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Myeloablative and Reduced-Intensity Conditioned Allogeneic Hematopoietic Stem Cell Transplantation in Myelofibrosis: A Retrospective Study by the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation

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A B S T R A C T

This retrospective study by the European Society for Blood and Marrow Transplantation analyzed the outcome of 2224 patients with myelofibrosis (MF) who underwent allogeneic stem cell transplantation (allo-SCT) between 2000 and 2014; 781 (35%) underwent myeloablative conditioning (MAC) and 1443 (65%) reduced-intensity conditioning (RIC). Median patient age was 52.9 years (range, 18 to 74 years) and 57.5 years (range, 21 to 76 years) in the MAC and RIC cohorts, respectively. Donor type was similar: matched sibling donors (MAC, 317 [41%]; RIC, 552 [38%]) and unrelated donors (MAC, 464 [59%]; RIC, 891 [62%]). Median time to both neutrophil and platelet ($>20 \times 10^9$/L) engraftment did not differ between cohorts. Rates of grade II to IV acute GVHD were 28% (MAC) and 31% (RIC; $P = NS$). Cumulative

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chronic GVHD rates (limited/extensive) were 22%/27% (MAC) and 19%/31% (RIC; $P = .10$). Cumulative incidences of nonrelapse mortality (NRM) at 1, 3, and 5 years were 25.5%, 32.2%, and 34.6% (MAC) and 26.3%, 32.8%, and 34.4% (RIC), respectively. There was a trend toward a higher relapse rate with RIC regimens compared with MAC ($P = .08$); rates at 1, 3, and 5 years were 10.9%, 17.2%, and 20.1% (MAC) and 14%, 19.7%, and 23.2% (RIC), respectively. No significant difference in 5-year probabilities of overall survival (OS) was noted: MAC (53.0%; 95% confidence interval [CI], 49.1% to 56.9%) and RIC (51.0%; 95% CI, 48.3% to 53.7%); $P = .78$. Regarding the composite end point of GVHD-free/relapse-free survival (GRFS), the unadjusted Kaplan-Meier estimate of 5-year GRFS was 32.4% (95% CI, 29.0% to 36.1%) in the MAC group and 26.1% (95% CI, 23.9% to 28.2%) in the RIC group ($P = .001$). In the MAC cohort, multivariable analysis confirmed worse OS and NRM with older age (>50 years), using an unrelated donor and a Karnofsky Performance Status of 80 or less. For the RIC cohort, worse OS and NRM were associated with age 60 to 70 years compared with younger recipients, use of a mismatched donor, and poor performance status. In conclusion, although similar OS rates existed for both cohorts overall, this study suggests that MAC should still be used for younger individuals suitable for such an approach due to a trend toward less relapse and an overall suggested advantage of improved GRFS, albeit this should be examined in a more homogeneous cohort. RIC allo-SCT still offers significant survival advantage in the older, fitter MF allograft patient, and optimization to reduce significant relapse and NRM rates is required.

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INTRODUCTION

Myelofibrosis (MF) is a chronic myeloproliferative neoplasm characterized by dysregulated hematopoiesis, bone marrow fibrosis, variable degrees of splenomegaly, an often-debilitating symptom burden, and an inherent risk of leukemic transformation [1]. Major advances in our understanding of disease pathogenesis over the past decade or so have led to the development of multiple novel therapeutic agents. The JAK1/JAK2 inhibitor, ruxolitinib (Novartis Pharmaceuticals, Basel, Switzerland), remains the only licensed drug and in many patients can lead to reductions in both disease-related symptomatology and splenomegaly [2,3]. However, responses may be heterogeneous and of variable duration, dosing may be limited by cytopenias, and this agent does not consistently modify disease biology [4]. Allogeneic stem cell transplantation (allo-SCT) remains the only curative approach, and over the past 15 years, there has been a steady increase in the number of procedures performed globally. The European Society for Blood and Marrow Transplantation (EBMT) registry reported on 149 transplantation episodes in 2003, which had risen significantly to 640 episodes in 2016. Conditioning regimens, such as myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC), have been heterogeneous in nature and direct comparisons in previously reported cohorts have been somewhat limited because of the overall numbers of patients analyzed (reviewed in McLornan et al. [5]). Historically, the nonrelapse mortality (NRM) with the use of MAC regimens was significant, particularly in those with increasing age. Moreover, the optimal conditioning intensity to use in younger individuals remains unknown. We hence conducted a retrospective EBMT registry analysis of a large cohort of MF allo-SCT recipients to describe outcomes in those patients undergoing both MAC and RIC preparative regimens.

