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Impact of reduced-intensity conditioning regimens on outcomes in diffuse large B-cell lymphoma undergoing allogeneic transplantation

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Abstract

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BACKGROUND: Reduced-intensity conditioning (RIC) regimens are frequently used for allogeneic hematopoietic cell transplantation (allo-HCT) in diffuse large B-cell lymphoma (DLBCL). However, the RIC regimen with the best risk/benefit profile for allo-HCT in DLBCL is not known. This is particularly important, as patients with DLBCL undergoing allo-HCT in the future would be enriched for those whose lymphoma has failed chimeric antigen receptor T-cell (CAR-T) therapy or other novel immunotherapies, with potentially more advanced disease and suboptimal performance scores. Using the CIBMTR database, we report the outcomes of the three most commonly used allo-HCT RIC regimens in DLBCL.

METHODS: 562 adult DLBCL patients in the CIBMTR registry undergoing allo-HCT using matched related or unrelated donors, between 2008–2016 were included in the analysis. Patients received one of the three RIC regimens: fludarabine/i.v. busulfan (~6·4mg/kg) (Flu/Bu), fludarabine/melphalan (140mg/m^2) (Flu/Mel140) or BCNU/etoposide/cytarabine/melphalan (BEAM).

FINDINGS: The study cohort was divided into three groups: Flu/Bu (n=151), Flu/Mel140 (n=296) and BEAM (n=115). Relative to Flu/Bu, the Flu/Mel140 (HR=2.33, 95%CI=1.42–3.82; p=0.001) and BEAM (HR=2.54, 95%CI=1.34–4.80; p=0.004) regimens were associated with a higher non-relapse mortality (NRM) risk. Although the risk of relapse with Flu/Mel140 was lower compared to Flu/Bu (HR=0.70, 95%CI=0.52–0.95; p=0.02), this did not translate in an improvement in progression-free (HR=1.04) or overall survival (HR=1.30). There was a significantly higher risk of grade 3–4 acute graft-versus-host disease with BEAM (HR=2.19, 95%CI=1.10–4.35; p=0.03) compared to Flu/Bu. In the chemosensitive subset, multivariate analysis showed a significantly higher mortality risk with Flu/Mel140 (HR=1.48, 95%CI=1.07–2.04, p=0.02) relative to Flu/Bu conditioning.

CONCLUSIONS: In the largest analysis comparing the impact of various RIC conditioning regimens on the survival of DLBCL patients undergoing allo-HCT, our results suggest that Flu/Bu is a better RIC choice in less fit or heavily pretreated patients due to lowest NRM risk.

Keywords

Reduced-intensity conditioning; diffuse large B-cell lymphoma; allogeneic hematopoietic cell transplant; survival

INTRODUCTION

Reduced-intensity conditioning (RIC) regimens account for the vast majority of allogeneic hematopoietic cell transplants (allo-HCT) performed for lymphomas in the U.S (1–8). Although the RIC regimens are generally associated with lower non-relapse mortality (NRM) rates relative to myeloablative conditioning (MAC) regimens, disease relapse remains the most common cause of treatment failure in lymphoma patients undergoing allo-HCT (9–12). However, even among regimens generally considered to be “reduced-intensity,” there is a spectrum of dose-intensities varying from regimens at the lower end of intensity spectrum (relying predominately on alloreactive immunological effects to eradicate disease) to higher-intensity options (that depend on both cytoreductive and immunological mechanisms to control disease). A recent Center for International Blood & Marrow Transplant Research (CIBMTR) analysis compared commonly used RIC regimens in non-

Hodgkin lymphomas (NHL) (13). The study compared fludarabine/I.V. busulfan (~6.4mg/kg) (Flu/Bu), fludarabine/melphalan (140mg/m^2) (Flu/Mel140), fludarabine/cyclophosphamide (Flu/Cy) and Flu/Cy+2Gy total body irradiation (Flu/Cy/2GyTBI) and found that Flu/Mel140 was associated with high NRM and inferior overall survival (OS) relative to the other RIC regimens (13). However, the study was not limited to DLBCL and included all NHL histologies. More importantly, BEAM (BCNU/etoposide/cytarabine/melphalan [BEAM]) a commonly used regimen in DLBCL, was not included in that analysis. In the future, DLBCL patients undergoing allo-HCT will be enriched for patients who have progressed despite chimeric antigen receptor T-cell (CAR-T) therapy or other novel immunotherapies, with potentially more advanced disease, compromised organ function, and suboptimal performance status. Defining a RIC platform with the best risk/benefit ratio is thus increasingly important.

We report here a registry analysis, comparing the outcomes of the three most commonly used RIC regimens in DLBCL patients undergoing allo-HCT in the United States, using the observational database of CIBMTR.

METHODS

Data source

The CIBMTR is a working group of more than 380 transplantation centers worldwide that contribute detailed data on HCT to a statistical center at the Medical College of Wisconsin (MCW). Participating centers are required to report all transplantations consecutively and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. The MCW and National Marrow Donor Program, Institutional Review Boards approved this study.

The CIBMTR collects data at two levels: Transplant Essential Data (TED) and Comprehensive Report Form (CRF) data. TED-data includes disease type, age, gender, pre-HCT disease stage and chemotherapy-responsiveness, date of diagnosis, graft type, conditioning regimen, post-transplant disease progression and survival, development of new malignancy, and cause of death. All CIBMTR centers contribute TED-data. More detailed disease and pre- and post-transplant clinical information are collected on a subset of registered patients selected for CRF data by a weighted randomization scheme. TED- and CRF-level data are collected pre-transplant, 100-days, and six months post-HCT and annually thereafter or until death. Data for the current analysis were retrieved from CIBMTR (TED and CRF) report forms.

