

# Thiotepa 10 mg/kg Treatment Regimen Is Superior to Thiotepa 5 mg/kg in TBF Conditioning in Patients Undergoing Allogeneic Stem-Cell Transplantation

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## Abstract

**A study evaluating the optimal dose of myeloablation in thiotepa, busulfan, and fludarabine (TBF) conditioning included 29 patients who received TBF conditioning before allogeneic stem-cell transplantation. Thirteen patients received 5 mg/kg thiotepa; the remaining 16 patients received 10 mg/kg. Patients deemed fit to receive 10 mg/kg conditioning had better overall and progression-free survival than those who received 5 mg/kg, with no additional toxicities.**

**Introduction:** The optimal intensity of myeloablation with a reduced-toxicity conditioning regimen to decrease relapse rate after allogeneic stem-cell transplantation without increasing transplant-related mortality (TRM) has not been well established. **Materials and Methods:** We compared outcomes between 5 mg/kg (T5) and 10 mg/kg (T10) thiotepa-based conditioning regimens in 29 adults who underwent allogeneic stem-cell transplantation for hematologic malignancies. **Results:** After a median follow-up of 11 months, TRM was 0% and 14% at 100 days and 1 year, respectively, with TRM observed only in the T5 group ( $P = .016$ ). The relapse incidence at 1 year was 20%. No patient had disease in first complete remission at the time of transplantation. At 1 year, progression-free and overall survival were 30% versus 87% ( $P = .012$ ) and 46% versus 87% ( $P = .008$ ) in the T5 and T10 groups, respectively. In univariate and multivariate analysis, only age at transplantation and total dose of thiotepa had a significant impact on TRM, overall, and progression-free survival. **Conclusion:** Patients deemed fit to receive T10-based conditioning for allogeneic stem-cell transplantation to treat high-risk hematologic malignancies had better overall and progression-free survival than those who received T5 with no additional toxicities. Patients should be stratified before conditioning, and those judged fit should receive T10, while the others should consider alternative reduced-intensity conditioning regimens.

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**Keywords:** Dose intensity, Hematological malignancies, High risk, Reduced toxicity conditioning regimens

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## Introduction

Allogeneic stem-cell transplantation (allo-SCT)<sup>1</sup> is a well-established treatment modality for high-risk hematopoietic malignancies. Even though standard myeloablative conditioning regimens are associated with decreased incidence of relapse, they are associated with increased risk of toxicities, graft-versus-host disease (GVHD), and transplant-related mortality (TRM).<sup>2</sup> This led to the development of reduced-intensity conditioning (RIC), which decreased both toxicities and TRM, but this came at the cost of increasing risk of relapse after allo-SCT. Reduced-toxicity conditioning has recently emerged as a solution to this problem. This combines the favorable antitumor effect of myeloablation with the

benefit of lower TRM of RIC.<sup>3</sup> However, the optimal intensity of myeloablation with a reduced-toxicity conditioning regimen to decrease relapse rate after allo-SCT without increasing TRM has not been well established.

Thiotepa is an alkylating compound with both antineoplastic activity<sup>4</sup> and immunosuppressive properties, as well as the ability to penetrate the blood–brain barrier.<sup>5,6</sup> Thiotepa has been subsequently incorporated into chemotherapeutic protocols used for hematologic malignancies and allo-SCT. However, few studies have focused on analyzing the benefit of thiotepa in the pre–allo-SCT conditioning in a specific disease category. Early studies reported on the use of thiotepa in the conditioning regimen before autologous SCT, mainly in patients with lymphoma, replacing carmustine and thus reducing lung toxicity (TECAM–thiotepa; etoposide, cytoxan, Ara-C, and melphalan), with good results.<sup>7</sup> Subsequently, thiotepa was incorporated into pre–allo-SCT conditioning regimens using matched donors for both malignant and nonmalignant indications.

