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Blinatumomab for First-Line Treatment of Children and Young Persons With B-ALL

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DOI https://doi.org/10.1200/JCO.23.01392

ABSTRACT

PURPOSE We tested whether blinatumomab (Blina) is effective as a toxicity-sparing alternative to first-line intensive chemotherapy in children and young persons (CYP) with B-ALL who were chemotherapy-intolerant or chemotherapy-resistant.

METHODS Data were collected for consecutive CYP (age 1-24 years) with Philadelphia chromosome–positive or Philadelphia chromosome–negative B-ALL who received Blina as first-line therapy. Blina was given as replacement for post-remission intensive chemotherapy to patients with chemotherapy intolerance or resistance. Blina responders received further chemotherapy (Blin-CT) or first remission hematopoietic stem-cell transplant (Blin-HSCT) if indicated. Event-free survival (EFS) and overall survival (OS) of the Blin-CT group were compared with those of matched controls treated with standard chemotherapy in the UKALL 2003 trial. Events were defined as death, relapse, or secondary cancer.

RESULTS From February 2018 to February 2023, 105 patients were treated, of whom 85 were in the Blin-CT group and 20 were in the Blin-HSCT group. A majority of Blin-CT patients received Blina for chemotherapy intolerance (70 of 85, 82%), and the group had a higher-risk profile than unselected patients with B-ALL. Blina was well tolerated with only one patient having a grade 3/4–related toxicity event, and of the 60 patients who were minimal residual disease–positive pre-Blina, 58 of 60 (97%) responded. At a median follow-up of 22 months, the 2-year outcomes of the 80 matched Blin-CT group patients were similar to those of 192 controls (EFS, 95% [95% CI, 85 to 98] *v* 90% [95% CI, 65 to 93] and OS, 97% [95% CI, 86 to 99] *v* 94% [95% CI, 89 to 96]). Of the 20 in the HSCT group, three died because of transplant complications and two relapsed.

CONCLUSION Blina is safe and effective in first-line treatment of chemotherapy-intolerant CYP with ALL.

ACCOMPANYING CONTENT

Protocol

Accepted September 18, 2023
Published November 15, 2023

J Clin Oncol 00:1-8
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INTRODUCTION

While 90% of children and young persons (CYP) with ALL are cured with contemporary risk-stratified intensive chemotherapy schedules, there is growing recognition of the associated acute and long-term toxicities[1] and their impact on mortality and health-related quality of life (HRQOL).[2] Importantly, the efficacy of therapy is compromised in a substantial minority who cannot continue protocol-mandated schedules because of toxicity,[3,4] while patients with pre-existing comorbidities, such as Down or Li-Fraumeni syndrome, have inferior outcomes due in part to toxicity.[5-7] Strategies to minimize toxicities could therefore not only mitigate treatment-related mortality and improve HRQOL but also reduce the risk of relapse.[8]

Blinatumomab (Blina), a CD3-/CD19-directed bispecific T-cell engager, is more effective and less toxic than intensive chemotherapy for CYP in the relapse setting.[9-11] Adults have a better outcome when Blina is added to a first-line chemotherapy backbone, regardless of their minimal residual disease (MRD) status.[12-14] Furthermore, preliminary data

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CONTEXT

Key Objective
Is blinatumomab (Blina) safe and effective as replacement for first-line chemotherapy in children and young adults with B-ALL who have intolerance or resistance to chemotherapy.

Knowledge Generated
Minimal residual disease responses are seen in 97% of children and young persons with B-ALL given Blina as replacement for parts of first-line chemotherapy. The 2-year event-free survival of Blina-treated patients is similar to that of historical controls treated with intensive chemotherapy alone.

Relevance *(S. Bhatia)*
These findings provide the rationale for testing the efficacy of Blina for first-line treatment in children with B-ALL.*

*Relevance section written by *JCO* Associate Editor Smita Bhatia, MD, MPH, FASCO.

suggest that Blina in combination with tyrosine kinase inhibitors such as dasatinib or ponatinib is highly effective as chemotherapy-free treatment of Philadelphia (Ph+) ALL in the elderly setting.[15-17]

Hence, we tested whether Blina was a less toxic and equally effective alternative to first-line postremission chemotherapy in CYP who had chemotherapy intolerance or resistance.

METHODS

Study Design and Participants

Patients were eligible for first-line Blina if they were age between 1 and 24 years and receiving treatment on pediatric regimens for Ph+/Ph− B-ALL and had chemotherapy-intolerant or chemotherapy-resistant disease (Table 1). Patients were planned for further chemotherapy (Blin-CT group) or CR1 hematopoietic stem-cell transplant (HSCT), if indicated (Blin-HSCT group), after Blina (Fig 1).

Consecutive eligible patients were treated according to a consensus guideline, approved by the UK Children's Cancer and Leukaemia Group (CCLG; see the Protocol, online only), after discussion in a national advisory panel, at 24 centers across the United Kingdom and the Republic of Ireland. Blina was given according to its licensed indication for persistent MRD or outside this indication on a special need basis after approval by individual institution's drug and therapeutics committees. The basis for such approvals was the inability to deliver effective therapy, compromising the patient's chance of cure. Treating clinicians obtained consent after counseling patients and caregivers of the risk and benefits of this approach. After October 2021, the guideline was amended to recommend that all patients with Down syndrome (DS) should receive prophylactic levetiracetam during Blina therapy.

