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Peripheral blood stem cell transplantation from haploidentical and unrelated *versus* related donors for acute leukemia in children, adolescents and young adults (CAYA): A competing risk analysis

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Summary

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only potentially curative treatment for acute leukemia. Various parameters have significant impact on the final results of HSCT, such as donor type, stem cell source, and the applied conditioning regimen. In the absence of HLA-matched related or unrelated donors, haploidentical donors present a possible alternative for the patients with indications for HSCT. The present single-center study compared the outcomes of HSCT from different donor types using a radiation-free MAC regimen. We compared the results of unmanipulated peripheral blood stem cell transplantation (PBSCT) from matched, or mismatched related, and unrelated donors with those from haploidentical donors in the children, adolescents and young adults (CAYA) treated for acute leukemia.

Patients and methods

In this retrospective study performed since 2014 to 2021, we have evaluated the clinical outcomes among CAYA patients with acute leukemia who underwent peripheral blood T cell-replete HSCT from haploidentical donors *versus* unrelated donors (including 10/10 or 9/10 HLA-matched), and *versus* related donors (including 10/10 or 9/10 HLA-matched). The myeloablative conditioning for HSCT was performed as irradiation-free regimen including busulfan and cyclophosphamide. GvHD prophylaxis was based on administration of cyclosporine A in all the patients, accomplished by rabbit anti-human thymocyte globulin in HSCT from unrelated and haploidentical donors, and post-transplant cyclophosphamide in cases of haploidentical donors. For statistical evaluation, an adjusted multivariable proportional hazard Cox and competing risk analyses were used.

Results

Median follow-up time period was 28.7 months (95% CI: 21.9-34.9). Three-year overall survival rate (OS) and GvHD-free/relapse-free survival (GFRFS) rate were 68.81% (95% CI: 60.08%-76.01%) and 44.19% (95% CI: 35.52%-52.49%), respectively. The patients who underwent HSCT from unrelated HLA-matched donors had the lowest OS and GFRFS compared to other donor types. The 3-year non-relapse mortality (NRM) in all patients was 7.84% (95% CI 4.36-12.62). Adjusted multivariable modeling of OS showed that the hazard of death in patients who had undergone HSCT from an unrelated donor, was 3.6 times more than for the patients who underwent HSCT from their haploidentical donors (P=0.05). Likewise, the hazard of NRM after HSCT from unrelated donors was 6 times more than with haploidentical donors (P=0.002). However, the relapse incidence was not significantly different between the two mentioned groups.

Conclusions

In this study, HSCT from haploidentical donors was associated with superior survival rates compared to HSCT from unrelated HLA-matched donors. Hence, haploidentical transplantation with peripheral blood stem cells could be a practical and valuable clinical option that offers a reasonable opportunity for the disease control in CAYA patients with acute leukemia requiring HSCT and lacking matched available donors.

Keywords

Acute leukemia, allogeneic hematopoietic stem cell transplantation, matched related donors, unrelated donors, haploidentical donors, clinical outcomes.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only available curative option for acute leukemia nowadays. Many different parameters have significant impact on the final results of HSCT, especially on the more recently defined graft-versus-host disease (GvHD)-free/relapse-free survival (GFRFS) rate, including the pre-HSCT characteristics, such as disease profile at diagnosis and the disease status at the time of transplant, as well as the peri-HSCT factors, i.e. donor type, stem cell source, implemented conditioning regimen and potential post-transplant complications. Aiming to reduce the relapse rates after HSCT, myeloablative conditioning (MAC) regimens at higher dose intensity using busulfan or total body irradiation (TBI) has shown promising results [1]. However, due to higher vulnerability of younger patients to adverse effects of therapeutic irradiation, MAC regimens without TBI are preferred [2, 3]. Moreover, in view of relative complexity for bone marrow collection procedure, along with potentially enhanced graft-versus-leukemia (GvL) effect, peripheral blood (PB) is the preferred source of stem cells for allogeneic HSCT ever more. On the other hand, the increasing number of transplants from human leukocyte antigen (HLA)-haploidentical donors in the patients with acute leukemia is performed due to the absence of suitable related or unrelated HLA-matched donors, thus raising the necessity of understanding, whether HSCT outcomes with this approach are similar to those of more common modes. Over last years, several reports have shown comparable outcomes between HSCT from haploidentical donors and historical HLA-matched related or unrelated donors [4-6]. Hence, additional reports regarding the comparison of different donor types could be a guide to the upcoming therapeutic strategies. To address this issue, we carried out a single-center study, using HSCT with radiation-free MAC regimen, in order to evaluate the results of unmanipulated peripheral blood stem cell transplantation (PBSCT) performed from matched and mismatched related and unrelated donors compared with haploidentical donors in children, adolescents and young adults (CAYA) affected by acute leukemia.

Patients and methods

Patient characteristics

Our study included 180 patients who underwent first allogeneic HSCT for acute leukemia in the CAYA HSCT Department of the Research Institute for Oncology, Hematology and Cell Therapy (RIOHCT), Tehran, Iran, between January 2014 and January 2021. All data were retrieved retrospectively from clinical records according to the policy approved by the Committee for Medical Ethics of Tehran University of Medical Sciences (TUMS) and after obtaining informed consent from the patients, or their legal guardians.

HSCT parameters

In all patients and their donors, high-resolution HLA molecular typing for HLA-A, -B, -C, -DRB1, and -DQB1 loci was performed. The first donor preference was a 10/10 HLA-matched related donor (MRD), or a 9/10 HLA-mismatched related donor (MMRD). In absence of related donors, an alternative donor including 10/10 HLA-matched unrelated donors (MUD), or 9/10 HLA-mismatched unrelated donors (MMUD), or a related haploidentical donor (Haplo) was chosen, depending on their availability and accessibility.

