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RESEARCH PAPER

Impact of conditioning regimen intensity on the outcomes of peripheral T-cell lymphoma, anaplastic large cell lymphoma and angioimmunoblastic T-cell lymphoma patients undergoing allogeneic transplant

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Summary

There have been no large studies comparing reduced-intensity/non-myeloablative conditioning (RIC/NMA) to myeloablative conditioning (MAC) regimens in T-cell non-Hodgkin lymphoma (T-NHL) patients undergoing allogeneic transplant (allo-HCT). A total of 803 adults with peripheral T-cell lymphoma, anaplastic large cell lymphoma and angioimmunoblastic T-cell lymphoma (age 18–65 years), undergoing allo-HCT between 2008–2019 and reported to the Center for International Blood and Marrow Transplant Research with either MAC ($n = 258$) or RIC/NMA regimens ($n = 545$) were evaluated. There were no significant differences between the two cohorts in terms of patient sex, race and performance scores. Significantly more patients in the RIC/NMA cohort had peripheral blood grafts, haematopoietic cell transplantation-specific

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comorbidity index (HCT-CI) of ≥3 and chemosensitive disease compared to the MAC cohort. On multivariate analysis, overall survival (OS) was not significantly different in the RIC/NMA cohort compared to the MAC cohort (hazard ratio (HR) = 1.01, 95% confidence interval (CI) = 0.79–1.29; $p = 0.95$). Similarly, non-relapse mortality (NRM) (HR = 0.85, 95% CI = 0.61–1.19; $p = 0.34$), risk of progression/relapse (HR = 1.29; 95% CI = 0.98–1.70; $p = 0.07$) and therapy failure (HR = 1.14; 95% CI = 0.92–1.41, $p = 0.23$) were not significantly different between the two cohorts. Relative to MAC, RIC/NMA was associated with a significantly lower risk of grade 3–4 acute graft-versus-host disease (HR = 0.67; 95% CI = 0.46–0.99, $p = 0.04$). Among chemorefractory patients, there was no difference in OS, therapy failure, relapse, or NRM between RIC/NMA and MAC regimens. In conclusion, we found no association between conditioning intensity and outcomes after allo-HCT for T-cell NHL.

KEYWORDS
allogeneic transplant, mature T-cell NHL, myeloablative conditioning, reduced-intensity conditioning

INTRODUCTION

Mature T-cell lymphomas are a heterogeneous group of aggressive neoplasms that constitute approximately 15% of all non-Hodgkin lymphomas (NHLs) in adults.[1] The most common subtypes within mature nodal T-cell lymphomas are peripheral T-cell lymphoma–not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T-cell lymphomas (AITLs). With the exception of ALCL (especially the anaplastic lymphoma kinase [ALK] positive subset), disease relapse following first-line treatment in mature nodal T-cell lymphomas is expected in the majority of patients. In the relapsed/refractory setting, available therapy options typically do not provide durable disease control[2–4] and allogeneic haematopoietic cell transplant (allo-HCT) remains the only potentially curative option.[5–9] In fact, with the rapidly declining utilization of allo-HCT for aggressive B-cell lymphomas, T-cell NHL now constitutes the most common indication for allo-HCT for lymphomas in the United States and Europe.[10]

The allo-HCT conditioning regimens have a spectrum of dose-intensities, ranging from regimens at the lower end of the intensity spectrum (relying predominately on immunological effects to eradicate disease) to higher-intensity options (depending on both cytoreductive and immunological mechanisms to control disease).[11] Reduced-intensity and non-myeloablative conditioning (RIC/NMA) regimens now account for the vast majority of allo-HCTs performed for lymphomas in the United States.[7,11–16] Although the RIC regimens are generally associated with a lower cumulative incidence of non-relapse mortality (NRM) relative to myeloablative conditioning (MAC) regimens, disease relapse remains the most common cause of treatment failure in patients with lymphoma undergoing allo-HCT. Retrospective studies comparing conditioning regimen intensities, including predominantly patients with B-cell NHL or classic Hodgkin lymphoma, generally show higher NRM rates, with high-intensity conditioning without a consistent survival benefit.[14,17–22]

There are sparse data directly comparing clinical outcomes of patients who have undergone RIC/NMA *versus* MAC allo-HCT for mature T-cell NHL.[23] Using the observational database of the Centre for International Blood and Marrow Transplant Research (CIBMTR), we report here the outcomes of PTCL-NOS, AITL and ALCL patients, according to the intensity of allo-HCT conditioning regimens.

