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Comparison of total body irradiation versus non-total body irradiation containing regimens for *de novo* acute myeloid leukemia in children

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ABSTRACT

With limited data comparing hematopoietic cell transplant outcomes between myeloablative total body irradiation (TBI) containing and non-TBI regimens in children with *de novo* acute myeloid leukemia, the aim of this study was to compare transplant-outcomes between these regimens. Cox regression models were used to compare transplant-outcomes after TBI and non-TBI regimens in 624 children transplanted between 2008 and 2016. Thirty two percent (n=199) received TBI regimens whereas 68% (n=425) received non-TBI regimens. Five-year non-relapse mortality was higher with TBI regimens (22% vs. 11%, $P<0.0001$) but relapse was lower (23% vs. 37%, $P<0.0001$) compared to non-TBI regimens. Consequently, overall (62% vs. 60%, $P=1.00$) and leukemia-free survival (55% vs. 52%, $P=0.42$) did not differ between treatment groups. Grade 2-3 acute graft *versus* host disease was higher with TBI regimens (56% vs. 27%, $P<0.0001$) but not chronic graft *versus* host disease. The 3-year incidence of gonadal or growth hormone deficiency was higher with TBI regimens (24% vs. 8%, $P<0.001$) but there were no differences in late pulmonary, cardiac or renal impairment. In the absence of a survival advantage, the choice of TBI or non-TBI regimen merits careful consideration with the data favoring non-TBI regimens to limit the burden of morbidity associated with endocrine dysfunction.



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Introduction

Hematopoietic cell transplant (HCT) is accepted as the standard of care for children and adolescents with high risk or relapsed/refractory acute myeloid leukemia (AML).¹⁻³ Total body irradiation (TBI) or busulfan (Bu) containing myeloablative conditioning regimens are commonly used to treat these patients.^{4,5} In 1992, a randomized trial in adults showed improved 2-year leukemia-free survival using conditioning with TBI-cyclophosphamide (Cy) compared to Bu-Cy using oral busulfan formulation, which was available at that time,⁶ however, there are limited data in children and adolescents. Intravenous Bu has subsequently been developed, which provides more consistent pharmacokinetics and reliable dosing.⁷ Further, pharmacokinetic targeting of intravenous Bu dosing reduces treatment-related toxicity.⁸ In the modern era, in adults, intravenous Bu-conditioning has been shown to be associated with improved non-relapse mortality, and overall and disease-free survival in comparison to TBI-containing regimens.^{9,10} However, acute graft *versus* host disease (GvHD),¹¹ acute liver injury,¹² pulmonary injury (*e.g.*, diffuse alveolar hemorrhage), and bloodstream infections^{13,14} are reported to be higher with TBI-containing compared to non-TBI regimens. Late complications, including secondary malignancies, endocrine, metabolic, renal, ocular, and neurocognitive complications are also higher with TBI-containing compared to non-TBI myeloablative regimens.¹⁵⁻¹⁷ Although TBI-containing regimens are associated with significant toxicity in children,¹⁸ many physicians continue to use TBI-containing regimens for transplantation for *de novo* AML in children and adolescents. In the absence of a randomized trial comparing TBI-containing *versus* non-TBI regimens in children, we utilized data on HCT reported to an observational registry, the Center for International Blood and Marrow Transplant Research (CIBMTR) to compare outcomes between the two treatment groups.

Methods

Patients

Data were reported prospectively to the CIBMTR, a voluntary working group of more than 450 transplant centers worldwide that contribute detailed data on allogeneic and autologous HCT. Participating centers report consecutive transplants and compliance is monitored by on-site audits. All patients are followed longitudinally until death or lost to follow-up. Eligible patients were aged ≤ 21 years undergoing first allogeneic transplantation with myeloablative conditioning for *de novo* AML in first or second complete remission between 2008 and 2016 and consented for research. Excluded were patients with an antecedent hematologic disorder or secondary AML, mismatched related donor transplant and non-calcineurin inhibitor GvHD prophylaxis regimens. Patients were broadly grouped into TBI-containing (TBI-Cy), TBI-Cy-fludarabine (Flu) and non-TBI (Bu-Cy and Bu-Flu) regimens. The study was approved by the Institutional Review Board of the National Marrow Donor Program.

