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Thiotepa-Based Regimens Are Valid Alternatives to Total Body Irradiation-Based Reduced-Intensity Conditioning Regimens in Patients with Acute Lymphoblastic Leukemia: A Retrospective Study on Behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

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A B S T R A C T

Total body irradiation (TBI) at myeloablative doses is superior to chemotherapy-based regimens in young patients with acute lymphoblastic leukemia (ALL) undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, in elderly and unfit

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patients, in whom reduced-intensity conditioning (RIC) regimens are preferred, whether a TBI-based or a chemotherapy-based approach is better is unexplored. Thiotepa can be used as part of ALL conditioning regimens. The current study aimed to compare transplantation outcomes after RIC with TBI-based or thiotepa-based regimens in patients with ALL. The study cohort comprised patients aged ≥40 years undergoing allo-HSCT for ALL in first complete remission between 2000 and 2020 who received an RIC regimen containing either TBI (4 to 6 Gy) or thiotepa. We identified a total of 265 patients, including 117 who received a TBI-based RIC regimen and 148 who received a thiotepa-based RIC regimen. Univariate analysis revealed no significant differences in the following transplantation outcomes for TBI versus thiotepa: relapse, 23% versus 28% (P = .24); nonrelapse mortality, 20% versus 26% (P = .61); leukemia-free survival, 57% versus 46% (P = .12); overall survival, 67% versus 56% (P = .18); graft-versus-host disease (GVHD)/relapse-free survival, 45% versus 38% (P = .21); grade II-IV acute GVHD, 30% in both groups (P = .84); grade III-IV acute GVHD, 9% versus 10% (P = .89). The sole exception was the incidence of chronic GVHD, which was higher in the recipients of TBI-based regimens (43% versus 29%; P = .03). However, multivariate analysis revealed no differences in transplantation outcomes between the 2 groups. In patients aged ≥40 years receiving RIC, use of a thiotepa-based regimen may represent a valid alternative to TBI-based regimens, as no differences were observed in the main transplantation outcomes.

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INTRODUCTION

Total body irradiation (TBI) at myeloablative doses represents an essential backbone of conditioning regimens in adult patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) for acute lymphoblastic leukemia (ALL) [1,2]. However, TBI is hampered by short- and long-term adverse effects that may negatively impact long-term survival [3]. Therefore, chemotherapy-based regimens represent a possible alternative. Thiotepa is a radiomimetic agent that has the peculiar characteristic of crossing the blood-brain barrier, thus exerting its antileukemic activity even in sanctuary sites [4,5]. Comparative studies in the adult setting have shown higher leukemia-free survival (LFS) and a lower relapse incidence (RI) when using TBI at myeloablative doses compared to thiotepa-containing myeloablative regimens [6]. However, a high proportion of patients are not eligible for a myeloablative regimen owing to their advanced age and/or associated comorbidities, and in these patients, a reduced-intensity conditioning regimen (RIC) is preferred [7,8]. Studies comparing transplantation outcomes with either TBI-based or thiotepa-based RIC regimens in adults undergoing allo-HSCT are lacking.

METHODS

This retrospective study is from the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT), a working group of more than 600 transplant centers, mostly located in Europe, that are required to report annually all consecutive transplantations and follow-up data. Data are entered, managed, and maintained in a central database with internet access; each EBMT center is represented in this database. There are no restrictions on centers for reporting data, except those required by law on patient consent and data confidentiality and accuracy. Quality control measures include several independent systems: confirmation of validity of the entered data by the reporting team, selective comparison of the survey data with MED-A data sets in the EBMT registry database, cross-checking with the National Registries, and regular in-house and external data audits. Patients provide informed consent authorizing the use of their personal information for research purposes. Each patient also provides consent for transplantation according to the ethical principles of the Declaration of Helsinki. The study was approved by the Institutional Review Board of the EBMT ALWP.

