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Influence of Donor Type (Sibling versus Matched Unrelated Donor versus Haploidentical Donor) on Outcomes after Clofarabine-Based Reduced-Intensity Conditioning Allograft for Myeloid Malignancies

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A B S T R A C T

Clofarabine-based reduced-intensity conditioning (RIC) regimens are well-established schedules for allograft in patients with myeloid malignancies. A retrospective study was conducted including all adults allografted in our department with such a regimen and disease with the aim to assess whether or not the donor type (matched sibling [MSD], matched unrelated [MUD], or haploidentical [haplo]) impacted outcomes. Between October 2009 and February 2018, 118 patients met the inclusion criteria. Thirty-six, 55, and 27 patients received a graft from an MSD, MUD, or haplo donor, respectively. Peripheral blood stem cells (PBSCs) were the source of graft for all patients. The median age of the entire cohort was 62 years (range, 20 to 73), and the median follow-up was 31 months (range, 4.5 to 106). All patients engrafted except 1 haplo recipient. Neutrophils ($>.5 \times 10^9$/L) and platelets (50×10^9/L) recoveries were significantly delayed in the haplo group ($P = .0003$ and $P < .0001$) compared with MSD and MUD. Acute grades II to IV or III to IV graft-versus-host disease (GVHD) incidences were similar between the 3 groups as well as the incidence of moderate or severe chronic GVHD. Also, similar 2-year overall survival (OS; 64.7% versus 73.9% versus 60.2%, $P = .39$), disease-free survival (DFS; 57.7% versus 70.9% versus and 53.6%, $P = .1$), and GVHD relapse-free survival (37.9% versus 54.3% versus 38.9%, $P = .23$) were observed between MSD versus MUD versus haplo groups. The same was true when considering only acute myeloid leukemia (AML) cases. In multivariate analysis the type of donor remained independent of outcomes in this series, whereas myelodysplastic syndrome (versus AML), high disease risk index, and older donor (≥50 years) were associated with lower OS and DFS. These data suggest that haplo donors are an acceptable alternative for patients receiving a clofarabine-based RIC PBSC allograft for myeloid malignancies who lack an MSD or a MUD.

INTRODUCTION

Haploidentical stem cell transplantations using high-dose post-transplant cyclophosphamide (PTCY) are increasingly used in patients lacking suitable matched donors [1]. The Baltimore reduced-intensity conditioning (RIC) regimen, combining fludarabine, low doses of cyclophosphamide and total body irradiation, followed by PCTY, has become a standard of care in this setting in some institutions [2]. Recently we reported the encouraging results of a "Clo-Baltimore" RIC regimen for myeloid malignancies where fludarabine was replaced by clofarabine and bone marrow by peripheral blood stem cells (PBSCs) as the source of graft [3]. Previously we also reported very good outcomes using a "CloB2A1/A2" RIC (clofarabine, busulfan, and antithymocyte globulin) regimen for patients with matched sibling (MSD) or matched unrelated (MUD) donors [4].

Clofarabine is a second-generation purine analogue [5], with a potentially higher antileukemic activity than fludarabine, especially in allotransplants for myeloid disorders [6,7]. Thus, clofarabine-based regimens currently represent a valid platform for allotransplant when considering acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), or myeloproliferative neoplasms.

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When comparing haploidentical (haplo) transplants with transplants from standard donors (MSD or MUD), almost all retrospective analyses have shown similar disease-free survival (DFS) or overall survival (OS), sometimes with the advantage of less severe acute or chronic graft-versus-host disease (GVHD) for the haplo group, allowing for better GVHD-free/relapse-free survivals (GRFS) [8-20]. This is also true when considering haplo donors versus cord blood (CB) transplants [8]. Although unclear, some studies suggest that haplo donors may be an even better choice than MSD for Hodgkin disease [21] or CB in some AML patients [22,23]. Considering our long experience of clofarabine-based RIC regimens and because to our knowledge no studies are available, we conducted a retrospective study with the aim to determine whether the type of donor (MSD versus MUD versus haplo) did or did not have an impact on post-transplant outcomes in patients allografted with such a regimen for myeloid malignancies.