Endpoint

Grades 2-3 acute GvHD, grade 3-4 acute GvHD, and chronic GvHD were defined using standard definitions.^{19,20} Relapse was defined as the recurrence of AML (morphologic, cytogenetic or molecular) and non-relapse mortality was defined as death in remission. Overall survival was defined where death from any

cause was considered an event. Leukemia-free survival was defined as being alive in continuous remission. Neutrophil recovery was defined as achieving a count of $\geq 0.5 \times 10^9/L$ for 3 consecutive days. Platelet recovery was defined as achieving a count of $\geq 20 \times 10^9/L$ without transfusions for 7 consecutive days. The day-100 incidence of veno-occlusive disease, systemic bacterial, viral and fungal infection were compared between the two treatment groups. The 5-year incidence of post-transplant interstitial pneumonitis, congestive heart failure, gonadal dysfunction, growth hormone deficiency and renal failure severe enough to warrant dialysis were compared between the two treatment groups.

Statistical methods

Patient-related, disease-related, and transplant-related outcomes were compared between treatment groups using Mann-Whitney tests (continuous variables) and Fisher's exact/Chi-square test (categorical variables). A *P*-value of < 0.05 was considered statistically significant. Cox regression models were built for acute and chronic GvHD, non-relapse mortality, relapse, overall and leukemia-free survival.²¹ The main effect (TBI-containing *vs.* non-TBI regimens) was forced in all models, and other covariates were retained in the final model if they met a significance level of less than 0.05. Forward stepwise selection was used to identify significant covariates. The interaction between the main effect and significant covariates was examined. Assessment of the proportional-hazards assumption was done by examining the coefficient of the logarithm of time from transplant to the last follow-up for each covariate. The coefficients for the covariates which violated the proportional hazards assumption were added as time-varying effects. The adjusted survival or cumulative incidence probabilities were calculated based on the final Cox models.^{22,23} Center effects were tested for non-relapse mortality, relapse, overall and leukemia-free survival using the score test.²⁴ All analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC).

Results

Patient, disease and transplant characteristics

Six hundred and twenty-four patients transplanted at 124 transplant centers were eligible and their characteristics are shown in Table 1. TBI-containing regimens included TBI-Cy (38%, 76 of 199) and TBI-Cy-Flu (62%, 123 of 199). Non-TBI regimens included Bu-Cy (76%, 322 of 425) and Bu-Flu (24%, 103 of 425). Bu pharmacokinetics with dose adjustments were performed for 80% (338 of 425) of non-TBI transplantations. Patient and disease characteristics differed by treatment group. TBI-containing regimens were less likely to be used for children aged 3 years and younger, for transplants in first complete remission and more likely with umbilical cord blood (67%). In very young children (age ≤ 3 years, $n=170$), only 19% (33 of 170) received a TBI regimen. Bone marrow was the predominant graft for non-TBI regimen transplants (48%). *In vivo* T-cell depletion with anti-thymocyte globulin was common with non-TBI regimens accounting for 52% of transplantations compared to only 11% with TBI-containing regimens. The predominant GvHD prophylaxis with TBI-containing regimens was cyclosporine with mycophenolate and for non-TBI regimen, tacrolimus or cyclosporine with methotrexate. There were no differences between treatment groups regarding performance score, hematopoietic co-morbidity index, sites at diagnosis and cytogenetic risk. Most transplant centers used both TBI-containing and non-

TBI regimens (n=57) or non-TBI regimens alone (n=53). Only 14 centers used TBI-containing regimens alone. Further, between 2012 and 2016, only a third of transplants used TBI-containing regimens. Non-TBI regimens were equally likely to be used between 2008 and 2011 and between 2012 and 2016. The median follow-up of patients who received TBI-containing regimens was 63 months (range, 3-122 months) and for those who received non-TBI regimens, 50 months (range, 3-122 months).

Table 1. Patient, disease and transplant characteristics.

