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Transplantation Conditioning Regimens and Outcomes after Allogeneic Hematopoietic Cell Transplantation in Children and Adolescents with Acute Lymphoblastic Leukemia

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Relapse is common after hematopoietic stem cell transplantation (HSCT) for acute lymphoblastic leukemia (ALL). Although 1200 cGy total body irradiation (TBI) and cyclophosphamide (Cy) is the standard conditioning regimen, attempts to reduce relapse have led to the addition of a second chemotherapeutic agent and/or higher dose of TBI. We examined HSCT outcomes in patients age <18 years with ALL, in second or subsequent remission or in relapse at transplantation. Most transplantations were performed with the patient in remission. Patients received grafts from an HLA-matched sibling or unrelated donor. Four treatment groups were created: (1) Cy + TBI ≤ 1200 cGy (n = 304), (2) Cy + etoposide + TBI ≤ 1200 cGy (n = 108), (3) Cy + TBI ≥ 1300 cGy (n = 327), and (4) Cy + etoposide + TBI ≥ 1300 cGy (n = 26). Neither TBI > 1200 cGy nor the addition of etoposide resulted in fewer relapses. The 5-year probability of relapse was 30% for group 1, 28% for group 2, 35% for group 3, and 31% for group 4. However, transplantation-related mortality was higher (35% versus 25%, $P = .02$) and overall survival lower (36% versus 48%, $P = .03$) in group 4 compared with group 3. Our findings indicate that compared with the standard regimen, neither TBI > 1200 cGy nor the addition of etoposide improves survival after HSCT for ALL.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is an accepted treatment for children with recurrent acute lymphoblastic leukemia (ALL) [1-3]. Transplantation conditioning regimens typically consist of total body irradiation (TBI), in doses ranging from 1000 to 1400 cGy, along with one or more chemotherapeutic agents. The standard conditioning regimen, developed based on empirical observations, is cyclophosphamide (Cy) 120 mg/kg and TBI 1200 cGy [4]. The Center for International Blood and Marrow Transplant Research (CIBMTR) has reported that non–irradiation-containing regimens are associated with higher relapse rates compared with TBI-containing regimens for ALL [5]. Attempts to decrease the risk of relapse after HCT by modulating transplantation conditioning have included increasing the TBI dose to >1200 cGy and/or adding a second chemotherapeutic agent, most commonly etoposide [6-8]. Others have attempted to decrease the intensity of the conditioning regimen, relying on immune modulation (ie, graft-versus-leukemia effect) for disease control [9]. Although reports on relatively few patients suggest acceptable leukemia-free survival, these regimens are used in <5% of HSCTs for pediatric ALL [10].

A review of myeloablative TBI-containing conditioning regimens for pediatric ALL reported to the CIBMTR identified 4 commonly used regimens: (1) TBI 1000 or 1200 cGy + Cy, (2) TBI 1000 or 1200 cGy + Cy + etoposide, (3) TBI 1320-1400 cGy + Cy, and (4) TBI 1320-1400 cGy + Cy + etoposide. In the present analysis, we sought to examine the effect of these 4 commonly used transplantation conditioning regimens on leukemia relapse, transplantation-related mortality, and overall survival in 765 children and adolescents with ALL.

PATIENTS AND METHODS

Data Source

The CIBMTR is a voluntary working group of more than 400 transplant centers worldwide that contribute detailed data on consecutive allogeneic and autologous HSCT to a statistical center at the Medical College of Wisconsin in Milwaukee or the National Marrow Donor Program Coordinating Center in Minneapolis. Participating centers are required to report all HSCTs consecutively; compliance is monitored by onsite audits. Patients are followed longitudinally. All patients and/or their guardians provide written informed consent. The Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Inclusion Criteria

This study included patients with ALL age <18 years at the time of HSCT who received a graft from an HLA-matched sibling or an unrelated donor. Unrelated donor grafts included bone marrow and umbilical cord blood. All HSCTs were performed between 1998 and 2007. All patients received myeloablative conditioning with a TBI-containing regimen (TBI ≥ 1000 cGy). Recipients of non–TBI-containing regimens were excluded.

Outcomes

The primary study outcome was relapse after HSCT. Relapse was defined as morphological reappearance of leukemic blasts. Other outcomes included transplantation-related mortality, defined as death not related to leukemia recurrence, and overall survival, defined as death from any cause. Surviving patients were censored at last follow-up.