Study Design and Eligibility Criteria

The current study included adult patients aged ≥40 years at the time of allo-HSCT, diagnosed with ALL, with available information on immunophenotype and Philadelphia (Ph) chromosome status and undergoing their first allo-HSCT in first complete remission (CR) using a RIC regimen. Only patients receiving either a thiotepa-based

(THIO group) or a TBI-based (TBI group) RIC regimen were included. In the THIO group, thiotepa doses of 5 and 10 mg/kg were included, whereas in the TBI group, only doses between 4 and 6 Gy were included. All donor types (except cord blood units) and both peripheral blood and bone marrow stem cell grafts were included. Ex vivo T cell depletion was an exclusion criterion. All transplantations were performed between 2000 and 2020. Transplantation outcomes were compared between the THIO and TBI groups.

Definitions

Performance status was graded according to the Karnofsky Performance Status (KPS) scale and was defined as poor when it was <90. The primary study endpoint was LFS, defined as the probability of being alive without evidence of relapse. Secondary endpoints included overall survival (OS), refined graft-versus-host disease (GVHD)/relapse-free survival (GRFS), cumulative incidence of engraftment, cumulative incidence of GVHD, RI, and nonrelapse mortality (NRM). Acute GVHD (aGVHD) was graded according to the modified Glucksberg criteria, and chronic GVHD (cGVHD) was graded according to the revised Seattle criteria [9,10].

Engraftment was defined as achieving an absolute neutrophil count $\geq .5 \times 10^9$/L for 3 consecutive days. OS was defined as the time from allo-HSCT to death, regardless of the cause. Refined GRFS was defined as being alive with neither grade III-IV aGVHD nor severe cGVHD nor disease relapse at any time point [11]. Relapse was defined as the presence of ≥5% BM blasts and/or reappearance of the underlying disease. NRM was defined as death without evidence of relapse or progression.

Statistical Analysis

The median value and range or interquartile range (IQR) were expressed for continuous data, and frequency and percentage for categorical data. Patient-, disease-, and transplantation-related characteristics of the 2 groups were compared using the chi-square or Fisher exact test for categorical data and the Kruskal-Wallis test for continuous data. The probabilities of LFS, OS, and GRFS were calculated using the Kaplan-Meier method and the log-rank test was used for univariate comparisons of survival [12].

Neutrophil engraftment, aGVHD, cGVHD, RI, and NRM were calculated using the cumulative incidence estimator to accommodate competing risks. For NRM, relapse was the competing event, and for RI, the competing risk was death without relapse. For studying aGVHD and cGVHD, relapse and death were the competing events. Multivariate analyses of the main outcomes were performed using the Cox proportional hazards model [13]. Most of the variables that differed significantly between the 2 groups and clinically relevant factors were included in the multivariate Cox models. The final Cox model included conditioning regimen, ALL subtype, age, year of transplantation, donor type, stem cell source, and female donor to male recipient combination. Results were expressed as hazard ratio (HR) with 95% confidence interval (CI). All *P* values were 2-sided. Statistical analyses were performed with R 4.0.2 (R Development Core Team).

RESULTS

Overall, 265 patients who met the inclusion criteria were identified, including 148 in the THIO group and 117 in the TBI group. Table 1 presents patient-, disease- and transplantation-related characteristics. The median patient age was 59 years (range, 40 to 75 years) in the THIO group versus 56 years (range, 40 to 72 years) for the TBI group ($P = .32$). The median year of transplantation was 2016 in both groups ($P = .09$). There were no differences in the distribution of diagnoses between the groups. Most patients were diagnosed with Ph-positive ALL (55% in the THIO group and 59% in the TBI group), with Ph-negative B-ALL and T-ALL diagnosed in 28% and 16%, respectively, in the THIO group and in 19% and 22%, respectively, in the TBI group ($P = .14$). Thiotepa was more frequently associated with busulfan and fludarabine (TBF; n = 88), whereas TBI was more frequently associated with cyclophosphamide and fludarabine (n = 52), fludarabine alone (n = 27), or cyclophosphamide alone (n = 17) (data not shown). Unrelated donors were more frequent in the TBI group (58% versus 44%; $P < .04$). A female donor for a male recipient was recorded in 14% of cases in both groups, whereas a longer interval from diagnosis to transplantation was seen in the THIO group (median, 7 months versus 6 months; $P < .01$).

