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Expanding transplant options to patients over 50 years. Improved outcome after reduced intensity conditioning mismatched-unrelated donor transplantation for patients with acute myeloid leukemia: a report from the Acute Leukemia Working Party of the EBMT

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ABSTRACT

The outcome of patients undergoing HLA-matched unrelated donor allogeneic hematopoietic cell transplantation following reduced-intensity conditioning or myeloablative regimens is reported to be equivalent; however, it is not known if the intensity of the conditioning impacts outcomes after mismatched unrelated donor transplantation for acute myeloid leukemia. Eight hundred and eighty three patients receiving reduced-intensity conditioning were compared with 1041 myeloablative conditioning regimen recipients in the setting of mismatched unrelated donor transplantation. The donor graft was HLA-matched at 9/10 in 872 (83.8%) and at 8/10 in 169 (16.2%) myeloablative conditioning recipients, while in the reduced-intensity conditioning cohort, 754 (85.4%) and 129 (14.6%) were matched at 9/10 and 8/10 loci, respectively. Myeloablative conditioning regimen recipients were younger, 70% being <50 years of age compared to only 30% in the reduced-intensity conditioning group (P=0.0001). Significantly, more patients had secondary acute myeloid leukemia (P=0.04) and Karnofsky Performance Status score <90% (P=0.02) in the reduced-intensity conditioning group. Patients <50 and ≥50 years were analyzed separately. On multivariate analysis and after adjusting for differences between the two groups, reduced-intensity conditioning in patients age ≥50 years was associated with higher overall survival (HR 0.78; P=0.01), leukemia-free survival (HR 0.82; P=0.05), and decreased non-relapse mortality (HR 0.73; P=0.03). Relapse incidence (HR 0.91; P=0.51) and chronic graft-*versus*-host disease (HR 1.31; P=0.11) were, however, not significantly different. In patients <50 years old, there were no statistically significant differences in overall survival, leukemia-free survival, relapse incidence, non-relapse mortality, and chronic graft-*versus*-host-disease between the groups. Our study shows no significant outcome differences in patients younger than 50 years receiving reduced-intensity *vs.* myeloablative conditioning regimens after mismatched unrelated donor transplantation. Furthermore, the data support the superiority of reduced-intensity conditioning regimens in older adults receiving transplants from mismatched unrelated donors.

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Introduction

Allogeneic hematopoietic cell transplantation (HCT) can provide extended leukemia-free survival (LFS) for the majority of patients with acute myeloid leukemia (AML).[1] However, only about 30-35% of patients have an HLA-matched sibling.[2-5] When an HLA-matched donor (related or unrelated) is not available or not suitable to donate, alternative donors may be considered if the patient is likely to benefit from allogeneic transplantation. Alternative donor sources include HLA-mismatched adult unrelated donors, unrelated umbilical cord blood (UCB), and mismatched related (family) members (haploidentical donor). Increasing numbers of patients are receiving alternative donor HCT, preference is given to a centers experience, physician preferences and participation in clinical trials.[6] Currently it is possible to find a stem cell source for virtually all patients who have an indication to receive HCT.[7,8]

Outcomes for matched or mismatched unrelated donor allografting have improved over time, likely because of, among other factors, better HLA-typing and matching and intensive supportive care.[9,10] Outcomes for matched unrelated donor allografting now appear comparable with those seen with matched sibling donor HCT.[3,4,11,12] Reduced-intensity conditioning (RIC) regimens have further extended the use of allogeneic HCT to older patients and those with significant pre-transplant comorbidities.[9,13,14]

Several previous studies comparing the clinical outcomes of RIC and MAC regimens after matched related or unrelated donor HCT in AML have shown similar outcomes;[13-16] however, it is unknown in patients receiving mismatched unrelated donor (MM-URD) HCT. Therefore, we explored whether there were outcome differences for adults with AML after RIC or MAC regimens in the setting of MM-URD HCT using data reported to the European Society for Blood and Marrow Transplantation (EBMT).

Methods

Study design and data collection

This was a retrospective multicenter analysis. Data were provided and approved for this study by the Acute Leukemia Working Party (ALWP) of the EBMT group registry. The latter is a voluntary working group of more than 500 transplant centers that are required to report all consecutive stem cell transplantations and follow-ups once a year. Audits are routinely performed to determine the accuracy of the data. Since 1990, patients have provided informed consent authorizing the use of their personal information for research purposes. Eligibility criteria for this analysis included adult patients (age >18 years) with AML, transplanted between 2000 and 2012, from a HLA-mismatched unrelated donor with bone marrow (BM) or G-CSF-mobilized peripheral blood (PB) stem cells. All donors were HLA-mismatched at one or two loci (9/10 or 8/10) (-A, -B, -C, DRB1, -DQB1). Recipients of a previous allogeneic or cord blood transplant were excluded. Variables collected included recipient and donor characteristics (age, gender, CMV serostatus), disease status at transplant, transplant related-factors including conditioning regimen, immunosuppression (*in vivo* T-cell depletion *vs.* none), stem cells source (BM or PB), GVHD prophylaxis, and outcome variables (acute and chronic GVHD, relapse, non-relapse mortality [NRM], LFS, overall survival [OS] and causes of death). Regimens were classified as MAC or RIC based on published criteria.[17] The list of institutions reporting data included in this study is provided in the *Online Supplementary Appendix*.

