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The Dilemma of Conditioning Intensity: When Does Myeloablative Conditioning Improve Outcomes for Allogeneic Hematopoietic Cell Transplantation

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The impact of conditioning intensity on different disease risk index (DRI) groups has not been evaluated. We retrospectively analyzed acute myelogenous leukemia (AML)/myelodysplastic syndrome (MDS) hematopoietic cell transplantation (HCT) recipients in 2 groups based on DRI, to assess the impact of conditioning intensity on overall survival (OS), disease free survival (DFS), relapse, and nonrelapse mortality (NRM).

A total of 380 patients with either high/very high (n = 148) or low/intermediate DRI (n = 232) myeloid malignancy (AML, n = 278; MDS, n = 102) were included in the analysis. Median follow-up for survivors was 35 months. Median age was 58 years (range, 18 to 75). Patient and transplant-related characteristics were 41% reduced-intensity conditioning (RIC), 59% myeloablative conditioning (MAC), 13% bone marrow graft, 29% matched related donor, 49% matched unrelated donor, 22% haploidentical donor, and 52% HCT-specific comorbidity index $\geq$ 3. Among patients with high/very high DRI, there was no difference in OS, DFS, relapse, and NRM between RIC and MAC conditioning groups. For low/intermediate risk DRI recipients of MAC had better 3-year OS estimate (69% versus 57%, $P = .001$), DFS (65% versus 51%, $P = .003$), and lower relapse (3-year cumulative incidence, 17% versus 32%; $P = .01$) but similar NRM (19% versus 17%, $P = .04$) to RIC recipients. On multivariable analysis MAC was associated with better DFS (hazard ratio [HR], .58; 95% confidence interval [CI], .39-.88; $P = .01$), lower relapse (HR, .56; 95% CI, .32 to .97; $P = .038$), and similar NRM (HR, 1.11; 95% CI, .54 to 2.26; $P = .781$) compared with RIC in the low/intermediate DRI group. Intensity had no impact on HCT outcomes in the high/very high DRI group.

MAC improves DFS and relapse compared with RIC among AML/MDS patients with low/intermediate DRI. The finding of no such benefit in high/very high DRI needs to be further explored in a larger cohort with a longer follow-up.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is an established curative therapy for patients with high-risk acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). The success of allogeneic HCT is highly dependent on multiple patient-, disease-, and transplant-related factors [1-3]. Historically, allogeneic HCT was based on high-intensity preparative regimens with an intent to achieve marrow aplasia. As the role of the graft-versus-leukemia benefit became more evident in curing myeloid malignancies, several reduced-intensity conditioning (RIC) regimens were studied and showed sustained engraftment, low regimen-related toxicity, and the ability to cure a significant proportion of patients with myeloid malignancies [4-6]. RIC transplant in AML and MDS is routinely performed for patients who cannot tolerate myeloablative conditioning (MAC) because of age or comorbidities and has been shown to yield 5-year survival rates close to 40% [7]. A common question on whether conditioning intensity affects outcomes after allogeneic HCT for patients with AML and MDS has been studied in retrospective and prospective trials with conflicting results [8-14]. Most retrospective studies and a recent phase III prospective trial by the European Society for Blood and Marrow Transplantation (EBMT) reported comparable survival after both RIC and MAC [8]. On the other hand, a recent phase III randomized trial by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) showed lower relapses and a

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nonstatistically significant improvement in overall survival (OS) among recipients of MAC compared with RIC [9].

We hypothesized that MAC can be of benefit for patients with AML and MDS with disease risk that has a relatively high potential of cure with chemotherapy such as low and intermediate disease risk index (DRI) groups. On the other hand, patients with high and very high DRI risk, with a very low potential of cure with cytotoxic chemotherapy, will get no benefit from the extra intensity associated with MAC regimens. For this purpose we assessed the impact of conditioning intensity among AML/MDS patients based on DRI in 2 separate groups: low/intermediate DRI and high/very high DRI.

METHODS

Objective and Definition

The objective of this single-institution retrospective analysis was to assess the impact of conditioning intensity based on the DRI among patients with AML or MDS who received allogeneic HCT, including all donor sources, between 2006 and 2016. Disease risk and conditioning intensity were assigned using previously published criteria [1,15-17].

