Blinatumomab is associated with better post-transplant outcome than chemotherapy in children with high-risk, first-relapse B-cell acute lymphoblastic leukemia irrespective of the conditioning regimen

Total body irradiation (TBI) is a key component of many conditioning regimens administered prior to allogeneic hematopoietic stem cell transplantation (alloHSCT) in patients with acute lymphoblastic leukemia (ALL). A recent, large randomized clinical study – FORUM – including patients with a donor matched for ≥9/10 HLA loci demonstrated that children with high-risk/relapsed ALL who received TBI plus etoposide as a conditioning regimen had a significantly higher (P<0.0001) 2-year probability of overall survival (0.91, 95% confidence interval [95% CI]: 0.86-0.95) than that of patients who received conditioning with chemotherapy (chemoconditioning; 0.75, 95% CI: 0.67-0.81) prior to alloHSCT.[1] Although effective, conditioning with TBI is associated with the risk of lifelong adverse effects, including impairment of growth, gonadal, thyroid and cognitive function, an increased incidence of cataracts, and secondary malignancies.[2-4] A novel approach aimed at providing an alternative to TBI-based conditioning is, therefore, desirable.

Blinatumomab is a bispecific T-cell engager that redirects CD3-positive T cells to engage and lyse CD19-positive target cells. A randomized, phase III trial (NCT02393859) demonstrated that treatment with one cycle of blinatumomab compared with standard intensive multidrug chemotherapy administered as the third consolidation course (HC3) prior to alloHSCT in pediatric high-risk, first-relapse B-cell ALL (B-ALL) resulted in an improvement in event-free survival and overall survival.[5,6] In order to better dissect the contribution of immediate pre-transplant treatment from the role played by the conditioning regimen, we performed a *post hoc* analysis aimed at evaluating the outcome of children with high-risk, first-relapse B-ALL from this phase III study who received either blinatumomab or chemotherapy (HC3) as the third consolidation course and for whom data on the type of conditioning regimen received (TBI or chemoconditioning) prior to alloHSCT were available.

Details of the study design, patients' eligibility, and treatment doses of blinatumomab and HC3 have been reported elsewhere.[5] High-risk first relapse has been defined earlier.[7,8] Patients who achieved or maintained a second complete remission after treatment with either blinatumomab or HC3 were assigned to receive TBI or chemoconditioning before alloHSCT. Myeloablative conditioning prior to alloHSCT consisted of TBI (12 Gy in 6 fractions) plus 60 mg/kg etoposide (1.8 g/m^2; maximum total dose 3.6 g) or chemoconditioning including fludarabine (30 mg/m^2 once a day for 5 consecutive days) plus thiotepa (5 mg/kg twice a day for 1 day) and either treosulfan (14 g/m^2 once a day for 3 consecutive days) or busulfan.[1] Busulfan was dosed once, twice, or four times a day according to local guidelines, age, and body weight, usually with therapeutic drug monitoring and pharmacokinetic dose adjustment. Time-to-event endpoints were summarized using the Kaplan-Meier method. Transplant-emergent adverse events were assessed by the clinicians per good clinical practice guidelines and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Acute and chronic graft-*versus*-host disease were assessed at each visit and graded according to the description by Glucksberg *et al*.[9] The study protocol was approved by the institutional review boards or independent ethics committees of all participating institutions. A Cox regression model was used to evaluate the effects of treatment with either blinatumomab or chemotherapy before alloHSCT and of the conditioning regimen on patients' outcome.

Of the 90 evaluable patients for whom data on the conditioning regimen administered were available, 51 received blinatumomab and 39 received HC3. Of the 51 patients treated with blinatumomab, 30 patients received TBI plus etoposide and 21 patients received chemoconditioning (5 of 21 patients received fludarabine + thiotepa + treosulfan; 16 of 21 received fludarabine + thiotepa + busulfan prior to alloHSCT). Of the 39 patients given HC3, 19 received TBI and 20 received chemoconditioning (16 patients received the busulfan-based regimen and the remaining 4 had the treosulfan-based preparation) before alloHSCT. The patients' demographics and baseline characteristics, including measurable residual disease (MRD), were well balanced between the blinatumomab and HC3 treatment groups prior to administration of TBI or chemoconditioning (Table 1). Fifty percent of patients treated with blinatumomab (25 of 51 patients) and 41% of patients treated with HC3 (16 of 39 patients) received a transplant from matched donors with an HLA match of ≥9/10, this representing the population of children eligible for the randomized trial conducted by the FORUM consortium. The remaining patients were eligible to be reported in the FORUM database. The median time elapsed between the last dose of blinatumomab and alloHSCT was 25 days (range, 8-67 days) and the median time between the last dose of HC3 and alloHSCT was 44 days (range, 20-107 days).

