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ORIGINAL ARTICLE

Matched unrelated or matched sibling donors result in comparable outcomes after non-myeloablative HSCT in patients with AML or MDS

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The impact of allelic HLA matching in patients with AML and myelodysplastic syndrome (MDS) who receive allogeneic PBSC after a reduced-intensity conditioning (RIC) regimen is unclear. From January 2000 to December 2010, 108 consecutive patients with AML ($n = 63$) and MDS ($n = 45$) received PBSC after RIC in our center, either from siblings ($n = 70$) or from matched unrelated donors (MUD; 10/10 high resolution, $n = 38$). Conditioning regimen was fludarabine based in 95% of patients and GvHD prophylaxis was mostly cyclosporine plus mycophenolate. Patient characteristics were similar between sibling and MUD for age (median 57 years), gender and disease distribution. Conditioning regimen (more anti-thymocyte globulin (ATG) in MUD), donor age (younger for MUD) and number of CD34 + cells infused (higher in MUD) were different. The median follow-up was 36 months (range 2–72). Engraftment, GvHD, TRM, relapse rate and OS at 3 years were comparable between sibling and MUD. After adjustment for age, cytogenetic risk, ATG and number of CD34 + cells infused, donor type still did not influence OS. In patients with AML or MDS, HSCT from MUD using PBSC after a RIC regimen led to similar outcomes than from Siblings.

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INTRODUCTION

Allogeneic hematopoietic SCT (HSCT) offers potentially curative treatment for a wide range of otherwise fatal hematological disorders. However, only one-third of the patients have a HLA-identical sibling donor (S). The success of unrelated HSCT is influenced by the degree of HLA compatibility between donor and patient.[1] The presence of donor–recipient mismatching is associated with increased risk of post-transplantation complications, including graft rejection, acute and chronic GvHD and mortality.[2–5]

A number of studies in the myeloablative setting have shown that matched related donors are superior to unrelated donors (URDs), mainly because the latter are associated with a greater risk of GvHD and TRM.[6–10] Improvements in HLA typing through the widespread use of molecular rather than serological typing has allowed identification and selection of donors who are truly matched at major HLA loci. As a consequence of improved HLA typing, according to recent study reports, survival rates after URD HSCT approach those achieved with siblings (S).[11–15]

Reduced-intensity conditioning (RIC) regimens are increasingly used to facilitate HSCT in patients with advanced age or medical comorbidity, primarily because RIC regimen are well tolerated and associated with less toxicity.[16–19] Unlike myeloablative HSCT where dose intensity intrinsically reduces tumor burden, RIC HSCT depends largely on the GVL effect. In RIC HSCT for AML and myelodysplastic syndrome (MDS), the relative benefits and risks of a sibling vs an unrelated 10/10 HLA allellically identical donor remain to be elucidated. To further address this question, we performed a retrospective cohort analysis comparing all consecutive patients who received a RIC HSCT from sibling and matched 10/10 HLA allellically identical URD at our institution since 2000.

PATIENTS AND METHODS

Study cohort

Patients aged $\geqslant 18$ years who underwent HSCT were identified from the computerized database at Saint-Louis Hospital Paris VII University (France) for this retrospective analysis. One hundred and eight consecutive patients were included. All patients had AML or MDS at the time of HSCT, underwent a non-myeloablative conditioning regimen, had either a matched sibling or URD with available high-resolution HLA typing data and received a first transplant between 2000 and 2010. Non-myeloablative conditioning regimen consisted in <8 Gy fractionated TBI and <8 mg/kg BU or i.v. equivalent.[20] For our analysis, AML and MDS at diagnosis were classified according to the 2001 World Health Organization classification.[21] Disease risks were defined according to published scores.[22–25] All patients were treated on protocols that were approved by the Institutional Review Board of Saint-Louis Hospital. Informed consent was obtained in accordance with the Declaration of Helsinki.

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HLA typing and matching

All related donors were HLA-matched siblings based on family studies. Histocompatibility testing and selection of URDs are described in detail elsewhere.[26] In brief, high-resolution typing methods for discriminating nucleotide differences encoded in exons 2 and 3 of class I HLA-A, C and B, and exon 2 of HLA-DRB1 and DQB1 included sequencing-based and oligonucleotide probe hybridization methods for human genomic DNA. Recipients and URDs were defined as matched ('10/10') if HLA-A, C, B, DRB1 and DQB1 were identical at the molecular level.