METHODS

Data source

The CIBMTR is a working group comprising over 380 transplantation centres worldwide that provide data regarding HCT to a statistical centre at the Medical College of Wisconsin (MCW), Milwaukee, Wisconsin. On-site audits ensure compliance of the participating transplant centres in reporting all transplantations consecutively. Additionally, the quality of data is further augmented through computerized affirmation of discrepancies, physicians' review of submitted data and on-site audits of participating centres. Observational studies are conducted by the CIBMTR in compliance with all pertinent federal regulations with regard to the protection of human research participants. All patients included in this analysis provided written consent. The International Review Board of MCW and the National Marrow Donor Program approved this study.

Patients

This analysis included adults between the ages of 18 and 65 years diagnosed with PTCL-NOS, ALCL and AITL, who

underwent RIC/NMA or MAC allo-HCT between 2008 and 2019. Patients 66 years and older were not included as patients at advanced age are less likely to receive MAC regimens. Eligible donors included haploidentical donors, human leucocyte antigen (HLA)-identical sibling donors and unrelated donors (MUD), matched at the allele-level at HLA-A, HLA-B, HLA-C and HLA-DRB1. Graft sources included bone marrow or peripheral blood. Graft-versus-host disease (GVHD) prophylaxis consisted of calcineurin inhibitor (CNI)-based approaches. Patients who received haploidentical HCT and did not receive post-transplant cyclophosphamide-based GVHD prophylaxis were excluded. The patients were divided into two cohorts: MAC and RIC/NMA regimens. Patients with *ex vivo* T-cell depletion were excluded. Patients receiving *in vivo* T-cell depletion with anti-thymocyte globulin were included.

Definitions and endpoints

The intensity of allo-HCT conditioning regimens was defined using consensus criteria.[24] Disease response at the time of allo-HCT was determined using the International Working Group criteria that was in use during the era of this analysis.[25–27] Patients not in complete or partial remission at the time of allo-HCT were considered chemorefractory. The primary endpoint was overall survival (OS). Death from any cause was considered an event. For progression-free survival (PFS), a patient was considered a treatment failure at the time of progression/relapse or death from any cause. Patients alive without evidence of disease relapse or progression were censored at the last follow-up. Secondary outcomes included NRM and progression/relapse. NRM was defined as death without evidence of prior lymphoma progression/relapse; relapse was considered a competing risk. Progression/relapse was defined as progressive lymphoma after HCT or lymphoma recurrence after a complete response (CR); NRM was considered a competing risk. Acute GVHD and chronic GVHD were graded using established clinical criteria.[28,29] Probabilities of PFS and OS were calculated using the Kaplan–Meier estimates. Neutrophil recovery was defined as the first of 3 successive days with an absolute neutrophil count of ≥500/μl after the post-transplantation nadir. Platelet recovery was considered to have occurred on the first of 3 consecutive days with a platelet count of 20 000/μl or higher, in the absence of platelet transfusion for 7 consecutive days. Death without the event was considered a competing risk for neutrophil and platelet recovery.

Statistical analysis

This study compared conditioning intensities, MAC *versus* NMA/RIC, in patients who underwent allo-HCT for PTCL-NOS, ALCL and AITL. The chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables were used to compare baseline characteristics. The Cox model was used for OS and PFS. The proportional cause-specific hazards model was used for GVHD, relapse and NRM, to account for competing risks.[30] The proportional hazards assumption was tested by examining a time-varying effect for each risk factor and each outcome. A forward stepwise selection was used to identify significant variables while conditioning intensity was kept in all models. The interaction between conditioning intensity and significant variables was checked. Variables tested in the regression models included conditioning intensity, patient-related variables, including patient age, sex, Karnofsky performance status, HCT comorbidity index (HCT-CI), disease-related characteristics, including time from diagnosis to HCT, lymphoma histology, history of autologous transplant and disease status at the time of allo-HCT as well as transplant-related factors including donor type, cytomegalovirus serostatus, use of total body irradiation in conditioning and year of transplant.

To further confirm the regression analysis results, we conducted propensity score matching. To calculate propensity scores, we used multiple imputation using R package smcfcs (https://rdocumentation.org/packages/smcfcs/) and Rubin's rule to handle missing covariates.[31,32] Using calculated propensity scores, we matched MAC and RIC/NMA cohorts using R package MatchIt (https://rdocumentation.org/packages/MatchIt) with a 1:2 matching ratio for MAC and NMA/RIC.[33] The marginal model was used to handle correlation within matched pairs.[34] In addition, we fitted regression models after restricting the patients to ≤50 years old. All statistical analyses were performed using SAS version 9.4 (SAS Institute) and R version 4.0.4 (R Foundation for Statistical Computing).