METHODS

This was a retrospective, multicenter, registry-based analysis approved by the Chronic Malignancies Working Party of the EBMT. The EBMT is a nonprofit scientific society representing more than 600 transplant centers mainly in Europe. Data are entered, managed, and maintained in a central database with Internet access; each EBMT center is represented in this database. There are no restrictions on centers for reporting data, except for those required by the law on patient consent, data confidentiality, and accuracy. All patients whose transplant data are reported to the EBMT by participating centers provide informed consent to use such information for anonymized research projects. Patient selection was performed by identifying adult patients (aged >18 years) who underwent first allo-SCT for MF between 2000 and 2014, using either MAC or RIC preparative regimens as defined by standard EBMT criteria [6]. Patient-, disease-, and transplant-related variables were expressed as median and range for continuous variables and frequencies for categorical variables. Overall survival (OS) was calculated from the date of transplant until death or last observation alive. For each separate regimen, identification of potential prognostic factors was undertaken. Probability curves for OS were calculated by the Kaplan-Meier method and groups compared using the log-rank test. Outcomes with competing events (disease relapse and NRM) were determined using the cumulative incidence function with Gray's test employed for comparison of groups. Identification of best models in the multivariable setting was performed using Cox regression or Fine and Gray methods as appropriate. All statistical tests were 2-sided, and significance was determined when $P \leq .05$. Analyses were performed using SPSS version 25 (SPSS, Inc., Chicago, IL) or R version 3.4.3 (R Foundation, USA).

RESULTS

Patient, Disease, and Transplant Characteristics

Of 2224 patients with MF who were included in this analysis, 781 (35%) underwent MAC and 1443 (65%) RIC preparative regimens between 2000 and 2014. Comparisons between patient, disease, and transplant characteristics in each cohort are shown in Table 1. Blast phase disease was excluded. Median patient age was 52.9 years (range, 18 to 74 years) and 57.5 years (range, 21 to 76 years) in the MAC and RIC cohorts, respectively. Of note, in the entire cohort, approximately one third of patients were aged >60 years at the time of allo-SCT (n = 717 [32%]), and only 37 (1.7%) were >70 years old. Regarding disease type, 650 patients (83%) in the MAC cohort had primary MF (PMF) and 131 (17%) secondary MF (SMF), and in the RIC cohort, 1066 (74%) patients had PMF and 377 (26%) SMF. Median times from diagnosis to allo-SCT in the MAC and RIC cohorts were 23.2 months (range, 1 to 394 months) and 31.0 months (range, 1 to 526 months), respectively. Data were available for the Lille score in only 626 (28.6%) patients and for dynamic International Prognostic Scoring System in 493 (22.1%) and hence were not included in analysis. Details of those receiving JAK inhibitor (JAKi) and splenectomy status (where known) are shown in Table 1. A significantly higher proportion of patients in the RIC cohort (32%) had reported comorbid conditions compared with the MAC group (13%) ($P < .001$). Approximately 60% of individuals in each cohort had a Karnofsky Performance Status (KPS) of 90% or greater. Given the database source, cytogenetic and mutational data were incomplete for a large proportion and hence not analyzed. Donor source for both cohorts was similar: MAC included 317 (41%) matched sibling donors (MSDs) and 464 (59%) unrelated donors (URDs), and the RIC cohort included 552 (38%) MSDs and 891 (62%) URDs. Most patients received peripheral blood-derived stem cells. A total of 94 patients (6.5%) in the RIC group had bone marrow-derived stem cells compared with 110 (14.1%) in the MAC group. No significant differences existed in donor age, sex mismatch, or cytomegalovirus (CMV) serostatus (donor/recipient) between either cohort. Given the multicenter nature, a wide variety of conditioning regimens was used (Table 1), but in the MAC group,

