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Higher total body irradiation dose-intensity in fludarabine/TBI-based reduced-intensity conditioning regimen is associated with inferior survival in non-Hodgkin lymphoma patients undergoing allogeneic transplantation.

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Abstract

INTRODUCTION—Disease relapse is the most common cause of therapy failure in non-Hodgkin lymphoma (NHL) patients undergoing reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (alloHCT). It is not known whether or not increasing total body irradiation (TBI) dose from 2Gy to 4Gy in RIC-platform can provide improved disease control without increasing non-relapse mortality (NRM). Using the CIBMTR database we evaluated the outcomes of NHL patients receiving RIC alloHCT with either fludarabine (Flu)/2Gy TBI vs. Flu/4Gy TBI.

METHODS—In the CIBMTR registry, 413 adult NHL patients underwent a first alloHCT using either a matched related or unrelated donor between 2008–2017, utilizing a RIC regimen with either Flu/2Gy TBI (n=349) or Flu/4Gy TBI (n=64). The primary endpoint was overall survival (OS). Secondary endpoints included acute (a) and chronic (c) graft-versus-host disease (GVHD), NRM, relapse/progression and progression-free survival (PFS).

RESULTS—At baseline the Flu/2Gy TBI cohort had significantly fewer patients with KPS ≥90 and significantly more patients had a higher HCT-CI. On multivariate analysis the two conditioning cohorts were not significantly different in terms of risk of grade 3–4 aGVHD or cGVHD. Compared to Flu/2Gy TBI, the Flu/4Gy TBI conditioning was associated with a significantly higher risk of NRM (HR 1.79, 95%CI=1.11–2.89, p=0.02), and inferior OS (HR 1.51, 95%CI=1.03–2.23, p=0.03). No significant differences were seen in the risk of relapse/progression (HR 0.78, 95%CI=0.47–1.29, p=0.33) or PFS (HR 1.09, 95%CI=0.78–1.54, p=0.61) between the two regimens. Comparing Flu/2Gy TBI vs. Flu/4Gy TBI cohorts the 5-year adjusted outcomes were; NRM (28% vs. 47%; p=0.005), relapse/progression (35% vs. 29%; p=0.28), PFS (37% vs. 24%; p=0.03) and OS (51% vs. 31%; p=0.001), respectively. Relapse was the most common cause of death in both cohorts.

CONCLUSIONS—In NHL patients undergoing Flu/TBI-based conditioning, augmenting TBI dose from 2Gy to 4Gy is associated with higher NRM and inferior OS, without any significant benefit in terms of disease control. 2Gy is optimal dose in the RIC Flu/TBI platform for lymphomas.

Keywords

fludarabine; TBI; reduced-intensity conditioning; allogeneic hematopoietic cell transplant

INTRODUCTION

Reduced-intensity conditioning (RIC) or non-myeloablative conditioning (NMA) regimens currently account for ~45% of all allogeneic hematopoietic cell transplants (alloHCT) performed in the United States (U.S)[1]. Owing to their lower intensity, these regimens are generally associated with a reduced risk of non-relapse mortality (NRM) and can be offered to older patients and those with significant comorbid conditions. Considering the median age at diagnosis of non-Hodgkin lymphoma (NHL) patients is 67 years,[2] it is not surprising that RIC/NMA regimens now account for the majority of alloHCT performed for this indication

in the U.S[3]. Unfortunately, disease relapse remains the most common cause of treatment failure in NHL patients undergoing alloHCT with lower-intensity conditioning platforms.[4–6]

The RIC/NMA conditioning approach with the best risk/benefit profile (NRM vs. relapse rate) in NHL patients remains controversial. A Center for International Blood & Marrow Transplant Research (CIBMTR) analysis[7] compared HCT outcomes among lymphoma patients undergoing alloHCT with either 2Gy total body irradiation (TBI)-based or non-TBI containing NMA conditioning alloHCT. The study found a higher risk of graft-versus-host disease (GVHD) with TBI-based approaches, but no difference in relapse risk or survival outcomes between the two approaches. Recent data for patients with non-malignant blood disorders undergoing alternative donor NMA alloHCT suggest that increasing the dose of TBI in transplant conditioning to 4Gy can substantially reduce the risk of graft failure, without negatively impacting NRM rates.[8] However, it is not known whether increasing TBI dose from 2Gy to 4Gy in RIC/NMA-platforms can provide improved disease control without increasing NRM in lymphoma patients. Using the CIBMTR database we evaluated the outcomes of NHL patients receiving RIC alloHCT with either fludarabine (Flu)/2Gy TBI vs. Flu/4Gy TBI.