The stem cell source was predominantly peripheral blood (81% in the THIO group and 94% in the TBI group; $P < .01$). The most frequently used GVHD prophylaxis regimen was cyclosporine with either methotrexate or mycophenolate mofetil in both groups. In vivo T cell depletion was used more frequently in the TBI group (54% versus 40%; $P < .03$). No imbalances were

Table 1
Patient, Disease, and Transplantation Characteristics According to Conditioning Regimen

Characteristic	THIO Group (N = 148)	TBI Group (N = 117)	*P* Value
Age at allo-HSCT, yr, median (range)	59 (40-75)	56 (41-72)	.32
Age 40-60 yr, n	98	78	
Age >60 yr, n	50	39	
Sex, female/male, n (%)	71 (48)/77 (52)	52 (44)/65 (56)	.57
Main diagnosis, n (%)			
Ph- B-ALL	42 (28)	22 (19)	.14
Ph+ B-ALL	82 (55)	69 (59)	
T-ALL	24 (16)	26 (22)	
Female donor to male recipient, n (%)	21 (14)	16 (14)	.89
Karnofsky Performance Status <90, n (%)	32 (23)	23 (22)	.81
Sorror score, n (%)			.19
0	52 (47)	42 (61)	
1-2	29 (26)	13 (19)	
≥ 3	30 (27)	14 (20)	
Missing	37	48	
Patient CMV serology, n (%)			.32
Negative	28 (19)	17 (15)	
Positive	117 (81)	99 (85)	
Missing	3	1	
Donor type, n (%)			<.04
HLA-identical sibling	52 (35)	36 (31)	
Unrelated donor	65 (44)	68 (58)	
Haploidentical	31 (21)	13 (11)	
Donor CMV serology, n (%)			.8
Negative	53 (38)	40 (36)	
Positive	88 (62)	71 (64)	
Missing	7	6	
Interval from diagnosis to allo-HSCT, mo, median (range)	7 (2-22)	6 (1-22)	< .01
Stem cell source, n (%)			<.01
BM	28 (19)	7 (6)	
PB	120 (81)	110 (94)	
Reason for choosing an RIC (as reported by centers), n			
Age of recipient	51	21	
Comorbid conditions	23	17	
Protocol driven	25	45	
Infection	3	-	
Not reported/missing	46	34	
TBI, n			
4 Gy	-	65	
6 Gy	-	52	
In vivo TCD, n (%)	58 (40)	63 (54)	<.03
GVHD prophylaxis, n (%)			-
CsA	8 (5)	6 (5)	
CsA + MTX	57 (39)	57 (49)	
CsA + MMF	52 (36)	35 (30)	
Other	29 (20)	19 (16)	
Missing	2	0	
Year of allo-HSCT, median (range)	2016 (2002-2020)	2016 (2000-2020)	.09
Follow-up, mo, median (range)	29 (25-37)	25 (24-36)	—

CMV indicates cytomegalovirus; BM, bone marrow; PB, peripheral blood; TCD, T cell depletion; CsA, cyclosporine A; MTX, methotrexate; MMF, mycophenolate mofetil.

Table 2
Cumulative Incidence of GVHD at 6 Months and 2 Years

Group	6-mo Grade II-IV aGVHD, % (95% CI)	6-mo Grade III-IV aGVHD, % (95% CI)	2-yr cGVHD, Any Grade, % (95% CI)	2-yr cGVHD, Extensive, % (95% CI)
THIO	30 (22-38)	10 (6-16)	29 (21-37)	13 (7-19)
TBI	30 (22-39)	9 (5-16)	43 (32-53)	13 (7-22)
P value	.84	.89	<.04	.99

observed for either Karnofsky Performance Status <90 (23% for the THIO group and 22% for the TBI group; $P = .81$) or Sorror score.

Univariate Analysis

Results of the univariate analysis are summarized in Tables 2 and 3.

Engraftment, aGVHD, and cGVHD

The cumulative incidence of day 60 neutrophil engraftment was 96.4% (95% CI, 91.2% to 98.6%) for the THIO group and 99.1% (95% CI, 89.5% to 99.9%) for the TBI group ($P = .30$), with a median time to neutrophil engraftment of 18 days (range, 7 to 42 days) and 19 days (range, 10 to 56 days), respectively ($P = .82$).

