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Haploidentical

Improved Outcomes of Haploidentical Hematopoietic Cell Transplantation with Total Body Irradiation-Based Myeloablative Conditioning in Acute Lymphoblastic Leukemia

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A B S T R A C T

The optimal myeloablative conditioning (MAC) for patients undergoing haploidentical hematopoietic cell transplantation (haplo-HCT) is unknown. We studied the outcomes of total body irradiation (TBI)-based versus chemotherapy (CT)-based MAC regimens in patients with acute lymphoblastic leukemia (ALL). The study included 427 patients who underwent first haplo-HCT with post-transplantation cyclophosphamide (PTCy), following TBI-based (n = 188; 44%) or CT-based (n = 239; 56%) MAC. The median patient age was 32 years. Fludarabine-TBI (72%) and thiotepa-busulfan-fludarabine (65%) were the most frequently used TBI- and CT-based regimens, respectively. In the TBI and CT cohorts, 2-year leukemia-free survival (LFS) was 45% versus 37% (P = .05), overall survival (OS) was 51% versus 47% (P = .18), relapse incidence (RI) was 34% versus 32% (P = .44), and nonrelapse mortality (NRM) was 21% versus 31% (P < .01). In the multivariate analysis, TBI was associated with lower NRM (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.33 to 0.86; P = .01), better LFS (HR, 0.71; 95% CI, 0.52 to 0.98; P =.04), and increased risk for grade II-IV acute graft-versus-host disease (GVHD) (HR, 1.59; 95% CI, 1.08 to 2.34; P = .02) compared with CT-based MAC. The type of conditioning regimen did not impact RI, chronic GVHD, OS, or GVHD-free, relapse-free survival after adjusting for transplantation-related variables. TBI-based MAC was associated with lower NRM and better LFS compared with CT-based MAC in patients with ALL after haplo-HCT/PTCy.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative treatment modality for patients with acute lymphoblastic leukemia (ALL) [1]. Multiple conditioning regimens are being used in practice. The goals of conditioning

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therapy before hematopoietic cell infusion are to eradicate residual leukemia clones and create a favorable immune environment to allow successful engraftment in a recipient. These regimens can be categorized based on their perceived regimen-related toxicities into myeloablative conditioning (MAC), reduced-intensity conditioning (RIC), or nonmyeloablative (NMA) conditioning [2]. Examples of MAC include total body irradiation (TBI) ≥5 Gy in a single dose or busulfan (Bu) >8 mg/kg. Multiple registry-based studies and a prospective randomized study have established the advantage of MAC in young, fit patients undergoing allo-HCT for acute leukemia [3-7]. TBI-based versus chemotherapy (CT)-based MAC has been compared in observational and prospective studies in patients undergoing allo-HCT from a full HLA-matched sibling donor (MSD) or a matched unrelated donor (MUD) [8-10]. TBI-based MAC appears to be associated with superior leukemia-free survival (LFS) owing to lower relapse incidence (RI) and comparable nonrelapse mortality (NRM) among patients with ALL [11-16].

Allo-HCT from a haploidentical related donor has emerged as a suitable alternative in the absence of an MSD or MUD [17-19]. In retrospective analyses, T cell-replete haploidentical related donor allo-HCT (haplo-HCT) with post-transplantation cyclophosphamide (PTCy) has shown comparable clinical outcomes to MUD allo-HCT, with a significantly lower risk of chronic graft-versus-host disease (cGVHD) [20-27]. The ideal MAC regimen for adult ALL patients undergoing haplo-HCT remains to be defined. Small single-center noncomparative retrospective studies have shown the safety and efficacy of TBI-based MAC in the setting of haplo-HCT [28,29].

In this study, we compared the outcomes of patients with ALL who underwent TBI-based versus CT-based MAC followed by haplo-HCT/PTCy. We used a transplantation registry database to study the factors impacting haplo-HCT outcomes to determine which patients would benefit from a TBI- or CT-based MAC regimen.

METHODS

Study Design and Data Collection

This was a retrospective multicenter analysis using the dataset of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT) registry. The EBMT is a voluntary working group of more than 600 transplantation centers that are required to report all consecutive stem cell transplantations and follow-ups once yearly. Audits are routinely performed to determine the accuracy of the data. Eligibility criteria for this analysis included adult patients age ≥18 years with ALL who underwent a first haplo-HCT with PTCy and a MAC regimen between 2010 and 2018. A haploidentical donor was defined as a ≥2 HLA-mismatched related donor. The exclusion criteria were receipt of allo-HCT from another donor type (MSD, MUD, mismatched-unrelated donor, or cord blood), previous history of allo-HCT, use of ex vivo T cell-depleted hematopoietic cell grafts, use of alemtuzumab or antithymocyte globulin, or lack of information on conditioning regimen. Data collected included recipient and donor characteristics (age, sex, cytomegalovirus serostatus), disease characteristics, disease status at transplantation, year of transplantation, type of conditioning regimen, stem cell source (bone marrow [BM] or peripheral blood [PB]), and GVHD prophylaxis regimen. The conditioning regimen was defined as MAC based on the reports from individual transplantation centers according to previously established EBMT criteria [2]. GVHD prophylaxis regimens were according to institutional protocols, but all patients received PTCy. Grading of acute GVHD (aGVHD) was performed using established criteria [30]. cGVHD was classified as limited or extensive according to published criteria [31]. For this study, all necessary data were collected according to the EBMT guidelines, using the EBMT minimum essential data forms. A list of institutions reporting data included in this study is provided in Supplementary Table S1.