We proceeded to HSCT if the result of a pre-HSCT bone marrow examination pointed to morphologically complete remission (CR), regardless of the minimal residual disease status. The HSCT procedure was based on irradiation-free MAC regimen including busulfan (a total dose of 3.2-4.8 mg/kg/day, according to patients' ideal body weight, from day -6 to -3), and cyclophosphamide (60 mg/kg/day, day -2 to -1). The GvHD prophylaxis was based on administration of cyclosporine A (CsA) in all the patients, and a short course of methotrexate (10 mg/m^2 on day +1, 6 mg/m2 on day

+3, +6, and +11) in HSCT from matched and mismatched related and unrelated donors, plus rabbit anti-human thymocytes globulins (ATG-Thymoglobuline, Sanofi, 2.5 mg/kg/day from days -3 to -1) in MMRD, MUD/MMUD and haplo-HSCT groups, and high-dose Pt-Cy treatment (40 mg/kg/day on days +3 and +4) in the Haplo group. We only included patients who received unmanipulated peripheral blood hematopoietic stem cells as graft source.

Considering hazards of CMV reactivation after HSCT, the patients were classified, according to their serological status, into low-risk (donor [D]-/recipient [R]-), intermediate-risk (D+/R-), or high-risk groups (D-/R+ or D+/R+) [7].

Definitions and endpoints

The main purpose of this study was to compare the survival rates of acute leukemia patients who had undergone allogeneic HSCT from different donor types. Overall survival (OS) was defined as the probability of survival, irrespective of the disease state at any point in time. GvHD-free/relapse-free survival (GFRFS) which is regarded as an endpoint more precisely reflective of health status and quality of life post-transplant, was defined as the probability of survival at complete remission of the disease, with sustained donor cell engraftment and absence of either grade III–IV acute GvHD, or chronic GvHD requiring immunosuppressive treatment [8]. Non-relapse mortality (NRM) was defined as probability of death without a relapse after HSCT. The relapse incidence (RI) was defined as the probability to develop a disease relapse.

Donor chimerism was determined on day +15, +30, +60 and +90 after HSCT, and then, if clinically indicated, in whole bone marrow mononuclear cells by means of quantitative PCR of informative short tandem repeats in the donor and recipient [9]. Sustained donor cell engraftment was defined at $>0.5\times10^9$/L neutrophils and $>20\times10^9$/L platelets for three consecutive days without blood transfusion support. Graft rejection was defined as a lack of initial engraftment of donor cells (primary), or loss of donor cell engraftment (secondary graft failure), regardless of peripheral cell blood counts. Acute GvHD (aGvHD) and chronic GvHD (cGvHD) were diagnosed and graded according to the published criteria [10, 11]. The mentioned HSCT outcomes were compared between the three categorized groups of different donor types, i.e., the patients transplanted from HLA-matched related (10/10), HLA-mismatched related (9/10) donors (MRD/MMRD), HLA-matched unrelated (10/10), HLA-mismatched (9/10) unrelated donors (MUD/MMUD), and HLA-haploidentical (Haplo) donors.

Statistical evaluation

The patients followed-up beyond 36 months were censored, for better comparison between the groups because some sub-groups had shorter follow-up periods than the other sub-groups. Homogeneity within 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 as follows: OS, GFRFS, relapse-associated, and non-relapse mortality incidence. Kaplan-Meier curves were derived to determine OS and GFRFS, having been compared with log-rank test. Median follow-up time was established by means of 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.

Variables in the multivariable OS and GFRFS were determined, as based on the P-values of <0.2 in the univariable Cox proportional hazards models. The proportionality of hazards assumption was checked using the global proportionality of hazard test based on Schoenfeld residuals in each of the three multivariable models. There were no deviations from the proportionality of hazards assumption in all multivariable models (results not shown). To account for informative censoring in presence of multiple endpoints, the competing risks in survival analysis were evaluated with nonparametric methods using the cumulative incidence competing risk method. CI for relapses and NRM were calculated by Gray's method. Death beyond relapses was considered a competing event for relapse, and the relapse was considered a competing event for NRM. The Fine-Gray proportional hazard regression model was used to assess the effects of covariates on the relapse frequency and NRM incidence. Like multivariate Cox proportional hazard regression, all the variables at P values of <0.2 in the univariate Fine-Gray proportional hazard regression were included in appropriate multivariate analyses. A two-sided P-value of <0.05 was considered to be statistically significant. The data evaluation was done with STATA version 16 and the packages "survival" and "cmprsk" in R software version 3.3.1.

Results

Patients

The study included 180 patients (120 males and 60 females) at a median age of 12 years (4 months to 24 years) at the time of HSCT, and 123 patients (68.3%) were transplanted at the age of ≤15 years. The donor types were as follows: matched (n=103) and mismatched (n=2) relatives including siblings (n=94) and other relatives (n=11) for a total of 105 cases (58.3%); matched (n=20) and mismatched (n=10) unrelated donors (a total of 30 patients, 16.7%), and haploidentical donors for 45 patients (25%). The patients' characteristics are summarized in Table 1.

The median follow-up time was 28.7 months for the patients enrolled into the study who were still alive at the end of the study (range: 21.9-34.9). A total of 96 patients presented with B-cell lineage acute lymphoblastic leukemia (ALL); 22 cases, with T-lineage ALL, and 62 patients had acute myeloblastic leukemia (AML). A total of 12 patients suffered from Ph chromosome-positive ALL. All the patients were in complete hematological remission before HSCT, including 93 patients (51.7%) transplanted in their first complete remission (CR1), 67 patients (37.2%) in the second complete remission (CR2), and 20 patients (11.1%) had experienced more than 2 relapses before HSCT. A pre-HSCT cytomegalovirus (CMV) serology showed that more than 90% of the patients were at high risk (recipient [R]+, donor [D]+) for CMV reactivation after HSCT.