Variable	TBI- regimens	Non-TBI regimens	P-value
Sex			0.94
Male/female	101 (51%) / 98 (49%)	217 (51%) / 208 (49%)	
Age			<0.001
≤ 3 years	33 (17%)	137 (32%)	
4 – 10 years	49 (25%)	93 (22%)	
11 – 21 years	117 (59%)	195 (46%)	
Performance score			0.06
90 - 100	168 (84%)	376 (88%)	
≤ 80	26 (13%)	47 (11%)	
Not reported	5 (3%)	2 (<1%)	
HCT co-morbidity index			0.55
≤ 2	172 (86%)	375 (88%)	
≥ 3	25 (13%)	43 (10%)	
Not reported	2 (1%)	7 (2%)	
Site(s) at diagnosis			0.14
Bone marrow only	132 (66%)	295 (69%)	
Bone marrow + central nervous system	52 (26%)	84 (20%)	
Bone marrow + other sites	12 (6%)	29 (7%)	
Not reported	3 (2%)	17 (4%)	
Cytogenetic risk			0.14
Favorable	29 (15%)	36 (8%)	
Intermediate	123 (62%)	285 (67%)	
Poor	41 (21%)	90 (21%)	
Not reported	6 (3%)	14 (3%)	
Disease status at transplant			0.006
1 st complete remission	107 (54%)	277 (65%)	
2 nd complete remission	92 (46%)	148 (35%)	
Donor			
HLA-matched sibling	17 (9%)	123 (29%)	
HLA-matched unrelated donor	34 (17%)	109 (26%)	
HLA-mismatched unrelated donor	14 (7%)	32 (8%)	
HLA-matched unrelated cord blood	21 (11%)	29 (7%)	
HLA-mismatched unrelated cord blood	101 (51%)	99 (23%)	
Unrelated cord blood (not reported)	12 (6%)	33 (8%)	
Graft versus host disease prophylaxis			<0.001
Tacrolimus + mycophenolate	7 (4%)	42 (10%)	
Tacrolimus + methotrexate	40 (20%)	139 (33%)	
Tacrolimus alone	4 (2%)	8 (2%)	
Cyclosporine + mycophenolate	119 (60%)	77 (18%)	
Cyclosporine + methotrexate	20 (10%)	115 (27%)	
Cyclosporine alone	9 (5%)	44 (10%)	
Anti-thymocyte globulin	22 (11%)	221 (52%)	<0.001
Transplant period			<0.001
2008 – 2011	133 (67%)	192 (45%)	
2012 – 2016	66 (33%)	233 (55%)	

TBI: total body irradiation; HCT: hematopoietic cell transplant.

Hematopoietic recovery

The median time to neutrophil recovery was 20 days and 17 days after TBI-containing and non-TBI regimens, respectively ($P=0.04$). The corresponding time to platelet recovery were 38 days and 30 days, $P=0.002$. Consequently, the day-28 incidence of neutrophil recovery was lower after TBI-containing (79%, 95% Confidence Interval [CI]: 73–84) compared to non-TBI regimens (85%, 95% CI: 82–88), $P=0.04$. Similarly, day-100 incidence of platelet recovery was also lower after TBI-containing (81%, 95% CI: 75–86) compared to non-TBI regimens (87%, 95% CI: 84–90), $P=0.002$.

Acute and chronic graft versus host disease

Grade 2-3 acute GvHD risk was higher with TBI-containing compared to non-TBI regimens (Table 2). The day-100 incidence of grade 2-3 acute GvHD were 56% (95% CI: 49–63) and 27% (95% CI: 22–30), respectively, $P<0.0001$. Compared to HLA-matched sibling donors, risks were higher with HLA-matched unrelated (hazard ratio [HR] 3.03, 95% CI: 1.75–5.25, $P<0.0001$), HLA-mismatched unrelated (HR 4.12, 95% CI: 2.18–7.77, $P<0.0001$), HLA-matched cord blood (HR 3.02, 95% CI: 1.44–6.34, $P=0.0035$) and HLA-mismatched cord blood (HR 2.95, 95% CI: 1.57–5.56, $P=0.0008$). Grade 3-4 acute GvHD risk did not differ between the treatment groups (Table 2). Compared to bone marrow grafts, risk of acute GvHD was higher with peripheral blood (HR 3.22, 95% CI: 1.72–6.03, $P=0.003$) and cord blood (HR 2.24, 95% CI: 1.29–3.88, $P=0.0041$). Chronic GvHD risk also did not differ between treatment groups (Table 2). The 5-year incidence of chronic GvHD was 37% (95% CI: 30–44) and 30% (95% CI: 26–35) after TBI-containing and non-TBI regimens. Chronic GvHD risks were higher in patients aged 11–21 years compared to those aged ≤3 years (HR 1.78, 95% CI: 1.13–2.81,