METHODS

Patients

This retrospective study included all adult patients (≥18 years old) with a myeloid malignancy allografted at our institution after a clofarabine-based RIC regimen whatever the type of donor. All patients received PBSCs as source of graft.

This study was approved by the ethical review board of Nantes University Hospital. All patients provided informed consent, and data were collected from ProMISe (Project Manager Internet Server), an internet-based system shared by all European transplantation centers.

Clofarabine-Based RIC Conditioning Regimens

Patients allografted with MSDs or MUDs received a CloB2A1/A2 RIC regimen consisting of clofarabine 30 mg/m^2/day for 4 to 5 days (Clo), busulfan 3.2 mg/kg/day for 2 days (B2), and 2.5 mg/kg/day of rabbit antithymocyte globulin for 1 or 2 days (A1 or A2) [4,6]. Patients allografted with a haplo donor received a Clo-Baltimore regimen consisting of clofarabine 30 mg/m^2/day on days −6 to −2, cyclophosphamide 14.5 mg/kg on day −6, and low-dose total body irradiation 2 Gy on day −1 [3].

All patients received cyclosporine + mycophenolate mofetil as GVHD prophylaxis, except MSD recipients, who were given cyclosporine alone. Haplo recipients received PTCY 50 mg/kg/day on days +3 and +4.

Statistical Analyses

The clinical outcomes studied were OS, DFS, GRFS, relapse incidence, nonrelapse mortality (NRM), acute GVHD incidence (grades II to IV and III to IV), chronic GVHD incidence, and hematologic recoveries. OS was defined as the time from day 0 of allogeneic stem cell transplantation to death or last follow-up for survivors. DFS was defined as time from day 0 of allogeneic stem cell transplantation to time without evidence of relapse or disease progression censored at the date of death or last follow-up. Neutrophils and platelets recoveries were defined as the first day of 3 consecutive days with neutrophils $> .5 \times 10^9$/L and platelets $> 50 \times 10^9$/L. Relapse was defined as any event related to recurrence of the disease. NRM was defined as death from any cause without previous relapse or progression. Acute and chronic GVHD were diagnosed and graded according to standard criteria [24,25]. GRFS was defined as patients alive with no previous grades III to IV acute GVHD, or moderate to severe chronic GVHD, or relapse [26].

Probabilities of OS and leukemia-free survival were calculated using the log-rank test and Kaplan-Meier graphic representation. Cumulative incidence functions [27] were used to estimate relapse incidence and NRM in a competing risk setting. Survival probabilities are presented as percentages and 95% confidence intervals (CIs).

Univariate analyses were performed using the log rank test for OS, DFS, and GRFS and the Gray test for cumulative incidence function. Characteristics considered for univariate analysis were age (< or ≥60 years), gender (male versus female), disease (AML versus MDS), disease status at transplant (complete remission [CR] versus active), type of donor (MSD versus MUD versus haplo), and disease risk index (DRI) [28] (intermediate versus high). Comparison of survivals according to the type of donor (MSD versus MUD versus haplo) was also performed for AML patients.

Multivariate analyses were performed using the Cox proportional-hazard model. Factors with $P < .20$ by univariate analysis or of interest for the study were included in the multivariate analysis.

All tests were 2-sided, and $P < .05$ was considered as indicating a statistically significant association. Analyses were performed in July 2018 using the Medcalc statistical software (Ostend, Belgium).

RESULTS

Outcomes of the Entire Cohort

Between October 2009 and February 2018, 118 patients fulfilled inclusion criteria, including 68 men and 50 women. The median age was 62 years (range, 20 to 73). Most patients were diagnosed with AML (n = 78, including 2 granulocytic sarcoma), then MDS (n = 31), and other myeloid diseases (n = 9). Most patients was in CR at transplant (first CR, 77; second CR, 14; third CR, 1). Thirteen and 7 patients had been allotransplanted or autotransplanted previously. Thirty-six patients had MSDs, 55 MUDs, and 27 had haplo donors. The median CD34$^+$ PBSC dose infused was 7.39×10^6/kg of recipient (range, 2.49 to 12.9). The outcomes of some patients were reported previously [3,4] but were updated for the present study. Patient characteristics are given in Table 1.

