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Comparative Effectiveness of Busulfan and Fludarabine versus Fludarabine and 400 cGy Total Body Irradiation Conditioning Regimens for Acute Myeloid Leukemia/Myelodysplastic Syndrome

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A B S T R A C T

Allogeneic hematopoietic cell transplantation conditioning regimen intensity has varied for patients with acute myeloid leukemia and myelodysplastic syndrome. A comparative effectiveness analysis was performed to assess outcomes of busulfan and fludarabine (BuFlu) versus those of fludarabine and 400 cGy total body irradiation (FluTBI) conditioning. Thirty-three subjects received BuFlu and 38 received FluTBI. The BuFlu group received more red blood cell transfusions ($P = .02$) and had a longer time to platelet recovery ($P = .004$). There were no differences between the regimens regarding incidence of acute or chronic graft-versus-host disease (GVHD), quality of life, or 2-year outcome estimates for relapse (48; 95% confidence interval [CI], 30 to 64 and 50; 95% CI, 33 to 65), nonrelapse mortality (29; 95% CI, 14 to 45 and 29; 95% CI, 15 to 44), relapse-free survival (27; 95% CI, 13 to 43 and 29; 95% CI, 16 to 44), and overall survival (35; 95% CI, 19 to 51; and 37; 95% CI, 22 to 52), respectively. These comparable outcomes have implications for health care resource utilization. Future prospective investigation comparing these regimens with larger patient cohorts and additional strategies to prevent relapse and limit toxicities as well as cost-effectiveness analyses are warranted.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (alloHCT) is a potentially curative treatment modality for acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) [1-4]. However, myeloablative conditioning regimens are typically not considered for older patients and those with significant comorbidities because of the high rate of nonrelapse mortality (NRM) [5,6]. Reduced-intensity conditioning (RIC) has therefore become a well-established approach for such patients [7-9], but disease relapse has been a major cause of treatment failure [5,10]. As such, investigation of conditioning regimen dose intensity has been explored among RIC in an effort to optimize outcomes [6,11].

We have previously compared 200 cGy versus 400 cGy total body irradiation (TBI) with fludarabine for RIC and did not observe a significant difference in survival [11]. Disease relapse continued to be the most common cause of death after transplantation. In an effort to further intensify conditioning for AML and MDS patients to potentially decrease relapse and improve outcomes, we then utilized busulfan and fludarabine (BuFlu). This approach has been proposed to be myeloablative but with reduced toxicity and preferable for older patients with or without busulfan dose adjustment [12].

The objective of this study was to retrospectively compare the effectiveness of BuFlu and fludarabine with 400 cGy TBI (FluTBI) alloHCT conditioning for adult patients with AML and MDS.

PATIENTS AND METHODS

From March 2004 through April 2010, 38 patients (23 AML, 15 MDS) underwent T cell–replete RIC alloHCT with 400 cGy TBI and fludarabine at the Cleveland Clinic in Cleveland, Ohio. Our analysis compared outcomes with 33 patients (20 AML, 13 MDS) conditioned with BuFlu without busulfan

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dose adjustment from July 2010 to December 2013. Patients were required to have an HLA-matched related donor or an 8/8 HLA–matched unrelated donor by DNA-based typing (HLA-A, -B, -Cw, -DR), as previously described [13-15]. The study was approved by the Cleveland Clinic's institutional review board.

Treatment

Patients received parenteral busulfan (100 mg/m^2/day on days –5, –4, –3, –2) without dose adjustment and fludarabine (40 mg/m^2/day on days –5, –4, –3, –2) (BuFlu) or fludarabine (30 m^2/day on days –5, –4, –3) and 400 cGy TBI (200 cGy on days –1 and 0) (FluTBI). The TBI dose was administered as previously described [11]. All patients received T cell–replete grafts with peripheral blood progenitor cells. The BuFlu transplantations were all performed as inpatient procedures while FluTBI transplantations were performed as outpatient procedures. The patients in the FluTBI group had daily monitoring of their blood counts, except on Sundays, as an outpatient until they had hematopoietic recovery. Graft-versus-host disease (GVHD) prophylaxis was similar between the groups and consisted of mycophenolate mofetil and a calcineurin inhibitor except for 3 patients in the BuFlu group who received tacrolimus with methotrexate (Table 1). Other supportive care measures were administered as previously described [11]. Donors received granulocyte colony–stimulating factor 10 mcg/kg subcutaneous daily for peripheral blood progenitor cell mobilization. Leukapheresis began on the fifth day of granulocyte colony–stimulating factor administration and continued for 2 or 3 days.