Acute and chronic GvHD

Criteria for diagnosis and grading of acute and chronic GvHD have been reported previously.[27,28]

Statistical analysis

Clinical outcomes were engraftment, acute GvHD grade II–IV, disease relapse/progression, TRM, PFS and OS. All time-to-event outcomes were counted from the date of transplant to the date of event or date of last follow-up, except engraftment and acute GvHD that were arbitrarily censored at 200 days. TRM was considered as any cause of death occurring before disease relapse/progression. Death was considered as a competing risk in analyses of engraftment and acute GvHD. TRM and relapse/progression were considered to be mutually competing risks. OS and PFS functions were estimated using Kaplan–Meier product-limit estimator. For competing risks analyses, cumulative incidence functions were estimated using usual methodology.[29] Characteristics of patients receiving related vs matched unrelated stem cells were compared using Wilcoxon rank-sum and Fisher's exact tests. Factors associated with outcome were analyzed using Gray's test (acute GvHD), proportional hazards models for the cause-specific hazard[30] (relapse/progression and TRM) and Cox proportional hazards models. The proportional hazards assumption was checked by examination of Schoenfeld residuals and Grambsch and Therneau's lack-of-fit test.[31] Given the median follow-up, it was decided to present probability estimates at 36 months, except when otherwise stated. All tests were two-sided and *P*-values $\leqslant 0.05$ were considered as indicating significant association. Considering that several tests were performed at a 0.05 significant threshold and given that in adjusted analysis five variables were tested for OS and three for non-relapse mortality, 0.4 significant associations will be expected by chance only. Analyses were performed using the R statistical software version 2.10.1.

RESULTS

Patient characteristics

Between January 2000 and December 2010, a total of 108 consecutive patients with AML ($n=63$) or MDS ($n=45$) met the inclusion criteria. Patient characteristics according to the type of donor were similar for age (median 57 years), gender and disease distribution. In particular, cytogenetic disease risk and pre-transplant Gratwohl score were comparable in the two groups. Conversely, use of anti-thymocyte globulin (ATG) in conditioning regimen (more in matched unrelated donor (MUD): 69% vs 43%, $P=0.016$), donor age (younger for MUD: 30 vs 52 years, $P<0.0001$) and number of CD34+ cells infused (higher in MUD: 7 vs 6.5×10^6/kg, $P=0.022$) were different (Table 1).

Engraftment, acute and chronic GvHD

The median follow-up was 36 months (range 2–72). All patients engrafted. The cumulative incidence of acute GvHD was 41%: 40% with HLA matched sibling donor and 44% for MUD ($P=0.58$). The cumulative incidence of chronic GvHD at 3 years was 48%: 49% with HLA matched sibling donor and 45% with MUD ($P=0.66$). No risk factor was associated with either acute or chronic GvHD despite a trend for a higher rate of acute GvHD for donor aged <45 years vs $\geqslant45$ years (51% vs 34%, $P=0.055$) as well as a lower rate of chronic GvHD in patients with AML vs MDS (41% vs 59%, $P=0.077$) and in those who received ATG in the conditioning regimen (54% vs 43%, $P=0.067$) (Table 2).