RESULTS

Baseline characteristics

A total of 803 patients from 122 different CIBMTR reporting transplant centres, including 545 receiving RIC/NMA and 258 patients receiving MAC regimens, met the eligibility criteria of this analysis (Table 1). Three NHL histologies were included in this analysis; 52% with PTCL-NOS, 31% with ALCL and 17% with AITL were in the MAC cohort. In patients who received RIC/NMA regimens, 45%, 27% and 28% had PTCL-NOS, ALCL and AITL, respectively. The median age of patients was significantly lower [46 years (range 18–66 years)] in the MAC cohort compared to [54 years (range 18–66 years) in patients who underwent RIC/NMA conditioning. There were no significant differences between the MAC and RIC/NMA cohorts in terms of sex, race and Karnofsky performance scores. Significantly more patients in the RIC/NMA cohort had peripheral blood grafts (92% vs 87%), history of prior autologous HCT (39% vs 16%), HCT-CI of ≥3 (40% vs 29%) and chemosensitive disease before allo-HCT (87% vs 79%; Table 1). Matched siblings as donors (54% vs 44%), total body irradiation (TBI) containing conditioning (66% vs 28%) and CNI plus methotrexate as GVHD prophylaxis (71% vs 45%) were more frequent in the MAC cohort.

TABLE 1 Baseline patient characteristics

Characteristic	MAC	RIC/NMA	p^1
No. of patients	258	545	
Patient age, median (range)	46 (18–65)	54 (18–65)	<0.01[a]
Male sex, *n* (%)	169 (66)	346 (63)	0.58[b]
Karnofsky performance score – ≥90 *n* (%)	158 (61)	310 (57)	0.17[b]
Not reported	3 (1)	17 (3)	
Patient race, *n* (%)			0.09[b]
Caucasian	190 (74)	438 (80)	
African American	30 (12)	44 (8)	
Asian/Pacific islander	12 (4)	30 (5)	
Missing	26 (10)	33 (6)	
Peripheral blood graft, *n* (%)	224 (87)	504 (92)	0.01[b]
Donor type, *n* (%)			<0.01[b]
Matched sibling donors	140 (54)	238 (44)	
Haploidentical donors	22 (9)	69 (13)	
MUD with ATG	25 (10)	98 (18)	
MUD without ATG	71 (28)	140 (26)	
HCT-CI 3 or more, *n* (%)	75 (29)	220 (40)	<0.01[b]
Lines of prior therapy – median (min-max)	2 (1–5)	2 (1–5)	0.28[b]
Remission status, *n* (%)			<0.01[b]
Complete remission[2]	110 (43)	279 (51)	
Partial remission	93 (36)	196 (36)	
Chemoresistant	55 (21)	70 (13)	
TBI in conditioning, *n* (%)			<0.01[b]
TBI-containing	169 (66)	155 (28)	
TBI-free	89 (34)	390 (72)	
Conditioning regimens, *n* (%)			
CY/TBI	122 (47)	1 (<1)	
Bu/CY	35 (14)	–	
Flu/Bu	46 (18)	134 (25)	
Flu/TBI ± others	20 (7)	59 (11)	
Flu/Mel ± others	–	187 (34)	
Flu/CY/TBI	1 (<1)	70 (13)	
Others	34 (14)	94 (17)	
GVHD prophylaxis, *n* (%)			<0.01[b]
Post-CY ± other(s)	22 (9)	69 (13)	
CNI + MMF ± other(s) (except post-CY)	26 (10)	153 (28)	
CNI + MTX ± other(s) (except MMF, post-CY)	184 (71)	246 (45)	
CNI + other(s) (except MMF, MTX, post-CY)	18 (7)	66 (12)	
CNI alone	8 (3)	11 (2)	
Lymphoma histology, *n* (%)			<0.01[b]
PTCL-NOS	134 (52)	243 (45)	
ALCL	81 (31)	147 (27)	
AITL	43 (17)	155 (28)	
History of autologous transplant, *n* (%)	40 (16)	214 (39)	<0.01[b]
Median time from diagnosis to HCT, *n* (%)	12 (3–208)	15 (2–247)	<0.01[a]
Follow-up median (min-max)	62 (3–145)	60 (3–145)	

Abbreviations: ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; Bu, busulfan; CNI, calcineurin inhibitor; CY, cyclophosphamide; Flu, fludarabine; GVHD, graft versus host disease; HCT, haematopoietic cell transplant; mel, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; MUD, unrelated donors; PTCL-NOS, peripheral T cell lymphoma- not other specified; TBI, total body irradiation.