Two of 51 patients (4%) treated with blinatumomab experienced cytokine release syndrome. Cyclosporine and meth-

otrexate were commonly administered for graft-*versus*-host disease prophylaxis at the investigators' discretion. The incidence of transplant-emergent adverse events in patients treated with blinatumomab was comparable with that of patients treated with HC3.[5] One patient each in the HC3 and blinatumomab groups experienced graft failure.

The Kaplan-Meier analysis of both overall and event-free survival showed that survival in patients treated with blinatumomab, regardless of subsequent treatment with TBI or chemoconditioning, was better than the survival of patients treated with HC3 followed by TBI or chemoconditioning (Figure 1A, B). Twenty-four of 39 (62%) patients given HC3 and 15 of 51 (29%) blinatumomab-treated patients relapsed after transplantation. Treatment after relapse was heterogenous and included chemotherapy, inotuzumab and chimeric antigen receptor-modified T cells and allowed the rescue of a proportion of patients. In detail, eight of the 24 HC3-treated patients (33%) who relapsed are alive, as are ten of the 15 (66%) allocated to the blinatumomab arm. The Kaplan-Meier estimates for event-free survival at 36 and 48 months after transplantation (35.5%, 95% CI: 20.9-50.4% in both cases) indicated a higher probability of an event with HC3 than with blinatumomab (63.8%, 95% CI: 48.8-75.4% at 36 months and 60.2%, 95% CI: 44.4-72.8% at 48 months) irrespective of subsequent conditioning. Among patients treated with blinatumomab, there was not a statistically significant difference in event-free survival between patients who received TBI or chemoconditioning (Figure 1B).

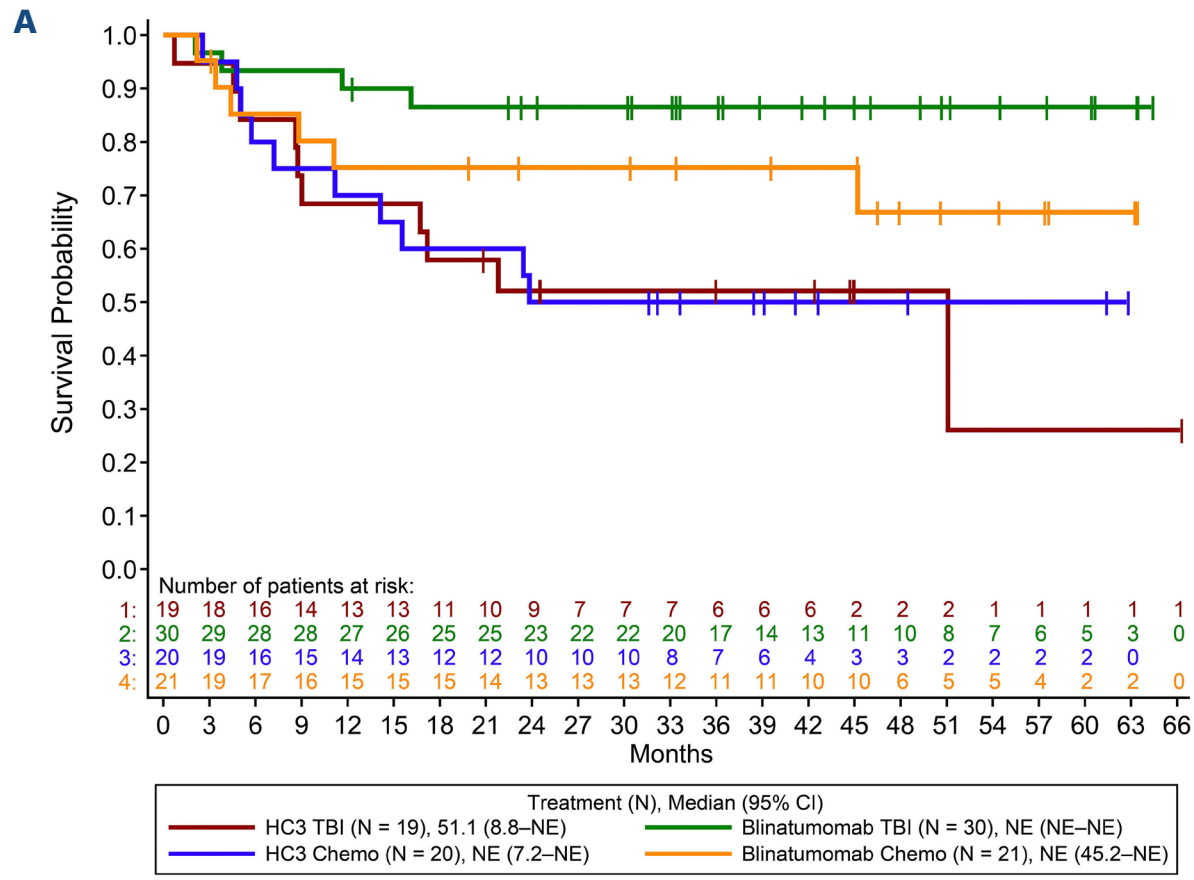
The Kaplan-Meier 100-day estimate of mortality after alloHSCT was 3.9% (95% CI: 1.0-14.8%) in the blinatumomab arm and 5.1% (95% CI: 1.3-19.0%) in the HC3 arm (Table 2). Among patients treated with blinatumomab, the 2 year Kaplan-Meier estimate for overall survival was numerically greater in patients who received conditioning with TBI (86.5%, 95% CI: 68.0-94.7%) than in patients who received chemoconditioning (75.2%, 95% CI: 50.3-88.9%) (Table 2). The difference in favor of TBI persisted at the 4-year timepoint after transplantation. Neither the pre-transplant treatment nor the type of conditioning regimen used influenced the occurrence of acute or chronic graft-*versus*-host disease (*data not shown*). Results from a multivariate Cox regression model for overall survival showed that pre-transplant treatment with blinatumomab was correlated with a statistically significant better outcome (hazard ratio=0.33 [0.15-0.72]; *P*=0.005), while the use of TBI did not reach a statistically significant value (*data not shown*). Results from the current analysis demonstrate that children with high-risk, first-relapse B-ALL receiving blinatumomab as the third consolidation course before alloHSCT had better estimated 2-year overall survival and event-free survival compared with patients who received HC3, irrespective of