Table 1. Characteristics of the 108 patients according to the donor type

Variable	*Siblings* (N = *70*)	*Matched unrelated* (N = *38*)	P
Age at transplant, median (range) years	55 (20–67)	57 (24–68)	0.13
Gender, n (%)			0.84
Female	25 (36)	13 (33)	
Male	45 (64)	25 (67)	
Disease, n (%)			0.31
AML	43 (62)	20 (51)	
MDS	27 (38)	18 (49)	
Status at HSCT for AML, n (%)			0.65
CR1	28 (65)	15 (75)	
CR⩾2	9 (21)	4 (20)	
Non-CR	6 (14)	1 (5)	
Status at HSCT for MDS, n (%)			0.54
CR1	12 (44)	6 (33)	
Non-CR	15 (56)	12 (67)	
Time from diagnosis to HSCT for AML patients in CR1, median (range) months	5.5 (3.4–9.5)	6.1 (4.2–10.6)	0.014
Cytogenetic risk for AML[a]*, n (%)*			0.69
Favorable	3 (7)	0 (0)	
Intermediate	31 (72)	16 (80)	
Poor	9 (21)	4 (20)	
Cytogenetic risk for MDS[b]*, n (%)*			0.49
Intermediate/low	22 (81)	12 (68)	
High	5 (19)	6 (32)	
IPSS for MDS, n (%)			0.94
Low	3 (13)	4 (21)	
Intermediate 1	8 (35)	5 (26)	
Intermediate 2	10 (43)	8 (42)	
High	2 (9)	2 (11)	
Disease according to EBMT score[c]*, n (%)*			0.66
0	48 (69)	24 (63)	
1	11 (16)	5 (13)	
2	11 (16)	9 (24)	
Donor age, median (range) years	52 (27–72)	30 (16–63)	<0.0001
Donor/recipient CMV status, n (%)			0.020
Negative/Negative	16 (23)	11 (28)	
Negative/Positive	10 (14)	14 (36)	
Positive/Negative	17 (24)	4 (11)	
Positive/Positive	27 (39)	9 (24)	
Conditioning/GVHD prophylaxis			
Fludarabine, *n* (%)[d]	68 (97)	35 (92)	0.34
TBI < 4 Gy, *n* (%)	21 (30)	8 (21)	0.37
Anti-thymoglobulin, *n* (%)	31 (44)	26 (68)	0.026
CsA + MMF, *n* (%)	56 (80)	29 (77)	0.81
Graft composition			
Nucleated cells, median (range) $\times 10^8$/kg	10.3 (3.4–23.3)	10.1 (4.3–21.9)	0.24
CD34+, median (range) $\times 10^6$/kg	6.6 (1.1–14.4)	7.0 (3.6–20.9)	0.024
CD3+, median (range) $\times 10^6$/kg	23.4 (7.8–53.5)	25.9 (7.4–63.6)	0.37

Abbreviations: EBMT = European Group for Blood and Marrow Transplantation; HSCT = hematopoietic SCT; IPSS = International Prognostic Scoring System; MMF = mycophenolate mofetil; MDS = myelodysplastic syndrome. [a]According to Grimwade *et al.*[22] [b]According to Greenberg *et al.*[23] [c]According to Gratwohl *et al.*[25] [d]Fludarabine plus BU, $n=34$ and 25; Fludarabine plus Melphalan, $n=12$ and 3, respectively.

Table 2. Association of variables with acute and chronic GvHD

Variable	*Acute GvHD 2–4*		*Chronic GvHD*		
	CIF (95% CI)	P	*36 months CIF (95% CI)*	*HR (95% CI)*	P
Donor		0.47			0.79
Sibling	39% (27–50)		49% (35–62)	1	
Matched unrelated	44% (28–59)		47% (28–64)	0.92 (0.48–1.73)	
Recipient age		0.68			0.62
$<$55 years	41% (27–55)		50% (33–65)	1	
$\geqslant$55years	41% (28–53)		47% (32–61)	0.86 (0.47–1.57)	
Gender		0.72			0.29
Female	42% (26–57)		50% (28–68)	1	
Male	40% (29–52)		49% (35–61)	1.42 (0.75–2.69)	
Disease		0.33			0.077
AML	37% (25–49)		41% (27–55)	1	
MDS	47% (32–61)		59% (40–74)	1.73 (0.94–3.18)	
Cytogenetic risk		0.55			0.96
Standard	40% (29–50)		50% (37–62)	1	
High risk	46% (25–64)		43% (20–64)	1.02 (0.47–2.20)	
EBMT score		0.58			0.13
0	43% (32–54)		45% (32–58)	1	
1–2	36% (21–52)		54% (34–71)	1.62 (0.87–3.02)	
Donor age		0.055			0.87
$<$45 years	51% (35–65)		44% (27–60)	1	
$\geqslant$45 years	34% (23–46)		51% (35–64)	0.95 (0.51–1.77)	
Donor CMV status		0.89			0.84
Negative	39% (26–53)		48% (31–63)	1	
Positive	42% (29–55)		48% (33–61)	1.07 (0.58–1.94)	
Anti-thymoglobulin		0.55			0.067
No	43% (29–57)		54% (39–67)	1	
Yes	39% (26–51)		43% (23–62)	0.56 (0.30–1.04)	

Abbreviations: CIF = cumulative incidence function; CI = confidence interval; EBMT = European Group for Blood and Marrow Transplantation; HR = hazard ratio; MDS = myelodysplastic syndrome.