Table 1
Patient, Disease, and Transplant Characteristics

Characteristic	MAC (n = 781)	RIC (n = 1443)
Age, median (range), yr	52.8 (18-74)	57.5 (21-76)
Sex, n (%)		
Male	494 (63)	913 (63)
Female	287 (37)	530 (37)
Disease: primary MF, n (%)	650 (83)	1066 (74)
Post-ET or post-PV MF	131 (17)	377 (26)
Disease stage, n (%)		
Responding or stable	150 (19.2)	270 (18.7)
Relapse, refractory, progression	284 (36.4)	522 (36.2)
Untreated	302 (38.7)	548 (38.0)
Other	45 (5.8)	103 (7.1)
Duration of disease pre-HSCT, median (range), mo	23.1 (1-394)	31.2 (1-526)
Presence of comorbidities, n (%)		
Yes	105 (13)	459 (32)
No	210 (27)	323 (22)
Missing	466 (60)	661 (46)
KPS, n (%)		
100	150 (19)	356 (25)
90	315 (40)	501 (35)
80	142 (18)	279 (19)
<80	44 (6)	108 (8)
Missing	130 (17)	199 (13)
Previous JAK inhibitor, n (%)		
Yes	34 (4.3)	136 (9.4)
No	443 (56.7)	954 (66.1)
Missing	304 (39)	353 (24.5)
Splenectomy, n (%)		
Yes	69 (8.8)	135 (9.4)
No	257 (32.9)	664 (46)
Missing	455 (58.3)	644 (44.6)
HLA matching, n (%)		
Matched sibling	317 (40.6)	552 (38.3)
Matched unrelated	60 (7.7)	101 (7)
Mismatched unrelated	19 (2.4)	41 (2.8)
Unrelated; match unspecified	385 (49.3)	749 (51.9)
Donor/recipient sex, n (%)		
M/M	333 (42.6)	610 (42.3)
F/M	146 (18.7)	291 (20.2)
M/F	169 (21.6)	308 (21.3)
F/F	112 (14.3)	216 (15)
Missing	21 (2.7)	18 (1.2)
Stem cell source, n (%)		
Bone marrow	110 (14)	94 (4)
Peripheral blood	671 (86)	1382 (96)
CMV serostatus (D:R), n (%)		
−/−	204 (26)	429 (29.7)
−/+	156 (20)	264 (18.3)
+/−	81 (10.4)	158 (11)
+/+	289 (37)	546 (37.8)
Missing	51 (6.6)	46 (3.2)
Conditioning regimen, n (%)		
Fludarabine and busulfan	369 (47.2)	820 (56.8)
Fludarabine and melphalan	—	284 (19.7)
Busulfan and cyclophosphamide	130 (16.6)	—
Cyclophosphamide + TBI	110 (14.1)	—
Other	172 (22.1)	339 (23.5)
HSCT era, n (%)		
2000-2004	120 (8.3)	117 (15)
2005-2009	393 (27.2)	208 (26.6)
2010-2014	930 (64.4)	450 (58.4)

ET indicates XXX; PV, XXX; TBI, total body irradiation; HSCT, hematopoietic stem cell transplantation.

the 2 most common regimens were fludarabine and busulfan (Flu + Bu) with myeloablative dosages of busulfan (n = 369 [42%]) and busulfan and cyclophosphamide (n = 130 [16.6%]), whereas in the RIC setting, the most frequent were Flu + Bu (n = 820 [57%]), fludarabine and melphalan (Flu + Mel; n = 284 [20%]), and Flu and antithymocyte globulin (n = 67 [5%]), with others collectively accounting for the remaining 18%. Total body irradiation-based conditioning was used in 133 (17%) cases in the MAC cohort. Median follow-up period was 3.99 (0.1 to 18.1) years for the MAC cohort and 4.20 (0.1 to 16.2) years for the RIC cohort.