Ethics Approval and Consent to Participate

All required data for the current survey were collected according to EBMT guidelines. The scientific board of the Acute Leukemia Working Party of the EBMT approved this study. Also, the study protocol was approved by the institutional review board at each site and complied with country-specific regulatory requirements. All patients gave informed consent to use their anonymized personal information for research purposes. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Statistical Analysis

The study endpoints were overall survival (OS), LFS, RI, NRM, engraftment, aGVHD, and cGVHD incidence, as well as GVHD-free, relapse-free survival (GRFS). All endpoints were measured from the time of transplantation. OS was defined as time to death from any cause. LFS was defined as survival with no evidence of relapse or progression. We used modified GRFS criteria and GRFS events were defined as the first event among grade III-IV aGVHD, extensive cGVHD, relapse, and death from any other cause [32,33].

Patient, disease, and transplantation-related characteristics were compared between the 2 groups (TBI and CT cohorts) using the Mann-Whitney *U*test for numerical variables, chi-square, or Fisher's exact test for categorical variables. The probabilities of OS, LFS, and GRFS were calculated using the Kaplan-Meier (KM) estimator. The RI and NRM were calculated using cumulative incidence curves in a competing-risk setting, with death in remission treated as a competing event for relapse. The median duration of follow-up was calculated using the reverse KM estimator, with being alive as the event and death censored. Early death was considered a competing event for engraftment. To estimate the cumulative incidence of aGVHD or cGVHD, relapse and death were considered as competing events. Univariate analyses were done using the log-rank test for LFS and OS, while Gray's test was used for cumulative incidence. Multivariate analyses were performed with the Cox proportional hazards regression model. All variables differing significantly between the 2 groups, or potential risk factors were included in the model. All p-values were two-sided with a type 1 error rate fixed at 0.05. Statistical analyses were performed with SPSS 24.0 (SPSS Inc, Chicago, IL, USA) and R 3.4.1 [R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.]

Data Sharing Statement

Please contact the EBMT for the original data used for this study (www.ebmt.org).

RESULTS

Patient, Transplantation, and Disease Characteristics

Baseline patient, transplantation, and disease characteristics were comparable in the 2 study cohorts (Table 1). A total of 427 patients met the study inclusion criteria. TBI-based MAC was used in 188 patients (44%), and CT-based MAC was used in 239 (56%). Overall, the median patient age was 31 years, and 36% were female. The Karnofsky Performance Status (KPS) score was ≥90 points in 72% of the patients, and the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) was 0 in 68% of the patients. The median duration of follow-up after haplo-HCT was 20.7 months (IQR, 11.7 to 35.3 months) in the TBI cohort and 26.2 months (IQR, 10.2 to 41.0 months) in the CT cohort (P= .59). The primary diagnosis was B cell ALL in 291 patients (75%). Philadelphia chromosome-positive disease was reported in 91 patients (27%). The disease status before haplo-HCT was complete remission (CR) 1 in 208 patients (49%), ≥CR2 in 135 (32%), and advanced in 84 (20%). The most common TBI- and CT-based MAC regimens were fludarabine-TBI (Flu-TBI; n = 136; 72% of the TBI cohort) and thiotepa-Bu-Flu (TBF; n = 156; 65% of the CT cohort), respectively. The median i.v. Bu dose (n = 210 patients) was 9.6 mg/kg (range, 9.6 to 12.8 mg/kg). Two patients received oral Bu, one with a total dose of 12 mg/kg and the other with a total dose of 16 mg/kg. The median thiotepa dose (n = 176 patients) was 10 mg/kg (range, 5 to 20 mg/kg). The median TBI dose was 12 Gy (range 7.5 to 16 Gy) in 188 patients. A complete list of the conditioning regimens is provided in Supplementary Table S2.

There was a trend toward frequent use of TBI-MAC in high-volume centers (≥10 cases/center) compared with low-volume centers (P= .008). Cyclosporine A plus mycophenolate mofetil was the most common GVHD prophylaxis regimen (in 68% of TBI patients and 61% of CT patients). There was no statistically significant difference between the 2 cohorts in the proportion of patients who received PB grafts versus BM grafts (P= .72).