All patients engrafted except 1 haplo recipient, who died of infection before engraftment. The median times for neutrophils and platelets recoveries were 16 days (range, 8 to 53) and 12.5 days (range, 7 to 99), respectively.

With a median follow-up of 31 months (range, 4.5 to 106) for surviving patients, 2-year OS, DFS, and GRFS were 69.3% (range, 61% to 78%), 62.9% (range, 54% to 72%), and 45.7% (range, 37% to 56%), respectively. The 2-year incidence of relapse was 22.8% and 2-year NRM 11%. The incidences of day 100 grades II to IV and III to IV acute GVHD were 43.2% and 16.1%, respectively. The incidence of 2-year moderate + severe chronic GVHD was 15.2%. Thirty-nine patients died, with the main causes of death relapse (n = 23, 58%) and then infection (n = 9), GVHD (n = 5), thrombotic microangiopathy (n = 1), and dermatomyositis (n = 1).

Comparison of Outcomes between Recipients Allografted with MUDs versus MSDs versus Haplo Donors

The 3 groups shared similar characteristics (Table 1), except regarding ABO compatibility (less frequent in the MUD group, 42% versus MSD 69% versus haplo 67%; $P = .02$), median CD34$^+$ graft PBSCs (lower in the haplo group, $P = .02$), and a previous history of allograft (haplo, n = 7; MUD, n = 6; MSD, n = 0; $P = .005$). Also, although the same proportion of patients in CR was observed in the 3 groups, less patients were in first CR in the haplo group (52% versus 65% for MUD and 75% for MSD, $P = .02$). Donors were significantly younger in the MUD group (median, 30 years versus MRD 63 years versus haplo 43 years; $P < .001$). Finally, post-transplant donor lymphocyte infusion or maintenance were less frequent in the haplo group (3 patients [11%] versus MUD 18 patients [33%] versus MRD 12 patients [33%], $P = .08$).

The median length of stay was significantly higher for the haplo group: 31 days (range, 23 to 135) versus MUD 25 days (range, 14 to 38) versus MRD 25.5 days (range, 18 to 70; $P < .001$; MUD versus MRD, $P = .26$). Neutrophils and platelets recoveries were significantly delayed in the haplo group (19 days [range, 8 to 27] versus MUD 15 days [range, 10 to 31] versus MSD 15 days [range, 10 to 53], $P = .0003$; and 31 days [range, 14 to 99] versus 12 days [range, 7 to 55] versus 11 days [range, 9 to 28], $P < .0001$; respectively).

Day 100 acute grades II to IV or III to IV GVHD incidences were similar between the 3 groups at 34.5% and 14.5% for MUD, 50% and 22% for MSD, and 48% and 11% for haplo ($P = .18$ for grades II to IV and $P = .45$ for grades III to IV) as well as moderate + severe chronic GVHD incidences (MUD 16%, MSD 14%, haplo 15%; $P = .94$).

With a median follow-up of 34.2 (range, 6 to 74), 21.4 (range, 7 to 53), and 33.7 (range, 4.5 to 106) months for patients allografted with MUDs, MSDs, or haplo donors,