Table 2. Results of multivariate analysis

Outcome	Events/Number	Hazard Ratio (95% CI)	P-value
Grade 2-4 acute GvHD*			
TBI-containing regimen	109/196	1.00	
Non-TBI regimen	112/420	0.44 (0.33 – 0.58)	<0.0001
Grade 3-4 acute GvHD			
TBI-containing regimen	34/196	1.00	
Non-TBI regimen	53/420	0.69 (0.44 – 1.08)	0.10
Chronic GvHD*			
TBI-containing regimen	70/198	1.00	
Non-TBI regimen	116/422	0.82 (0.59 – 1.13)	0.23
Non-relapse mortality [†]			
TBI-containing regimen	42/199	1.00	
Non-TBI regimen	46/425	0.53 (0.35 – 0.81)	0.003
Relapse [‡]			
TBI-containing regimen	43/199	1.00	
Non-TBI regimen	149/425	1.46 (1.04 – 2.07)	0.03
Leukemia-free survival ^{***}			
TBI-containing regimen	85/199	1.00	
Non-TBI regimen	195/425	1.01 (0.78 – 1.31)	0.95
Overall survival [†]			
TBI-containing regimen	73/199	1.00	
Non-TBI regimen	159/425	0.98 (0.74 – 1.30)	0.91

GvHD: graft versus host disease; TBI: total body irradiation; CI: Confidence Interval; TBI: total body irradiation; *adjusted for age, donor type and GvHD prophylaxis; † adjusted for age; ‡adjusted for age and site(s) at diagnosis and ***adjusted for age and cytogenetic risk.

$P=0.01$) and 4–10 years (HR 2.29, 95% CI: 1.57–3.33, $P<0.0001$). Chronic GvHD was higher with HLA-mismatched cord blood compared to HLA-matched sibling donors (HR 2.04, 95% CI: 1.10–3.67, $P=0.02$). Chronic GvHD risks did not differ between other donor groups (*data not shown*).

Non-relapse mortality and relapse

Non-relapse mortality was higher with TBI-containing regimens (Table 2, Figure 1A). The 1- and 5-year incidence of non-relapse mortality with TBI-containing regimens were 17% (95% CI: 12–22) and 22% (95% CI: 16–28). The corresponding incidence with non-TBI regimens were 8% (95% CI: 6–11) and 11% (95% CI: 8–15). Compared to patients aged 4–10 years, non-relapse mortality was higher in patients aged 11–21 years (HR 1.99, 95% CI: 1.15–3.46, $P=0.01$) but not in those aged ≤ 3 years (HR 1.71, 95% CI: 0.85–3.44, $P=0.13$). Infections were higher with TBI-containing compared to non-TBI regimens (Table 3A). Venooclusive disease was lower with TBI-containing regimens (Table 3A). Patients who survived at least 1 year after transplantation in remission were evaluable for organ dysfunction (Table 3B). Endocrine dysfunction (thyroid or gonadal) was higher with TBI-containing regimens. Pulmonary, cardiac and renal complications did not differ between treatment groups.