Table 1
Baseline Patient, Disease, and Transplantation Characteristics

Characteristic	CT Cohort (N = 239)	TBI Cohort (N = 188)	*P* Value
Follow-up (reverse KM), mo, median (IQR)	26.2 (10.2-41.0)	20.7 (11.7-35.3)	.59
Patient age at haplo-HCT, yr, median (range) [IQR]	32.1 (18.1-65.3) [24.9-46]	32 (18.1-68.2) [23.6-44.4]	.41
Year of haplo-HCT, median (range)	2016 (2010-2018)	2016 (2011-2018)	.96
Philadelphia chromosome status, n (%)			
Negative	138 (72.6)	114 (74.5)	.70
Positive	52 (27.4)	39 (25.5)	
Missing	49	35	
Immunophenotype, n (%)			
B cell	162 (73.0)	129 (76.8)	.39
T cell	60 (27.0)	39 (23.2)	
Missing	17	20	
Donor age, yr, median (range) [IQR]	39 (8.2-74.3) [26.9-50.6]	40.3 (13.2-67) [28.6-50.7]	.98
Missing, n	39	14	
Disease status before haplo-HCT, n (%)			
CR1	113 (47.3)	95 (50.5)	.65
≥CR2	80 (33.5)	55 (29.3)	
Advanced	46 (19.3)	38 (20.2)	
Patient sex, n (%)			
Male	146 (61.3)	129 (68.6)	.12
Female	92 (38.7)	59 (31.4)	
Missing	1	0	
Donor sex, n (%)			
Male	123 (51.5)	114 (60.6)	.06
Female	116 (48.5)	74 (39.4)	
Missing	0	0	
Female donor to male recipient, n (%)			
No	165 (69.3)	138 (73.4)	.36
Yes	73 (30.7)	50 (26.6)	
Missing	1	0	
Patient CMV serostatus, n (%)			
Negative	57 (24.0)	36 (19.6)	.28
Positive	181 (76.1)	148 (80.4)	
Missing	1	4	
Donor CMV serostatus, n (%)			
Negative	52 (22.5)	50 (27.5)	.25
Positive	179 (77.5)	132 (72.5)	
Missing	8	6	
Graft source, n (%)			
BM	130 (54.4)	99 (52.7)	.72
PB	109 (45.6)	89 (47.3)	
KPS score, n (%)			
<90	61 (26.9)	53 (29.0)	.64
≥90	166 (73.1)	130 (71.0)	
Missing	12	5	
HCT-CI score, n (%)			
0	106 (68.0)	77 (68.8)	.99
1 or 2	21 (13.5)	15 (13.4)	
≥3	29 (18.6)	20 (17.9)	
Missing	83	76	
GVHD prophylaxis, n (%)			
CSA	5 (2.1)	5 (2.7)	<.01*
CSA + MTX	5 (2.1)	2 (1.1)	
CSA + MMF	146 (61.1)	128 (68.1)	
MMF + Tacrolimus	49 (20.5)	45 (23.9)	
Other	34 (14.2)	8 (4.3)	
Conditioning regimen, n (%)			
TBF	156 (65.3)	0	
Flu-TBI	0	136 (72.3)	
BuFlu	27 (11.3)	0	
FluCyTBI	0	20 (10.6)	
FluBuCy	24 (10.0)	0	
CyTBI	0	16 (8.5)	
Other CT-MAC	32 (13.4)	0	
Other TBI-MAC	0	16 (8.5)	

CSA indicates cyclosporine A; MTX, methotrexate; MMF, mycophenolate mofetil.
* By Fisher's exact test.

Univariate Analysis of TBI versus CT Outcomes

The cumulative incidence of absolute neutrophil count >500 cells/μL at 30 days after transplantation was higher in the TBI cohort compared with the CT cohort (92% versus 84%; *P* = .08). Graft failure or loss was reported in 6 patients (3%) who received TBI-based MAC and in 19 (8%) who received CT-based MAC (*P*= .09, Fisher's exact test). Univariate analysis showed that TBI-based MAC was associated with a better 2-year LFS compared with CT-based MAC (45% versus 37%; *P*= .05) (Supplementary Table S3, Figure 1). There was no

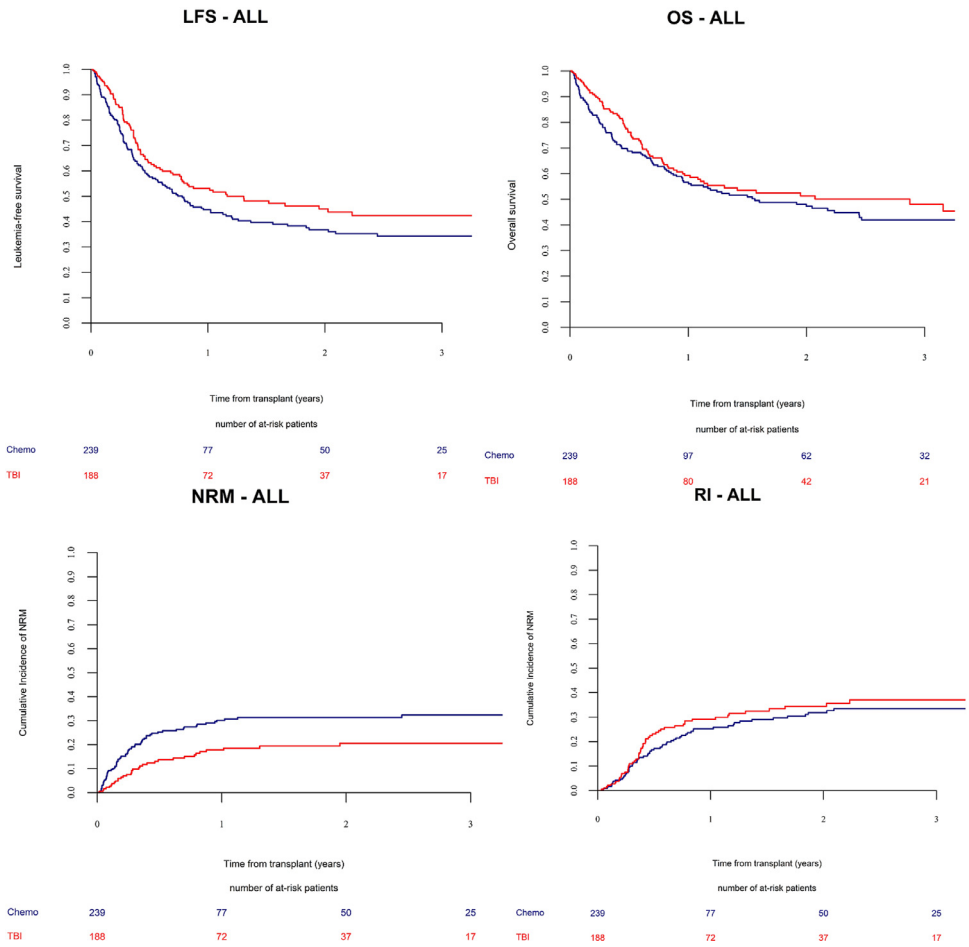

Figure 1. Transplantation outcomes in the TBI and CT cohorts.

statistically significant difference in 2-year RI (*P*= .44), OS (*P*= .18), or GRFS (*P*= .32) between the 2 cohorts (Supplementary Figure S1). TBI was associated with a trend toward an increased incidence of 100-day grade II-IV aGVHD (38% versus 30%; *P*= .07), but the difference was not statistically significant. Type of conditioning did not impact 100-day grade III-IV aGVHD, 2-year overall cGVHD, or extensive cGVHD rates.