Statistical analysis

The primary end points of the study were OS and LFS. Secondary endpoints included: disease relapse incidence (RI), NRM, engraftment and incidences and severity of acute and chronic GVHD. The starting point for time-to-event analysis was "date of transplantation". OS was defined as the time to death from any cause. Surviving patients were censored at the time of their last follow-up. LFS was defined as survival without relapse or progression. Patients surviving in continuous CR were censored at the time of last follow-up. RI was defined as time to onset of leukemia recurrence. NRM was the competing risk, and patients surviving in continuous complete remission were censored at the last contact. NRM was defined as death without relapse/progression (relapse was the competing risk). The probabilities of OS and LFS were calculated by using the Kaplan-Meier estimator. The probabilities of chronic GVHD, NRM, and relapse were calculated by using the cumulative incidence estimator to accommodate competing risks. For chronic GVHD, death without the event was the competing risk. The 2 groups according to the conditioning regimen were compared by the Chi-square test for qualitative variables, whereas the Mann-Whitney test was applied for continuous parameters. Univariate comparisons were done using the log-rank test for OS, LFS, and the Gray's test for RI, NRM and chronic GVHD cumulative incidences. Multivariate analyses were performed using logistic regression for acute GVHD and Cox proportional hazards model for all other endpoints. All factors known as potentially related to the outcome were included in the final model. All tests were two-sided. The type I error rate was fixed at 0.05 for the determination of factors associated with time to event outcomes. Statistical analyses were performed with SPSS 22.0 (IBM Corp., Armonk, NY, USA) and R 3.1.1 software packages (R Development Core Team, Vienna, Austria).

Results

Patient, disease and transplant characteristics

Details of patients, disease and transplant characteristics are summarized in Table 1.

One thousand nine hundred and twenty four patients with AML were included in the study. One thousand and forty one patients received MAC and 883 RIC regimens before MM-URD HCT between 2000 and 2012.

RIC recipients were older with a median age of 57 years (range, 18-75) in comparison to 43 years (range, 18-72) for the MAC group (P<0.0001). Only thirty percent of the patients were ≤50 years of age in the RIC group *versus* 70% in the MAC group (P<0.0001). The median time from diagnosis to transplant was similar in the MAC and RIC groups (240 *vs.* 235 days, respectively; P=0.89). The median follow-up of surviving patients in the MAC group was 27 (IQR, 12-48) months, while that of the RIC group was 23 (IQR, 5-44) months (P=0.004). Significantly higher numbers of patients had secondary AML (13 *vs.* 10%, P=0.04) and KPS<90% (30 *vs.* 25%, P=0.02) in the RIC group. There were no significant differences in the distribution of advanced disease and poor risk cytogenetic among regimens. The proportions of CMV positive recipients and donors were similar in the MAC and RIC groups (67% *vs.* 66%; P=0.84 and 44% *vs.* 45%; P=0.52, respectively).

Commonly used MAC regimens were TBI based (n=369), BuCy (n=354) and Bu-Flu (n=143); in the RIC group the most commonly used regimens were low dose TBI based (n=275), Bu-Flu (n=312) and Flu-Mel (n=178).

Among the MAC recipients, 872 (83.8%) received 9/10 and 169 (16.2%) 8/10 HLA-matched donors, and in the RIC cohort, 754 (85.4%) received 9/10 and 129 (14.6%) 8/10 matched donors (P=0.33). The percentage of patients receiving *in vivo* T-cell depletion was not significantly different between the two groups (P=0.18, Table 1).

In the MAC group bone marrow was used more frequently as the stem cell source (20 *vs.* 9%; P<0.0001). Apart from *in vivo* T-cell depletion, GvHD prophylaxis consisted of the combination of one calcineurin inhibitor with mycophenolate mofetil (MMF) alone, or in association with methotrexate (MTX). A calcineurin inhibitor + MMF and/or MTX were used in 96% and 95% of the patients in the MAC and RIC groups, respectively. The choice of conditioning and GvHD prophylaxis was dependent on transplant center protocols and strategies for transplantation.