TRM, relapse and OS

During follow-up, 47 patients died (29 from relapse and 18 from TRM). The 3-year cumulative incidence of TRM was 19% (95% CI 11–27): 17% with HLA-matched sibling donor and 22% with MUD ($P = 0.55$). Recipient's gender and disease (AML vs MDS) were both associated with TRM in univariate analysis (Table 3).

The 3-year cumulative incidence of relapse was 40% (95% CI 29–50): 45% with HLA matched sibling donor and 31% with MUD ($P = 0.34$; Figure 1). There was no difference between both the groups regarding disease risk (cytogenetic and EBMT (the European Group for Blood and Marrow Transplantation) score). Only recipient's gender was significantly associated with relapse risk (Table 3).

The 3-year OS was 46%, similar between HLA-matched sibling donor and MUD (Figure 2), with a 3-year OS of 45% (95% CI: 33–61) and 49% (95% CI: 34–71), respectively (Table 3). Patients with high-risk cytogenetics (only 13% of patients) had poorer survival (26% vs 52%, $P = 0.083$; Figure 3), whereas EBMT score did not influence OS.

For adjusted analysis, we should ideally adjust on all unbalanced factors (donor age, CMV status, use of ATG and number of CD34+ cells infused) and prognostic factors (gender and cytogenetic risk for OS; CMV status and disease for TRM). Moreover, we consider age as potential adjustment factor. As donor and recipient age were mildly correlated, we tried a model with recipient age instead of donor age and this model fitted the data better. After adjustment for recipient age, cytogenetic risk, ATG, number of $CD34^+$ cells infused, recipient's gender and CMV status, type of donor still did not influence OS (HR: 0.92, 95% CI: 0.46–1.84, $P = 0.82$). Table 3 presents univariate analysis for TRM, relapse and OS. For TRM, as only 17 events was observed, the analysis was restricted to models with two variables as using more variables appeared somewhat unstable. Adjusting for age, MDS was the only factor increasing TRM (HR 3.4; 95% CI 1.2–9.5; $P = 0.02$); there was no model in which the donor effect was significant.

DISCUSSION

Our findings support two major conclusions. First, the likelihood of OS and disease-free survival at 3 years following reduced intensity allogeneic HSCT in this particular high-risk AML and MDS population is about 45% and 40%, respectively. This suggests that almost half of adult patients with AML/MDS are or will likely be cured with this treatment modality. Second, our data indicate that HSCT from unrelated HLA allellically matched '10/10' donors led to outcomes post HSCT similar to those from HLA-identical sibling donors in patients with AML/MDS.

Patient's age in our study was comparable with other reports of allogeneic HCT after RIC, (median age, 57 years vs 56,[32] 58[33] and

Table 3. Association of variables with TRM, relapse and OS

Variable	*Relapse/progression*			*TRM*			*OS*		
	CIF (95% CI)	*HR (95% CI)*	P	*CIF (95% CI)*	*HR (95% CI)*	P	*Estimate (95% CI)*	*HR (95% CI)*	P
Donor									
Sibling	45% (31–58)	1		17% (8–27)	1		45% (33–61)	1	
Matched unrelated	31% (15–48)	0.70 (0.34–1.45)	0.34	22% (9–38)	1.35 (0.51–3.54)	0.55	49% (34–71)	0.99 (0.54–1.82)	0.98
Recipient age									
<55 years	39% (24–55)	1		21% (10–35)	1		45% (31 to 64)	1	
⩾55 years	40% (26–54)	0.93 (0.49–1.79)	0.83	17% (8–28)	0.81 (0.31–2.09)	0.66	48% (36–65)	0.91 (0.51–1.63)	0.76
Gender									
Female	31% (15–49)	1		10% (2–24)	1		62% (47–83)	1	
Male	44% (31–57)	2.21 (1.04–4.69)	0.039	23% (13–34)	3.54 (1.01–12.3)	0.047	39% (28–54)	2.23 (1.13–4.40)	0.020
Disease									
AML	41% (27–54)	1		11% (4–21)	1		51% (39–68)	1	
MDS	38% (23–54)	1.02 (0.53–1.97)	0.95	29% (15–45)	2.77 (1.02–7.52)	0.045	39% (25–60)	1.24 (0.70–2.20)	0.46
Cytogenetic risk									
Standard	37% (26–49)	1		18% (10–27)	1		52% (41–66)	1	
High risk	51% (24–73)	1.38 (0.65–2.95)	0.40	21% (6–44)	1.37 (0.44–4.20)	0.59	26% (11–59)	1.77 (0.93–3.36)	0.083
EBMT score									
0	41% (28–53)	1		16% (8–27)	1		47% (35–63)	1	
1–2	38% (21–55)	1.03 (0.52–2.05)	0.94	23% (10–40)	1.56 (0.59–4.11)	0.37	44% (29–68)	1.21 (0.66–2.21)	0.53
Donor age									
<45 years	36% (20–52)	1		23% (10–38)	1		47% (33–67)	1	
⩾45 years	43% (29–56)	1.09 (0.55–2.14)	0.81	16% (8–27)	0.60 (0.23–1.57)	0.30	46% (34–63)	0.84 (0.47–1.51)	0.57
Donor CMV status									
Negative	39% (25–54)	1		24% (13–38)	1		44% (31–62)	1	
Positive	40% (25–54)	0.87 (0.46–1.66)	0.67	13% (5–25)	0.43 (0.16–1.15)	0.092	48% (35–67)	0.74 (0.42–1.32)	0.31
Anti-thymoglobulin									
No	38% (25–52)	1		22% (12–34)	1		45% (33–61)	1	
Yes	44% (25–61)	1.03 (0.54–1.98)	0.92	14% (5–26)	0.61 (0.22–1.64)	0.32	48% (34–69)	0.86 (0.48–1.54)	0.61