The cumulative incidence of 180-day grade II-IV aGVHD was 30% in both groups ($P = .84$), and the cumulative incidence of grade III-IV aGVHD was 10% (95% CI, 6% to 16%) in the THIO group and 9% (95% CI, 5% to 16%) in the TBI group ($P = .89$). A higher cumulative incidence of cGVHD of all grades at 2 years was seen in the TBI compared with the THIO group (43% [95% CI, 32% to 53%] versus 29% [95% CI, 21% to 37%] ; $P < .04$), but the cumulative incidence of extensive cGVHD was 13% in both groups ($P = .99$).

In the multivariate analysis, no significant differences were observed for either aGVHD or cGVHD according to the conditioning regimen used (Table 4). Considering TBI as the reference group, the HR for grade II-IV aGVHD was .97 (95% CI, .60 to 1.56; $P = .89$) while for cGVHD of all grades it was .71 (95% CI, .44 to 1.15; $P = .17$). Of note, for cGVHD, regardless of the conditioning regimen used, female donor to male recipient, year of allo-HSCT, and the use of matched sibling donors versus unrelated donors were variables independently associated with cGVHD.

Relapse and NRM

With a median follow-up of 29 months (range, 25 to 37 months) for the THIO group and 25 months (range, 24 to 36 months) for the TBI group, no differences were observed between the 2 groups in the cumulative incidence of relapse or NRM, with relapse at 28% (95% CI, 20% to 36%) in the THIO group and 23% (95% CI, 15% to 33%) in the TBI group ($P = .24$) and NRM at 26% (95% CI, 19% to 34%) and 20% (95% CI, 12% to 29%), respectively ($P = .61$) (Figure 1). The main causes of death in the THIO and TBI groups were recurrence of ALL (43% in both groups), infections (22% and 23%, respectively) and GVHD (15% and 23%, respectively).

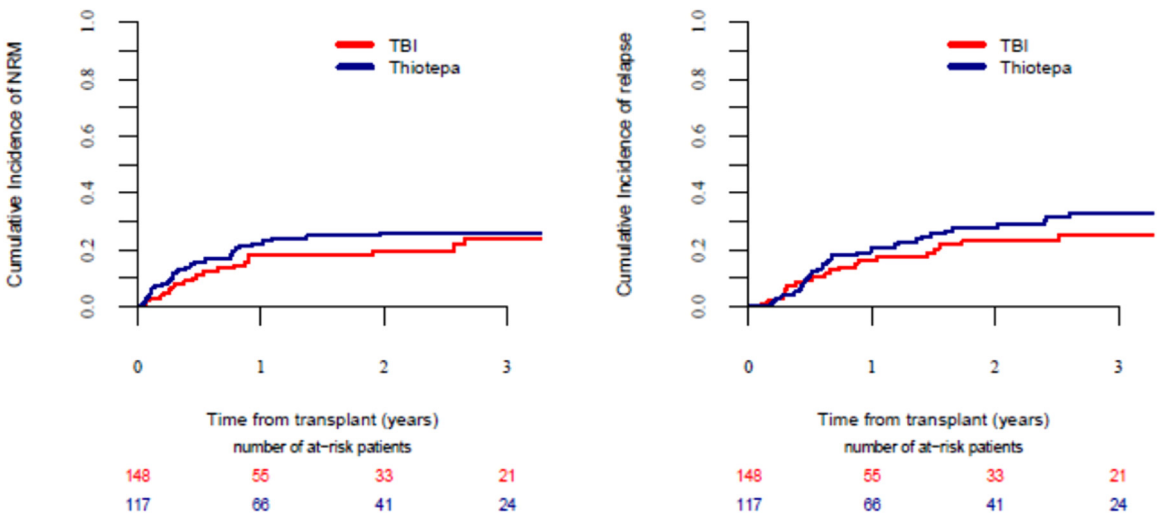

Figure 1. Survival outcomes according to thiotepa or TBI use. (A) Cumulative incidence of NRM. (B) Cumulative incidence of relapse.

