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Comparison of Reduced Intensity and Nonmyeloablative Conditioning for Adults with Acute Myeloid Leukemia Undergoing Allogeneic Hematopoietic Cell Transplantation in First or Second Remission

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Abstract

Reduced intensity conditioning (RIC) and nonmyeloablative (NMA) conditioning regimens have expanded use of allogeneic hematopoietic cell transplantation (HCT) in AML to include older and medically less-fit patients, but relative efficacies and toxicities remain poorly defined. Here, we analyzed outcomes from 343 adults transplanted in remission after RIC (n=137) or NMA (n=206) conditioning between 2006 and 2021. The characteristics of RIC and NMA HCT patients were similar except that RIC patients were younger and their time between most recent remission achievement and allografting was shorter. There were no significant differences in relapse risk, relapse-free survival (RFS), overall survival (OS), and non-relapse mortality (NRM) between RIC and NMA HCT patients, both overall (relapse: hazard ratio [HR]=0.80, *P*=0.27; RFS: HR=0.93, *P*=0.61; OS: HR=0.93, *P*=0.66; NRM: HR=1.13, *P*=0.59) and when patients were stratified by pre-HCT measurable residual disease (MRD) status. After multivariable adjustment, there was no statistically significant association between conditioning intensity and relapse (HR=0.69, *P*=0.088), RFS (HR=0.86, *P*=0.37), OS (HR=0.89, *P*=0.49), or NRM (HR=1.37, *P*=0.19). In this non-randomized cohort of adults undergoing allografting for AML in first or second remission at

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AUTHORSHIP CONTRIBUTIONS:

R.B.W., B.M.S., and R.S. conceptualized and designed this study and participated in data analysis and interpretation and drafting of the manuscript. B.M.S., M.U.O., H.J.D., and R.S. contributed to the provision of study material, patient recruitment, and acquisition of data. M.O. conducted all statistical analyses and participated in data interpretation. C.O., E.R.A., G.S., and C.D. contributed to the collection and assembly of data. All authors revised the manuscript critically and gave final approval to submit for publication.

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our center, we could not detect differences in outcomes between those assigned to RIC and those assigned to NMA conditioning.

INTRODUCTION

Many patients with acute myeloid leukemia (AML) are older and/or have comorbid illnesses [1]. The development of a spectrum of reduced intensity conditioning (RIC) and nonmyeloablative (NMA) conditioning regimens over the last 25 years has expanded the use of allogeneic hematopoietic cell transplantation (HCT) to include such patients. By providing an immunologic graft-versus-leukemia (GVL) effect with lower regimen-related toxicities than myeloablative conditioning (MAC) regimens, they now offer a potentially curative treatment option for those more vulnerable patients [2–5]. To date, despite their routine use, their relative efficacies and toxicities of RIC *vs.* NMA conditioning regimens remain poorly defined. Limited data from earlier retrospective studies suggested differences in outcomes might be relatively small although nominally perhaps slightly worse with NMA conditioning relative RIC [6, 7]. In a recent retrospective analysis of 1,088 patients by the EBMT, no differences were observed with respect to risk of relapse, relapse-free survival (RFS), overall survival (OS), or non-relapse mortality (NRM) between those receiving a RIC regimen (fludarabine 30 mg/m^2 × 5 days, intravenous busulfan 0.8 mg/kg 4 times daily × 2 days, with/without *in vivo* T cell depletion) and those receiving NMA conditioning (fludarabine 30 mg/m^2 × 5 days, 2 Gy of total body irradiation [TBI]) [8]. In one relatively small randomized phase 2 trial, relapses were less common among the 69 adults who received a RIC regimen (fludarabine 30 mg/m^2 × 5 days, oral busulfan 1 mg/kg 4 times daily × 2 days, and rabbit anti-thymocyte globulin [ATG]) compared to the 70 patients who received NMA conditioning (fludarabine 30 mg/m^2 × 5 days, 2 Gy of TBI); on the other hand, NRM was higher with the RIC regimen, resulting in overall and progression-free survival estimates at 5 years that were not statistically significantly different between the 2 arms [9]. Here, we retrospectively examined outcomes after RIC and NMA HCT in a cohort of 343 adults who underwent allogeneic HCT for AML in first or second remission at our institution.

PATIENTS AND METHODS

Study cohort

We identified all adults ≥18 years of age with AML (2016 WHO criteria [10]) who underwent either RIC or NMA conditioning and received a first allograft while in first or second remission (i.e. <5% blasts in bone marrow) between 5/2006 and 10/2021. In previous publications, we have reported partial results from 330 of the 343 patients included in this study cohort [11–18]. The HCT-specific comorbidity index (HCT-CI) and TRM score were calculated as described [14, 19, 20]. Related or unrelated donors were selected by high-resolution HLA-typing. Post-HCT maintenance therapy was not typically done except in a small subset of patients with *FLT3*-mutated AML after midostaurin was approved in 2017. Information on post-HCT outcomes was captured via the Long-Term Follow-Up Program through medical records from our outpatient clinic and local clinics that provided primary care for patients in addition to records obtained on patients on research studies. All patients

were treated on Institutional Review Board-approved research protocols (all registered with ClinicalTrials.gov) or standard treatment protocols and gave consent in accordance with the Declaration of Helsinki. Follow-up was current as of October 3, 2022.

Classification of disease risk, treatment response, and post-HCT outcomes

The 2022 European LeukemiaNet criteria [1] were used to assign cytogenetic risk at diagnosis. Only the cytogenetic component of the risk classification could be used for risk assessment because molecular data at time of diagnosis were lacking in many patients. Cytogenetically normal AML was considered in patients with a normal karyotype regardless of how many metaphases were available for analysis [11–13, 21]. Secondary AML was defined using the 2022 ELN criteria [1]. Treatment responses were categorized as proposed by the ELN [1] except that post-HCT relapse was defined as emergence >5% blasts by morphology or MFC in blood or bone marrow, emergence of cytogenetic abnormalities seen previously, or presence/emergence of any level of disease if leading to a therapeutic intervention. The overall burden of acute graft-versus-host disease (GVHD) was measured with average acute GVHD Activity Index scores [22]. Chronic GVHD was diagnosed using 2014 National Institutes of Health (NIH) consensus criteria [23]. Peripheral blood CD3 chimerism data were categorized as done by Craddock *et al.* [24].

