IJHOSCR

Original Article

International Journal of Hematology-Oncology and Stem Cell Research

Selection of Suitable Alternative Donor in the Absence of Matched Sibling Donor: A Retrospective Single-Center Study to Compare between Haploidentical, 10/10 and 9/10 Unrelated Donor Transplantation

Maryam Barkhordar, Amir Kasaeian, Sahar Tavakoli, Mohammad Vaezi, Hossein Kamranzadeh Foumani, Tannaz Bahri, Davood Babakhani , Leila Mirzakhani, Ashraf Mousavi, Seied Asadollah Mousavi, Ardeshir Ghavamzadeh

Hematology, Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran

Corresponding Author: Seied Asadollah Mousavi, Hematology, Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran
Tel/Fax: +98 88004141
Email: bmtcontact633@gmail.com

Received: 10, Sep 2020
Accepted: 29, Nov, 2020

ABSTRACT

Background: Finding a suitable donor at the optimal time is one of the most challenging issues in many transplant centers. We evaluated the clinical outcomes of 248 patients with acute leukemia and without matched sibling donors (MSD) who underwent alternative transplantation, including haploidentical (n=118), 10/10 matched unrelated (MUD, n=91), 9/10 mismatched unrelated (MMUD, n=21), and 9/10 mismatched related (MMRD, n=18) between January 2010 and November 2019 in our center.
Materials and Methods: The myeloablative conditioning regimen was used in most of the patients. Both post-transplant cyclophosphamide (40mg/kg at +3, +4) and pre-transplant ATG were used in most of Haploidentical transplantations. Patients with unrelated donors received ATG as a part of the conditioning regimen.
Results: The median follow-up was 31.83 months. No significant difference in probability of 3-year leukemia-free survival (LFS) and overall survival (OS) as well as 3-year relapse incidence (RI) were noted between donor sources.
A significant difference was found in the 3-year cumulative incidence (CI) of non-relapse mortality (NRM) among the donor sources: 37.89%, 24.20%, 24.30%, and 11.48%, for Haplo, 9/10 MMUD, 10/10 MUD, and 9/10 MMRD (p=0.02). Using the multivariable Cox model, the advanced age of patients and Major-ABO mismatched, were two risk factors independently associated with lower OS and DFS as well as higher NRM, whereas male donor and AML disease compared to ALL were associated with a better OS and DFS.
Conclusion: Given that no significant differences were observed in the overall outcome of Haplo with other alternative transplantations, suggesting that Haploidentical transplantation is a suitable, accessible, and inexpensive option.

Keywords: Allogeneic stem cell transplantation; Haploidentical; Mismatched related donor; Mismatched unrelated donor; Cox proportional hazards models

Copyright © 2021 Tehran University of Medical Sciences. This work is licensed under a Creative Commons Attribution-Noncommercial 4.0 International license (http:// creativecommons.org/licenses/by-nc/4.0). Non-commercial uses of the work are permitted, provided the original work is properly cited.

INTRODUCTION

Over recent years, much progress has been made in stem cell transplant procedures and their supportive measures[1,2]. However, finding a suitable donor at the optimal time is one of the most challenging issues in transplant centers.

A transplant from an HLA-matched related donor (MRD) as the first choice is available for only a third of transplant candidates, so most patients have to use an alternative donor[3].

Since the compatibility of HLA is the highest priority to determine the ideal alternative donor, matched unrelated donor (MUD) is often the next preferred graft source after MRD,[4,5] and the outcomes of the MUD is comparable with those of MRD[6,7].

Alternative options, when access to a matched related or unrelated donor is not possible, are mismatched related or unrelated donors (MMUD, MMRD), cord blood units, and haploidentical hematopoietic stem cell transplantation (haplo-HSCT).

Recent improvements in the outcome of haplo-HSCT are similar to those of unrelated transplants[8]. Other benefits such as finding a donor more quickly and the possibility of recurring donations for donor lymphocyte infusions (CD3+) or boost (CD34+),[9-11] has led to a growing by about 300 percent in the use of haplo-HSCT in Europe and China.[12]

Moreover, using high-dose post-transplantation cyclophosphamide to induce immune tolerance after haplo-HSCT contributes to reducing GvHD incidence, resulting in significantly improved outcomes.[13-15]

With the increasing popularity of haplo-HSCT, several retrospective comparative studies have recently evaluated the outcome among haplo, MRD, MUD, and MMUD. The combined data was in favor of similar outcomes for haplo-HSCT and other alternative transplantations[15-17], some reports have also shown comparable outcomes between haplo-HSCT and MSD.[17-19]

Therefore, this prompted us to perform a retrospective study, comparing the outcomes of haplo-HSCT to 10/10 MUD, 9/10 MMUD, and 9/10 MMRD HSCT in our center.