Study Population

Three hundred eighty patients who underwent a first allogeneic HCT for AML or MDS using an HLA-identical sibling donor (MRD, n = 124); 8/8 HLA-A, -B, -C, and -DRB1 allele matched volunteer unrelated donor (MUD, n= 161); or T cell–replete haploidentical graft using post-transplant cyclophosphamide (n = 95) at our center were included in this analysis. The transplants were performed consecutively between January 2006 and December 2016. This time frame was chosen to allow a minimum of 12 months of post-transplant follow-up for surviving patients. Haploidentical donors (HIDs) were selected based on our center's criteria that makes patients eligible for HIDs if there is no suitable MRD or MUD donor or such a donor is not available within an acceptable time frame. Transplants using cord blood or grafts that were ex vivo T cell depleted were excluded from the analysis. Cord blood recipients were excluded because we only performed RIC cord blood in the identified time period. Patients were analyzed in 2 separate groups based on DRI: low/intermediate (n = 232) and high/very high (n = 148).

Treatment Regimens

The conditioning regimen intensity was assigned based on standard published criteria. Patients were labeled as MAC recipients if they received total body irradiation $\geq$ 8 Gy fractionated or a busulfan dose > 8 mg/kg p.o. or i.v. equivalent [16,17]. RIC haploidentical transplant regimens used included the Johns Hopkins University protocol [18] or a locally developed regimen at our institution that consisted of fludarabine 30 mg/m^2 on days −6 to −2, melphalan 140 mg/m^2 on day −1, and cyclophosphamide 50 mg/kg on days +3 and +4. MAC haploidentical transplantation was performed using 2 different regimens that were consecutively developed at our institution [19,20]. Regimen 1 consisted of fludarabine 25 mg/m^2 i.v. once per day on days −6 to −2, busulfan 110 to 130 mg/m^2 i.v. once per day on days −7 to −4, and cyclophosphamide 14.5 mg/kg i.v. once per day on days −3 and −2 and 50 mg/kg once per day on days +3 and +4. Regimen 2 included fludarabine 30 mg/m^2 once per day on days −7 to −5, total body irradiation 150 cGy twice daily on days −4 to −1 (total dose, 1200 cGy) with the same post-transplant therapy as regimen 1. Supportive care and infectious disease prophylaxis were similar between all donor types with the exception of extended quinolone therapy (until day 100) among haploidentical recipients for BK cystitis prophylaxis.

Covariates

Patient-, disease-, and transplant-related variables were prospectively documented and obtained for this analysis from our comprehensive institutional database. Clinical factors examined included age (<50, 50 to 59, and ≥60 years), sex, race, year of transplant (2006 to 2010, 2011 to 2013, 2013 to 2016), diagnosis (AML, MDS), conditioning intensity (RIC/nonablative, MAC), donor type (MRD, MUD, HID), graft source (bone marrow or peripheral blood stem cells), HCT-specific comorbidity index [2], donor–recipient sex match, donor–recipient cytomegalovirus (CMV) status, Center for International Blood and Marrow Transplant Research risk score, and DRI [1].

Endpoints

Outcomes analyzed were OS (time from transplantation to death), disease-free survival (DFS; survival without evidence of relapse of the underlying malignancy after transplantation), nonrelapse mortality (NRM), relapse/progression of malignancy, and acute and chronic graft-versus-host disease (GVHD). Because of the possibility of delayed onset of clinical acute GVHD after transplantations performed using RIC/nonablative regimens, maximum cumulative incidence of acute GVHD was assessed at 6 months after transplantation. Chronic GVHD was classified as mild, moderate, or severe by the 2005 National Institutes of Health consensus criteria [21]. Acute and chronic GVHD were prospectively evaluated, graded, and documented by a single practitioner within the program. All endpoints were analyzed for each DRI group separately, low/intermediate DRI and high/very high DRI.

Statistical Analysis

The association between patient characteristics and conditioning intensity was evaluated by the Wilcoxon rank sum test for continuous characteristics and Fisher's exact test for categorical characteristics. The Kaplan-Meier method was used to estimate probabilities of OS and DFS. The cumulative incidences of NRM, relapse, and acute and chronic GVHD were computed to accommodate competing risks. NRM and relapse were considered as competing risks. Death was considered as the competing risk for GVHD endpoints. Log-rank test and Gray's test were used to compare survival probabilities and cumulative incidence probabilities, respectively. The Cox model was used to model the hazard functions of OS and DFS and cause-specific hazard functions of NRM, relapse, and GVHD endpoints.