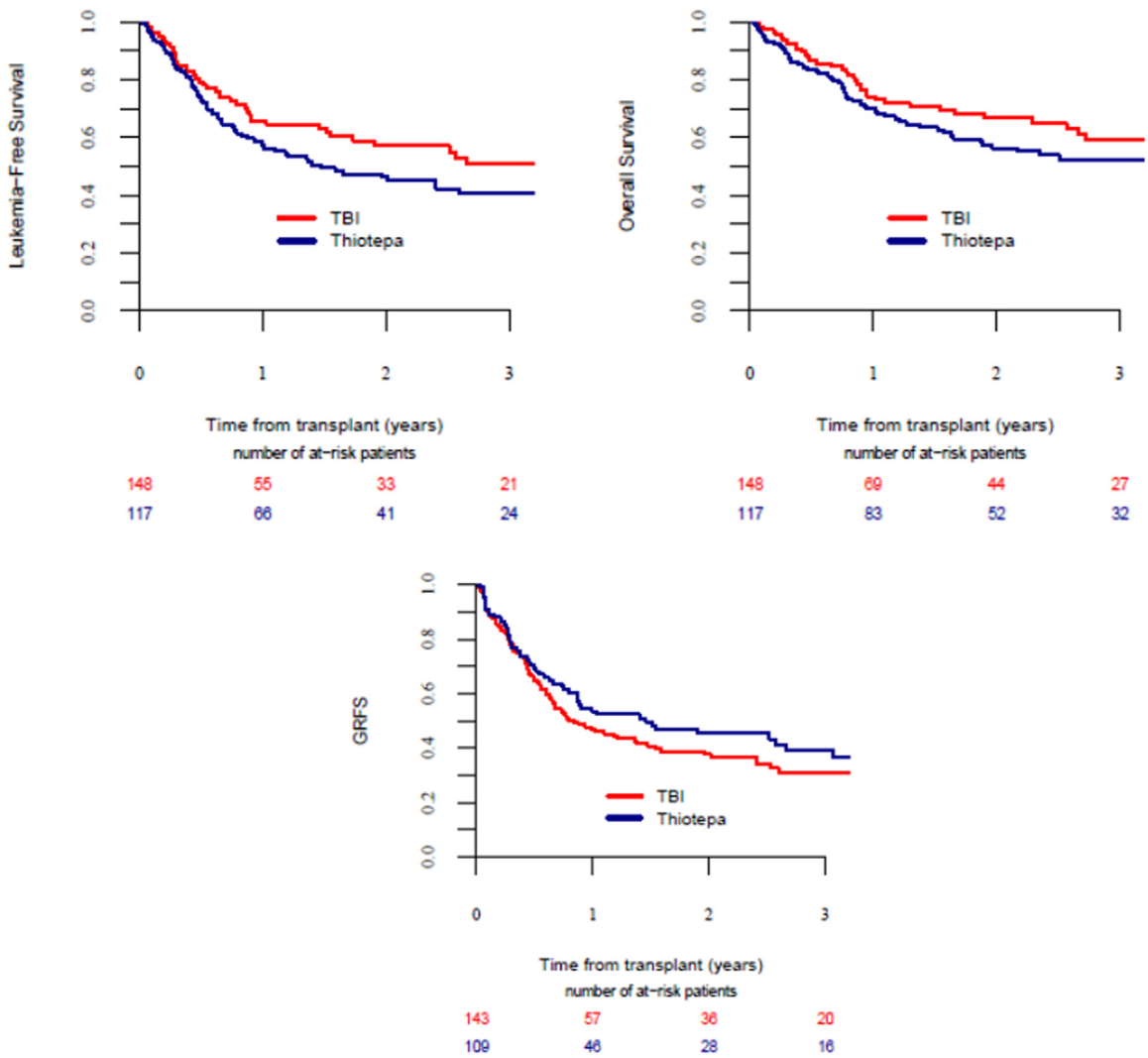

Figure 2. Survival outcomes according to thiotepa or TBI use. (A) LFS. (B) OS. (C) GRFS.