A subgroup analysis of patients age <40 years (n = 279) showed no statistically significant differences in RI, LFS, or OS between the 2 cohorts but lower NRM in the TBI cohort (18.7% versus 27.6%; *P*= .04). A similar analysis for patients who were not in CR1 (≥CR2 or advanced-disease status; n = 219) before haplo-HCT showed no difference in RI, LFS, or OS between the 2 cohorts but lower NRM in the TBI cohort (22% versus 35.6%; *P*= .02). Unfortunately, we did not have information on measurable residual disease (MRD) status before transplantation in most patients, and thus we were not able to perform a separate outcome analysis by MRD status.

NRM and Causes of Death

Univariate analysis showed a lower 2-year NRM in the TBI cohort compared with the CT cohort (21% versus 31%; *P*< .01) compared to CT (Figure 1). A total of 78 patients in the TBI cohort and 114 patients in the CT cohort died during the study period. Table 3 presents the cumulative incidence for the main causes of death in the 2 cohorts, with the competing risk of death from another cause for all endpoints. Disease relapse was a common cause of death in both cohorts. The cumulative incidence of GVHD-related death was lower in the TBI cohort (20% versus 31%; *P* = .004) (Table 3). There was no statistically significant difference in other causes of death between the 2 groups, but the rate of infection-related deaths was lower in the TBI cohort (13% versus 16%; *P*= .53). Death due to veno-occlusive disease (VOD) was reported in 4 patients in the TBI cohort and in 8 patients in the CT cohort. Death due to graft failure/rejection and second malignancy was reported in 3 and 2 CT patients, respectively (Supplementary Table S4).

Multivariate Analysis of TBI versus CT Outcomes

A Cox regression model was used to investigate the individual effects of baseline, patient, and transplantation characteristics on the outcome measures (Table 2). TBI was associated with lower NRM (HR, 0.53; 95% CI, 0.33 to 0.86; *P*= .01) and better LFS (HR, 0.71; 95% CI, 0.52 to 0.98; *P*= .04) compared with CT. TBI was also associated with a higher risk of grade II-IV aGVHD (HR, 1.59; 95% CI, 1.08 to 2.34; *P*= .02). There were no associations between MAC regimen type and rates of RI, OS, aGVHD III-IV, overall cGVHD, or GRFS. The use of PB grafts was associated with higher NRM, resulting in lower LFS, OS, and GRFS. Advanced disease and ≥CR2 status at the time of haplo-HCT were associated with higher RI, resulting in lower LFS, OS, and GRFS. A post hoc subgroup analysis focused on the 2 most common conditioning regimens (Flu-TBI versus TBF) was performed. The multivariate analysis results were consistent with the entire population, but the difference did not reach significance in terms of LFS and aGVHD (Supplementary Table S5).

Table 2
Multivariate Analysis of Outcomes Based on Patient, Disease, and Transplantation Characteristics

Outcome	Relapse		NRM		LFS		OS		Grade II-IV aGVHD		cGVHD	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
TBI vs CT	0.9 (0.59-1.39)	.65	0.53 (0.33-0.86)	.01	0.71 (0.52-0.98)	.04	0.77 (0.54-1.08)	.13	1.59 (1.08-2.34)	.02	0.88 (0.55-1.4)	.58
Patient age (per 10 yr)	1.02 (0.84-1.25)	.81	1.06 (0.87-1.28)	.59	1.04 (0.9-1.19)	.62	1.07 (0.92-1.24)	.36	0.9 (0.76-1.07)	.25	0.98 (0.81-1.17)	.79
Philadelphia chromosome-positive	0.4 (0.2-0.82)	.01	1.32 (0.78-2.23)	.31	0.8 (0.53-1.2)	.28	0.81 (0.52-1.25)	.33	1.04 (0.65-1.65)	.88	0.98 (0.56-1.73)	.95
Disease status at haplo-HCT (CR1, reference)												
≥CR2	2.43 (1.39-4.24)	<.01	1.47 (0.87-2.49)	.15	1.83 (1.26-2.67)	<.01	1.69 (1.12-2.55)	.01	1 (0.64-1.57)	1	1.46 (0.87-2.47)	.15
Advanced	5.02 (2.89-8.71)	<.01	1.53 (0.82-2.84)	.18	2.92 (1.96-4.33)	<.01	2.63 (1.72-4.01)	<.01	1.26 (0.76-2.08)	.37	1.22 (0.6-2.46)	.58
KPS ≥90	0.98 (0.62-1.57)	.94	0.73 (0.45-1.18)	.2	0.85 (0.61-1.18)	.33	0.75 (0.52-1.06)	.11	1.25 (0.8-1.93)	.32	0.85 (0.52-1.4)	.53
PB versus BM graft source	1.39 (0.9-2.15)	.14	1.6 (1.01-2.53)	.03	1.44 (1.05-1.97)	.02	1.5 (1.07-2.1)	.02	1.64 (1.11-2.43)	.01	1.15 (0.72-1.83)	.56
Female donor to male recipient versus other	1.09 (0.69-1.73)	.71	0.9 (0.54-1.51)	.69	0.98 (0.7-1.39)	.93	0.92 (0.64-1.35)	.68	1.12 (0.74-1.71)	.59	1.54 (0.95-2.5)	.08
Year of haplo-HCT	0.93 (0.82-1.04)	.20	0.98 (0.86-1.12)	.76	0.96 (0.88-1.05)	.33	0.95 (0.86-1.04)	.28	0.92 (0.83-1.03)	.16	0.91 (0.79-1.05)	.2
Centers with ≥10 patients	1.09 (0.67-1.77)	.73	0.76 (0.42-1.38)	.37	0.97 (0.67-1.4)	.85	0.96 (0.65-1.43)	.85	0.58 (0.34-0.97)	.04	1.28 (0.73-2.22)	.39