Table 1. Characteristics of the patients and transplant procedure

Parameters of the patients and transplants		Total (n=180)	Haplo (n=45)	MUD/MMUD (n=30)	MRD/MMRD (n=105)	Pvalue
Gender	Female	60 (33.3%)	12 (26.7%)	10 (33.3%)	38 (36.2%)	0.526
	Male	120 (66.7%)	33 (73.3%)	20 (66.7%)	67 (63.8%)	
Leukemia type	B-ALL	96 (53.3%)	20 (44.4%)	23 (76.7%)	53 (50.5%)	0.070
	T-ALL	22 (12.2%)	7 (15.6%)	1 (3.3%)	14 (13.3%)	
	AML	62 (34.4%)	18 (40.0%)	6 (20.0%)	38 (36.2%)	
WBC at diagnosis ($\times 10^9$/l)	≤50	69 (59.0%)	18 (62.1%)	14 (58.3%)	37 (57.8%)	0.984
	50-100	19 (16.2%)	5 (17.2%)	4 (16.7%)	10 (15.6%)	
	>100	29 (24.8%)	6 (20.7%)	6 (25.0%)	17 (54.7%)	
Disease status at HSCT	CR1	93 (51.7%)	17 (37.8%)	11 (36.7%)	65 (61.9%)	0.021
	CR2	67 (37.2%)	23 (51.1%)	15 (50.0%)	29 (27.6%)	
	CR≥3	20 (11.1%)	5 (11.1%)	4 (13.3%)	11 (10.5%)	
Relapse site	No relapse	94 (52.2%)	18 (40%)	11 (36.7%)	65 (61.9%)	0.084
	BM/BM+	62 (34.4%)	22 (48.9%)	14 (46.7%)	26 (24.8%)	
	Extramedullary	24 (13.3%)	5 (11.1%)	5 (16.7%)	14 (13.3%)	
Age at HSCT (year)	≤15	123 (68.3%)	26 (57.8%)	23 (76.7%)	74 (70.5%)	0.174
	>15	57 (31.7%)	19 (42.2%)	7 (23.3%)	31 (29.5%)	
R/D blood group matching	Matched	113 (62.8%)	36 (80%)	9 (30%)	68 (64.8%)	0.001
	Major MM	42 (23.3%)	4 (8.9%)	11 (36.7%)	27 (25.7%)	
	Minor MM	25 (13.9%)	5 (11.1%)	10 (33.3%)	10 (9.5%)	
Donor age (year)	≤30	128 (71.5%)	22 (50%)	13 (43.3%)	93 (88.6%)	0.001
	>30	51 (28.5%)	22 (50%)	17 (56.7%)	12 (11.4%)	
$CD34^+$ Cell dose infused ($\times 10^6$/kg)	≤ 6	125 (70.2%)	19 (42.2%)	23 (76.7%)	83 (80.6%)	0.001
	6-8	24 (13.5%)	6 (13.3%)	5 (16.7%)	13 (12.6%)	
	>8	29 (16.3%)	20 (44.4%)	2 (6.7%)	7 (6.8%)	
$CD3^+$ Cell dose infused ($\times 10^6$/kg)	≤ 250	79 (44.4%)	12 (26.7%)	19 (63.3%)	48 (46.6%)	0.006
	>250	99 (55.6%)	33 (73.3%)	11 (36.7%)	55 (53.4%)	

Notes: ALL: acute lymphoblastic leukemia, AML: acute myeloblastic leukemia, BM: bone marrow, BM+: involvement of bone marrow together with other sites, CR: complete remission, Haplo: HLA-haploidentical donors, MM: mismatched, MRD/MMRD: HLA-matched related and HLA-mismatched related donors, MUD/MMUD: HLA-matched unrelated and HLA-mismatched unrelated donors, R/D: recipient/donor, WBC: white blood cell.

Table 2. Engraftment terms and GVHD incidence for the different donor types

		Total	Haplo	MUD/MMUD	MRD/MMRD	P-value
Neutrophil recovery	Mean duration (95% CI)	11.34 (11.10-11.58)	12.20 (11.76-12.64)	12.17 (11.71-12.63)	10.73 (10.43-11.03)	0.000
	N (%)	180 (100%)	45 (100%)	30 (100%)	105 (100%)	
Platelet recovery	Mean duration (95% CI)	14.70 (12.64-16.76)	14.67 (11.89-17.45)	16.21 (10.99-21.42)	14.30 (11.31-17.30)	0.809
	N (%)	176 (97.7%)	42 (93.3%)	29 (96.6%)	105 (100%)	
Grade II-IV acute GvHD	Cumulative incidence at day 100 (SE)	23.8% (4.5)	10.5% (7.0)	31.6% (11.8)	27.3% (6.0)	0.845
	N (%)	70 (38.9%)	17 (37.8%)	13 (43.3%)	40 (38.1%)	0.860
Chronic GvHD	Cumulative incidence at 3 years (SE)	20.3% (3.9)	7.0% (5.0)	22.5% (10.3)	23.3 (4.9)	0.105
	N (%)	27 (15%)	2 (4.4%)	4 (13.3%)	21 (20%)	0.048

Notes: GvHD: graft-versus-host disease, Haplo: HLA-haploidentical donors, MM: mismatched, MRD/MMRD: HLA-matched related and HLA-mismatched related donors, MUD/MMUD: HLA-matched unrelated and HLA-mismatched unrelated donors.