Relapse risks were lower in TBI-containing regimens (Table 2, Figure 1B). The 1- and 5-year incidence of relapse with TBI-containing regimens were 15% (95% CI: 11–22) and 23% (95% CI: 17–29). The corresponding relapse incidence with non-TBI regimens were 26% (95% CI: 22–31) and 37% (95% CI: 32–42), $P<0.0001$. Relapse risks did not differ between patients aged 4–10 and 11–21 years (HR 1.17, 95% CI: 0.82–1.69, $P=0.39$). Relapse was higher in patients aged ≤ 3 years compared to those aged 4–10 years (HR 2.49, 95% CI: 1.68–3.69, $P<0.0001$) and 11–21 years (HR 2.12, 95% CI: 1.51–2.98, $P<0.0001$). Compared to bone marrow and central nervous system involvement at diagnosis,

relapse risks were higher in patients with bone marrow involvement alone (HR 1.93, 95% CI: 1.27–2.93, $P=0.002$) and bone marrow with extramedullary site(s) excluding central nervous system involvement (HR 1.88, 95% CI: 1.01–3.50, $P=0.04$). Acute grade 2–4 GvHD was associated with lower relapse risk (HR 0.63, 95% CI: 0.44–0.89, $P=0.008$) but this was independent of conditioning regimen. The effect of acute grade 3–4 (HR 0.65, 95% CI: 0.39–1.09, $P=0.10$) and chronic GvHD (HR 0.74, 95% CI: 0.48–1.15, $P=0.19$) on relapse did not meet the level of significance that was set a priori.

Overall and leukemia-free survival

There were no differences in overall or leukemia-free survival by treatment groups (Table 2, Figure 2A and B). Age was associated with both overall and leukemia-free survival and cytogenetic risk with leukemia-free survival. Compared to patients aged 4–10 years, survival was lower for those aged 11–21 years (HR 1.82, 95% CI: 1.28–2.59, $P<0.0001$) and ≤ 3 years (HR 2.79, 95% CI: 1.90–4.10, $P<0.0001$). Survival was also lower in patients aged ≤ 3 years compared to those aged 11–21 years (HR 1.52, 95% CI: 1.14–2.08, $P=0.005$). Compared to favorable cytogenetics, leukemia-free survival was lower with intermediate risk (HR 1.85, 95% CI: 1.10–3.09, $P=0.0198$) and poor risk (HR 2.46, 95% CI: 1.42–4.27, $P=0.0013$). The 5-year overall survival was 61% (95% CI: 54–68) and 61% (95% CI: 56–66) after TBI-containing and non-TBI containing regimens. The corresponding leukemia-free survival was 53% (95% CI: 46–60) and 53% (95% CI: 48–58).

Transplant period

As the current analysis included patients transplanted between 2008 and 2016, we tested for an effect of transplant period (2012–2016 vs. 2008–2011) on non-relapse mortality (HR 0.75, 95% CI 0.48–1.21, $P=0.21$), relapse (HR 1.04, 95% CI: 0.78–1.41, $P=0.78$), overall (HR 0.93, 95% CI: 0.71–1.22, $P=0.62$) and leukemia-free survival (HR 0.96,