Patients

Included in this analysis are adult (≥18 years) DLBCL patients undergoing their first RIC allo-HCT between 2008 and 2016. Eligible donors included either HLA-identical sibling donors or unrelated donors (URD) matched at the allele-level at HLA-A, HLA-B, HLA-C,

and HLA-DRB1. Graft source was limited to mobilized peripheral blood stem cells. Graft-versus-host disease (GVHD) prophylaxis was limited to calcineurin inhibitor (CNI)-based approaches. The study cohort was divided into three most commonly used RIC regimens (Flu/Bu, Flu/Mel140, and BEAM) for DLBCL in the United States. Patients in the Flu/Bu cohort received a uniform intravenous busulfan dose of ~6.4mg/m^2. The Flu/Mel140 cohort was limited to a melphalan dose of 140mg/m^2. Allo-HCT recipients could have received *in vivo* T-cell depletion with antithymocyte globulin (ATG) or alemtuzumab. Patients receiving *ex vivo* graft manipulation were excluded. Patients receiving bone marrow grafts (n=28) were excluded due to small numbers.

Definitions and Study Endpoints

The intensity of allo-HCT conditioning regimens was determined using the existing consensus criteria (14). Disease response at the time of HCT was assessed using the International Working Group criteria in use during the era of this analysis (15).

The primary endpoint was OS; death from any cause was considered an event, and surviving patients were censored at last follow up. Secondary endpoints included cumulative incidence of acute GVHD, chronic GVHD, NRM, progression/relapse, progression-free survival (PFS), and time to neutrophil and platelet recovery. NRM was defined as death without evidence of lymphoma progression/relapse; relapse was considered a competing risk. Progression/relapse was defined as progressive lymphoma after HCT or lymphoma recurrence after a complete remission; NRM was considered a competing risk. For 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 last follow-up. Acute GVHD and chronic GVHD were graded using established clinical criteria (16, 17). Neutrophil recovery was defined as the first of 3 successive days with an absolute neutrophil count 500/μL after post-transplant 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. For GVHD and hematopoietic recovery, death without the event was considered a competing risk.

Statistical Analysis

The study compared three RIC/NMA conditioning platforms: Flu/Bu vs Flu/Mel140 vs BEAM cohorts. Associations among patient-, disease-, and transplant-related variables and outcomes of interest were evaluated using Cox proportional hazards regression for PFS, and OS, the proportional cause-specific hazards model for chronic GVHD, relapse, NRM, and logistic regression for acute GVHD. The forward stepwise selection was used to identify covariates that influenced outcomes. Covariates with a $P<0.05$ were considered significant. The proportional hazards assumption for Cox regression and the cause-specific hazards model was tested by evaluating time-varying effects for each risk factor and each outcome. Variables that violated the proportional hazards assumption were added using the piecewise proportional hazards models. Interactions between the main effect and significant covariates were examined. Center effect was tested using the score test for relapse, NRM, PFS, and OS and the generalized linear mixed model for acute GVHD (18). The variables considered in multivariate analysis are shown in (Table S1). Adjusted PFS and OS, and adjusted

cumulative incidence rates for relapse and NRM were created based on the final model (19, 20). The cumulative incidence was calculated for hematopoietic recovery and GVHD. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline characteristics

The overall patient population (N=562) was divided into three cohorts; 151 received Flu/Bu, 296 received Flu/Mel140, and 115 received BEAM. The baseline patient-, disease-, and transplantation-related characteristics are shown in Table 1. There were no significant differences between the three cohorts in terms of patient's gender, HCT-comorbidity index (HCT-CI), donor type, donor/recipient sex match, donor/recipient CMV match, and prior median lines of chemotherapy before allo-HCT. Significantly more patients in the Flu/Bu (45%) cohort were ≥ 60 years of age compared to Flu/Mel140 (33%) or BEAM cohorts (20%; P=0.004). There were significantly more patients in the Flu/Bu and Flu/Mel140 cohorts who had a Karnofsky performance score (KPS) of ≥ 90, chemosensitive disease at allo-HCT, and a history of prior autologous HCT (auto-HCT) relative to the BEAM cohort (Table 1). ATG/alemtuzumab use in conditioning was more frequently used in Flu/Bu (35%) and BEAM (38%) cohorts, while rituximab with conditioning was predominantly used in the BEAM (49%) cohort. Patients in the BEAM cohort had a significantly shorter time from diagnosis to transplant compared with Flu/Bu and Flu/Mel140 groups. Among total transplants reported each year, the proportion of patients receiving Flu/Mel140 increased from 2012 onward (Table 1).

Hematopoietic recovery

The cumulative incidence of neutrophil recovery at day 28 was 99% (95%CI=96–100) in the Flu/Bu group compared to 97% (95%CI=95–99) and 94% (95%CI=89–98) in the Flu/Mel140 and BEAM cohorts respectively (p=0.17; Table 2). The cumulative incidence of platelet recovery at day 100 was significantly higher in Flu/Bu group [99% (95%CI=97–100)] compared to Flu/Mel140 [89% (95%CI=85–93)] and BEAM groups [89% (95%CI=82–94)] (p<0.001; Table 2).