[1]Hypothesis testing: [a]Kruskal–Wallis test; [b]Pearson chi-square test.

[2]Five patients (2%) in myeloablative conditioning (MAC) and six (1%) in, reduced intensity conditioning/non-myeloablative (RIC/NMA) groups were in CR1(1st complete response) after one prior line of therapy at the time of allo-HCT.

There was no significant difference in the baseline characteristics of the propensity-score-matched patient subset (n = 360), except for higher median age in the RIC/MAC cohort (53 years vs 49 years) (Table S1).

Overall survival

On univariate analysis, the OS was 61% and 57% at 3 and 5 years in the MAC cohort, respectively. The respective figures for patients receiving RIC/NMA regimens were 64% and 59% (Figure 1A; Table 2). Among patients with chemoresistant disease before allo-HCT, the 5-year OS was 55% and 49% in the MAC and RIC/NMA cohorts, respectively (p = 0.55; Table 3). On multivariate analysis, after adjusting for all independently significant covariates (Karnofsky performance status, history of autologous transplant and year of transplant) the OS was not significantly different in the RIC/NMA cohort relative to the MAC cohort (HR = 1.01, 95% CI = 0.79–1.29, p = 0.95; Table 4).

There were 322 reported deaths. The most common cause of death was primary disease in 41% and 33% of patients in MAC and RIC/NMA, respectively. GVHD accounted 18% and 20% of deaths in MAC and RIC/NMA cohorts respectively, while infections accounted for 15% and 18% of deaths in similar order (details in Table S2).

Non-relapse mortality

On univariate analysis (Table 2), the NRM at 100-days was significantly higher in the MAC cohort (11%) compared to the RIC/NMA cohort (7%; p = 0.04; Figure 1B). The 5-year NRM in similar order was 24% and 23%, respectively. In the chemoresistant subset (Table 3) the 5-year NRM in the MAC and RIC/MAC cohorts was 19% and 25% (p = 0.42), respectively. After adjusting for all independently significant covariates (age, Karnofsky performance status and year of transplant) on multivariate analysis the NRM risk was not significantly lower after RIC/NMA compared to MAC (HR = 0.85, 95% CI = 0.61–1.19; p = 0.34; Table 4).

Relapse and progression-free survival

The cumulative incidence of progression/relapse at 5 years was the same in both cohorts at 31% (p = 0.93; Figure 1C; Table 2). Among the chemoresistant cohort, the 5-year cumulative incidence of progression/relapse was 49% following MAC compared to 40% following RIC/NMA (p = 0.81; Table 3). On multivariate analysis (Table 4), the risk of progression/relapse was not significantly higher with RIC/NMA relative to MAC (HR = 1.29; 95% CI = 0.98–1.70; p = 0.07) cohorts.