Abbreviations: CIF = cumulative incidence function; EBMT = European Group for Blood and Marrow Transplantation; HR = hazard ratio; MDS = myelodysplastic syndrome.

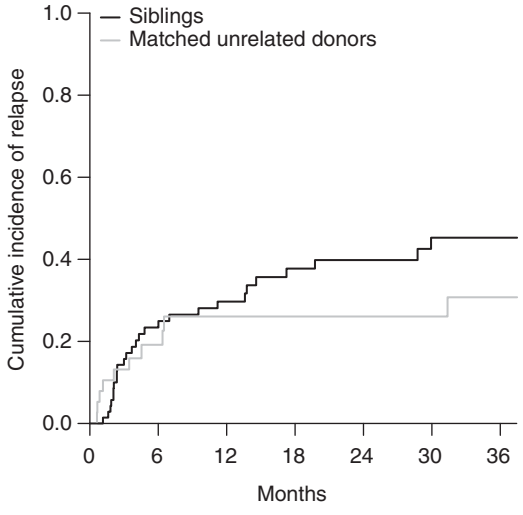

Figure 1. Relapse rate according to the donor type.

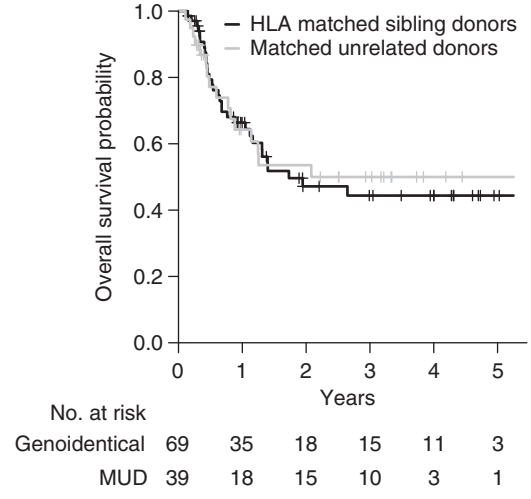

Figure 2. OS according to the donor type (Tick marks denote censored observations). MUD = matched unrelated donor.

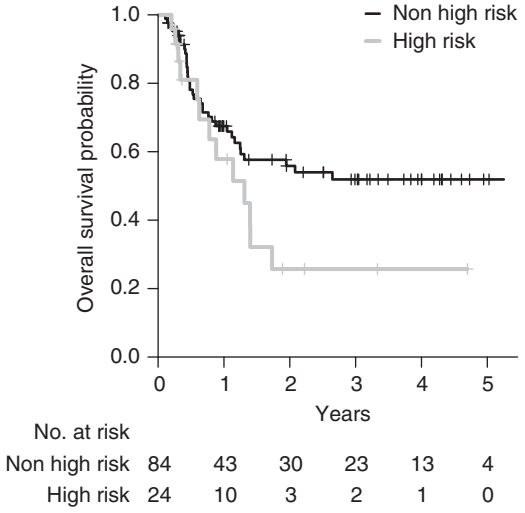

Figure 3. OS according to the cytogenetic risk (Tick marks denote censored observations).