Thiotepa has become an integral part of the thiotepa, busulfan, and fludarabine (TBF) conditioning regimen, which is being used with increasing frequency for alternative donor transplantations, including haploidentical stem-cell transplantation and cord-blood transplants.<sup>8</sup> However, to our knowledge, no studies have investigated the optimal dose of thiotepa. In an attempt to assess the optimal dose of thiotepa, we retrospectively compared the transplantation outcomes of patients who received 5 mg/kg thiotepa (T5) as part of their TBF conditioning versus those who received 10 mg/kg thiotepa (T10).

## Materials and Methods

In this retrospective study conducted at the American University of Beirut Medical Center, we included 29 consecutive patients with hematologic malignancies who received allo-SCT with TBF conditioning between January 2015 and December 2016. This study was approved by the American University of Beirut Medical Center institutional review board. We included adult patients who had Karnofsky scores of > 70% and who underwent transplantation either from a matched sibling donor (MSD) or from a haploidentical donor with TBF conditioning. All donors were mobilized using granulocyte colony-stimulating factor, and stem cells were collected from peripheral blood. Neutrophil recovery is defined as the first of 3 days with neutrophil count > 500/mm<sup>3</sup>, and platelet recovery was defined as the first of 3 consecutive days with platelet count > 50 × 10<sup>3</sup>/mm<sup>3</sup> without platelet transfusion. Patients and transplant characteristics are reported in Table 1.

### Conditioning and GVHD Prophylaxis

All patients received a myeloablative conditioning regimen consisting of thiotepa 5 mg/kg per day infused on days –7 and/or –6 (T10 group) or on day –6 only (T5 group), fludarabine 30 mg/m<sup>2</sup> infused on day –5 to day –2; and busulfan 130 mg/m<sup>2</sup> infused on day –5 to day –3. Our strategy is based on a risk-adapted approach to allo-SCT by adjusting the intensity of the conditioning regimen according to age, disease risk, and existing comorbidities, and by implementing appropriate posttransplantation prophylactic maintenance therapy. In an attempt to decrease posttransplantation complications in older patients and in heavily pretreated patients, there was a tendency to provide them with a lower dose (T5). The

choice of thiotepa dose between 5 mg/kg per day on day –6 (T5) or 5 mg/kg per day on days –7 and –6 (T10) was not prospectively defined. All patients received intravenous rabbit anti–thymocyte globulin (ATG; Thymoglobulin; Genzyme, Lyon, France) at a dose of 2.5 mg/kg per day on day –2 and day –1. Fourteen patients (48%) and 15 patients (52%) received a total thiotepa dose of 5 mg/kg or 10 mg/kg, respectively. Comparative characteristics for the 2 groups are listed in Table 1. GVHD prophylaxis for patients who received transplants from haploidentical donors consisted of posttransplantation cyclophosphamide 50 mg/kg per day on day +3 and day +5, cyclosporine initiated at 1.5 mg/kg on day +6 and readjusted according to level, and mycophenolate mofetil 500 mg every 6 hours beginning on days +6 to +28. Patients who received transplants from a MSD received only cyclosporine as GVHD prophylaxis as of day –3.

### Posttransplantation Maintenance Therapy

Posttransplantation therapy was planned in all nonlymphoma patients starting between day +30 and day +60 after allo-SCT with administration of dasatinib 50 mg daily or imatinib 400 mg daily for up to 5 years for patients with Philadelphia-positive acute lymphoblastic leukemia (ALL), sorafenib 400 mg twice daily for up to 2 years for *FLT3* internal tandem duplication–mutated acute myeloid leukemia (AML), 5-azacytidine 32 mg/m<sup>2</sup> per day for 5 days a month for up to 5 years for myeloid malignancies,<sup>9</sup> and monthly intrathecal cytarabine 100 mg for up to 12 months for ALL. Seventy-two percent of patients were slated to receive posttransplantation therapy. However, only 20 patients (69%) received their planned therapy after allo-SCT, including 7 patients (24%) who received 5-azacytidine,<sup>9</sup> 4 (14%) sorafenib,<sup>10,11</sup> 4 (14%) dasatinib, and 5 (17%) intrathecal cytarabine.<sup>12</sup> Two patients experienced early relapse before day 100 and did not receive maintenance therapy after allo-SCT. The other 7 patients with lymphoma did not receive posttransplantation maintenance therapy.

