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Cord Blood

Reduced-Intensity versus Myeloablative Conditioning in Cord Blood Transplantation for Acute Myeloid Leukemia (40-60 years) across Highly Mismatched HLA Barriers—On Behalf of Eurocord and the Cellular Therapy & Immunobiology Working Party (CTIWP) of EBMT

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A B S T R A C T

The use of myeloablative conditioning (MAC) in umbilical cord blood transplantation (UCBT) has been associated with high nonrelapse mortality (NRM) in patients aged >40 years, especially those having a high HLA disparity, thus limiting wider applications. We hypothesized that the NRM advantage of reduced-intensity conditioning (RIC) and higher graft-versus-leukemia effect associated with greater HLA disparities would expand its use for patients (aged 40 to 60 years) without compromising efficacy and compared outcomes between RIC and MAC regimens. In total, 288 patients aged 40 to 60 years, with de novo acute myeloid leukemia, receiving UCBT with at least 2 HLA mismatches with RIC (n = 166) or MAC (n = 122) regimens were included. As compared to RIC, the MAC cohort included relatively younger patients, having received more single UCBT, with lower total nucleated cell counts and more in vivo T cell depletion. Median time to neutrophil engraftment, infections (bacterial, viral, and fungal), and grade II to IV acute and chronic graft-versus-host disease were similar in both groups. In the multivariate analysis, overall survival (hazard ratio [HR], 0.98; $P = .9$), NRM (HR, 0.68; $P = .2$), and relapse (HR, 1.24; $P = .5$) were not different between RIC and MAC. Refractory disease was associated with worse survival. Outcomes of UBCT for patients aged 40 to 60 years having ≥2 HLA mismatches are comparable after the RIC or MAC regimen.

Allogeneic hematopoietic stem cell transplantation from HLA identical sibling is the treatment of choice for selected patients with acute myeloid leukemia with high-risk features as well as in relapsed settings [1,2]. However, for patients who lack a suitable HLA identical donor, unrelated cord blood transplantation (UCBT) is a valid alternative to HLA-matched unrelated bone marrow or peripheral blood stem cell (PBSC) transplantation, particularly for patients at high risk of disease relapse who urgently need a transplantation [3-6].

During the past 2 decades, there has been an increase in the use of the reduced-intensity conditioning (RIC) regimen, which mainly relies on the graft-versus-leukemia (GVL) effect rather than conditioning intensity to eradicate the disease. On the basis of a prospective study, the myeloablative conditioning (MAC; including reduced toxicity) regimen is still generally preferred for younger individuals [7] while using PBSCs both related and unrelated donors, but it is limited by high nonrelapse mortality (NRM) in older patients, thereby promoting the usage of novel RIC regimens in this subgroup of patients

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[8,9]. Due to cord blood stem cell properties, a strong GVL effect is reported in UBCT recipients [10]. This could suggest that conditioning intensity might be proportionally less important following UCBT in regards to the risk of relapse [5,11,12]. However, large registry data in UCBT showed no advantage of using RIC over MAC (reduced NRM was counterbalanced by an increased incidence of relapses) [13]. Also, very similar to PBSCs, the use of MAC in UCBT was associated with a higher risk of NRM in patients older than 40 years, especially in case of higher HLA disparity (allele level) [14-18], thus restricting wider applications due to limitations of finding a nearly matched cord donor [5,17].

PATIENTS AND METHODS

This study was approved by Eurocord and the Cellular Therapy & Immunobiology Working Party (CTIWP) of European Society for Blood and Marrow Transplantation (EBMT). Patients and donors treated at EBMT-affiliated centers routinely provide informed consent authorizing the use of their personal information for research purposes.