MATERIALS AND METHODS

The clinical records of all ALL and AML patients transplanted from haploidentical, one Locus miss-matched unrelated, one locus miss-matched related, and full matched unrelated donors between Jan. 2010 and Nov. 2019 were reviewed. All patients were followed up until death, relapse, or the end of the expected follow-up time which was May 2020.

Patients followed-up beyond 3 years were censored to better compare the two groups because the one Locus miss-matched unrelated group had a shorter follow-up period than the other three groups.

This retrospective analysis was approved by the institutional review board of Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran.

Homogeneity between treatment pairs was evaluated using the Chi-square test or Fisher exact test for qualitative variables and Student's T-test or Wilcoxon rank-sum test for continuous variables.

The endpoints were OS, DFS, relapse and non-relapse mortality incidence, and also engraftment incidence.

Kaplan–Meier curves were derived to determine OS and DFS, and were compared through the log-rank test at each landmark. Median follow-up time was established with the reverse Kaplan-Meier method.

After selection of baseline characteristics and clinical variables based on univariable Cox proportional hazards models, multivariable Cox proportional hazards models were fitted. Multivariable predictors of OS and DFS were determined based on the P-values at or below 0.2 in the univariable Cox proportional hazards models.

The proportionality of hazards assumption was checked using the global proportionality of hazards test based on Schoenfeld residuals in each of the three multivariable models. There was no departure from the proportionality of hazards assumption in all multivariable models (results not shown).

To account for the informative censoring in the presence of multiple endpoints, competing risks survival analysis was performed utilizing nonparametric methods using the cumulative incidence competing risk method. CI of relapse and NRM were calculated by Gray's method. Death

without relapse was considered as a competing event for relapse, and relapse was considered as a competing event for NRM.

Cumulative incidence function was also used to express neutrophil and platelet engraftment failure incidence in competing risks setting where death before any of these events or before day 30 was regarded as its competing event.

Fine-Gray proportional hazard regression model used to assess the effects of covariates on relapse incidence and NRM incidence. Like multivariate Cox PH regression, all variables with a P-value at or below 0.2 in the univariate Fine-Gray proportional hazard regression were included in the corresponding multivariate analyses.

A two-sided P-value of 0.05 or lower was considered to be statistically significant. Analyses were done with STATA version 11.2 and Packages "survival" and "cmprsk" in R software version 3.3.1.

RESULTS

A total of 248 patients with acute leukemia who did not have suitably MRD were included: 118 patients underwent an unmanipulated haplo-HSCT, 91 a 10/10 unrelated donor, 21 a 9/10 unrelated donor, and 18 a 9/10 related donor HSCT.

Patients' and donors' characteristics

Patient's and donors' characteristics are shown in Table 1. The myeloablative conditioning regimen comprised of busulfan and cyclophosphamide in combination with ATG is used in most patients receiving alternative transplantations in our center. *For in vivo* T cell depletion (TCD) rabbit ATG, 2.5 mg/kg/day is given for 3 days (-3,-2,-1) in haplo and 9/10 MMUD, and for 2 days (-2,-1) in 10/10 MUD and 9/10 MMRD according to our center protocol.

All patients received cyclosporine A (CSA) and methotrexate (MTX) for GvHD prophylaxis. However, in haplo-HSCT, CSA and high-dose post-transplant cyclophosphamide (PTCy, 40mg/kg at +3,+4) were used to prevent GvHD.

Allelic typing for locus A, B, C, DRB1, and DQB1 is available for all patients and donors. Among 38 patients receiving a 9/10 donor, 18 (47.4 %) were mismatched in locus A, 3 (7.9%) in locus B, 3 (7.9 %) in locus C, 9 (23.6 %) in locus DRB1, and 5 (13.2 %) in locus DQB1.

Neither grades II-IV acute GvHD nor extensive chronic GvHD percentage differ between donor types.

LFS and OS

The median follow-up for the global population was 31.83 months (95% CI: 6.05 - 57.62). It was 18.2 (8.59–27.8) for haplo-HSCT and 60.15 (34.5–85.79) for MUD 10/10. The probability of 3-year LFS was 41.18% (95% CI: 31.44–50.65) for haplo-HSCT, 47.14% (95% CI: 23.24–67.88) for 9/10 MMUD, 50.52% (95% CI: 38.73–61.17) for 10/10 MUD and 65.48% (95% CI: 38.69–82.79) for 9/10 MMRD, respectively (Figure 1). The probability of OS at 3 years was 40.28% (30.51–49.84), 45% (20.93–66.52), 54.20% (42.30–64.66), and 70.1% (42.32–86.35) for haplo-HSCT, 9/10 MMUD, 10/10 MUD, and 9/10 MMRD (Figure 2). No significant difference in the probability of 3-year LFS and OS was noted among donor types.