Multivariate analysis showed no differences in NRM and relapse according to the conditioning regimen used (Table 4). With TBI as the reference group, the HR was 1.38 (95% CI, .79 to 2.40; $P = .26$) for RI and 1.13 (95% CI, .64 to 1.99; $P = .67$) for NRM. Of note, a greater risk of NRM was observed in recipients of unrelated donors compared to HLA-identical sibling donors (HR, 2.12; 95% CI, 1.11 to 4.06; $P < .03$).

OS, LFS, and GRFS

No between-group differences were observed in univariate analyses for LFS, OS, and GRFS (Figure 2). Higher probabilities of LFS, OS, and GRFS were observed in the TBI group compared to the THIO group, but the differences did not reach statistical significance ($P = .12$ for LFS, $P = .18$ for OS, and $P = .21$ for GRFS). The same held true in the multivariate analysis (Table 4): HR for LFS, 1.24 (95% CI, .84 to 1.84; $P = .28$); HR for OS: 1.28 (95% CI, .83 to 1.96; $P = .26$); HR for GRFS, 1.18 (95% CI, .83 to .66; $P = .35$). Regardless of the conditioning regimen, the use of grafts from HLA-identical sibling donors was associated with lower LFS (HR, 1.63; 95% CI, 1.05 to 2.62; $P < .03$) compared to unrelated donors, whereas a diagnosis of T-ALL compared to Ph-negative B-ALL was associated with both a better LFS (HR, .53; 95% CI, .29 to .98; $P < .05$) and OS (HR, .49; 95% CI, .26 to .92; $P < .03$). Furthermore, Ph-positivity was associated with a better OS compared to Ph-negative B-ALL (HR, .52; 95% CI, .32 to .84; $P < .01$).

DISCUSSION

Despite major improvements in transplantation outcomes for patients with ALL, the use of TBI or chemoconditioning-based MAC regimens is associated with high NRM, reaching nearly 36% at 2 years in patients age 35 to 40 years [14]. Furthermore, unfavorable disease characteristics,

Table 3
Two-Year Survival Outcomes

Group	LFS, % (95% CI)	OS, % (95% CI)	GRFS, % (95% CI)	RI, % (95% CI)	NRM, % (95% CI)
THIO	46 (37-55)	56 (47-65)	38 (29-46)	28 (20-36)	26 (19-34)
TBI	57 (46-67)	67 (56-75)	45 (35-55)	23 (15-33)	20 (12-29)
P value	.12	.18	.21	.24	.61

Table 4
Multivariate Analysis for Transplantation Outcomes

Outcome	HR (95% CI)	*P* Value
LFS		
TBI vs THIO	1.24 (.84-1.84)	.28
Ph-negative vs Ph-positive B-ALL	.65 (.42-1.01)	.06
Ph-negative B-ALL vs T-ALL	.53 (.29-.98)	<.05
Incremental age (× 10 yr)	1.11 (.85-1.45)	.46
Year of allo-HSCT	.97 (.92-1.01)	.16
MSD vs UD	1.63 (1.05-2.52)	<.03
MSD vs TCR-Haplo donor	.78 (.40-1.53)	.47
Female donor to male recipient vs other sex combinations	.87 (.49-1.52)	.62
PB vs BM	.58 (.34-1.00)	.06
OS		
TBI vs THIO	1.28 (.83-1.96)	.26
Ph-negative vs Ph-positive B-ALL	.52 (.32-.84)	<.01
Ph-negative B-ALL vs T-ALL	.49 (.26-.92)	<.03
Incremental age (×10 yr)	1.15 (.85-1.55)	.37
Year of allo-HSCT	.96 (.91-1.01)	.12
MSD vs UD	1.50 (.94-2.39)	.09
MSD vs TCR-Haplo donor	.64 (.30-1.39)	.26
Female donor to male recipient vs other sex combinations	.86 (.46-1.60)	.63
PB vs BM	.65 (.35-1.18)	.16
GRFS		
TBI vs THIO	1.18 (.83-1.66)	.35
Ph-negative vs Ph-positive B-ALL	.70 (.47-1.05)	.08
Ph-negative B-ALL vs T-ALL	.63 (.37-1.07)	.09
Incremental age (× 10 yr)	1.06 (.84-1.34)	.63
Year of allo-HSCT	.97 (.93-1.02)	.25
MSD vs UD	1.12 (.77-1.64)	.55
MSD vs TCR-Haplo donor	.65 (.36-1.15)	.14
Female donor to male recipient vs other sex combinations	.99 (.62-1.56)	.95
PB vs BM	.67 (.41-1.1)	.12
RI		
TBI vs THIO	1.38 (.79-2.40)	.26
Ph-negative vs Ph-positive B-ALL	.55 (.30-1.01)	.06
Ph-negative B-ALL vs T-ALL	.65 (.29-1.44)	.29
Incremental age (× 10 yr)	.90 (.63-1.29)	.56
Year of allo-HSCT	.97 (.90-1.03)	.31
MSD vs UD	1.26 (.69-2.28)	.45
MSD vs TCR-Haplo donor	.77 (.32-1.83)	.55
Female donor to male recipient vs other sex combinations	.92 (.44-1.91)	.82
PB vs BM	.48 (.23-1.00)	.06
NRM		