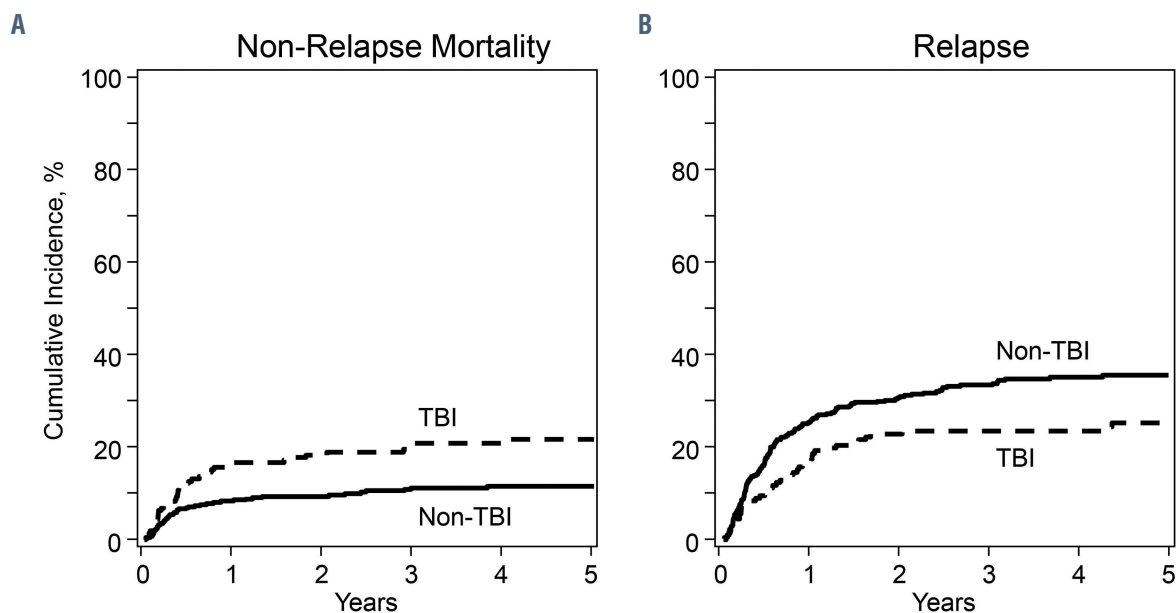


Figure 1. Non-relapse mortality and relapse. (A) Cumulative incidence of non-relapse mortality with total body irradiation (TBI)-containing and non-TBI regimens, (B) cumulative incidence of relapse with TBI-containing and non-TBI regimens.

95% CI: 0.75–1.23, $P=0.15$) and found none. We also examined for differences in infection rates by transplant period and observed lower rate of fungal infection between 2012 and 2016 compared to the earlier period in patients who received TBI-containing (2% vs. 8%) and non-TBI (1% vs. 4%) regimens.

Subset analysis

In a subset analysis limited to patients who received Bu-Cy and Bu-Flu, we examined for an effect of anti-thymocyte globulin on grade 2-4 acute GvHD (HR 0.68, 95% CI: 0.44–1.03, $P=0.07$), grade 3-4 acute GvHD (HR 0.93, 95% CI: 0.51–1.70, $P=0.82$), chronic GvHD (HR 0.75, 95% CI:

0.50–1.12, $P=0.16$), non-relapse mortality (HR 1.09, 95% CI: 0.60–1.99, $P=0.78$), relapse (HR 1.07, 95% CI: 0.77–1.50, $P=0.68$), overall (HR 1.24, 95% CI: 0.90–1.72, $P=0.19$) and leukemia-free survival (HR 1.05, 95% CI: 0.78–1.40, $P=0.75$) and found none.

Discussion

To our knowledge this is the largest study to compare TBI and non-TBI intravenous Bu containing regimens in children and adolescents with *de novo* AML. Non-relapse mortality was higher with TBI regimens, and relapse was

Table 3A. Day-100 incidence of veno-occlusive disease and systemic infection.

Outcome	TBI-containing regimen		Non-TBI regimen		P-value
	N eval	Probability (95% CI)	N eval	Probability (95% CI)	
VOD	197	8% (4-12)	422	15% (11-18)	0.03
Bacterial bloodstream infection	199	47% (40-54)	425	30% (26-35)	<0.001
Viral bloodstream infection	199	43% (36-50)	425	30% (26-34)	0.001
Fungal bloodstream infection	199	6% (3-9)	425	2% (1-4)	0.04

TBI: total body irradiation; VOD: veno-occlusive disease; CI: Confidence Interval; eval: evaluated.

Table 3B. 3-year incidence of organ dysfunction in patients who were alive and in remission for at least 1-year post-transplant

Outcome	TBI-containing regimen		Non-TBI regimen		P-value
	N eval	Probability (95% CI)	N eval	Probability (95% CI)	
Interstitial pneumonitis / Idiopathic pneumonia syndrome	129	5% (2-9)	267	7% (4-11)	0.36
Endocrine dysfunction (gonadal or growth hormone)	125	24% (17-32)	265	8% (5-12)	<0.001
Cardiac failure, renal failure requiring dialysis	129	5% (2-9)	267	3% (1-5)	0.26

Number of events: gonadal dysfunction TBI n=28 of 125; non-TBI n=29 of 265; growth hormone deficiency TBI n=14 of 129, non-TBI n=7 of 265; cardiac failure TBI n=3 of 129, non-TBI n=1 of 267; renal failure TBI n=4 of 129, non-TBI n=7 of 267. TBI: total body irradiation; CI: Confidence Interval; n: number; eval: evaluated.