Engraftment and GvHD

Conditioning regimen specific engraftment and GvHD data are summarized in Table 2. Ninety five percent of patients in the MAC group engrafted *versus* 96% in the RIC group (P=0.45). The median day to absolute neutrophil count (ANC) >500/μL was 16 in both groups. The percentage of grade II-IV (33% *vs.* 32%; P=0.55) and III-IV (12% *vs.* 14%; P=0.38) acute GvHD were not significantly

Table 1. Patients, disease and transplant characteristics.

Patient characteristics	MAC (n=1041)	RIC (n=883)	P
Recipient age at HCT (median, IQR), years	43 (32-52)	57 (47-63)	$<10^{-4}$
<50	731 (70.2%)	267 (30.2%)	
≥50	310 (29.8%)	616 (69.8%)	
Recipient gender, n (%)			0.52
Male	523 (50.2%)	455 (51.7%)	
Female	518 (49.8%)	425 (48.3%)	
Unknown	0	3	
Interval from diagnosis to HCT (median, IQR), days	240 (158-478)	235 (156-505)	0.89
Donor age (years, range)	36 (19-70)	35 (20-61)	0.66
Donor gender, n (%)			0.7
Male	651 (64.3%)	567 (65.2%)	
Female	361 (35.7%)	303 (34.8%)	
Unknown	29	13	
Female donor to male recipient, n (%)	157 (15.5%)	132 (15.2%)	0.86
Disease status at HCT, n (%)			0.14
CR1	523 (50.2%)	408 (46.2%)	
≥CR2	261 (25.1%)	226 (25.6%)	
Active disease	257 (24.7%)	249 (28.2%)	
Secondary AML	104 (10%)	115 (13%)	0.04
Karnofsky at HCT, <90%, n (%)	230/917 (25.1%)	236/787 (30%)	0.02
Patient positive CMV serology	670/1008 (66.5%)	573/868 (66%)	0.84
Donor positive CMV serology	444/1014 (43.8%)	393/868 (45.3%)	0.52
Human leukocyte antigen matching			0.33
9/10 match	872 (83.8%)	754 (85.4%)	
8/10 match	169 (16.2%)	129 (14.6%)	
Stem cells source			<0.0001
BM	207 (19.5%)	84 (9.5%)	
PB	834 (80.1%)	799 (90.5%)	
Conditioning regimen, n			
Bu-Cy	354		
Bu-Flu	143	312	
Flu-Mel	36	178	
TBI-MAC	369		
TBI-RIC		275	
Others regimens	139	118	
In vivo T-cell depletion, n (%)	841/1029 (81.7%)	734/878 (83.6%)	0.18

AML: acute myeloid leukemia; CMV: cytomegalovirus; CR: complete remission; RIC: reduced intensity conditioning; MAC: myeloablative conditioning; HCT: allogeneic stem cell transplantation; BM: bone marrow; PB: peripheral blood; Bu- busulfan; Cy: cyclophosphamide; Flu: fludarabine; Mel: melphalan; TBI: total body irradiation; some percentages do not add up to 100% because of rounding.

different between the groups. As shown in Table 3, in multivariate analysis, the factors associated with increased risk of grade II-IV acute GvHD were active disease (OR 1.48; 95% CI, 1.05-2.11; *P*=0.03) in patients <50 years and female donor to male recipient (OR 1.56; 95% CI, 1.04-2.35; *P*=0.03) in patients ≥50 years. *In vivo* T-cell depletion was associated with a decreased risk of acute GVHD in patients in both the <50 years (OR 0.67; 95% CI, 0.47-0.97; *P*=0.03) and ≥50 years groups (OR 0.70; 95% CI, 0.48-1.03; *P*=0.07).

The two-year cumulative incidence of chronic GVHD was higher after the RIC regimen (34% [95% CI, 31-38] *vs.* 29% [95% CI, 26-32] in the MAC, *P*=0.04) (Table 4). In multivariate analysis, chronic GVHD was not significantly different between MAC and RIC in patients <50 years (HR 0.91; 95% CI, 0.66-1.26; *P*=0.58) and in ≥50 years groups (HR 1.31; 95% CI, 0.95-1.81; *P*=0.11). The factor associated with chronic GVHD were female donor to male recipient (HR 1.49; 95% CI, 1.08-2.07; *P*=0.02) and *in vivo* T-cell depletion (HR 0.51; 95% CI, 0.37-0.68; *P*=0.00001) in patients <50 years and (HR 0.63; 95% CI, 0.45-0.89; *P*=0.01) in patients ≥50 years (Table 3).

NRM

There was no difference in NRM at 2 years between the MAC and RIC groups in univariate analysis- (28%; 95% CI, 25-30 after MAC *vs.* 27%; 95% CI, 24-30 after RIC; *P*=0.76) (Table 4). When analyzing patients <50 and ≥50 years separately, only the older cohort in the MAC group showed a higher risk of NRM (36%; 95% CI, 30-41 for MAC *vs.* 30%; 95% CI, 24-35; *P*=0.05) (Table 4).