Patient Selection and Treatment Characteristics

Inclusion criteria for this analysis were patients with de novo acute myeloid leukemia (any disease status), 40 to 60 years of age, undergoing single or double UCBT with 2 or more HLA mismatches in EBMT centers between 2005 and 2018. In total, 134 (54.5%) patients received in vivo T cell depletion with anti-thymocyte globulin (ATG). Patients were conditioned with either RIC or MAC [19]. Both groups received HLA mismatched cords (at least at 2 loci—HLA A/B at antigen level and DRB1 at allelic level). The most common MAC used was fludarabine, busulfan, and thiotepa (70%), while the commonest RIC regimen consisted of cyclophosphamide, fludarabine, and total body irradiation (TBI) less than 6 Gy (70%). Graft-versus- host disease (GVHD) prophylaxis consisted of calcineurin inhibitors and mycophenolate (MMF) in 190 (66%) patients. The choice of conditioning regimen and GVHD prophylaxis was dependent on transplant center protocols.

Cytogenetic abnormalities were classified according to the Medical Research Council classification [20]. Leukemia-free survival (LFS) was defined as the interval from the time of transplant to either relapse or death while in remission. Overall survival (OS) was defined as the time to death from any cause. Engraftment was defined as the first 3 consecutive days with an absolute neutrophil count over 0.5×10^9/L. Acute and chronic GVHD was diagnosed and graded according to standard criteria, respectively [21].

Statistical Methods

The Kruskal-Wallis test was used to assess continuous variables and chi-square was used for categorical variables. Univariate analyses were performed using Gray's test for cumulative incidence functions and the log-rank test for OS and LFS. To study acute and chronic GVHD, we considered relapse and death to be competing events. Variables considered in univariate analyses were type of conditioning regimen (RIC versus MAC), median year of UCBT, recipient weight, median age, age group ($\leq$50 or $>$50), sex, graft type (double of single UCBT), disease status (remission versus no remission), cytogenetic risk, cytomegalovirus serology, performance status, ABO matching, TBI, ATG, use of busulfan, GVHD prophylaxis (cyclosporine + MMF $\pm$ other versus other), median total nucleated cell count (TNC), and median CD34.

Probabilities of OS and LFS were calculated using the Kaplan-Meier estimate. A Cox proportional hazard models was used for multivariate regressions. Variables differing significantly between the 2 groups or factors associated with significant outcome in the univariate analysis were included in the multivariate Cox models. Results were expressed as the hazard ratio (HR) with the 95% confidence interval (CI). All tests were 2-sided. The type I error rate was fixed at 0.05 for the determination of factors associated with time-to-event outcomes. Statistical analysis was performed using R 3.4.0 (R Core Team, Vienna, Austria) and SPSS 22 (SPSS, Inc., Chicago, IL).

RESULTS

Patients

A total of 288 patients (122 MAC and 166 RIC) were included in the analysis. Median follow-up was 33 (3.2 to 155.2) and 47 (3.2 to 149.9) months for the MAC and RIC groups (P = .21), respectively. Baseline demographic and clinical data are outlined in Table 1. As compared to RIC, the MAC group included relatively younger patients (median age 47 versus 53 years, $P \leq .001$), having had received more single UCBT (73.8% versus 28.9%, $P \leq .001$), a lower TNC (3.9 versus 4.7, $P \leq .001$), and more in vivo T cell depletion using ATG (86.6% versus 27.6, $P \leq .001$). More patients in the RIC group received standard cyclosporine/MMF-based prophylaxis (82.5% versus 43.4%, $P < .001$) (Table 1).

Engraftment and GVHD

There was no difference between the 2 groups for median time to neutrophil engraftment (RIC, 21 [3 to 54] versus MAC, 22 [11 to 50] days; P = .3) (Table 2). Seventeen patients (13.9%) in the MAC group had engraftment failure as compared to 29 (17.5%) in the RIC group (P = .62). Grade II to IV acute GVHD (aGVHD) and all grade chronic GVHD (cGVHD) were comparable between the groups (30.6% versus 37.6%, P = .221, and 31.8% versus 27.2%, P = .28, for MAC versus RIC, respectively). Among patients with GVHD, the proportion of patients with grade III to IV aGVHD and extensive cGVHD was also similar (37% versus 42% and 67% versus 48%, MAC versus RIC, respectively). Factors predicting lower aGVHD in multivariate analysis (MVA) were the use of ATG and TNC $<4.3 \times 10^7$/kg. Factors predicting a higher incidence of cGVHD were use of busulfan-based regimens, which were mainly myeloablative (Table 3).