Short tandem repeat analysis for T cell chimerism was performed on peripheral blood samples as previously described [11]. The hematopoietic cell transplantation-specific comorbidity index was used to assess patients' pretransplantation comorbidities [16]. Patients were also categorized into 3 risk groups based upon the American Society of Blood and Marrow Transplantation Request for Information classification system: low risk (patients in first complete remission [CR] before transplantation), intermediate risk (patients in CR2 or CR3 before transplantation) or high risk (patient never treated, in primary induction failure, or in relapse) [17].

Quality of Life

Quality of life (QoL) was assessed using the Functional Assessment of Cancer Therapy – Bone Marrow Transplantation tool [18],which includes 5 domains (physical well-being, social well-being, emotional well-being, functional well-being, additional concerns), a trial outcome index, and a total score. Higher scores represent better QoL. The assessment was performed at 4 time points: at baseline (before transplantation) and on days +100, +180, and +365.

Definitions

Complete donor chimerism for T cells was defined as achievement of ≥95% DNA of donor origin in the T cell–enriched fraction. *Mixed chimerism* was defined as ≥1% and <95% DNA of donor origin in the T cell–enriched fraction. *Post-transplantation neutrophil recovery* was defined as absolute neutrophil count ≥500/μL for 3 consecutive days and *platelet recovery* was defined as platelet count ≥20,000/μL without platelet transfusions for 7 consecutive days. Graft rejection included a failure of hematopoietic recovery by day 30 after transplantation or a sustained decline in absolute neutrophil count <500/μL after initial hematopoietic engraftment in the absence of relapsed or progressive AML/MDS. The diagnosis of GVHD was determined clinically and typically confirmed by biopsy when possible. Standard criteria were used for classifying acute and chronic GVHD [19,20]. Overall survival (OS) was estimated from the time of transplantation until death from any cause. Relapse-free survival (RFS) was estimated from transplantation until the date of relapse or death from any cause. *NRM* was defined as death from any cause other than disease progression or relapse.

Statistical Analysis

Categorical variables were compared between conditioning regimens using the chi-square test. Continuous variables were compared using the Wilcoxon rank sum test. OS and RFS were estimated using the Kaplan-Meier method and compared using the log-rank test [21]. All other time-related outcomes were estimated using the cumulative incidence method and compared using the Gray test. The crude number and percentage of events corresponding to each outcome are described as frequency counts and percentages, which are not adjusted for length of follow-up. Outcome estimates at selected time points are described as the estimate and 95% confidence interval (CI) of the estimate.

QoL scores were compared between conditioning regimens using repeated measures analysis of variance, which assessed differences between regimens, differences over time, and the interaction between regimen and time. If an interaction was present ($P < .05$), then QoL differences between regimens were not constant over time and comparisons were made at each time point. If the interaction was not significant, then a single P value was calculated to compare regimens across all time points. Analyses were done using SAS Software (SAS Institute, Inc, Cary, NC), version 9.4. All statistical tests were 2-sided and $P < .05$ was used to indicate statistical significance. No multivariate analysis was performed because of the sample size of the study cohorts.

RESULTS

Patient and Transplantation Characteristics

Baseline characteristics are shown in Table 1. Patients who received BuFlu conditioning were older than those who received the FluTBI regimen (median, 65; range, 34 to 73 versus median, 61; range, 44 to 70 years, $P = .027$). Two of the patients in the FluTBI group had received prior autologous hematopoietic cell transplantations for non-Hodgkin lymphoma. There were no other differences in baseline characteristics between BuFlu and FluTBI conditioning.

Outcomes

Post-transplantation outcomes are shown in Table 1. Since the study cohorts were from sequential time periods, the median duration of follow-up after transplantation was significantly longer for the FluTBI group at 80 months (range, 44 to 111) than for those in the BuFlu group (median, 26; range, 18 to 56 months; $P = .002$). Subjects who received BuFlu conditioning received more red blood cell (RBC) transfusions (median, 4; range, 0 to 22 versus 2; range, 0 to 34; $P = .019$) but not more platelet transfusions than the FluTBI group. Time to platelet recovery was longer for those conditioned with BuFlu (median, 16; range, 10 to 83 versus 12; range, 8 to 57 days; $P = .004$), but there was no difference in time to neutrophil recovery (median, 12; range, 6 to 25 versus 11; range, 1 to 21 days; $P = .12$).