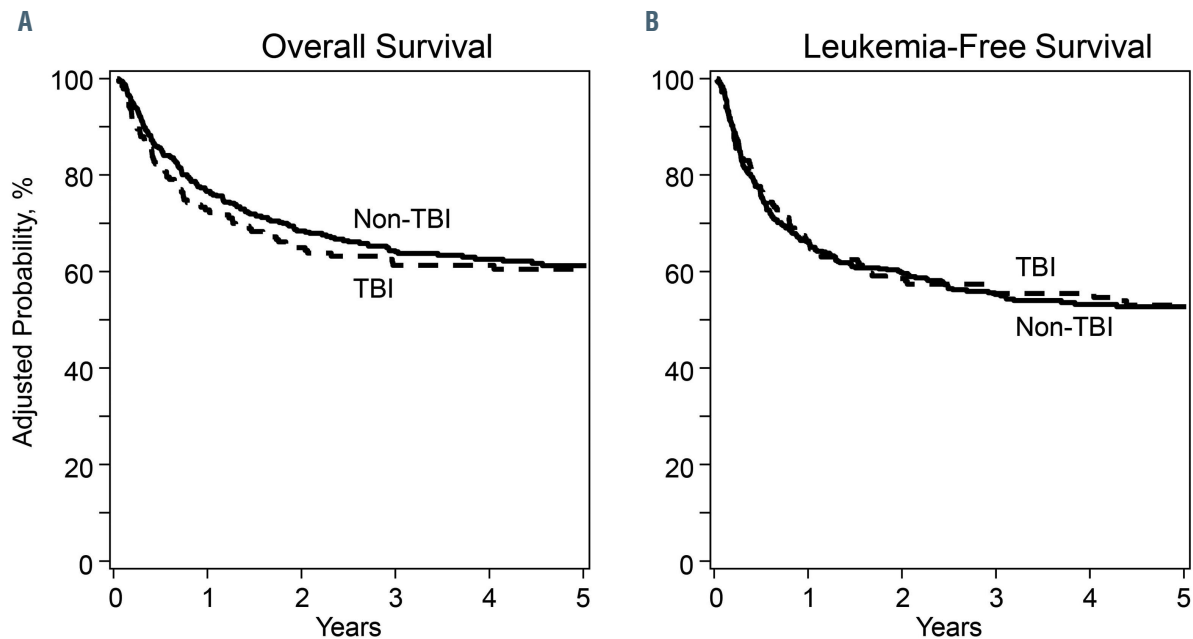


Figure 2. Leukemia-free survival and overall survival. (A) Probability of overall survival with total body irradiation (TBI)-containing and non-TBI regimens, (B) probability of leukemia-free survival with TBI-containing and non-TBI regimens.

higher with non-TBI regimens, negating an advantage for overall or leukemia-free survival. The net contribution of non-relapse mortality or relapse for either treatment group was not sufficient to lead towards an overall or leukemia-free survival advantage. Our findings are in keeping with another pediatric study from Japan that also failed to show differences in overall and leukemia-free survival between TBI-containing and non-TBI Bu regimens.¹ We hypothesize there are several factors that influenced relapse risks including acute grade 2-4 GvHD. TBI regimens were largely used with cord blood transplants and TBI-Cy-Flu was the predominant regimen. Others have reported lower relapse with TBI-Cy-Flu regimen compared to other TBI- and non-TBI containing regimens for cord blood transplant.²⁵ The higher incidence of bacterial, viral and fungal infections with the TBI-containing regimens within the first 3 months after transplantation likely contributed to early transplant-related mortality. Whether this is an effect of the conditioning regimen or the type of donor is challenging to differentiate as TBI regimens were predominantly used for cord blood transplants. In the subset, limited to transplants between 2012 and 2016, the incidence of bacterial and viral infections was also higher with TBI-regimens and consistent with the main analysis. However, the incidence of invasive fungal infection decreased to 2% with TBI regimens and 1% with non-TBI regimens for transplants between 2012 and 2016 ($P=0.89$) although this had negligible effect on non-relapse mortality (HR 1.18, $P=0.72$). A higher 5-year overall survival recorded with TBI-Cy-Flu compared to non-TBI regimens may be acceptable for some considering cord blood transplant even though growth hormone and gonadal deficiency is higher with TBI-Cy-Flu regimen.²⁵ For transplantations with HLA-matched sibling or adult unrelated donors intravenous Bu-Cy or Bu-Flu is preferred.^{26,27} A recent study from the European Society for Blood and Marrow Transplant (EBMT) observed lower relapse and higher leukemia-free survival for AML in first complete remission with Bu-Cy-melphalan compared to Bu-Cy and TBI-Cy.²⁸ Our study did not include the Bu-Cy-melphalan regimen.