However, multivariate analysis demonstrated that compared to the haplo-HSCT (reference), MMRD 9/10 had a better LFS and OS (Table 2).

In multivariate analysis for OS, patient's age at transplant and major-ABO mismatched compared to ABO-matched (reference) were the two predictive factors associated with lower OS (HR = 1.03, 1.73) (Table 2).

Male donors compared to female and AML (as primary diagnosis) compared to ALL were associated with a better OS. (HR=0.63, 0.65) (Table 2).

Similarly, in multivariate analysis for LFS, male donor and AML disease were two protective factors (HR = 0.62, 0.6) while recipient's age and major-ABO mismatched were the hazard factors independently associated with lower LFS. (HR = 1.03, 1.68).

Relapse incidence and non-relapse mortality

The relapse incidence (RI) at 3 years were not significantly among between haplo, 9/10 MMUD, 10/10 MUD, and 9/10 MMRD: 16.53% (95% CI:

10.04–24.42%), 26.14% (95% CI: 8.59-48.02%), 15.80% (95% CI: 13.43–32.24%), and 23.33% (95% CI: 6.83–45.42%) (p=0.59) (Figure 3).

In multivariate analysis for RI, AML (as primary diagnosis) compared to ALL was the only protective factor associated with lower RI (HR=0.43, *P*<10-3) (Table 3).

A significant difference was found in the 3-year CI of NRM among the donor sources: 37.89% (32.23–51.51), 24.20% (8.39–44.38), 24.30% (17–36), and 11.48% (1.74–31.44), for haplo, 9/10 MMUD, 10/10 MUD, and 9/10 MMRD, (p=0.02) (Figure 4). These results were also confirmed in a multivariate analysis, showing that 9/10 MMRD was associated with lower hazard for NRM compared to the haplo (reference) (HR=0.23, 95% CI: 0.08-0.71, *P*=0.01). Multivariate analysis demonstrated that both patient's and donor's age and major-ABO mismatched were the risk factors associated with higher NRM (HR=1.03, *P*<10-3), (HR=1.02, *P*=0.002) and (HR = 1.64, p = 0.02), respectively (Table 3).

The 30-day cumulative incidence of engraftment was not significantly different among donor types (p=0.145). It was 81.35% (95% CI: 72.99–87.34%) for haplo, 85.71% (95% CI: 58.54–95.65%) for 9/10 MMUD, 87.91% (95% CI: 78.96–93.21%) for 10/10 MUD and 100% for 9/10 MMRD, respectively (Figure 5).

Table 1: Baseline characteristics of patients and donors

		Haplo	MUD10/10	MMUD9/10	MMRD9/10	P
N		118	91	21	18	
Donor Age Median (IQR)		36 (25-43)	30 (25-40)	27 (26-41)	38 (29-46)	0.36
Median MNC dose*10^8/kg (IQR)		8.5 (7-9)	7.1 (4-8)	6.3 (5.9-8)	7.8 (5.5-8)	0.0001
Median CD34*10^8/kg (IQR)		5.6 (4-8)	5.3 (3-7)	4.9 (3.5-6.2)	5.5 (4-8)	0.21
Median CD3*10^8/kg (IQR)		322 (233-386)	204 (85-250)	257 (156-300)	220 (137-318)	0.0001
Patient. Age(y) Median (IQR)		26 (18-34)	19 (12-32)	20 (17-33)	23 (10-36)	0.06
Months from DX to HSCT Median (IQR)		14 (9-23)	14 (11-23)	18 (13-55)	10 (7-12)	0.0018
Acute GvHD, Grad(2-4)		54 (58%)	42 (52%)	10 (52%)	13 (76%)	0.29
Chronic GvHD, Extensive		51 (63%)	38 (57%)	11 (78%)	8 (50%)	0.36
ABO Matching	Matched	66 (55.97%)	25 (27.5%)	8 (38.1%)	10 (55.6%)	< 0.001
	Minor mismatched	22 (18.6%)	32 (35.2%)	11 (52.4%)	4 (22.2%)	
	Major mismatched	30 (25.4%)	34 (37.4%)	2 (9.5%)	4 (22.2%)	
Primary Disease	AML	76 (64%)	50 (55%)	7 (33%)	12 (66%)	0.046
	ALL	42 (35%)	41 (45%)	14 (66%)	6 (33%)	
Pre HSCT Disease Status	CR1	41 (34.7%)	52 (57%)	8 (38%)	13 (72%)	0.006
	CR2	60 (51%)	29 (32%)	9 (43%)	5 (27%)	
	CR3	17 (14.4%)	10 (11%)	4 (19%)	0	
Causes of Death	Relapse	17(26.5%)	18(45%)	5(50%)	3(60%)	0.42
	Infection	19 (29.7%)	12 (30%)	2 (20%)	0	
	PGF	16 (25%)	6 (15%)	1 (10%)	1 (20%)	
	GvHD	6 (9.3%)	2 (5%)	0	0	
	Unknown	6 (9.3%)	2 (5%)	2 (20%)	1 (20%)	

