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Fludarabine/Busulfan versus Fludarabine/Melphalan Conditioning in Patients Undergoing Reduced-Intensity Conditioning Hematopoietic Stem Cell Transplantation for Lymphoma

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A B S T R A C T

There is at present little data to guide the choice of conditioning for patients with lymphoma undergoing reduced-intensity conditioning (RIC) allogeneic stem cell transplantation (SCT). In this study, we compared the outcomes of patients undergoing RIC SCT who received fludarabine and melphalan (FluMel), the standard RIC regimen used by the Spanish Group of Transplantation, and fludarabine and busulfan (FluBu), the standard RIC regimen used by the Dana-Farber Cancer Institute/Brigham and Women's Hospital. We analyzed 136 patients undergoing RIC SCT for lymphoma with either FluBu (n = 61) or FluMel (n = 75) conditioning between 2007 and 2014. Median follow-up was 36 months. The cumulative incidence of grades II to IV acute graft-versus-host disease (GVHD) was 13% with FluBu and 36% with FluMel ($P = .002$). The cumulative incidence of nonrelapse mortality (NRM) at 1 year was 3.3% with FluBu and 31% with FluMel ($P < .0001$). The cumulative incidence of relapse at 1 year was 29% with FluBu and 10% with FluMel ($P = .08$). The 3-year disease-free survival rate was 47% with FluBu and 36% with FluMel ($P = .24$), and the 3-year overall survival rate was 62% with FluBu and 48% with FluMel ($P = .01$). In multivariable analysis, FluMel was associated with a higher risk of acute grades II to IV GVHD (HR, 7.45; 95% CI, 2.30 to 24.17; $P = .001$) and higher risk of NRM (HR, 4.87; 95% CI, 1.36 to 17.44; $P = .015$). The type of conditioning was not significantly associated with relapse or disease-free survival in multivariable models. However, conditioning regimen was the only factor significantly associated with overall survival: FluMel conditioning was associated with a hazard ratio for death of 2.78 (95% CI, 1.23 to 6.27; $P = .014$) compared with FluBu. In conclusion, the use of FluBu as conditioning for patients undergoing SCT for lymphoma was associated with a lower risk of acute GVHD and NRM and improved overall survival when compared with FluMel in our retrospective study. These results confirm the differences between these RIC regimens in terms of toxicity and efficacy and support the need for comparative prospective studies.

INTRODUCTION

Reduced-intensity conditioning (RIC) regimens were developed to decrease the early nonrelapse mortality (NRM) associated with myeloablative conditioning regimens, which has allowed more patients to be considered for allogeneic stem cell transplantation (SCT) [1,2]. According to current consensus criteria, a wide spectrum of conditioning regimens with different dose intensities, as well as different hematologic and nonhematologic toxicities, are considered as "reduced intensity" [3-5]. Because of the paucity of prospective data

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comparing these RIC regimens, there is great variety in the conditioning regimens used by different transplant centers worldwide [6,7].

RIC regimens are very often used in patients undergoing SCT for lymphoma, given the absence of comparative data suggesting a benefit with myeloablative regimens [8,9]. Fludarabine with low to intermediate doses of busulfan (FluBu) and fludarabine with intermediate doses of melphalan (FluMel) are 2 widely used RIC regimens. The Spanish transplant group Grupo Español de Trasplante Hematopoyético (GETH) has previously reported that patients undergoing either regimen had 1-year progression-free and overall survival (OS) rates of 60% and 55%, respectively [10]. The standard RIC regimen from GETH is FluMel for lymphoid diseases (whereas FluBu is used for myeloid malignancies) [11,12]. In contrast, the standard RIC regimen at the the Dana-Farber Cancer Institute/Brigham and Women's Hospital (DFCI/BWH) for patients diagnosed with lymphoma has been FluBu [13,14]. Although only a few studies have compared the outcomes of patients receiving FluMel or FluBu, these studies have suggested that FluMel might induce a higher response rate but also a higher NRM, leading to an OS that does not appear to differ between the 2 approaches [15-18]. Only 1 of these studies has specifically examined this question in patients with lymphoma [16]. In this study, patients underwent RIC SCT with FluBu, FluMel, or fludarabine and treosulfan. The 3-year NRM with FluBu and FluMel was 24% and 54% respectively, without a significant difference in OS. We undertook a retrospective comparison of the 2 conditioning regimens using data from separate centers with different institutional standards in an effort to limit the selection bias typically associated with such comparisons.

