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Allogeneic Stem Cell Transplantation in Patients >40 Years of Age With Acute Lymphoblastic Leukemia: Reduced Intensity Versus Myeloablative Conditioning

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Background. The outcome in older patients with acute lymphoblastic leukemia (ALL) remains unsatisfactory due to high relapse and nonrelapse mortality (NRM) rates. Allogeneic stem cell transplantation (alloHSCT) as postremission therapy has an important role in reducing relapse rate, albeit its application is limited in older adult patients due to alloHSCT-related morbidity and mortality. Reduced-intensity conditioning (RIC) alloHSCT has been developed as a less toxic conditioning regimen, but comparative studies with myeloablative conditioning (MAC) are limited in patients with ALL. **Methods.** In this retrospective study, RIC-alloHSCT (n = 111) was compared with MAC-alloHSCT (n = 77) in patients aged 41 to 65 y with ALL in first complete remission. MAC was predominantly applied by combining high-dose total body irradiation and cyclophosphamide, whereas RIC mainly consisted of fludarabine and 2 Gy total body irradiation. **Results.** Unadjusted overall survival was 54% (95% confidence interval [CI], 42%-65%) at 5 y in MAC recipients compared with 39% (95% CI, 29%-49%) in RIC recipients. Overall survival and relapse-free survival were not significantly associated with type of conditioning after adjusted for the covariates age, leukemia risk status at diagnosis, donor type, and donor and recipient gender combination. NRM was significantly lower after RIC (subdistribution hazard ratio: 0.41, 95% CI, 0.22-0.78; $P = 0.006$), whereas relapse was significantly higher (subdistribution hazard ratio: 3.04, 95% CI, 1.71-5.40; $P < 0.001$). **Conclusions.** Collectively, RIC-alloHSCT has resulted in less NRM, but it was also found to be associated with a significantly higher relapse rate. These results suggest that MAC-alloHSCT may provide a more effective type of consolidation therapy for the reduction of relapse and that RIC-alloHSCT may be restricted to patients at higher risk for NRM.

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INTRODUCTION

The outcome in adult patients with acute lymphoblastic leukemia (ALL) has gradually improved over the past decades.[1,2] The introduction of pediatric-based induction and consolidation chemotherapy has improved outcomes in younger adult patients with ALL.[3-7] Additionally, the application of allogeneic hematopoietic stem cell transplantation (alloHSCT) as postremission therapy in younger adult patients with poor-risk ALL in first complete remission (CR1) has resulted in survival rates of approximately 40% to 60%, depending on various risk factors including age, comorbidity status, type of donor, and residual disease status.[8-14] The graft-versus-leukemia (GVL) effect of alloHSCT is strong in ALL, as shown in previous studies,[11,12,15] and appears to reduce the relapse rate by approximately 50% compared with maintenance or high-dose chemotherapy followed by autologous transplantation.

However, the outcome in patients with ALL aged >40 y is still unsatisfactory due to higher chemotherapy-associated toxicity and mortality and also due to a higher relapse rate.[16] Additionally, alloHSCT as postremission therapy has been less frequently applied because of alloHSCT-related morbidity and mortality in patients aged >40 y. Particularly myeloablative conditioning (MAC) alloHSCT is associated with a higher rate of nonrelapse mortality (NRM).[17,18] However, since the introduction of less-toxic, reduced-intensity conditioning (RIC) regimens, alloHSCT was more frequently applied in patients aged >40 y, for which development started approximately 25 y ago.[1,19] Position statement of the European Society for Blood and Marrow Transplantation (EBMT) considers RIC-alloHSCT in older patients with ALL as encouraging.[20] In the Netherlands, RIC-alloHSCT was gradually introduced and applied in patients with ALL CR1 beyond the age of 40 y as from 2001 onward. Meanwhile, MAC-alloHSCT was not completely abandoned by most Dutch transplantation centers, allowing us to compare these modalities in a retrospective study.

In the present study, we addressed the question of whether RIC-alloHSCT in adult patients with CR1 ALL aged >40 y has resulted in improved outcomes compared with recipients of MAC-alloHSCT.