Statistical Analysis

Patient, disease, and transplant characteristics of the 4 treatment groups were compared using the χ^2 test for categorical variables. The probability of overall survival was calculated with the Kaplan-Meier estimator [11]. The probabilities of transplantation-related mortality and

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Table 1
Patient, Disease, and Transplant Characteristics

	Cy		Cy + Etoposide		*P* Value
	TBI ≤ 1200 cGy	TBI ≥ 1320 cGy	TBI ≤ 1200 cGy	TBI ≥ 1320 cGy	
Number	304	327	108	26	
Age at HSCT, years, n (%)					NS
≤10	171 (56)	197 (60)	71 (66)	14 (54)	
11-18	133 (44)	130 (40)	37 (34)	12 (46)	
Sex, n (%)					NS
Male	200 (65)	214 (65)	66 (61)	14 (54)	
Female	104 (32)	113 (35)	42 (39)	12 (46)	
Performance score, n (%)					<.0001
<90%	47 (15)	40 (12)	28 (26)	8 (31)	
≥90%	244 (80)	253 (77)	78 (72)	17 (65)	
Not reported	13 (4)	34 (10)	2 (2)	1 (4)	
Recipient cytomegalovirus status, n (%)					.002
Positive	169 (56)	145 (45)	35 (32)	11 (42)	
Negative	133 (44)	177 (54)	71 (66)	15 (58)	
Not reported	2 (1)	5 (1)	2 (2)	—	
National Cancer Institute risk score, n (%)					NS
Normal	105 (35)	124 (38)	47 (44)	8 (26)	
High	164 (54)	152 (46)	47 (44)	16 (58)	
Not reported	35 (12)	51 (16)	14 (13)	2 (16)	
Cytogenetic risk group, n (%)					NS
Intermediate risk	231 (76)	229 (70)	81 (75)	13 (50)	
High risk	10 (3)	17 (5)	2 (2)	3 (12)	
Not reported	63 (21)	81 (25)	25 (23)	10 (38)	
Duration of first remission, n (%)					NS
≤36 months	201 (66)	213 (65)	66 (61)	17 (65)	
>36 months	103 (34)	114 (35)	42 (39)	9 (35)	
Disease status, n (%)					NS
Second complete remission	227 (75)	219 (67)	78 (72)	16 (62)	
Third complete remission	55 (18)	71 (22)	21 (19)	5 (19)	
Relapse	22 (7)	37 (11)	9 (8)	5 (19)	
Donor source, n (%)					<.0001
HLA-matched sibling					
Bone marrow	103 (34)	19 (6)	15 (14)	10 (38)	
Cord blood	4 (1)	6 (2)	3 (3)	1 (4)	
Unrelated					
Matched	47 (15)	66 (20)	18 (17)	4 (15)	
Mismatched	82 (27)	106 (32)	29 (27)	10 (38)	
Cord blood	68 (22)	132 (40)	42 (39)	3 (12)	
Graft-versus-host disease prophylaxis, n (%)					<.0001
Cyclosporine + methotrexate	186 (61)	139 (43)	56 (52)	11 (42)	
Cyclosporine ± steroid	77 (25)	124 (38)	26 (24)	13 (50)	
Tacrolimus + methotrexate	32 (11)	54 (17)	15 (14)	0 (0)	
Tacrolimus ± other	4 (1)	7 (2)	6 (6)	1 (4)	
Methotrexate + other	5 (2)	3 (1)	5 (5)	1 (4)	
Year of transplantation, n (%)					<.0001
1998-1999	73 (24)	41 (13)	30 (28)	10 (38)	
2000-2004	160 (53)	173 (53)	56 (52)	14 (54)	
2005-2007	71 (23)	113 (35)	22 (20)	2 (8)	
Follow-up of surviving patients; median (range), months	50 (3-133)	44 (2-119)	46 (3-130)	53 (34-93)	

NS indicates not significant.

relapse were calculated with the cumulative incidence estimator [12]. For transplantation-related mortality, relapse was the competing event, and for relapse, transplantation-related mortality was the competing event. Log-transformation was used to derive 95% confidence intervals (CIs). Multivariate models were built using Cox proportional hazards regression models for transplantation-related mortality, relapse, and overall mortality [13]. Models were built using the backward stepwise selection procedure and confirmed using the forward stepwise selection procedure. The proportional hazards assumption was tested for each variable individually; all variables met this assumption. A *P* value ≤.05 was considered statistically significant.