Table 1. Patients' demographics and characteristics.

Variable	Total body irradiation		Chemoconditioning		Overall	
	HC3 N=19	Blinatumomab N=30	HC3 N=20	Blinatumomab N=21	HC3 N=39	Blinatumomab N=51
Age						
Years, median (range)	6.0 (3-16)	6.0 (3-17)	5.0 (1-17)	5.0 (1-17)	5.0 (1-17)	6.0 (1-17)
Distribution, N (%)						
1-9 years	13 (68.4)	21 (70.0)	16 (80.0)	15 (71.4)	29 (74.4)	36 (70.6)
10-18 years	6 (31.6)	9 (30.0)	4 (20.0)	6 (28.6)	10 (25.6)	15 (29.4)
Male, N (%)	6 (31.6)	14 (46.7)	7 (35.0)	13 (61.9)	13 (33.3)	27 (52.9)
Stem cell source, N (%)						
Peripheral blood	4 (21.1)	13 (43.3)	7 (35.0)	8 (38.1)	11 (28.2)	21 (41.2)
Bone marrow	14[a] (73.7)	14 (46.7)	11[a] (55.0)	12[a] (57.1)	25[a] (64.1)	26[a] (51.0)
Cord blood	2 (10.5)	3 (10.0)	3 (15.0)	2 (9.5)	5 (12.8)	5 (9.8)
Donor type, N (%)						
Matched sibling	4 (21.1)	6 (20.0)	6 (30.0)	6 (28.6)	10 (25.6)	12 (23.5)
HLA loci matching ≥9/10	3 (75.0)	6 (100.0)	4 (66.7)	4 (66.7)	7 (70.0)	10 (83.3)
HLA loci matching 10/10	3 (75.0)	6 (100.0)	4 (66.7)	4 (66.7)	7 (70.0)	10 (83.3)
Matched unrelated donor	7 (36.8)	12 (40.0)	5 (25.0)	6 (28.6)	12 (30.8)	18 (35.3)
HLA loci matching ≥9/10	6 (85.7)	10 (83.3)	3 (60.0)	5 (83.3)	9 (75.0)	15 (83.3)
HLA loci matching 10/10	2 (28.6)	5 (41.7)	2 (40.0)	4 (66.7)	4 (33.3)	9 (50.0)
Haploidentical parental donor[b]	4[c] (21.1)	9 (30.0)	9 (45.0)	6[d] (28.6)	13[c] (33.3)	15[d] (29.4)
Mismatched sibling	0 (0.0)	0 (0.0)	1 (5.0)	1 (4.8)	1 (2.6)	1 (2.0)
Mismatched unrelated donor	4 (21.1)	3 (10.0)	2 (10.0)	5 (23.8)	6 (15.4)	8 (15.7)