PATIENTS AND METHODS

Patients

A total of 188 patients with ALL between 41 and 65 y of age, who underwent a first alloHSCT in CR1 in the Netherlands between 2001 and 2015 were retrospectively included. Induction treatment was given within or according to 3 consecutive prospective trials of the Haemato Oncology Foundation for Adults in the Netherlands (HOVON; HOVON-37, HOVON-71, and HOVON-100). The HOVON-71 and HOVON-100[21-23] protocols were based on a (semi)intensive, pediatric-inspired treatment regimen. Minimal residual disease (MRD) monitoring was partially applied during the study period; however, treatment choices were not based on MRD results.

Data were provided by the Dutch Stem Cell Transplantation Working Group of HOVON. Patients were classified according to leukemia risk (standard or high risk), based on clinical, cytogenetic, and molecular profile of ALL (**Table S1, SDC,** http://links.lww.com/TP/C804). Patients with an incomplete risk status were considered as standard risk. The HOVON trials had been approved by the ethics committees of the participating institutions and were conducted in accordance with the Declaration of Helsinki.

Transplantation Protocols

Patients were considered for alloHSCT when either classified as having a standard risk disease and a fully matched sibling donor or as high-risk patients with also alternative donor sources (a matched-related or -unrelated donor, a mismatched donor, or cordblood units).

AlloHSCT was performed according to standard guidelines and general procedures operational in the 8 academic centers in the Netherlands. The choice of MAC versus RIC was based on the age of the patient and the preference of the treatment site. Three of the 8 transplant centers had switched to RIC after that conditioning modality had been introduced in medical practice, 3 transplant centers used both conditioning strategies with decision-making based on patient fitness and leukemia risk, whereas the remaining 2 centers maintained and preferred to apply MAC protocols. MAC was mainly applied as the combination of high-dose total body irradiation (TBI) and high-dose cyclophosphamide, whereas RIC was mainly given according to the Seattle regimen (fludarabine and 2-Gy TBI dose).[24] Graft-versus-host disease (GVHD) prevention was applied according to local protocols by mainly using calcineurin inhibitor with or without mycophenolate mofetil (>80% of patients).

Endpoints

The primary endpoint of the study was overall survival (OS), according to the type of conditioning regimen received. Secondary endpoints were relapse-free survival (RFS), cumulative incidence of NRM, and relapse and incidence of GVHD.

Statistical Methods

Patient-, disease-, and transplant-related variables were compared between MAC and RIC groups. The Kaplan-Meier method was used to estimate survival. OS and RFS were measured from the date of transplantation. The event for OS was death, whatever the cause, and patients were censored at the date of the last contact, if alive. The events for RFS were death in CR1, designated as NRM, or leukemia relapse. The reverse Kaplan-Meier method was used to calculate the median time to follow-up. The cumulative risks of relapse and NRM over time were calculated as competing risks. Univariable and multivariable Cox regression analyses were performed to evaluate the association of type of conditioning regimen with OS and with RFS, whereas the Fine and Gray method[25] was used for NRM and relapse. Based on the results of the univariable analysis ($P < 0.05$; **Table S2, SDC,** http://links.lww.com/TP/C804), in the multivariable analysis, type of conditioning regimen was adjusted for age (continuous) and donor type (sib versus nonsib). Furthermore, donor and recipient gender combination as remaining factor of the EBMT risk score[26] and leukemia risk status at diagnosis (high versus standard) was added to the model. Based on the results

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of the multivariable Cox regression, we plotted the estimated OS Cox proportional hazards regression (**Figure S1, SDC,** http://links.lww.com/TP/C804.) All *P* were based on log-likelihood ratio tests. *P* values have not been adjusted for multiple testing. Previously described analyses were also performed for the *BCR-ABL1*–positive and *BCR-ABL1*–negative subgroups separately. All analyses were performed with Stata Statistical Software: Release version 16.0 (StataCorp LP, College Station, TX).