Detection of MRD by multiparameter flow cytometry

All patients underwent bone marrow aspirate analysis with ten-color flow cytometry as part of the pre-HCT work-up as described [12, 13, 25–30]. As done before, any detectable MRD was considered positive [11–13, 25–29, 31–33].

Statistical analysis

Unadjusted probabilities of RFS (events=relapse and death) and OS (event=death) were estimated using the Kaplan-Meier method, and probabilities of relapse and NRM as well as acute and chronic GVHD were summarized using cumulative incidence estimates. NRM was defined as death without prior relapse and was considered a competing risk for relapse, while relapse was a competing risk for NRM. Death was considered a competing risk for acute and chronic GVHD. OS, RFS, NRM, relapse, and acute/chronic GVHD were measured from date of transplant; patients last known to be alive without event were censored at date of last contact. Associations with RFS and OS were assessed using Cox regression; cause-specific regression models were used for relapse and NRM, and acute/chronic GVHD. Covariates associated with outcomes of interest with $P<0.1$ in univariate models were included in multivariable models with the exclusion of the TRM score due to collinearity with age and performance status. Besides conditioning intensity, covariates evaluated were: age at time of HCT, HCT comorbidity index, ECOG performance status, TRM score, white blood cell (WBC) count at time of diagnosis, cytogenetic risk group at time of AML diagnosis, type of AML at diagnosis (secondary *vs.* de novo), first or second remission at time of HCT, pre-HCT MRD, cytogenetics at time of HCT, peripheral blood counts at the time of HCT (recovered *vs.* not recovered), HLA matching, donor type, and type of GVHD prophylaxis. Missing disease risk, cytogenetic, and CD3 chimerism data were accounted for as separate categories. Categorical patient characteristics were compared using Fisher's exact test and quantitative characteristics were compared with the Wilcoxon

rank sum test. Two-sided *P*-values are reported. Statistical analyses were performed using R (http://www.r-project.org).

RESULTS

Characteristics of study cohort

We identified 425 adults meeting the inclusion criteria for our study. Of these, 10 did not agree to their data being used for research purposes, 4 did not undergo MRD testing at our institution during the pre-HCT work-up, 44 received unrelated cord blood as stem cell source, and 24 received either HLA-haploidentical allografts (n=22) or 2 antigen mismatched allografts (n=2), leaving 343 patients for analysis. Two hundred-six patients underwent NMA conditioning consisting of 2–3 Gy of TBI (low-dose TBI; L-TBI) in combination with fludarabine [34] except in 1 patient where TBI alone was used. One hundred thirty-seven patients received RIC regimens: clofarabine with L-TBI (n=40) [35]; melphalan/fludarabine with (n=42) or without (n=18) L-TBI; cyclophosphamide/thiotepa/fludarabine/L-TBI (n=19); busulfan (2 days)/fludarabine (n=14); fludarabine with 4–4.5 Gy TBI (n=3); and cladribine/cytarabine/G-CSF/mitoxantrone with L-TBI (n=1). Table 1 summarizes the characteristics of this study population, donors, and HCTs, both overall and separately for the 206 NMA HCT and 137 RIC patients. RIC patients were statistically significantly younger then NMA HCT patients at the time of HCT (P=0.0014), had a lower TRM score (P=0.0092), were more likely to have received high-dose cytarabine-containing therapy during induction (P=0.0095), and their time between most recent remission achievement and allografting was shorter (P=0.0022). RIC and NMA HCT patients also differed significantly in the type of GVHD prophylaxis used. On the other hand, there were no differences regarding HCT-CI score, ECOG performance status, cytogenetic disease risk, donor type, HLA matching, and stem cell source, and statistically similar portions of patients had secondary AML, second remission, pre-HCT flow cytometric evidence of residual disease, residual cytogenetic abnormalities at the time of HCT, and incompletely recovered neutrophil and/or platelet counts. Donor lymphocyte infusions were infrequently used in either RIC or NMA HCT patients (4% *vs.* 8%, P=0.19).

T cell chimerism, acute and chronic GVHD

A significantly higher proportion of RIC patients achieved full peripheral blood CD3 chimerism between day 20 and 40 compared to NMA HCT patients (61% vs 16%, P<0.001; Table 1). Whereas the cumulative incidence of grade 3 or 4 acute GVHD was not statistically different for RIC and NMA HCT patients (P=0.24), chronic GVHD was observed earlier on average in NMA than RIC patients (P=0.02; Figure 1). Point estimates of 100-day grade 3 or 4 acute GVHD were 12% (95% confidence interval: 7–18%) for RIC and 8% (5–13%) for NMA HCT patients; estimates of 18-month chronic GVHD were 34% (26–42%) for RIC and 47% (40–54%) for NMA HCT patients, respectively (Table 2).