All patients were hospitalized to receive BuFlu while all FluTBI transplantations were performed in the outpatient setting. Hence, not unexpectedly, patients who received BuFlu regimen were hospitalized more days in the first 100 days after transplantation (median, 22; range, 8 to 79 versus 10; range, 0 to 53 days; $P < .001$) as well as in the first year after transplantation (median, 40; range, 8 to 126 versus 16; range, 0 to 94 days; $P = .001$). In addition, the number of days alive and not hospitalized in the first 100 days after transplantation was significantly more for the FluTBI patients than for those who received BuFlu (90; range, 7 to 100 versus 78; range, 9 to 92 days; $P < .001$). However, this difference was no longer present at 1-year follow-up. Although the median number of hospitalizations was comparable for both regimens at 100 days, this was greater for the BuFlu subjects compared with those conditioned with FluTBI at 1 year (median, 3; range, 1 to 6 versus 2; range, 0 to 11; $P = .044$).

Regarding the time of initial hospitalization for FluTBI patients, 8 (21%) occurred within 1 week, 14 (37%) within 2 weeks, 19 (50%) within 3 weeks, and 23 (61%) within 4 weeks of the transplantation. Since the FluTBI group was not hospitalized initially for transplantation, an analysis regarding days of hospitalization was performed that excluded the days of the initial transplantation admission for the BuFlu group. As compared to the FluTBI patients, the BuFlu group then had fewer days in the hospital (median, 10; range, 0 to 53 days versus median, 1; range, 0 to 63 days; $P = .021$). However, when assessing the groups in the first 365 days, the 2 were comparable with regards to days of hospitalization (BuFlu median, 20 days; range, 0 to 113 days versus FluTBI median, 16 days; range, 0 to 94 days; $P = .73$).