RESULTS

Patient Characteristics

We identified 188 patients with newly diagnosed ALL, aged between 41 and 65 y, receiving alloHSCT in CR1 between 2001 and 2015. Patient and transplant characteristics are summarized in Table 1. The MAC regimen was applied in 77 transplants (41%), whereas RIC was used in 111 patients (59%). The median follow-up time of patients still alive was 78 mo (interquartile range: 37–138) and 55 mo (interquartile range, 43–102) in the MAC and RIC group, respectively. Significant differences between MAC and RIC recipients were observed with respect to age (median 47 versus 55 y; $P < 0.001$) and year of transplantation (median 2009 versus 2010, respectively, $P = 0.007$). Alternative donors were less often used in MAC-alloHSCT patients (39% versus 58%, $P = 0.009$), and high EBMT scores (≥3) were less frequent in MAC patients (53% versus 68%, $P = 0.037$) compared with RIC patients. In vivo lymphocyte depletion (using either alemtuzumab or antithymocyte globulin) was more frequently applied in MAC patients compared with RIC patients (40% versus 27%, $P = 0.041$). Other leukemia risk parameters were not significantly different between the groups. *BCR-ABL1* fusion was detected in 31% of the patients in the MAC group and in 41% of patients in the RIC group ($P = 0.100$). Comorbidity data were not available in this study.

Survival Analysis

Unadjusted OS at 5 y was 54% (95% confidence interval [CI]: 42%-65%) and 39% (95% CI, 29%-49%) in recipients of MAC and RIC, respectively. Unadjusted RFS was 51% (95% CI, 39%-61%) and 36% (95% CI, 27%-45%), respectively, after MAC and RIC (Figure 1A and B). Subgroup analyses of *BCR-ABL1*–positive and –negative patients showed no significant difference between MAC and RIC recipients according to OS and RFS (**Table S3, SDC,** http://links.lww.com/TP/C804). Univariable analyses showed no significant association between conditioning type and OS (hazard ratio [HR]: 1.32; 95% CI, 0.88-1.99; $P = 0.176$, RIC versus MAC) or RFS (HR: 1.45; 95% CI, 0.98-2.13; $P = 0.063$, RIC versus MAC; **Table S2, SDC,** http://links.lww.com/TP/C804). No significant association was found between year of transplantation and outcome (**Table S2, SDC,** http://links.lww.com/TP/C804).

Multivariable Analysis

The results of the multivariable analyses with adjustment for the covariates conditioning type, age, leukemia risk status at diagnosis, donor type, and donor–recipient gender combination are shown in Table 2. There was no significant association between conditioning type and OS or RFS. OS was exclusively associated with increasing age at diagnosis (HR: 1.04; 95% CI, 1.01-1.08; $P = 0.010$). The conditioning regimen (subdistribution hazard ratio [SHR]: 0.41; 95% CI, 0.22-0.78; $P = 0.006$, RIC versus MAC), increasing age (SHR: 1.06; 95% CI, 1.01-1.11; $P = 0.021$), and donor type (SHR: 2.20; 95% CI, 1.13-4.27; $P = 0.021$, alternative donor versus HLA-identical sibling) were independently associated with NRM. Moreover, the conditioning regimen (SHR: 3.04; 95% CI, 1.71-5.40; $P < 0.001$, RIC versus MAC) and donor type (SHR: 0.44; 95% CI, 0.25-0.78; $P = 0.005$, alternative donor versus HLA-identical sibling) were significantly associated with relapse. No significant association between leukemia risk status at diagnosis and outcome was found.

Graft-versus-host Disease

Incidences of grade II to IV acute GVHD after RIC-alloHSCT and MAC-alloHSCT were comparable, 42% in MAC patients and 36% in RIC patients ($P = 0.119$). Incidences of chronic limited and chronic extensive GVHD were 21% and 19% in MAC-alloHSCT recipients, respectively, and 11% and 42% in RIC-alloHSCT, respectively ($P = 0.002$; **Table S4, SDC,** http://links.lww.com/TP/C804).

DISCUSSION

In the present retrospective study, we addressed the question whether RIC-alloHSCT in patients aged >40 y has resulted in improved outcome compared with MAC-alloHSCT. Although NRM was reduced, no improvement in OS and RFS was observed, mainly due to a counterbalancing higher relapse rate after RIC-alloHSCT. Only a few previous retrospective clinical trials comparing RIC-alloHSCT and MAC-alloHSCT in adult ALL patients are available.[27-31] Most of them also suggest that patients receiving RIC may experience a higher risk of relapse compared with patients receiving MAC. Marks et al[27] reported no significant higher relapse rate in RIC patients, although a trend (35% in RIC versus 26% in MAC, $P = 0.08$) toward a higher relapse rate was suggested. Tanaka et al[30] found a higher relapse rate in RIC-alloHSCT patients, but no difference in NRM and survival. The explanation for these differences in outcome might be the type of RIC used. The studies performed used different RIC regimens. The Center for International Blood and Marrow Transplant Research has defined a wide range of regimens as RIC.[32] All regimens that include a <5-Gy single dose TBI or <8-Gy fractionated dose TBI and also various chemotherapy regimens were designated as RIC. Retrospective analysis of the Acute Leukemia Working Party of the EBMT compared 3 RIC regimens (fludarabine/busulfan, fludarabine/melphalan, and fludarabine-TBI), showing similar transplant outcomes.[33] In our study, the Seattle regimen was predominantly applied.[24] Of all RIC regimens reported, the fludarabine 2-Gy TBI regimen has a relatively low antileukemic cytotoxic effect. AlloHSCT using that regimen predominantly depends on the immunotherapeutic allogeneic GVL effect. Although the GVL effect is operational in ALL, our results stress that preceding cytotoxic effects of the conditioning regimen are significant.