The following variables were considered in multivariate analysis: conditioning intensity, age, patient sex, race, diagnosis, stem cell source, donor type, HCT-specific CI, DRI, Center for International Blood and Marrow Transplant Research risk, patient CMV, donor sex, donor CMV, tacrolimus-containing GVHD prophylaxis, methotrexate-containing GVHD prophylaxis, and year of transplant. Conditioning intensity was retained in the models. Other variables were evaluated by the forward stepwise algorithm. A variable was selected if its significance was below the 5% threshold. Proportionality of selected variables was tested by including time-dependent covariate, $Z \times \log(t)$, in Cox models. No violation of proportionality was detected.

Two-sided P values were reported, and $P < .05$ was considered to be significant. All statistical analyses were performed by using the SAS software (version 9.4; SAS Institute, Cary NC).

RESULTS

Low/Intermediate Risk DRI Cohort

Patient characteristics

A total of 232 patients with AML (n = 170) or MDS (n = 62) with a low (n = 11) or intermediate (n = 221) DRI received their first allogeneic HCT after RIC (n = 98, 42%) or MAC (n = 134, 58%) conditioning (Table 1). Patient and disease characteristics between recipients of RIC and MAC were significant for a higher percentage of males in the RIC group (63% versus 47% for RIC versus MAC, $P = .017$), higher percentage of AML diagnosis in the MAC group (81% versus 63% for MAC versus RIC, $P = .004$), and more use of methotrexate for GVHD prophylaxis in the MAC group (78% versus 55% for MAC versus RIC, $P < .001$).

Survival and incidence estimates

The 3-year probability of OS and DFS was 57% and 51% for RIC and 69% and 65% for MAC. The Kaplan-Meier estimates showed better OS ($P = .001$) and DFS ($P = .003$) with MAC compared with RIC (Figure 1). RIC recipients had a higher cumulative incidence of relapse than MAC (32% versus 17% at 3 years, $P = .01$). The cumulative incidence of NRM at 3 years was similar between the 2 groups (19% for MAC versus 17% for RIC, $P = .40$). There was no difference in cumulative incidence of grades II to IV acute GVHD (38% for RIC versus 37% for MAC, $P = .92$) or moderate to severe chronic GVHD at 3 years (30% for RIC versus 42% for MAC, $P = .23$).

Multivariate analysis

The factors that affected OS in a multivariable analysis were age and year of transplant. Patients ≥ 60 years old had had worse OS than patients <50 years old (hazard ratio [HR], 2.19; 95% confidence interval [CI], 1.13 to 4.24; $P = .02$). MAC had a significant impact on DFS and relapse compared with RIC. MAC recipients had better DFS (HR, .58; 95% CI, .39 to .88; $P = .01$) and a lower relapse incidence (HR, .56; 95% CI, .32 to .97; $P = .038$) compared with RIC (Table 2). The Cox model on grades II to IV acute GVHD and moderate to severe chronic

Table 1
Characteristics by Conditioning Intensity in AML/MDS with Low/Intermediate DRI