Table 1
Patient Characteristics and Post-Transplantation Outcomes

Variable	FluTBI (n = 38)	BuFlu (n = 33)	*P* Value
Age at transplantation, median (range), yr	61 (44-70)	65 (34-73)	.027
Gender			
Male	23 (61)	22 (67)	.59
Female	15 (39)	11 (33)	
Race			
Caucasian	36 (95)	32 (97)	.64
All others	2 (5)	1 (3)	
Prior autologous HCT	2 (5)	0 (0)	.18
Performance status (n = 34, 33)*			
Good	31 (91)	29 (88)	.66
Poor	3 (9)	4 (12)	
Prior chemotherapy regimens, median (range)	2 (1-7)	2 (1-4)	.74
HCT-CI			
Low (0)	10 (26)	4 (12)	.21
Intermediate (1-2)	13 (34)	10 (30)	
High (≥3)	15 (40)	19 (58)	
Diagnosis			
AML	23 (61)	20 (61)	.99
MDS	15 (39)	13 (39)	
ASBMT RFI			
Low	18 (48)	19 (58)	.17
Intermediate	10 (26)	3 (9)	
High	10 (26)	11 (33)	
Time from diagnosis to transplantation, median (range), mo	7 (1.4-246.4)	6 (2.8-61.1)	.47
Donor relationship			
Sibling	20 (53)	19 (58)	.68
Unrelated	18 (47)	14 (42)	
Donor-to-recipient gender (n = 36, 33)			
Female to Female	5 (14)	3 (9)	.84
Female to Male	9 (25)	7 (21)	
Male to Female	9 (25)	8 (24)	
Male to Male	13 (36)	15 (45)	
CMV serostatus			
D+/R+	8 (21)	13 (39)	.39
D+/R–	2 (5)	2 (6)	
D–/R+	20 (53)	13 (39)	
D–/R–	8 (21)	5 (15)	
$CD34^+$ dose, median (range), $\times 10^6$/kg	5.43 (2.21-11.94)	5.02 (1.81-10.34)	.90
Total nucleated cell dose, median (range), $\times 10^8$/kg	7.91 (3.43-28.55)	8.46 (4.47-16.33)	.42
GVHD prophylaxis regimen			
MTX-based			.12
FK/MTX	-	3 (9)	
MMF-based			
CSA/MMF	19 (50)	18 (55)	
FK/MMF	19 (50)	12 (36)	
No. of RBC transfusions, median (range)	2 (0-34)	4 (0-22)	.019
No. of platelet transfusions median (range)	1 (0-71)	1 (0-20)	.61
Days to neutrophil recovery (n = 29, 33), median (range)	11 (1-21)	12 (6-25)	.12
Days to platelet recovery (n = 29, 26), median (range)	12 (8-57)	16 (10-83)	.004
Hospitalized for transplantation	0 (0)	33 (100)	<.001
Hospital admissions in the first 100 post-transplantation days (including transplantation admission), median (range)	1 (0-5)	2 (1-4)	.16
Days alive and not in the hospital in the first 100 post-transplantation days, median (range)	90 (7-100)	78 (9-92)	<.001
Hospital admissions in the first 365 post-transplantation days (including transplantation admission), median (range)	2 (0-11)	3 (1-6)	.044
Days alive and not in the hospital in the first 365 post-transplantation days, median (range)	307 (7-365)	292 (9-357)	.18
Post-transplantation events (>1 possible)			
Subsequent allogeneic HCT	5 (13)	1 (3)	—
T cell CD chimerism	29/37 (78)	26/32 (81)	.83
Graft failure	3 (8)	3 (9)	.87
Grade 2-4 acute GVHD	13 (34)	17 (52)	.24
Grade 3-4 acute GVHD	3 (8)	6 (18)	.21
Any chronic GVHD	16 (42)	14 (42)	.91
Extensive chronic GVHD	8 (21)	13 (39)	.06
CMV infection	12 (32)	13 (39)	.66
Fungal infection	2 (5)	1 (3)	.83
Neutropenic fever	2 (5)	3 (9)	.52
Disease relapses	20 (53)	17 (52)	.96
Relapse deaths	14 (37)	12 (36)	.86
Nonrelapse deaths	18 (47)	9 (27)	.56
Deaths from all causes	32 (84)	21 (64)	.73
Relapse or death	32 (84)	25 (76)	.95
100-Day mortality	5 (13)	3 (9)	.59
Follow-up, patients who are alive (n = 6, 12) median (range), mo	80 (43.9-111.1)	26 (17.8-55.8)	.002
Cause of death, patients who died (n = 32, 21)			
Relapse	14 (44)	12 (57)	—
Infection	4 (12)	3 (14)	
Nonpulmonary organ failure	3 (9)	1 (5)	
Acute GVHD	1 (3)	2 (10)	
Chronic GVHD	2 (6)	1 (5)	
Multiorgan failure	3 (9)	-	
Pulmonary	2 (6)	1 (5)	
Other†	3 (9)	-	
Unknown	-	1 (5)	

Data presented are n (%) unless otherwise indicated.
HCT-CI indicates hematopoietic cell transplantation-specific comorbidity index; ASBMT RFI, American Society for Blood and Marrow Transplantation Request for Information classification; CMV, cytomegalovirus; D, donor; R, recipient; MTX, methotrexate; FK, tacrolimus; MMF, mycophenolate; CSA, cyclosporine.
* Performance state poor: Eastern Cooperative Oncology Group performance status >1 or Karnofsky performance status <80.
† Other: 1 hemorrhage, 1 secondary malignancy, 1 accident.