[a]One patient received stem cells from peripheral blood in addition to bone marrow. [b]Haploidentical father or mother or both. [c]Three patients received stem cells from a second source in addition to a haploidentical donor, one patient received stem cells from a matched unrelated donor, one patient received stem cells from a mismatched unrelated donor, and one patient received a transplant from a matched sibling. [d]One patient received a transplant from a mismatched sibling and one patient received a transplant from a mismatched unrelated donor. HC3: third consolidation course with chemotherapy; HLA: human leukocyte antigen.

treatment with TBI plus etoposide or chemoconditioning. Persistence of MRD after induction with chemotherapy and prior to alloHSCT has been demonstrated to be predictive of recurrence of B-ALL.[7,10-13] A recently published *post hoc* analysis of data from a randomized phase III study[6] demonstrated that a higher proportion of patients with high-risk, first-relapse B-ALL with MRD had undetectable disease after receiving blinatumomab as their third consolidation course compared with patients treated with HC3. As patients included in the current analysis were drawn from the



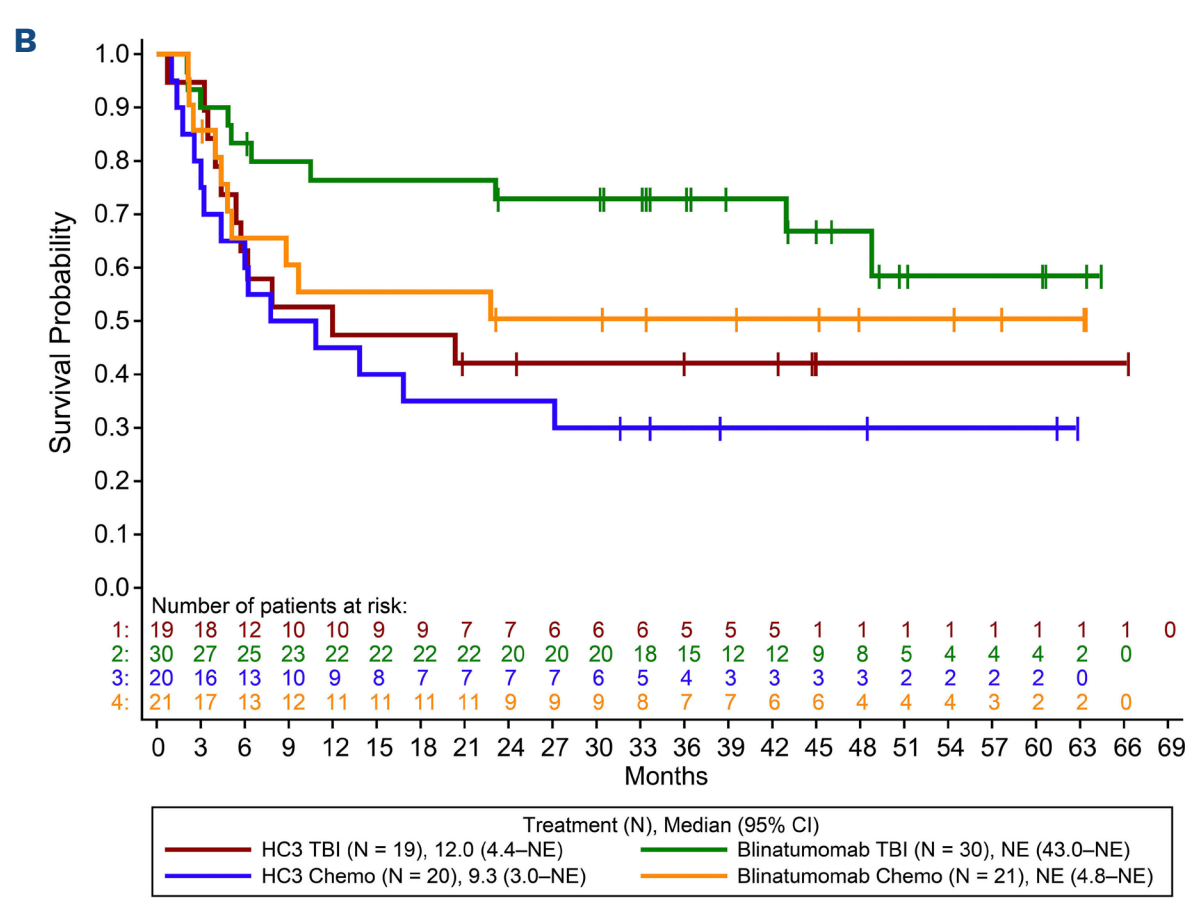


Figure 1. Post-transplant survival according to type of third consolidation and conditioning regimen. (A, B) Kaplan-Meier analysis for overall survival (A) and event-free survival (B) following allogeneic hematopoietic stem cell transplant in patients with high-risk, first-relapse B-cell acute lymphoblastic leukemia who received blinatumomab or chemotherapy as the third consolidation course and subsequently received either total body irradiation or chemotherapy as their conditioning regimen. The log-rank P value for all four subgroups was 0.0147 in (A) and 0.0568 in (B). Censor indicated by |. N: number of patients included in the analysis; 95% CI: confidence interval; HC3: third consolidation course of chemotherapy; TBI: total body irradiation; NE: not estimable; chemo: chemotherapy.

Table 2. Overall survival following allogeneic hematopoietic stem cell transplant in patients with high-risk, first-relapse B-cell acute lymphoblastic leukemia who received blinatumomab or chemotherapy as the third consolidation course and subsequent myeloablative total body irradiation or chemoconditioning.

	TBI		Chemoconditioning		Overall	
	HC3 N=19	Blinatumomab N=30	HC3 N=20	Blinatumomab N=21	HC3 N=39	Blinatumomab N=51
Mortality following alloHSCT						
KM estimate at 100 days, %	5.3	3.3	5.0	4.8	5.1	3.9
95% CI	0.8-31.9	0.5-21.4	0.7-30.5	0.7-29.3	1.3-19.0	1.0-14.8
Patients' status at last follow-up, N (%)						
Dead	10 (52.6)	4 (13.3)	10 (50.0)	6 (28.6)	20 (51.3)	10 (19.6)
Alive	9 (47.4)	26 (86.7)	10 (50.0)	15 (71.4)	19 (48.7)	41 (80.4)