The variables for transplantation conditioning regimen—TBI ≤ 1200 cGy (1000 or 1200 cGy) + Cy versus TBI ≤ 1200 cGy + Cy + etoposide versus TBI ≥ 1320 (1320 or 1350 or 1400 cGy) + Cy versus TBI ≥ 1320 + Cy + etoposide—were included in all steps of model building regardless of the level of significance. Other variables tested were included in the final model when significant; these included patient age (≤10 years versus >10 years), National Cancer Institute risk score (standard risk versus high risk), cytogenetic risk (standard risk versus high risk), duration of first remission (≤36 months versus >36 months), patient performance score (90-100 versus ≤80), donor and graft source (HLA-matched sibling [bone marrow/cord blood] versus HLA-matched unrelated donor bone marrow versus HLA-mismatched unrelated donor bone marrow versus unrelated cord blood), recipient cytomegalovirus serostatus (positive versus negative), and year of transplantation (1998-1999 versus 2000-2004 versus 2005-2007). There was no significant effect of transplantation center on survival. All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient, Disease, and Transplant Characteristics

Patient, disease, and transplant characteristics by treatment group are presented in Table 1. Sixteen of 412 patients (4%) who received TBI ≤ 1200 cGy were given 1000 cGy, and the remaining patients were given TBI 1200 cGy. Eighty-four of the 353 patients (24%) who received TBI ≥ 1320 cGy were given 1320 cGy, 145 (41%) were given 1350 cGy, and 124 (35%) were given 1400 cGy. Almost all patients received Cy 120 mg/kg regardless of TBI dose; 87% of those who received etoposide as a second agent received either 40 mg/kg or 60 mg/kg. Although there were no significant differences in patient age among the 4 treatment groups, patients who

Table 2
Results of Multivariate Analysis

	HR (95% CI)	*P* Value
Relapse		
TBI ≤ 1200 cGy + Cy + etoposide versus TBI ≤ 1200 cGy + Cy	0.97 (0.63-1.48)	.87
TBI ≥ 1320 cGy + Cy + etoposide versus TBI ≥ 1320 cGy + Cy	1.01 (0.49-2.09)	.97
TBI ≥ 1320 cGy + Cy versus TBI ≤ 1200 cGy + Cy	1.13 (0.85-1.50)	.41
TBI ≥ 1320 cGy + Cy + etoposide versus TBI ≤ 1200 cGy + Cy + etoposide	1.19 (0.54-2.61)	.67
Transplantation-related mortality		
TBI ≤ 1200 cGy + Cy + etoposide versus TBI ≤ 1200 cGy + Cy	1.06 (0.70-1.60)	.78
TBI ≥ 1320 cGy + Cy + etoposide versus TBI ≥ 1320 cGy + Cy	2.36 (1.17-4.76)	.02
TBI ≥ 1320 cGy + Cy versus TBI ≤ 1200 cGy + Cy	0.73 (0.53-1.01)	.06
TBI ≥ 1320 cGy + Cy + etoposide versus TBI ≤ 1200 cGy + Cy + etoposide	1.63 (0.77-3.45)	.20
Overall mortality		
TBI ≤ 1200 cGy + Cy + etoposide versus TBI ≤ 1200 cGy + Cy	1.10 (0.82-1.50)	.52
TBI ≥ 1320 cGy + Cy + etoposide versus TBI ≥ 1320 cGy + Cy	1.79 (1.07-2.99)	.03
TBI ≥ 1320 cGy + Cy versus TBI ≤ 1200 cGy + Cy	0.87 (0.69-1.09)	.23
TBI ≥ 1320 cGy + Cy + etoposide versus TBI ≤ 1200 cGy + Cy + etoposide	1.40 (0.81-2.43)	.23

received etoposide in addition to TBI and Cy were more likely to have a performance score <90. Disease characteristics, including National Cancer Institute risk score, cytogenetic risk, time from diagnosis to transplantation, and disease status at transplantation, were similar across the treatment groups. There were differences among the groups in the choice of conditioning regimen; recipients of TBI ≥ 1320 + Cy + etoposide (group 4) were more likely to have received an HLA-matched sibling transplant, less likely to have received an umbilical cord blood transplant, more likely to have received methotrexate-containing graft-versus-host disease prophylaxis, and more likely to have undergone HSCT before 2005. The median follow-up of surviving patients in all treatment groups was 4 years.