In multivariate analysis, NRM was not significantly different between the MAC and RIC in patients <50 years (HR 0.91; 95% CI, 0.65-1.26; *P*=0.56), however in the ≥50 years group, the RIC regimen was independently associated with decreased NRM (HR 0.73; 95% CI, 0.56-0.97; *P*=0.03). The other factors associated with NRM were active disease and secondary AML in those <50 ((HR 1.86; 95% CI, 1.32-2.62; *P*=0.0004; HR 1.65; 95% CI, 1.06-2.58; *P*=0.03, respectively) and ≥50 years (HR 1.45; 95% CI, 1.06-1.98; *P*=0.02; HR 1.41; 95% CI, 1.01-1.96; P=0.04, respectively) and CMV seropositivity (HR 1.37; 95% CI, 1.01-1.86; *P*=0.04) in patients <50 years and age at HCT (by +10 years) (HR 1.15; 95% CI, 1.04-1.28; *P*=0.01) in patients ≥50 years (Table 3).

Relapse

There was no difference in RI at 2 years between the MAC and RIC groups in univariate analysis (30%; 95% CI, 27-33; after MAC *vs.* 33%; 95% CI, 30-36 after RIC; *P*=0.11) (Table 4). When analyzing patients <50 and ≥50 years separately, an advantage of receiving a MAC regimen in reducing relapse risk was only observed in the younger cohort (<50 years) (30%; 95% CI, 26-34 for MAC *vs.* 40%; 95% CI, 33-46; *P*=0.008) (Table 4);

In multivariate analysis, RI was not different between MAC and RIC in both <50 years and ≥50 years groups (Table 3).

The factors associated with RI were active disease in both <50 (HR 2.96; 95% CI, 2.25-3.88; *P*<0.0001) and ≥50 years group (HR 2.46; 95% CI, 1.85-3.27; *P*<0.0001), CMV positive recipients (HR 0.78; 95% CI, 0.60-1.00; *P*=0.05) and higher HLA- mismatching (8/10 *vs.* 9/10) (HR 0.69; 95% CI, 0.48-1.00; *P*=0.05) in patients ≥50 years (Table 3).

Leukemia-free survival

There was no difference in LFS at 2 years between the MAC and RIC groups in univariate analysis (43%; 95% CI, 39-46; after MAC *vs.* 40%; 95% CI, 36-44 after RIC; *P*=0.34) (Table 4). When analyzing patients <50 and ≥50 years separately, an advantage was seen for LFS in the MAC group only for younger patients (<50 years) (46%; 95% CI, 42-50 for MAC *vs.* 39%; 95% CI, 32-45; *P*=0.05) and in the RIC group for the older patients (34%; 95% CI, 29-40 for MAC *vs.* 40%; 95% CI, 36-45; *P*=0.03) (Table 4).

In multivariate analysis, LFS was not significantly different between MAC and RIC in patients <50 years (HR 1.02; 95% CI, 0.83-1.26; *P*=0.83). Among older cohorts (age ≥50), there was an advantage of RIC regimen with higher LFS (HR 0.82; 95% CI, 0.68-1.00; *P*=0.05). The other factors associated with LFS were active disease in <50 (HR 2.48; 95% CI, 2.00-3.06; $P<10^{-4}$) and ≥50 years groups (HR 1.93; 95% CI, 1.56-2.38; $P<10^{-4}$) and secondary AML (HR 1.36; 95% CI, 1.00-1.85; *P*=0.05) in patients <50 years and age at HCT (by +10 years) (HR 1.09; 95% CI, 1.02-1.17; *P*=0.02) in patients ≥50 years (Table 3).

Overall survival

There was no difference in OS at 2 years between the MAC and RIC groups in univariate analysis (45%; 95% CI, 42-49; after MAC *vs.* 45%; 95% CI, 41-48 after RIC; *P*=0.81) (Table 4). When analyzing patients <50 and ≥50 years separately, RIC had an advantage in older cohorts (37%; 95% CI, 31-43 for MAC *vs.* 45%; 95% CI, 40-49; *P*=0.01) (Table 4).

In multivariate analysis, OS was not significantly different between MAC and RIC in patients <50 years old (HR 0.96; 95% CI, 0.77-1.19; *P*=0.71). Among older cohorts (age ≥50), there was an advantage of RIC regimen with higher OS (HR 0.78; 95% CI, 0.66-0.95; *P*=0.01). The other factors associated with OS were active disease in patients <50 (HR 2.37; 95% CI, 1.90-2.95; *P*<0.0001) and ≥50 years old (HR 1.82; 95% CI, 1.46-2.26; *P*<0.0001), secondary AML (HR 1.41; 95% CI, 1.03-1.94; *P*=0.03), higher HLA-mismatching (8/10 *vs.* 9/10) (HR 1.27; 95% CI, 1.01-1.61; *P*=0.05) in patients <50 years old and age at HCT (by +10 years) (HR 1.14; 95% CI, 1.05-1.22; *P*=0.0008) in patients ≥50 years (Table 3).