	All (N = 232)	RIC (n = 98)	MAC (n = 134)	*P*
Median age, yr (min, max)	55 (18, 75)	63 (24, 75)	50 (18, 65)	.099
Male sex	125 (54)	62 (63)	63 (47)	.017
Race				.051
White	193 (83)	87 (89)	106 (79)	
Black	31 (13)	7 (7)	24 (18)	
Other/unknown	8 (4)	4 (4)	4 (3)	
Diagnosis				.004
AML	170 (73)	62 (63)	108 (81)	
MDS	62 (27)	36 (37)	26 (19)	
Cell source				.745
Bone marrow	49 (21)	22 (22)	27 (20)	
Peripheral blood	183 (79)	76 (78)	107 (80)	
Donor type				.271
MRD	71 (31)	27 (28)	44 (33)	
MUD	109 (47)	44 (45)	65 (48)	
HID	52 (22)	27 (28)	25 (19)	
HCT-specific comorbidity index				.232
0-2	118 (51)	45 (46)	73 (54)	
>=3	114 (49)	53 (54)	61 (46)	
Center for International Blood and Marrow Transplant Research risk				.047
Low	144 (62)	55 (56)	89 (66)	
Intermediate	44 (19)	17 (17)	27 (20)	
High	44 (19)	26 (27)	18 (13)	
DRI				.125
Low	11 (5)	2 (2)	9 (7)	
Intermediate	221 (95)	96 (98)	125 (93)	
Donor–recipient sex match				1.000
F–M	48 (21)	20 (20)	28 (21)	
Donor–recipient CMV				.331
+/+	97 (42)	39 (40)	58 (43)	
−/−	44 (19)	22 (22)	22 (16)	
+/−	22 (9)	6 (6)	16 (12)	
−/+	69 (30)	31 (32)	38 (28)	
GVHD prophylaxis, tacrolimus	218 (94)	87 (89)	131 (98)	.009
GVHD prophylaxis, methotrexate	158 (68)	54 (55)	104 (78)	<.001
Year of transplant				.277
2006-2010	58 (25)	29 (29)	29 (22)	
2011-2013	74 (32)	32 (33)	42 (31)	
2014-2016	100 (43)	37 (38)	63 (47)	
Median follow-up of survivors, mo (min, max)	36.6 (5.2, 143.6)	34.8 (5.2, 143.6)	36.6 (5.2, 141.7)	.374

Values are n (%) unless otherwise defined.

GVHD showed that MUD recipients had higher incidence of acute grades II to IV GVHD than MRD (HR, .30 for MRD versus MUD; 95% CI, .17 to .55; $P < .001$) and higher moderate to severe GVHD compared with MRD (HR, .59 MRD versus MUD; 95% CI, .48 to .98; $P = .04$) and HID (HR, .43 HID versus MUD; 95% CI, .36 to .87; $P = .015$).

High/Very High Risk DRI Cohort

Patient characteristics

A total of 148 patients diagnosed with AML (n = 113) or MDS (n = 35) with a high (n = 137) and very high (n = 11) DRI received their first allogeneic HCT between 2006 and 2016. Among 113 AML patients, 37 were in first complete remission, 8 in second complete remission, 58 in primary induction failure, and 16 with relapsed disease. Patient and transplant characteristics are shown in Table 3. Ninety-one patients received MAC, and compared with RIC, MAC recipients were younger (49 versus 64 years, $P < .001$), more likely to have an AML diagnosis (88% versus 58%, $P < .001$), more likely to have received a peripheral blood stem cell graft (93% versus 79%, $P = .01$), more likely to have a better HCT-specific comorbidity index score (66% MAC versus 40% RIC had HCT-specific comorbidity index 0 to 2, $P = .004$), and more likely to have received methotrexate as part of their GVHD prophylaxis (Table 3). The median follow-up for survivors was 42.7 months (range, 12 to 134.6).

Survival and incidence estimates

The 3-year OS and DFS estimates were not significantly different between the 2 conditioning groups at 50% and 44% for

Table 2
Cox Models for OS, DFS, NRM, and Relapse in Patients with Low/Intermediate DRI

Factor	Effect	HR	95% CI	*P*
Cox model for OS				
Intensity	MAC vs. RIC	.75	.44-1.27	.277
Age	50-59 vs. <50	1.20	.64-2.26	.565
	≥60 vs. <50	2.19	1.13-4.24	.020
Year of transplant	2011-2013 vs. 2005-2010	.74	.45-1.22	.237
	2014-2016 vs. 2005-2010	.46	.25-.86	.014
Cox model for DFS				
Intensity	MAC vs. RIC	.58	.39-.88	.010
Year of transplant	2011-2013 vs. 2005-2010	.70	.44-1.12	.137
	2014-2016 vs. 2005-2010	.50	.29-.85	.010
Cox model for relapse				
Intensity	MAC vs. RIC	.56	.32-.97	.038
Year of transplant	2011-2013 vs. 2005-2010	.60	.32-1.11	.104
	2014-2016 vs. 2005-2010	.33	.17-.67	.002
Cox model for NRM				
Intensity	MAC vs. RIC	1.11	.54-2.26	.781
Age	50-59 vs. <50	1.53	.62-3.79	.353
	≥60 vs. <50	3.35	1.32-8.52	.011