## Results

### Engraftment and Chimerism

All 29 patients had neutrophil engraftment at a median of 14 days (range, 10–18 days), while 23 (96%) had platelet engraftment at a median of 13 days (range, 8–48 days). Twenty-seven patients (93%) experienced full donor chimerism on the day +30 evaluation; one patient had 94% donor chimerism on day +30, experienced disease relapse on day +55, and died of disease on day +76. At day 100 after allo-SCT, 27 patients (97%) were alive, with 26 of them (90%) with disease in complete remission and full donor chimerism. The remaining patient had disease that failed to respond to platelet engraftment and died with progressive disease from *Acinetobacter baumannii* sepsis on day +23 after transplantation.

### Acute and Chronic GVHD

The cumulative incidence of grade II–IV acute GVHD (aGVHD) was 31% in the T5 group versus 19% in the T10 group. Three patients (23%) had grade II and 1 (8%) had grade III aGVHD in the T5 group, versus 1 patient (6%) with grade II and 2 (13%) with grade III aGVHD in the T10 group. Two patients (6%), one in each group, developed chronic GVHD (cGVHD). There was no significant difference between dose of thiotepa, and

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**Table 1** Patient and Transplant Characteristics

Characteristic	Total	T5	T10	P
Patients	29 (100%)	13 (45%)	16 (55%)	NS
<b>Age (Years), median (range)</b>				
At diagnosis	36 (21-64)	43 (24-64)	36 (21-54)	NS
At transplantation	37 (21-65)	43 (25-65)	37 (21-55)	NS
<b>Sex</b>				.017 <sup>a</sup>
Female	9 (31%)	1 (8%)	8 (50%)	
Male	20 (69%)	12 (92%)	8 (50%)	
<b>Disease Type</b>				
AML	12 (42%)	5 (38%)	7 (44%)	NS
ALL	9 (31%)	2 (15%)	7 (44%)	NS
HL	3 (10%)	1 (8%)	2 (13%)	NS
NHL	4 (14%)	4 (31%)	0	.0184 <sup>a</sup>
MDS	1 (3%)	1 (8%)	0	NS
<b>Karyotype</b>				NS
Normal	20 (69%)	11 (85%)	9 (56%)	
Abnormal	9 (31%)	2 (15%)	7 (44%)	
<b>Molecular Abnormalities</b>				
<i>FLT3</i>	4 (14%)	1 (8%)	3 (19%)	NS
<i>NPM1</i>	5 (17%)	1 (8%)	4 (25%)	NS
Ig	3 (10%)	1 (8%)	2 (13%)	NS
TCR	2 (6%)	1 (8%)	1 (6%)	NS
CR-ABL	4 (14%)	1 (8%)	3 (19%)	NS
<b>Disease Risk Index</b>				
Intermediate	15 (52%)	5 (38%)	10 (63%)	NS
High	14 (48%)	8 (62%)	6 (38%)	NS
HCT-CI	0 (0%-2%)	0 (0%-1%)	0 (0%-2%)	NS
<b>Type of Donor</b>				
Haplo	18 (62%)	8 (62%)	10 (63%)	NS
Matched sibling donor	11 (38%)	5 (38%)	6 (38%)	NS
<b>Status at Transplantation</b>				
CR	22 (76%)	9 (69%)	13 (81%)	NS
CR1	14 (49%)	5 (38%)	9 (56%)	NS
CR2	5 (17%)	1 (8%)	4 (25%)	NS
CR <sub>≥</sub> 3	3 (10%)	3 (23%)	0	.0466
PR	3 (10%)	3 (23%)	0	.0466
PD	4 (14%)	1 (8%)	3 (19%)	NS
<b>Molecular Status at Transplantation</b>				
Positive	7 (24%)	4 (31%)	3 (19%)	NS
Negative	22 (76%)	9 (69%)	13 (81%)	NS
PBSC	29 (100%)	13 (100%)	16 (100%)	NS
CD34 × 10 <sup>6</sup> /kg, median (range)	7.74 (4.4-10.37)	7.04 (5.22-10.37)	7.74 (4.4-10.22)	NS
CD3 × 10 <sup>9</sup> /kg, median (range)	2.085 (1.12-8.38)	2.11 (1.12-3.87)	2.085 (1.5-8.38)	NS
ANC > 500/mm <sup>3</sup> /cu.mm; days, median (range)	14 (10-18)	14 (12-18)	14 (10-18)	NS
Platelets > 50 K/mm <sup>3</sup> days, median (range)	13 (8-48)	13 (8-25)	13 (10-48)	NS
<b>GVHD Prophylaxis</b>				
CS	29 (100%)	13 (100%)	16 (100%)	NS
MMF	18 (62%)	8 (62%)	10 (63%)	NS
Dead at last follow-up	8 (28%)	6 (46%)	2 (13%)	.0526 <sup>a</sup>
TRM	4 (14%)	4 (31%)	0	.016 <sup>a</sup>