Engraftment, Graft-versus-Host Disease, and NRM

Time to neutrophil engraftment was documented for 94% of MAC and 92% of RIC cohorts with a median time of 17 and 18 days, respectively ($P = .85$). The median time to platelet engraftment ($>20 \times 10^9$/L) was not significantly different between cohorts (MAC 20 days and RIC 19 days; $P = .73$). Regarding graft failure, this occurred in a total of 73 patients (9.5%) in the MAC cohort and 194 (13.6%) patients in the RIC cohort ($P = .005$), suggesting a significantly higher risk for RIC platforms. Acute and chronic graft-versus-host disease (GVHD) status was documented in 96% and 79% of the entire cohort, respectively. Rates of grade II to IV acute GVHD were 28% in the MAC cohort and 31% in the RIC cohort, with grades III to IV accounting for 12% and 16%, respectively, while the proportions of patients with chronic GVHD (limited/extensive) were 22%/27% (MAC) and 19%/31% (RIC). Cumulative incidences of NRM at 1, 3, and 5 years were similar between both cohorts: 25.5%, 32.2%, and 34.6% (MAC) and 26.3%, 32.8%, and 34.4% (RIC); Figure 1. The most frequent causes of NRM in the MAC and RIC cohorts are shown in Table 2, and univariate/multivariable analysis of factors affecting NRM is demonstrated in Supplementary Tables S1 and S2.

OS and Relapse-Free Survival

No significant difference in 5-year probabilities of survival (OS) between either approach was noted: MAC (53.0%; 95% confidence interval [CI], 49.1% to 56.9%) and RIC (51.0%; 95% CI, 48.3% to 53.7%); $P = .78$, (Figure 1). There was no difference in outcomes as determined by disease type (PMF versus SMF) and, where information was available, splenectomy versus no splenectomy pre-alloSCT. Univariable/multivariable outcome analysis for both MAC and RIC cohorts is shown in Supplementary Tables S3 and S4. There was a trend toward a higher relapse rate with RIC preparative regimens overall, with rates at 1, 3, and 5 years of 14%, 19.7%, and 23.2% compared with 10.9%, 17.2%, and 20.1% for MAC ($P = .08$; Figure 1), respectively. Regarding donor matching, adverse outcome was associated with use of Mismatched Unrelated Donor in the RIC setting, with a median survival of only 1.2 years (range, 0.07 to 2.3) compared with 3.5 years for Matched Unrelated Donor (MUD) (range, 0 to 7.6). No OS difference was noted between the most frequent RIC regimens (Flu + Bu versus Flu + Mel versus other; $P = .29$) or any of the most frequent myeloablative regimens (busulfan and cyclophosphamide versus Flu + Bu versus other; $P = .84$). Univariable

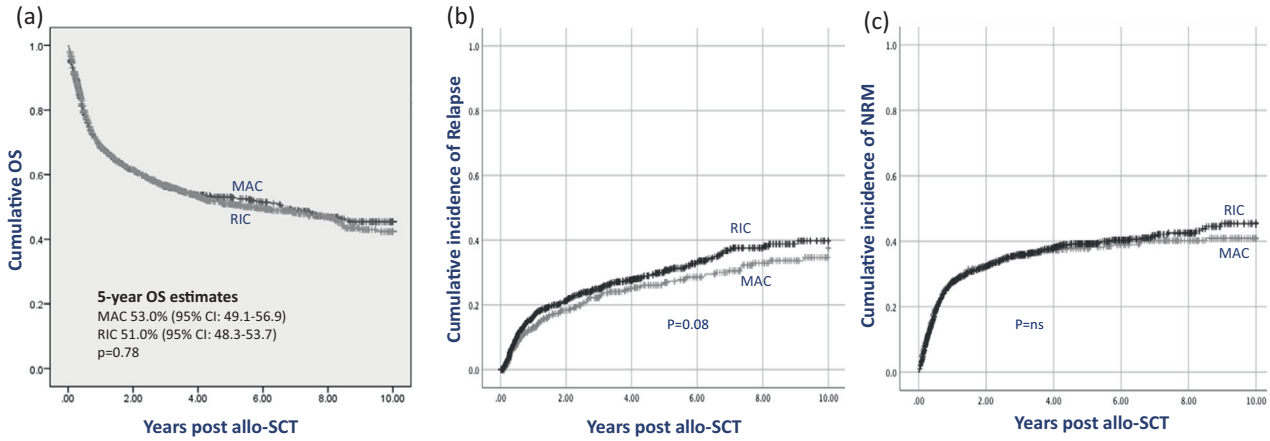

Figure 1. Outcome analysis for both RIC and MAC cohorts. (A) OS as determined by intensity of conditioning regimen. (B) Relapse and (C) nonrelapse mortality rates as determined by intensity of conditioning regimen.

