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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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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.