METHODS

Data sources

The CIBMTR is a working group of more than 500 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 a new malignancy, and cause of death. All CIBMTR centers contribute TED-data. More detailed disease and pre- and post-transplant clinical information is 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) patients with NHL, undergoing their first Flu/TBI-based RIC/ NMA alloHCT between 2008 and 2017. Eligible donors included either

HLA-identical sibling donors or adult unrelated donors (URD) matched at the allele-level at HLA-A, -B, -C and -DRB1. All the patients received peripheral blood as the graft-source and GVHD prophylaxis was limited to calcineurin inhibitor (CNI)-based approaches.

Definitions and Study Endpoints

Response to the last line of therapy before alloHCT was determined using the International Working Group criteria in use during the era of this analysis[9]. The primary endpoint was overall survival (OS); death from any cause was considered an event and surviving patients were censored at last contact. Secondary endpoints included NRM, progression/relapse, progression-free survival (PFS), acute and chronic GVHD. 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 response (CR); 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. Neutrophil recovery was defined as the first of 3 successive days with absolute neutrophil count (ANC) ≥500/μL after post-transplantation nadir. Platelet recovery was considered to have occurred on the first of three consecutive days with platelet count 20,000/μL or higher, in the absence of platelet transfusion for 7 consecutive days. For neutrophil and platelet recovery, death without the event was considered a competing risk. Acute GVHD[10] and chronic GVHD[11] were graded using standard criteria. Primary and secondary graft failures were considered as a single outcome. Primary graft failure was defined as failure to achieve an ANC of ≥500/μL for 3 consecutive days or donor chimerism < 5% (peripheral blood CD3+ or bone marrow). Secondary graft failure was defined as initial donor engraftment followed by graft loss, evidenced by a persistent decline in the ANC (≥500/μL) or loss of donor chimerism < 5% or a second transplantation in patients with documented clinical remission[12].

Statistical analysis

The Flu/2Gy TBI cohort was compared against the Flu/4Gy TBI cohort. Probabilities of PFS and OS were calculated as described previously[13]. Cumulative incidence of NRM and lymphoma progression/relapse were calculated to accommodate for competing risks[14]. Associations among patient-, disease-, and transplantation-related variables and outcomes of interest were evaluated using multivariable Cox proportional hazards regression. A forward stepwise selection was used to identify covariates that influenced outcomes. Covariates with a $p<0.05$ were considered statistically significant. The proportional hazards assumption for Cox regression was tested by adding a time-dependent covariate for each risk factor and each outcome. Interactions between the main effect and significant covariates (e.g. remission status, lymphoma subtype) were examined and none were found. Results are expressed as hazard ratio (HR). The center effect was examined using the random effect score test[15] for OS, PFS, relapse, and NRM. There was no center effect noted for any of the outcomes. The variables considered in multivariable regression analysis include conditioning regimen (main effect), patient age, Karnofsky performance status (KPS), HCT-comorbidity index (HCT-CI), race, lymphoma histology, remission status at HCT, history of prior autologous HCT, interval between diagnosis and HCT, donor type, GVHD prophylaxis, use of *in vivo* T-cell

depletion, donor-recipient cytomegalovirus serostatus and year of HCT. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Characteristics

A total of 413 NHL patients were included in the analysis, of whom 349 patients received RIC with Flu/2Gy TBI and 64 received Flu/4Gy TBI. The baseline patient-, disease- and transplantation-related characteristics are shown in Table 1. The two groups had no significant differences in terms of patient age, gender, race, lymphoma subtypes, median interval between diagnosis and allogeneic HCT, remission status at HCT, history of prior autologous HCT, *in vivo* T-cell depletion use with conditioning, donor type, and donor-recipient CMV serostatus. The proportion of patients with KPS ≥90% was higher in Flu/4Gy TBI cohort compared to Flu/2Gy TBI group (79.7% vs. 60.5%; p=0.01). A greater proportion of patients in Flu/2Gy TBI group had an HCT-comorbidity index (HCT-CI), ≥3 (43.3% vs 21.9%; p=0.003) and CNI/mycophenolate mofetil-based GVHD prophylaxis (96% vs 85.9%; p=0.004) compared to the Flu/4Gy TBI cohort. Median follow-up of survivors was 59.4months in the Flu/2Gy TBI group and 48.5months in the Flu/4Gy TBI group.