**Table 1** Continued

Characteristic	Total	T5	T10	P
Acute GVHD	1 (3%)	1 (8%)	0	NS
Infection	3 (10%)	3 (23%)	0	.0466 <sup>a</sup>
Death progression	4 (14%)	2 (15%)	2 (13%)	.8791

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; ANC = absolute neutrophil count; CR = complete remission; CR1 = first complete remission; CR2 = second complete remission; CR<sub>≥3</sub> = third or more complete remission; CS = cyclosporine; GVHD = graft-versus-host disease; HCT-CI = Hematopoietic Cell Transplantation Comorbidity Index; HL = human leukocyte antigen; MDS = myelodysplastic syndromes; MMF = mycophenolate mofetil; NHL = non-Hodgkin lymphoma; PBSC = peripheral blood stem cell; PD = progressive disease; PR = partial response; T5 = 1 day's thiotepa conditioning at 5 mg/kg total dose; T10 = 2 days' thiotepa conditioning at 10 mg/kg total dose; TRM = transplant-related mortality.

<sup>a</sup>Statistically significant.

there was no difference according to transplant source (haplo-identical or MSD) (Table 2).

### Overall Survival, Progression-Free Survival, and TRM

After a median follow-up of 11 months (range, 1-26 months), 21 patients (72%) were alive with disease in complete remission, with negative minimal residual disease and full donor chimerism. Eight patients (28%) had died by last follow-up, 4 patients (14%) from disease progression and 4 patients (14%) from TRM. Three patients (10%) experienced relapsed before 1 year after allo-SCT, with 163 days (range, 55-236 days) as the median time to progression. Two of these patients were transplanted for ALL in second complete remission, and one patient was transplanted for AML in first complete remission. The causes of death are listed in Table 2. The 100-day TRM was 0, and the 1-year TRM was 14%. Interestingly, the 1-year TRM was 31% versus 0 in patients receiving a total dose of thiotepa of 5 mg/kg and 10 mg/kg, respectively ( $P = .03$ ). The posttransplantation complications are listed in Table 2.