Abbreviations: Haplo: haploidentical donors; MUD: matched unrelated donors; MMUD: mismatched unrelated donors; MMRD: mismatched related donors; HSCT: hematopoietic stem cell transplantation; CR, complete remission; PGF: poor graft function

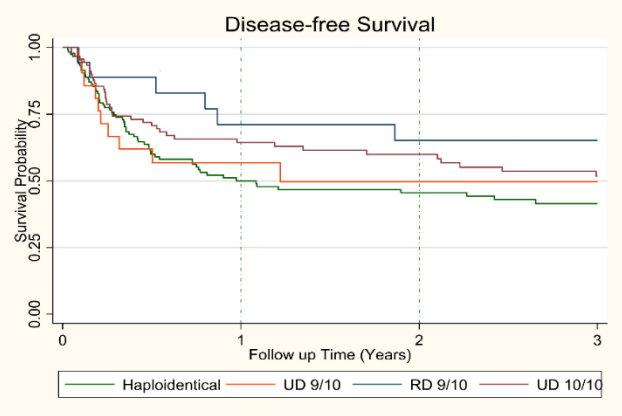

Figure 1. Kaplan-Meier estimates of leukemia-free survival (LFS)

Table 2: Univariate and Multivariate regression models for OS and LFS

	Univariable OS		**Multivariable OS**		**Univariable LFS**		**Multivariable LFS**	
	HR (95 % CI)	**P**	**HR (95 % CI)**	**P**	**HR (95 % CI)**	**P**	**HR (95 % CI)**	**P**
Matching								
Haplo	Ref.	---	Ref.	---	Ref.	---	Ref.	---
UD 9/10	0.94 (0.48 - 1.83)	0.848	0.95 (.46 1.95)	0.884	0.95 (0.49 - 1.86)	0.889	1.07 (0.52 - 2.19)	0.862
UD10/10	0.67 (0.44 - 1.00)	0.053	0.81 (0.51 1.30)	0.379	0.73 (0.49 - 1.09)	0.122	0.89 (0.56 - 1.40)	0.460
RD 9/10	0.38 (0.15 - 0.95)	0.039	0.44 (0.17 - 1.12)	0.014	0.47 (0.20 - 1.10)	0.081	0.55 (0.23 - 1.31)	0.055
Recipient age	1.02 (1.01 - 1.04)	<0.0001	1.03 (1.02 - 1.05)	<0.0001	1.02 (1.01 - 1.03)	0.001	1.03 (1.02 - 1.05)	< 0.001
Donor age	1.02 (1.00 - 1.03)	0.033	1.01 (0.99 - 1.03)	0.199	1.01 (1.00 - 1.03)	0.506	1.01 (0.99 - 1.03)	0.302
ABO Match								
Match	Ref.	---	Ref.	---	Ref.	---	Ref.	---
Minor	1.15 (0.73 - 1.81)	0.552	1.27 (0.76 - 2.11)	0.365	1.17 (.75 - 1.82)	0.491	1.24 (0.75 - 2.05)	0.400
Major	1.34 (0.86 - 2.07)	0.195	1.73 (1.05 - 2.86)	0.031	1.36 (.88 - 2.10)	0.167	1.68 (1.04 - 2.74)	0.035
Remission								
CR1	Ref.	---	Ref.	---	Ref.	---	Ref.	---
CR2	1.48 (1.00 - 2.21)	0.052	1.32 (0.85 - 2.05)	0.211	1.44 (0.98 - 2.12)	0.066	1.36 (0.89 - 2.09)	0.153
CR3/PIF	1.31 (0.73 - 2.35)	0.365	1.04 (0.53 - 2.03)	0.902	1.27 (0.71 - 2.27)	0.412	1.05 (0.54 - 2.03)	0.893
Disease								
ALL	Ref.	---	Ref.	---	Ref.	---	Ref.	---
AML	0.80 (0.55 - 1.15)	0.228	0.65 (0.42 - 1.00)	0.05	0.75 (.52 - 1.08)	0.119	0.60 (.39 - 0.91)	0.017
Sex matching (D-R)								
F-F	Ref.	---	Ref.	---	Ref.	---	Ref.	---
F-M	0.79 (0.47 - 1.33)	0.383	0.74 (0.42 - 1.28)	0.278	0.81 (0.49 - 1.36)	0.437	0.73 (0.42 - 1.27)	0.264
M-F	0.74 (0.41 - 1.33)	0.312	0.66 (0.35 - 1.24)	0.198	0.72 (0.40 - 1.30)	0.276	0.60 (0.32 - 1.13)	0.026
M-M	0.58 (0.34 - 0.99)	.046	0.63 (0.35 - 1.12)	0.027	0.63 (0.37 - 1.06)	0.081	0.62 (0.35 - 1.10)	0.010