Table 2. Conditioning regimen specific engraftment and GvHD data.

	MAC (n=1041)	RIC (n=883)	*P*
Engraftment			
Yes	976 (95.2%)	826 (95.9%)	0.45
No	49 (4.8%)	35 (4.1%)	
Unknown, n	16	22	
Acute GvHD			
Grade II-IV, n (%)	330/997 (33.1%)	271/852 (31.8%)	0.55
Grade III-IV, n (%)	122/997 (12.2%)	116/852 (13.6%)	0.38
Chronic GvHD*	29.2% [26-32.3]	34.2% [30.6-37.8]	0.04
Limited, n	119	125	
Extensive, n	123	88	
Unknown, n	7	23	

*GvHD: graft-versus-host disease; *2-year cumulative incidence; RIC: reduced intensity conditioning; MAC: myeloablative conditioning; some percentages do not add up to 100% because of rounding.*

Interaction between the conditioning regimen and HLA-mismatch

There is no significant interaction between the conditioning regimen and the degree of HLA-mismatch (P=0.32) or status at transplant (P=0.29). Interactions remained insignificant when data were analyzed separately for patients <50 (P=0.30 and P=0.82 with HLA-mismatches and with status at transplant, respectively) and ≥50 years (P=0.38 and P=0.29 for HLA mismatch and status at transplant, respectively). Results were similar among HLA-mismatched pairs, and recipients with advanced disease, although this study was not designed to detect potential differences within these subsets.

Discussion

This large, multicenter, registry study did not show significant outcome difference between transplant recipients who received RIC and those who received MAC regimen followed by HLA MM-URD HCT for AML in patients younger than 50 years. Moreover, data support the superiority of RIC regimen in patients ≥50 years receiving transplant from a MM-URD. This finding is novel and clinically very important since many older adults are not transplanted due to the lack of a 10/10 HLA-matched donor.

We investigated patient, disease, and transplantation factors affecting survival, LFS, relapse, and NRM in a well-

Table 3. Multivariate analysis- comparison between RIC *vs.* MAC regimen and significant factors associated with outcome.

	P Age <50 years	HR (95% CI)		*P* Age ≥50 years	HR (95% CI)
Relapse					
RIC *vs.* MAC	0.50	1.10 (0.84-1.43)	RIC *vs.* MAC	0.51	0.91 (0.70-1.20)
Active disease (ref CR1)	$<10^{-4}$	2.96 (2.25-3.88)	Active disease (ref CR1)	$<10^{-4}$	2.46(1.85-3.27)
			CMV+ donor	0.05	0.78 (0.60-1.00)
			HLA-match 8/10 *vs.* 9/10	0.05	0.69 (0.48-1.00)
NRM					
RIC *vs.* MAC	0.56	0.91 (0.65-1.26)	RIC *vs.* MAC	0.03	0.73 (0.56-0.97)
Active disease (ref CR1)	0.0004	1.86 (1.32-2.62)	Active disease (ref CR1)	0.02	1.45 (1.06-1.98)
Secondary AML	0.03	1.65 (1.06-2.58)	Secondary AML	0.04	1.41 (1.01-1.96)
CMV+ patient	0.04	1.37 (1.01-1.86)	Age at SCT (+10 years)	0.01	1.15 (1.04-1.28)
Acute GvHD*					
RIC *vs.* MAC	0.27	0.83 (0.59-1.16)	RIC *vs.*MAC	0.29	1.20 (0.86-1.67)
Active disease (ref CR1)	0.03	1.48 (1.05-2.11)	Female▶male	0.03	1.56 (1.04-2.35)
In vivo T-cell depletion	0.03	0.67 (0.47-0.97)	*In vivo* T-cell depletion	0.07	0.70 (0.48-1.03)
Chronic GVHD					
RIC *vs.* MAC	0.58	0.91 (0.66-1.26)	RIC *vs.* MAC	0.11	1.31 (0.95-1.81)
Female▶male	0.02	1.49 (1.08-2.07)	*In vivo* T-cell depletion	0.01	0.63 (0.45-0.89)
In vivo T-cell depletion	0.00001	0.51 (0.37-0.68)			
LFS					
RIC *vs.* MAC	0.83	1.02 (0.83-1.26)	RIC *vs.* MAC	0.05	0.82 (0.68-1.00)
Active disease (ref CR1)	$<10^{-4}$	2.48 (2.00-3.06)	Active disease (ref CR1)	$<10^{-4}$	1.93 (1.56-2.38)
Secondary AML	0.05	1.36 (1.00-1.85)	Age at SCT (+10 years)	0.02	1.09 (1.02-1.17)
OS					
RIC *vs.* MAC	0.71	0.96 (0.77-1.19)	RIC *vs.* MAC	0.01	0.78 (0.66-0.95)
Active disease (ref CR1)	$<10^{-4}$	2.37 (1.90-2.95)	Active disease (ref CR1)	$<10^{-4}$	1.82 (1.46-2.26)
Secondary AML	0.03	1.41 (1.03-1.94)	Age at SCT (+10 years)	0.0008	1.14 (1.05-1.22)
HLA-match 8/10 *vs.* 9/10	0.05	1.27 (1.01-1.61)			