The median overall survival (OS) and progression-free survival (PFS) have not yet been reached. The 1-year PFS and OS were 60% and 65%, respectively. There is no statistical difference in term of PFS, OS, and TRM between patients transplanted from sibling donors or haplo-identical donors. Interestingly, the 1-year PFS and OS probabilities were 31% versus 87% ( $P = .012$ ) and 46% versus 87% ( $P = .008$ ), respectively, for patients in the T5 and T10 groups (Figures 1 and 2). In univariate and multivariate analysis, donor type (MSD vs. haplo-identical), disease (acute leukemia vs. lymphoma), disease status at transplantation (first complete remission vs. others), Hematopoietic Cell Transplantation Comorbidity Index, and disease risk index (intermediate vs. high) had no statistically significant impact on TRM, PFS, and OS, probably because of the small sample size. On the other hand, in univariate analysis, increased age at transplantation and total dose of thiotepa had a statistically significant impact on TRM, PFS, and OS. However, only dose of thiotepa remained significant in the multivariate analysis (OS  $P = .001$ , PFS  $P = .003$ , and TRM  $P = .023$ ).

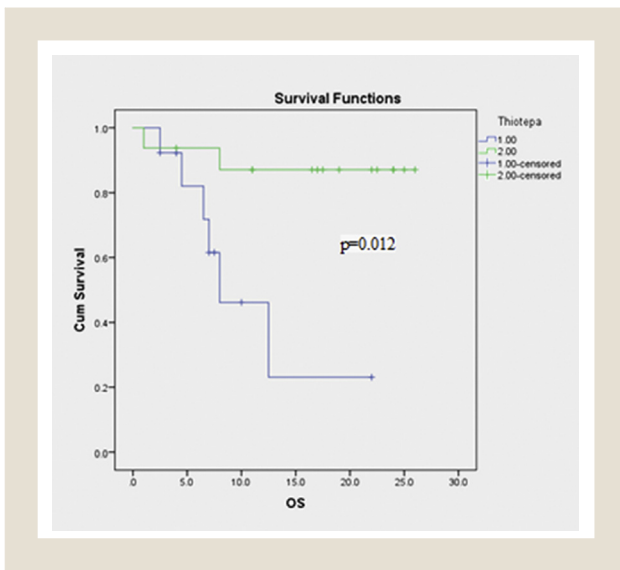
**Table 2** Complications After Transplantation

Complication	Total	T5	T10	P
Patients	29 (100%)	13 (45%)	16 (55%)	NS
<b>Infectious Complications</b>				
CMV	21 (72%)	10 (77%)	11 (69%)	NS
Days to CMV reactivation	32 (5-76)	31 (24-76)	32 (5-60)	
EBV (day), median (range)	8 (28%)	5 (38%)	3 (19%)	NS
Days to EBV	46 (27-117)	46 (31-90)	46 (27-117)	
BKV	11 (38%)	4 (31%)	7 (44%)	NS
Days to BKV	32 (5-90)	40 (40-90)	32 (5-62)	
HHV6	3 (10%)	1 (8%)	2 (13%)	NS
Days to HHV6	42 (22-61)	41	42 (22-61)	
JC-PML	2 (7%)	1 (8%)	1 (6%)	NS
Time to reactivation	246 (102-390)	390	102	
<b>Noninfectious Complications</b>				
VOD	1 (3%)	0	1 (6%)	NS
aGVHD	7 (24%)	4 (31%)	3 (19%)	NS
Grade II	4 (14%)	3 (23%)	1 (6%)	NS
Grade III-IV	3 (10%)	1 (8%)	2 (13%)	NS
cGVHD limited	1 (3%)	0	1 (6%)	NS
cGVHD extensive	1 (3%)	1 (8%)	0	NS

Abbreviations: aGVHD = acute graft-versus-host disease; BKV = BK virus; cGVHD = chronic graft-versus-host disease; CMV = cytomegalovirus; EBV = Epstein-Barr virus; haplo = haplo-identical stem-cell transplantation; hem-cystitis = hemorrhagic cystitis; HHV6 = human herpesvirus 6; JC-PML = JC virus progressive multifocal leukoencephalopathy; T5 = 1 day's thiotepa conditioning at 5 mg/kg total dose; T10 = 2 days' thiotepa conditioning at 10 mg/kg total dose; VOD = veno-occlusive disease.