Abbreviations: OS, overall survival; LFS, leukemia-free survival; HR, hazard ratio; CI, confidence interval; CR, complete remission; D-R, Donor- Recipient; F: female; M: male

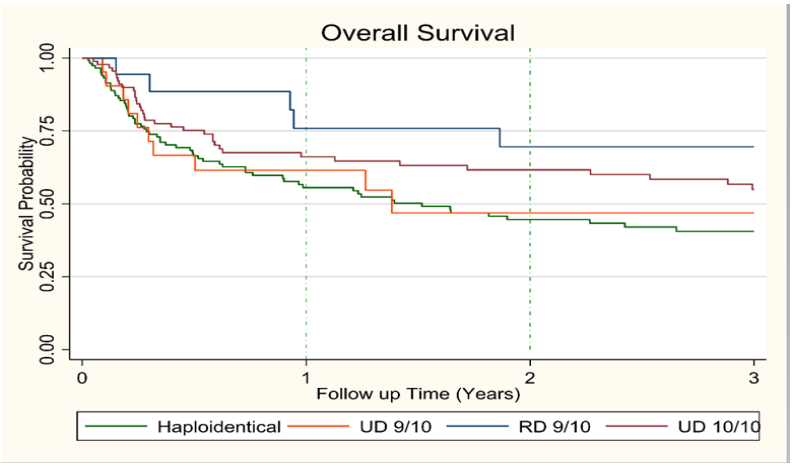

Figure 2. Kaplan-Meier estimates of overall survival (OS)

Table 3: Univariate and Multivariate regression models for RI and NRM

	Univariable RI		Multivariable RI		Univariable NRM		Multivariable NRM	
	HR (95 % CI)	P	HR (95 % CI)	P	HR (95 % CI)	P	HR (95 % CI)	P
Matching								
Haplo	Ref.	---	Ref.		Ref.		Ref.	---
UD 9/10	1.89 (0.91 - 3.90)	0.087	1.48 (0.71 - 3.11)	0.298	0.58 (0.30 - 1.13)	0.107	0.73 (0.36 - 1.48)	0.381
UD10/10	1.30 (0.82 - 2.09)	0.266	1.30 (0.78 - 2.15)	0.309	0.57 (0.40 - 0.81)	0.002	0.72 (0.49 - 1.07)	0.102
RD 9/10	1.47 (0.68 - 3.18)	0.330	1.62 (0.71 - 3.68)	0.251	0.23 (0.08 - 0.61)	0.003	0.24 (0.08 - 0.71)	0.010
Recipient age	1.00 (.99 - 1.02)	0.322	---	---	1.20 (1.01 - 1.03)	< 0.001	1.03 (1.01 - 1.04)	< 0.001
Donor age	0.99 (0.971 - 1.00)	0.127	0.98 (0.96 - 1.00)	0.059	1.03 (1.01 - 1.04)	< 0.001	1.02 (1.01 - 1.04)	0.002
ABO Matching								
Match	Ref.	---	Ref.	---	Ref.	---	Ref.	---
Minor	1.17 (0.70 - 1.95)	0.551	---	---	1.20 (0.81 - 1.78)	0.357	1.45 (0.93 - 2.28)	0.104
Major	1.30 (0.78 - 2.15)	0.313	---	---	1.34 (0.91 - 1.96)	0.139	1.64 (1.08 - 2.50)	0.021
Remission								
CR1	Ref.	---	Ref.	---	Ref.		Ref.	---
CR2	1.42 (0.89 - 2.27)	0.136	1.55 (0.95 - 2.51)	0.076	1.29 (0.92 - 1.80)	0.139	1.04 (0.72 - 1.50)	0.837
CR3/PIF	2.04 (1.12 - 3.72)	0.019	1.29 (0.64 - 2.61)	0.469	0.82 (.45 - 1.49)	0.514	0.72 (0.38 - 1.35)	0.308
Disease								
ALL	Ref.	---	Ref.	---	Ref.	---	Ref.	---
AML	0.38 (0.25 - 0.59)	< 0.0001	0.43 (0.26 - 0.69)	< 0.001	1.80 (.85 - 1.64)	0.318		
Sex matching (D-R)								
F-F	Ref.	---	Ref.	---	Ref.	---	Ref.	---
F-M	0.82 (0.43 - 1.56)	0.543	---	---	0.87 (0.55 - 1.36)	0.543	0.85 (0.54 - 1.34)	0.481
M-F	1.07 (0.55 - 0.09)	0.842	---	---	0.63 (0.37 - 1.09)	0.101	0.46 (0.25 - 0.87)	0.016
M-M	1.00 (0.55 - 1.84)	0.987	---	---	0.55 (0.34 - 0.88)	0.013	0.62 (0.37 - 1.04)	0.070