Hematopoietic recovery and GVHD

The day 28 cumulative incidence of neutrophil recovery for the Flu/2Gy TBI group was 97.4% (95%CI=95.4–98.8) compared 95.3% (95%CI=88.1–99.3) for the Flu/4Gy TBI group (p=0.48; Table 2). The day 100 cumulative incidence of platelet recovery in the same order was 97.4% (95%CI=95.4–98.8) and 100% (95%CI=0–100) (p=0.15; Table 2), respectively. There was no difference in the risk of graft failure between the two cohorts.

On univariate analysis, the cumulative incidence of grade II-IV acute GVHD at day 180 (Table 2) in the Flu/2Gy TBI cohort was 46.6% (95%CI=41.4–51.9), compared to 50% (95%CI=37.4–62.6) in the Flu/4Gy TBI (p=0.63). The corresponding rates of grades III-IV acute GVHD were 14.7% (95%CI=11.1–18.6) vs. 18.3% (95%CI=9.6–29.1), respectively (p=0.50). On multivariable regression analysis (Table 3), the two cohorts were not significantly different in terms of risk of grade III-IV acute GVHD (odds ratio=1.29, 95%CI=0.63–2.64, p=0.49). On univariate analysis, the cumulative incidence of chronic GVHD at 1-year (Table 3) in Flu/2Gy TBI cohort was 53.3% (95%CI=47.9–58.7) compared to 64.7% (95%CI=51.8–76.7) in the Flu/4Gy TBI (p=0.10). On multivariable regression analysis (Table 3), the two cohorts were not significantly different in terms of risk of chronic GVHD (HR=1.35, 95%CI=0.97–1.88, p=0.08).

NRM and relapse/progression

The adjusted cumulative incidence of NRM at 5-years was 28% (95%CI=23–33) and 47% (95%CI=35–59) in the Flu/2Gy TBI and Flu/4Gy TBI groups, respectively (p=0.005; Figure 1a, Table 2). On multivariable regression analysis, Flu/4Gy TBI was associated with a significantly higher risk of NRM (HR=1.79, 95%CI=1.11–2.89, p=0.02) (Table 3). In

addition, HCT-CI >3, was independently predictive of higher risk of NRM (HR=2.25; Table 3).

The adjusted cumulative incidence of relapse/progression at 5-years was 37% (95%CI=30–40) and 29% (95%CI=18–40) in the Flu/2Gy TBI and Flu/4Gy TBI groups, respectively (p=0.28; Figure 1b, Table 2). On multivariable regression analysis (Table 3), the two cohorts were not significantly different in terms of risk of relapse/progression (HR=0.78, 95%CI=0.47–1.29, p=0.33). Partial remission (HR=2.30) or resistant disease (HR=2.49) as remission status before HCT were associated with a significantly higher risk of disease relapse/progression, while matched unrelated donor HCT was independently associated with a lower risk of relapse/progression (HR=0.60; Table 3).

Progression-free Survival & Overall Survival

The 5-year adjusted PFS in the Flu/2Gy TBI and Flu/4Gy TBI groups was 37% (95%CI=31–42) and 24% (95%CI=14–34), respectively, p=0.03 (Figure 1c, Table 2). On multivariable regression analysis (Table 3), PFS between the two cohorts was not significantly different (HR=1.09, 95%CI=0.78–1.54, p=0.61). Partial remission (HR=1.72) or resistant disease (HR=1.99) as remission status before HCT were independently associated with a significantly worse PFS (Table 3).