Table 1
Patient Characteristics

	All Patients(N = 118)	MSD Group(n = 36)	MUD Group(n = 55)	Haplo Group(n = 27)	P*
Median follow-up, mo (range)	31 (4.5-106)	34.2 (6-74)	33.7 (4.5-106)	21.4 (7-53)	
Gender, male/female	68/50	20/16	34/21	14/13	.66
Median age, yr (range)	62 (20-73)	63 (32-71)	61 (20-72)	62 (33-73)	.69
Disease					
AML†	78	22	41	15	.13
Myelodysplastic syndrome	31	11	12	8	
Myelofibrosis	2	0	1	1	
Chronic myeloid leukemia	1	0	0	1	
MDS/myeloproliferative disease	3	1	1	1	
Plasmacytoid dendritic cell neoplasm	1	0	0	1	
Biphenotypic leukemia	2	2	0	0	
Disease status					
First CR	77	27	36	14	.02
Second CR	14	0	11	3	.16
Third CR	1	0	0	1	
Active disease	26	9	8	9	
CR vs. active					
Previous allograft	13	0	6	7	.005
Previous autograft	7	2	1	4	.06
DRI [28]					
Low	70	25	30	15	.14
Intermediate	43	8	24	11	
High	5	3	1	1	
Very high					
Not applicable					
European LeukemiaNet 2010 criteria for AML					
Favorable		1	4	4	.14
Intermediate 1 + 2		16	28	6	
High		4	8	5	
Donor					
Median age, yr (range)	42 (19-76)	63 (22-76)	30 (19-49)	43 (26-71)	<.001
Haplo (son, daughter, sister, brother, father, nephew)				(10, 2, 7, 4, 2, 2)	
MSD					
MUD			54		
Mismatch unrelated 9/10		36	1		
CMV status recipient/donor					
−/−	56	13	25	18	.09
−/+	10	4	3	3	
+/+	25	11	10	4	
+/−	27	8	17	2	
ABO compatibility					
Compatibility	66	25	23	18	.02
Minor incompatibility	31	4	21	6	
Major incompatibility	21	7	11	3	
Median PBSC graft, $CD34^+$ cells $\times 10^6$/kg					
	7.39 (2.49-12.9)†	7.94 (3.46-12.9)	7.87 (2.78-12.12)	6.62 (2.49-10.04)	.02
Conditioning regimen					
CloB2A2 [4]		13	19	0	
CloB2A1 [4]		21	30	0	
"Clo-Baltimore" [3]		2	6	27	.08
Maintenance postgraft or DLI					
5'-Azacytidine		1	3	1	
DLI (mixed chimerism/persistence of MRD)		6 (5/1)	5 (4/1)	1 (1/0)	
5'-Azacytidine + DLI		4	10	1	
Sorafenib		1	0	0	

CMV indicates cytomegalovirus; DLI, donor lymphocyte infusion; MRD, minimal residual disease.
* Comparison between patients allografted with an MSD vs. a MUD vs. a haplo donor.
† Including 2 granulocytic sarcoma.

respectively, rates of 2-year OS were 73.9% (range, 62% to 87%), 64.7% (range, 50% to 83%), and 60.3% (range, 43% to 83%; $P = .39$) (Figure 1), of DFS were 70.9% (range, 59% to 84%), 57.7% (range, 43% to 76%), and 53.6% (range, 37% to 77%; $P = .1$) (Figure 2), and of GRFS were 54.3% (range, 41% to 70%), 37.9% (range, 24% to 57%), and 38.9% (range, 23% to 63%; $P = .23$) (Figure 3) and were similar between the 3 groups. The same was observed regarding 2-year NRM (14% versus 11% versus 18.5%, respectively; $P = .63$).

Comparison of Survivals between AML Recipients Allografted with MUD versus MSD versus Haplo Donor

There was no difference in terms of European LeukemiaNet 2010 classification [29] for AML patients between the 3 groups. Again, similar 2-year survivals were observed between these 3 groups: OS: MUD (n = 40) 75.1% (range, 62% to 90%) versus MSD (n = 21) 71.4% (range, 54% to 93%) versus haplo (n = 15) 66.6% (range, 46% to 95%; $P = .45$); DFS: 70.8% (range, 57% to 87%) versus 66.6% (range, 49% to 90%) versus 66.6% (range, 46% to 95%; $P = .38$); and GRFS: 56% (range, 41% to 75%) versus 38% (range, 22% to 65%) versus 40% (range, 21% to 74%; $P = .12$).

Univariate and Multivariate Analysis for Survivals

In univariate analysis (Table 2) the type of donor, type of disease (AML versus MDS), gender, age, and disease status were not associated with GRFS, DFS, or OS. Conversely, intermediate DRI was associated with better 2-year DFS (70.3% [range, 60% to 82%] versus high DRI 52% [range, 38% to 69%], $P = .03$) and OS (76.5% [range, 66% to 87%] versus high 55.7% [range, 42% to 73%], $P = .009$). Also, younger donors (<50 years) were associated with better 2-year GRFS (52.7% [range, 41% to 66%] versus 33.3% [range, 21% to 51%], $P = .01$), DFS (67.7% [range, 57% to 79%] versus 50.8% [range, 37% to 69%], $P = .02$) and OS (77% [range, 67% to 87%] versus 51.8% [range, 37% to 70%], $P = .01$).

