ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

e-ISSN 2329-0358
© Ann Transplant, 2019; 24: 350-358
DOI: 10.12659/AOT.916004

Received: 2019.03.03
Accepted: 2019.03.25
Published: 2019.06.14

ABO Blood Type Incompatibility Is Not a Risk Factor of Outcomes for Acute Myeloid Leukemia (AML) Patients After Unmanipulated Haplo-Identical Peripheral Blood Hematopoietic Stem Cell Transplantation

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Source of support: This work was supported by the Beijing Natural Science Foundation (No. 7162175)

Background: Haplo-identical hematopoietic stem cell transplantation (HSCT) has provided potential donors for patients lacking available HLA-matched donors. ABO blood type compatibility has been reported to be associated with HSCT outcomes. However, few studies have investigated the role of ABO compatibility in haplo-identical HSCT of AML patients.

Material/Methods: We retrospectively analyzed 42 adult acute myeloid leukemia (AML) patients who received unmanipulated haplo-identical peripheral blood HSCT at the Chinese PLA General Hospital between Jan 2013 and Dec 2017. We analyzed the role of ABO compatibility in engraftment, transfusion requirements, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) viremia, acute graft-versus-host disease (GVHD), overall survival (OS), transplantation-related mortality (TRM), relapse, chronic GVHD, and post-transplant lymphoproliferative disorder (PTLD).

Results: There were no significant differences between the ABO-matched group and the ABO-mismatched group in terms of engraftment, transfusion requirements, CMV and EBV viremia, OS, TRM, relapse, PTLD, and chronic GVHD. Univariate analysis revealed ABO incompatibility is not an independent risk factor of engraftment, transfusion requirements, CMV and EBV viremia, OS, TRM, relapse, PTLD, and chronic GVHD. We found a significantly higher cumulative incidence of aGVHD in the matched group compared with the mismatched group (80.95% *vs.* 42.86%, p=0.020). In multivariate analysis, ABO mismatch was associated with decreased risk of acute GVHD within 100 days after transplant (hazard ratio 0.492, 95% confidence interval 0.2123–1.14). However, the difference was not statistically significant (p=0.099).

Conclusions: This study demonstrated ABO incompatibility is not an independent risk factor of outcomes for AML patients who received unmanipulated haplo-identical peripheral blood HSCT. ABO compatibility might have limited value in haplo-identical donor selection.

MeSH Keywords: **Blood Group Incompatibility • Haploidy • Hematopoietic Stem Cell Transplantation • Leukemia, Myeloid, Acute**

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/916004

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Background

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) can be a lifesaving method for patients with hematological malignances. However, most of these patients lack HLA-matched donors [1,2]. HLA haplo-identical HSCT is gaining increasing appreciation worldwide and is providing potential donors for almost every HSCT recipient candidate [3,4]. Since a recipient candidate is most likely to have more than 1 haplo-identical potential donor, choosing the optimal donor is of great importance.

Factors such as donor-specific antibodies (DSA), donor age, donor sex, ABO compatibility, killer-cell immunoglobulin-like receptors (KIR)-ligand mismatch, non-inherited maternal antigen (NIMA) mismatch, type of donor, and cytomegalovirus (CMV) status should be considered when selecting the best donor in unmanipulated haplo-identical HSCT [5]. However, the role of ABO compatibility between patient and donor in HSCT is still unclear. Several studies [6–14] indicated ABO incompatibility as a risk factor for poor outcome. However, others [15–17] demonstrated a protective role or limited importance in HSCT. These reports contained a wide range of primary disease, conditioning regimens, donor sources, and stem cell sources. However, data on acute myeloid leukemia (AML) patients undergoing haplo-identical HSCT are limited. In this study, we retrospectively investigated the role of ABO compatibility in haplo-identical HSCT of AML patients.

Material and Methods

Study population

This was a retrospective, single-center analysis of 42 AML patients who received unmanipulated haplo-identical peripheral blood HSCT at the Chinese PLA General Hospital between Jan 2013 and Dec 2017. Inclusion criteria were: primary AML, patient and donor were more than 18 years old, 1st transplantation, granulocyte colony stimulating factor (G-CSF) mobilized unmanipulated peripheral blood HSCT, HLA 5/10 identical, and modified Bu/Cy+ATG conditioning regimen. All patients were followed up until Dec 31, 2018 or the day of death. This study was approved by the Ethics Committee of the Chinese PLA General Hospital. Identity information of patients and donors were concealed before analysis.