Table 2
Causes of Death in Both the MAC and RIC Cohorts

Characteristic	MAC, n (%)	RIC, n (%)
Relapse/disease progression	65 (19.1)	126 (19.3)
GVHD	77 (23.1)	208 (30.8)
Infection	103 (30.9)	186 (28.5)
Organ damage/failure/toxicity	29 (8.7)	45 (6.9)
Allo-SCT-related death, unspecified	12 (3.6)	22 (3.4)
Secondary malignancy/PTLD	13 (3.9)	24 (3.7)
Other	34 (10.2)	48 (7.4)

PTLD indicates post-transplant lymphoproliferative disorder.

analysis also confirmed that with regard to CMV serostatus, there was a worse 5-year OS in the RIC setting with a recipient CMV^+/donor CMV^- combination.

GVHD-Free, Relapse-Free Survival

Regarding the composite end point of GVHD-free, relapse-free survival (GRFS), the unadjusted Kaplan-Meier estimate of 5-year GRFS was 32.4% (95% CI, 29.0% to 36.1%) in the MAC group and 26.1% (95% CI, 23.9% to 28.2%) in the RIC group ($P = .001$).

Multivariable Outcome Analysis

In the MAC cohort, multivariable analysis confirmed worse OS and NRM with age older than >50 years, use of an unrelated donor compared to MSD, and a KPS of 80 or less. For the RIC cohort, worse OS and NRM were associated with age 60 to 70 years compared with younger recipients, use of a mismatched unrelated donor, a poor performance status with a KPS of 80 or less, and recipient comorbidities. Moreover, regarding CMV serostatus, in the RIC setting, the combination of recipient CMV^+/donor CMV^- was associated with a worse OS. Regarding risk of relapse, there were no significant variables on multivariable analysis in either the MAC or RIC cohort.

DISCUSSION

This analysis represents the largest multicenter retrospective study to date delineating outcomes in both MAC and RIC allo-SCT for MF. Despite advances in therapeutic options for MF, with many novel agents now in the clinical arena, allo-SCT remains the only curative approach for transplant-eligible patients. Optimal conditioning intensity for MF allo-SCT has not been compared prospectively on a large scale, likely due to the rarity of the disease and the historically low number of patients with MF moving into allo-SCT. In daily clinical practice, the outstanding question for the younger individual remains: do MAC approaches still confer an improved outcome over RIC? Historically, conventional MAC approaches have been considered to be associated with significant toxicity and indeed higher NRM rates. Moreover, the use of RIC platforms extends the potential of the transplant option to older and perhaps more frail candidates, particularly relevant for clinical practice given that the median age of onset of MF is in the sixth and seventh decades. Several small retrospective studies have been published comparing MAC versus RIC approaches. Patriarca et al. [7] analyzed 100 patients with MF who underwent allo-SCT between 1986 and 2006 on behalf of the Gruppo Italiano Trapianto di Midollo Osseo. Significant improvements in outcomes were seen over time (after 1986), and the intensity of the conditioning regimen did not significantly influence transplant outcome. The Nordic cooperative group, reporting on 92 patients, demonstrated that the 5–year OS, when adjusted for age, was 49% in the MAC cohort but significantly higher in the RIC cohort at 59% [8]. No differences existed with regard to day 100 transplant-related mortality. Foremost, our analyses confirm timely neutrophil and platelet engraftment in both the RIC and MAC cohorts, with most receiving peripheral blood-derived stem cells. Given the heterogeneity of the group, the effect of stem cell dose, if any, on outcome was not analyzed. Both acute and chronic GVHD rates did not differ between the MAC and RIC cohorts, but these remain heterogeneous groups. We did not detect any difference in 1-, 3-, and 5-year OS rates when comparing MAC and RIC cohorts with acceptable 5-year OS rates of >50% in both groups. Interestingly, this present study showed that there was no significant difference in NRM between both RIC and MAC cohorts, which differs from other earlier studies demonstrating higher toxicity rates and NRM with MAC approaches. Age was a strong predictor of survival in both the MAC and RIC cohorts, as shown above. Of note, only 37 patients were aged above 70 years (1.6%), although overall more than one third of the entire cohort was older than 60 years. As shown previously in the prospective EBMT RIC trial (n = 103), our study confirmed that use of a mismatched unrelated donor, particularly within the RIC setting, was associated with an adverse outcome compared with use of a MUD or MSD. Moreover, adverse OS was associated with the presence of recipient comorbidities in the RIC cohort and poor performance status; a KPS of <80% was associated with worse OS in both the RIC (median, 1.2 years; range, 0 to 2.8 years) and MAC (median, 1.2 years; range, 0 to 3.1 years) cohorts compared