The 5-year OS in the Flu/2Gy TBI and Flu/4Gy TBI cohorts was 51% (95%CI=46–57) and 31% (95%CI=20–41), respectively, p=0.001 (Figure 1d, Table 2). On multivariable regression analysis, Flu/4Gy TBI was associated with a significantly higher risk of mortality (HR=1.51, 95%CI=1.03–2.23, p=0.03) (Table 3). Other factors independently associated with a higher risk of mortality included; resistant disease (HR=1.69) as remission status before HCT and HCT-CI >3 (HR=1.73; Table 3).

Causes of Death

At last follow-up, 150 Flu/2Gy TBI cohort and 33 Flu/4Gy TBI cohort recipients had died (Table 4). Recurrent/progressive lymphoma was the primary cause of death in 55 (Flu/2Gy TBI patients (35.7%) and 10 Flu/4Gy TBI patients (30.3%). GVHD was the primary cause of death in 24 Flu/2Gy TBI cohort patients (15.6%) compared to 3 Flu/4Gy TBI cohort (9.1%) subjects. Infectious complications accounted for 6.5% (n=10) of deaths in Flu/2Gy TBI group and 3% (n=1) in the Flu/4GY TBI group.

DISCUSSION

Prospective, randomized studies assessing the relative importance of TBI dose-intensity within the context of RIC/NMA alloHCT conditioning regimens in NHL patients have not been performed. Hence, utilizing the observational database of the CIBMTR we compared 2Gy vs. 4Gy TBI conditioning in NHL patients and make several important observations. First, higher 4Gy TBI dose in Flu/TBI regimen was not associated with a higher risk of acute or chronic GVHD. Second, lower 2Gy TBI dose was not associated with a higher risk of graft failure. Third, Flu/4Gy TBI did not reduce the risk of disease relapse/progression or therapy failure. Finally, higher TBI dose intensity was associated with a higher risk of NRM and overall mortality.

Limited data are available comparing 2Gy TBI conditioning with 4Gy TBI in patients with myeloid malignancies[16]. In a single center, retrospective analysis, Sobecks et al.[17] compared outcomes of Flu/2Gy TBI (n=42) with Flu/4Gy TBI (n=40) in a heterogenous group of patients with hematological malignancies (predominantly myeloid disorders). The authors found no significant difference between the cohorts in terms of hematopoietic recovery, graft failure, GVHD and survival outcomes. While limited by sample size, interestingly in this analysis[17] the median survival of lymphoma patients receiving Flu/2Gy TBI (n=12) was 50months compared to 15months in subjects undergoing Flu/4Gy TBI (n=9) conditioning.

Increased doses of TBI in conditioning regimens have been associated with a higher risk of tissue injury and subsequently higher risk of GVHD. Prior CIBMTR data[7] comparing NMA alloHCT outcomes among lymphoma patients undergoing 2Gy TBI-based conditioning vs. non-TBI RIC approaches showed a higher risk of GVHD with TBI-containing approaches. In the current analysis, we found no increase in the risk of either acute or chronic GVHD with increasing TBI dose from 2Gy to 4Gy (Table 2), consistent with the data reported by Cleveland Clinic group[17]. In addition, unlike the recent data for non-malignant blood disorders, where 4Gy TBI containing conditioning approach in patients undergoing haploidentical transplantation was shown to substantially reduce the risk of graft failure[8], our analysis did not yield a similar benefits, albeit our patient population carries a vastly different clinical profile (NHL patients receiving HLA matched grafts).

In our current study 2Gy TBI dose in NHL patients was associated with superior OS due to the significantly lower NRM seen in this group. This is noteworthy considering the fact that the Flu/2Gy TBI cohort included more patients with a higher comorbidity burden, and worse performance score. Cause of death data (Table 4) suggest that this higher NRM does not appear to be related to a higher incidence of second malignancies or GVHD related mortality in the 4Gy TBI cohort, but due to other causes of death (that potentially can be a result of late effects of higher TBI dose). The nature of data reported to the registry precludes a more granular assessment of causes of death across two cohorts.

While the optimal RIC regimen for NHL patients is unknown, a recent CIBMTR report comparing various RIC regimens commonly utilized for NHL demonstrated a higher NRM and inferior OS with RIC platforms with relatively higher intensity (fludarabine/melphalan 140mg/m^2), compared to lower intensity RIC options (e.g. fludarabine/busulfan 6.4mg/kg iv, fludarabine/cyclophosphamide-based regimens)[18]. These data collectively along with our current analysis suggest that more intense conditioning options are unlikely to improve alloHCT outcomes in NHL patients.