*HR-hazard ratio; CR: complete remission; GvHD: graft-*versus*-host-disease; LFS: leukemia-free survival; NRM: non-relapse mortality; RIC: reduced intensity conditioning; MAC: myeloablative conditioning; OS: overall survival; Female▶male: female donor for male recipient.*

Table 4. Outcomes at 2 years, by age at transplantation.

Disease status	Patients group	RI	NRM	LFS	OS	cGvHD
All patients*	MAC	29.9% [27.2-32.9]	27.5% [24.7-30.4]	42.5% [39.2-45.7]	45.4% [42.1-48.7]	29.2% [26-32.3]
	RIC	33% [29.6-36.4]	27.1% [24.3-30]	39.9% [36.3-43.5]	44.6% [40.9-48.3]	34.2% [30.6-37.8]
	P	0.11	0.76	0.34	0.81	0.04
Age <50 years*~	MAC	29.9% [26.4-33.5]	24.1% [20.9-27.4]	45.9% [42-49.7]	48.8% [44.9-52.8]	31.2% [27.4-35]
	RIC	39.7% [33.3-46.1]	21.4% [18.3-24.6]	38.9% [32.3-45.4]	44.6% [37.8-51.3]	26.2% [20.4-32.5]
	P	0.008	0.50	0.05	0.24	0.18
Age ≥50 years*	MAC	29.8% [24.5-35.4]	35.8% [30.1-41.4]	34.3% [28.5-40.1]	37.1% [31.3-43]	24.3% [19-29.9]
	RIC	30% [26.2-34]	29.6% [24.2-35.3]	40.3% [36-44.6]	44.6% [40.2-49]	37.6% [33.2-42.1]
	P	0.95	0.05	0.03	0.01	0.0009

*Data are % (95% CI), unless otherwise specified; *2-year outcome; cGvHD: chronic graft-*versus*-host-disease; LFS: leukemia-free survival; NRM: non-relapse mortality; MAC: myeloablative conditioning; OS: overall survival; RI: relapse incidence; RIC: reduced intensity conditioning; ~higher advanced disease patients in RIC group (38% vs. 21% in MAC group, $P<10^{-4}$).*

characterized population of nearly 2000 adult AML patients receiving MAC or RIC MM-URD HCT. Overall, nearly 45% of patients (Figure 1,2) transplanted with MM-URD survived beyond 2 years and the intensity of the conditioning regimen did not significantly influence LFS or OS. Two-year survival after RIC regimen was favorable (45%) compared with MAC regimens (37%, *P*=0.01). Similarly, the risk of relapse was not different between the two groups in multivariate analysis. These promising results compare favorably with outcomes after HLA-matched donor transplant, yet the heterogeneity in the subjects likely contribute to the differences.[2,4,18] Another important finding is the worsening outcome with age in the older cohort which is consistent with many previous reports.[9]

Clear data on the value of the conditioning regimen intensity for AML are still lacking, though the use of RIC has extended the availability of allogeneic HCT to older patients.[13] Many retrospective studies have highlighted that the lower risks of NRM are offset by the increased rates of relapse in RIC with similar OS.[13,19-21] More recent studies note similar outcomes for those in complete remission.[22-24] An unanswered question is whether HLA match requirements should differ based on the conditioning regimen. With increasing numbers of reduced-intensity conditioning transplantations being performed for AML, our study is timely and explores the impact of HLA mismatching and the intensity of conditioning intensity in the current era.

It is possible that the historically higher relapse rate after RIC compared to MAC can be abrogated by the potent graft-*versus*-leukemia (GVL) effect induced by greater HLA disparity after RIC MM-URD transplant.[25,26] In multivariate analysis, our data showed that the relapse rate was not different between MAC and RIC in both <50 years and ≥50 years groups. However, in older patients (≥50 years), the superiority of the RIC regimen was due to the additional benefits of decreased NRM compared to patients receiving MAC.