60 years,[34] respectively); however, the current 3-year TRM rate of 19% was in the lower range in comparison to the rates reported by others, which ranged from 20% to 53% at 2 and 4 years.[35–37] One might have expected a higher rate of TRM compared with the 2-Gy TBI-based regimen reported by the Seattle group,[34,38,39] as the majority of our patients received a more intensive conditioning regimen (Fludarabine and BU). In our population, a more toxic RIC regimen did not translate into a higher rate of TRM for which the only associated factor was the disease (MDS). Of note, rates of TRM were similar between HLA-matched sibling donor and MUD. In more details, GvHD rates in our population (grade II–IV acute GvHD, 41%; chronic GvHD, 48% at 3 year) were also not statistically different between sibling and MUD. No risk factor was associated with either acute or chronic GvHD. This suggests that use of a 10 out of 10 molecularly HLA-matched graft led to a risk of acute GvHD comparable with that of a sibling transplant. This result is of particular importance as matched sibling donors can only be found for 15–25% of patients, and physicians still hesitate to refer older patients for unrelated HSCT as shown by Estey *et al.*[40] in a feasibility analysis of RIC regimens for patients >50 years with AML and high risk MDS. However, these results should be considered with caution as the conditioning regimen varied between sibling and MUD. More patients transplanted with a MUD received ATG in the conditioning regimen, which could impact GvHD rates. Indeed, the absence of ATG in the conditioning regimen in unrelated transplantation has been reported to increase chronic GvHD.[41,42] The strict comparison between sibling vs MUD with ATG vs MUD without ATG is thus not feasible because of the non-randomized status of our study.

As already pointed out in previous studies of RIC regimens in patients with AML or MDS, the leading cause of treatment failure was relapse.[32,33,43,44] The current study showed higher relapse rates in patients with high-risk disease, but the difference did not reach significance, probably because of the small number of patients in this category (only 13% of the overall population). Regarding the donor type, the 3-year cumulative incidence of relapse was 46% with HLA-matched sibling donor and 30% with MUD ($P=0.28$), with no difference between both the groups regarding disease risk. In the majority of studies including ours, most URD patients received ATG in the conditioning regimen that could have confounded relapse results. In patients transplanted for various disease, lower relapse and superior PFS in MUD—HLA 6/6 identical—compared with sibling have been found using a Flu/Bu conditioning without ATG.[45]

Our work has strengths and limitations. The strengths include the homogeneous cohort of AML/MDS patients enrolled in our center with specified diagnostic criteria, complete characteristics of the disease, homogeneous conditioning regimen, high-resolution HLA typing on 10 antigens, GvHD prophylaxis, supportive care and prospectively determined and defined clinical outcomes. We monitor our patients indefinitely at specified intervals, and our policy requires periodic assessment for adverse events like relapse and late toxicity. Our study is limited due to its retrospective nature and the relatively small number of patients within each of the two types of disease subcategories (AML and MDS). An important limitation of our study is its non-randomized setting, which offers the potential for the introduction of bias. Such bias could work both ways; only healthier patients are referred for matched URD transplants, or only those supposed to be at highest risk might be referred. To minimize this bias, we adjusted the statistical analysis for baseline differences in the various patient cohorts.

Acknowledging these limitations, our data indicate that allogeneic HSCT provides strictly identical long-term survival for patients with AML and MDS receiving grafts from matched (10 out of 10 alleles) URDs or matched sibling donor, including after adjustment for variables potentially impacting survival. Given these results, one may question the requirement for older sibling donors when healthier, younger MUDs are available. Until prospective studies are completed, this conclusion supports the recommendation to consider matched URD HSCT for similar indications as those currently put forward for matched related donor HSCT for AML and MDS patients after a RIC regimen.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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MR and RPL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author contributions: Conception and design: MR, RP, LA, GS, RPL. Provision of study materials and patients: MR, LA, NB, ER, JL, CH, AD, PF, HD, GS, RPL. Collection and assembly of the data: MR, RP, LA, GS, RPL. Data analysis and interpretation: MR, RP, LA, GS, RPL. Manuscript writing: MR, RP, LA, GS, RPL. Final approval of manuscript: MR, RP, LA, NB, ER, JL, CH, AD, PF, HD, GS, RPL.

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