NRM and Relapse

The 3-year cumulative incidence of NRM was significantly higher in the MAC group (MAC, 45.3% versus RIC, 23%; P = .001) (Figure 2A and Table 2). However, MVA did not confirm a statistically significant difference between the 2 groups (P = .2; HR, 0.68; 95% CI, 0.3 to 1.2; reference MAC) (Table 3). Disease relapse was the main cause of death in the RIC group (56%) as compared to MAC (33%). Patients receiving the MAC regimen succumbed more often to transplant-related complications (64%) (GVHD, 30%; infections, 36% [bacterial infection, 14%; unknown infections, 12%; viral infections, 8%; parasitic infections, 2%]). There was no difference in infective (bacterial, viral, or fungal) episodes/complications between the 2 groups. Veno-occlusive disease and idiopathic pneumonia were reported in MAC recipients only (MAC, 6%, 2% versus RIC, no veno-occlusive disease, no idiopathic pneumonia).

At 3 years, the cumulative incidence of relapse was significantly higher in the RIC group (41% versus 27%, P = .019) (Table 2 and Figure 2B). However, in MVA shown in Table 3, the difference no longer remained significant (P = .48; HR, 1.24; 95% CI, 0.47 to 2.3, reference MAC).

OS and LFS

There was no difference in 3-year OS or LFS between the 2 groups, OS (MAC, 31% versus RIC, 41%; P = .073) and LFS (MAC, 28% versus RIC, 36%; P = .28) (Figure 1A,B). In multivariate analyses, disease status prior to transplant (complete remission versus no remission) was the only factor that remained significant for OS and LFS ($P < .0001$; HR, 2.7; 95% CI, 1.7 to 4.08; $P \leq .0001$; HR, 3.03; 95% CI, 1.9 to 4.5, reference complete remission, for OS and LFS, respectively) (Table 3). There was no difference in impact of intensity of conditioning regimen when considering the use of TBI or ATG (data not shown).

DISCUSSION

Results of UCBT and related HLA haploidentical grafts have shown comparable outcomes to HLA matched or mismatched unrelated PBSC donors [3-5]. The use of myeloablative UCBT is standard for young patients but still highly limited by substantially increased NRM associated with HLA disparity (especially at the allele level) and increasing age [13]. There is a need to expand the utilization of UCBT across such barriers without compromising efficacy. Recently, it was shown that in case of