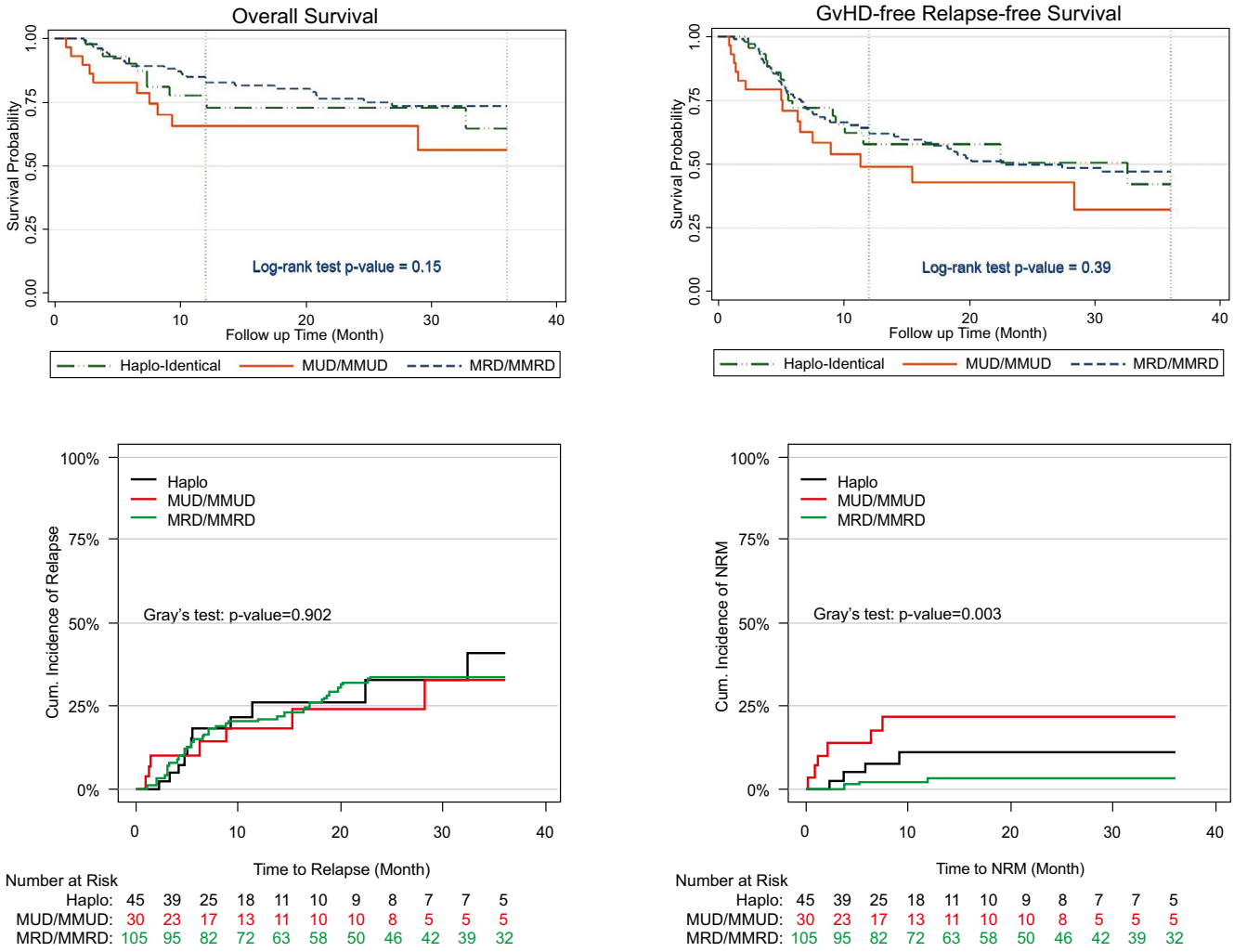

Figure 1. Clinical outcomes in the cohort of young patients subjected to HSCT from different types of donors. A. Overall survival, B. GvHD-free, relapse-free survival, C. Relapse incidence, D. Non-relapse mortality of patients included in the study. Abscissa, observation terms

Note: Haplo: HLA-haploidentical donors, MRD/MMRD: HLA-matched related and HLA-mismatched related donors, MUDMMUD: HLA-matched unrelated and HLA-mismatched unrelated donors.

Donor cell engraftment

All the patients (180/180) achieved neutrophil counts over 0.5×10^9/L at a median time of 11 days (range: 7-16). A total of 178 patients achieved platelet counts above 20×10^9/L, with a median time of 11 days (range: 0-130), and 4 patients died before the platelet engraftment (Table 2). The median time for neutrophil and platelet engraftment in Haplo *vs* MUD/MMUD *vs* MRD/MMRD was 12.20 and 14.67 days *vs* 12.17 and 16.21 days *vs* 10.73 and 14.30 days, respectively. Two patients from the Haplo group experienced secondary graft failure following CMV reactivation with high viral load after HSCT; one patient was successfully rescued by the second haploidentical HSCT from the same sibling donor, whereas other patient received a second allograft from other parent followed by sustained engraftment and hematopoietic recovery.

Acute and chronic GVHD

Grade II to IV of aGvHD was diagnosed in 70 patients (38.9%), being developed at the median term of 15 days after HSCT. Cumulative aGVHD incidence at day 100 was highest in the MUD/MMUD group compared to Haplo and MRD/MMRD, but this difference was not statistically significant [31.6% (±11.8) *versus* 10.5% (±7.0) *versus* 27.3% (±6.0), respectively (P=0.845)].

Among 165 patients who survived more than 100 days after HSCT, 27 patients (15%) developed cGvHD, and we observed lower incidence of 3-year cGVHD in the haploidentical group compared to the MUD/MMUD group [7.0% (±5.0) *versus* 22.5% (±10.3), respectively]. Table 2 represents the comparison for GvHD incidence in the 3 donor types.