In multivariate analysis (Table 3), donor type remained independent of outcomes in this series. AML (versus MDS) was independently associated with higher DFS (hazard ratio [HR], .41; 95% CI, 1.17 to .99; $P = .05$) and OS (HR, .39; 95% CI, .16-.96; $P = .04$). Conversely, high DRI status (OS: HR, 2.81; 95% CI, 1.36 to 5.79; $P = .005$; DFS: HR, 2.27; 95% CI, 1.16 to 4.45; $P = .017$), and older donor (≥50 years) (OS: HR, 2.37; 95% CI, 1.15 to 4.91; $P = .02$; DFS: HR, 2.27; 95% CI, 1.16 to 4.44; $P = .017$) were independently associated with lower OS and DFS. Younger donors and patients as well as female recipient were associated with better GFRS.

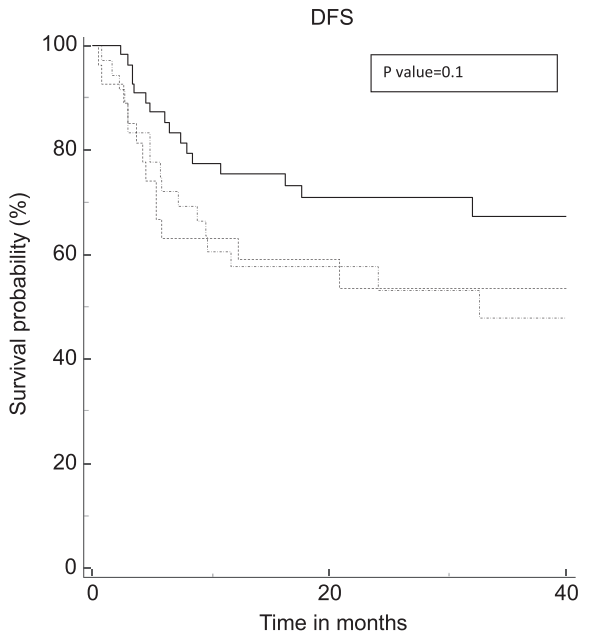

Figure 2. Comparison of DFS between patients receiving a clofarabine-based RIC allotransplant from matched sibling (*dot-dashed line*), matched unrelated (*full line*), or haplo (*dashed line*) donors.

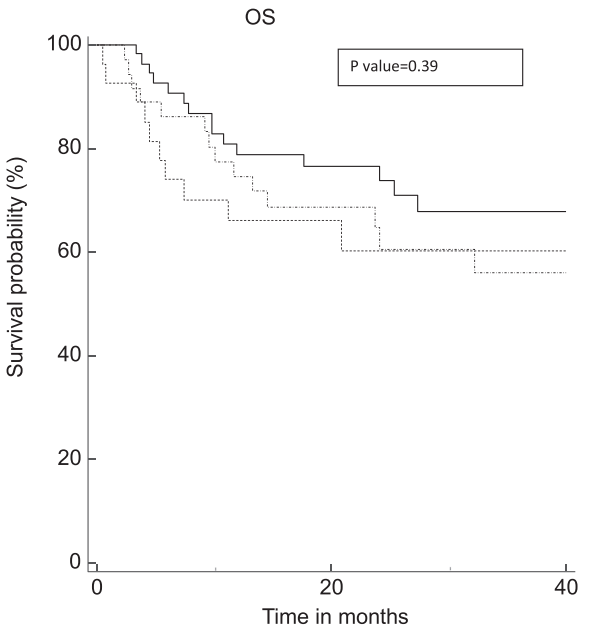

Figure 1. Comparison of OS between patients receiving a clofarabine-based RIC allotransplant from matched sibling (*dot-dashed line*), matched unrelated (*full line*), or haplo (*dashed line*) donors.