Table 1
Demographic Characteristics of the Study Population

Characteristic	Table 1	MAC (n = 122)	RIC (n = 166)	*P* Value
Follow-up for survivors in months	Median (range)	33 (3.3-155.2)	47.9 (3.2-149.9)	.215
Year UCBT	Median (range)	2011 (2005-2018)	2010 (2005-2018)	.034
Patient sex, No. (%)	Male	55 (45.1)	76 (45.8)	.906
	Female	67 (54.9)	90 (54.2)	
Age at UCBT, yr	Median (range)	47.8 (40.0-59.9)	53.2 (40.3-60.0)	<.001
Type of graft (graft type), No. (%)	Single	90 (73.8)	48 (28.9)	<.001
	Double	32 (26.2)	118 (71.1)	
Disease status, No. (%)	First CR	74 (61.7)	89 (54.6)	NP
	Second CR	30 (25.0)	48 (29.4)	
	>Second CR	1 (0.8)	5 (3.1)	
	Active or advanced disease	15 (12.5)	21 (12.9)	
	Missing	2	6	
Remission, No. (%)	CR	105 (87.5)	142 (87.1)	.924
	No CR	15 (12.5)	21 (12.9)	
	Missing	2	6	
Cytogenetic risk, No. (%)	Good or intermediate	65 (78.3)	111 (82.2)	.477
	Poor	18 (21.7)	24 (17.8)	
	Missing	39	31	
Performance status at transplant, No. (%)	KPS ≤80	21 (20.8)	19 (19.0)	.75
	KPS >80	80 (79.2)	81 (81.0)	
	Missing	21	66	
Delay in months from diagnosis to UCBT (considering only patients in CR)	Median (range)	6.5 (3.19-52.9)	7.3 (3.13-247.5)	.036
HLA matching (HLA STUDY), No. (%)	2 mismatches	111 (92.5)	148 (94.3)	NP
	3 mismatches	8 (6.7)	7 (4.5)	
	4 mismatches	1 (0.8)	2 (1.3)	
	At least 2 mismatches, but missing information for the second CB	2	9	
CMV (donor), No. (%)	Negative	34 (29.3)	60 (38.2)	.126
	Positive	82 (70.7)	97 (61.8)	
	Missing	6 9		
ABO match, No. (%)	Compatible or minor	48 (60.0)	78 (57.4)	.703
	Major incompatibility	32 (40.0)	58 (42.6)	
	Missing	42	30	
TBI in conditioning, No. (%)	No	83 (80.6)	28 (17.6)	<.001
	Yes	20 (19.4)	131 (82.4)	
	Missing	19	7	
Busulfan in conditioning, No. (%)	No	24 (19.7)	149 (89.8)	<.001
	Yes	98 (80.3)	17 (10.2)	
ATG, No. (%)	No	15 (13.4)	97 (72.4)	<.001
	Yes	97 (86.6)	37 (27.6)	
	Missing	10	32	
GVHD prophylaxis, No. (%)	Other GVHD prophylaxis	69 (56.6)	29 (17.5)	<.001
	CSA + MMF ± other	53 (43.4)	137 (82.5)	
Median TNC	Median (IQR)	3.9 (3.1-5.1)	4.7 (3.8-5.7)	<.001

(*continued*)

Table 1 (*Continued*)

Characteristic	Table 1	MAC (n = 122)	RIC (n = 166)	*P* Value
	Missing	12	21	
Median CD34	Median (IQR)	1.9 (0.5-7.0)	1.8 (1.4-2.7)	.903
	Missing	13	28	

CR indicates complete remission; KPS, Karnofsky performance status; CB, cord blood; CMV, cytomegalovirus; CSA, cyclosporine; IQR, interquartile range.

Table 2
Univariate Analysis for RIC versus MAC

Outcomes	Variables	Events	EFS at 4 yr	*P* Value
LFS	MAC	82	28%	.285
	RIC	107	36%	
OS	MAC	78	31%	.073
	RIC	96	41%	
		% 60 days	95% CI	*P* Value
Engraftment	MAC	86.1	(80-92.6)	.629
	RIC	82.5	(76.9-88.6)	
		% 3 years	(95% CI)	*P* Value
NRM	MAC	45.4	(36.9-56.0)	<.001
	RIC	23	(17.3-30.6)	
		% 3 years	(95% CI)	*P* Value
Relapse	MAC	27.8	(20.5-37.7)	.019
	RIC	41.3	(34.2-49.8)	
		% 100 days (95% CI)		*P* Value
aGVHD	MAC	30.6	(23.3-40.1)	.221
	RIC	37.6	(30.8-45.8)	
		% 3 years	(95% CI)	*P* Value
cGVHD	MAC	31.8	(23.8-42.4)	.280
	RIC	27.2	(21-35.3)	

EFS indicates Event-free survival.

mismatched unrelated donor transplants, the reduced NRM associated with the RIC regimen [8,9] and increased GVL effect associated with HLA disparity could be harnessed to expand indications in patients older than 40 years [22]. Since GVL may increase with the degree of HLA disparity, we took advantage of the large EBMT and Eurocord registries to determine whether the utility of highly HLA mismatched UCBT could be similarly expanded in patients aged 40 to 60 years by using the RIC regimen.