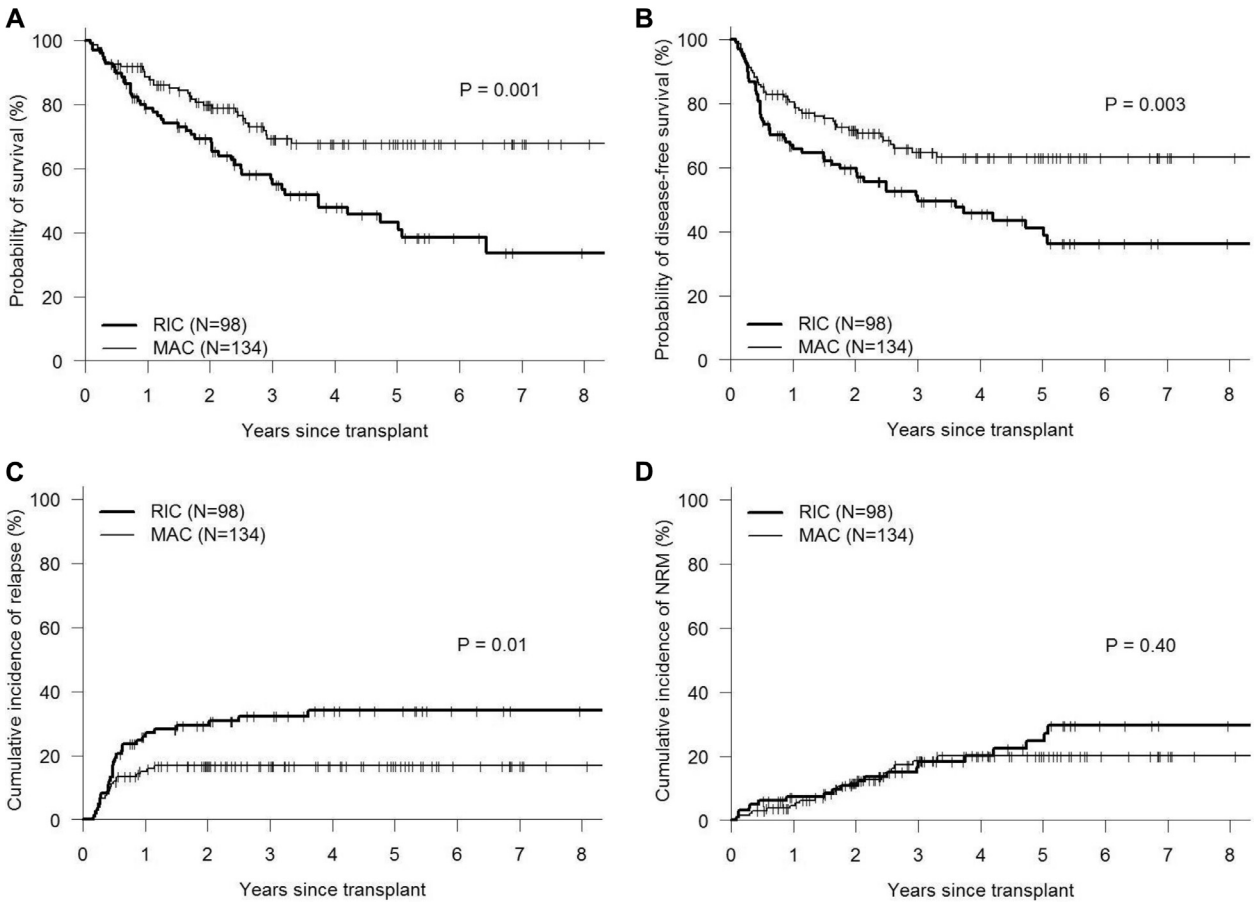

Figure 1. Probability of OS (A), DFS (B), cumulative incidence of relapse (C), and NRM (D) by conditioning intensity in patients with low/intermediate DRI.

MAC and 37% and 28% for RIC recipients, respectively (Figure 2) ($P = .18$ for OS, $P = .16$ for DFS). The cumulative incidence of relapse at 1 and 3 years was 32% and 40% for MAC versus 39% and 44% for RIC ($P = .84$). The cumulative incidence of NRM at 1 and 3 years was 10% and 16% for MAC versus 16% and 22% for RIC ($P = .16$).