Relapse incidence (RI)

The 1-year and 3-year RI of the entire study population was 20.47% (95% CI 14.66-26.97) and 33.85% (95% CI 25.81-41.98), respectively. The 3-year RI in patients of the Haplo group was higher when compared to MUD/MMUD and MRD/MMRD: 40.95% (95% CI 18.41-62.44) *versus* 32.94% (95% CI 11.92-56.01) *versus* 33.17% (95% CI 23.64-42.99), respectively (Table 3). This difference was not statistically

Table 3. One- and three-year relapse incidence (RI) and non-relapse mortality (NRM) following HSCT

		1-year RI (95% CI)	3-year RI (95% CI)	P-value	1 and 3-year NRM % (95% CI)	P-value
Leukemia type	B-ALL	22.78% (14.57-32.12)	34.87% (23.89-46.05)	0.902	10.24% (4.96-17.75)	0.497
	T-ALL	43.60% (21.45-63.92)	53.86% (24.62-76.09)		5.12% (0.30-21.80)	
	AML	8.70% (3.15-17.81)	25.22% (13.55-38.71)		5.05% (1.30-12.80)	
WBC at diagnosis ($\times 10^9$/l)	≤50	16.74% (8.44-27.46)	21.52% (11.55-33.52)	0.178	7.19% (2.22-16.18)	0.647
	50-100	24.88% (6.94-48.39)	35.64% (10.58-62.26)		10.52% (1.65-29.05)	
	>100	32.51% (15.86-50.38)	40.62% (18.89-61.45)		10.69% (2.60-25.43)	
Relapse site	No relapse	14.27% (7.76-22.69)	14.27% (7.76-22.69)	0.049	6.13% (2.24-12.82)	0.134
	BM/BM+	20.13% (10.17-32.49)	20.13% (10.17-32.49)		14.0% (5.99-25.31)	
	Extramedullary	44.71% (21.73-65.42)	44.71% (21.73-65.42)		4.82% (0.29-20.59)	
Disease status at HSCT	CR1	14.44% (7.85-22.95)	29.70% (19.09-41.07)	0.122	4.88% (1.57-11.14)	0.181
	CR2	30.14% (19.15-41.88)	40.24% (26.67-53.43)		12.94% (5.92-29.72)	
	CR≥3	15.31% (3.59-34.68)	29.80% (9.78-53.22)		5.0% (0.31-21.10)	
Gender	Male	25.42% (17.62-33.94)	39.47% (28.88-49.47)	0.035	6.39% (2.79-12.08)	0.318
	Female	10.73% (4.31-20.51)	23.63% (12.26-37.10)		10.68% (4.25-20.50)	
Age at HSCT (year)	≤15	21.36% (14.40-29.25)	34.73% (25.31-44.31)	0.582	4.31% (1.59-9.20)	0.01
	>15	18.44% (8.96-30.58)	32.32% (17.37-48.25)		16.48% (7.53-28.45)	
Donor type	Haplo	25.82% (12.12-41.94)	40.95% (18.41-62.44)	0.902	10.61% (3.21-23.14)	0.003
	MUD/MMUD	18.33% (6.36-35.18)	32.94% (11.92-56.01)		21.40% (8.36-38.36)	
	MRD/MMRD	19.69% (12.58-27.98)	33.17% (23.64-42.99)		3.06% (0.81-8.01)	
R/D ABO matching	Matched	18.12% (11.38-26.11)	35.81% (25.24-46.49)	0.979	5.65% (2.29-11.24)	0.427
	Major MM	22.51% (10.95-36.59)	29.43% (15.42-44.93)		10.13% (3.13-21.98)	
	Minor MM	26.76% (10.50-46.25)	32.73% (13.76-53.31)		13.58% (3.16-31.52)	
Donor age (year)	≤30	19.44% (12.84-27.07)	32.87% (23.64-42.38)	0.812	6.65% (3.08-12.12)	0.475
	>30	23.04% (12.12-36.01)	36.10% (20.91-51.51)		10.48% (3.77-21.16)	
CD34+ Cell dose infused ($\times 10^6$/kg)	≤6	23.21% (15.94-31.29)	34.39% (25.28-43.66)	0.318	6.84% (3.17-12.42)	0.137
	6-8	9.01% (2.23-21.81)	27.66% (9.81-49.09)		16.38% (5.55-32.24)	
	>8	25.22% (7.29-48.45)	53.26% (13.96-81.75)		0	
CD3+ Cell dose infused ($\times 10^6$/kg)	≤250	18.73% (10-78-28.39)	36.02% (23.13-49.06)	0.923	9.57% (4.14-17.75)	0.471
	>250	22.31% (14.24-31.51)	33.44% (22.99-44.21)		6.60% (2.67-13.01)	

Notes: ALL: acute lymphoblastic leukemia, AML: acute myeloblastic leukemia, BM: bone marrow, BM+: involvement of bone marrow together with other sites, CR: complete remission, Haplo: HLA-haploidentical donors, MM: mismatched, MRD/MMRD: HLA-matched related and HLA-mismatched related donors, MUDMMUD: HLA-matched unrelated and HLA-mismatched unrelated donors, NRM: non-relapse mortality, R/D: recipient/donor, RI: relapse incidence, WBC: white blood cell.

significant (P=0.902). In the Cox analysis, using both univariate and multivariate approaches, RI was not significantly different among the three donor type groups. In adjusted multivariable RI modeling, the hazard of relapse in the patients from MUD/MMUD group was only 10% lower than for the patients from Haplo group [HR=0.90 (95% CI 0.37-2.19), P=0.826].

Survival rates and post-HSCT complications

The 3-year OS and GFRFS rates for the entire study cohort were 68.81% (95% CI 60.08-76.01), and 44.19% (95% CI 35.52-54.49), respectively (Fig. 1). Patients in the MUD/MMUD group had the lowest OS and GFRFS compared to other donor types (Table 4).