Abbreviations: RI, relapse incidence; NRM, non-relapse mortality; HR, hazard ratio; CI, confidence interval; CR, complete remission; D-R, Donor- Recipient; F: female; M: male

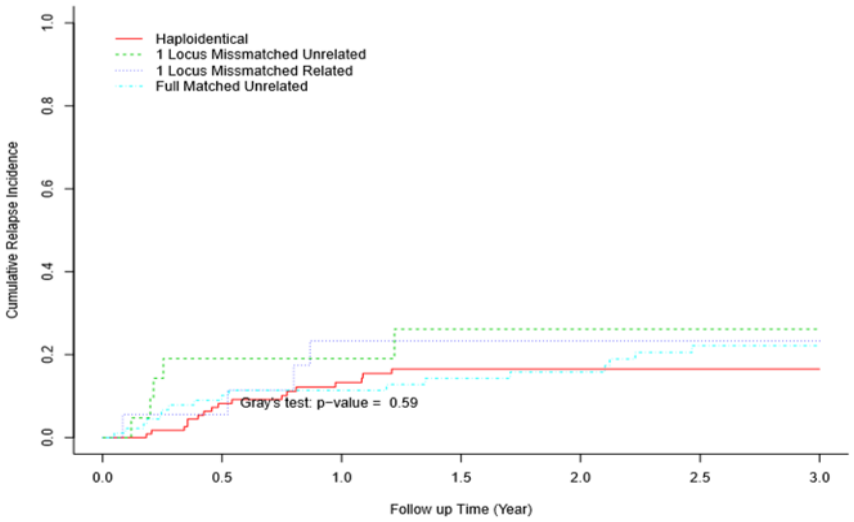

Figure 3. Cumulative incidence of relapse incidence (RI)

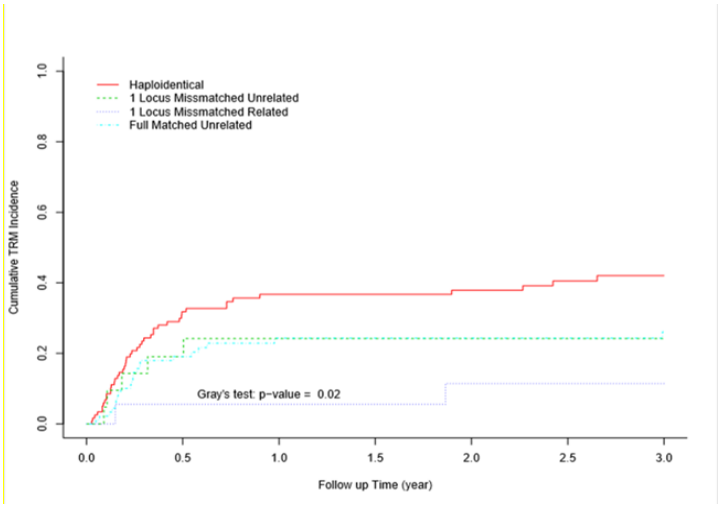

Figure 4. Cumulative incidence of non-relapse mortality (NRM)