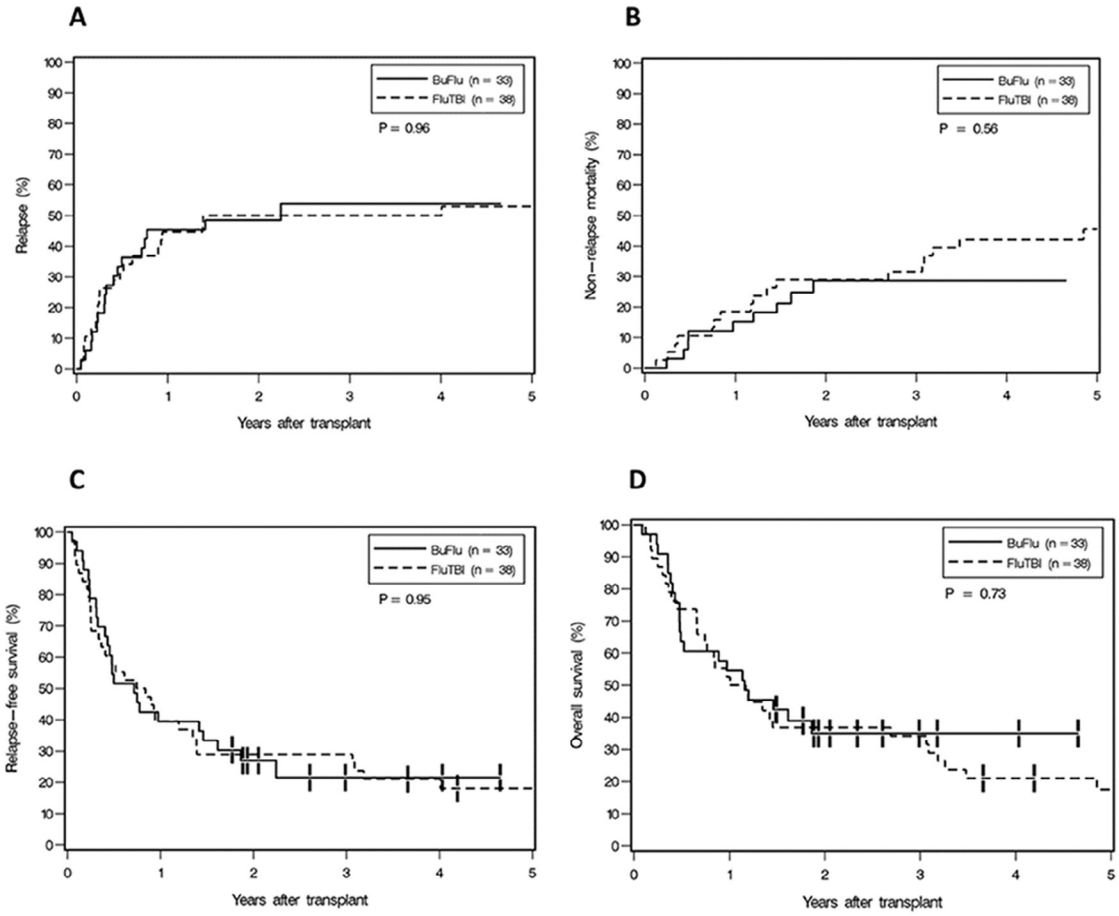

Figure 1. Comparison of BuFlu versus FluTBI cumulative incidences for (A) relapse and (B) NRM. Kaplan-Meier curves for (C) RFS and (D) OS.

The incidence of GVHD was comparable for the BuFlu and FluTBI groups: grades 2 to 4 acute GVHD (52% versus 34%, $P = .24$), grades 3 and 4 acute GVHD (18% versus 8%, $P = .21$), and chronic GVHD (42% versus 42%, $P = .91$). The respective cumulative incidence estimates were 30% (95% CI, 16 to 46%) versus 29% (95% CI, 15 to 44%) for grades 2 to 4 acute GVHD at day 100, 9% (95% CI, 2 to 22%) versus 5% (95% CI, 1 to 16%) for grades 3 and 4 acute GVHD at day 100, and 41% (95% CI, 23 to 58%) versus 38% (95% CI, 23 to 54%) for chronic GVHD at 2 years.

There were no differences between BuFlu and FluTBI conditioning for relapse (52% versus 53%, $P = .96$), relapse mortality (36% versus 37%, $P = .86$), NRM (27% versus 47%, $P = .56$), RFS (76% versus 84%, $P = .95$), or OS (64% versus 84%, $P = .73$) (Figure 1). Respective 2-year outcome estimates for BuFlu and FluTBI were 48% (95% CI, 30 to 64%) versus 50% (95% CI, 33 to 65%) for relapse, 36% (95% CI, 20 to 53%) versus 34 (95% CI, 20 to 49%) for relapse mortality, 29% (95% CI, 14 to 45%) versus 29% (95% CI, 15 to 44%) for NRM, 35% (95% CI, 19 to 51%) versus 37% (95% CI, 22 to 52%) for OS, and 27% (95% CI, 13 to 43%) versus 29% (95% CI, 16 to 44%) for RFS. The most common causes of death for those treated with BuFlu or FluTBI were relapse (57% versus 44%) and infection (14% versus 12%), respectively.

QoL

There was no difference in Functional Assessment of Cancer Therapy domain scores or total scores between conditioning regimens at baseline or any of the follow-up time points after transplantation (Table 2).