The 3-year OS rates were 73.58% (95% CI 62.98-81.59), 54.21% (95% CI 29.61-73.49), and 64.18% (95% CI 39.76-80.79) for MRD/MMRD, MUD/MMUD, and Haplo groups, respectively (P=0.08); The 3-year GFRFS rates were 47.11% (95% CI 36.48-57.02), 30.89% (95% CI 10.70-53.80), and 42.46% (95% CI 20.41-63.01) for MRD/MMRD, MUD/MMUD, and Haplo groups, respectively (P=0.26). In the Cox analysis, using both univariate and multivariate approaches, OS and GFRFS were not significantly different among the 3 donor type groups. Adjusted multivariable modeling of OS based on the variables selected in unadjusted univariate models (see Patients and methods) showed that hazard of death in the patients who received HSCT from MUD/MMUD was about 3.6 times higher than in cases of

Table 4. One- and three-year overall survival (OS) and GFRFS rates following HSCT in young patients

		1-year OS (95% CI)	3-year OS (95% CI)	P-value	1-year GFRFS (95% CI)	3-year GFRFS (95% CI)	P-value
Leukemia type	B-ALL	74.22% (63.38-82.29)	63.49 (51.0-73.61)	0.002	53.6% (42.32-63.62)	39.35% (27.77-50.71)	0.032
	T-ALL	59.48% (34.69-77.50)	47.59% (20.04-70.96)		47.03% (24.92-66.40)	35.27% (12.26-59.61)	
	AML	91.51% (80.76-96.38)	83.11% (68.06-91.49)		73.55% (59.91-83.18)	55.0% (39.83-67.82)	
WBC at diagnosis ($\times 10^9$/l)	≤50	83.93% (71.14-91.38)	78.69% (64.23-87.83)	0.145	61.78% (47.56-73.19)	54.07% (39.24-66.75)	0.133
	50-100	62.64% (34.15-81.57)	62.64% (34.15-81.57)		48.58% (22.13-70.78)	38.86% (14.09-63.39)	
	>100	70.83% (49.88-84.29)	70.83% (49.88-84.29)		44.87% (25.72-62.31)	34.9% (14.20-56.68)	
Relapse site	No relapse	86.54% (76.96-92.33)	79.11% (67.20-87.10)	0.010	68.47% (57.17-77.37)	49.39% (36.80-60.78)	0.053
	BM/BM+	72.53% (58.89-82.31)	57.92% (41.74-71.08))		53.15% (39.14-65.31)	38.24% (24.56-51.78)	
	Extra-medullary	61.48% (37.17-78.73)	53.80% (28.72-73.49)		40.45% (20.0-60.11)	40.45% (20.0-60.11)	
Disease status at HSCT	CR1	87.71% (78.32-93.21)	80.18% (68.25-88.01)	0.002	69.41% (58.11-78.23)	50.07% (37.35-61.51)	0.0358
	CR2	65.78% (52.22-76.34)	54.51% (39.23-67.47)		46.39% (33.22-58.54)	36.57% (23.60-49.61)	
	CR≥3	77.78% (50.52-91.17)	62.85% (34.19-81.80)		58.34% (33.65-76.59)	43.75% (19.98-65.42)	
Gender	Male	77.74% (68.55-84.54)	64.53% (53.15-73.81)	0.264	54.78% (44.79-63.71)	39.38% (29.02-49.56)	0.073
	Female	79.65% (66.11-88.24)	77.0% (62.71-86.38)		69.19% (55.03-79.68)	53.37% (37.77-66.71)	
Age at HSCT (year)	≤15	79.85% (71.18-86.17)	70.59% (60.21-78.73)	0.447	67.04% (57.55-74.87)	49.87% (39.34-59.51)	0.008
	>15	74.87% (59.71-85.01)	63.96% (45.94-77.36)		41.11% (26.73-54.94)	29.98% (15.99-45.31)	
Donor type	Haplo	77.55% (59.67-88.23)	64.18% (39.76-80.79)	0.082	58.23% (39.73-72.84)	42.46% (20.41-63.01)	0.268
	MUD/ MMUD	63.24% (42.01-78.50)	54.21% (29.61-73.49)		47.06% (26.87-64.91)	30.89% (10.70-53.80)	
	MRD/ MMRD	82.8% (73.76-88.96)	73.58% (62.98-81.59)		63.17% (52.90-71.80)	47.11% (36.48-57.02)	
R/D ABO matching	Matched	84.07% (75.20-89.98)	74.40% (63.09-82.71)	0.080	65.33% (55.22-73.69)	47.96% (36.76-58.31)	0.364
	Major MM	72.50% (55.76-83.77)	62.19% (44.04-75.96)		53.47% (36.47-67.81)	42.23% (25.27-58.26)	
	Minor MM	63.06% (39.29-79.65)	54.05% (28.17-74.17)		45.70% (24.45-64.71)	29.38% (9.70-52.57)	
Donor age (year)	≤30	80.85% (72.29-87.0)	71.63% (61.34-79.63)	0.308	61.43% (51.84-69.67)	45.04% (34.74-54.80)	0.872
	>30	72.95% (57.90-83.36)	62.48% (45.0-75.80)		55.47% (39.99-68.46)	42.13% (26.19-57.25)	
$CD34^+$ Cell dose infused ($\times 10^6$/kg)	≤6	76.53% (67.61-83.30)	66.88% (56.65-75.22)	0.654	55.43% (45.74-64.08)	42.85% (33.01-52.30)	0.593
	6-8	77.19% (57.40-88..62)	77.19% (57.40-88..62)		68.24% (48.41-81.77)	49.63% (27.06-68.70)	
	>8	92.31% (56.64-98.88)	63.30% (21.45-87.30)		68.32% (39.69-85.47)	42.70% (12.82-70.29)	
$CD3^+$ Cell dose infused ($\times 10^6$/kg)	≤250	73.48% (61.48-82.27)	66.13% (52.09-76.94)	0.446	60.14% (47.81-70.44)	39.51% (25.91-52.80)	0.601
	>250	81.91% (72.07-88.55)	69.97% (57.74-79.27)		58.26% (47.10-67.86)	47.20% (35.68-57.88)	

Notes: ALL: acute lymphoblastic leukemia, AML: acute myeloblastic leukemia, BM: bone marrow, BM+: involvement of bone marrow together with other sites, CR: complete remission, GFRFS: GvHD-free/relapse-free survival, Haplo: HLA-haploidentical donors, MM: mismatched, MRD/MMRD: HLA-matched related and HLA-mismatched related donors, MUD/MMUD: HLA-matched unrelated and HLA-mismatched.

