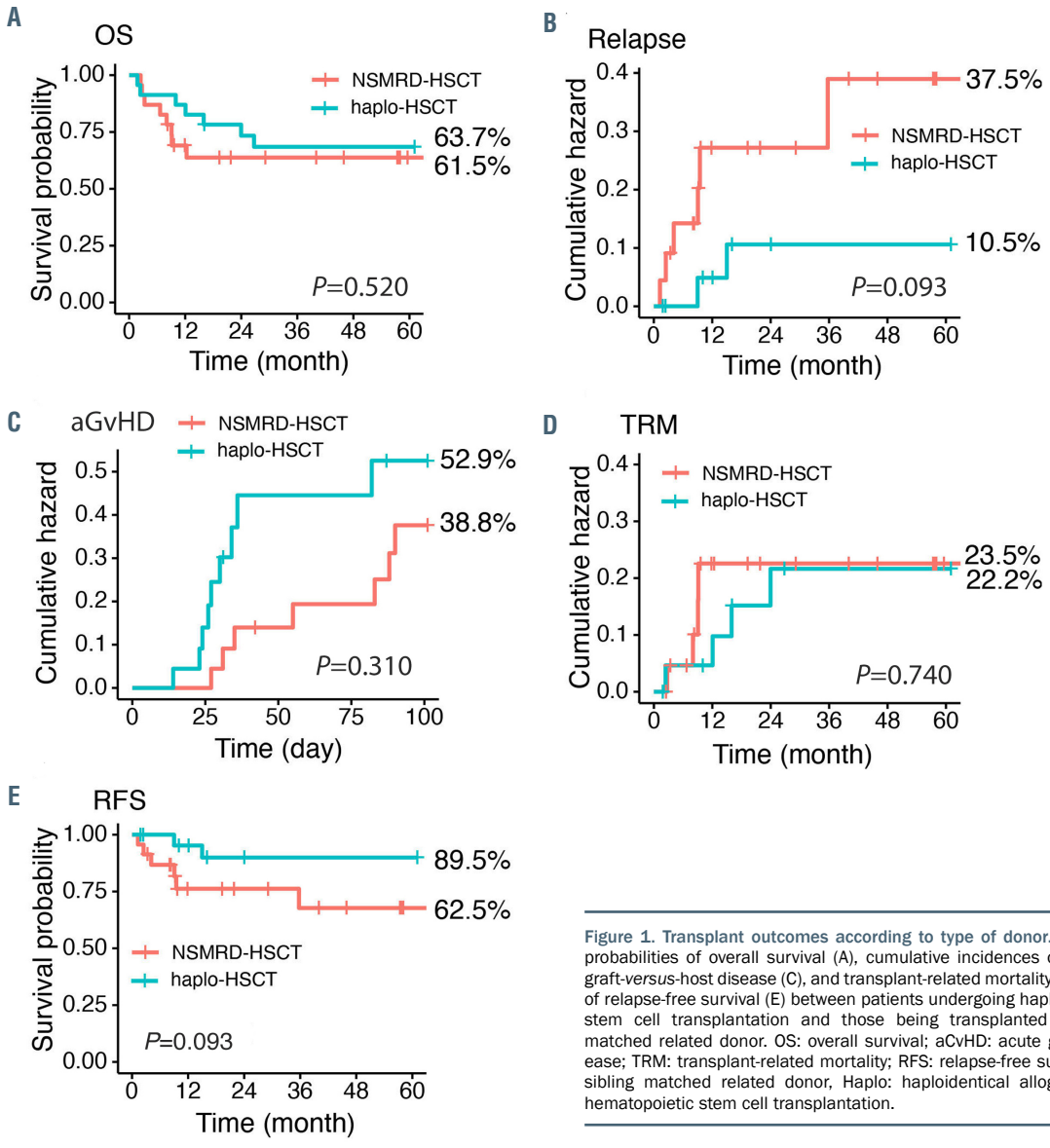

Figure 1. Transplant outcomes according to type of donor. (A-E) Differences in probabilities of overall survival (A), cumulative incidences of relapse (B), acute graft-*versus*-host disease (C), and transplant-related mortality (D) and probabilities of relapse-free survival (E) between patients undergoing haploidentical allogeneic stem cell transplantation and those being transplanted from a non-sibling matched related donor. OS: overall survival; aCvHD: acute graft-*versus*-host disease; TRM: transplant-related mortality; RFS: relapse-free survival; NSMRD: non-sibling matched related donor, Haplo: haploidentical allogeneic donor; HSCT: hematopoietic stem cell transplantation.