Relationship between conditioning intensity and post-HCT outcome

In our cohort, there were 114 relapses and 184 deaths, of which 88 were NRM events, that contributed to the probability estimates for relapse, OS, RFS, and NRM. The median (range) follow-up after HCT among survivors was 50.7 (10.3–192.5) months: 48.0 (10.3–120.5)

months for RIC and 58.3 (12.0–192.5) months for NMA HCT patients, respectively. There was no statistically significant difference in time to recovery of neutrophil counts after nadir to >500/μL (NMA HCT *vs*. RIC: 18 [95% confidence interval: 2–37] days *vs*. 16 [10–30] days; P=0.056), whereas time to recovery of platelet counts after nadir to >20,000/μL was slightly faster for NMA HCT (10 [6–48] days *vs*. 12 [8–33] days; P=0.0001). Across all patients, the 3-year estimates for relapse, RFS, and OS were 33%, 47% and 55%, respectively. These estimates were 29% (relapse), 49% (RFS), and 57% (OS) for RIC patients, and 35%, 45%, and 53% for NMA HCT patients (Table 2 and Figure 2). Consistent with all our previous studies [11–13, 25–29, 31, 33], outcomes were substantially better in patients without flow cytometric evidence of pre-HCT MRD relative to those in whom MRD was detected at that time. There were no statistically significant differences in relapse risks, RFS, OS, and NRM between RIC and NMA HCT patients. This was true for the cohorts overall and when patients were stratified by pre-HCT MRD status (Table 2, Figure 1, Figure 3). Nominally, 3-year relapse risks were slightly higher and 3-year NRM risks and 3-year RFS and 3-year OS slightly lower for NMA patients, although these differences did not reach statistical significance. 100-day NRM was statistically non-significantly higher in RIC as compared to NMA HCT patients (7% *vs*. 2%).

Conditioning intensity as independent prognostic factor

To study the relationship between conditioning regimen and post-HCT outcomes in more detail, we evaluated both univariate and multivariable regression models for the endpoints of relapse, RFS, OS, and NRM, accounting for the covariates noted in *Patients and Methods*. As summarized in Table 3, several covariates were associated with relapse (ECOG performance status, TRM score, cytogenetic risk, remission number, pre-HCT MRD status, karyotype at time of HCT, type of GVHD prophylaxis), RFS (ECOG performance status, TRM score, age at HCT, HCT-CI, WBC at diagnosis, cytogenetic risk, remission number, pre-HCT MRD status, karyotype at time of HCT, type of GVHD prophylaxis), OS (ECOG performance status, TRM score, age at HCT, HCT-CI, WBC at diagnosis, cytogenetic risk, remission number, pre-HCT MRD status, karyotype at time of HCT, ANC recovery, platelet count recovery, blood count recovery, HLA matching), or NRM (ECOG performance status, TRM score, age at HCT, HCT-CI, WBC at diagnosis, platelet count recovery, blood count recovery, HLA matching, donor type). On the other hand, conditioning intensity was not associated with any of these outcomes (relapse: P=0.27; RFS: P=0.61; OS: P=0.66; NRM: P=0.59). Similar qualitative findings to those from the univariate models were found in the multivariable models (Table 4). That is, after multivariable adjustment, there was no association between conditioning intensity and relapse (hazard ratio [HR]=0.69, P=0.088), RFS (HR=0.86, P=0.37), OS (HR=0.89, P=0.49), or NRM (HR=1.37, P=0.19) in our study cohort.

DISCUSSION

For younger and medically fit adults with AML, the recent prospective randomized BMT CTN 0901 trial demonstrated significantly improved disease-free survival with the use of MAC compared to RIC HCT, at least in patients with molecular MRD at the time of HCT [36–38]. This trial may define MAC as the current standard of care for such patients. On the

other hand, the optimal conditioning therapy before allogeneic HCT for older or medically less-fit adults with AML who may not tolerate myeloablative preparative regimens well remains debated. At our institution and many others, RIC and NMA conditioning regimens have been used for this purpose for an extended period to enable such adults access to allogeneic HCT. The NMA regimen used here nearly entirely depends on graft-vs.-leukemia effects for disease control. Underlying this RIC/NMA regimen diversity is the notion that conditioning intensification might also reduce the rates of post-HCT relapse across regimens considered less intense than MAC [6, 7, 9]. However, this potential benefit may be offset by an excess in regimen-related morbidity and mortality. Our findings presented herein are consistent with this balance between benefits and risks of higher intensity conditioning therapy among RIC and NMA conditioning regimens. Examining a larger cohort of patients, our data indicate that relapse rates are statistically non-significantly lower, whereas NRM risks are statistically non-significantly higher, after RIC relative to NMA conditioning. As a result, survival outcomes (i.e. RFS and OS estimates) after RIC and NMA HCT are very similar across the entire patient cohorts. These findings are consistent with those from a recent retrospective analysis of 535 RIC and 553 NMA HCT patients reporting no statistically significant differences in relapse risks, RFS, OS, or NRM [8].

In our cohort, we found chronic GVHD developed, on average, earlier in NMA HCT than RIC patients, whereas there was no difference in the incidence or timing of severe acute GVHD. The GVHD prophylaxis differed between RIC and NMA HCT patients, with a higher proportion of NMA HCT patients using a calcineurin inhibitor together with mycophenolate mofetil (MMF) with/without sirolimus rather than a calcineurin inhibitor with methotrexate with/without another drug compared to RIC patients. Approximately 10% of patients (13% of RIC *vs.* 8% of NMA HCT patients) received GVHD prophylaxis with post-HCT cyclophosphamide together with a calcineurin inhibitor with/without MMF or sirolimus. Interestingly, our multivariable analyses suggested a potential benefit of post-HCT cyclophosphamide compared to the other regimens regarding relapse risk and RFS. However, given the small number of patients, a larger cohort would be needed to better understand and characterize this potential benefit.

It is now well established that pre-HCT evidence of MRD, either immunophenotypically or by molecular means, identifies a subset of patients with increased risk of post-HCT relapse [39, 40]. We were therefore particularly interested in examining the relationship between RIC *vs.* NMA conditioning and outcomes in this patient subgroup. While limited by the relatively small number of patients with positive MRD before HCT, our data indicate that the similarity in survival outcomes with RIC and NMA conditioning extends to this subset of patients as well.