Acute and chronic GVHD

The cumulative incidence of grade II-IV acute GVHD at day 180 (Table 2) was 45% (95%CI=37–53) for Flu/Bu, 38% (95%CI=33–44) for Flu/Mel140 and 44% (95%CI=35–53) for BEAM (p=0.38). The corresponding rates of grades III-IV acute GVHD in similar order, were 13% (95%CI=8–19), 13% (95%CI=9–17) and 22% (95%CI=15–30), respectively, (p=0.10). After adjusting for GVHD prophylaxis and donor type, the multivariate analysis (Table 3) showed a significantly higher risk of grade III-IV acute GVHD with BEAM conditioning (HR=2.2, 95%CI=1.10–4.35, p=0.03) relative to the Flu/Bu cohort (Table 3).

The cumulative incidence of chronic GVHD at 1-year (Table 2) was 38% (95%CI=30–46) for Flu/Bu, 42% (95%CI=36–48) for Flu/Mel140 and 31% (95%CI=23–40) for BEAM (p=0.16). After adjusting for GVHD prophylaxis and ATG/alemtuzumab use in conditioning, the multivariate analysis (Table 3) showed no significant difference in the risk

of chronic GVHD in patients who received Flu/Mel140 (HR=1·09) or BEAM (HR=0·84) relative to Flu/Bu (Figure 1a).

NRM and relapse

The 4-year adjusted cumulative incidence of NRM for Flu/Bu, Flu/Mel140, and BEAM cohorts was 16%, 29%, and 25%, respectively (p=0.02, Table 2). After adjusting for age, HCT-CI, history of prior autologous HCT, remission status at allo-HCT and GVHD prophylaxis in multivariate analysis, Flu/Mel140 (HR=2.33, 95%CI=1.42–3.82, p=0.001) and BEAM (HR=2.54, 95%CI=1.34–4.80, p=0.004) conditioning regimens were associated with a significantly higher risk of NRM when compared to Flu/Bu (Table 3, Figure 1b).

The adjusted cumulative incidence of relapse/progression at 4-years for Flu/Bu, Flu/Mel140 and BEAM cohorts was 54%, 40%, and 42%, respectively (p=0.02, Table 2). After adjusting for age and remission status at allo-HCT, the multivariate analysis showed that the Flu/Mel140 cohort had a significantly lower risk of relapse/progression compared with the Flu/Bu cohort (HR=0.70, 95%CI=0.52–0.95, p=0.02) (Table 3, Figure 1c). Relative to Flu/Bu, the BEAM cohort was not associated with a significantly lower risk of relapse/progression (Table 3).

Progression-free survival

The 4-year adjusted PFS for the Flu/Bu, Flu/Mel140, and BEAM cohorts was 33%, 33%, and 34%, (p=0.95, Table 2). After adjusting for remission status at allo-HCT and GVHD prophylaxis, the multivariate analysis did not show a significantly improved PFS with Flu/Mel140 (HR=1.04) or BEAM (HR=1.07) relative to Flu/Bu conditioning (overall p=0.92; Table 3, Figure 1d).

Overall survival

The 4-year adjusted OS for the Flu/Bu, Flu/Mel140 and BEAM cohorts was 50%, 42%, and 41%, (p=0.31, Table 2). However, after adjusting for KPS, remission status at allo-HCT and history of prior autologous HCT, multivariate analysis did not show a significantly higher mortality risk with Flu/Mel140 (HR=1.30) or BEAM (HR=1.44) relative to Flu/Bu conditioning (overall p=0.11; Table 3, Figure 1e).

There was no center effect noted for NRM (p=0.80), relapse/progression (p=0.20), PFS (p=0.52) or OS (p=0.54).

Outcomes of chemosensitive patients at allo-HCT

The proportion of patients in complete or partial remission at the time of allo-HCT was higher in the Flu/Bu (85%) and Flu/Mel140 (85%) cohorts compared with the BEAM cohort (63%; p<0.01). We thus performed a subgroup analysis restricted to patients with chemosensitive disease. In the chemosensitive subset, after adjusting for significant covariates in the multivariate analysis, Flu/Mel140 (HR=2.19, 95%CI=1.26–3.81, p=0.005) and BEAM (HR=2.27, 95%CI=1.07–4.83, p=0.03) conditioning regimens remained associated with a significantly higher risk of NRM versus Flu/Bu (Table 4, Figure 2a). In line with the overall analysis (Table 3), the Flu/Mel140 cohort had a significantly lower risk

of relapse/progression compared with Flu/Bu cohort (HR=0.69, 95%CI=0.49–0.96, p=0.03) (Table 4, Figure 1b). Relative to Flu/Bu, the BEAM cohort was not associated with a significantly lower risk of relapse/progression. Neither the Flu/Mel140 (HR=1.02) nor BEAM (HR=1.02) cohort was associated with significantly improved PFS relative to the Flu/Bu cohort after adjusting for the significant covariates (overall p=0.99; Table 4, Figure 1c). After adjusting for KPS, HCT-CI, remission status at allo-HCT, and history of prior autologous HCT, multivariate analysis showed a significantly higher mortality risk with Flu/Mel140 (HR=1.48, 95%CI=1.07–2.04, p=0.02) relative to Flu/Bu conditioning. The mortality risk was not significantly different with BEAM (HR=1.56, 95%CI=0.98–2.46, p=0.059) compared to Flu/Bu conditioning (Table 4, Figure 1d). The adjusted NRM, relapse/progression, PFS, and OS outcomes are provided in Table S2.