HSCT procedure

The haplo-identical HSCT procedure used in our clinical center had been reported previously [18,19]. In brief, donors were mobilized with G-CSF for 5 days before stem cells were harvested and transplanted; the modified Bu/Cy+ATG conditioning regimen consisted of busulfan, carmustine, cytarabine, cyclophosphamide, and ATG (rabbit anti-human thymocyte immunoglobulin); and all patients were given cyclosporine A, mycophenolate mofetil, and methotrexate triple graft-versus-host disease (GVHD) prophylaxis.

Definitions

Neutrophil and PLT engraftment were defined as sustained achievement of an absolute neutrophil count over 0.5×10^9/L and platelet count over 20×10^9/L, respectively. CMV and Epstein-Barr virus (EBV) were detected by quantitative-PCR, and CMV and EBV viremia were defined as at least 2 consecutive virus DNAs positive in the blood. RBC and PLT units were the amount of red blood cells and platelets transfused in transplantation wards.

Statistical analysis

Overall survival (OS) was calculated by Kaplan-Meier method and the log-rank test was used to compare survival curves. Quantitative data were compared by *t* test or Mann-Whitney U test. Proportion was compared by Fisher's exact probability method. Cumulative incidence curves of relapse, acute GVHD, chronic GVHD, and post-transplant lymphoproliferative disorder (PTLD) were compared by competing risk model. Univariate analysis and multivariate analysis were conducted by Fisher's exact probability method, Cox regression, and competing risk regression. Parameters were included into multivariate analysis when p value <0.1 in univariate analysis. All tests were 2-sided and the type I error rate was 0.05. Statistical analyses were performed with SPSS and R studio software.

Results

Patient characteristics

Overall, 42 patients were included in this retrospective study with a median follow-up period of 18.4 months (range 1.3–70.4 months). Patient characteristics are summarized in Table 1. The patients' ages ranged from 18 to 59 years old, with a median of 34 years old, and 28 (66.67%) of the patients were male. The AML FAB subtype included M0, M1, M2, M4, and M5, and 4 patients' FAB subtype were not available. There were 10 (23.81%) patients diagnosed as relapse/refractory AML before transplant; 4 (9.52%) patients were low risk at diagnosis, 23 (54.76%) were intermediate risk, 13 (30.95%) were high risk, and 2 patients' data were not available. There were 34 (80.95%) patients in first complete remission (CR1), 2 (4.76%) patients were in second complete remission (CR2), 2 (4.76%) patients were in third complete remission (CR3), and 4 (9.52%) patients were in active disease before transplant. Two (4.76%) patients

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Table 1. Patient characteristic before and after transplant.

Patient age median (range)	34	(18–59)
Male patient number (percent)	28	(66.67)
FAB subtype number (percent)		
M0	2	(4.76)
M1	2	(4.76)
M2	17	(40.48)
M4	6	(14.29)
M5	11	(26.19)
NA	4	(9.52)
Relapse/refractory number (percent)	10	(23.81)
Risk stratification number (percent)		
Low	4	(9.52)
Intermediate	23	(54.76)
High	13	(30.95)
NA	2	(4.76)
Disease status number (percent)		
CR1	34	(80.95)
CR2	2	(4.76)
CR3	2	(4.76)
Active	4	(9.52)
CNS leukemia number (percent)	2	(4.76)
Donor age median (range)	35.5	(18–66)
Male donor number (percent)	31	(73.81)
Donor type number (percent)		
Parent	17	(40.48)
Child	13	(30.95)
Sibling	11	(26.19)
Other	1	(2.38)
Female to male number (percent)	11	(26.19)
DLI number (percent)	11	(26.19)
MNC median (range)	9.758 (5.41–21.37) $\times 10^8$/kg	
CD34 median (range)	3.9 (1.15–10.5) $\times 10^6$/kg	
Neutrophil engraftment median day (range)	11	(9–20)
Platelet engraftment within 30 days number (percent)	37	(88.10)
CMV anemia number (percent)	38	(90.48)
EBV anemia number (percent)	24	(47.14)
RBC unit median(range)	6.5	(0–37.5)
PLT unit median (range)	6	(1–30)

NA – not available; CR – complete remission; CNS – central nervous system; DLI – donor lymphocyte infusion; MNC – mononuclear cell; CD34 – CD34 positive cell; CMV – cytomegalovirus; EBV – Epstein-Barr virus; RBC – red blood cell; PLT – platelet.