As strengths, ours was a retrospective study done at a single institution with uniform and consistent, standardized supportive care. Almost all patients received intensive chemotherapy to achieve an initial remission, and all but 3 patients received peripheral blood as stem cell source. Because none of the RIC or NMA HCT patients received *in vivo* T cell depletion with ATG or alemtuzumab, the GVL effects were balanced across the conditioning intensity groups. Several limitations need to be acknowledged. As one limitation, this is a retrospective analysis of patients assigned to RIC or NMA conditioning in a (largely) non-

randomized fashion. In the 2006–2021 period, patients with AML were routinely assigned to myeloablative conditioning if felt tolerable. For the other patients, several factors, including age, comorbidity assessments, and trial availability influenced the decision between RIC and NMA conditioning. As a second limitation, several types of RIC regimens were used. It is possible that relative risks/benefits differ between individual RIC regimens, but the relatively small number of patients transplanted with any given RIC regimen precluded any analysis of relative merits of one *vs.* another regimen. As another shortcoming, no uniform treatment strategies were pursued when AML was detected at the submicroscopic or microscopic level following HCT. Therapies were selected largely based on discretion/preference of the clinical HCT team, and included expedited withdrawal of immunosuppressive agents, infusion of donor lymphocytes, treatment with azanucleosides or molecularly targeted agents (e.g., tyrosine kinase inhibitors), administration of intensive chemotherapy, or various combinations thereof used simultaneously or sequentially. However, treatment decisions regarding post-HCT AML therapies at the time of relapse were not typically informed by the conditioning intensity. As a fourth limitation, our ability to account for disease risk was limited because mutational profiles were only available for a small subset of patients and could therefore not be included.

Acknowledging these limitations, our data indicate that outcomes for adults with AML undergoing allografting while in morphologic remission are similar after RIC and NMA conditioning. The lack of overt overall benefit with RIC over NMA conditioning could be used to support the routine use of NMA conditioning therapies in patients felt to be poor candidate for MAC-based allogeneic HCT. Considering that the intensification of conditioning with agents typically used in RIC regimens does not appear to substantially reduce the risks of post-HCT relapse relative to NMA conditioning, our data provide the rationale to explore the value of alternative intensification strategies, for example using antigen-specific immunotherapeutics and/or small molecule inhibitors, to improve HCT outcomes in these patients with AML, with particular emphasis, but not limitation, to patients with MRD or other high-risk features (e.g. adverse cytogenetic risk or second remission; see results from multivariable analyses) before HCT.

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DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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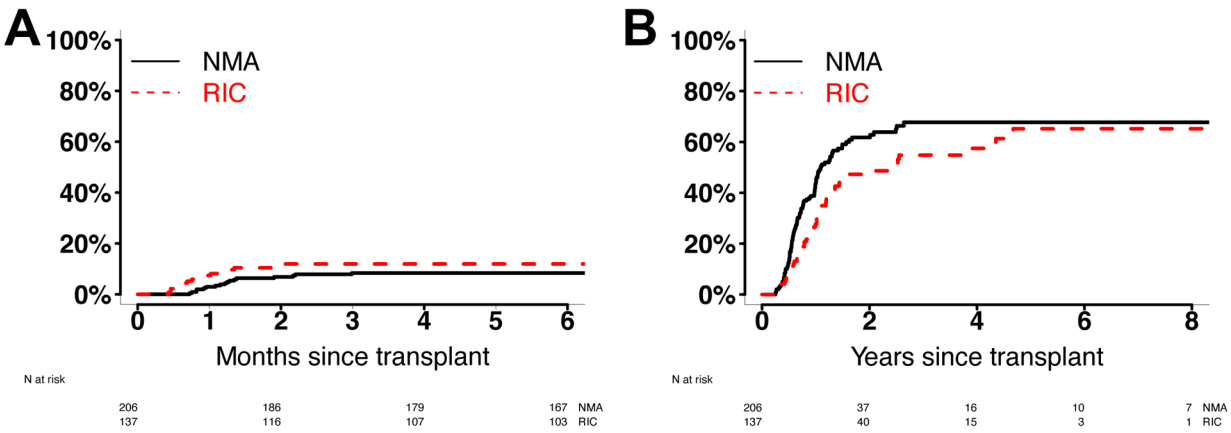

Figure 1. Cumulative incidences of acute and chronic GVHD, stratified by conditioning intensity.

Estimate of (**A**) grade 3 and 4 acute GVHD and (**B**) chronic GVHD, shown separately for RIC (n=137) and NMA (n=206) conditioning, respectively.