Relapse

In multivariate analysis, the risk of relapse was similar among the 4 treatment groups (Table 2). The 5-year probability of relapse was 30% (95% CI, 25%-35%) for group 1, 28% (95% CI, 19%-37%) for group 2, 35% (95% CI, 29%-40%) for group 3, and 31% (95% CI, 15%-48%) for group 4 (Figure 1). Relapse risk was similar in patients receiving TBI (any dose) + Cy + etoposide and those receiving TBI (any dose) + Cy (hazard ratio [HR], 0.9; 95% CI, 0.66-1.34; $P = .72$). However, relapse risk was associated with patient sex, duration of first remission, and disease status at transplantation, with higher risk in females (HR, 1.5; 95% CI, 1.2-2.0; $P = .003$), patients with first remission lasting less than 36 months (HR, 2.96; 95% CI, 2.13-4.17; $P < .001$), and patients in third complete remission or relapse at the time of transplantation (HR, 1.6; 95% CI, 1.2-2.2; $P = .001$).

Transplantation-Related Mortality

The risk of transplantation-related mortality differed by conditioning regimen (Table 2). Compared with recipients of

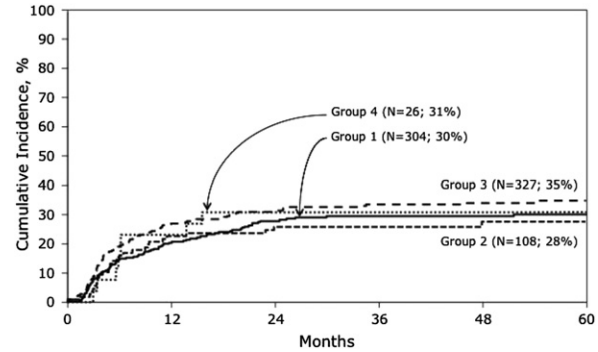

Figure 1. Probability of relapse by conditioning regimen. Group 1: TBI ≤ 1200 cGy + Cy; group 2: TBI ≤ 1200 cGy + Cy + etoposide; group 3: TBI ≥ 1300 cGy + Cy; group 4: TBI ≥ 1300 cGy + Cy + etoposide.

TBI ≥ 1320 cGy + Cy (group 3), those who received TBI ≥ 1320 cGy + Cy + etoposide (group 4) were at greater risk for transplantation-related mortality. The addition of etoposide to TBI ≤ 1200 cGy + Cy (group 2) was not associated with increased risk compared with TBI ≤ 1200 cGy + Cy alone (group 1) (HR, 1.06; 95% CI, 0.70-1.60; $P = .78$). The 5-year cumulative incidence of transplantation-related mortality was 25% (95% CI, 21%-31%) for group 1, 32% (95% CI, 23%-41%) for group 2, 25% (95% CI, 20%-30%) for group 3, and 35% (95% CI, 18%-52%) for group 4 (Figure 2). The risk of transplantation-related mortality was not higher in recipients of TBI (any dose) + Cy + etoposide compared with recipients of TBI (any dose) + Cy (HR, 1.37; 95% CI, 0.97-1.92; $P = .07$). Age >10 years (HR, 1.93; 95% CI, 1.45-2.56; $P < .001$) was associated with a higher risk of transplantation-related mortality. Compared with recipients of an HLA-matched sibling transplant, the risk of transplantation-related mortality was greater in recipients of matched unrelated donor bone marrow (HR, 3.26; 95% CI, 1.77-6.02; $P < .001$), mismatched unrelated donor bone marrow (HR, 4.07; 95% CI, 2.34-7.08; $P < .001$), and umbilical cord blood (HR, 5.30; 95% CI, 3.04-9.25; $P < .001$) transplants.