Multivariate analysis

The multivariate analysis on OS showed that male gender had worse OS compared with female gender (HR, 1.72; 95% CI, 1.10 to 2.70; $P = .018$). Conditioning intensity did not impact OS, DFS, relapse, or NRM by multivariate analysis (Table 4). Patients who were transplanted between 2014 and 2016 had a lower relapse rate than patients who received their transplant in 2005 to 2010 (HR, .42; 95% CI, .21 to .81; $P = .01$).

DISCUSSION

This analysis shows that conditioning intensity improves disease control among AML and MDS patients with low/intermediate DRI but has no significant impact on patients with high/very DRI. The low/intermediate DRI risk group included early stage AML with favorable or intermediate cytogenetics and MDS with intermediate risk cytogenetics [1]. Patients with intermediate risk AML can achieve a long-term DFS of 30% to 35% using chemotherapy alone as consolidation [22]. We hypothesized that patients in the low/intermediate DRI risk will benefit from intensifying the conditioning regimen because their disease is potentially curable by chemotherapy. On the other hand, patients in the high/very high DRI with very low likelihood of cure with chemotherapy alone will not benefit from intensifying the conditioning regimen because their transplant benefit is derived mostly from the immune effect of the graft. High intensity provided better relapse rates and higher DFS among low/intermediate DRI group with similar NRM compared with RIC.

A recent BMT CTN randomized phase III study ceased accrual before finishing planned enrollment because of high relapse incidence seen with RIC. Among 272 enrolled patients the relapse rate for RIC compared with MAC was 48% versus 13.5% ($P < .001$), and treatment-related mortality was higher with MAC (15.8% versus 4.4%, $P = .002$), resulting in a trend for a higher OS with MAC at 18 months (77.5% versus 67.7%, $P = .07$ for MAC versus RIC). In this study 42% of patients had high-risk disease based on cytogenetic features [9,23]. The superior effect of survival was seen mainly in AML patients but not in MDS. This study differs from our analysis in that it was not powered to detect impact of conditioning intensity on disease risk, and the most commonly used RIC was fludarabine with low-dose busulfan, which has been shown to have a higher relapse rate compared with fludarabine/melphalan [24]. Most of our population received fludarabine/melphalan, accounting for 66% of RIC transplants in the high/very high DRI recipients and for 71% in low/intermediate DRI cohort.

The EBMT conducted a prospective, multicenter, open label, randomized phase III trial that compared busulfan-based RIC with MAC in patients with MDS or secondary AML. Among 129 patients enrolled on this trial, there was no difference in OS or relapse-free survival between MAC and RIC. The 2-year relapse-free survival and OS rates after MAC were 58% (95% CI, 46% to 71%) and 63% (95% CI, 51% to 75%) compared with 62%

Table 3
Characteristics by Conditioning Intensity in AML/MDS with High/Very High DRI

	All	MAC	RIC	*P*
	(N = 148)	(n = 91)	(n = 57)	
Median age, yr (min, max)	55.5 (18, 77)	49 (18, 63)	64 (44, 77)	<.001
Male sex	76 (51)	49 (54)	27 (47)	.501
Race				.063
White	119 (80)	68 (75)	51 (89)	
Black	23 (16)	19 (21)	4 (7)	
Other/unknown	6 (4)	4 (4)	2 (4)	
Diagnosis				<.001
AML	113 (76)	80 (88)	33 (58)	
MDS	35 (24)	11 (12)	24 (42)	
Cell source				.018
Bone marrow	18 (12)	6 (7)	12 (21)	
Peripheral blood	130 (88)	85 (93)	45 (79)	
Donor type				.151
MRD	53 (36)	38 (42)	15 (26)	
MUD	52 (35)	30 (33)	22 (39)	
Haplo	43 (29)	23 (25)	20 (35)	
HCT-specific comorbidity index				.004
0-2	83 (56)	60 (66)	23 (40)	
≥3	65 (44)	31 (34)	34 (60)	
Center for International Blood and Marrow Transplant Research risk				.021
Low	41 (28)	18 (20)	23 (40)	
Intermediate	8 (5)	5 (5)	3 (5)	
High	99 (67)	68 (75)	31 (55)	
DRI				.205
High	137 (93)	82 (90)	55 (96)	
Very high	11 (7)	9(10)	2 (4)	
Donor–recipient sex match				.485
F–M	22 (15)	12 (13)	10 (18)	
Donor–recipient CMV				.205
+/+	58 (40)	33 (37)	25 (44)	
−/−	24 (16)	18 (20)	6 (11)	
+/−	13 (9)	10 (11)	3 (5)	
−/+	52 (35)	29 (32)	23 (40)	
GVHD prophylaxis, tacrolimus	143 (97)	91 (100)	52 (91)	.008
GVHD prophylaxis, methotrexate	94 (64)	66 (73)	28 (49)	.005
Year of transplant				.004
2006-2010	56 (38)	43 (47)	13 (23)	
2011-2013	41 (28)	25 (27)	16 (28)	
2014-2016	51 (34)	23 (25)	28 (49)	
Median follow-up of survivors, mo (min, max)	42.7 (5.5, 134.6)	57.6 (5.5, 134.6)	24.1 (6.4, 128.1)	.019