DISCUSSION

The current study compared the effectiveness of BuFlu and FluTBI conditioning for adult patients with AML and MDS, as used at our institution. The BuFlu regimen utilized was myeloablative and fludarabine with 400 cGy TBI was RIC [22]. Except for a greater red blood cell transfusion requirement, longer time to platelet recovery, and more days of inpatient hospitalization for those treated with BuFlu, there were no other significant differences in outcomes in comparison to FluTBI. Furthermore, QoL assessments were similar for both regimens at multiple time points after transplantation.

Prior retrospective and prospective analyses have demonstrated less toxicity and lower NRM but higher relapse rates for RIC as compared with myeloablative conditioning. This has resulted in similar OS between these approaches [5,10]. Similar to our analysis, a retrospective report from the Japan Society for Hematopoietic Cell Transplantation also observed no difference in survival or NRM when comparing low-dose TBI (≤400 cGy) and fludarabine with non-TBI approaches, including busulfan- and melphalan-based regimens [23]. A retrospective comparison of RIC versus myeloablative conditioning from French investigators reported significantly lower NRM for RIC but similar adjusted relapse rate and OS [24]. Another multicenter French study prospectively compared oral busulfan, fludarabine, and rabbit antithymocyte globulin (ATG) to fludarabine and 200 cGy TBI for patients with hematologic malignancies, including some with AML and MDS [25]. Although the BuFlu/ATG group had a higher

Table 2
QoL Assessment with the FACT-BMT Scoring System

QoL Score/Time	FluTBI Number (Mean ± SD)	BuFlu Number (Mean ± SD)	*P* (1)	*P* (2)
Physical well-being; interaction *P* = .08, time *P* = .005			.69	
Baseline	27 (22.7 ± 4.6)	29 (23.3 ± 4.8)		
Day 100	12 (21.7 ± 6.1)	19 (22.7 ± 5.6)		
Day 180	8 (23.9 ± 2.5)	14 (23.2 ± 4.1)		
Day 365	8 (22.8 ± 2.7)	6 (18.9 ± 8.3)		
Social well-being; interaction *P* = .23, time *P* = .42			.39	
Baseline	27 (24.4 ± 3.7)	29 (24.5 ± 3.3)		
Day 100	12 (22.6 ± 4.5)	19 (25.8 ± 2.5)		
Day 180	8 (24.3 ± 3.3)	14 (24.4 ± 3.8)		
Day 365	8 (25.4 ± 1.7)	6 (25.5 ± 2.4)		
Emotional well-being; interaction *P* = .22, time *P* = .02			.49	
Baseline	27 (17.8 ± 4.1)	29 (18.6 ± 4.6)		
Day 100	12 (17.6 ± 5.1)	19 (20.8 ± 3.8)		
Day 180	8 (18.8 ± 3.4)	14 (20.6 ± 3.1)		
Day 365	8 (21.0 ± 1.6)	6 (20.0 ± 4.3)		
Functional well-being; interaction *P* = .016				
Baseline	27 (19.2 ± 6.0)	29 (17.2 ± 6.6)		.21
Day 100	12 (18.0 ± 7.0)	19 (19.7 ± 5.3)		.87
Day 180	8 (21.3 ± 4.3)	14 (19.7 ± 6.2)		.83
Day 365	8 (22.4 ± 3.7)	6 (18.3 ± 7.1)		.28
Additional concerns; interaction *P* = .39, time *P* < .001			.95	
Baseline	27 (69.7 ± 10.3)	27 (70.7 ± 10.0)		
Day 100	12 (70.3 ± 12.6)	19 (71.4 ± 9.5)		
Day 180	8 (70.2 ± 13.5)	14 (71.2 ± 10.0)		
Day 365	8 (70.1 ± 7.1)	6 (66.5 ± 14.6)		
Trial outcome index; interaction *P* = .10, time *P* = .06			.88	
Baseline	27 (111.6 ± 18.1)	29 (107.6 ± 23.3)		
Day 100	12 (110.0 ± 23.9)	19 (113.7 ± 17.2)		
Day 180	8 (115.3 ± 16.6)	14 (114.0 ± 19.0)		
Day 365	8 (115.3 ± 10.8)	6 (103.7 ± 29.0)		
Total score; interaction *P* = .031				
Baseline	27 (153.9 ± 23.0)	29 (150.7 ± 27.9)		.46
Day 100	12 (150.1 ± 31.3)	19 (160.3 ± 21.6)		.50
Day 180	8 (158.4 ± 19.2)	14 (159.0 ± 24.3)		.31
Day 365	8 (161.6 ± 10.5)	6 (149.1 ± 35.2)		.41