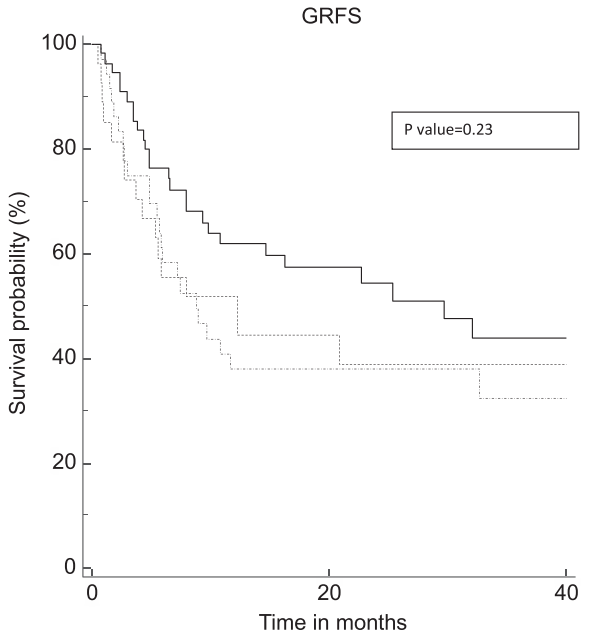

Figure 3. Comparison of GRFS between patients receiving a clofarabine-based RIC allotransplant from matched sibling (*dot-dashed line*), matched unrelated (*full line*), or haplo (*dashed line*) donors.

Table 2
Univariate Analysis

	2-Year GRFS	2-Year DFS	2-Year OS
Age < 60 yr, n = 48	47.8 (35-65)	63.5 (51-79)	72.7 (60-87)
vs. ≥60 yr, n = 70	44.2 (31-56) *P* = .79	62.7 (52-75) *P* = .75	64.8 (54-77) *P* = .28
	HR, .93 [.56-1.5]	HR, .91 [.50-1.64]	HR, .71 [.37-1.34]
Gender, female, n = 50	54.7 (41-71)	68.2 (56-83)	71.5 (59-86)
vs. male, n = 68	38.8 (28-52) *P* = .06	59.0 (48-72) *P* = .20	65.2 (54-78) *P* = .55
	HR, .63 [.38-1.04]	HR, .69 [.38-1.23]	HR, .83 [.44-1.55]
Disease, AML, n = 76	46.2 (35-59)	67 (57-78)	70 (60-81)
vs. others, n = 42	42.8 (29-61) *P* = .35	52.3 (38-70) *P* = .17	60.8 (46-78) *P* = .12
	HR, .77 [.46-1.31]	HR, .63 [.34-1.19]	HR, .61 [.31-1.18]
vs. MDS, n = 31	39.1 (25-60) *P* = .31	51.8 (36-72) *P* = .19	57.4 (42-78) *P* = .07
	HR, .74 [.41-1.32]	HR, .62 [.31-1.23]	HR, .49 [.23-1.02]
DRI, intermediate, n = 70	49.0 (38-62)	70.3 (60-82)	76.5 (66-87)
vs. high, n = 43	42.2 (29-60) *P* = .26	52.0 (38-69) *P* = .03	55.7 (42-73) *P* = .009
	HR, .74 [.44-1.25]	HR, .51 [.27-.94]	HR, .40 [.20-.80]
Disease status, CR, n = 92	44.4 (34-56)	64.6 (55-75)	70.1 (61-80)
vs. active, n = 26	49 (32-72) *P* = .96	56.6 (40-79) *P* = .54	65.9 (48-88) *P* = .70
	HR, .93 [.51-1.69]	HR, .90 [.44-1.86]	HR, .99 [.46-2.17]
Type of donors, MSD, n = 36	37.9 (24-57)	57.7 (43-76)	64.7 (50-83)
vs. MUD, n = 55	54.3 (41-70)	70.9 (59-84)	73.9 (62-87)
vs. haplo, n = 27	38.9 (23-63) *P* = .23	53.6 (37-77) *P* = .1	60.2 (43-83) *P* = .39
Donor age < 50 yr, n =n76	52.7 (41-66)	67.7 (57-79)	77 (67-87)
≥50 yr, n = 48	33.3 (21-51) *P* = .01	50.8 (37-69) *P* = .02	51.8 (37-70) *P* = .01
	HR, .56 [.34-.85]	HR, .51 [.28-.94]	HR, .50 [.26-.97]

Values are percents with ranges in parentheses and HRs with 95% CIs in brackets.