(95% CI, 50% to 74%) and 76% (95% CI, 66% to 87%) after RIC ($P = .58$ ad $P = .08$ respectively). This study had a higher NRM after RIC compared with that reported in the BMT CTN study. NRM rate was 17% in the EBMT study versus 4.5% in the BMT CTN trial, and the EBMT study had a lower relapse rate of 17% after RIC compared with 48% in the BMT CTN trial. There was no relapse benefit for increasing intensity for advanced disease in a multivariate analysis [8]. A similar finding to the EBMT study was also reported previously from a multicenter German study. In the randomized German trial that closed early because of slow accrual, patients with AML in complete remission had similar OS, DFS, NRM, and relapse after total body irradiation–based RIC compared with standard high-dose total body irradiation MAC [25]. A follow-up analysis after a median time of 9.9 years revealed similar incidence of late relapses with RIC compared with MAC [26]. DRI was not 1 of the assessed variables in both these studies. One cannot explain the different findings between these trials and BMT CTN based on disease risk without a comparison of both populations. One major difference between the BMT CTN and EBMT studies is that the EBMT study included secondary AML in its study population as opposed to the BMT CTN trial, which that included de novo AML.

We tried to dissect the benefit of conditioning intensity by studying its impact on different disease risk groups. We did a multivariate analysis on the total patient population where conditioning intensity did not predict OS or DFS. Our analysis has limitations that are inherent to its retrospective nature. The choice of conditioning regimen intensity at our center, aside from age requirement (<60 years for MAC), is left at the discretion of the transplant physician. RIC recipients were older and had higher comorbidities than MAC patients. As we suggested, we found that patients with low/intermediate DRI risk tended to benefit more from increasing the intensity

Table 4
Cox Models for OS, DFS, NRM, and Relapse in Patients with High/Very High DRI

Factor	Effect	HR	95% CI	*P*
Cox model for OS				
Intensity	MAC vs. RIC	.68	.43-1.08	.102
Sex	Male vs. female	1.72	1.10-2.70	.018
Cox model for DFS				
Intensity	MAC vs. RIC	.80	.52-1.23	.306
Cox model for relapse				
Intensity	MAC vs. RIC	.71	.42-1.21	.203
Year of transplant	2011-2013 vs. 2006-2010	.61	.33-1.12	.109
	2014-2016 vs. 2006-2010	.42	.21-.81	.010
Cox model for NRM				
Intensity	MAC vs. RIC	.54	.26-1.13	.110