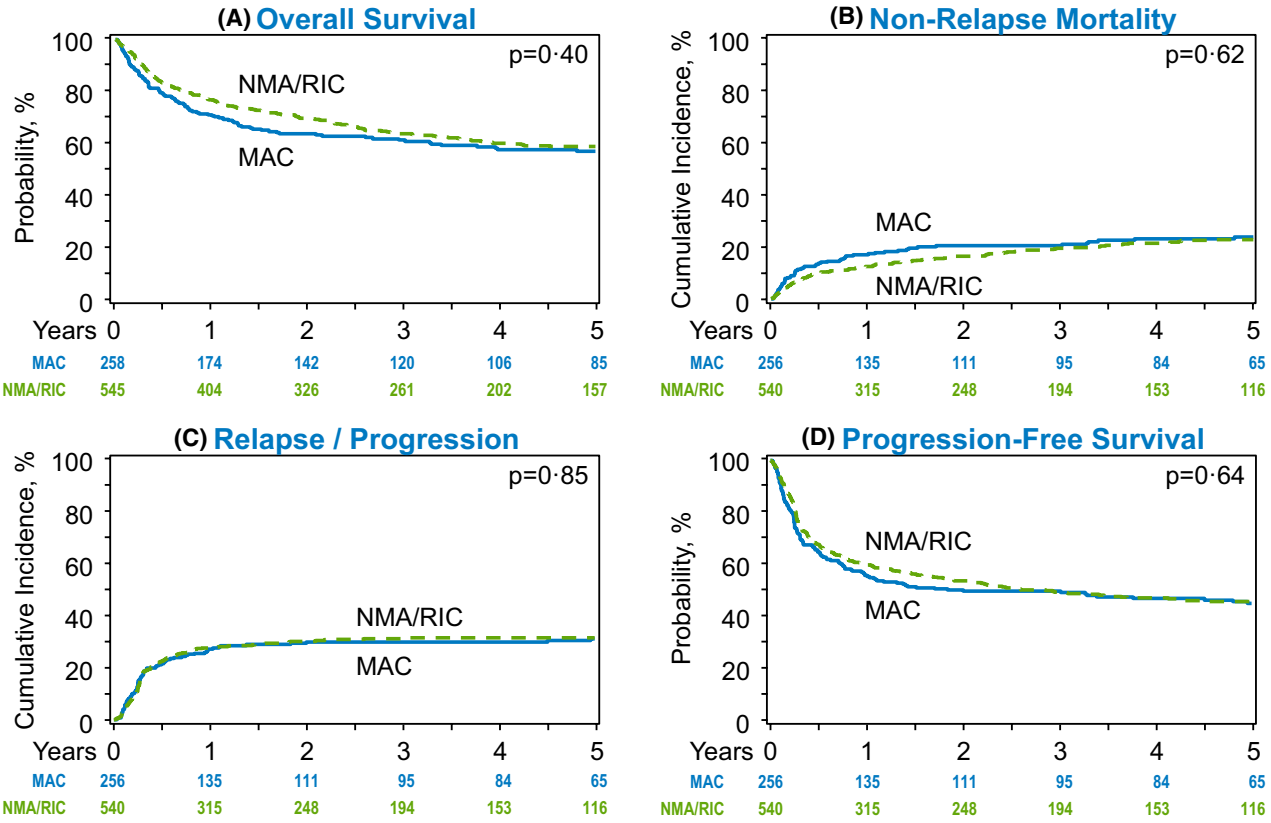

FIGURE 1 (A) Overall survival, (B) non-relapse mortality, (C) relapse/progression and (D) progression-free survival through 5-years of patients receiving myeloablative (MAC) and non-myeloablative (NMA)/reduced-intensity conditioning (RIC) regimen prior to an allo-HCT for peripheral T-cell lymphoma, anaplastic large cell lymphoma and angioimmunoblastic T-cell lymphoma [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Univariate outcomes of patients with peripheral T-cell lymphoma, anaplastic large cell lymphoma and angioimmunoblastic T-cell lymphoma who received MAC versus RIC/NMA conditioning regimens prior to allo-HCT

	MAC (n = 258)		RIC/NMA (n = 545)		
Outcomes	***n***	**Probability (95% CI)**	***n***	**Probability (95% CI)**	***p***
Neutrophil recovery	258		541		
30-day		95 (92–97)		97 (95–98)	0.34
Platelet recovery	250		535		
100-day		87 (83–91)		94 (91–96)	0.005
Grade 2–4 acute GVHD	245		510		
180-day		41 (35–48)		36 (32–40)	0.16
Grade 3–4 acute GVHD	245		510		
180-day		18 (14–23)		13 (10–16)	0.08
Chronic GVHD	244		520		
1-year		41 (35–47)		43.9 (40–48)	0.42
2-year		50 (44–57)		51.9 (47–56)	0.70
NRM	256		540		
100-day		11 (8–16)		7 (5–9)	0.04
1-year		17 (13–22)		12 (10–15)	0.09
3-year		20 (16–26)		19 (16–23)	0.73
5-year		24 (19–30)		23 (19–27)	0.76
Progression/relapse	256		540		
1-year		27 (22–33)		28 (24–31)	0.91
3-year		30 (24–36)		31 (27–35)	0.69
5-year		31 (25–37)		31 (28–36)	0.93
PFS	256		540		
1-year		56 (50–62)		60 (56–64)	0.26
3-year		50 (44–56)		50 (45–54)	0.93
5-year		45 (39–52)		46 (41–50)	0.86
Overall survival	258		545		
1-year		71 (65–76)		77 (73–80)	0.09
3-year		61 (55–67)		64 (59–68)	0.52
5-year		57 (51–63)		59 (54–63)	0.64

Abbreviations: GVHD, graft-versus-host disease; MAC, myeloablative conditioning; NMA, non-myeloablative; NRM, non-relapse mortality; PFS, progression-free survival; RIC, reduced intensity conditioning.