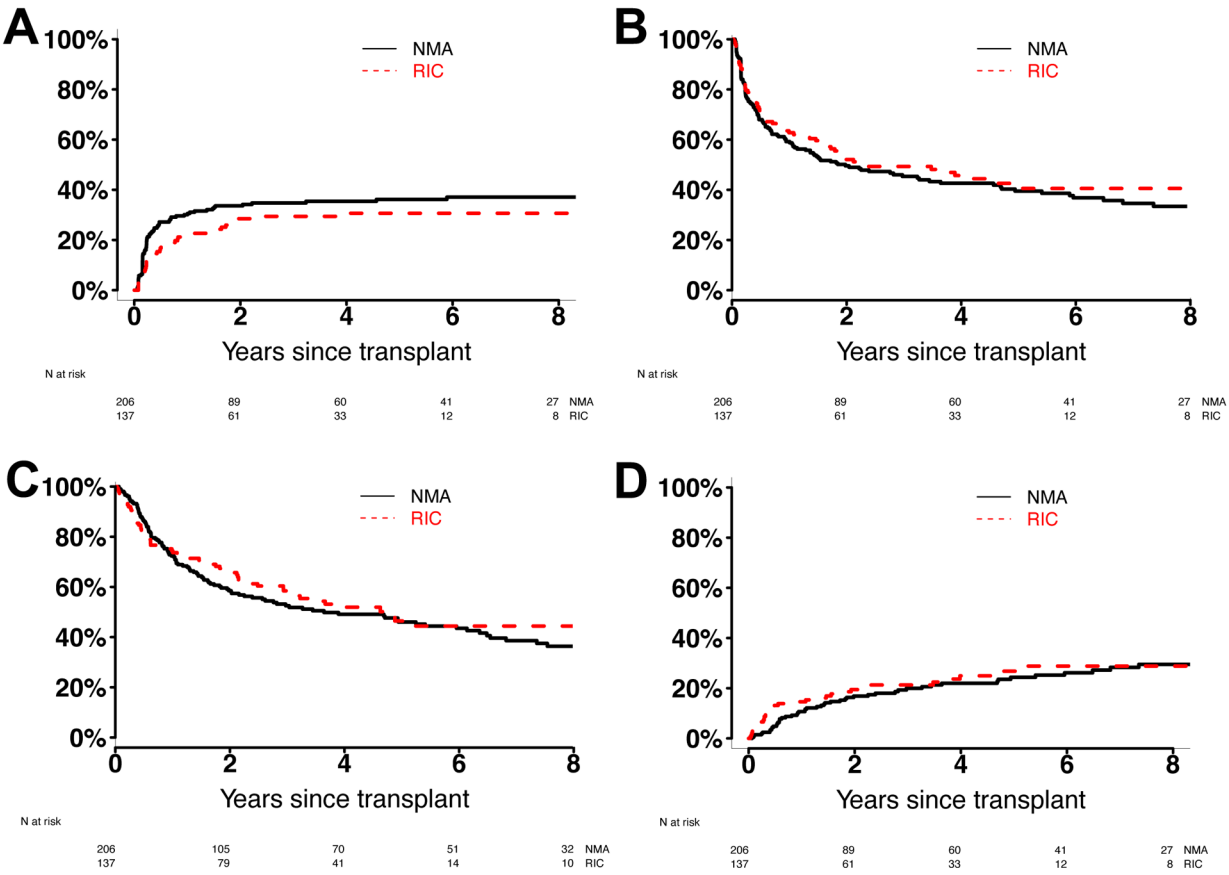

Figure 2. Post-HCT outcomes for 343 adults with AML undergoing allogeneic HCT while in first or second morphologic remission after RIC or NMA conditioning, stratified by conditioning intensity.

(**A**) Risk of relapse, (**B**) relapse-free survival, (**C**) overall survival, and (**D**) risk of non-relapse mortality, shown separately for RIC (n=137) and NMA (n=206) conditioning, respectively.

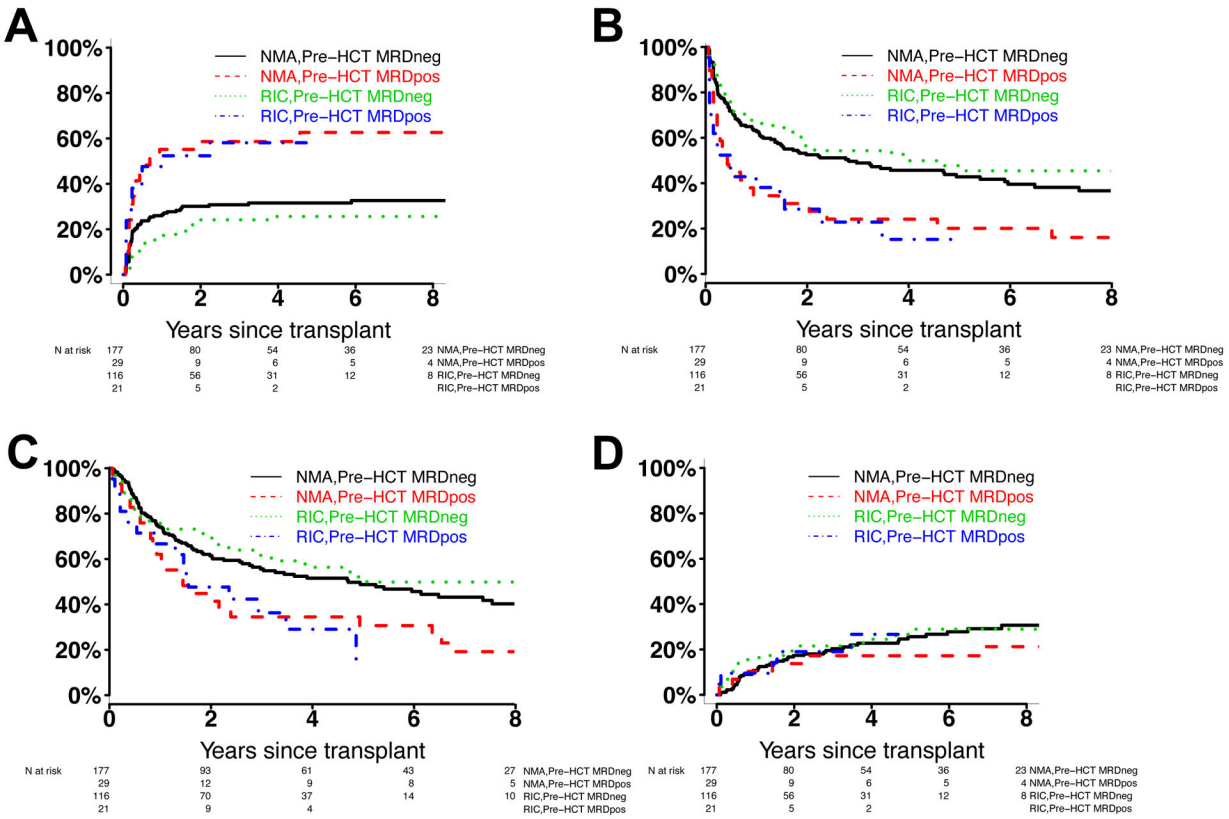

Figure 3. Post-HCT outcomes for 343 adults with AML undergoing allogeneic HCT while in first or second morphologic remission after RIC or NMA conditioning, stratified by conditioning intensity and pre-HCT MRD status.

(**A**) Risk of relapse, (**B**) relapse-free survival, (**C**) overall survival, and (**D**) risk of non-relapse mortality, shown separately for RIC (n=137) and NMA (n=206) conditioning, respectively.

TABLE 1.