METHODS

One hundred thirty-six patients undergoing RIC SCT for lymphoma between 2007 and 2014 at 1 of the participating institutions were included. Clinical factors were extracted from the database of the different participating centers and by medical chart review when needed. This study was approved by the institutional review board of all participating centers.

The FluBu regimen consisted of fludarabine 30 mg/m^2 daily administered i.v. on days –9 to –5, plus busulfan at a total dose of 3.2 to 6.4 mg/kg given i.v. at the DFCI/BWH (and 8 mg/kg i.v. in 6 patients receiving this regimen at the GETH centers). The FluMel regimen consisted of fludarabine 30 mg/m^2 daily administered i.v. on days –9 to –5, followed by melphalan 70 mg/m^2 daily administered i.v. on days –3 and –2. All 55 patients from DFCI/BWH received FluBu, whereas 75 patients received FluMel and 6 patients received FluBu from GETH. These 6 patients had previously received an autologous stem cell transplant with carmustine, etoposide, cytarabine, and melphalan as the conditioning regimen.

Graft-versus-host disease prophylaxis was with sirolimus plus tacrolimus or a calcineurin inhibitor plus methotrexate (MTX). For the former group, sirolimus was administered as a loading dose of 6 mg p.o. on day –6, followed by 4 mg daily from day –5 onward (GETH regimen) or at a loading dose of 12 mg on day –3, followed by 4 mg daily from day –2 onward (DFCI/BWH regimen). Tacrolimus for this group was started on day –3 at a dose of .02 mg/kg/day as a continuous i.v. infusion or .05 mg/kg twice daily orally. The levels of both drugs were monitored from day –1, and doses were adjusted to target 3 to 12 ng/mL. Prophylaxis with calcineurin inhibitor/MTX was based on the combination of either cyclosporine at a dose of 1 mg/kg per day i.v. from days –7 to –2 and then 3 mg/kg per day i.v. or orally from day –1 onward (target level, 150 to 300 ng/mL) or tacrolimus at a dose of .03 mg/kg/day as a continuous i.v. infusion or .05 mg/kg p.o. twice daily, plus MTX at 15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6, and +11 (or 5 mg/m^2 at DFCI/BWH).

Acute and chronic GVHD were graded according to standard criteria [19,20]. Response and relapse were determined based on clinician assessment using routine clinical and radiographic methods.

Statistical Analysis

For continuous variables, intergroup differences were compared using Student *t*-test or the Mann-Whitney U test, depending on the type of distribution. The chi-square test was used to compare categorical variables. Probabilities of OS and disease-free survival (DFS) were calculated using the Kaplan-Meier method, and unadjusted comparisons were made using the log-rank test. Relapse, NRM, and GVHD probabilities were analyzed in a competing risk framework using the cumulative incidence nonparametric estimator and were compared by the Gray test [21].

Events analyzed were calculated from the time of transplantation as follows. NRM was defined as death due to any cause (GVHD related or other), without prior relapse or progression of the underlying disease. The relapse incidence was analyzed from transplant until the time of relapse or progression. DFS was calculated from transplant until disease relapse or death; patients alive and free of disease at their last follow-up were censored. OS was calculated from transplant until death from any cause, and surviving patients were censored at the last follow-up. Patients who engrafted and survived more than 100 days were assessable for chronic GVHD. In acute or chronic GVHD, the day of onset was analyzed as time to event in an assessable patient.

Adjusted effects on NRM, relapse, GVHD, DFS, and OS were estimated in terms of hazard ratios (HRs) by Cox models [22]. Covariates included into the multivariate analysis were chosen based on clinical relevance as well as statistical significance in univariate analysis ($P < .1$). These variables were age, type of conditioning, GVHD prophylaxis, disease risk index (DRI) as described by Armand et al. [23], previous transplant, and type of donor. Data were analyzed using SPSS.V.15 (SPSS Inc, Chicago, IL, USA) and the CMPRSK package in R 2.4.1 (R Core Team 2013, Vienna, Austria) for the analyses of cumulative incidence curves in the framework of competing risk. Differences were considered to be statistically significant for 2-sided $P < .05$. Confidence intervals (CIs) refer to 95% boundaries.