Outcomes of chemoresistant patients at allo-HCT

The proportion of patients with chemoresistant disease at the time of allo-HCT was higher in the BEAM cohort (36%) compared with Flu/Bu (11%) and Flu/Mel140 (14%) cohorts (p<0.001). In the chemoresistant subset, after adjusting for significant covariates in the multivariate analysis, BEAM (HR=9.65, 95%CI=1.93–48.21, p=0.006) conditioning regimen was associated with a significantly higher risk of NRM relative to Flu/Bu (Table S3). The Flu/Mel140 (HR=0.61) and BEAM (HR=0.59) cohorts were not associated with a significantly lower risk of relapse/progression relative to Flu/Bu cohort (overall p=0.41; Table S3). Finally, on multivariate analysis, after adjusting for significant covariates, neither of the RIC regimens (Flu/Mel 140 or BEAM) were associated with an improvement in PFS (overall p=0.80) or OS (overall p=0.35) compared with Flu/Bu cohort (Table S3).

Causes of death

The most common cause of death in all the cohorts was recurrent/progressive lymphoma; 57% (n = 72) with Flu/Bu, 41% (n=158) with Flu/Mel140, and 51% (n=34) with BEAM. Infectious complications and GVHD were other common causes of death (Table 5).

DISCUSSION

Prospective randomized controlled studies comparing outcomes among various RIC regimens in DLBCL have not been performed. Here, we report the largest registry analysis of DLBCL patients undergoing RIC allo-HCT with either Flu/Bu, Flu/Mel140 or BEAM conditioning, and make several important observations. First, the probability of platelet recovery was lower following more intense RIC (i.e. Flu/Mel140 and BEAM) relative to Flu/Bu. Second, BEAM conditioning was associated with a significantly higher risk of grade 3–4 acute GVHD. Third, BEAM and Flu/Mel140 were associated with a significantly higher NRM risk relative to Flu/Bu conditioning. Fourth, the risk of relapse was significantly lower following Flu/Mel140 conditioning but did not translate into survival benefit due to higher NRM. Lastly, none of these regimens provided a PFS or OS benefit in the overall study population, but in chemosensitive patients, Flu/Bu was associated with significantly reduced mortality risk.

Unlike myeloid disorders, where the benefit of conditioning intensity in younger and fit patients is well established (21, 22), in lymphomas, the benefit for higher intensity regimens remains debatable. Whether MAC offers an advantage over RIC options in NHL patients undergoing allo-HCT has been examined. A CIBMTR analysis for patients with chemosensitive DLBCL showed no difference in 5-year PFS and OS between MAC and RIC/NMA regimens (5, 11). Similarly, even in patients with chemorefractory DLBCL, the intensity of conditioning regimens (MAC vs. RIC) does not appear to impact survival outcomes (5, 12, 23). Although BEAM is considered as a MAC regimen by the European Society for Blood and Marrow Transplantation (EBMT), it is categorized as RIC by CIBMTR based on the consensus criteria (14). While prior CIBMTR studies have reported the outcomes of MAC vs RIC/NMA, there are limited comparative data published on the relative efficacy and toxicity of the individual RIC regimens commonly used in DLBCL. A multicenter retrospective study (n=136) compared outcomes of two RIC regimens (Flu/Mel with Flu/Bu) in lymphomas and showed that Flu/Bu was associated with a significantly lower risk of acute GVHD and NRM and improved OS relative to Flu/Mel (24). However, the study was limited by a small sample size of aggressive NHLs (n=65) and did not include BEAM as a conditioning regimen. A recent CIBMTR study reported the outcome of four RIC/NMA regimens: Flu/Bu, Flu/Mel140, Flu/Cy, and Flu/Cy/2GyTBI, in NHL patients (13). In that study, relative to Flu/Bu, Flu/Mel140 was associated with a significantly higher risk of NRM translating to inferior OS (HR=1.34, 95%CI=1.13–1.59; $p<0.001$) (13). However, that study included all NHL histologies (B-cell NHL including aggressive and indolent NHLs and T-cell NHL) and did not include BEAM conditioning, a commonly used RIC regimen in DLBCL. In the current study, we compared the three commonly used RIC regimens (Flu/Bu, Flu/Mel140 and BEAM) in DLBCL and found that Flu/Mel140 and BEAM were associated with a significantly higher risk of NRM compared to Flu/Bu. In line with the previous study, the risk of relapse was significantly lower with Flu/Mel140; however, this did not translate into survival benefit in the current study.

A recent single-center retrospective study (n=70) evaluated the outcomes of R-BEAM (n=47) versus other RIC regimens (n=23; Flu/Bu/TBI +/− rituximab and Flu/Mel/TBI +/− rituximab) in DLBCL patients (25). In the study, the cumulative incidence of grade 3–4 acute GVHD was significantly higher in the R-BEAM group relative to the RIC cohort, however, there was no difference in the cumulative incidence of relapse, NRM, or survival outcomes between the two cohorts. Relative to R-BEAM, the other regimens in the RIC cohort had a similar 3-year risk of relapse (25.5% versus 17.4%), NRM (39.7% versus 39.1%), and OS (34.4% versus 43.5%). One of the major limitations of the study was the small sample size that precluded robust multivariable modeling. Another important drawback was the imbalance between the groups, especially the RIC cohort that was predominantly comprised of the Flu/Bu/TBI +/− rituximab. Of note, the addition of TBI to the RIC regimens in the study likely increased the toxicity (8, 26).