Previous studies[34-39] have suggested an important role for myeloablative TBI in reducing the relapse rate in ALL. RIC

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TABLE 1.

Patient and transplant characteristics

Parameters	MAC-alloHSCT N (%)	RIC-alloHSCT N (%)	Total N (%)	*P*
Total no. of patients	77 (41)	111 (59)	188 (100)	
Follow-up in mo, median (IQR)	78 (37–138)	55 (43–102)		
Sex				0.251
Male	49 (64)	64 (58)	113 (60)	
Female	28 (36)	47 (42)	75 (40)	
Age, y, median (range)	47 (41–62)	55 (41–65)	51(41–65)	<0.001
ALL type				0.081
B-ALL	61 (79)	100 (90)	161 (86)	
T-ALL	13 (17)	10 (9)	23 (12)	
Unknown	3 (4)	1 (1)	4 (2)	
Leukemia risk status				0.197
Standard risk	39 (51)	48 (43)	87 (46)	
High risk	38 (49)	63 (57)	101 (54)	
BCR-ABL1 positive	24 (31)	46 (41)	70 (37)	0.100
Time diagnosis alloHSCT, median (range)	6(3–12)	6 (4–11)	6 (3–12)	0.205
Year of transplantation, median (range)	2009 (2001–2015)	2010 (2003–2015)	2010 (2001–2015)	0.008
Donor type				0.009
HLA-id SIB	47 (61)	47 (42)	94 (50)	
Alternative donor	30 (39)	64 (58)	94 (50)	
Matched UD	17 (57)	30 (47)	47 (50)	
Mismatched UD	7 (23)	20 (31)	27 (29)	
Mismatched RD	1 (3)	0 (0)	1 (1)	
Unknown	5 (17)	14 (22)	19 (20)	
Female donor male recipient	14 (18)	19 (17)	33 (18)	0.522
Other	63 (82)	90 (81)	153 (81)	
Unknown	0 (0)	2 (2)	2 (1)	
Donor source				0.003
Bone marrow	10 (13)	2 (2)	12 (6)	
Peripheral blood	65 (84)	100 (90)	165 (88)	
Cord blood	2 (3)	9 (8)	11 (6)	
EBMT score				0.037
2	36 (47)	34 (31)	70 (37)	
≥3	41 (53)	75 (68)	116 (62)	
Incomplete	0 (0)	2 (2)	2 (1)	
TBI dose given, Gy	65 (84)	100 (90)	165 (88)	
2	1 (1)	91 (82)	92 (49)	
4	0 (0)	9 (8)	9 (5)	
8	1 (1)	0 (0)	1 (1)	
9	46 (60)	0 (0)	46 (24)	
10	4 (5)	0 (0)	4 (2)	
12	13 (17)	0 (0)	13 (7)	
In vivo T-cell depletion	31 (40)	30 (27)	61 (32)	0.041
Patient CMV serology				0.448
Negative	24 (31)	38 (34)	62 (33)	
Positive	48 (62)	70 (63)	118 (63)	
Unknown	5 (6)	3 (3)	8 (4)	
Donor CMV serology				0.944
Negative	37 (48)	56 (50)	93 (49)	
Positive	35 (45)	48 (43)	83 (44)	
Unknown	5 (6)	7 (6)	12 (6)	

ALL, acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplantation; B-ALL, B-cell ALL; CMV, cytomegalovirus; EBMT, European Society for Blood and Marrow Transplantation; HLA-id SIB, HLA-identical sibling donor; IQR, interquartile range; MAC, myeloablative conditioned; RD, related donor; RIC, reduced intensity conditioning; T-ALL, T-cell ALL; TBI, total body irradiation; UD, unrelated donor.