with those with better Performance Status (PS), indicating that strategies to optimize PS pre-allo-SCT are warranted. This may be a role for JAKi therapy pretransplant. Regarding relapse, there was a trend toward improved RFS in the MAC arm, although relapse rates in both groups remained significant as highlighted above. Data were not available on detailed post-transplant approaches in this cohort, although it is clear with such relapse rates that strategies to reduce relapse, through perhaps optimal conditioning intensity choice, close measurable residual disease monitoring, and adoptive immunotherapeutic approaches, should be mandated. We did not note any effect on OS in splenectomized versus nonsplenectomized recipients, albeit the information regarding splenectomy status was available in only 1125 patients. This is in keeping with what was described in the retrospective Center for International Blood and Marrow Transplant Research study but contrasts, at least in part, to the recently published retrospective French cooperative group study, whereby there was no evidence of an association between pretransplant splenectomy and either NRM or relapse risk, but a suggestion toward improved OS [9,10]. Conditioning regimens were varied, and in particular, RIC regimens remained highly heterogeneous with regard to intensity. Of particular note, we detected no significant difference in OS in the RIC arm between the 2 most commonly used regimens: Flu + Bu and Flu + Mel, akin to a recently published retrospective comparison [11].

Donor (D) and recipient (R) CMV status affected survival outcomes; compared with a CMV R−/D− combination (median survival, 8 years), survival was markedly inferior in those who were CMV seropositive and received a graft from a CMV-negative donor (R+/D−) (median survival, 3.4 years; range, 2 to 4.7 years). Similar survival outcomes between cases who were CMV R+/D+ and R−/D + were noted, and these were superior to the R+/D− combination. We can only hypothesize in this retrospective study why the R +/D− cohort did worse. Of note, as previously described, CMV seropositivity correlates strongly with advancing age. In present-day practice, CMV disease is rare given standard pre-emptive strategies, so perhaps these findings are reflective of indirect CMV mechanisms whereby these patients may have higher severe GVHD rates, and this aspect should be analyzed in a more recent and homogeneous cohort of MF-alloSCT recipients. Last, regarding GRFS, our study suggests a statistically significant benefit for MAC versus RIC platforms in MF, which should be considered when deciding upon conditioning intensity in fit young patients.

Limitations to conclusions from our study are those inherent to registry-based, retrospective analyses and include a lack of clarity for physician choice of regimen intensity, incomplete data for cytogenetics and molecular profiles (hence an inability to calculate accurate and current molecular prognostic scoring systems), and a lack of detail and incomplete data on type of recipient comorbidities and degree of HLA matching for all URDs. We acknowledge that more patients in the MAC cohort had incomplete information on performance status, splenectomy status, comorbidities, and the use of JAK inhibitors, and hence the conclusions of our study need to be considered with this in mind. Moreover, relapse and progression are as captured and reported by the individual transplant centers. However, this is the largest reported study to date of allo-SCT outcome for patients with MF, and we can see that despite the time span of inclusion, both MAC and RIC regimens are associated with acceptable 5-year OS rates in >50% of cases. Use of a mismatch URD still confers an adverse outcome, and in the current era, comparison to outcomes using haploidentical donors should be investigated when a transplant-eligible patient lacks a MSD or MUD. Patient selection remains paramount as both comorbidities and poor KPS are associated with more adverse outcomes, and perhaps there is a role of JAKi agents to improve PS pre-allo-SCT. Graft failure rates appeared higher with the use of RIC regimens. Our data suggest a trend toward less relapse and a significant reduction in GRFS in those receiving MAC regimens, so in younger, fitter individuals who would tolerate this approach, they should still continue to be considered for MAC platforms. Our data also confirm the benefit of transplant with RIC regimens, which extends this therapeutic option to older and less fit individuals—we saw no difference in OS between both groups. Optimization to reduce the significant relapse and NRM rates is required with both approaches.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.06.034.

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