Table 3
Multivariate Analysis

	HR (Exp b)	95% CI	*P*
GRFS			
Type of donor (haplo vs. MUD vs. MRD)	.86	.58-1.27	.44
Age < 60 yr (vs. ≥60 yr)	.97	.95-.99	.04
AML (vs. MDS)	.55	.25-1.19	.13
Male (vs. female)	1.74	1.03-2.97	.04
CR (vs. active disease)	.76	.30-1.92	.56
High DRI (vs. intermediate)	1.39	.81-2.38	.23
Donor age ≥ 50 yr (vs. <50 yr)	2.12	1.17-3.84	.01
DFS			
Type of donor (haplo vs. MUD vs. MRD)	.95	.60-1.49	.82
Age < 60 yr (vs. ≥60 yr)	.99	.97-1.02	.74
AML (vs. MDS)	.41	1.17-.99	.05
Male (vs. female)	1.28	.69-2.38	.43
CR (vs. active disease)	.50	.17-1.47	.21
High DRI (vs. intermediate)	2.27	1.16-4.45	.017
Donor age ≥ 50 yr (vs. <50 yr)	2.27	1.16-4.44	.017
OS			
Type of donor (haplo vs. MUD vs. MRD)	.82	.51-1.33	.43
Age < 60 yr (vs. ≥60 yr)	1.02	.98-1.05	.24
AML (vs. MDS)	.39	.16-.96	.04
Male (vs. female)	1.21	.63-2.35	.56
CR (vs. active disease)	.48	.16-1.41	.18
High DRI (vs. intermediate)	2.81	1.36-5.79	.005
Donor age ≥ 50 yr (vs. <50 yr)	2.37	1.15-4.91	.02

DISCUSSION

This retrospective study demonstrates that survivals are not statistically different between allografted patients receiving MSD, MUD, or haplo donor grafts in the course of a clofarabine-based RIC allotransplant for myeloid diseases, especially AML, which was the largest group in this study. Of note, although neutrophil and platelet recoveries were significantly delayed in the haplo group, no increased incidence of acute or chronic GVHD was noted in this latter group.

Our results regarding survivals are in accordance with previous studies reporting other conditioning regimens and comparing various types of donors, including haplo [8-20]. We also confirm here the good survivals for AML patients allografted with clofarabine as part of the RIC regimen [4]. Clofarabine-based RIC regimens for myeloid malignancies are now considered as a valid alternative to standard of care RIC regimens. When considering matched donors, the comparison of clofarabine-based versus fludarabine-based RIC regimens showed that the former can likely provide longer survival and may become a new standard of care RIC regimen for allotransplanted AML patients. Indeed, in a retrospective study conducted on behalf of the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire, we showed that the 2-year OS was significantly higher for CloB2A2 patients versus FB2A2 patients (74.3% [range, 60.5% to 88%] versus 55.8% [range, 49.5% to 62.2%], *P* = .03). This was confirmed by multivariate analysis. However, when considering AML and MDS patients separately, the benefit of the CLOB2A2 regimen was restricted to AML patients [6]. When considering haplo donors, using a Clo-Baltimore regimen for myeloid malignancies where fludarabine is replaced by clofarabine as part of the Baltimore regimen, we demonstrated an 18-months OS and DFS of 66.2% ± 9% and 59% ± 9.5% [3], respectively, whereas less than 15% of 2-year event-free survival was obtained with the Baltimore regimen [2]. In another AML study [13] using different types of RIC regimens (Baltimore, cyclophosphamide-

fludarabine-busulfan or thiotepa-fludarabine-busulfan), the 31 haplo recipients achieved a 2-year OS and progression-free survival of 70% and 67%, respectively, suggesting that our clofarabine-based RIC regimen is at least as efficacious as a fludarabine-busulfan or thiotepa-fludarabine-busulfan RIC regimen for haplo transplants.