In this registry-based analysis, some important limitations should be considered. Any observational study comparing different interventions is subject to preferences of the treating centers/physicians owing to the complex criteria for selection that underlie the choice of a given intervention. Our analysis cannot adjust for unknown variables that could have prompted a given center or a physician to pick one conditioning option over the other. Since CIBMTR does not capture donor cell chimerism at TED level data, in the current analysis we cannot assess any possible differences in donor cell chimerism kinetics between the two cohorts. We caution extrapolating these observations to patients with myeloid malignancies

(where benefit conditioning dose intensity is well established) to other TBI-based RIC platforms in NHL. We did not include patients receiving Flu/cyclophosphamide/TBI based conditioning in the current analysis since 4Gy TBI dose was rarely reported with that regimen in CIBMTR registry. Our study included a variety of NHL subtypes (that have varying degrees of relapse risk), but we found no interaction between the main effect (the two conditioning regimens) and lymphoma subtype for any of the outcomes analyzed (i.e. the impact of conditioning regimen did not vary according to NHL histology), justifying inclusion of different NHL subtypes in this analysis. Small sample size of 4Gy TBI group is another limitation to acknowledge.

In conclusion, our analysis provides compelling evidence of the higher toxicity and lack of a survival advantage with the use of a higher 4Gy TBI dose in NHL patients undergoing Flu/TBI-based conditioning as part of their RIC. 2Gy TBI should be considered the optimal dose in this setting.

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Highlights

- Augmentation of TBI dose from 2Gy to 4Gy for NHL patients undergoing RIC alloHCT is associated with higher NRM and inferior OS
- Higher dose of TBI does not result in improved disease control.

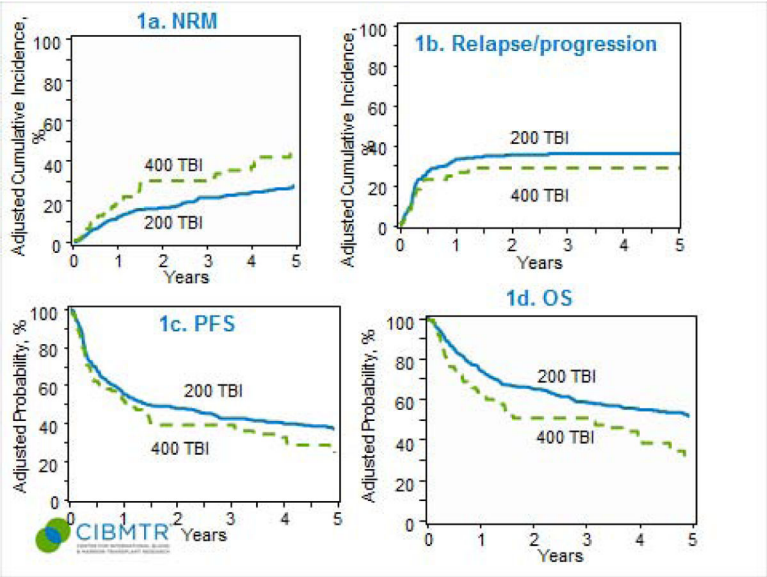

Figure 1.

Adjusted transplantation outcomes of patients receiving Flu/4Gy TBI (interrupted lines) and Flu/2Gy TBI (solid line) regimens. 1a: Cumulative incidence of Relapse. 1b: Cumulative incidence of non-relapse mortality. 1c: Progression-free survival. 1d: Overall survival.

Table 1.

Baseline characteristics for NHL patients receiving first alloHCT and Flu/2Gy vs. Flu/4Gy TBI in conditioning during 2008–2017