Historically, DLBCL was the most common indication for allo-HCT in NHL, but with newly available options, these numbers are decreasing. The advent of CD19 CAR T-cell therapy has revolutionized the treatment of relapsed/refractory DLBCL patients with good response rates (27–29). Bispecific antibodies have also shown promising activity in multiply relapsed DLBCL patients including those with do not respond or progress following CAR-T cell

therapy (30). Thus, in the future, patients undergoing allo-HCT will be enriched for those who are potentially heavily pretreated. Hence, defining a RIC platform with the best risk/benefit ratio is increasingly important in current practice. Our results suggest that Flu/Bu is a better RIC platform in less fit or heavily pretreated patients due to the lowest NRM risk, and reduced risk of mortality (particularly in patients with chemosensitive disease).

We would like to acknowledge that the consensus criteria allows a wide array of regimens to be classified as RIC, with some at the lower spectrum of intensity (e.g. Flu/Bu and associated lower NRM risk), while others are at the high end of intensity spectrum (e.g. Flu/Mel140 and BEAM) with much higher NRM risk, in elderly DLBLC patients. Any observational study comparing different interventions is subject to the preferences of the treating centers/physicians owing to the complex criteria for selection of the conditioning regimen. However, we did not notice any center effect, in this analysis. We acknowledge that the patients in the BEAM cohort were probably enriched for those who were not candidates for auto-HCT, likely due to chemoresistance. To address this bias, we did a subgroup analysis of the three RIC regimens and evaluated the outcomes of the chemosensitive patients at allo-HCT. The results were generally in line with the main analysis except for significantly higher risk of mortality with Flu/Mel140. When restricting the analysis to patients with chemoresistant at allo-HCT, the BEAM cohort had a significantly higher risk for NRM relative to Flu/Bu, however, there was no survival (PFS or OS) benefit seen with any of the RIC regimens in this analysis. These results are in line with a previously published CIBMTR study that showed no survival benefit with higher conditioning regimen intensity in chemorefractory patients at allo-HCT (12). While it has been previously shown that the addition of rituximab to RIC regimens improved PFS (1), we cannot examine the effect of rituximab at conditioning in our study as only a few patients received rituximab at conditioning (n=90). More importantly, it was predominantly used with BEAM conditioning (n=56) thereby precluding additional analysis. The reason for more frequent use of rituximab with BEAM conditioning (compared with Flu/Bu and Flu/Mel140) in our study is not clear. While this is likely a reflection of center policies, it is plausible that the high percentage of chemoresistant patients in the BEAM cohort could have been the driving factor behind the addition of rituximab to BEAM. Lastly, as alemtuzumab-BEAM was shown to be toxic by other groups, we tried to evaluate the toxicity associated with this. However, only 13 patients in the current study received alemtuzumab-BEAM precluding any additional evaluation.

Our analysis is the largest comparative study evaluating outcomes of commonly used RIC regimens in DLBCL patients. Although Flu/Mel140 was associated with a significantly lower risk of relapse, this did not translate into superior survival due to significantly higher NRM. Similarly, BEAM was associated with a significantly higher risk of NRM. Although all the regimens evaluated provided comparable survival outcomes in the overall patient population, Flu/Bu provided superior survival relative to Flu/Mel140 in chemosensitive patients. In the absence of prospective randomized studies in the field, our results suggest that Flu/Bu is a better RIC platform in less fit or heavily pretreated patients due to the lowest NRM risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

1. Reduced-intensity conditioning regimen with the best risk/benefit profile for allo-HCT in DLBCL is not known. This is important, as patients with DLBCL undergoing allo-HCT in the future would be enriched for those whose lymphoma has failed chimeric antigen receptor T-cell therapy or other novel immunotherapies, with potentially more advanced disease and suboptimal performance scores.
2. Our results suggest that Flu/Bu is a better RIC choice in less fit or heavily pretreated patients due to the lowest NRM risk.

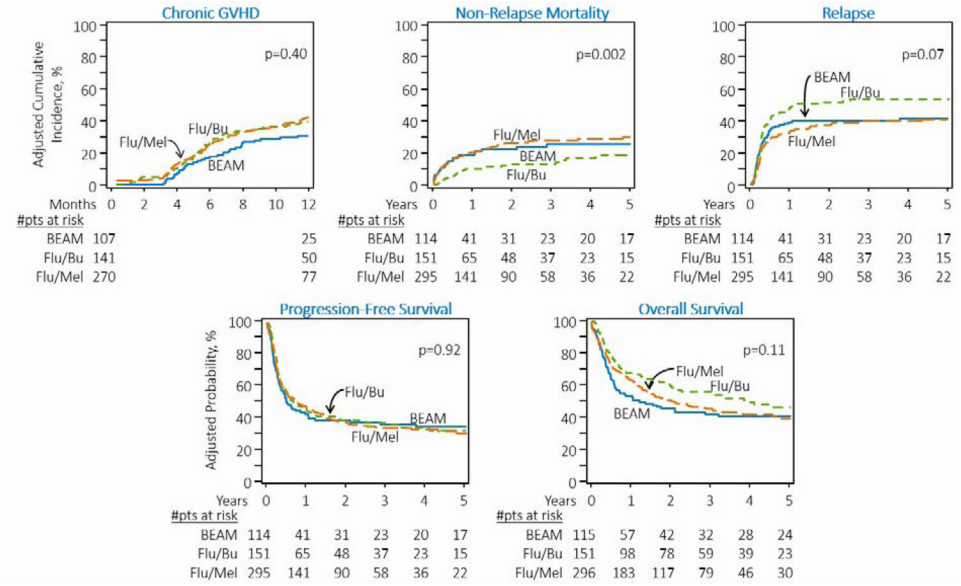

Figure 1:

Adjusted transplantation outcomes of DLBCL patients receiving RIC regimens. A) Cumulative incidence of chronic graft-versus-host-disease. B) Cumulative incidence of non-relapse mortality. C) Cumulative incidence of lymphoma relapse/progression. D) Progression-free survival. E) Overall survival

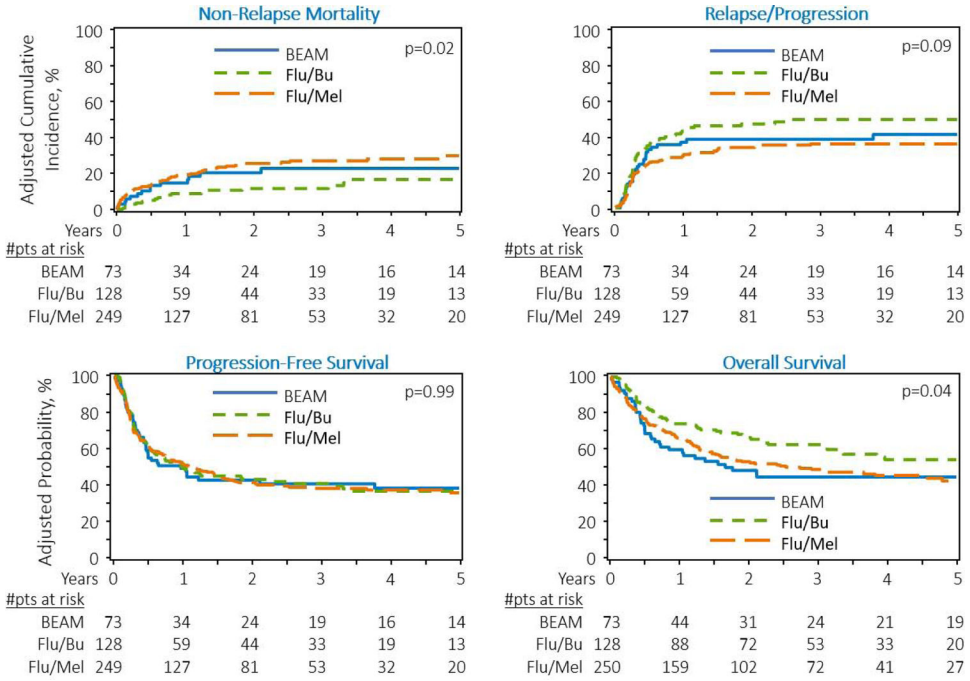

Figure 2:

Adjusted transplantation outcomes of chemosensitive DLBCL patients receiving RIC regimens. A) Cumulative incidence of non-relapse mortality. B) Cumulative incidence of lymphoma relapse/progression. C) Progression-free survival. D) Overall survival

Table 1.

Baseline characteristics of DLBCL patients receiving RIC/NMA conditioning regimens followed by allo-HCT between 2008–2016

	Flu/Bu N (%)	Flu/Mel 140 N (%)	BEAM N (%)	p-value
Number of patients	**151**	**296**	**115**	
Median patient age, years (range)	59 (25–72)	56 (22–73)	53 (22–69)	0.004
≥60	68 (45)	99 (33)	23 (20)	
Male sex	87 (58)	190 (64)	74 (64)	0.36
Karnofsky performance score ≥ 90	83 (55)	175 (59)	45 (39)	<0.001
Missing	1 (1)	6 (2)	10 (9)	
HCT-CI				0.06
0	34 (23)	98 (33)	41 (36)	
1–2	51 (34)	72 (24)	35 (30)	
≥3	64 (42)	118 (40)	35 (30)	
Missing	2 (1)	8 (3)	4 (4)	
Patient race				0.04
Caucasian	142 (94)	257 (87)	98 (85)	
Other	9 (6)	39 (13)	17 (15)	
Remission at HCT				<0.001
CR	68 (45)	126 (43)	37 (32)	
PR	60 (40)	124 (42)	36 (31)	
Resistant	16 (11)	42 (14)	41 (36)	
Untreated/Unknown	4 (3)	3 (1)	0	
Not reported	3 (2)	1 (0.3)	1 (1)	
History of prior auto-HCT	83 (55)	133 (45)	11 (10)	<0.001
Donor type				0.25
Matched related donor	70 (46)	153 (52)	65 (57)	
Matched unrelated donor	81 (54)	143 (48)	50 (43)	
Median time from diagnosis to HCT, months (range)	34 (3–340)	27 (<l-386)	14 (2–258)	<0.001
GVHD prophylaxis				<0.001
CNI + MMF+−other (s)	40 (26)	39 (13)	34 (30)	
CNI + MTX+−other (s)	96 (64)	176 (60)	62 (54)	
CNI + other (s)	15 (10)	81 (27)	19 (16)	
ATG/alemtuzumab use in conditioning	53 (35)	71 (24)	44 (38)	0.005
Rituximab use in conditioning	2 (1)	32 (11)	56 (49)	<0.001
Donor/recipient sex match				0.29
F-M	25 (17)	69 (23)	20 (17)	
Other combinations	126 (83)	227 (77)	94 (82)	
Missing	0	0	1 (1)	
Donor/recipient CMV match				0.93