RESULTS

Patient characteristics are shown in Table 1 and Supplementary Table 1. Sixty-one patients received FluBu and 75 received FluMel. Median follow-up was 36 months (26 versus 47 months, respectively; $P = .05$). No significant differences were observed between the 2 groups in terms of type of donor, source of stem cells, or disease status. Eighty-five percent of patients receiving FluBu had non-Hodgkin lymphoma as compared with 62% who received FluMel ($P = .008$). In addition, according to the DRI, which is based on diagnosis

Table 1
Patients Characteristics (N = 136)

	FluBu (n = 61)	FluMel (n = 75)	*P*
Male gender	41 (67.2%)	49 (65.3%)	.081
Median age	42 (SD, 12.3)	48.2 (SD, 12.3)	.073
Diagnosis			
Hodgkin lymphoma	9 (14.8%)	26 (34.7%)	.017
Indolent non-Hodgkin	17 (27.9%)	19 (25.3%)	
lymphoma	35 (57.4%)	30 (40%)	
Aggressive non-Hodgkin			
lymphoma			
DRI			
Low	24 (39.3%)	32 (43.8%)	.002
Intermediate	36 (59%)	27 (37%)	
High or very high	1 (1.6%)	14 (19.2%)	
Type of donor*			
Related	25 (41.0%)	36 (48.0%)	.413
Unrelated	36 (59.0%)	39 (52.0%)	
Source of stem cells			
Bone marrow	—	2 (2.7%)	.502
Peripheral blood	61 (100%)	73 (97.3%)	
Disease status at SCT			
Complete remission	31 (56.4%)	38 (53.5%)	.073
Partial remission	20 (36.4%)	18 (25.4%)	
Active disease or progression	4 (7.3%)	15 (21.1%)	
GVHD prophylaxis			
CNI-MTX	42 (68.9%)	34 (45.3%)	.006
SIRO-TKR	19 (31.1%)	41 (54.7%)	
Prior autologous SCT	33 (54%)	51 (68%)	.069

SD indicates standard deviation; CNI, calcineurin inhibitor; SIRO, sirolimus; TKR, tacrolimus.

* All related donors were HLA identical; for unrelated donors, all were 8/8 identical except for 1 7/8 allele HLA matched at A, B, C, and DRB1.

and disease status at SCT [23], 1.6% of patients receiving FluBu were categorized as high or very high risk of relapse as compared with 19.2% of those receiving FluMel ($P = .002$). With regards to GVHD prophylaxis, the combination of sirolimus and tacrolimus (± MTX) was used in 31.1% and 54.7% of patients receiving FluBu and FluMel, respectively ($P = .006$).

Transplant Toxicities: Engraftment, GVHD, and NRM

Median time to neutrophil engraftment was slower with FluMel, 15 days versus 12 days with FluBu ($P < .001$). Patients receiving FluBu displayed a significantly lower risk of mucositis as compared with those receiving FluMel: 6 of 61 patients (19%) versus 54 of 72 patients (75%), respectively ($P < .001$). The cumulative incidence of grades II to IV acute GVHD was 18% (95% CI, 10% to 31%) with FluBu and 41% (95% CI, 41% to 54%) with FluMel ($P = .002$) (Figure 1A). The respective values for grades III to IV acute GVHD were 9.8% (95% CI, 4.6% to 21.2%) and 16% (95% CI, 9.5% to 27%), respectively ($P = .26$). In multivariable analysis (Table 2), only the type of conditioning significantly influenced the risk of grades II to IV acute GVHD (HR with FluMel, 7.45; 95% CI, 2.30% to 24.17; $P = .001$). The risk of overall chronic GVHD was 73% (95% CI, 62% to 86%) with FluBu and 62% (95% CI, 51% to 77%) with FluMel ($P = .13$) (Figure 2A). Extensive chronic GVHD was 56% (95% CI, 44% to 71%) and 41.6% (95% CI, 30% to 57%) for FluBu and FluMel, respectively ($P = .07$; Figure 2B).

The cumulative risk of NRM at 1 year was 3.3% (95% CI, .8% to 13%) with FluBu and 31% (95% CI, 22% to 43.7%) with FluMel ($P < .0001$; Figure 3A). Causes of death are specified in Table 2. In multivariable analysis (Table 3), only type of conditioning significantly influenced the risk of NRM (HR with FluMel, 4.87; 95% CI, 1.36 to 17.44; $P = .015$).

Overall Outcomes: Relapse, DFS, and OS

A trend toward a higher risk of relapse was observed at 1 year after SCT for patients receiving FluBu, 29% (95% CI, 19% to 44%) as compared with 10% (95% CI, 5% to 20%) with FluMel ($P = .08$) (Figure 3B). In multivariable analysis, prior SCT (HR, .38; 95% CI, .15 to .99; $P = .048$) and type of donor (HR for unrelated donor, .36; 95% CI, .16 to .8; $P = .013$) significantly influenced the risk of relapse (Table 3).