had central nervous system (CNS) leukemia and all were controlled before transplant. The donors' ages ranged from 18 to 66 years old, with a median of 35.5 years. The majority of the donors were male (31, 73.81%). The donor type included parent (17, 40.48%), child (13, 30.95%), sibling (11, 26.19%), and other (1, 2.38%). Eleven (26.19%) of the transplants were female-to-male. Eleven (26.19%) patients received post-transplant prophylactic donor lymphocyte infusion (DLI). The amount of CD34 cells transplanted was 1.15~10.5×10^6/kg, with a median of 3.9×10^6/kg, and the number of mononuclear cells (MNC) was 5.41~21.37×10^8/kg, with a median of 9.758×10^8/kg.

All patients achieved hematopoietic chimerism within 30 days after transplant and all achieved neutrophil engraftment by post-transplant day 20 (median 11 days, range 9–20 days). However, only 37 (88.10%) of the patients achieved PLT (platelet) engraftment by day 30. Two patients failed to achieve PLT engraftment, 1 patient engrafted on day 35, 1 on day 65, and 1 engrafted after 100 days. Thirty-eight (90.48%) of the patients had CMV viremia and 24 (47.14%) had EBV viremia within 3 months after transplant.

The 5-year OS was 57.14% (24/42) (Figure 1A). Eighteen patients died, and the causes of mortality were GVHD, infection, CNS problems, lung bleeding, and leukemia relapse. The 5-year cumulative incidence of transplant-related mortality (TRM), relapse, and post-transplant lymphoproliferative disorder (PTLD) were 32.60% (Figure 1B), 15.04% (Figure 1C), and 7.14% (Figure 1D), respectively. The 4-year cumulative incidence of chronic graft-versus-host disease (cGVHD) was 58.44% (Figure 1E). We analyzed acute graft-versus-host disease (aGVHD) within 100 days after transplant. The cumulative incidence of aGVHD was 61.90% (Figure 1F). Since no grade III-IV aGVHDs within 100 days after transplant were observed in our study, we further analyzed grade II aGVHD. The cumulative incidence of grade II aGVHD was 19.31%.

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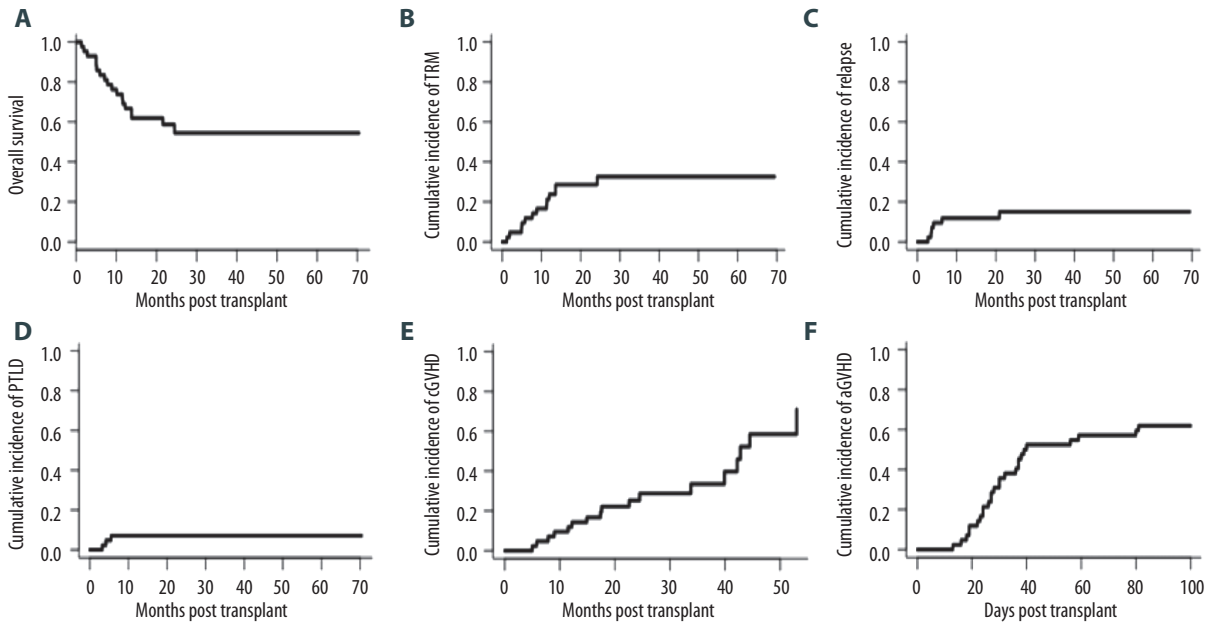