	Flu/Bu N (%)	Flu/Mel 140 N (%)	BEAM N (%)	p-value
Donor-/recipient+	42 (28)	79 (27)	33 (29)	
Others	108 (71)	212 (71)	81 (70)	
Not reported	1 (1)	5 (2)	1 (1)	
Year of transplant				0.03
2008	12 (7.9)	12 (4.1)	12 (10.4)	
2009	14 (9.3)	29 (9.8)	14 (12.2)	
2010	8 (5.3)	33 (11.1)	11 (9.6)	
2011	14 (9.3)	23 (7.8)	13 (11.3)	
2012	22 (14.6)	31 (10.5)	11 (9.6)	
2013	29 (19.2)	36 (12.2)	18 (15.7)	
2014	24 (15.9)	40 (13.5)	10 (8.7)	
2015	13 (8.6)	45 (15.2)	17 (14.8)	
2016	15 (9.9)	47 (15.9)	9 (7.8)	
Median number of lines of chemotherapy (range)	2 (1–5)	3 (1–5)	3 (1–5)	0.37
Median follow-up of survivors (range), months	48 (4–100)	37 (2–101)	60 (3–96)	

Abbreviations: DLBCL- Diffuse large B-cell lymphoma; RIC/NMA- Reduced Intensity Conditioning/Non-myeloablative; allo-HCT- Allogeneic hematopoietic cell transplantation; Flu/Bu- Fludarabine/Busulfan; Flu/Mel- Fludarabine/Melphalan; BEAM- BCNU/etoposide/cytarabine/melphalan; HCT-CI- Hematopoietic Cell Transplantation Specific Comorbidity Index; auto-HCT- Autologous Hematopoietic cell transplantation; GVHD- Graft versus Host Disease; CNI- Calcineurin inhibitor; MMF- Mycophenolate mofetil; MTX- methotrexate; ATG- Anti-Thymocyte Globulin.

Table 2.

Engraftment, GVHD and adjusted transplant outcomes

	Flu/Bu (N = 151)		Flu/Mel 140 (N = 296)		BEAM (N = 115)		
Outcomes	**N**	**Prob (95% Cl)**	**N**	**Prob (95% Cl)**	**N**	**Prob (95% Cl)**	**P Value**
Neutrophil recovery	148		293		115		
28-days		99 (96–100)%		97 (95–99)%		94 (89–98)%	0.17
Platelet recovery	145		288		114		
100-days		99 (97–100)%		89 (85–93)%		89 (82–94)%	<0.001
Grade II-IV acute GVHD	143		284		110		
6 months		45 (37–53)%		38 (33–44)%		44 (35–53)%	0.38
Grade III-IV acute GVHD	143		283		110		
6 months		13 (8–19)%		13 (9–17)%		22 (15–30)%	0.10
Chronic GVHD	141		270		107		
1-year		38 (30–46)%		42 (36–48)%		31 (23–40)%	0.16
Adjusted NRM	151		295		114		
1-year		10 (5–14)%		20 (16–25)%		19 (11–26)%	0.002
4-year		16 (10–23)%		29 (23–34)%		25 (17–34)%	0.02
Adjusted Progression/relapse	151		295		114		
1-year		49 (41–56)%		33 (28–39)%		39 (31–48)%	0.007
4-year		54 (46–62)%		40 (35–46)%		42 (33–51)%	0.02
Adjusted PFS	151		295		114		
1-year		44 (37–52)%		46 (41–52)%		42 (34–51)%	0.75
4-year		33 (26–41)%		33 (27–38)%		34 (25–43)%	0.95
Adjusted OS	151		296		115		
1-year		68 (61–75)%		63 (58–69)%		53 (44–63)%	0.07
4-year		50 (41–58)%		42 (36–48)%		41 (31–51)%	0.31

Abbreviations: N- Number; Prob- Probability; CI- Confidence Interval; GVHD- Graft versus Host Disease; Flu/Bu- Fludarabine/Busulfan; Flu/Mel- Fludarabine/Melphalan; BEAM- BCNU/etoposide/cytarabine/melphalan; NRM- Non-Relapse Mortality; PFS- Progression Free Survival; OS- Overall Survival

Table 3.