The 3-year DFS rate was 47% (95% CI, 31% to 61%) in patients receiving FluBu and 36% (95% CI, 25% to 48%) in patients receiving FluMel ($P = .24$; Figure 4A). Only type of donor significantly influenced DFS in multivariable models (for unrelated donor, HR, .52; 95% CI, .30 to .89; $P = .017$). Finally, 3-year OS rates were 62% (95% CI, 49% to 72%) with FluBu and 48% (95% CI, 36% to 59%) with FluMel ($P = .01$) (Figure 4B). Considering the different median follow-up of the FluBu and Flu Mel cohorts (26 versus 47 months, respectively), we also compared OS, censoring follow-up at the time when the last event in the FluBu group occurred. Results were similar to the previous analysis (61% versus 48%, $P = .02$). In multivariable analysis, FluMel conditioning was the only factor significantly associated with worsening OS (HR, 2.78; 95% CI, 1.23 to 6.27; $P = .014$) (Table 4).

Table 2
Causes of Death by Conditioning Regimen

	FluBu N = 20	FluMel N = 40
Disease	12 (60)	12 (30)
Infection	3 (15)	16 (40)
GVHD (± infection)	2 (10)	9 (22.5)
Sinusoidal obstruction syndrome	0	1 (2.5)
Other	3 (15)	2 (5)

Values are number of cases with percents in parentheses.

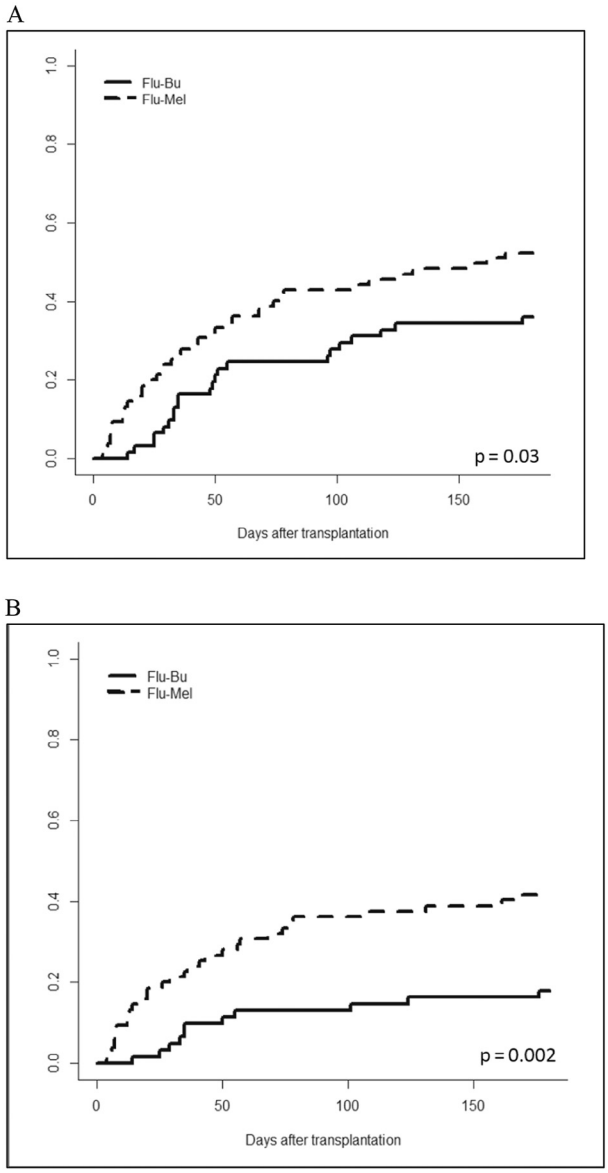

Figure 1. (A) Cumulative incidence of overall acute GVHD. The cumulative incidence of overall acute GVHD was 36% (95% CI, 25% to 50%) with FluBu and 52% (95% CI, 42% to 65%) with FluMel. (B) Cumulative incidence of grades II to IV acute GVHD. The cumulative incidence of grades II to IV acute GVHD was 18% (95% CI, 10% to 31%) with FluBu and 41% (95% CI, 41% to 54%) with FluMel.

Finally, we analyzed the impact of the conditioning regimen on OS when stratified by the DRI. As shown in Figure 5, patients with low or intermediate DRI scores receiving FluBu had a significantly better 3-year OS rate (62%; 95% CI, 45% to 75%) when compared with FluMel (49%; 95% CI, 35% to 62%; $P = .02$). The number of patients with high or very high DRI score was too small for analysis.