Unlike previous studies comparing RIC and MAC regimens for UCBT [13], wherein RIC was associated with substantially increased relapses and reduced NRM in comparison to MAC, our study showed no statistical difference in outcomes between the 2 cohorts when adjusting in the multivariate analyses. In a large retrospective Center for International Blood and Marrow Transplant Research and Eurocord analysis, NRM increased exponentially with every degree of high-resolution HLA disparity [14]. Similarly, the effects of high-resolution allele-level HLA mismatches and association with higher NRM and increased GVL [15,16] were shown in a large Japanese registry study, separately for pediatric and adult cohorts.

The OS and LFS in the present study were similar for both groups and comparable to other studies [14-16]. A Japanese group [16] showed significant reduction in OS after 5 or greater degree of allele-level HLA mismatches in a cohort of

Table 3
Multivariate Analysis of Factors Affecting OS, EFS, NRM, Relapse, and GVHD

Characteristic	*P* Value	HR	95% CI, Exp(B) Inferior	Superior
OS				
RIC (RIC versus MAC)	.931	.983	.663	1.458
Graft type (double versus single)	.060	.697	.479	1.015
Remission (no CR versus CR)	.000	2.703	1.791	4.080
ATG (ATG versus no ATG)	.774	1.063	.699	1.617
LFS				
RIC (RIC versus MAC)	.838	1.040	.713	1.517
Graft type (double versus single)	.125	.749	.518	1.083
ATG (ATG versus no ATG)	.726	1.075	.718	1.609
Remission (no CR versus CR)	.000	3.003	1.990	4.531
NRM				
RIC (RIC versus MAC)	.202	.685	.383	1.225
ATG (ATG versus no ATG)	.533	1.235	.636	2.397
Graft type (double versus single)	.235	.699	.387	1.263
Year of transplant (>2010 or ≤2010)	.193	1.370	.853	2.201
CSA ± MMF versus others	.751	.917	.539	1.562
Relapse				
RIC (RIC versus MAC)	.476	1.244	.682	2.268
Remission (no CR versus CR)	.000	5.384	3.295	8.796
TBI (yes versus no)	.625	1.204	.572	2.535
Bu (yes versus no)	.703	1.182	.500	2.795
CSA_MMF (CSA + MMF ± other versus other)	.458	1.232	.710	2.136
Year of transplant (>2010 or ≤2010	.268	.791	.523	1.198
Acute GVHD				
RIC (RIC versus MAC)	.350	.755	.418	1.362

(*continued*)

Table 3 (*Continued*)

Characteristic	*P* Value	HR	95% CI, Exp(B) Inferior Superior	
Sex (female versus male)	.099	.676	.425	1.076
CMV (yes versus no)	.906	.972	.609	1.551
ATG (ATG versus no ATG)	.002	.382	.210	.696
TNC (>4.3 versus ≤4.3)	.013	1.819	1.136	2.914
Chronic GVHD				
RIC (RIC versus MAC)	.907	.965	.528	1.763
Year of transplant (>2010 versus ≤2010)	.026	1.685	1.063	2.671
Bu (yes versus no)	.058	1.781	.980	3.238

Bu indicates busufan.