Multivariable analysis of DLBCL patients receiving RIC conditioning regimens

	N	OR	OR Lower CI	OR Upper CI	p-value
Grade 3–4 acute GVHD					
Conditioning regimen					
Flu/Bu	143	1			0.06[1]
Flu/ Mel 140	283	1.26	0.68	2.35	0.47
BEAM	110	2.19	1.10	4.35	0.03
Grade 3–4 acute GHVD adjusted for significant covariates: GVHD prophylaxis and donor type.					
Chronic GVHD					
Conditioning regimen					
Flu/Bu	143	1			0.40[1]
Flu/ Mel 140	279	1.09	0.80	1.47	0.59
BEAM	108	0.84	0.56	1.27	0.41
Chronic GVHD adjusted for significant covariates: GVHD prophylaxis and ATG/alemtuzumab use in conditioning.					
Non-relapse mortality					
Conditioning regimen					
Flu/Bu	151	1			0.002[1]
Flu/ Mel 140	296	2.33	1.42	3.82	0.001
BEAM	115	2.54	1.34	4.80	0.004
NRM adjusted for significant covariates: age, HCT-CI, remission status at HCT, prior auto-HCT, and GVHD prophylaxis					
Progression/relapse					
Conditioning regimen					
Flu/Bu	151	1			0.07[1]
Flu/ Mel 140	296	0.70	0.52	0.95	0.02
BEAM	115	0.81	0.56	1.19	0.29
Progression/relapse adjusted for significant covariates: age and remission at HCT.					
Progression free survival					
Conditioning regimen					
Flu/Bu	151	1			0.92[1]
Flu/ Mel 140	296	1.04	0.81	1.35	0.75
BEAM	115	1.07	0.78	1.45	0.69
Progression free survival adjusted for significant covariates: remission at HCT and GVHD prophylaxis.					
Overall survival					
Conditioning regimen					
Flu/Bu	151	1			0.11[1]
Flu/ Mel 140	296	1.30	0.98	1.73	0.07
BEAM	115	1.44	0.99	2.10	0.05

	N	OR	OR Lower CI	OR Upper CI	p-value
Overall survival adjusted for significant covariates: KPS, remission status at HCT, and prior auto-HCT.					

Abbreviations: DLBCL- Diffuse large B-cell lymphoma; RIC- Reduced Intensity Conditioning; allo-HCT- Allogeneic hematopoietic cell transplantation; Flu/Bu- Fludarabine/Busulfan; Flu/Mel- Fludarabine/Melphalan; BEAM- BCNU/etoposide/cytarabine/melphalan; HCT-CI- Hematopoietic Cell Transplantation Specific Comorbidity Index; auto-HCT- Autologous Hematopoietic cell transplantation; GVHD- Graft versus Host Disease; CNI- Calcineurin inhibitor; MMF- Mycophenolate mofetil; MTX- methotrexate; ATG- Anti-Thymocyte Globulin.

[1] Overall P values show whether the main effect was significant based on the Wald test in the final model. The other P values are from pairwise comparisons between two conditioning regimens. All pairwise comparisons were from the Wald test.

Please see Table S1 in the supplementary appendix for the co-variates included in the multivariable analysis.

Table 4.

Multivariable analysis of chemosensitive DLBCL patients receiving RIC conditioning regimens

	N	OR	OR Lower CI	OR Upper CI	p-value
Non-relapse mortality					
Conditioning regimen					
Flu/Bu	128	1			0.02[1]
Flu/ Mel 140	250	2.19	1.26	3.81	0.005
BEAM	73	2.27	1.07	4.83	0.03
NRM adjusted for significant covariates: age, HCT-CI, remission status at HCT, prior auto-HCT, and GVHD prophylaxis.					
Progression/relapse					
Conditioning regimen					
Flu/Bu	128	1			0.09[1]
Flu/ Mel 140	250	0.69	0.49	0.96	0.03
BEAM	73	0.81	0.52	1.27	0.36
Progression/relapse adjusted for significant covariates: age and remission at HCT.					
Progression free survival					
Conditioning regimen					
Flu/Bu	128	1			0.99[1]
Flu/ Mel 140	250	1.02	0.77	1.36	0.87
BEAM	73	1.02	0.70	1.48	0.93
Progression free survival adjusted for significant covariates: remission at HCT and GVHD prophylaxis.					
Overall survival					
Conditioning regimen					
Flu/Bu	128	1			0.04[1]
Flu/ Mel 140	250	1.48	1.07	2.04	0.02
BEAM	73	1.56	0.98	2.46	0.059
Overall survival adjusted for significant covariates: KPS, HCT-CI, remission status at HCT, and prior auto-HCT.					

Abbreviations: DLBCL- Diffuse large B-cell lymphoma; RIC- Reduced Intensity Conditioning; allo-HCT- Allogeneic hematopoietic cell transplantation; Flu/Bu- Fludarabine/Busulfan; Flu/Mel- Fludarabine/Melphalan; BEAM- BCNU/etoposide/cytarabine/melphalan; HCT-CI- Hematopoietic Cell Transplantation Specific Comorbidity Index; auto-HCT- Autologous Hematopoietic cell transplantation; GVHD- Graft versus Host Disease

[1]Overall P values show whether the main effect was significant based on the Wald test in the final model. The other P values are from pairwise comparisons between two conditioning regimens. All pairwise comparisons were from the Wald test.

Table 5.

Cause of death

	Flu/Bu	Flu/Mel 140	BEAM
Number of patients	72	158	67
Primary disease	41 (57)	65 (41)	34 (51)
Infection	6 (8)	16 (10)	5 (8)
GVHD	4 (6)	8 (5)	8 (12)
IpN	1 (1)	1 (1)	0
Organ failure	1 (1)	12 (8)	3 (5)
Second malignancy	0	1 (1)	1 (1)
Hemorrhage	0	1 (1)	1 (1)
Vascular	0	1 (1)	0
Other HCT related cause, NOS	13 (18)	30 (19)	9 (13)
Not reported	6 (8)	23 (15)	6 (9)

Abbreviations: Flu/Bu- Fludarabine/Busulfan; Flu/Mel- Fludarabine/Melphalan; BEAM- BCNU/etoposide/cytarabine/melphalan; GVHD- Graft versus Host Disease; IPn, Idiopathic pneumonia syndrome; HCT- Hematopoietic Cell Transplantation