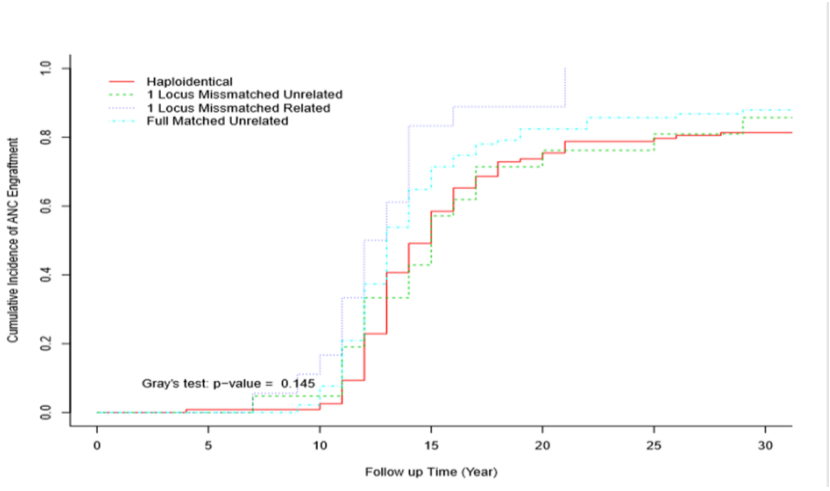

Figure 5. Cumulative incidence (CI) of ANC engraftment

DISCUSSION

In the present study, we analyzed and compared the outcomes of HSCT in patients with Acute Leukemia undergoing alternative donor transplantation between 2010 and 2019. Due to lack of a MSD, patients underwent haploidentical, MUD, MMUD, and MMRD transplantation.

No statistically significant difference was observed in LFS and OS among these alternative transplant groups. Our findings are consistent with other similar studies that have compared the HSCT outcome between different types of donors.[15-17]

However, in multivariate analysis, the best clinical outcome was observed in the MMRD.

According to our study, age and sex of donor, primary diagnosis, donor sex, and ABO-matching are the predictive factors, which are independently associated with the outcome of HSCT and must be considered for the optimal donor selection.

The effect of ABO-mismatched on the outcome of patients following HSCT remains controversial, but our findings show that in cases undergoing alternative HCT, major-ABO mismatched transplantation has been associated with the inferior outcome due to higher transplant-related mortality.

Although haplo-HSCT recipients did not experience worse outcomes compared to other alternative transplants, at the Gray test, 3-year NRM was significantly higher in haplo-HSCT (38%) compared with both unrelated groups (24%). The 3-year CI of relapse was not different, but a trend for lower relapse incidence was observed in haplo-HSCT compared to unrelated donors. One hypothesis to explain the lower relapse rate in haplo-HSCT patients is that the median CD3+ cell dose was significantly higher in haplo-HSCT than other alternative sources for HSCT (Table 1).

Although usually one of the two methods of PTCy or ATG is used to prevent GvHD in haplo-HSCT, the combination of ATG and PTCy in haplo-HSCT has been reported in some studies with lower rates of GvHD and acceptable rate of relapse.[20,21]

The haplo-HSCT protocol at our center also contains a combination of a modified dose of PTCy (40mg/kg at +3, +4) plus ATG.

Since the most common cause of death following haplo-HSCT in our report was the infection, it can be concluded that the combination of ATG and PTCy appears to have contributed to increasing infectious complications.

Some reports comparing the effects of ATG and PTCy on the outcome of haplo-HSCT recipients found that PTCy protocol was associated with lower NRM and may be higher disease recurrence[22,23], while in vivo TCD with ATG was a hazard factor associated with a higher incidence of NRM and infection[24].

Due to the growing need for HLA-haploidentical bone marrow transplantation, it is suggested that more efforts must be focused on the management of post-HSCT complication, especially CMV infection that remains the major cause of post-transplantation mortality in high-risk patients.[25]

For this reason, it is necessary to pay more attention to prevent high-risk infections, pre-emptive therapy for CMV, timely diagnosis and treatment of viral and fungal infections, and if possible, early immunosuppression cessation.

We also have some difficulties with access to certain new drugs such as second and third-line antiviral in patients with CMV refractoriness or severe cytopenia following ganciclovir.

Another problem we encountered in this study is that the exact time of GvHD onset was not determined in some cases, so it was not possible to calculate the cumulative incidence of acute and chronic GvHD.

Although haplo-HSCT is usually performed as a salvage treatment for advanced stage of disease in the absence of suitable unrelated donor, the results of the current study were not significantly different from those of unrelated, especially in terms of DFS.

CONCLUSION

The importance of early referral to haplo-HSCT, especially those who need an urgent transplant procedure, is recommended to prevent high-risk patients from developing recurrence or therapy-related toxicities.

CONFLICT OF INTEREST

There are no conflicts of interest to report.

ACKNOWLEDGEMENT

We would like to thank all physicians, nurses and fellows serving in BMT wards, and also our data registry team providing data for this study.

REFERENCES

1. Gratwohl A, Pasquini MC, Aljurf M, et al. Worldwide Network for Blood and Marrow Transplantation (WBMT). One million haemopoietic stem-cell transplants: a retrospective observational study. Lancet Haematol. 2015; 2(3):e91-e100.

2. Passweg JR, Baldomero H, Bader P, et al. Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. Bone Marrow Transplant. 2017; 52(6):811-817.