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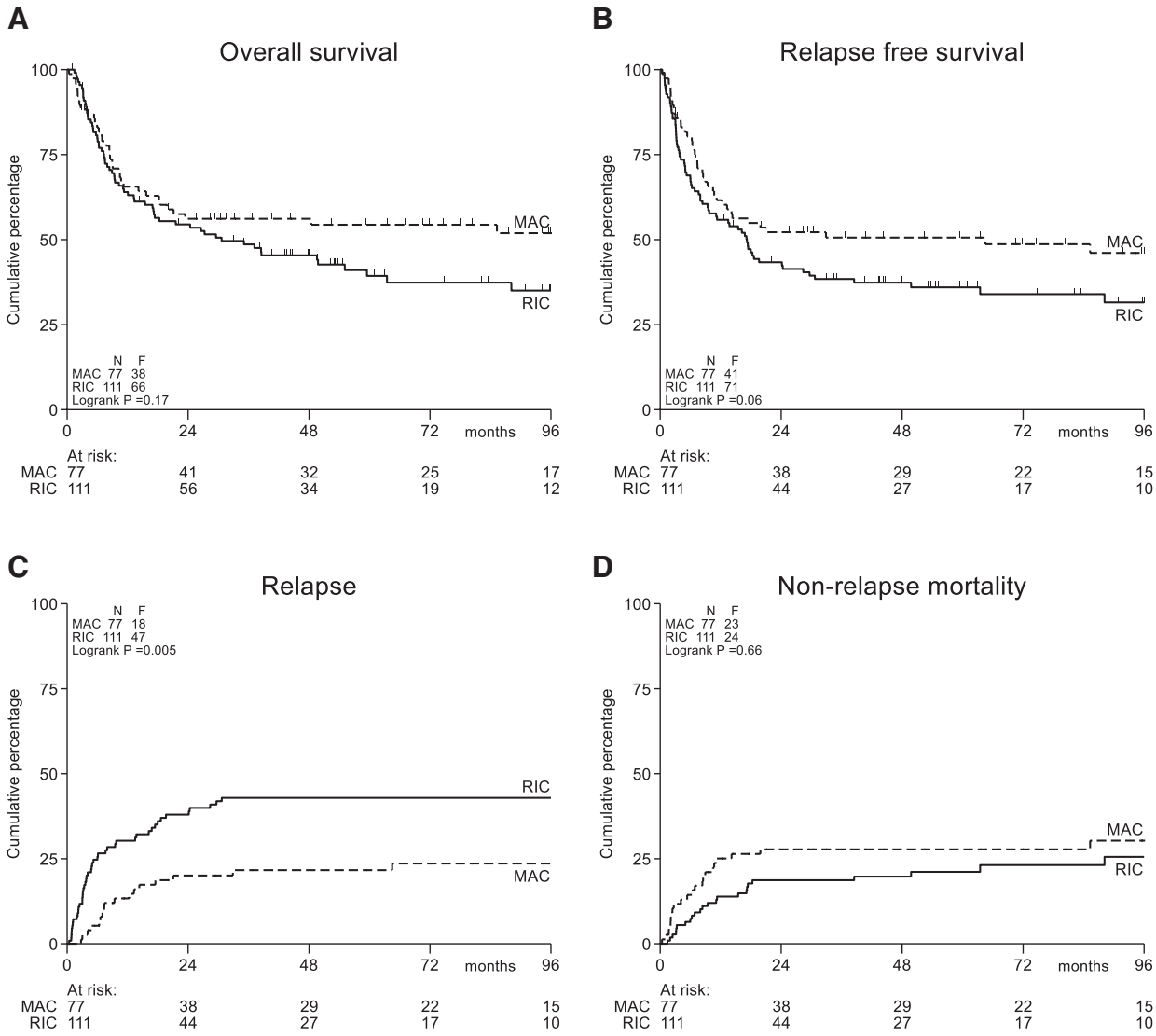

FIGURE 1. Outcome of allogeneic transplantation by conditioning type. Kaplan-Meier estimates of OS (A) and RFS (B), and cumulative incidence of relapse (C) and NRM (D) of patients with ALL in CR1 from the start of transplantation. The cumulative incidences of relapse and NRM over time were calculated as competing risks according to the Fine and Gray method.[25] ALL, acute lymphoblastic leukemia; CR1, complete remission; MAC, myeloablative conditioning; NRM, nonrelapse mortality; OS, overall survival; RFS, relapse-free survival; RIC, reduced intensity conditioning.