Overall survival (KM) in days						
Median	1,558	NE	NE	NE	1,558	NE
95% CI	267-NE	NE-NE	220-NE	1,379-NE	431-NE	NE-NE
Range	22-1,558	63-492	78-727	67-1,379	22-1,558	63-1,379
KM estimate, %						
At 24 months	52.1	86.5	50.0	75.2	50.9	82.0
95% CI	28.0-71.6	68.0-94.7	27.1-69.2	50.3-88.9	34.4-65.3	68.3-90.2
At 48 months	52.1	86.5	50.0	66.8	50.9	77.9
95% CI	28.0-71.6	68.0-94.7	27.1-69.2	39.1-84.1	34.4-65.3	61.8-87.9

TBI: total body irradiation; HC3: third consolidation course with chemotherapy; alloHSCT: allogeneic hematopoietic stem cell transplant; KM: Kaplan-Meier; 95% CI: 95% confidence interval; NE: not estimable.

same phase III study, the deeper MRD remission (i.e., $<10^{-4}$ leukemic blasts) observed with blinatumomab explains the numerically longer overall survival observed in patients treated with blinatumomab compared with that in patients treated with HC3, irrespective of subsequent conditioning. Although the best overall survival was observed in patients given blinatumomab followed by the TBI-containing regimen, this finding also suggests that blinatumomab consolidation (and the resulting lower leukemia burden even in patients who were already MRD-negative before the randomization) could render chemoconditioning a possible alternative in patients who are ineligible to receive TBI. In addition, the use of blinatumomab before alloHSCT can reduce the risk of pre-transplant bacterial/fungal colonization and tissue toxicity which can result in a higher risk of life-threatening or even fatal events after transplantation.

A limitation of this analysis is that the generalizability of the findings to routine clinical practice could be limited by the sample size evaluated and the *post hoc* nature of the analysis. The ongoing FORUM study with more than 1,700 registered ALL children will provide a clearer picture of the benefit of using blinatumomab before alloHSCT in the real word.[1]

Overall, this analysis demonstrates that blinatumomab as the third course of consolidation improved both overall and event-free survival after alloHSCT in pediatric high-risk, first-relapse B-ALL irrespective of the conditioning therapy employed (TBI or chemoconditioning) prior to alloHSCT as compared with the survival of patients treated with HC3. Further prospective studies are needed to evaluate whether TBI could be substituted by chemoconditioning in patients with high-risk, first-relapse B-ALL who are treated with blinatumomab and who become MRD-negative before transplantation.

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Contributions

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Data-sharing statement

Qualified researchers may request data from Amgen clinical studies.

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