P (1): overall comparison of conditioning regimens if interaction with time is not statistically significant; *P*(2), comparisons of conditioning regimens at each time point if interaction is statistically significant.
FACT-BMT indicates Functional Assessment of Cancer Therapy – Bone Marrow Transplantation.

response rate and lower relapse rate, these patients had a higher incidence of grades 2 to 4 acute GVHD and NRM with comparable progression-free survival and OS. A prospective, German, multicenter randomized phase III trial comparing RIC versus myeloablative conditioning for patients with intermediate-risk or high-risk AML did not find a difference in NRM, relapse, leukemia-free survival, or OS [26].

However, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0901 trial that was a randomized comparison of high versus RIC observed a statistically significant advantage in RFS with myeloablative conditioning (68%; 95% CI, 59% to 75% versus 47%; 95% CI, 39% to 55%; $P < .01$), but no difference in OS at the time of the most recent report [10]. Those receiving RIC transplantations had significantly less grades II to IV acute GVHD and better 100-day and 1-year QoL. Based on this information, the early stopping of the 0901 study does not necessarily mean that RIC regimens are inferior. It is possible that patients on this study may have experienced morbidity and/or mortality from myeloablation that is not captured by the RFS endpoint. Moreover, there could be a tradeoff between morbidity/mortality due to relapse with RIC versus morbidity/mortality due to transplantation with myeloablation. In addition, we do not yet know whether longer RFS with myeloablation translates into more durable remissions (ie, "cures"), given that most patients are undergoing transplantation for disease that is thought to be refractory to chemotherapy.

Our study did not corroborate the findings of the BMT CTN 0901 trial but had much longer follow-up and specifically compared only 2 regimens. In particular, the BuFlu regimen used for myeloablative conditioning in our patients has been considered a reduced-toxicity approach in contrast to busulfan/cyclophosphamide or 1200 cGy to 1420 cGy TBI/cyclophosphamide that were included as well for those treated on the BMT CTN 0901 trial [12]. The increased intensity of these regimens in contrast to BuFlu may have accounted for the lower relapse rate and improved RFS as well as the differences in acute GVHD and QoL compared with those associated with RIC. This is supported by the finding of a much higher relapse rate for our BuFlu patients than that reported for the myeloablative cohort of the BMT CTN 0901 trial (52% versus 14%, respectively). However, the relapse rates for both conditioning regimens in the current study were comparable to that observed for the RIC group of the BMT CTN 0901 trial as well as for RIC BuFlu with ATG as reported by the Cancer and Leukemia Group B 100103 (Alliance for Clinical Trials in Oncology)/Blood and Marrow Transplant Clinical Trial Network 0502 [27].

In our trial, busulfan was administered parenterally without dose adjustment. Although targeted busulfan dosing may be reasonable to consider, predictable systemic busulfan exposure may be achieved by parenteral administration without pharmacokinetic monitoring [28].

Limitations of this retrospective analysis included the modest sample size and cohorts from sequential time periods, with longer follow-up for the FluTBI group. However, all subjects were treated at a single institution and supportive care measures were similar for both transplantation conditioning regimens. The majority of patients in both study cohorts had high baseline comorbidity index scores that may have contributed to NRM.

Some prior reports have observed that patients receiving RIC had more rapid recovery of QoL compared with those who received myeloablative conditioning [29-31]. We found that QoL was similar for those conditioned with BuFlu or FluTBI when assessed at multiple time points after transplantation, as previously suggested [32]. This finding would be consistent with the classification of myeloablative conditioning with reduced toxicity for the BuFlu regimen that we utilized [12]. However, given the limited amount of QoL data in our study cohorts, particularly with patient drop out at later time points after transplantation, further investigation with larger sample sizes is appropriate to consider.

We conclude that FluTBI and BuFlu conditioning for alloHCT result in comparable outcomes for adult AML and MDS. The need for more RBC transfusions and days of inpatient hospitalization with BuFlu has implications for health care resource utilization. Future prospective studies with larger patient cohorts and cost-effectiveness analyses comparing these regimens as well as other conditioning strategies are warranted. Since disease relapse remains the predominant cause of treatment failure for these regimens additional approaches, such as post-transplantation maintenance therapy with novel agents and adoptive cellular therapies, are appropriate to consider in an effort to further improve outcomes.

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