The 5-year PFS of patients receiving MAC and RIC/NMA was 45% and 46%, respectively (p = 0.86; Table 2). The respective figures for the chemoresistant subgroup were 32% and 35% (Table 3). On multivariate analysis, the risk of therapy failure (inverse of PFS) was not significantly different following RIC/NMA relative to MAC (HR = 1.14; 95% CI = 0.92–1.41, p = 0.23; Table 4).

RIC *versus* NMA regimens

There was no difference in the survival outcomes of patients receiving RIC *versus* NMA conditioning regimens. The 5-year NRM, relapse, PFS and OS of patients receiving RIC *versus* NMA conditioning regimens was 23% vs 22%; 31% vs 34%; 46% vs 44% and 59% vs 58%, respectively (all p-values non-significant).

Haematopoietic recovery

The cumulative incidence of neutrophil recovery at day 30 was not significantly different between the RIC/NMA cohort (97%) and the MAC cohort (95%; p = 0.34; Table 2). The cumulative incidence of platelet recovery at day 100 was significantly higher in the RIC/NMA cohort at 94% compared to 87% in the MAC cohort (p = 0.005).

Acute and chronic GVHD

On univariate analysis, the day 180 cumulative incidence of grade 3–4 acute GVHD following MAC and RIC was 18% and 13%, respectively (p = 0.08, Table 2; Figure 2). On multivariate analysis, relative to MAC, RIC/NMA was associated with a significantly lower risk of grade 3–4 acute GVHD

TABLE 3 Subgroup univariate outcomes: chemoresistant patients

	MAC ($n = 55$)		NMA/RIC ($n = 70$)		
Outcomes	***n***	**Probability (95% CI)**	***n***	**Probability (95% CI)**	***p***
NRM	55		70		0.47
100-day		11 (4–21)		14 (7–24)	0.57
1-year		14 (7–25)		17 (9–27)	0.69
3-year		16 (8–28)		19 (11–29)	0.72
5-year		19 (9–31)		25 (15–37)	0.42
Progression/relapse	55		70		0.56
1-year		42 (29–55)		40 (29–52)	0.88
3-year		44 (31–57)		40 (29–52)	0.72
5-year		49 (35–63)		40 (29–52)	0.36
PFS	55		70		0.98
1-year		44 (31–57)		43 (31–54)	0.89
3-year		40 (27–53)		41 (29–52)	0.94
5-year		32 (20–46)		35 (23–46)	0.81
Overall survival	55		70		0.74
1-year		66 (53–77)		65 (54–76)	1.00
3-year		62 (48–74)		55 (43–67)	0.48
5-year		55 (41–68)		49 (37–62)	0.55

Abbreviations: MAC, myeloablative conditioning; NMA, non-myeloablative; NRM, non-relapse mortality; PFS, progression-free survival; RIC, reduced intensity conditioning.

(HR = 0.67; 95% CI = 0.46–0.99, $p = 0.04$; Table 4). The 2-year cumulative incidence of chronic GVHD following MAC and RIC was 50% and 51.9%, respectively ($p = 0.70$, Table 2). On multivariate analysis, the risk of chronic GVHD was not significantly different following RIC/NMA compared to MAC (HR = 0.98; 95% CI = 0.79–1.21, $p = 0.83$; Table 4).

Propensity-score-matched subset

Multivariate analysis on a propensity-score-matched subset (Table S1) showed results concordant with multivariate analysis in the overall study population, with no statistically significant differences between the MAC and RIC/NMA cohorts in terms of chronic GVHD, NRM, relapse risk, survival outcomes, and lower grade 3–4 acute GVHD risk among the RIC/NMA recipients (Table 5).

Outcomes of patients in complete or partial remission at the time of allo-HCT are shown in Table S3. Multivariate analysis restricted to patients ≤50 years of age (Table S4) showed results in line with overall study population.

DISCUSSION

In this large registry analysis, we evaluated the impact of conditioning regimen intensity on the outcomes of 803 patients with mature nodal T-cell lymphomas undergoing an allo-HCT in 122 CIBMTR reporting transplant centres. We found no significant difference with regard to OS, PFS and cumulative incidences of NRM and relapse among patients receiving MAC or RIC/NMA regimens. There was, however, a significant reduction in the risk of grade 3–4 acute GVHD in patients who received RIC/NMA compared to MAC regimens.