# Thiotepa Treatment Regimen

**Figure 1 OS (Months) by Thiotepa Dose Intensity (T5 vs. T10)**

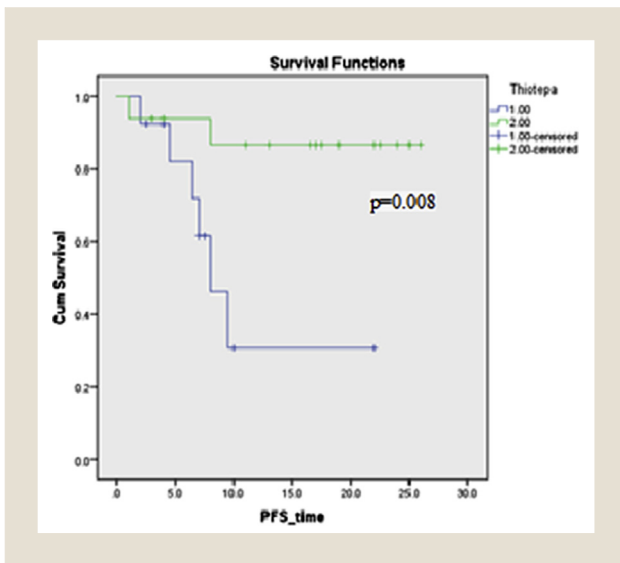


Abbreviations: 1 = T5 group; 2 = T10 group; Cum survival = cumulative survival; OS = overall survival; T10 = 10 mg/kg; T5 = 5 mg/kg.

## Discussion

In the 1990s, Bacigalupo et al<sup>13</sup> reported on the use of thiotepa in patients with advanced leukemia undergoing myeloablative conditioning. The 2-year OS was 57% and the TRM was 29%. Rosales and colleagues used thiotepa (5 mg/kg per day for 2 days) in addition to the standard busulfan/cyclophosphamide regimen with comparable results and moderate toxicity rates. Thiotepa was later included in RIC regimens in an effort to intensify the antileukemic effect and reduce the relapse rates, which were higher after RIC compared to the myeloablative regimens.<sup>14,15</sup> Indeed, Bacigalupo

**Figure 2 PFS (Months) by Thiotepa Dose Intensity (T5 vs. T10)**



Abbreviations: 1 = T5 group; 2 = T10 group; Cum survival = cumulative survival; PFS = progression-free survival; T10 = 10 mg/kg thiotepa dose; T5 = 5 mg/kg thiotepa dose.

et al<sup>16</sup> were able to show an impressive outcome of thiotepa-based RIC regimens at 10-year follow-up.

To our knowledge, ours is the first study to assess the impact of thiotepa dose intensity in TBF-based conditioning regimens. Full engraftment was observed in all cases, suggesting a sufficient immunosuppressive activity of both doses of thiotepa with fludarabine in combination with intermediate doses of busulfan and ATG. The incidence of aGVHD was comparable between the T5 and T10 groups. Our study showed that the increased dose intensity of thiotepa does not correlate with increased TRM. In our study, we observed a 1-year TRM of 14%. Surprisingly, all TRM cases were observed in the T5 group and none in the T10 group. This can be explained by the older population, haploidentical donors, and higher number of lines of therapy in the T5 group. However, in univariate and multivariate analysis, a lower dose of thiotepa was the only factor associated with increased TRM.

Recently the GELATMO trial, which included only patients with high-risk relapsed or refractory aggressive B-cell lymphoma receiving RIC allo-SCT from related donors using 5 mg/kg thiotepa, reported a higher TRM at 100 days and 1 year of 22% and 28%, respectively.<sup>17</sup> However, in our study of comparable high-risk lymphoma patients, the type of disease (lymphoid vs. myeloid) had no impact on transplantation outcomes.