Table 3
Cumulative Incidence of Major Causes of Death

Cause of Death	CT, %	TBI, %	*P* Value
Infection	15.7 (11.1-21.1)	12.8 (8.2-18.5)	.53
GVHD	31.1 (24.9-37.4)	20.3 (14.3-26.9)	.004
Disease relapse	18.7 (13.3-25)	19.1 (13-26.2)	.87
Veno-occlusive disease	3.4 (1.6-6.3)	2.3 (0.8-5.5)	.45
Interstitial pneumonitis	2 (0.7-4.8)	1.8 (0.5-4.8)	.75
Multiorgan failure	1.8 (0.6-4.2)	1.8 (0.3-6.2)	.45

DISCUSSION

In this multi-institutional registry-based observational study of patients with ALL who underwent haplo-HCT with PTCy, a TBI-based MAC regimen was associated with significantly lower NRM, resulting in better LFS, compared to with CT-based MAC. We also found TBI-based MAC to be safe and to lead to comparable RI, OS, and GRFS compared with CT-based MAC. There was an increased risk for grade II-IV aGVHD with TBI-based MAC but no significant impact on cGVHD rates compared to CT-based MAC.

The intensity of conditioning regimens plays an important role in relapse prevention after allo-HCT [5]. Four prospective, randomized trials have compared Bu/Cy with Cy/TBI in myeloid malignancies [34-37]. All patients in these trials received BM grafts from MSDs. The results were not consistent across these trials. In some studies, Cy/TBI performed better than Bu/Cy [34,35]. whereas in other studies, the 2 regimens were comparable [36,37]. TBI may have a selective advantage over CT-based conditioning in patients with lymphoid malignancies [1]. Preclinical animal studies have shown little effect of Bu on lymphoid organs, whereas TBI was able to suppress B cell and T cell activity [38].

TBI-based MAC also may reduce the risk of central nervous system relapse. A single-center study showed better LFS and OS with TBI-MAC compared with Bu-based MAC in ALL patients age <40 years [39]. A registry-based study showed an increased RI (HR, 1.78; $P = .03$) and similar OS with thiotepa-based MAC versus TBI-based MAC in ALL patients [13]. A similar analysis limited to T-ALL patients who underwent matched donor allo-HCT in the EBMT database showed the superiority of TBI-based conditioning in younger adults (age <35 years), with better LFS and OS compared with CT-based MAC [12]. The Center for International Blood and Marrow Transplant Research (CIBMTR) compared i.v. Bu-based MAC with TBI-based MAC in ALL patients who underwent allo-HCT from MSD or MUD and found lower NRM and cGVHD and similar OS with Bu-based regimens compared with TBI-based regimens [40]. There has been no prospective trial comparing TBI-based versus CT-based MAC in adult ALL patients. The variation in these study results could be related to differences in GVHD prophylaxis, disease characteristics, and the use of T cell depletion. We note that none of these studies had TBF as their main CT-MAC regimen, as used in the present study. Previous EBMT studies have shown comparative outcomes with TBF-based versus Bu-based conditioning in the setting of matched donor allo-HCT in patients with acute myelogenous leukemia (AML) [41,42].

The experience with TBI-based MAC in the setting of T cell-replete haplo-HCT is limited to small studies in a heterogeneous patient population. A group from Peking University retrospectively compared the outcomes of patients with AML and ALL who received TBI-based MAC or CT-based MAC in the setting of T cell-replete haplo-HCT, using antithymocyte globulin and combined granulocyte colony-stimulating factor-mobilized PB

plus BM grafts [43]. In that study, TBI was associated with a lower incidence of liver toxicity and hemorrhagic cystitis compared with CT, with no significant difference in LFS, OS, NRM, or RI. Recently, PTCy has emerged as an important in vivo T cell depletion strategy that significantly reduces the risk of cGVHD by eliminating alloreactive donor T cells and promoting graft tolerance in the setting of haplo-HCT [44]. PTCy also may help reduce the risk of cGVHD, which is greater after TBI-based MAC, as reported in the previous CIBMTR study [40]. In our study, TBI was associated with an elevated risk of grade II-IV aGVHD but not of more clinically significant grade III-IV aGVHD when used with PTCy. More importantly, the incidence of cGVHD, which has been shown to significantly impair the quality of life in long-term allo-HCT survivors, was comparable in the 2 study cohorts [45]. We also noted a lower cumulative incidence of GVHD-related deaths in TBI recipients, which could be due to center effect and other unmeasured factors, such as number of organs involved and response to GVHD therapies.