	Flu/2Gy TBI N=349	Flu/4Gy TBI N=64	P-value
Number of centers	55	8	
Median Patient age (range)	57.7 (20.4–77.1)	55.3 (22.7–72.9)	0.67
Male gender (%)	231 (66.2)	50 (78.1)	0.06
Patient race (%)			0.15
Caucasian	313 (89.7)	55 (85.9)	
Other[1]	14 (4)	1 (1.6)	
Not reported	22 (6.3)	8 (12.5)	
Karnofsky performance score ≥90 (%)	211 (60.5)	51 (79.7)	0.01
Lymphoma subtypes (%)			0.09
Follicular lymphoma	87 (24.9)	13 (20.3)	
Diffuse large B-cell lymphoma	107 (30.7)	11 (17.2)	
Mantle cell lymphoma	74 (21.2)	20 (31.3)	
Other B-cell	23 (6.6)	7 (10.9)	
T-cell NHL	58 (16.6)	13 (20.3)	
HCT-CI (%)			0.003
0	90 (25.8)	26 (40.6)	
1–2	89 (25.5)	23 (35.9)	
≥ 3	151 (43.3)	14 (21.9)	
Missing	19 (5.4)	1 (1.6)	
Prior autoHCT (%)	186 (53.3)	33 (51.6)	0.80
Median time from diagnosis to HCT, mons (range)	40.9 (1.4–250.8)	32.9 (4.4–165.6)	0.60
Donor type (%)			0.38
Matched related donor	157 (45)	25 (39.1)	
Matched unrelated donor	192 (55)	39 (60.9)	
Remission at HCT (%)			0.92
Complete remission	174 (49.9)	35 (54.7)	
Partial remission	117 (33.5)	21 (32.8)	
Resistant	46 (13.2)	6 (9.4)	
Untreated/Unknown	12 (3.4)	2 (3.1)	
ATG/alemtuzumab in conditioning (%)	10 (2.9)	3 (4.7)	0.44
Rituximab with conditioning (%)	38 (10.9)	0	0.005
GVHD prophylaxis (%)			0.004
CNI + MMF +- other(s)	335 (96)	55 (85.9)	
CNI + MTX +- other(s)	9 (2.6)	7 (10.9)	
CNI + other(s) (except MMF, MTX)	5 (1.4)	2 (3.1)	
CMV donor negative/recipient positive (%)	100 (28.7)	18 (28.1)	0.99
Follow-up - median (min-max)	59.4 (3.22–122.2)	48.55 (3.78–96.88)	

Abbreviations: HCT-hematopoietic cell transplantation; HCT-CI- HCT comorbidity index; ATG-anti-thymocyte globulin; CMV-cytomegalovirus; CNI-calcineurin inhibitors; GVHD; graft-versus-host disease; MTX-methotrexate; MMF-mycophenolate mofetil

[1]Patient race - other: **Flu/2GyTBI**: 14: 5 African American; 5 Asian; 2 Bi-racial; 1 Native American; 1 Native Pacific Islander. **Flu/4Gy TBI**: 1 African American.

Table 2:

Engraftment, graft-versus-host disease and adjusted HCT outcomes.

		Flu/2Gy TBI (N = 349)		Flu/4Gy TBI (N = 64)	
Outcomes	**N**	**Probability (95% CI)**	**N**	**Probability (95% CI)**	**P Value**
Neutrophil recovery	348		64		
28 days		97.4 (95.4–98.8)%		95.3 (88.1–99.3)%	0.48
Platelet recovery	346		63		
100-day		97.4 (95.4–98.8)%		100 (0–100)%	0.15
Acute grade II-IV GVHD	342		61		
6 months		46.6 (41.4–51.9)%		50 (37.4–62.6)%	0.63
Acute grade III-IV GVHD	342		61		
6 months		14.7 (11.1–18.6)%		18.3 (9.6–29.1)%	0.50
Chronic GVHD	342		62		
1-year		53.3 (47.9–58.7)%		64.7 (51.8–76.7)%	0.10
2-year		66 (60.7–71.1)%		68.4 (55.6–79.9)%	0.73
Graft failure	348		64		
100-day		0.6 (0.1–1.6)%		1.6 (0–6.2)%	0.54
1-year		1.8 (0.6–3.5)%		3.2 (0.3–8.9)%	0.55
Adjusted Non-relapse mortality	345		63		
1-year		13 (9–16)%		20 (12–28)%	0.10
3-year		22 (18–27)%		30 (21–40)%	0.12
5-year		28 (23–33)%		47 (35–59)%	0.005
Adjusted Relapse/progression	345		63		
1-year		32 (28–37)%		25 (14–35)%	0.22
3-year		35 (30–40)%		29 (18–40)%	0.31
5-year		35 (30–40)%		29 (18–40)%	0.28
Adjusted Progression-free survival	345		63		
1-year		55 (50–60)%		52 (42–62)%	0.55
3-year		42 (37–47)%		39 (29–49)%	0.56
5-year		37 (31–42)%		24 (14–34)%	0.03
Adjusted overall survival	349		64		
1-year		74 (70–79)%		64 (54–73)%	0.04
3-year		59 (53–64)%		51 (41–61)%	0.18
5-year		51 (46–57)%		31 (20–41)%	0.001