DISCUSSION

In the current study we compared the outcomes of patients undergoing RIC SCT for lymphoma with either FluBu or FluMel conditioning. Patients who received FluBu had sig-

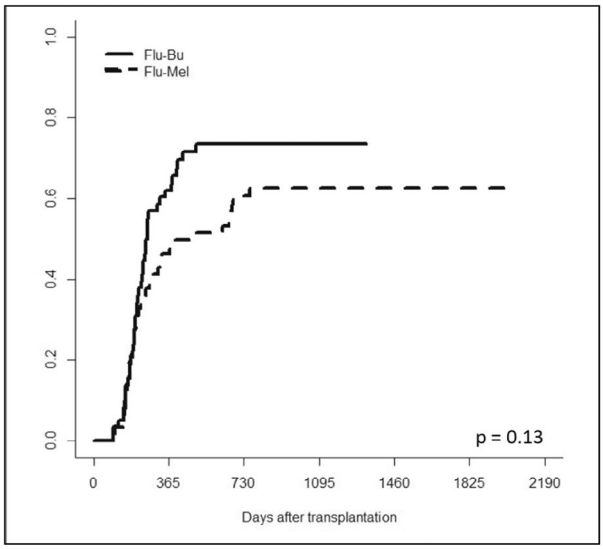

Figure 2. (A) Cumulative incidence of overall chronic GVHD. The cumulative incidence chronic GVHD was 73% (95% CI, 62% to 86%) with FluBu and 62% (95% CI, 51% to 77%) with FluMel. (B) Cumulative incidence of extensive chronic GVHD. The cumulative incidence of extensive chronic GVHD was 56% (95% CI, 44% to 71%) with FluBu and 41.6% (95% CI, 30% to 57%) with FluMel.

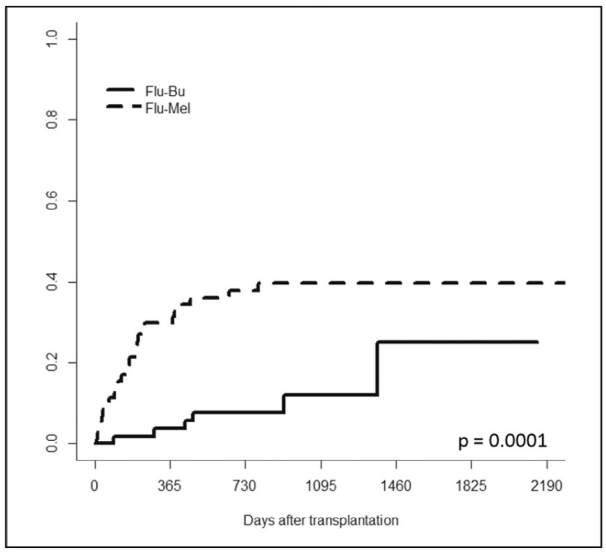

Figure 3. (A) Cumulative incidence of NRM. The cumulative risk of NRM at 1 year was 3.3% (95% CI, .8% to 13%) with FluBu and 31% (95% CI, 22% to 43.7%) with FluMel. (B) Cumulative incidence of relapse. The cumulative incidence of relapse at 1 year post-transplant was 29% (95% CI, 19% to 44%) with FluBu and 10% (95% CI, 5% to 20%) with FluMel.

nificantly lower acute GVHD and NRM; despite a trend toward an increased risk of relapse, this translated into a better OS with FluBu compared with FluMel. Remarkably, patients receiving FluBu displayed a significantly lower risk of mucositis as compared with FluMel. Thus, although both regimens are considered RIC, their toxicity patterns greatly differ, especially in the oral mucosa. Considering the key role of this organ in the pathophysiology of GVHD and especially in the cytokine release involved in acute GVHD development [24,25], this different toxicity profile might at least in part explain the higher risk of acute GVHD among patients receiving FluMel. Moreover, as shown in Table 2, the higher NRM observed with FluMel can be mostly attributed to the difference in risk of acute GVHD between both subgroups. By contrast, no significant differences were found in terms of chronic GVHD, which supports the concept that chronic GVHD is not simply a progression of acute GVHD. Chronic GVHD is a complex process involving the survival and expansion of donor T and B cells, which depends on variables not directly involved in acute GVHD.