There is a paucity of data comparing MAC *versus* RIC/NMA in patients with T-cell NHL. In a prior, smaller CIBMTR study (1996–2006; allo-HCT $n = 126$),[6] where 59 patients received MAC and 36 RIC/NMA regimens, disease

TABLE 4 Multivariate analysis of patients with PTCL, ALCL and AITL patients receiving allo-HCT during 2008–2019

	n	**HR (95% CI)**	***P***	**Overall *P***
Grade 2–4 acute GVHD				
MAC	245	1		0.09
NMA/RIC	510	0.81 (0.64–1.03)	0.09	
Grade 3–4 acute GVHD				
MAC	245	1		0.04
NMA/RIC	510	0.67 (0.46–0.99)	0.04	
Grade 3–4 acute GHVD adjusted for significant covariate: donor type				
Chronic GVHD				
MAC	244	1		0.83
NMA/RIC	520	0.98 (0.79–1.21)	0.83	
Chronic GVHD adjusted for significant covariates: donor type, time from diagnosis to transplant				
Non-relapse mortality				
MAC	256	1		0.34
NMA/RIC	540	0.85 (0.61–1.19)	0.34	
NRM adjusted for significant covariates: age, KPS, and year of transplant				
Progression/relapse				
MAC	256	1		0.07
NMA/RIC	540	1.29 (0.98–1.70)	0.07	
Progression/relapse adjusted for significant covariates: disease status, NHL histology, History of autologous transplant				
Progression free survival				
MAC	256	1		0.23
NMA/RIC	540	1.14 (0.92–1.41)	0.23	
Progression free survival adjusted for significant covariates: NHL histology disease status, history of autologous transplant, year of transplant				
Overall survival				
MAC	258	1		0.95
NMA/RIC	545	1.01 (0.79–1.29)	0.95	
Overall survival adjusted for significant covariates: KPS, history of autologous transplant, year of transplant				

Abbreviations: ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; GVHD, graft versus host disease; HR, hazard ratio; KPS, karnofsky performance score; MAC, myeloablative conditioning; NMA, non-myeloablative; NRM, non-relapse mortality; PTCL-NOS, peripheral T cell lymphoma- not other specified; RIC, reduced intensity conditioning.

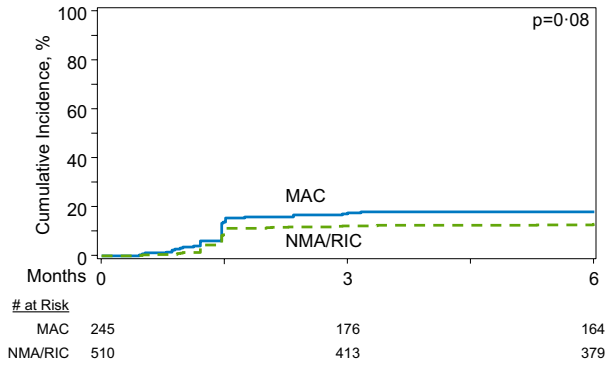

FIGURE 2 Cumulative incidence of grade 3–4 acute graft-versus-host disease GVHD in patients receiving myeloablative (MAC) and non-myeloablative (NMA)/reduced-intensity conditioning (RIC) regimens [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 5 Multivariate analysis of outcomes: propensity-score matched data

	n	HR (95% CI)	*p* (overall)
Grade 2–4 acute GVHD			
MAC	182	1	0.37
RIC/NMA	156	0.86 (0.62–1.20)	
Grade 3–4 acute GVHD			
MAC	182	1	0.02
RIC/NMA	156	0.49 (0.26–0.91)	
Chronic GVHD			
MAC	190	1	0.45
RIC/NMA	166	1.12 (0.83–1.51)	
Non-relapse mortality			
MAC	190	1	0.79
RIC/NMA	166	0.94 (0.58–1.50)	
Progression/relapse			
MAC	190	1	0.48
RIC/NMA	166	1.14 (0.80–1.62)	
Progression free survival			
MAC	190	1	0.87
RIC/NMA	166	1.02 (0.77–1.35)	
Overall survival			
MAC	192	1	0.96
RIC/NMA	168	0.99 (0.72–1.36)	

Abbreviations: GVHD, graft-versus-host disease; HR, hazard ratio; MAC, myeloablative conditioning; NMA, non-myeloablative; NRM, non-relapse mortality; RIC, reduced intensity conditioning.