Figure 1. Outcomes of all patients. (**A**) Overall survival; (**B**) TRM (transplant-related mortality); (**C**) relapse; (**D**) PTLD (post-transplant lymphoproliferative disease); (**E**) cGVHD (chronic graft-versus-host disease); (**F**) aGVHD (acute graft-versus-host disease).

Table 2. Donors' and patients' ABO blood type in ABO-matched and mismatched group.

ABO match n=21	ABO mismatch n=21		
	Major n=12	Minor n=7	Bi-direction n=2
A to A n=7	A to O n=4	A to AB n=1	A to B n=2
B to B n=7	B to O n=1	B to AB n=1	
O to O n=7	AB to A n=4	O to A n=3	
	AB to B n=3	O to B n=2	

ABO incompatibility is not an independent risk factor of transplant outcomes

Patients were divided into ABO blood type matched and mismatched groups according to their blood type cross-matching (Table 2): 21 patients were in the ABO-matched group and the other 21 were in the mismatched group. The ABO mismatched group included major mismatch (n=12), minor mismatch (n=7), and bidirectional mismatch (n=2). The characteristics of the patients in the 2 groups are summarized in Table 3. The median follow-up time was 18 (range 1.3–70.4) months in the ABO-matched group and 18.8 (range 2.8–44.1) months in the ABO mismatched group. There were no significant differences in baseline characteristics between ABO-matched and mismatched patients except for patient age and donor type (Table 3). In the matched group, patients were younger compared with the mismatched group (matched 32 (18–48) *vs.* mismatched 40 (21–59), p=0.047). The donor type proportion was also significantly different between the 2 groups (p=0.018). Most donors were a sibling (42.9%) in the matched group and a child (47.6%) in the mismatched group.

We analyzed neutrophil engraftment, PLT engraftment, RBC unit, PLT unit, and CMV viremia and EBV viremia after transplant and found no significant differences between the matched and mismatched groups (Table 3). Univariate analysis showed ABO compatibility was not an independent risk factor of neutrophil engraftment, PLT engraftment, RBC unit, PLT unit, CMV viremia, and EBV viremia after transplant (Table 4).

We also found no statistically significant differences between the matched and mismatched groups regarding to OS, TRM, relapse, and PTLD (Figure 2A–2D). Neither of the groups reached median overall survival. The 3-year overall survival was 57.1% in the matched group and 50.8% in the mismatched group. The 3-year cumulative incidence of TRM was

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Table 3. Characteristics of patients before and after transplant in ABO-matched and mismatched groups.

	ABO match n=21	ABO mismatch n=21	p Value
Patient age median (range),year	32 (18–48)	40 (21–59)	0.047
Male patient number (percent)	16 (76.2)	12 (57.1)	0.326
FAB subtype number (percent)			0.582
M0	0 (0)	2 (9.5)	
M1	1 (4.8)	1 (4.8)	
M2	11 (52.4)	6 (28.6)	
M4	2 (9.5)	4 (19.0)	
M5	5 (23.8)	6 (28.6)	
NA	2 (9.5)	2 (9.5)	
Relapse/refractory number (percent)	4 (19.0%)	6 (28.6)	0.719
Risk stratification number (percent)			0.315
Low	4 (19.0)	0 (0.0)	
Intermediate	10 (47.6)	13 (61.9)	
High	6 (28.6)	7 (33.3)	
NA	1 (4.8)	1 (4.8)	
Disease status number (percent)			0.844
CR1	17 (80.95)	17 (80.95)	
CR2	1 (4.76)	1 (4.76)	
CR3	0 (0.0)	2 (9.52)	
Active	3 (14.29)	1 (4.76)	
CNS leukemia number (percent)	1 (4.8)	1 (4.8)	1
Donor age median (range)	36 (21–63)	35 (18–66)	0.531
Male donor number (percent)	14 (66.7)	17 (81%)	0.484
Donor type number (percent)			0.018
Parent	9 (42.9)	8 (38.1)	
Child	3 (14.3)	10 (47.6)	
Sibling	9 (42.9)	2 (9.5)	
Other	0 (0.0)	1 (2.4)	
Female to male number (percent)	7 (33.33)	2 (9.52)	0.130
DLI number (percent)	7 (33.3)	4 (19.0)	0.484
MNC median (range)	8.66×10^8/kg ($5.41–16.50\times10^8$/kg)	10.10×10^8/kg ($6.43–21.37\times10^8$/kg)	0.400
CD34 median (range)	4.4×10^6/kg ($2.16–10.50\times10^6$/kg)	3.599×10^6/kg ($1.15–7.98\times10^6$/kg)	0.305
Neutrophil engraftment median day (range)	12 (9–20)	11 (10–17)	0.183
Platelet engraftment within 30 days number (percent)	20 (95.24)	17 (80.95)	0.343
RBC unit median (range)	5.5 (0–37.5)	8 (0–20)	0.728
PLT unit median (range)	7 (1–15)	4 (1–30)	0.84
CMV anemia number (percent)	21 (100.00)	17 (80.95)	0.107
EBV anemia number (percent)	15 (71.43)	9 (42.86)	0.118