Demographic and clinical characteristics of study cohort, stratified by conditioning intensity (RIC *vs.* NMA HCT)

	RIC (n=137)	NMA (n=206)	All patients (n=343)	*P*-value
Median age at HCT (range), years	63.7 (22.6–74.9)	66.0 (20.0–80.9)	65.0 (20.0–80.9)	0.0014
Female gender, n (%)	65 (47)	79 (38)	144 (58)	0.12
Median WBC at diagnosis (range), x10^3/μL	5.9 (0.2–347.5)	3.3 (0.3–295.0)	3.9 (0.2–347.5)	0.41
HCT Comorbidity Index, n (%)				0.16
0–1	37 (27)	60 (29)	97 (28)	
2–3	53 (39)	60 (29)	113 (33)	
≥4	47 (34)	86 (42)	133 (39)	
ECOG performance status, n (%)				0.71
0–1	125 (91)	185 (90)	310 (90)	
2–3	12 (9)	21 (10)	33 (10)	
Median TRM score (range)	2.19 (0.09–17.7)	3.07 (0.37–25.4)	2.70 (0.09–25.4)	0.0092
Cytogenetics at diagnosis, n (%)				0.93
Favorable	4 (3)	9 (4)	13 (4)	
Intermediate	93 (68)	135 (66)	228 (66)	
Adverse	34 (25)	53 (26)	87 (25)	
Missing	6 (4)	9 (4)	15 (4)	
Secondary AML, n (%)	32 (23)	58 (28)	90 (26)	0.38
Initial induction therapy, n (%)				
HMA	2 (1)	9 (4)	11 (3)	0.0095
HMA/venetoclax	2 (1)	2 (1)	4 (1)	
Intensive (intermediate)*	61 (45)	121 (59)	182 (53)	
Intensive (high)*	72 (53)	74 (36)	146 (43)	
Disease status at HCT, n (%)				0.16
First remission	106 (77)	172 (83)	278 (81)	
Second remission	31 (23)	34 (17)	65 (19)	
Median remission duration before HCT (range), days	84 (11–576)	107 (16–788)	97 (11–788)	0.0022
Pre-HCT MRD status, n (%)				0.76

	RIC (n=137)	NMA (n=206)	All patients (n=343)	*P*-value
MRD^{neg}	116 (85)	177 (86)	293 (85)	
MRD^{pos}	21 (15)	29 (14)	50 (15)	
Median % abnormal blasts (range)	0.61 (0.007–5.0)	0.21 (0.01–5.0)	0.40 (0.007–5.0)	0.56
Cytogenetics before HCT, n (%)				0.88
Normalized karyotype	44 (32)	71 (34)	115 (34)	
Abnormal karyotype	26 (19)	36 (17)	62 (18)	
Non-informative karyotype **/missing	67 (49)	99 (48)	166 (48)	
Recovered ANC before HCT***, n (%)	117 (85)	189 (92)	306 (89)	0.076
Recovered platelet count before HCT***, n (%)	92 (67)	129 (63)	221 (64)	0.42
Recovered peripheral blood counts before HCT***, n (%)	89 (65)	125 (61)	214 (62)	0.43
Unrelated donor, n (%)	110 (80)	164 (80)	274 (80)	1.00
HLA matching, n (%)				0.26
10/10 HLA-identical related donor	27 (20)	40 (19)	67 (20)	
10/10 HLA-matched unrelated donor	96 (70)	132 (64)	228 (66)	
9/10 HLA-matched donor	14 (10)	34 (17)	48 (14)	
Source of stem cells, n (%)				0.063
PB	134 (98)	206 (100)	340 (99)	
BM	3 (2)	0 (0)	3 (1)	
GVHD prophylaxis, n (%)				<0.001
CNI + MMF ± sirolimus	94 (69)	188 (91)	282 (82)	
CNI + MTX ± other	25 (18)	0 (0)	25 (7)	
PTCy-based	18 (13)	17 (8)	35 (10)	
Other	0 (0)	1 (<1)	1 (<1)	
Donor lymphocyte infusion, n (%)	6 (4)	17 (8)	23 (7)	0.19
PB CD3 chimerism, day +20–40, n (%)				<0.001
Full (≥95%)	83 (61)	32 (16)	115 (34)	
Mixed (<95%)	29 (21)	150 (73)	179 (52)	
Missing	25 (18)	24 (12)	49 (14)	

*Intermediate intensity: 7+3 or similar regimen; high intensity: high-dose cytarabine containing regimen.

** Normal cytogenetics in patient with cytogenetically normal AML or missing cytogenetics at diagnosis.

*** Recovered: ANC ≥1,000/μL and platelets ≥100,000/μL; not recovered: ANC <1,000/μL and/or platelets <100,000/μL.

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; BM, bone marrow; CNI, calcineurin inhibitor; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; HMA, hypomethylating agent; MMF, mycophenolate mofetil; MRD, measurable residual disease; MTX, methotrexate; PB, peripheral blood; PTCy, post-transplantation cyclophosphamide; RIC, reduced-intensity conditioning; TRM, treatment-related mortality; WBC, total white blood cell count.

TABLE 2.

Outcome probabilities (with 95% confidence interval) stratified by conditioning intensity and pre-HCT MRD status

	Relapse at 3 years	RFS at 3 years	OS at 3 years	NRM at 100 days	NRM at 3 years	Grade 3/4 aGVHD at 100 days	cGVHD at 18 months
All patients							
All (n=343)	33% (28–38%)	47% (42–53%)	55% (49–60%)	4% (2–7%)	21% (16–25%)	10% (7–13%)	42% (37–47%)
MRD^{neg} (n=280)	28% (23–33%)	51% (45–57%)	58% (52–64%)	4% (2–6%)	21% (16–26%)	9% (6–13%)	43% (37–49%)
MRD^{pos} (n=50)	58% (43–71%)	24% (14–39%)	35% (24–52%)	6% (2–15%)	18% (9–30%)	12% (5–23%)	36% (23–49%)
RIC							
All (n=137)	29% (22–37%)	49% (41–59%)	57% (49–67%)	7% (3–12%)	21% (15–29%)	12% (7–18%)	34% (26–42%)
MRD^{neg} (n=109)	24% (17–33%)	54% (46–65%)	62% (53–72%)	6% (3–11%)	22% (14–30%)	10% (5–16%)	34% (26–43%)
MRD^{pos} (n=21)	58% (33–77%)	23% (10–51%)	36% (20–65%)	10% (2–27%)	19% (6–39%)	24% (8–44%)	33% (14–54%)
NMA HCT							
All (n=206)	35% (28–41%)	45% (39–53%)	53% (46–60%)	2% (1–5%)	20% (15–26%)	8% (5–13%)	47% (40–54%)
MRD^{neg} (n=171)	31% (24–38%)	49% (42–57%)	56% (48–64%)	2% (1–5%)	20% (15–27%)	9% (5–14%)	49% (41–56%)
MRD^{pos} (n=29)	59% (38–74%)	24% (13–46%)	34% (21–57%)	3% (0–15%)	17% (6–33%)	3% (1–15%)	38% (20–56%)