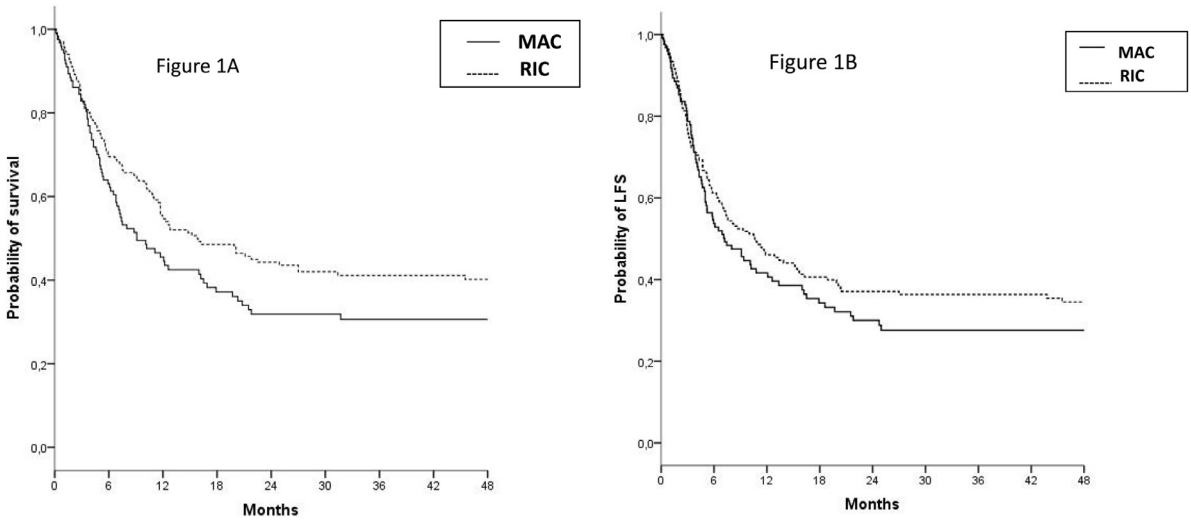

Figure 1. (A) NRM between RIC (n = 166; NRM, 23%) and MAC (n = 122; NRM, 45.4%; $P \leq .001$). (B) Relapse RIC (n = 166; relapse, 41.3%) versus MAC (n = 122; relapse, 27.8%; $P = .019$).

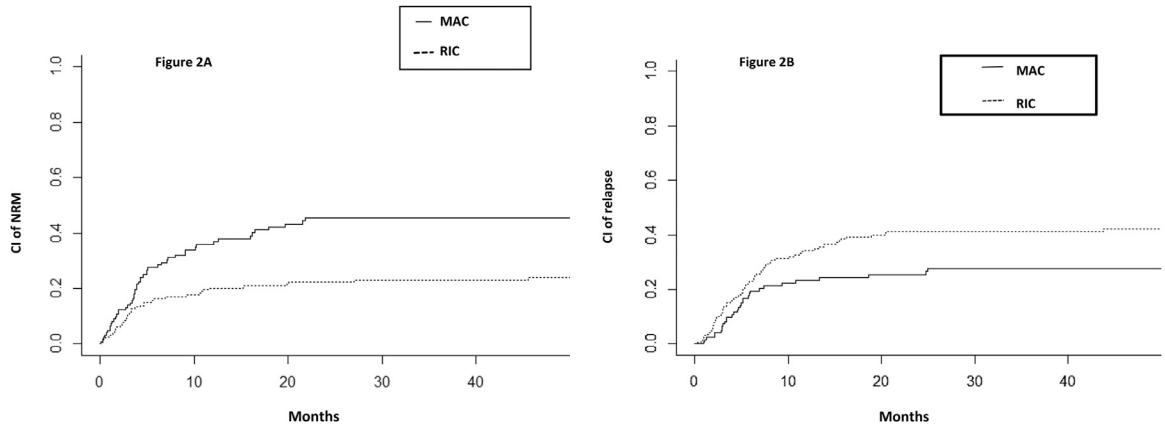

Figure 2. (A) OS between RIC (n = 166; OS, 41%) and MAC (n = 122; OS, 31%; $P = .073$). (B) LFS between RIC (n = 166; LFS, 36%) and MAC (n = 122; LFS, 28%; $P = .28$).