3. Ballen KK, King RJ, Chitphakdithai P, et al. The National Marrow Donor Program 20 years of unrelated donor hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2008; 14(9 suppl):2-7.

4. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood. 2007;110(13):4576–83.

5. Bray RA, Hurley CK, Kamani NR, et al. National marrow donor program HLA matching guidelines for unrelated adult donor hematopoietic cell transplants. Biol Blood Marrow Transplant. 2008; 14(9 Suppl):45-*53*.

6. Segal E, Martens M, Wang HL, et al. Comparing outcomes of matched related donor and matched unrelated donor hematopoietic cell transplants in adults with B-cell acute lymphoblastic leukemia. Cancer. 2017; 123(17):3346-3355.

7. Brissot E, Labopin M, Stelljes M, et al. Comparison of matched sibling donors versus unrelated donors in allogeneic stem cell transplantation for primary refractory acute myeloid leukemia: a study on behalf of the Acute Leukemia Working Party of the EBMT. J Hematol Oncol. 2017; 10(1):130.

8. Ciurea SO, Zhang MJ, Bacigalupo AA, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. Blood. 2015; 126(8):1033-1040.

9. Saito AM, Cutler C, Zahrieh D, et al. Costs of allogeneic hematopoietic cell transplantation with high-dose regimens. Biol Blood Marrow Transplant. 2008; 14(2):197–207.

10. Svahn BM, Alvin O, Ringden O, et al. Costs of allogeneic hematopoietic stem cell transplantation. Transplantation. 2006;82(2):147–53.

11. Khera N, Emmert A, Storer BE, et al. Costs of allogeneic hematopoietic cell transplantation using reduced intensity conditioning regimens. Oncologist. 2014;19(6):639–644.

12. Passweg JR, Baldomero H, Bader P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. Bone Marrow Transplant. 2016; 51(6):786-92.

13. Luznik L, Jalla S, Engstrom LW, et al. Durable engraftment of major histocompatibility complex-incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and

posttransplantation cyclophosphamide. Blood. 2001; 98(12):3456-64.
14. Cieri N, Greco R, Crucitti L, et al. Post-transplant cyclophosphamide and sirolimus after haploidentical hematopoietic stem cell transplantation using a treosulfan-based myeloablative conditioning and peripheral blood stem cells. Bio Blood Marrow Transplant. 2015; 21(8):1506–14.
15. Ciurea SO, Zhang MJ, Bacigalupo A, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. Blood. 2015; 126(8):1033-40.
16. Piemontese S, Ciceri F, Labopin M. A comparison between allogeneic stem cell transplantation from unmanipulated haploidentical and unrelated donors in acute leukemia. J Hematol Oncol. 2017; 10:24.
17. Raiola AM, Dominietto A, di Grazia C, et al. Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts. Biol Blood Marrow Transplant. 2014; 20(10):1573–9.
18. Luo Y, Xiao H, Lai X, et al. T-cell-replete haploidentical HSCT with low-dose anti-T-lymphocyte globulin compared with matched sibling HSCT and unrelated HSCT. Blood. 2015; 124(17):2735–2743.
19. Lu DP, Dong L, Wu T, et al. Conditioning including antithymocyte globulin followed by unmanipulated HLA-mismatched/haploidentical blood and marrow transplantation can achieve comparable outcomes with HLA identical sibling transplantation. Blood. 2006; 107(8):3065–73.
20. Dawsari G, Hassanein M, Rasheed W, et al. Addition of ATG to myeloablative haplo conditioning with post-transplantation cyclophosphamide might decrease the risk of GVHD and TRM without increasing the risk of relapse. Blood. 2016;128(22):5871.
21. Lin CC, Chen TT, Lo WJ, et al. Post-transplant cyclophosphamide (PTCy) with anti-thymocyte globulin (ATG) as GVHD prophylaxis is effective in haploidentical peripheral stem cell transplantation and without increasing risk of relapse. Blood. 2017; 130 (Supplement 1): 1978.
22. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant. 2008; 14(6):641-50
23. Ruggeri A, Sun Y, Labopin M, et al. Post-transplant cyclophosphamide versus anti-thymocyte globulin as graft- versus-host disease prophylaxis in haploidentical transplant. Haematologica, 2017; 102(2):401-410.
24. Piemontese S, Ciceri F, Labopin M, et al. A survey on unmanipulated haploidentical hematopoietic stem cell transplantation in adults with acute leukemia. Leukemia. 2015; 29(5):1069-75.
25. Green M.L, Leisenring W, Xie H, et al. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: A retrospective cohort study. Lancet Haematol. 2016; 3(3):e119–27.