NA – not available; CR – complete remission; CNS – central nervous system; DLI – donor lymphocyte infusion; MNC – mononuclear cell; CD34 – CD34 positive cell; CMV – cytomegalovirus; EBV – Epstein-Barr virus; RBC – red blood cell; PLT – platelet.

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Table 4. Univariate analysis of clinical characteristics and outcomes in terms of ABO compatibility (match *vs.* mismatch).

Outcomes	p Value
OS	0.606
Relapse	0.4
TRM	0.68
grade II aGVHD	0.78
cGVHD	0.35
PTLD	0.55
Neutrophil engraft within 11 days	1.000
PLT engraft within 30 days	0.343
RBC ≤6.5 units	0.538
PLT ≤6 units	0.215

OS – overall survival; TRM – transplant-related mortality; aGVHD – acute graft-versus-host disease; cGVHD – chronic graft-versus-host disease; PTLD – post-transplant lyphoproliferative disease; PLT – platelet; RBC – red blood cell.

37.4% in the matched group and 28.6% in the mismatched group. We also found the 3-year cumulative incidence of relapse was 9.5% in the matched group and 20.6% in the mismatched group. Furthermore, we found the 3-year cumulative incidence of PTLD was 9.52% in the matched group and 4.76 in the mismatched group. Univariate analysis showed ABO compatibility was not an independent risk factor of OS, TRM, relapse, and PTLD (Table 4).

We then analyzed GVHD after transplant. The 4-year cumulative incidence of cGVHD was 59.4% in the matched group and 56.3% in the mismatched group. As shown in Figure 2E, there were no significant differences between the matched and mismatched groups in terms of cGVHD. We further analyzed grade II aGVHD and found no significant difference between the 2 groups (matched 22.93%, mismatched 17.46%, p=0.788). Univariate analysis also showed ABO compatibility was not an independent risk factor of cGVHD and grade II aGVHD (Table 4). However, we found a significantly higher cumulative incidence of aGVHD in the matched group compared with the mismatched group (80.95% *vs.* 42.86%, p=0.020, Figure 2F). We included ABO compatibility, patient age, donor age, and donor type into multivariate analysis according to the results of univariate analysis (Table 5). ABO incompatibility was associated with decreased risk of aGVHD within 100 days after transplant (HR0.492, 95%CI0.2123–1.14, Table 6), but the difference was not statistically significant (p=0.099, Table 6). These results indicated ABO compatibility was not an independent risk factor of aGVHD and cGVHD.