GvHD occurred in five out of the 13 patients in the ATG low-dose group and five out of the ten patients in the ATG high-dose group. The cumulative incidence of chronic GvHD was 43.4% at 2 years (95% CI: 23.9% to 65.1%). Three patients died of transplant-related causes, which included infection (n=1) and extensive chronic GvHD (n=2). Six patients had relapsed at a median time of 5 months (range, 2 to 9) after HSCT and ultimately died. The estimated 2-year overall survival and relapse-free survival for the whole cohort were 61.5% (95% CI: 44.3% to 86.2%) and 62.5% (95% CI: 43.4% to 78.2%), respectively. There was no significant difference in overall survival (P=0.68) and relapse-free survival (P=0.53) between the two groups treated with different doses of ATG.

To further compare outcomes by donor type, we performed a propensity-matched analysis in which each patient who underwent NSMRD-HSCT was matched 1:1 with a control patient who received a contemporaneous transplant from a mismatched haplo-donor (Table 2). Age, gender, diagnosis, Disease Risk Index Group,[7] donor and recipient blood type, and relationship were selected as factors for propensity-matched analysis. All selected patients were negative for donor-specific anti-HLA antibodies. The results for patients who underwent haplo-HSCT from mismatched donors, the overall survival (63.7% *vs.* 61.5%, P=0.520), relapse-free surival (89.5% *vs.* 62.5%, P=0.093) and transplant-related mortality (22.2% *vs.* 23.5%, P=0.740) did not show any statistically significant differences from those for patients with NSMRD-HSCT (Figure 1A, D, E). However, patients who underwent NSMRD-HSCT showed trends to a higher relapse rate (37.5% *vs.* 10.5%, P=0.093) (Figure 1B) and lower cumulative incidence of grade II-IV acute GvHD (38.8% *vs.* 52.9%, P=0.310) than patients who accepted haplo-HSCT with mismatched donors (Figure 1C). So, it seems that outcomes after NSMRD-HSCT were closer to those of sibling transplantation (*Online Supplementary Table S1, Online Supplementary Figure S1*).

The probability of finding a fully matched non-sibling related donor through an extended family search is high in regions in which consanguineous marriage is frequently practiced. In a retrospective analysis from Iran by Hamidieh and colleagues, outcomes of 109 patients transplanted from fully matched other-relative donors were reported, and were comparable to those of transplantation from matched sibling donors.[8] As consanguineous marriage is prohibited in China, the chance of

Table 2. Patients' baseline and transplant characteristics before and after matching on the propensity score.

Variables	Before matching			After matching		
	Haplo (n=782)	NSMRD (n=23)	*P*	Haplo (n=23)	NSMRD (n=23)	*P*
Age (years), median (IQR)	38.98 (27.48, 47.46)	37.45 (27.02, 50.65)	0.810	33.44 (27.26, 53.39)	37.45 (27.02, 50.65)	0.693
Gender, n (%)			0.491			0.749
Female	346 (44)	8 (35)		6 (26)	8 (35)	
Male	436 (56)	15 (65)		17 (74)	15 (65)	
Diagnosis, n (%)			0.013			0.212
Acute lymphocytic leukemia	228 (29)	7 (30)		3 (13)	7 (30)	
Acute myeloid leukemia	393 (50)	9 (39)		11 (48)	9 (39)	
Mixed phenotype acute leukemia	24 (3)	0 (0)		0 (0)	0 (0)	
Myelodysplastic syndrome	137 (18)	7 (30)		9 (39)	7 (31)	
Disease risk index*, n (%)			0.819			0.890
Low risk	161 (21)	4 (17)		3 (13)	4 (17)	
Intermediate risk	424 (56)	14 (61)		14 (61)	14 (61)	
High and very high risk	197 (25)	5 (22)		6 (26)	5 (22)	
Donor-recipient relationship, n (%)			0.296			0.914
Daughter	197 (25)	3 (13)		3 (13)	3 (13)	
Son	280 (36)	8 (35)		8 (35)	8 (35)	
Father	240 (31)	8 (35)		10 (43)	8 (35)	
Mother	65 (8)	4 (17)		2 (9)	4 (17)	
Donor-recipient ABO group match, n (%)			0.799			0.085
Matched	434 (55)	14 (61)		8 (35)	14 (61)	
Major mismatched	142 (18)	5 (22)		8 (35)	5 (22)	
Minor mismatched	161 (21)	4 (17)		3 (13)	4 (17)	
Major+minor mismatched	45 (6)	0 (0)		4 (17)	0 (0)	
Donor-recipient HLA disparities, n (%)			–			–
5/10	214 (27)	–		15 (65)	–	
6/10	80 (10)	–		5 (11)	–	
7/10	218 (28)	–		2 (8)	–	
8/10	270 (35)	–		1 (4)	–	
9/10	270 (35)	–		0 (0)	–	
10/10	0 (0)	23 (100)		0 (0)	23 (100)	