The protective effect of *in vivo* T-cell depletion on the incidence of GVHD without compromising transplant outcome was reaffirmed in our study.[27] Given the multiple

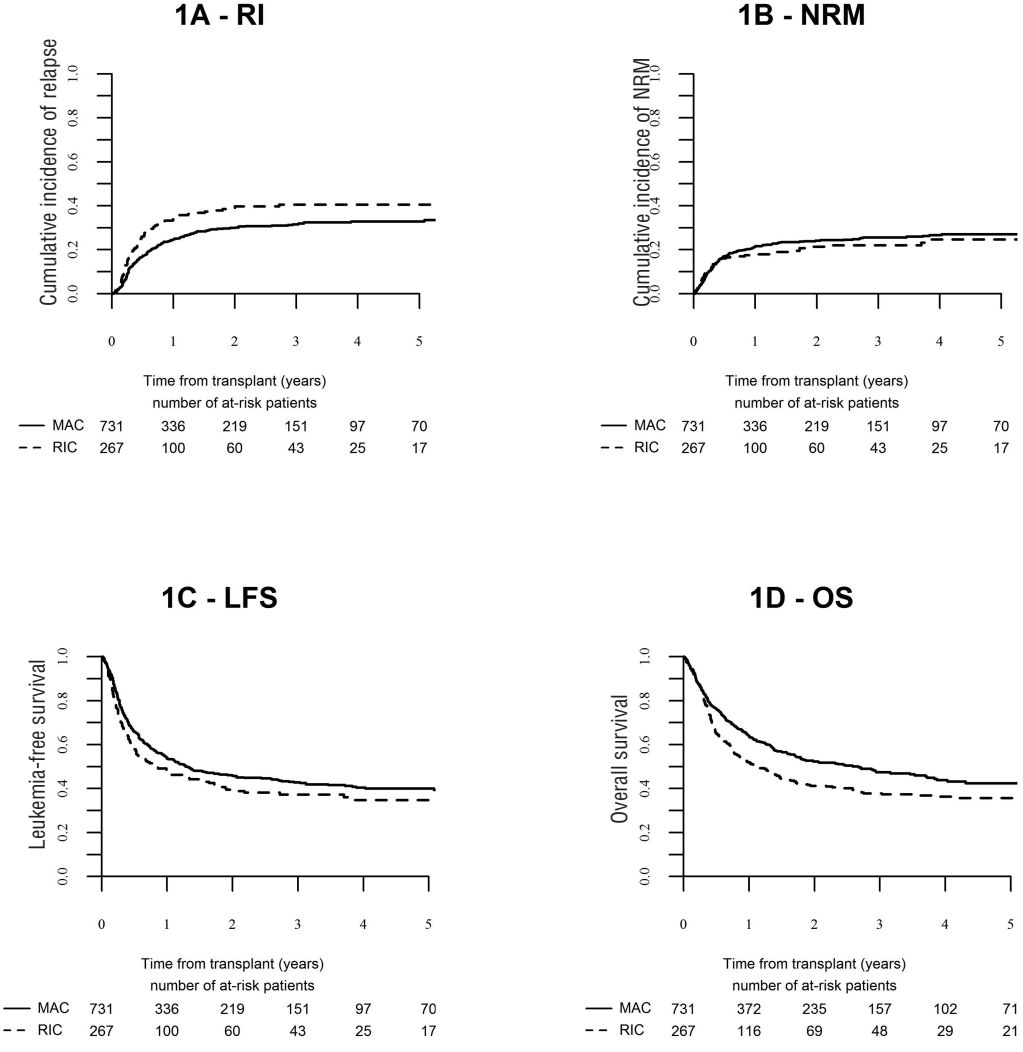

Figure 1. Probability of overall survival (OS), leukemia-free survival (LFS), non-relapse mortality (NRM) and relapse incidence (RI) after myeloablative or reduced intensity conditioning regimen for acute myeloid leukemia (age <50 years) after mismatched unrelated donor transplantation.

adverse long-term implications of chronic GVHD on survival and quality of life (QOL) this is an important observation.[28,29] Chronic GVHD can impair QOL and is associated with significant morbidity and mortality among HCT recipients. However, the costs, economic burden and resource utilizations to manage long term complications associated with cGVHD have not been well described.[30] More research is needed to better understand the costs of GVHD to patients, centers and the health care system and to determine if the lower incidence and severity of GVHD with *in vivo* T-cell depletion leads to long-term resource savings.

Recently presented results of a randomized trial within the Blood and Marrow Transplant Clinical Trials Network 0901 showed that RIC regimens result in higher relapse rates and lower TRM compared to MAC, with a statistically significant advantage in relapse-free survival for patients receiving MAC regimens.[31] The study is closed to accrual and reports of the study data are unlikely to answer questions in patients receiving MM-URD HCT. Despite the inherent limitations of our retrospective registry study and in the absence of the prospect for prospective data in the near future, it is reasonable to consider RIC regimen for patients receiving MM-URD HCT for AML in transplant-indicated patients.