relapse was more frequent with RIC (3-year relapse MAC vs RIC = 32% vs 40%), while NRM was higher with MAC (3-year NRM: MAC vs RIC = 32% vs 27%), with OS favouring lower-intensity approaches (3-year OS: MAC vs RIC = 39% vs 52%). A recent retrospective study from Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) included 285 patients with T-cell NHL transplanted during 2006–2014.[23] Of these patients, 62% received RIC regimen while 38% received MAC. The 2-year relapse rate was 22% in the MAC group and 17% in the RIC group. The 2-year NRM in similar order was 21% and 24%, respectively. In addition, no significant difference between MAC and RIC for OS (p = 0.5) or event-free survival (p = 0.55) was seen. Of note, in addition to common nodal variants of T-cell NHL (i.e. PTCL-NOS, AITL, ALCL), the French analysis also included a sizeable subset of rare T-cell and NK-cell subtypes. In a more homogenous cohort, our analysis reports concordant finding, but in addition shows a higher risk of severe acute GVHD following MAC regimens.

Higher intensity conditioning regimens can, in theory, provide post-transplant disease control among refractory patients, to allow time for graft-versus-lymphoma effects to develop. An important observation from our current analysis is that, even among the subset of patients with refractory disease at allo-HCT (n = 125; Table 3), MAC regimens provided no significant benefit in terms of reducing the risk of disease relapse, PFS or OS. These observations are in line with earlier data for refractory aggressive B-cell NHL, where MAC has not been conclusively shown to provide better disease control.[19,35–37] In addition, a prior registry study limited to AITL patients undergoing allo-HCT did not suggest a benefit of MAC over RIC/NMA approaches.[38] The current analysis (2008–2019; n = 803; upper age limit 65 years; limited to PTCL-NOS; AITL, ALCL), allowed us to also interpret modern allo-HCT outcomes in T-cell NHL, relative to historical data reported by the earlier CIBMTR study[6] (1996–2006; n = 126; upper age limit 60 years; limited to PTCL-NOS; AITL, ALCL). These two analyses suggest that among patients receiving MAC regimens, the 3-year NRM rates have improved from 32% to 20% and 3-year OS from 39% to 61%. Among patients receiving RIC/NMA regimens, the 3-year NRM has improved from 27% to 19%, and 3-year OS from 52% to 64%.

A recent registry analysis from the Spanish GETH/GELTAMO Centres[39] evaluated 201 patients with mature T and natural killer (NK) T-cell neoplasia who received allo-HCT in Spanish centres over the course of 25 years (1995–2018). Out of 201 patients in their study, 28 were diagnosed with PTCL-NOS, 43 with AITL and 23 with ALCL. The majority of patients in their study had undergone peripheral blood allo-HCT, as with our analysis. Approximately 74% received RIC and 26% had received MAC regimens. Post-transplant cyclophosphamide was used as GVHD prophylaxis in 22.4% of cases. The 2-year OS and PFS were 65.5% and 58.2% respectively, largely similar to our findings. They found a significant difference in HR for the type of conditioning regimen employed (RIC vs MAC; HR 1.8; 95% CI, 1.2–2.8; p = 0.008) on univariate Cox analysis for PFS, which was not noted in our cohort.

Our analysis has several important limitations. We excluded patients older than 65 years of age to focus on an age range where both low and high intensity conditioning approaches could be considered by transplant physicians. The cohort comparisons based on registry data is one of the

major limitations of the study. These data cannot account for the reasons a particular conditioning approach was selected for a given patient. We used propensity-score matching to balance the distribution of important covariates between the cohorts and reduce the effects of confounding variables. Differences in practice across various centres can impact survival outcomes, therefore, we examined centre effect and found none in this particular analysis. Our study is underpowered to detect small effect sizes. Histological diagnosis was not centrally reviewed for this study. Patients included in this study had the three most common mature T-cell NHL histologies. There was a lack of interaction between main effect and the three subtypes, arguing against a differential effect of various conditioning regimens relative to NHL histologies.

In this large, registry analysis of PTCL-NOS, ALCL and AITL subtypes of NHL comparing various conditioning regimen intensity, we found no significant difference in survival outcomes of patients who received RIC/NMA or MAC regimens, although the latter was associated with a higher risk of grade 3–4 acute GVHD. No advantage of MAC platforms was seen, even in the subset of patients with refractory disease at the time of allo-HCT.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

MS and MH: conception and design; YC and MH: collection and assembly of data;. YC and KWA: data analysis; All authors: interpretation of data; MS and MH: first draft of manuscript; All authors: initial revision of manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

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