Abbreviations: Hematopoietic cell transplantation; MRD, measurable residual disease; NMA, nonmyeloablative; NRM, non-relapse mortality; OS, overall survival; RFS, relapse-free survival; RIC, reduced-intensity conditioning.

TABLE 3.

Univariate regression models of entire study cohort

	Relapse		Relapse-free survival		Overall survival		Non-relapse mortality	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Conditioning intensity								
NMA (n=206)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
RIC (n=137)	0.80 (0.55–1.18)	0.27	0.93 (0.70–1.24)	0.61	0.93 (0.69–1.27)	0.66	1.13 (0.73–1.74)	0.59
Age at HCT (per 10 years)	1.10 (0.91–1.35)	0.33	1.18 (1.01–1.37)	0.039	1.25 (1.06–1.47)	0.0088	1.28 (1.00–1.64)	0.047
Gender								
Female (n=144)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Male (n=199)	1.02 (0.70–1.48)	0.92	1.25 (0.94–1.66)	0.12	1.34 (0.99–1.81)	0.055	1.65 (1.05–2.57)	0.028
HCT Comorbidity Index								
0–1 (n=97)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
2–3 (n=113)	1.42 (0.88–2.29)	0.15	1.48 (1.02–2.16)	0.039	1.48 (0.99–2.22)	0.056	1.58 (0.86–2.89)	0.14
≥4 (n=133)	1.23 (0.76–1.98)	0.40	1.50 (1.04–2.15)	0.028	1.82 (1.24–2.67)	0.0022	1.93 (1.10–3.38)	0.022
Performance status								
0–1 (n=310)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
2–3 (n=33)	3.26 (1.94–5.50)	<0.001	3.63 (2.45–5.38)	<0.001	3.88 (2.59–5.80)	<0.001	4.21 (2.32–7.67)	<0.001
TRM score	1.08 (1.02–1.14)	0.0097	1.13 (1.08–1.17)	<0.001	1.16 (1.11–1.21)	<0.001	1.19 (1.13–1.26)	<0.001
WBC at diagnosis (per 10,000/μL)	1.01 (0.98–1.05)	0.35	1.03 (1.00–1.05)	0.017	1.04 (1.01–1.06)	0.0027	1.04 (1.01–1.07)	0.0083
Cytogenetic risk								
Favorable/intermediate (n=241)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Adverse (n=87)	2.40 (1.64–3.52)	<0.001	1.79 (1.32–2.41)	<0.001	1.76 (1.29–2.40)	<0.001	1.12 (0.67–1.87)	0.67
Type of AML								
De novo (n=253)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Secondary (n=90)	1.42 (0.96–2.10)	0.081	1.24 (0.91–1.67)	0.17	1.05 (0.77–1.45)	0.74	1.02 (0.63–1.64)	0.93
Disease status								
First remission (n=278)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Second remission (n=65)	1.82 (1.19–2.77)	0.0056	1.63 (1.17–2.27)	0.0042	1.54 (1.09–2.17)	0.015	1.37 (0.79–2.36)	0.18
Pre-HCT MRD status								
MRD^{neg} (n=293)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	

	Relapse		Relapse-free survival		Overall survival		Non-relapse mortality	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
MRD^{pos} (n=50)	2.88 (1.90–4.38)	<0.001	2.22 (1.58–3.12)	<0.001	1.88 (1.33–2.67)	<0.001	1.41 (0.77–2.60)	0.27
Pre-HCT karyotype								
Normalized (n=115)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Not normalized (n=62)	1.75 (1.08–2.84)	0.024	1.75 (1.20–2.55)	0.0037	1.89 (1.26–2.81)	0.0019	1.73 (0.95–3.17)	0.076
Pre-HCT ANC *								
Recovered (n=306)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Not recovered (n=37)	1.37 (0.80–2.36)	0.25	1.42 (0.94–2.13)	0.092	1.56 (1.03–2.36)	0.036	1.48 (0.80–2.72)	0.21
Pre-HCT platelet counts *								
Recovered (n=221)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Not recovered (n=122)	0.84 (0.57–1.25)	0.34	1.25 (0.94–1.65)	0.13	1.40 (1.05–1.88)	0.024	1.99 (1.31–3.03)	0.0012
Pre-HCT blood counts *								
Recovered (n=214)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Not recovered (n=129)	0.83 (0.56–1.22)	0.34	1.19 (0.90–1.57)	0.22	1.35 (1.01–1.81)	0.042	1.86 (1.22–2.83)	0.0037
HLA matching								
10/10 related donor (n=67)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
10/10 unrelated donor (n=228)	0.84 (0.54–1.30)	0.43	1.16 (0.81–1.68)	0.42	1.19 (0.81–1.75)	0.38	2.06 (1.05–4.04)	0.036
9/10 matched (n=48)	0.75 (0.39–1.46)	0.40	1.61 (1.01–2.57)	0.045	1.89 (1.15–3.09)	0.012	4.31 (2.02–9.19)	<0.001
Donor type								
Related (n=69)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Unrelated (n=274)	0.76 (0.50–1.16)	0.21	1.17 (0.83–1.67)	0.37	1.21 (0.84–1.76)	0.30	2.42 (1.25–4.69)	0.009
GVHD prophylaxis								
CNI+MMF±sirolimus ** (n=283)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
CNI+MTX±other (n=25)	1.10 (0.57–2.11)	0.77	1.09 (0.66–1.79)	0.74	1.08 (0.65–1.81)	0.76	1.07 (0.49–2.33)	0.86
PTCy (n=35)	0.38 (0.16–0.95)	0.037	0.54 (0.29–0.99)	0.046	0.53 (0.26–1.07)	0.077	0.80 (0.34–1.85)	0.60

* Recovered: ANC ≥1,000/μL and platelets ≥100,000/μL; not recovered: ANC <1,000/μL and/or platelets <100,000/μL.