(*continued*)

Table 4 (*Continued*)

Outcome	HR (95% CI)	*P* Value
TBI vs THIO	1.13 (.64-1.99)	.67
Ph-negative vs Ph-positive B-ALL	.78 (.41-1.49)	.45
Ph-negative B-ALL vs T-ALL	.41 (.15-1.07)	.07
Incremental age (× 10 yr)	1.41 (.94-2.13)	.1
Year of allo-HSCT	.97 (.9-1.04)	.37
MSD vs UD	2.12 (1.11-4.06)	<.03
MSD vs TCR-Haplo donor	.74 (.25-2.16)	.58
Female donor to male recipient vs other sex combinations	.79 (.33-1.9)	.6
PB vs BM	.72 (.32-1.63)	.43
Grade II-IV aGVHD		
TBI vs THIO	.97 (.60-1.56)	.89
Ph-negative vs Ph-positive B ALL	1.02 (.57-1.82)	.95
Ph-negative B-ALL vs T-ALL	1.02 (.49-2.12)	.97
Incremental age (× 10 yr)	1.04 (.74-1.46)	.82
Year of allo-HSCT	.97 (.92-1.03)	.4
MSD vs UD	.91 (.53-1.57)	.74
MSD vs TCR-Haplo donor	1.05 (.5-2.18)	.9
Female donor to male recipient vs other sex combinations	1.11 (.58-2.1)	.75
PB vs BM	1.07 (.51-2.24)	.86
cGVHD		
TBI vs THIO	.71 (.44-1.15)	.17
Ph-negative vs Ph-positive B-ALL	.76 (.42-1.38)	.37
Ph-negative B-ALL vs T-ALL	1.46 (.73-2.89)	.28
Incremental age (×10 yr)	.87 (.63-1.20)	.41
Year of allo-HSCT	.93 (.88-.99)	<.03
MSD vs UD	.48 (.28-.83)	<.01
MSD vs TCR-Haplo donor	.60 (.29-1.24)	.17
Female donor to male recipient vs other sex combinations	1.84 (1.07-3.18)	<.03
PB vs BM	1.08 (.47-2.46)	.86

such as the presence of adverse cytogenetics, and increasing age have been reported in one-half of adults aged ≥40 years. The development of RIC regimens incorporating lower doses of TBI and reduced-toxicity chemotherapies has allowed older and less fit patients to benefit from allo-HSCT, lowering NRM [15].