Previous experience with TBI-based MAC in haplo-HCT/PTCy has been limited to single-center retrospective studies [28,29,46]. Solomon et al. [29] studied outcomes of 82 patients with various hematologic malignancies (ALL, n = 27) who underwent haplo-HCT/PTCy after conditioning with fludarabine plus TBI (12 Gy) and found a 4-year OS of 67%, disease-free survival of 60%, RI of 27%, and NRM of 13% [29]. Bacigalupo et al. [46] analyzed the outcomes of 148 patients (TBI, n = 56) after MAC haplo-HCT/PTCy and found an NRM of 13% and an incidence of aGVHD grade II-IV of 24% for the whole study population. A recent CIBMTR analysis by Solomon et al. [14] including 526 patients who underwent MAC haplo-HCT (TBI, n = 222; CT, n = 304) for AML, ALL, or myelodysplastic syndrome found no difference in disease-free survival between TBI-based MAC and CT-based MAC. However, this study was not designed to investigate TBI versus CT outcomes, and the majority of patients had a myeloid malignancy. We recently compared TBI-based and CT-based MAC in AML haplo-HCT/PTCy recipients and found an increased risk of cGVHD with TBI-MAC but similar RI, NRM, LFS, and OS in the 2 cohorts [47]. Differences in baseline demographic characteristics of the study populations and in the potential impact of pre-HCT therapies may explain the discrepancies between these 2 studies. The combination of multiple alkylating agents during conditioning may increase the risk of hepatic injury [10], especially in the recipients of PTCy. In our study, TBI-based MAC was associated with relatively fewer VOD-related deaths compared to CT-based MAC (albeit not statistically significant), with TBF the most common regimen, which included 3 alkylating drugs with PTCy.

In the present study, the cumulative incidence of graft failure was higher in the CT cohort compared with the TBI cohort, likely related to better host immunosuppression with TBI-MAC. These results are in line with previous retrospective reports [48,49]. The lower NRM with TBI in our study appears to be driven by fewer GVHD-related and infection-related deaths. It is plausible that TBI-MAC in the setting of PTCy may result in better immune reconstitution compared with CT-based MAC, as indicated by the greater neutrophil engraftment and lower incidence of graft failure in this analysis. Further studies are needed to prospectively compare subsets of T cells, B cells, and natural killer cells at various time points after TBI-based MAC versus CT-based MAC.

Our analysis was limited by the study's retrospective nature. Our inability to adjust for unknown or unmeasured factors might have affected the transplantation outcomes. In addition, some prognostic groups had a small number of patients, reducing the statistical power in the multivariate analysis. Information on MRD, exposure to tyrosine kinase inhibitor therapy, donor chimerism, and comorbidities other than KPS and HCT-CI were missing in a subset of the patients included in the study. There was also marked heterogeneity in the TBI dose and schedule among the EBMT centers, as noted in our previous study [50]. We relied on standard EBMT conditioning regimen criteria and reports from transplantation centers about specific conditioning regimen intensity. The limited follow-up duration might have resulted in underestimation of the long-term adverse effects of TBI, such as cardiovascular events and second malignancies. The database lacked information on the incidence of VOD and hemorrhagic cystitis, 2 common complications seen after MAC haplo-HCT with PTCy. Bazarbachi et al. [27] recently reported no impact of RIC versus MAC in patients with T cell ALL after haplo-HCT with PTCy, but the limited number of TBI-MAC cases did not allow a separate outcome analysis of patients with T cell ALL in our study. We noted an interaction between choice of conditioning regimen and volume of cases per center. There is a possibility that high-volume (and thus more experienced) centers may have lower NRM compared with low-volume centers.

In conclusion, in this registry-based study, the use of TBI-based MAC was associated with improved LFS and reduced NRM compared with CT-based MAC in patients with ALL who underwent T cell-replete haplo-HCT with PTCy. However, the choice of conditioning regimen did not impact other outcomes, such as RI, OS, and GRFS. A prospective study with uniform conditioning regimens is warranted to validate these findings.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2020.10.008.

REFERENCES

1. Maffini E, Saraceni F, Lanza F . Treatment of adult patients with relapsed/refractory B-cell Philadelphia-negative acute lymphoblastic leukemia. *Clin Hematol Int*. 2019;1:85–93.
2. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant*. 2009;15:1628–1633.
3. Sibai H, Falcone U, Deotare U, et al. Myeloablative versus reduced-intensity conditioning in patients with myeloid malignancies: a propensity score-matched analysis. *Biol Blood Marrow Transplant*. 2016;22:2270–2275.
4. Ringdén O, Labopin M, Ehninger G, et al. Reduced intensity conditioning compared with myeloablative conditioning using unrelated donor transplants in patients with acute myeloid leukemia. *J Clin Oncol*. 2009;27:4570–4577.
5. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;;35:1154–1161.