Overall Survival

Overall mortality risk also differed by transplantation conditioning regimen (Table 2). Recipients of TBI ≥ 1320 cGy who received Cy + etoposide had a higher mortality risk compared with those who received Cy alone. However, mortality risk was not higher in recipients of TBI ≤ 1200 cGy

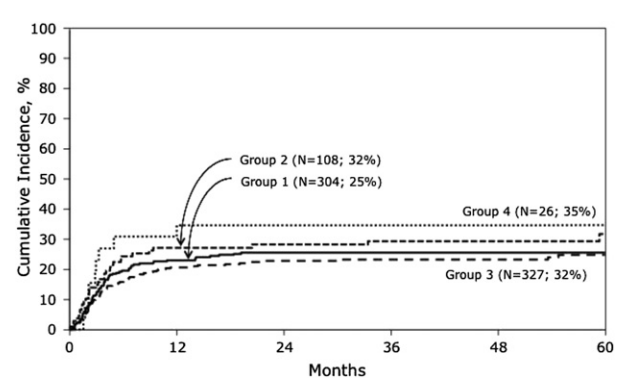

Figure 2. Probability of transplantation-related mortality by conditioning regimen. Group 1: TBI ≤ 1200 cGy + Cy; group 2: TBI ≤ 1200 cGy + Cy + etoposide; group 3: TBI ≥ 1300 cGy + Cy; group 4: TBI ≥ 1300 cGy + Cy + etoposide.

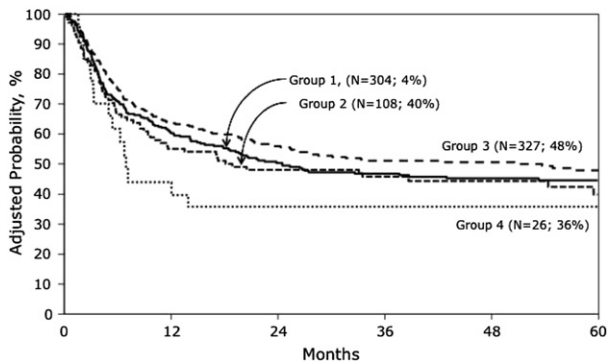

Figure 3. Probability of overall survival by conditioning regimen adjusted for patient age, duration of first complete remission, disease status at transplantation, and donor HLA match. Group 1: TBI ≤ 1200 cGy + Cy; group 2: TBI ≤ 1200 cGy + Cy + etoposide; group 3: TBI ≥ 1300 cGy + Cy; group 4: TBI ≥ 1300 cGy + Cy + etoposide.

who received Cy + etoposide compared with those who received Cy alone (HR, 1.10; 95% CI, 0.82-1.50; $P = .52$). Overall mortality risk was not higher in recipients of TBI (any dose) + Cy + etoposide compared with recipients of TBI (any dose) + Cy (HR, 1.24; 95% CI, 0.96-1.59; $P = .09$). Mortality risk was higher in patients age >10 years (HR, 1.05; 95% CI, 1.22-1.85; $P < .001$), those with a duration of first remission ≤36 months (HR, 1.69; 95% CI, 1.35-2.11; $P < .001$), and those undergoing HSCT in third remission or in relapse (HR, 1.41; 95% CI, 1.14-1.74; $P = .002$). Compared with recipients of HLA-matched sibling transplants, overall mortality risk was higher in recipients of mismatched unrelated donor bone marrow (HR, 1.72; 95% CI, 1.27-2.34; $P < .001$) and umbilical cord blood (HR, 1.87; 95% CI, 1.36-2.57; $P < .001$) transplants, but not in recipients of matched unrelated donor bone marrow transplants (HR, 1.34; 95% CI, 0.94-1.92; $P = .11$). The 5-year probability of overall survival was 44% (95% CI, 38%-50%) for group 1, 40% (95% CI, 30%-50%) for group 2, 48% (95% CI, 42%-54%) for group 3, and 36% (95% CI, 19%-53%) for group 4 (Figure 3).

DISCUSSION

In the present analysis, we examined for an effect on relapse after HSCT from different TBI-containing myeloablative conditioning regimens in children and adolescents with ALL. The patients were divided into 4 groups based on TBI dose and chemotherapeutic agents. Neither TBI ≥ 1200 cGy nor the addition of etoposide to Cy was associated with decreased risk of relapse. However, transplantation-related and overall mortality risks were higher with TBI ≥ 1320 cGy + Cy + etoposide compared with TBI ≥ 1320 cGy + Cy alone. In patients receiving lower-dose TBI (1000 or 1200 cGy), the addition of etoposide was not associated with increased mortality risk.

The addition of a second chemotherapeutic agent for children and adolescents receiving myeloablative TBI-based conditioning for enhanced leukemia control is not supported by these data. On the contrary, the addition of a second chemotherapeutic agent to a TBI ≥ 1320 cGy + Cy regimen increases the risk of mortality and should be avoided.