3500 adult patients receiving UCBT. Similarly, Eapen et al. [14] showed survival differences with a higher degree of HLA mismatches at high resolution among patients receiving UCBT. As expected, OS and LFS in both groups were lower in comparison to other recent studies in UCBT (RIC versus MAC), including younger patients. In a prospective multicenter study in 57 patients having received standard MAC UCBT, the 3-year disease-free survival was 50% [23], and 2-year disease-free survival in a prospective study of 79 patients using standard RIC UCBT was 35% [12].

Graft rejection has been a major barrier in UCBT, especially when using HLA-mismatched cords [14] in comparison to fully matched UCBT. HLA matching is an important factor to the success of the UCBT and should be carefully considered during the donor searching process.

Several strategies to improve engraftment and decrease graft failure have been described with promising results, including different platforms for progenitor cell expansion or the use of agents to enhance homing, among others. Although some of the approaches are still under

investigation, they offer hope for improved outcomes after UCBT, including for patients at a higher risk of graft failure such as those receiving HLA-mismatched UCBT. Surprisingly, in our study, there was no difference in engraftment kinetics and graft rejection between the 2 groups. This can be explained by a significantly higher use of double cords and higher median TNC count [23,24] in the RIC group as compared to MAC, which could have counterbalanced the reduction in the intensity of conditioning. GVHD has not been a major obstacle for UCBT. Similar to reported literature [15,17], we reported comparable and low acute and chronic GVHD incidences in the RIC and MAC groups. This could possibly be explained by a predominantly naive repertoire of cord blood donors [25]; however, data on immune recovery were not available in our study.

Historically, the use of RIC in UCBT has been associated with the double cord blood platform as developed by investigators from the University of Minnesota. In line with these findings, the group of RIC patients in our study more frequently received double UCBT to overcome the cell dose limitation when a single UCB unit with adequate TNC count was not available [26]. Importantly, we confirmed similar outcomes between single and double UCBT for older patients, as previously reported in prospective trials accruing children and young adults [27]. Similar to all previous studies, disease status prior to transplant was significantly associated with overall outcome [12,13,23].

Previous studies showed a detrimental impact of ATG on NRM and OS in patients given double UCBT after MAC [28] or RIC [29], despite the association with in vivo T cell depletion with a reduced risk of aGVHD. The use of ATG in patients receiving UCBT should be done cautiously, preferably in the setting of clinical trials. Studies of individualized ATG dosing could be helpful in investigation of the optimal dose schedule of ATG to improve outcomes.

Our study is limited by its design being retrospective and the imbalance of the 2 groups for risk factors known to be associated with outcome: RIC patients more frequently received double UCBT without ATG. These differences were carefully adjusted for in the multivariate analysis. Also, differences in practices as regards to conditioning regimen as well as GVHD prophylaxis across various centers need to be taken into account. Although considering mismatches at standard HLA A/B and DRB1 is standard practice in most of the centers, our study is limited by the fact that we have not taken into account additional and clinically relevant mismatches such as for HLA C [16].

How these results will compare with hematopoietic cell transplantation from haploidentical or unrelated donor should be further investigated. So far, data available in literature from single centers and registry studies [3,4] revealed comparable outcomes of UCBT and mismatched related or unrelated donor transplantation, but this should be carefully considered in a homogeneous cohort and uniform conditioning regimen and GVHD prophylaxis (ie, with post-transplant cyclophosphamide).

In summary, the use of UCBT with 2 or greater HLA mismatches is still limited, and in this setting, RIC showed comparable outcomes to MAC in patients aged 40 to 60 years. There is a need to find other means of reducing NRM without increasing relapses by achieving better disease control prior to transplant, designing better pretransplant strategies, avoiding use of ATG, and not solely relying on modulation of the intensity of conditioning.

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