A recent registry study performed by the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) using heterogeneous combinations and doses of thiotepa-based conditioning regimens for allo-SCT in patients with ALL in matched sibling and matched unrelated donors reported a TRM of 12% and 25% at 100 days and 1 year, respectively.<sup>18</sup> The relapse rate at 1 year was 33%. The 1-year PFS and OS were 57% and 66%, respectively. Furthermore, another registry study from the same group that compared thiotepa-based conditioning to cyclophosphamide and total-body irradiation for allo-SCT in patients with AML in complete remission showed comparable outcome between the two groups. The aGVHD was observed in 25%, cGVHD in 40%, and TRM in 24%, with a relapse rate of 17% after a thiotepa-based regimen.<sup>19</sup> However, none of these 2 large studies investigated the impact of thiotepa dose intensities on outcomes.

Our approach seemed to fulfill its objective to exert a broad-spectrum antitumor activity because at last follow-up, 72% were alive and had disease in complete remission, with 1-year PFS and OS of 60% and 65%, respectively. Although longer follow-up is needed, our results are encouraging for patients with progressive or residual disease.

In a similar study with comparable population investigating the outcome of 10 mg/kg thiotepa-based conditioning regimens in 33 patients with high-risk hematologic malignancies reported a TRM of 6% and 27% in patients receiving bone marrow and peripheral blood stem cells (PBSC) as a graft source, respectively.<sup>14</sup> They also reported a 3% incidence of aGVHD grade III-IV and cGVHD of 69% in PBSC and 23% in bone marrow graft. However, patients in this study did not receive ATG. Conversely, in our study, we report a lower incidence of TRM and cGVHD (6%) but a higher incidence of aGVHD grade III-IV (10%) in our patients overall and in those receiving 10 mg/kg thiotepa (13%). This may be explained by the exclusive use of PBSC in our study.

**Table 3** Comparison of Our Study With Other Similar Studies

Characteristic	El-Cheikh (2017) <sup>9</sup>	Eder (2017) <sup>18</sup>	Eder (2016) <sup>19</sup>	Raiola (2000) <sup>14</sup>	GELATMO
Type of study	<ul style="list-style-type: none"> <li>Retrospective</li> <li>Single center</li> <li>29 patients</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective</li> <li>Multicenter</li> <li>323 patients</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective</li> <li>Multicenter</li> <li>121 patients</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective</li> <li>Multicenter</li> <li>33 patients</li> </ul>	<ul style="list-style-type: none"> <li>Prospective</li> <li>Multicenter</li> <li>18 patients</li> </ul>
Conditioning regimens	TBF + ATG	TBF/TF/TB/MelF/TMEl/other	TCy/TBF/other	TCy	TMelF + Y-90— ibrutumomab + rituximab
Conditioning intensity	T5/T10	RIC/MAC	RIC/MAC	T10	T5 RIC
Age at transplantation (years), median (range)	37 (21-65)	43 (18-76)	42 (18-65)	52 (43-60)	50 (32-63)
Disease type	Myeloid and lymphoid	ALL	AML	Myeloid and lymphoid	Refractory relapsed B-cell lymphoma
Donor type	MSD/Haplo	MSD-MUD	MSD-MUD	MSD	MSD
Stem-cell source	PBSC	BM/PBSC	BM/PBSC	BM/PBSC	BM/PBSC
aGVHD	24%	27%	25%	52%	72%
cGVHD	6%	36%	41%	45%	59%
Relapse incidence	1 year: 20%	1 year: 33%	2 year: 17%	2 year: 43%	1 year: 26%
Transplant-related mortality	Day100: 0% 1 year: 14%	Day100: 12% 1 year: 25%	2 years: 24%	2 years: 22%	Day100: 22% 1 year: 28%
Progression-free survival	1 year: 60%	1 year: 57%	2 year: 59%	2 year: 60%	1 year: 50%
Overall survival	1 year: 65%	1 year: 66%	2 year: 61%	2 year: 72%	1 year: 55%

Abbreviations: aGVHD = acute graft-versus-host disease; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; ATG = antithymocyte globulin; B = busulfan; BM = bone marrow; cGVHD = chronic graft-versus-host disease; Cy = cyclophosphamide; F = fludarabine; haplo = haploidentical stem-cell transplantation donor; MAC = myeloablative conditioning; Mel = melphalan; MSD = matched sibling donor; MUD = matched unrelated donor; PBSC = peripheral blood stem cells; RIC = reduced-intensity conditioning; T = thiotepa; T5 = 5 mg/kg thiotepa dose; T10 = 10 mg/kg thiotepa dose.