Few other studies are available comparing both regimens. In this regard, Shimoni et al. [15] compared FluBu and FluMel conditioning regimens in 151 patients diagnosed with different hematologic malignancies. In this study, patients received cyclosporine plus short-course MTX as GVHD prophylaxis with the addition of antithymocyte globulin (ATG) for patients receiving an unrelated donor SCT. Transplant-related toxicities, including grades II to IV acute GVHD and NRM, were higher among patients receiving FluMel. Although the type of conditioning did not influence survival in multivariate analysis, among patients transplanted in remission, OS was significantly better with FluBu than FluMel (72%

Table 3
Multivariate Analysis for Grades II to IV Acute GVHD, NRM, and Relapse

	Grades II to IV Acute GVHD		NRM		Relapse	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.01 (.98-1.04)	.554	1.02 (.99-1.05)	.243	.98 (.95-1.00)	.085
Conditioning (FluMel)	7.45 (2.30-24.17)	**.001**	4.87 (1.36-17.44)	**.015**	1.03 (.39-2.70)	.950
DRI		.453		.453		.561
Low (Ref)	1.00		1.00		1.00	
Intermediate	.78 (.42-1.45)	.425	.71 (.33-1.55)	.390	1.47 (.69-3.15)	.315
High or very high	.52 (.17-1.59)	.255	1.35 (.52-3.49)	.531	.96 (.25-3.64)	.951
GVHD prophylaxis*	.49 (.20-1.21)	.120	.79 (.30-2.04)	.624	.71 (.31-1.63)	.418
Prior transplant	.33 (.10-1.10)	.071	.72 (.15-3.61)	.694	.38 (.15-0.99)	**.048**
Type of donor (unrelated)	2.19 (.89-5.37)	.088	.87 (.34-2.23)	.777	.36 (.16-0.80)	**.013**

Bold values indicate statistical significance.
* For sirolimus/tacrolimus.

and 36%, respectively; $P = .03$). Similarly, patients transplanted with active disease experienced higher NRM but lower relapse rates with FluMel, resulting in equivalent OS. More recently, the same group [16] compared Flu plus treosulfan (FluTreo), FluBu, and FluMel, with the same GVHD prophylaxis as in their previous study, in a series of 144 lymphoma patients undergoing SCT over a 13-year period. Rates of 3-year survival were 67%, 74%, and 48% after Flu plus treosulfan, FluBu, and FluMel, respectively, in chemosensitive disease ($P = .14$) and 34%, 11%, and 17% in chemorefractory disease ($P = .08$). In this study, FluMel was associated with shortened OS mostly because of a higher NRM. Baron et al. [17] compared the outcomes of 394 patients diagnosed with acute myeloid leukemia who received FluBu or FluMel. FluMel was associated with a lower relapse incidence (HR, .5; $P = .01$) and a trend toward a higher NRM with similar leukemia-free survival and OS. Thus, although FluMel provided better disease control, the 2 regimens resulted in similar OS. Finally, Damlaj et al. [18] compared FluBu with FluMel in a series of 134 patients diagnosed with acute myeloid leukemia or myelodysplastic syndrome who received a calcineurin inhibitor plus MTX as GVHD prophylaxis. FluBu was associated with increased risk of relapse. In that study, the risk of acute and chronic GVHD as well as NRM and survival were similar, whereas a better progression-free survival was observed among patients receiving FluMel (65% versus 51% with FluBu, $P = .03$).

In contrast to most of the previously published studies, our analysis focused specifically on patients diagnosed with lymphoma. Given that patients with lymphoma may have a different relapse risk and different treatment history compared with patients with myeloid diseases and that, moreover, lymphoid malignancies and myeloid malignancies may not be similarly susceptible to alkylating agents, it is possible that the balance of risks and benefits of a given conditioning regimen could be different in patients with lymphoma than in patients with myeloid diseases. There are also some important differences between our study and the other study focused on lymphoma patients [16]. First, in the current series, a significant proportion of patients received sirolimus plus tacrolimus as GVHD prophylaxis. According to prior studies, this combination may favorably influence clinical outcomes as compared with other prophylaxis strategies [26-28], especially among patients with lymphoma, because of a potential antilymphoma effect that might contribute to a decreased risk of relapse [29], although this effect was not confirmed in a prospective trial [30]. In addition, no patient received ATG with conditioning, which has also been shown to impact outcome in RIC SCT [31]. The rate of chronic GVHD is high in both cohorts in this study, a condition that remains a source of morbidity and decreased quality of life in patients post-transplant. For this reason, ATG should be evaluated in cohorts such as ours, possibly in a comparative study evaluating the potential benefit of combining sirolimus plus ATG as GVHD prophylaxis in an attempt to take advantage of both the antilymphoma effect of the former and the effect in preventing chronic GVHD of the latter [32-34]. It is also important to note other RIC regimens have been used in lymphoma with good effect, including 1 regimen of Flu, cyclophosphamide, and rituximab [35].