6. Mohty M, Labopin M, Volin L, et al. Reduced-intensity versus conventional myeloablative conditioning allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. *Blood*. 2010;116:4439–4443.
7. Bachanova V, Marks DI, Zhang MJ, et al. Ph+ ALL patients in first complete remission have similar survival after reduced intensity and myeloablative allogeneic transplantation: impact of tyrosine kinase inhibitor and minimal residual disease. *Leukemia*. 2014;28:658–665.
8. Litzow MR, Pérez WS, Klein JP, et al. Comparison of outcome following allogeneic bone marrow transplantation with cyclophosphamide-total body irradiation versus busulphan-cyclophosphamide conditioning regimens for acute myelogenous leukaemia in first remission. *Br J Haematol*. 2002;119:1115–1124.
9. Eder S, Labopin M, Arcese W, et al. Thiotepa-based versus total body irradiation-based myeloablative conditioning prior to allogeneic stem cell transplantation for acute myeloid leukaemia in first complete remission: a retrospective analysis from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Eur J Haematol*. 2016;96:90–97.
10. Nagler A, Rocha V, Labopin M, et al. Allogeneic hematopoietic stem-cell transplantation for acute myeloid leukemia in remission: comparison of intravenous busulfan plus cyclophosphamide (Cy) versus total-body irradiation plus Cy as conditioning regimen–a report from the acute leukemia working party of the European group for blood and marrow transplantation. *J Clin Oncol*. 2013;31:3549–3556.
11. Bunin N, Aplenc R, Kamani N, Shaw K, Cnaan A, Simms S. Randomized trial of busulfan vs total body irradiation containing conditioning regimens for children with acute lymphoblastic leukemia: a Pediatric Blood and Marrow Transplant Consortium study. *Bone Marrow Transplant*. 2003;32:543–548.
12. Cahu X, Labopin M, Giebel S, et al. Impact of conditioning with TBI in adult patients with T-cell ALL who receive a myeloablative allogeneic stem cell transplantation: a report from the acute leukemia working party of EBMT. *Bone Marrow Transplant*. 2016;51:351–357.
13. Eder S, Canaani J, Beohou E, et al. Thiotepa-based conditioning versus total body irradiation as myeloablative conditioning prior to allogeneic stem cell transplantation for acute lymphoblastic leukemia: a matched-pair analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Am J Hematol*. 2017;92:997–1003.
14. Solomon SR, St Martin A, Shah NN, et al. Myeloablative vs reduced intensity T-cell-replete haploidentical transplantation for hematologic malignancy. *Blood Adv*. 2019;3:2836–2844.
15. Potdar RR, Gupta S, Giebel S, et al. Current status and perspectives of irradiation-based conditioning regimens for patients with acute leukemia undergoing hematopoietic stem cell transplantation. *Clin Hematol Int*. 2019;1:19–27.
16. Pavlù J, Labopin M, Niittyvuopio R, et al. Measurable residual disease at myeloablative allogeneic transplantation in adults with acute lymphoblastic leukemia: a retrospective registry study on 2780 patients from the acute leukemia working party of the EBMT. *J Hematol Oncol*. 2019;12:108.
17. Passweg JR, Baldomero H, Bader P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. *Bone Marrow Transplant*. 2016;51:786–792.
18. Kanakry CG, Fuchs EJ, Luznik L. Modern approaches to HLA-haploidentical blood or marrow transplantation. *Nat Rev Clin Oncol*. 2016;13:10–24.
19. Shem-Tov N, Peczynski C, Labopin M, et al. Haploidentical vs. unrelated allogeneic stem cell transplantation for acute lymphoblastic leukemia in first complete remission: on behalf of the ALWP of the EBMT. *Leukemia*. 2020;34:283–292.
20. Ciurea SO, Zhang MJ, Bacigalupo AA, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. *Blood*. 2015;126:1033–1040.
21. Bashey A, Zhang X, Jackson K, et al. Comparison of outcomes of hematopoietic cell transplants from T-replete haploidentical donors using post-transplant cyclophosphamide with 10 of 10 HLA-A, B, C, DRB1, and DQB1 allele-matched unrelated donors and hla-identical sibling donors: a multivariable analysis including Disease Risk Index. *Biol Blood Marrow Transplant*. 2016;22:125–133.
22. McCurdy SR, Kasamon YL, Kanakry CG, et al. Comparable composite endpoints after HLA-matched and HLA-haploidentical transplantation with post-transplantation cyclophosphamide. *Haematologica*. 2017;102:391–400.
23. Solomon SR, Sizemore CA, Zhang X, et al. Impact of donor type on outcome after allogeneic hematopoietic cell transplantation for acute leukemia. *Biol Blood Marrow Transplant*. 2016;22:1816–1822.
24. Queralt Salas M, Law AD, Lam W, et al. Safety and efficacy of haploidentical peripheral blood stem cell transplantation for myeloid malignancies using post-transplantation cyclophosphamide and anti-thymocyte globulin as graft-versus-host disease prophylaxis. *Clin Hematol Int*. 2019;1:105–113.
25. Tegla C, Choi J, Abdul-Hay M, Cirrone F, Cole K, Al-Homsi AS. Current status and future directions in graft-versus-host disease prevention following allogeneic blood and marrow transplantation in adults. *Clin Hematol Int*. 2020;2:5–12.
26. Santoro N, Ruggeri A, Labopin M, et al. Unmanipulated haploidentical stem cell transplantation in adults with acute lymphoblastic leukemia: a study on behalf of the Acute Leukemia Working Party of the EBMT. *J Hematol Oncol*. 2017;10:113.
27. Bazarbachi A, Labopin M, Angelucci E, et al. Haploidentical transplantation with post-transplantation cyclophosphamide for T cell acute lymphoblastic leukemia: a report from the European Society for Blood and Marrow Transplantation Acute Leukemia Working Party. *Biol Blood Marrow Transplant*. 2020;26:936–942.