Our observations are in contrast with the findings of Duerst et al. [14] in their study of 41 children with ALL and abute myelogenous leukemia conditioned with TBI 1200-1400 cGy + Cy + etoposide. Duerst et al. observed a single fatal regimen-related toxicity in their series, and recurrent leukemia was the predominant cause of treatment failure. In that study, the etoposide dose was 30 mg/kg, whereas in the present study, most patients (87%) received an etoposide dose >30 mg/kg. The difference in mortality risk between the present study and the study of Deurst et al. may be related to the different etoposide doses. Because only 17 of our patients received a dose of 30 mg/kg, we were unable to test for an effect of etoposide dose on mortality risk. Others have reported a decreased risk of relapse with regimens consisting of TBI and etoposide alone. For example, a large series from the CIBMTR [15] that compared TBI dose (<1300 cGy versus ≥1300 cGy) with Cy or etoposide in children and adults with ALL in first or second complete remission found that for patients in second complete remission, relapse and mortality risks were lower in those who received TBI (any dose) and etoposide compared with those who received TBI < 1300 cGy and Cy. In an ongoing clinical trial conducted by the International Berlin-Frankfurt-Muenster group for allogeneic HSCT in children and adolescents with ALL (NCT01423747), the recommended regimen is TBI 1200 cGy and etoposide 60 mg/kg for recipients of matched related and unrelated donor grafts and etoposide 40 mg/kg for recipients of mismatched related and unrelated donor grafts. We were unable to test for an effect of TBI + etoposide alone versus TBI + Cy alone, because our study cohort contained too few children who received etoposide alone. In another study focusing on pediatric ALL, Gassas et al. [8] compared the addition of etoposide or Cy to TBI 1200 cGy and concluded that both regimens were equally effective. We tested for an effect when etoposide was added to the TBI ≤ 1200 cGy + Cy regimen, and found none. It is plausible that the excess mortality risk observed with the addition of etoposide to higher-dose TBI is a result of the additive effect of higher-dose TBI and a second chemotherapeutic agent. Although the actual etiology behind the excess mortality is unknown, our observations suggest that neither a TBI dose >1200 cGy nor the addition of a second chemotherapeutic agent is necessary.

Several factors besides conditioning regimen are associated with leukemia relapse. Consistent with other reports [16], duration of first remission and disease status at transplantation were important predictors of relapse in our series. We found no significant difference in relapse risk with the addition of etoposide. Our findings are in contrast with a previous report indicating that TBI-containing regimens with etoposide alone were associated with superior leukemia control posttransplantation [15]. Patient age varies among studies, however, with our series limited to children and adolescents, and the reported differences in risk may be related to differences in the biology of pediatric and adult ALL and/or differences in intensity of up-front chemotherapy regimens used to induce a second remission.

In the present study, along with conditioning regimen, patient age and donor source also affected survival. Older age and transplantation of unrelated donor grafts were associated with higher mortality risk. Although they predict mortality, patient age and donor source are not modifiable factors. The data presented herein span the period 1998-2007. Concurrent with improvements in supportive care and donor selection, survival rates are not different after HLA-matched sibling and matched unrelated donor transplantation [17]. In the absence of a suitably matched related donor, physicians should defer to recommended guidelines for selection of unrelated donors, that is, transplantation of

bone marrow from an 8/8 or a 7/8 HLA-matched adult donor or a mismatched umbilical cord blood unit with an adequate cell dose [18]. Of note, in our series, the effect of conditioning regimen on transplantation-related and overall mortality was independent of patient age and donor source. Patients who received TBI $\geq$ 1320 cGy + Cy + etoposide were more likely to have a performance score <90. Because poor performance score predicts survival, this variable was retained in the final multivariate model, implying that the observed adverse effect on mortality is independent of performance score.

In the present study, as in any study using data collected by a registry, several unknown or unmeasured factors also might have influenced outcomes. However, we performed a carefully controlled analysis adjusting for patient, disease, and transplant characteristics known to be associated with leukemia relapse and survival after HSCT. Our findings suggest that the addition of etoposide to a TBI $\geq$ 1320 cGy + Cy conditioning regimen increases mortality risk and should be avoided in children and adolescents with ALL. Given the known higher risk of second malignant neoplasm with a TBI dose $\geq$1300 cGy [19,20], in the absence of data that demonstrate an advantage for either lower relapse or higher survival, a TBI dose >1200 cGy should be avoided in children with ALL.

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