Haplo: haploidentical allogeneic hematopoietic stem cell donor; NSMRD: non-sibling 10/10 HLA-matched related donor; IQR: interquartile range; HLA: human leukocyte antigen. *Risk was defined according to the refined Disease Risk Index of the Center for International Blood and Marrow Transplant Research.[7]

finding such donors is very low, and we believe that the scenario is totally different in our study. Although the donor and recipient are 10/10 HLA-matched, theoretically, they only have one identical haplotype, while the other should be defined as a matched haplotype. On the haplotype-matched chromosome, there may be donor-recipient mismatching at additional HLA alleles (such as HLA-DPB1) and non-HLA-linked immune-related genes with polymorphisms (such as TNFA and MICA). These differences may affect the outcome of transplantation.[9,10] However, whether further matching at the haplotype level has a significant impact on clinical outcomes is controversial.[11]

The relapse risk and GvHD incidence in the control group were 10.5% and 52.9%, respectively, which are similar to those in a previous report.[5] Although the dose of ATG in the NSMRD cohort was relatively low, there was a trend toward a higher relapse rate and lower GvHD rate in these patients than in patients in the control group, but this trend did not reach statistical significance due to the sample size. Our results suggest that these unique donors are less immunogenic and more similar to HLA-matched sibling donors. The outcome of allo-HSCT from these donors might be different. However, a previous study from the Beijing group indicated that with the advent of the ATG protocol, the degree of HLA disparity on the unshared HLA haplotype was not significantly correlated with transplant outcomes, but HLA typing was only performed at the HLA-A, HLA-B, and HLA-DR loci, and only three cases (0.2%) with 6/6 HLA-matched related donors were involved in their study.[12]

ATG has been widely used for the prevention of GvHD in matched unrelated donor HSCT and haplo-HSCT. However, at high doses, ATG may lead to an increase in fatal infections, relapse, or delayed engraftment due to delayed immune reconstitution of T cells.[13] Therefore, the optimal ATG dose remains unclear and should be determined on the basis of a balance of advantages and disadvantages of ATG. The Chinese Society of Hematology recommends that the dose of ATG should be 10.0 mg/kg in haplo-HSCT.[6] Given the trend to a lower rate of GvHD observed in NSMRD-HSCT, the lack of significant difference between the groups treated with ≤6.0 or >6.0 mg/kg ATG, and the absence of fatal cases of acute GvHD in the low-dose group, it is reasonable to speculate that the immunosuppression should not be too

deep in this situation. Meanwhile, although a high dose of ATG may not be required, a reduced dose of ATG may still be necessary. In the research by Hamidieh *et al*. mentioned above, although both haplotypes were identical in the recipient and donor, more than 85% of patients had received ATG in the conditioning regimen, but the authors did not describe the dose.[8]

Although nonmalignant hematologic diseases, such as aplastic anemia and paroxysmal nocturnal hemoglobinuria, were not included in this study, according to the immunological specificities of NSMRD, such donors should be the first choice for patients with these diseases. However, in the clinical setting of hematologic malignancies, especially in patients with a high risk of relapse, the choice of these donors must be made with caution. Similarly to what was observed in our study, recent studies have shown that, as a consequence of the potential strong graft-*versus*-leukemia effects, haplo-HSCT, compared to HLA-mathced HSCT, can provide equivalent or even better long-term survival in high-risk leukemia patients because of a lower relapse rate.[14,15]

The limitations of this study include its retrospective nature and the small sample size. Whether the results could be extrapolated to haplo-HSCT using a post-transplant cyclophosphamide-based regimen is unclear. However, we believe that our data are a useful supplement to the donor selection recommendations for haplo-HSCT and that individualized treatment with adjustment of the dosage of ATG is reasonable for patients undergoing NSMRD-HSCT.

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