28. Raiola AM, Dominietto A, Ghiso A, et al. Unmanipulated haploidentical bone marrow transplantation and posttransplantation cyclophosphamide for hematologic malignancies after myeloablative conditioning. *Biol Blood Marrow Transplant*. 2013;19:117–122.
29. Solomon SR, Solh M, Zhang X, Morris LE, Holland HK, Bashey A. Fludarabine and total-body irradiation conditioning before ablative haploidentical transplantation: long-term safety and efficacy. *Biol Blood Marrow Transplant*. 2019;25:2211–2216.
30. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995;15:825–828.
31. Shulman HM, Sullivan KM, Weiden PL, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. *Am J Med*. 1980;69:204–217.
32. Ruggeri A, Labopin M, Ciceri F, Mohty M, Nagler A. Definition of GvHD-free, relapse-free survival for registry-based studies: an ALWP-EBMT analysis on patients with AML in remission. *Bone Marrow Transplant*. 2016;51:610–611.
33. Kanate AS, Nagler A, Savani B . Summary of scientific and statistical methods, study endpoints and definitions for observational and registry-based studies in hematopoietic cell transplantation. *Clin Hematol Int*. 2020;2:2–4.
34. Blaise D, Maraninchi D, Archimbaud E, et al. Allogeneic bone marrow transplantation for acute myeloid leukemia in first remission: a randomized trial of a busulfan-Cytoxan versus Cytoxan-total body irradiation as preparative regimen: a report from the Group d'Etudes de la Greffe de Moelle Osseuse. *Blood*. 1992;79:2578–2582.
35. Ringdén O, Ruutu T, Remberger M, et al. A randomized trial comparing busulfan with total body irradiation as conditioning in allogeneic marrow transplant recipients with leukemia: a report from the Nordic Bone Marrow Transplantation Group. *Blood*. 1994;83:2723–2730.
36. Devergie A, Blaise D, Attal M, et al. Allogeneic bone marrow transplantation for chronic myeloid leukemia in first chronic phase: a randomized trial of busulfan-cytoxan versus cytoxan-total body irradiation as preparative regimen: a report from the French Society of Bone Marrow Graft (SFGM). *Blood*. 1995;85:2263–2268.
37. Clift RA, Radich J, Appelbaum FR, et al. Long-term follow-up of a randomized study comparing cyclophosphamide and total body irradiation with busulfan and cyclophosphamide for patients receiving allogenic marrow transplants during chronic phase of chronic myeloid leukemia. *Blood*. 1999;94:3960–3962.
38. Buckner CD, Dillingham LA, Giddens Jr WE, Thomas ED. Toxicologic and marrow transplantation studies in rhesus monkeys given dimethyl myleran. *Exp Hematol*. 1975;3:275–288.
39. Sakellari I, Gavriilaki E, Chatziioannou K, et al. Long-term outcomes of total body irradiation plus cyclophosphamide versus busulfan plus cyclophosphamide as conditioning regimen for acute lymphoblastic leukemia: a comparative study. *Ann Hematol*. 2018;97:1987–1994.
40. Kebriaei P, Anasetti C, Zhang MJ, et al. Intravenous busulfan compared with total body irradiation pretransplant conditioning for adults with acute lymphoblastic leukemia. *Biol Blood Marrow Transplant*. 2018;24:726–733.
41. Saraceni F, Labopin M, Hamladji RM, et al. Thiotepa-busulfan-fludarabine compared to busulfan-fludarabine for sibling and unrelated donor transplant in acute myeloid leukemia in first remission. *Oncotarget*. 2017;9:3379–3393.
42. Saraceni F, Beohou E, Labopin M, et al. Thiotepa, busulfan and fludarabine compared to busulfan and cyclophosphamide as conditioning regimen for allogeneic stem cell transplant from matched siblings and unrelated donors for acute myeloid leukemia. *Am J Hematol*. 2018;93:1211–1219.
43. Fu H, Xu L, Liu D, et al. Total body irradiation and cyclophosphamide plus antithymocyte globulin regimen is well tolerated and promotes stable engraftment as a preparative regimen before T cell-replete haploidentical transplantation for acute leukemia. *Biol Blood Marrow Transplant*. 2014;20:1176–1182.
44. Luznik L, O'Donnell PV, Fuchs EJ. Post-transplantation cyclophosphamide for tolerance induction in HLA-haploidentical bone marrow transplantation. *Semin Oncol*. 2012;39:683–693.
45. Goerner M, Gooley T, Flowers ME, et al. Morbidity and mortality of chronic GVHD after hematopoietic stem cell transplantation from HLA-identical siblings for patients with aplastic or refractory anemias. *Biol Blood Marrow Transplant*. 2002;8:47–56.
46. Bacigalupo A, Dominietto A, Ghiso A, et al. Unmanipulated haploidentical bone marrow transplantation and post-transplant cyclophosphamide for hematologic malignanices following a myeloablative conditioning: an update. *Bone Marrow Transplant*. 2015;50(suppl 2):S37–S39.

47. Dholaria B, Labopin M, Angelucci E, et al. Impact of total body irradiation-vs chemotherapy-based myeloablative conditioning on outcomes of haploidentical hematopoietic cell transplantation for acute myelogenous leukemia [e-pub ahead of print]. *Am J Hematol*. 2021. https://doi.org/10.1002/ajh.25934. Accessed Jan 12, 2021.
48. Olsson RF, Logan BR, Chaudhury S, et al. Primary graft failure after myeloablative allogeneic hematopoietic cell transplantation for hematologic malignancies. *Leukemia*. 2015;29:1754–1762.
49. Monaco F, Scott BL, Chauncey TR, et al. Total body irradiation dose escalation decreases risk of progression and graft rejection after hematopoietic cell transplantation for myelodysplastic syndromes or myeloproliferative neoplasms. *Haematologica*. 2019;104:1221–1229.
50. Giebel S, Miszczyk L, Slosarek K, et al. Extreme heterogeneity of myeloablative total body irradiation techniques in clinical practice: a survey of the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Cancer*. 2014;120:2760–2765.