Published data support any one of three alternative donor HCT options for the patients without matched donors considered optimal.[2,4,32-34] Only through the conduct of well-designed clinical trials can we understand and appreciate the complexities of donor choice and their impact on outcome after HCT for AML. Unfortunately, there are no ongoing trials that compare outcomes after MM-URD with that of related mismatched or UCB transplantation. Therefore, in the absence of any prospect of such a comparative study, our data support the use of RIC MM-URD HCT for patients with AML when a suitably matched donor is unavailable.

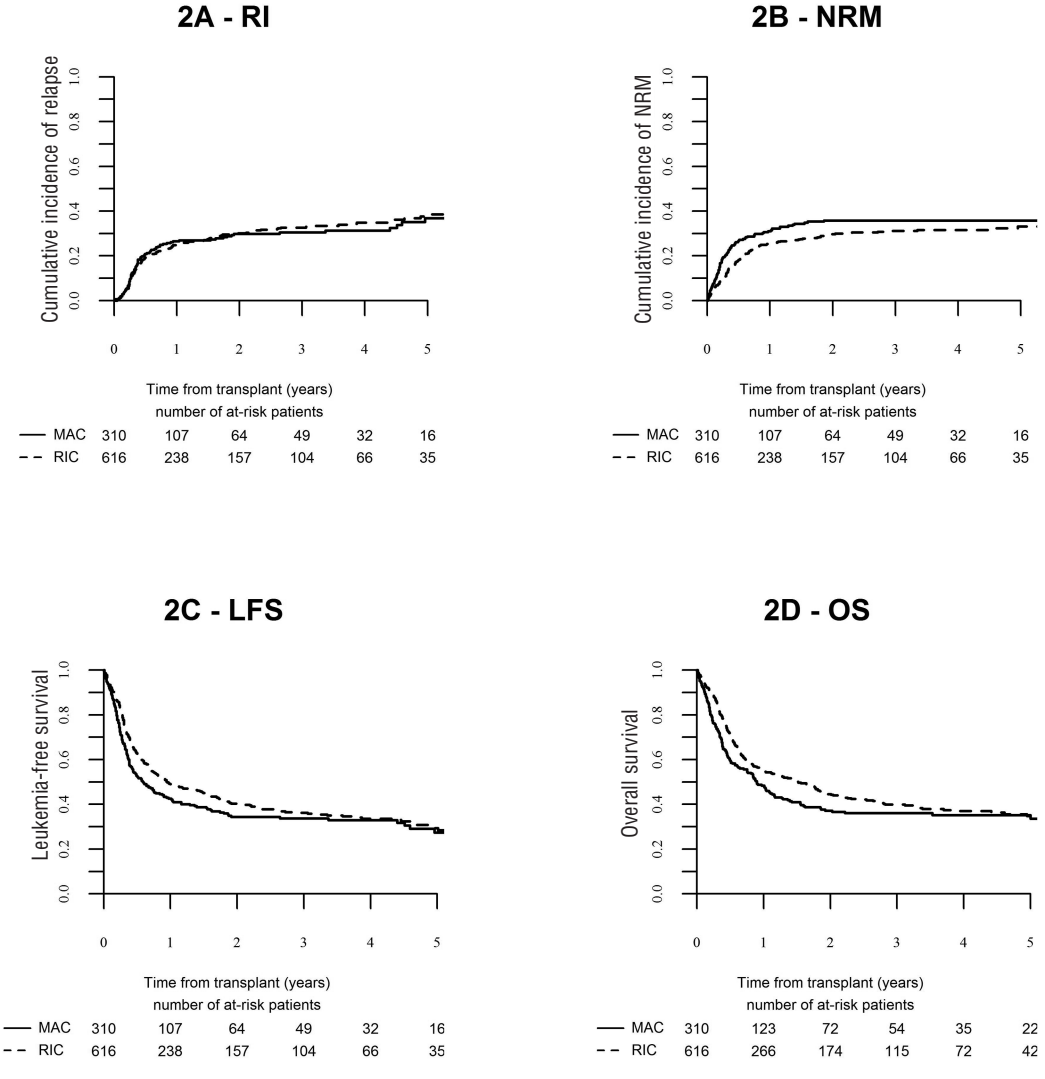

Figure 2. Probability of overall survival (OS), leukemia-free survival (LFS), non-relapse mortality (NRM) and relapse incidence (RI) after myeloablative or reduced intensity conditioning regimen for acute myeloid leukemia (age ≥50 years) after mismatched unrelated donor transplantation.

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