Abbreviations: GVHD=graft-versus-host disease; CI = confidence interval; N = number.

Table 3:

Multivariable Analysis Results

	N	OR	OR Lower CI	OR Upper CI	p-value
Grade 3–4 acute GVHD **					
Main effect					
Flu/2GY TBI	342	1			0.49
Flu/4GY TBI	61	1.29	0.63	2.64	0.49
Chronic GVHD					
Main effect					
Flu/2GY TBI	344	1			0.08
Flu/4GY TBI	63	1.35	0.97	1.88	0.08
Non-relapse mortality					
Main effect					
Flu/2GY TBI	344	1			0.02
Flu/4GY TBI	63	1.79	1.11	2.89	0.02
HCT-CI					
0	114	1			0.01
1 to 2	109	1.48	0.84	2.60	0.17
3+	165	2.25	1.36	3.73	0.0003
missing	19	1.52	0.57	4.01	0.40
Progression/relapse					
Main effect					
Flu/2GY TBI	349	1			0.33
Flu/4GY TBI	64	0.78	0.47	1.29	0.33
Remission at HCT					
Complete remission	209	1			<0.0001
Partial remission	138	2.30	1.56	3.38	<.0001
Resistant	52	2.49	1.52	4.08	0.0003
Untreated/Unknown	14	2.26	0.96	5.29	0.06
Donor type					
Matched related donor	182	1			0.004
Matched unrelated donor	231	0.60	0.43	0.85	0.004
Progression-free survival					
Main effect					
Flu/2GY TBI	349	1			0.61
Flu/4GY TBI	64	1.09	0.78	1.54	0.61
Remission at HCT					
Complete remission	209	1			0.0001
Partial remission	138	1.72	1.30	2.28	0.0002

	N	OR	OR Lower CI	OR Upper CI	p-value
Resistant	52	1.99	1.37	2.89	0.0003
Untreated/Unknown	14	1.30	0.60	2.79	0.50
Overall survival					
Main effect					
Flu/2GY TBI	349	1			0.03
Flu/4GY TBI	64	1.51	1.03	2.23	0.03
HCT - CI					
0	116	1			0.04
1 to 2	112	1.31	0.86	2.00	0.21
3+	165	1.73	1.18	2.54	0.01
missing	20	1.44	0.72	2.90	0.31
Remission at HCT					
Complete remission	209	1			0.05
Partial remission	138	1.20	0.87	1.65	0.28
Resistant	52	1.69	1.11	2.55	0.01
Untreated/Unknown	14	0.55	0.17	1.74	0.31

Abbreviations: HCT-CI- HCT comorbidity index;

** Acute GVHD models used logistic regression.

Table 4.

Causes of death.

	Flu/2Gy TBI	Flu/4Gy TBI
Total number of deaths (%)	**150**	**33**
Primary disease	55 (35.7)	10 (30.3)
Infection	10 (6.5)	1 (3)
Acute respiratory distress syndrome/idiopathic pneumonia syndrome	5 (3.2)	1 (3)
Graft-versus-host disease	24 (15.6)	3 (9.1)
Organ Failure	20 (13)	5 (15.2)
Second malignancy	2 (1.3)	0
Other[1]	30 (19.5)	10 (30.3)
Not reported	8 (5.2)	3 (9.1)

[1]Other:

Flu/2GY TBI: 24 other HCT related cause, NOS; 1 encephalopathy and stroke; 1 hypoxic respiratory failure; 1 stroke; 1 pulmonary embolism; 1 toxic encephalopathy; 1 acute left basal ganglia stroke.

Flu/4GY TBI: 7 other HCT related cause, NOS; 1 septic shock; 1 suicide; 1 possible MI.