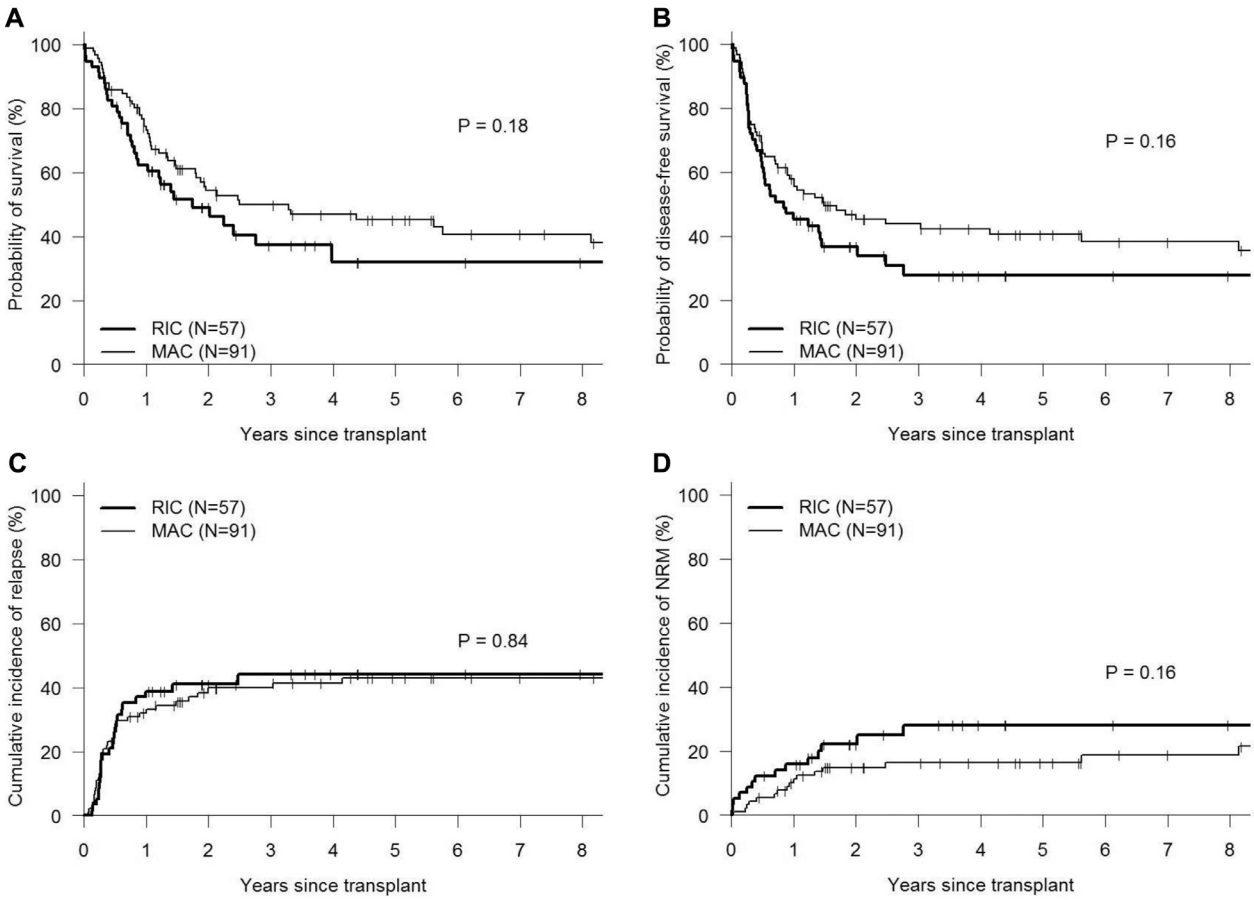

Figure 2. Probability of OS (A), DFS (B), cumulative incidence of relapse (C), and NRM (D) by conditioning intensity in patients with high/very high DRI.

of the chemotherapy regimen. As for patients with high/very high DRI, avoiding the toxicity of MAC and focusing on post-transplant strategies to help reduce relapse may be a more beneficial strategy [27-29].

There are a few limitations to the findings in the high/very high DRI risk group. First, RIC patients in the high/very high DRI group had a shorter follow-up duration compared with MAC (24.1 versus 57.6 months, $P = .019$). This difference in follow-up may underscore the late relapses that can occur in RIC recipients. Although most relapses occurred in the first 2 years after HCT in the MAC group (Figure 2c), we previously reported that late relapses are more common after high/very high DRI patients compared with low/intermediate DRI irrespective of the conditioning intensity [30]. Second, the number of patients in the high/very high DRI risk group was smaller than the low/intermediate DRI cohort, and the sample size may have limited the power to detect a difference in the high/very high DRI group. Our analysis is also limited by the fact that it only included certain disease types (AML/MDS) and donor types (no cord blood transplantation or T cell–depleted grafts). This limits the findings of this analysis to the current population and cannot be generalized to all disease subtypes and transplant subtypes.

In conclusion, our study shows that MAC followed by allogeneic HCT resulted in better DFS and relapse rates than RIC among AML and MDS patients with low/intermediate DRI. MAC and RIC resulted in equivalent survival, relapse, and DFS in the high/very high DRI group, a finding that needs to be further established in a larger cohort.

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