HSCT from haploidentical donors, and this difference was statistically significant (P=0.05). Moreover, in those patients who received HSCT from MRD/MMRD, the hazard of death was 12 percent higher than for those who received HSCT from haploidentical donors [HR=1.12, (95% CI 0.34-3.67), P=0.84].

The 3-year NRM in all patients was 7.84% (95% CI 4.36-12.62). The patients who underwent MUD/MMUD HSCT showed significantly higher NRM compared to the patients who received Haplo and MRD/MMRD transplants (Table 3): 21.40% (95% CI 8.36-38.36) *versus* 10.61% (95% CI 3.21-23.14) *versus* 3.06% (95% CI 0.81-8.01), respectively (P=0.003).

Considering the causes of NRM among patients from MUD/MMUD group who died in the disease remission, we observed six cases of infection and one case of heart failure. In the Haplo group, one patient deceased from NRM had aGvHD, and four others developed infection. In the MRD/MMRD group, one patient was lost due to aGvHD, three patients died with infectious complications, and one case, due to unknown reason.

Adjusted multivariable modeling of NRM showed that hazard of death in the patients who received HSCT from MUD/MMUD was 6 times higher than the hazard of death for the patients who received HSCT from haploidentical donors. This difference was statistically significant (P=0.002). In those patients who received HSCT from MRD/MMRD, the hazard of death was not higher than in those who received HSCT from haploidentical donors (P=0.23).

Although the estimated risk of CMV reactivation prior to HSCT was high in most patients, CMV reactivation after HSCT was detected in a total of 61 cases (33.9%). CMV reactivation after HSCT occurred significantly more often in Haplo and MUD/MMUD group compared with the MRD/MMRD group (55.6% and 43.3% *versus* 21.9%, respectively, P=0.001). Worth of note, the CMV reactivation post-HSCT was associated with decreased OS and GFRFS in all three groups, being, however, statistically non-significant (P=0.09).

Hemorrhagic cystitis (HC) was another documented complication post-HSCT which occurred in 36 patients (20%), and it mostly affected the patients from Haplo and MUD/MMUD groups compared with MRD/MMRD group (35.6% and 33.3% *versus* 9.5%, respectively, P=0.000). Sinusoidal obstruction syndrome (SOS) was documented in only 5 patients, i.e. one case from Haplo group, two patients transplanted with MUD/MMUD grafts, and two, from the MRD/MMRD group.

Discussion

Allogeneic HSCT has augmented the potential of cure in patients with acute leukemia [12-15]. Although HLA-compatible related and unrelated donors have been traditionally used for treating acute leukemia patients requiring an allograft, there remains a significant proportion of patients for whom HLA-identical acceptable donor is not available. For these patients, the use of a haploidentical donor combined with alloreactive T cell elimination by Pt-Cy is the most widely adopted strategy [16]. Our study has shown that, for children, adolescents and young adults (CAYA) affected by acute leukemia, haploidentical HSCT followed by Pt-Cy may offer a better and more accessible chance of cure in terms of NRM and survival rates when compared with HSCT from unrelated donors who are hardly available, especially in the COVID-19 pandemic era.

Different studies reported that haploidentical HSCT could provide similar results to those of MUD and MMUD [17-19]. Several reports have shown, at least, comparable outcomes between Haplo and historical MRD, MUD, and MMUD series [20-23]. In our work, in consistence with most studies, the MRD/MMRD group had the best survival rates within the three donor types. Nevertheless, surprisingly, the survival rates were higher in the Haplo group compared to MUD/MMUD group.

Saglio et al., using a TBI-based conditioning regimen, have reported similar OS rates for Haplo and MUD/MMUD in CAYA patients [24]. In our study, OS rates were much higher in Haplo group compared to the MUD/MMUD group. Likewise, in our patients who had undergone haploidentical HSCT, GFRFS was higher and NRM was much lower than the results attained after HSCT from MUD/MMUD.

In terms of GvHD, it has been emphasized that Pt-Cy is able to significantly eliminate alloreactive T cells and, therefore, to reduce the incidence of GvHD, especially its acute form [25]. In addition, ATG has been shown to reduce the rates of severe acute and chronic GvHD in cases of matched or mismatched, unrelated allogeneic HSCT [26, 27]. Chronic GvHD is the leading cause of late complications and death after allogeneic HSCT. Usage of peripheral blood stem cells as a graft source presents a sufficient risk factor for its development, since the T-cell levels in allografts are higher than those in bone marrow [28-30]. Low incidence of GvHD, particularly chronic GvHD, in our patients, as compared to other reports in the literature, despite application of MAC regimen, along with usage of peripheral blood stem cells, could be attributed to high doses of ATG in the conditioning regimen for HSCT in the patients undergoing Haplo and MUD/MMUD HSCT. In our study, the rates of acute and chronic GvHD were even lower in the Haplo group than among the patients in MUD/MMUD group. This could be ascribed to dual *in vivo* T-cell depletion caused by ATG and Pt-Cy in the Haplo group. However, adoption of the highly effective GvHD prophylaxis may potentially lead to increased risk of relapse. It seems to be true in our study, as we had the highest relapse incidence (RI) in the Haplo group. However, one should note that the difference in RI among our three donor types was not statistically significant. It is presumed that HLA disparity could be considered a contributing factor to allo-reactivity and GvL [31]. In the matched donor transplant setting, the frequency of donor T-cell precursors directed against leukemia-specific antigens mediating GvL may be more limited [32]. Other studies with less rigorous GvHD prophylaxis strategies compared to our approaches, have reported similar RI in Haplo and MUD/MMUD HSCT [24, 34].