Table 4
Multivariate Analysis for DFS and OS

	DFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	.99 (.97-1.01)	.493	1.00 (.98-1.03)	.723
Conditioning (FluMel)	1.28 (.77-2.13)	.339	2.78 (1.23-6.27)	**.014**
DRI		.767		.296
Low (Ref)	1.00		1.00	
Intermediate	1.17 (.70-1.94)	.556	1.17 (.66-2.08)	.592
High or very high	1.25 (.60-2.61)	.549	1.89 (.85-4.20)	.119
GVHD prophylaxis*	.87 (.51-1.50)	.623	.58 (.30-1.13)	.110
Prior transplant	.77 (.47-1.28)	.314	.60 (.25-1.46)	.260
Type of donor (unrelated)	.52 (.30-0.89)	**.017**	1.09 (.58-2.06)	.786

Bold values indicate statistical significance.
* For sirolimus/tacrolimus.

The limitations of the present work include its retrospective nature, which raises the possibility of unmeasured confounders. In particular, we did not analyze comorbidity index. However, we have attempted to limit the possible bias of this type of study by drawing the 2 cohorts from separate institutions where conditioning choice primarily reflects institutional standard rather than patient-specific choice. We also note the high NRM in the FluMel cohort as compared with FluBu. This could be related to a higher comorbidity index in the FluMel cohort or to the higher proportion of patients with high or very high DRI score included in the FluMel cohort. As previously reported, the DRI might adversely impact not only the risk of relapse but also NRM [23]. Nevertheless, in the current study, the type of conditioning significantly influenced NRM in multivariate analysis independently of the DRI and prior autografting. Furthermore, because this study included consecutive patients transplanted over a long time period at 2 separate institutions, it seems unlikely that a difference in comorbid burden could account for our findings. It is possible that there are nonmeasurable differences between the 2 cohorts based on the fact that the transplants occurred in 2 different transplant practices. We cannot account for this as a potential confounder but have performed a comparison of patients receiving the same FluBu conditioning at both places to try to look for any differences