TABLE 2.

Results of the multivariable analyses

	Overall survival			Relapse-free survival			Nonrelapse mortality			Relapse		
Independent variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**SHR**	**95% CI**	***P***	**SHR**	**95% CI**	***P***
Conditioning type												
RIC (N = 111) vs MAC (N = 77)	1.07	0.68-1.68	0.766	1.37	0.89-2.12	0.152	0.41	0.22-0.78	0.006	3.04	1.71-5.40	0.000
Age at diagnosis[a]	1.04	1.01-1.08	0.010	1.02	0.99-1.05	0.290	1.06	1.01-1.11	0.021	0.98	0.94-1.02	0.267
Risk status												
High risk (N = 101) vs standard risk (N = 87)	0.77	0.51-1.15	0.201	0.92	0.62-1.36	0.665	1.00	0.55-1.82	0.996	0.96	0.57-1.62	0.879
EBMT score												
Alternative donor (N = 94) vs HLA-id SIB (N = 94)	1.16	0.75-1.78	0.500	0.88	0.58-1.33	0.548	2.20	1.13-4.27	0.021	0.44	0.25-0.78	0.005
Female donor male recipient (N = 33) vs other (N = 153)	1.13	0.66-1.91	0.661	1.01	0.61-1.67	0.965	0.99	0.44-2.21	0.980	1.01	0.56-1.82	0.978

[a]Linear with estimates of HRs for 1 y difference.

CI, confidence interval; EBMT, European Society for Blood and Marrow Transplantation; HLA-id SIB, HLA-identical sibling donor; HR, hazard ratio; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; SHR, subdistribution hazard ratio.

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regimens including a higher TBI dose might reduce relapse rate more effectively, and preferably prospective studies are needed to address this issue. The balance between an effective antileukemic dose and acceptable NRM associated with that dose is still to be established. The ongoing phase II, randomized clinical trial by Marks et al in patients with ALL aged between 40 and 70 y, comparing the conditioning regimens cyclophosphamide and TBI versus fludarabine and melphalan, has been designed to address this question (EudraCT number: 2017-004800-23).

In this study, according to national guidelines, all patients with ALL were considered for alloHSCT, whereas only patients with high-risk disease classified for alternative donor sources. The choice of MAC or RIC conditioning was mainly based on patient age and the local protocol of the transplantation centers. Three of the 8 transplant centers had switched to the use of MAC after the introduction of RIC, 2 centers applied both conditioning strategies and their decision-making depended on both patient fitness and leukemia risk, whereas the remaining 3 centers preferred to apply MAC protocols. That policy reflects selection bias, which may have affected the results in our retrospective study. Additionally, recently published data have clearly shown that reaching MRD negativity before alloHSCT is a very important determinant for outcome,[40] especially in patients receiving RIC-alloHSCT in which outcome is most dependent on the allogeneic GVL effect.[41] Therefore, the achievement of a negative status of MRD before RIC-alloHSCT may be recommended. Unfortunately, MRD was not routinely measured before alloHSCT, in particular during the early years of the period under study. Therefore, this important question could not be addressed, the unknown pre-alloHSCT MRD status hampers the interpretation of a higher relapse rate after RIC-alloHSCT. Apart from these limitations, the retrospective nature and differences with respect to patient characteristics in both groups are also noted. Finally, information about comorbidities was not available in the current database, whereas comorbidities are important in the decision to apply an RIC versus MAC regimen.

In conclusion, application of RIC-alloHSCT after a fludarabine and 2 Gy TBI regimen reduced NRM in adult patients with ALL aged >40 y. As suggested by our population-based registry study,[1] that reduction of NRM has allowed for a wider application of alloHSCT in older and medically less fit patients. However, the higher relapse rate observed with RIC-alloHSCT suggests that more intensive conditioning regimens such as a higher, possibly fractionated dose of TBI should be explored, preferably in prospective randomized studies.

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