The alkylating agent thiotepa is used extensively in transplantation conditioning regimens and has found wide application in hematologic malignancies with central nervous system involvement [4,5]. Therefore, owing to its radiomimetic properties and its ability to cross the blood-brain barrier, several centers use thiotepa as an alternative to TBI in both the MAC and RIC settings for allo-HSCT in ALL [6,16]. Although Eder et al. [6] showed that the use of thiotepa-based MAC regimens is associated with inferior transplantation outcomes compared to TBI-based MAC regimens, no comparative analysis of the 2 RIC regimens has been reported to date [6]. Therefore, we used data from the EBMT registry to explore this issue. Interestingly, we observed no differences in any transplantation outcome when using thiotepa or TBI at 4 to 6 Gy, highlighting that both strategies may represent a valid option when choosing the conditioning regimen for the elderly or for patients with comorbidities considered not eligible for MAC. At 2 years, we observed a NRM of 26% for the THIO group compared to 20% for TBI group, in line with results recently reported from the UKALL14 study, where the use of a fludarabine, melphalan, and alemtuzumab-based conditioning regimen resulted in a 4-year NRM of 20% [17]. Similar to the aforementioned study, infection was the main cause of NRM in both the TBI and THIO groups.

Our study adds to the growing body of literature on RIC regimens for allo-HSCT in ALL, where the best regimen remains to be defined. Peric et

al. [18] previously compared 3 RIC regimens in 427 patients age <45 years—fludarabine with melphalan or busulfan and TBI at 2 Gy—and showed no differences among the 3 [18]. Importantly, although in that study, RI was as high as 40% and LFS was 42% to 45% at 2 years, we observed more encouraging results, with a lower RI of 28% and 23% and higher LFS of 46% and 57% in the THIO and TBI groups, respectively. However, comparisons between the 2 studies are difficult, and differences may depend not only on the conditioning regimens used (with TBI regimens at higher doses in our study), but also on the year of allo-HSCT, with our study including more recent transplant recipients, who may have benefited from the recent improvements in both ALL treatment and allo-HSCT procedures.

Interestingly, more than one-half of the patients in the THIO group received TBF as the conditioning regimen. The latter, initially introduced using cord blood and then with expanded use in the haploidentical setting, has found widespread use in allo-HSCT with all donor types and in various hematologic malignancies [19,20]. Banet et al. [16] recently reported the efficacy and feasibility of TBF (both MAC and RIC) in allo-HSCT for ALL (mostly B-ALL, with only 7% T-ALL) in patients aged from 17 to 72 years. They included all disease status and observed very favorable outcomes with a 5-year NRM of 15% and an RI of 28% [16]. Taken together, these results further highlight that chemoconditioning-based regimens represent a valid alternative to TBI, also facilitating the logistics of administration generally associated with TBI.

Of note, in our series, the use of TBI was also associated with a higher incidence of cGVHD (43%, compared to 29% in the THIO group), but this difference was not observed in the multivariate analysis, where female donor to male recipient, use of unrelated donors, and year of allo-HSCT were independently associated with the risk of cGVHD.

Our results also show no differences in transplantation outcomes between the use of HLA-identical and haploidentical sibling donors, suggesting that alternative graft sources can be considered for elderly or frail patients who lack an HLA-identical sibling donor and who are considered eligible for RIC allo-HSCT. Despite this, our results must be taken with caution considering the sample size, although they are in line with a previous study from our group showing no differences in survival in patients age ≥18 years who underwent transplantation from an HLA-identical or haploidentical sibling donor with both MAC and RIC regimens [21].

Importantly, we also report a higher probability of OS in Ph^+ compared to Ph^- ALL and a trend toward a lower RI and higher probability of LFS. This result in part reflects the different behavior of these 2 B-ALL entities and the significant impact that TKI may have on transplantation outcomes, with recent debates and therapeutic advances in the Ph^+ ALL field that even call into question the use of allo-HSCT in patients with Ph^+ ALL in first CR attaining MRD negativity [22].

Our study has several limitations, including those inherent to a registry-based retrospective analysis, coupled with sample size limitations and lack of comprehensive information concerning disease-related genomic characteristics or MRD information. Several factors may have guided the choice to perform HSCT in those patients in first CR, thus precluding stratifications and subanalyses that might have influenced final outcomes independently from conditioning regimens. Furthermore, an important study bias is related to patient selection and to factors guiding the decision to use an RIC regimen.

CONCLUSION

Our study highlights that in patients with ALL who are not considered eligible for MAC regimens, both TBI-based and thiotepa-based regimens represent valid alternatives, providing acceptable long-term disease control and survival.

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