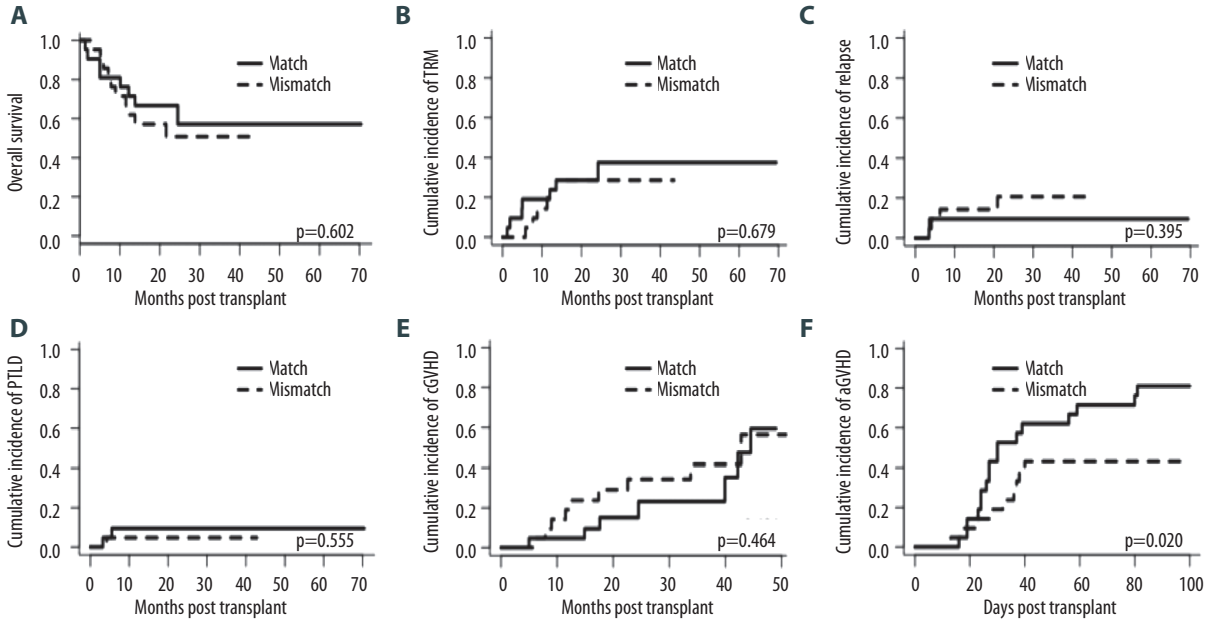

Figure 2. Outcomes of patients in ABO match and mismatch group. (**A**) Overall survival; (**B**) TRM (transplant-related mortality); (**C**) Relapse; (**D**) PTLD (post-transplant lymphoproliferative disease); (**E**) cGVHD (chronic graft-versus-host disease); (**F**) aGVHD (acute graft-versus-host disease).

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Table 5. Univariate analysis of aGVHD within 100 days after transplant.

Parameters	p Value
ABO compatibility	0.022
Patient age	0.022
Patient sex	0.97
FAB subtype	0.65
Relapse/refractory	0.63
Risk stratification	0.84
Disease status	0.6
Donor age	0.076
Donor gender	0.21
Donor type	0.0041
Female to male	0.62
MNC amount	0.97
CD34 amount	0.3

MNC – mononuclear cell; CD34 – CD34 positive cell.

Table 6. Multivariate analysis of aGVHD within 100 days after transplant.

Parameters	HR (95% CI)	p Value
ABO compatability	0.492 (0.2123–1.14)	0.099
Patient age	1.031 (0.9319–1.14)	0.550
Donor age	0.951 (0.8631–1.05)	0.310
Donor type	0.175 (0.0175–1.76)	0.140

HR – hazard ratio; CI – confidence interval.

Discussion

HLA-haplo-identical hematopoietic stem cell transplantation is an alternative transplant option for the majority of patients with hematological disease lacking matched donors. However, complications, including graft failure and GVHD, have limited its use [20]. Improvements of the HSCT procedure, including conditioning regimens, graft manipulation, and GVHD prevention, have reduced the risk of lethal graft failure and GVHD [21]. Haplo-identical HSCT is more viable and time-saving since each patient usually has more than 1 available donor who are ready and willing to donate enough stem cells. Thus, it is possible for a patient and doctor to choose the optimum donor. In addition to DSA, donor age, donor sex, KIR-ligand mismatch, NIMA mismatch, type of donor, and CMV status, ABO compatibility was also reported to be an important factor in selecting the best donor in haplo-HSCT[5]. Delayed red blood cell engraftment and GVHD can be complications of ABO-mismatch HSCT [22]. However, published studies have reported the controversial role of ABO compatibility in selecting HSCT donors. Moreover, few studies have focused on the role of ABO compatibility in haplo-identical donor selecting.