Our conditioning regimen was feasible, with comparable efficacy in both lymphoma and leukemia patients. We emphasize that we used ATG for 2 consecutive days in the haploidentical stem-cell transplantation setting with posttransplantation cyclophosphamide because of the use of PBSC graft in all patients. We aimed to reduce the risk of GVHD, successfully showing a low incidence of acute grade II-IV GVHD and cGVHD (24% and 6%), respectively, without increasing the incidence of relapse, as has been shown in conventional allo-SCT.<sup>20-22</sup> These results seem to compare favorably with those of other reports, which cite a cumulative incidence of 14% to 31% of acute grade II-IV GVHD and 0% to 38% of severe cGVHD without ATG.<sup>23-29</sup> Despite the use of ATG in patients with intermediate to high disease risk index, the 1-year relapse incidence was 20% in both MSD and haploidentical stem-cell transplantation groups. Overall, ATG in haploidentical stem-cell transplantation with this TBF conditioning was associated with low rates of GVHD without compromising outcomes. A comparison between our study and other similar studies is listed in Table 3.

This low risk of relapse could be related to the maintenance therapy received in the posttransplantation setting, such as the early administration of the hypomethylating agent 5-azacytidine in AML patients, which has been reported from our and other groups to be well tolerated and to result in a low incidence of GVHD.<sup>9,30</sup> Different reports suggest that *FLT3* tyrosine kinase inhibitors could also be effective for cases of *FLT3* internal tandem duplication in the posttransplantation setting.<sup>10,31</sup>

Interestingly, our data showed that on univariate and multivariate analysis, only increased age at transplantation and thiotepa dose had a statistically significant impact on TRM, PFS, and OS;

however, it could also be related to the lower dose of thiotepa provided to some older patients. Compared to MSD allo-SCT, toxicities and GVHD were not increased, and survival was not inferior in patients who underwent haploidentical stem-cell transplantation. Interestingly, the haploidentical group had a lower incidence of aGVHD than the MSD group despite the use of PBSC rather than bone marrow graft. Thus, there seems to be no benefit in searching for an unrelated donor when a haploidentical donor is easily and quickly available, especially in Middle Eastern countries, where patients have little chance to find a donor in international registries.

## Conclusion

Acknowledging the retrospective nature of our study and the small sample size, these results suggest that patients deemed fit to receive T10-based conditioning for allo-SCT in high-risk hematologic malignancies had better OS and PFS than those who received T5-based conditioning with no additional toxicities. Therefore, patients should be stratified before conditioning, and those judged fit should receive T10, while the others should consider alternative RIC conditioning regimens. An alternative way of tailoring the treatment regimen to older patients is reduction of busulfan to 2 days instead of decreasing thiotepa. However, the effect of the total dose of thiotepa on transplantation outcomes needs to be confirmed in a larger study.

## Clinical Practice Points

- The optimal intensity of myeloablation in TBF conditioning to decrease risk of relapse after allo-SCT without increasing TRM has not been established.

# Thiotepa Treatment Regimen

- In this retrospective study, we compared outcomes for patients receiving 2 different doses of thiotepa (5 vs. 10 mg/kg) as part of a TBF conditioning regimen.
- Patients who were fit to receive 10 mg/kg thiotepa had better OS and PFS than those who received 5 mg/kg, with no additional toxicities.
- Even though standard myeloablative conditioning regimens are associated with decreased incidence of relapse, they are associated with increased risk of toxicities, GVHD, and TRM.

## Disclosure

The authors have stated that they have no conflict of interest.

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