** Includes 1 patient who only received CNI + sirolimus.

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; BM, bone marrow; CNI, calcineurin inhibitor; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; MMF, mycophenolate mofetil; MRD, measurable residual disease; MTX, methotrexate; NMA, nonmyeloablative; PB, peripheral blood; PTCy, post-transplantation cyclophosphamide; RIC, reduced-intensity conditioning; WBC, total white blood cell count.

TABLE 4.

Multivariable regression models of entire study cohort

	Relapse		Relapse-free survival		Overall survival		Non-relapse mortality	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Conditioning intensity								
NMA	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
RIC	0.69 (0.45–1.06)	0.088	0.86 (0.61–1.20)	0.37	0.89 (0.64–1.24)	0.49	1.37 (0.86–2.20)	0.19
Age at HCT (per 10 years)	1.14 (0.93–1.41)	0.21	1.21 (1.02–1.43)	0.026	1.25 (1.05–1.49)	0.014	1.13 (0.87–1.46)	0.36
HCT Comorbidity Index								
0–1	Not included in		1 (Reference)		1 (Reference)		1 (Reference)	
2–3	model		1.40 (0.96–2.06)	0.083	1.47 (0.96–2.23)	0.074	1.99 (1.06–3.73)	0.031
≥4			1.25 (0.85–1.84)	0.25	1.63 (1.08–2.45)	0.02	2.22 (1.23–4.00)	0.0081
ECOG performance status								
0–1	1 (Reference)		1 (Reference)		1 (Reference)		Not included in	
2–3	2.88 (1.66–5.02)	<0.001	3.94 (2.55–6.09)	<0.001	3.95 (2.53–6.19)	<0.001	model	
WBC at diagnosis (per 10,000/μL)	Not included in model		1.04 (1.01–1.06)	0.0015	1.05 (1.03–1.08)	<0.001	1.04 (1.01–1.07)	0.013
Cytogenetic risk								
Favorable/intermediate	1 (Reference)		1 (Reference)		1 (Reference)		Not included in	
Adverse	2.37 (1.43–3.93)	<0.001	1.54 (1.04–2.29)	0.032	1.85 (1.22–2.81)	0.004	model	
Type of AML								
De novo	Not included in		Not included in		Not included in		Not included in	
Secondary	model		model		model		model	
Disease status								
First remission	1 (Reference)		1 (Reference)		1 (Reference)		Not included in	
Second remission	2.33 (1.46–3.70)	<0.001	1.71 (1.17–2.49)	0.0055	1.35 (0.91–2.02)	0.14	model	
Pre-HCT MRD status								
MRD^{neg}	1 (Reference)		1 (Reference)		1 (Reference)		Not included in	
MRD^{pos}	2.11 (1.32–3.34)	0.0016	1.96 (1.34–2.89)	<0.001	1.48 (0.99–2.22)	0.058	model	
Pre-HCT karyotype								
Normalized	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Not normalized	1.37 (0.68–1.95)	0.60	1.58 (1.03–2.42)	0.061	1.51 (0.95–2.39)	0.082	1.43 (0.74–2.80)	0.29

	Relapse		Relapse-free survival		Overall survival		Non-relapse mortality	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Pre-HCT ANC *								
Recovered	Not included in		Not included in		1 (Reference)		Not included in	
Not recovered	model		model		1.19 (0.73–2.15)	0.49	model	
Pre-HCT platelet counts *								
Recovered	Not included in		Not included in		1 (Reference)		1 (Reference)	
Not recovered	model		model		1.23 (0.88–1.72)	0.23	1.79 (1.14–2.80)	0.011
Pre-HCT blood counts *								
Recovered	Not included in		Not included in		Not included in		Not included in	
Not recovered	model		model		model		model	
HLA matching								
10/10 related donor	Not included in		1 (Reference)		1 (Reference)		1 (Reference)	
10/10 unrelated donor	model		1.13 (0.77–1.68)	0.53	1.10 (0.73–1.65)	0.66	1.78 (0.88–3.63)	0.11
9/10 matched			1.29 (0.77–2.17)	0.33	1.50 (0.88–2.56)	0.13	3.16 (1.37–7.29)	0.0068
Donor type								
Related	Not included in		Not included in		Not included in		Not included in	
Unrelated	model		model		model		model	
GVHD prophylaxis								
CNI+MMF±sirolimus **	1 (Reference)		1 (Reference)		Not included in		Not included in	
CNI+MTX±other	1.65 (0.77–3.52)	0.19	1.34 (0.74–2.44)	0.33	model		model	
PTCy-based	0.48 (0.19–1.21)	0.12	0.73 (0.38–1.40)	0.34				

*Recovered: ANC ≥1,000/μL and platelets ≥100,000/μL; not recovered: ANC <1,000/μL and/or platelets <100,000/μL.

**Includes 1 patient who only received CNI + sirolimus.

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; BM, bone marrow; CNI, calcineurin inhibitor; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; MMF, mycophenolate mofetil; MRD, measurable residual disease; MTX, methotrexate; NMA, nonmyeloablative; PB, peripheral blood; PTCy, post-transplantation cyclophosphamide; RIC, reduced-intensity conditioning; WBC, total white blood cell count.