Hematopoietic recovery was lower with TBI-containing regimens. We hypothesize the lower recovery rates are in part explained by the predominant use of umbilical cord blood graft with TBI-containing regimens and in part, by use of intravenous Bu for all patients and pharmacokinetic data available for 80% of patients in the non-TBI group. Higher neutrophil but not platelet recovery with intravenous Bu containing regimens compared to TBI-containing regimens has been reported in adults with acute leukemia.¹⁰

Consistent with other reports, TBI-containing regimens were associated with higher incidence of thyroid and growth hormone deficiency compared to non-TBI regimens.^{21,22} Although not studied in the current analysis, others have recorded higher risk of cataracts, neuropsychological and cognitive abnormalities with TBI-containing regimens.²²⁻²⁴ The 5-year incidence of cardiac failure and renal failure were modest (<10%) but did not differ between treatment groups. Although not the focus of the current study, two recent publications studied the association between myeloablative conditioning regimens and second neoplasm. Those reports did not record a higher risk with TBI-containing compared to non-TBI regimens.^{27,29}

There are limitations to studying the effect of transplant conditioning regimen in a retrospective cohort. First, we do not know the factors that influenced choice of conditioning regimen other than in the youngest age group (≤ 3 years), approximately 70% of those who received TBI regimen were in second complete remission. Although we performed a carefully controlled analyses there may be unknown or unmeasured factors that may have influenced the outcomes recorded. Second, over the course of the study, effective molecular flow cytometric measures of detectable disease in patients in complete remission after transplantation³⁰ although it can be argued that the effect of minimal residual disease (MRD) would be consistent across both treatment groups. Among 166 patients for whom MRD status was available, 6 of 33 (18%) patients who received TBI and 17 of 133 (13%) patients who received non-TBI regimens were MRD negative at transplantation. Third, we know most patients who received Bu had pharmacokinetic dose adjustments, but we do not have data on dose adjustments to examine whether an increase or decrease to the prescribed Bu dose was associated with outcomes. Our study spanned a 9-year period, a strength considering our sample size, but leukemia-free and overall survival may be influenced by transplant period. A careful analysis failed to find an effect of transplant period on outcomes other than a lower incidence of invasive fungal infection with TBI regimens.

Our findings are relevant regarding a discussion on the choice of TBI-containing or non-TBI regimen when considering allogeneic transplantation for children and adolescents with *de novo* AML. In the absence of a survival advantage with either regimen group, the non-TBI regimens, Bu-Cy or Flu-Bu, are preferred although when considering umbilical cord blood transplantation TBI-Cy-Flu may be preferred.²⁵

Disclosures

No conflicts of interest to disclose.

Contributions

CED, SMD, KWA, AEK, JL and ME designed the study; SB-S prepared the study file, KWA and YH analyzed the data; CED, SMD, KWA, YH and ME interpreted the results; CED drafted the manuscript; SMD, KWA, YH, AEK, JL, SB-S, HA-A, NB, JC, SG, NG, RH, NRL, JL, MM, TO, TP, AS, PS, LW and ME critically reviewed and edited the manuscript; all authors approved the final version.

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