With respect to transplant toxicity, our data confirm that the patients undergoing Haplo HSCT have much lower

NRM rates compared to patients undergoing MUD/MMUD HSCT, and the rates of complications, such as hemorrhagic cystitis and sinusoidal obstruction syndrome, seem to be comparable within the two groups. Previous studies comparing NRM rates in Haplo (with Pt-Cy) with MRD and MUD transplants (with standard GvHD prophylaxis) have reported inconsistent results. Meanwhile, some studies reported a higher NRM rates in Haplo HSCT [17, 35, 36].

This study was limited by its retrospective design, inability to adjust for unknown factors, the heterogeneity for conditioning regimens and supportive therapy that could affect the study outcomes.

Conclusions

Our study shows that inclusion of ATG into the myeloablative conditioning regimen before transplantation of peripheral blood stem cells from MUD/MMUD and Haplo donors is associated with reduced rates of chronic GvHD and graft failure, concomitantly. The rates of OS and GFRFS were higher in the Haplo group compared to MUD/MMUD, hence, our data supports the view that haploidentical HSCT with peripheral blood stem cells is a practical and valuable clinical option that offers CAYA patients with acute leukemia requiring HSCT and lacking matched available donors, a reasonable opportunity for the disease control. However, further progress is necessary to decrease the relapse rate in these patients.

Declarations

The study was approved by the Committee on Medical Ethics of Tehran University of Medical Sciences (TUMS) and informed consent was obtained from patients or their legal guardians. Authors provide a consent for publication. Primary data and materials are available on request.

Authors' contributions: TR designed and coordinated the study, and managed the patients. AK, MR and NA participated in the management of patients. AK carried out statistical evaluation. SA conceived of the study. All the authors read and approved the final manuscript.

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Competing Interests

None of the authors have any relevant conflict of interest to disclaim about the present article. No funding support for the study is declared.

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Трансплантация гемопоэтических клеток периферической крови от гаплоидентичных и неродственных доноров при острых лейкозах у детей, подростков и молодых взрослых: анализ конкурентного риска

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Резюме

Трансплантация аллогенных гематопоэтических клеток (алло-ТГСК) является единственной потенциальной возможностью излечения острого лейкоза. Многие параметры существенно влияют на конечный исход ТГСК, в т.ч. тип донора, источник стволовых клеток и применяемый режим кондиционирования. При отсутствии HLA-совместимого родственного донора, возможными кандидатами могут быть неродственные совместимые или гаплоидентичные доноры для пациентов с показаниями к ТГСК. Для того, чтобы сопоставить исходы ТГСК от доноров различного типа с кондиционированием без облучения, мы сравнили в рамках одноцентрового исследования результаты трансплантации интактных ГСК периферической крови от совместимых и несовместимых, родственных и неродственных доноров, и гаплоидентичных доноров реципиентам детского, подросткового возрастов и молодым взрослым с острыми лейкозами.

Пациенты и методы

В данном ретроспективном исследовании, проводившемся с 2014 по 2021 г., мы оценивали исходы ТГСК с реплецией Т-лимфоцитов от гаплоидентичных

доноров или неродственных доноров (совместимость – 10/10 или 9/10), а также в сравнении с неродственными донорами у пациентов с острыми лейкозами этих возрастных групп. Кондиционирование при ТГСК проводили с применением миелоаблативного режима с бусульфаном и циклофосфамидом и без ионизирующего облучения. Профилактика РТПХ включала назначение циклоспорина А всем пациентам, кроличий антитимоцитарный глобулин для неродственных и гаплоидентичных доноров, и циклофосфамид при ТГСК от гаплоидентичных доноров. Статистическую обработку проводили с помощью многовариантного пропорционального анализа рисков по Коксу и анализ конкурирующих рисков.

Результаты

Средний срок наблюдения составлял 28,7 мес. (95% CI: 21,9-34,9). Трехлетняя общая выживаемость (ОВ) и выживаемости без РТПХ и рецидивов были, соответственно, 68,81% (95% CI: 60,08%-76,01%) и 44.19% (95% CI: 35,52%-52,49%). Пациенты после ТГСК от неродственных совместимых доноров имели более низкие уровни ОВ и выживаемости без РТПХ и рецидивов по сравнению с другими типами доноров. Трехлетние показатели безрецидивной летальности (NRM) среди всех пациентов составляли 7,84% (95% CI 4,36-12,62). Адаптированное многовариантное моделирование общей выживаемости показало, что риск гибели пациентов после ТГСК от неродственного донора был в 3,6 раза выше, чем у пациентов, получивших ТГСК от гаплоидентичных доноров (P=0.05). Аналогично, риск безрецидивной смертности (NRM) после ТГСК от неродственных доноров был в 6 раз выше, чем при ТГСК от гаплоидентичных доноров (P=0.002). Однако частота рецидивов не различалась существенно между двумя указанными группами.

Выводы

В данном исследовании показано, что ТГСК от гаплоидентичных доноров была ассоциирована с более высокими уровнями выживаемости, по сравнению с ТГСК от неродственных совместимых доноров. Таким образом, ТГСК от гаплоидентичных доноров может быть предложена в качестве практичной и ценной клинической опции, для пациентов молодых возрастов с острыми лейкозами в случае отсутствия совместимых доноров.

Ключевые слова

Острый лейкоз, аллогенная трансплантация гемопоэтических клеток, совместимые родственные доноры, неродственные доноры, гаплоидентичные доноры, клинические исходы.