In this study, we demonstrated ABO incompatibility is not an independent risk factor of transplant outcomes after unmanipulated haplo-identical peripheral blood HSCT. Univariate analysis showed ABO compatibility is not an independent risk factor of neutrophil engraftment, PLT engraftment, RBC unit, PLT unit, CMV viremia, EBV viremia, OS, TRM, relapse, PTLD, and cGVHD after transplant (Table 4). We found a significantly higher cumulative incidence of aGVHD in the ABO-matched group compared with the mismatched group (80.95% *vs.* 42.86%, p=0.020, Figure 2F). However, multivariate analysis showed ABO incompatibility is not an independent risk factor of aGVHD (HR 0.492, 95%CI 0.2123–1.14, p=0.099, Table 6). Collectively, our results indicate ABO incompatibility, including major mismatch, minor mismatch, and bidirectional-mismatch, is not an independent risk factor of clinical outcome after unmanipulated haplo-identical peripheral blood HSCT.

Several published studies demonstrated that ABO incompatibility is a risk factor for delayed engraftment and poor outcome. Stussi et al. [11] found an RBC engraftment delay in a major ABO mismatched group compared with the matched group. They also found bidirectional and minor ABO mismatches are associated with poor survival and higher incidence of aGVHD, respectively. In pediatric SCT, Svennilson et al. [13] demonstrated ABO mismatch is a risk factor for acute GVHD (grade II–IV). Ramirez et al. [14] reported that ABO major mismatch was one of the variables associated with delayed platelet recovery. Vaezi et al. [10] found minor and bidirectional mismatched patients were transfused significantly more blood than were matched patients. For HSCT outcomes, Watz et al. [7] found that passenger lymphocyte syndrome (PLS) after minor ABO mismatch HSCT and the persistent or recurring recipient type ABO (PRABO) antibodies after major ABO mismatch HSCT are risk factors of poor survival and high incidence of TRM. Grube et al. [12] found minor ABO-mismatch is an independent risk factor for TRM. Hefazi et al. [6] also demonstrated that major and bidirectional ABO mismatch is associated with higher incidence of non-relapse mortality (NRM) and shorter disease-free survival (DFS) and OS. Logan et al. [8] also demonstrated that ABO major and minor mismatch are associated with poor transplant outcomes. Collectively, these studies indicate that an ABO-matched donor, if available, is the best choice for HSCT.

Several other studies also demonstrated ABO compatibility is of limited use in selecting HSCT donors. Brierley et al. [9] found transfusion requirements and transplant outcomes, including

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survival, NRM, relapse, and acute GVHD, are not affected by ABO mismatch. In the study conducted by Blin and colleagues [15], hematopoietic reconstitution and GVHD were not influenced by ABO mismatch, and they also found major ABO mismatch is associated with decreased relapse rate in acute leukemia patients. Kudek et al. [17] also found ABO compatibility does not affect engraftment, transfusion requirement, and transplant outcomes in patients after umbilical cord blood transplant.

The published reports mentioned above included a wide variety of diseases, conditioning regimens, donor types, and stem cell sources. However, data on AML patients undergoing haploidentical HSCT are limited. Chang et al. [23] retrospectively analyzed factors correlating with hematopoietic recovery in 133 pediatric patients (including AML patients) after unmanipulated HLA-mismatched/haplo-identical blood and marrow transplantation; their univariate analysis revealed ABO compatibility was not a risk factor of neutrophil engraftment and platelet engraftment. The study reported by Canaani et al. [16] was a retrospective, multicenter study containing 837 AML patients receiving HLA haplo-identical bone marrow or G-CSF mobilized peripheral blood stem cell transplantation. In patients transplanted with bone marrow, minor ABO mismatch was associated with higher incidence of grade II–IV aGVHD and major ABO mismatch was associated with poor survival. Moreover, they found ABO mismatch does not affect the clinical outcome of patients receiving haplo-identical peripheral blood HSCT.

In the present study, we retrospectively analyzed 42 adult AML patients who underwent unmanipulated haplo-identical peripheral blood HSCT. Our results, which agree with those of Canaani, indicated ABO blood type compatibility is not an independent risk factor of clinical outcome. We also demonstrated ABO mismatch does not affect engraftment, transfusion requirements, and viremia. However, we did not further investigate the role of ABO mismatching subgroups due to the limited number of patients.

Conclusions

This retrospective study, focusing on adult AML patients who received haplo-identical G-CSF mobilized unmanipulated peripheral blood HSCT, demonstrated ABO blood type incompatibility between patient and donor is not an independent risk factor of engraftment, transfusion requirements, viremia, and clinical outcomes.

Conflicts of interest

None.

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