Using PBSCs, we obtained similar incidences of severe acute or chronic GVHD with haplo donors, suggesting that haplo PBSCs can be a valid alternative to bone marrow as a source of graft. The use of PBSCs instead of bone marrow is still debated in the haplo transplant setting. However, besides a suspected higher occurrence of GVHD (nor observed here), it may also allow an increase in the rate of engraftment [30] and speed up neutrophil and platelet recoveries [31] as well as reduce the incidence of relapse, especially in AML cases [31]. Thus, PBSCs and PTCY are far from being deleterious and may even be beneficial in some circumstances. Indeed, this combination seems to be highly effective in transplants with matched donors at least in terms of chronic GVHD, as reported by our group [3] and others [32,33]. One way to improve these GVHD results could be to associate antithymocyte globulin to PTCY in both haplo and matched transplants. We are currently testing this approach by using our "CloB2A1/A2" RIC platform [4] followed by PTCY in both lymphoid and myeloid malignancies.

There was a trend for better survivals with MUDs. It may be explained by the fact that donors were significantly younger in this group. Indeed, younger donors (<50 years) were significantly associated with better GRFS, DFS, and OS in our series. Older donors are generally associated with clonal or deficient hematopoiesis, which can also explain why patients receiving PBSCs from such donors had lower survivals. Our results suggest that a younger MUD or haplo donor may be better than an older sibling donor and should be chosen preferentially. As the number of MUD and MRD patients receiving post-transplant donor lymphocyte infusion or maintenance, this does not explain the trend for the better outcome for MUD patients. However, a postgraft therapy strategy may be envisaged to improve the results in the haplo group [34].

Moreover, patients with MDS had worse outcomes than those diagnosed with AML. This is probably explained by the fact that MDS patients were older (median 64 years versus 60.5 for AML, $P = .05$) and mostly presented with a more aggressive (complex karyotype 39% versus 18% for AML, $P = .04$) and high-burden (active disease at transplant 61% versus only 1% for AML, $P < .001$) disease at transplant.

Here we do not report our experience with patients receiving CB transplant with a clofarabine-based RIC regimen. Indeed, only 4 recipients so far in our department have received such a Minneapolis-like regimen [35] where fludarabine was replaced by clofarabine, combining clofarabine 30 mg/m^2 for 5 days + cyclophosphamide 50 mg/kg for 1 day + low-dose 2 Gy total body irradiation followed by double CB transplantation. All CB cases died at 1, 8, 9, and 11.5 months post-transplant, respectively (infection, 1; relapse, 2; chronic GVHD, 1). Although none of them survived allotransplant, the series is too small to conclude on the inefficacy of this procedure. It must also be kept in mind that CB transplant, even if its incidence is decreasing in adults, remains a valid alternative in case of urgent transplantation in patients with no matched or haplo donors or as a salvage option in patients presenting with primary or secondary graft failure after haplo transplants [36]. Moreover, emerging haplo-CB transplants could present some advantage over CB transplant alone [37]. Interestingly, we showed that high DRI [28] is also a feature of poor prognostic value on survivals in the setting of clofarabine-based RIC allotransplant [10,11,38].

Finally, as infections and leukemia relapse resulting from slow immune reconstitution after transplants with PTCY may be an issue, the immunologic impact as well as kinetics of immune reconstitution are likely to be of importance to improve outcomes after haplo transplant [39]. Indeed, we have shown that the combination of clofarabine and PTCY can improve early natural killer T cell and γ/δ T cells subset reconstitution, which can explain our good and comparable results in terms of relapse and GVHD in this group compared with transplants with standard matched allotransplants [40]. In conclusion, these data confirm that because no difference was observed in terms of outcomes, haplo donors represent a valid alternative for patients receiving a clofarabine-based RIC PBSC allograft for patients with myeloid malignancies for whom no matched donor can be identified.

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