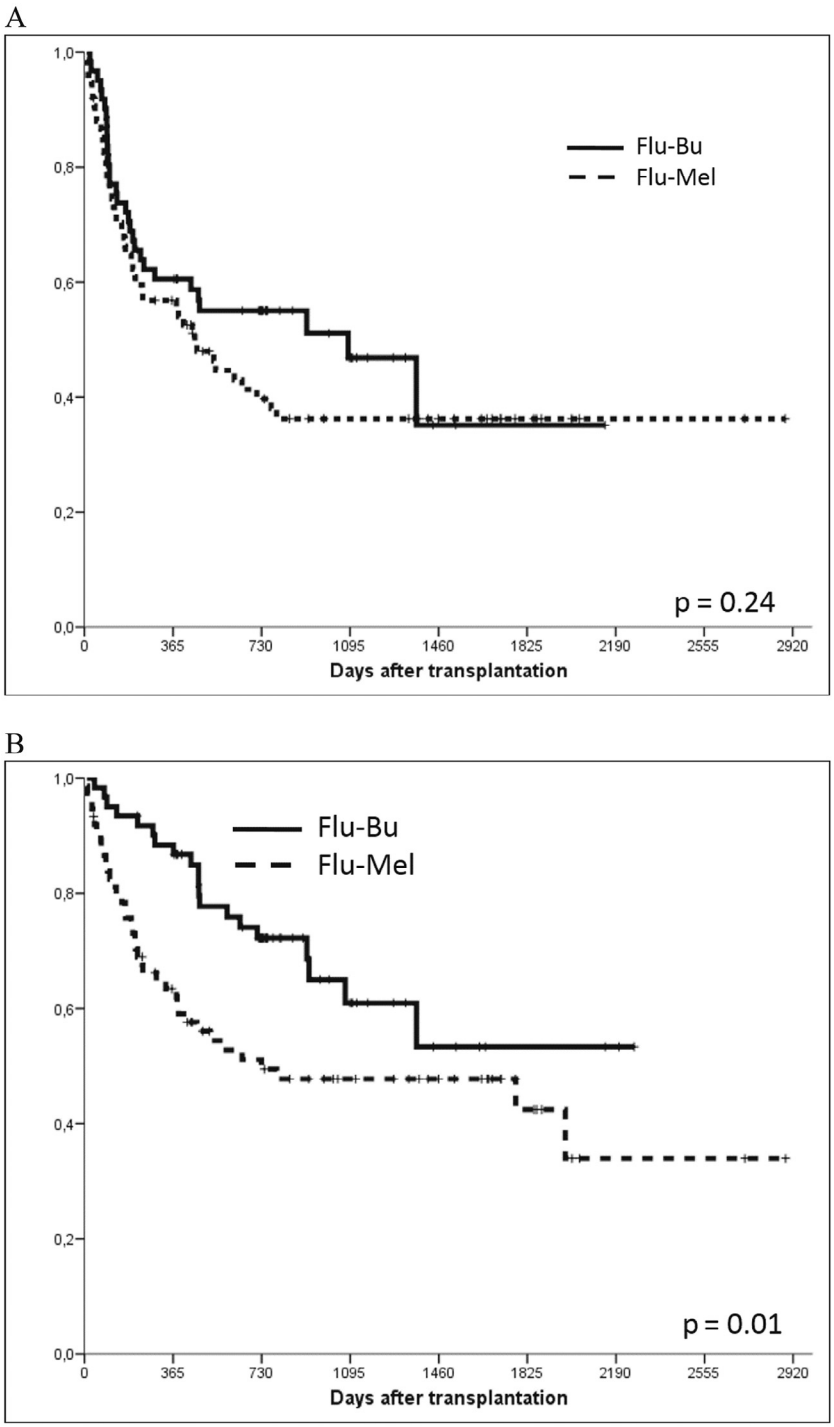

Figure 4. (A) The 3-year DFS were 47% (95% CI, 31% to 61%) with FluBu and 36% (95% CI, 25% to 48%) with FluMel. (B) The 3-year OS rates were 62% (95% CI, 49% to 72%) with FluBu and 48% (95% CI, 36% to 59%) with FluMel.

based on center effect. Although the numbers are too small for formal analysis, we found no significant differences between GVHD, NRM, and survival outcomes between patients receiving FluBu within the GETH centers and those receiving FluBu at DFCI/BWH (data not shown).

In conclusion, in this analysis the use of FluBu conditioning was associated with a significantly lower NRM and better OS than FluMel conditioning for patients with lymphoma undergoing RIC SCT, especially for low and intermediate DRI scores. These results confirm the differences between these RIC regimens in terms of toxicity and efficacy and support the need for comparative prospective studies.

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Conflict of interest statement: There are no conflicts of interest to report.

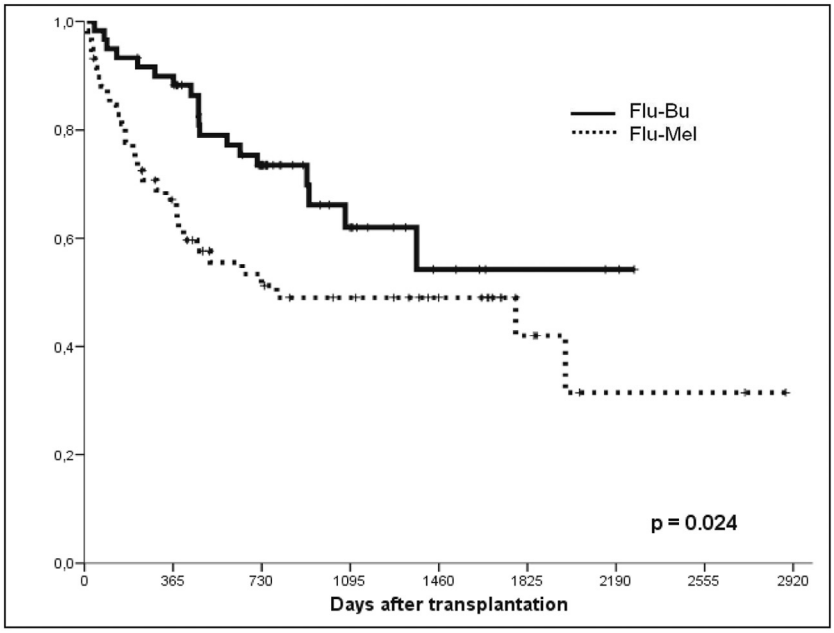

Figure 5. OS for Patients with low or intermediate DRI score. The 3-year OS rate was 62% (95% CI, 45% to 75%) with FluBu and 49% (95% CI, 35% to 62%) with FluMel for patients with low or intermediate DRI score.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2016.07.006.

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