The guideline specified that, before receiving Blina, patients with CNS3 status at diagnosis should have responded to intrathecal therapy and be CNS2/1, and infections should be appropriately managed.

Clinical, laboratory, treatment, toxicity, and outcome data were collected through a tumor board referral pro forma and follow-up questionnaires.

To assess whether Blina was as effective as chemotherapy, we compared the outcomes of the CT group with those of a matched control group treated on the UKALL 2003 trial.[19,20] All induction failures, induction deaths, and cases where patients were transplanted in first remission were excluded from the 2,632 available control patients. Cases were matched to a maximum of three controls by sex, DS status, cytogenetic risk group,[21] National Cancer Institute (NCI) risk group, end-of-induction MRD (<0.01%, 0.01%-0.1%, >0.1%), and age (1-4 years, 5-9 years, 10-14 years, 15-26 years). Because of the rarity of high-risk genetics (including Ph+), these cases were matched only by specific cytogenetic abnormalities.

Procedures

Blina was given postinduction or mid-/postconsolidation as one to two 28-day cycles via continuous intravenous infusion, with a 1- to 2-week treatment break between cycles (Fig 1). Intrathecal methotrexate was given on days 1, 15, and 28 of cycle 1 and days 15 and 28 of cycle 2. Bone marrow assessments for MRD were performed on days 15 and 28 of each cycle, with the day 15 assessment of cycle 2 omitted if patients were MRD-negative at the end of cycle 1. MRD was tested by quantitative immunoglobulin/T-cell receptor rearrangements, flow cytometry, or, in a majority, both. A reduction in MRD to <0.01% or maintenance of MRD negativity was defined as a Blina response, and such patients proceeded with further planned therapy. Patients who had persistent MRD of equal to or greater than 0.01% were considered to have failed

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TABLE 1. Indications for Blinatumomab in Chemotherapy and HSCT Groups

Indication	Detail
Chemotherapy group: 85 patients	
Severe toxicity (n = 53)	18 sepsis (6 = G3, 12 = G4), the majority (n = 11) of whom required intensive care
	13 invasive fungal infection (6 = G3, 7 = G4), including CNS (n = 2), pulmonary mucormycosis (n = 1), and biopsy-proven disseminated aspergillus (n = 4)
	Seven severe pancreatitis (5 = G3, 2 = G4), associated with typhlitis (n = 4)
	Seven severe typhlitis (3 = G3, 4 = G4) requiring ileostomy (n = 2) or TPN (n = 2)
	Three grade 3/4 encephalopathy
	Two G3 CNS thrombosis
	Two G4 liver failure requiring intensive care
	One G4 CNS hemorrhage
Comorbidities (n = 16)	Eight Down syndrome
	Two Li-Fraumeni
	Six others[a] (Bloom syndrome, overgrowth syndrome with PIK3CA mutation, Rett syndrome, Schimke immuno-osseous dysplasia, 7q11.21-23 duplication, 11q duplication)
EOC MRD >0.05% (n = 10)	Not suitable for HSCT because of poor patient performance status, comorbidities, or lack of suitable donor
Persistent MRD + HR cyto (n = 5)	Two Ph+
	Two KMT2A
	One near haploid
Jehovah's witness (n = 1)	Refused blood products
HSCT group: 20 patients	
Refractory postconsolidation (n = 17)	Six MRD >5%
	Four MRD 1%-5%
	Seven MRD 0.05%-1%
Refractory postinduction (n = 2)	One Ph+ ALL and one Ph-like ALL with MRD >5%
Pre-existing condition (n = 1)	Immunodeficiency syndrome (Omenn syndrome) requiring further HSCT[18]

NOTE. Grading as per CTCAE.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; Cyto, cytogenetics; EOC, end of consolidation; G, grade; HR, high risk; HSCT, hematopoietic stem-cell transplant; MRD, minimal residual disease; Ph, Philadelphia; TPN, total parental nutrition.
[a]Further details of some of these cases are presented in the study by Ramdeny et al.[18]

Blina and went on to receive salvage chemotherapy, HSCT, or chimeric antigen receptor T-cell therapy (CART) depending on clinician choice.

Blina was incorporated within a UKALL chemotherapy backbone.[19] Depending on their performance status and previous toxicity, responders in the Blin-CT group received either a single delayed intensification followed by maintenance or maintenance alone. Responders planned for HSCT could proceed after one cycle if they were MRD-negative depending on donor availability and performance status.

Statistical Analysis

Event-free survival (EFS) and overall survival (OS) were evaluated. EFS was defined as the time from diagnosis to relapse, death, secondary cancer, or last contact for those who were event-free, and OS was defined as the time from diagnosis to death by any cause or last contact if alive.

Survival rates were calculated and plotted using the Kaplan-Meir method. All survival rates are quoted at 2 years and were compared using the log-rank test. The proportion of cases and controls in subgroups were compared using the χ^2 test. All analyses were performed using Intercooled Stata 15.1 (Stata Corporation, College Station, TX).

Ethics Statement

Written consent was obtained for treatment. The study did not require institutional review board (IRB) approval as it was an audit of patients treated on a national guideline. Audits are exempt from needing IRB approvals in the United Kingdom as they are a means of ensuring that patients are being treated optimally according to the guideline.

RESULTS

From February 1, 2018, to February 24, 2023, 105 consecutive patients from 24 centers across the United Kingdom and the

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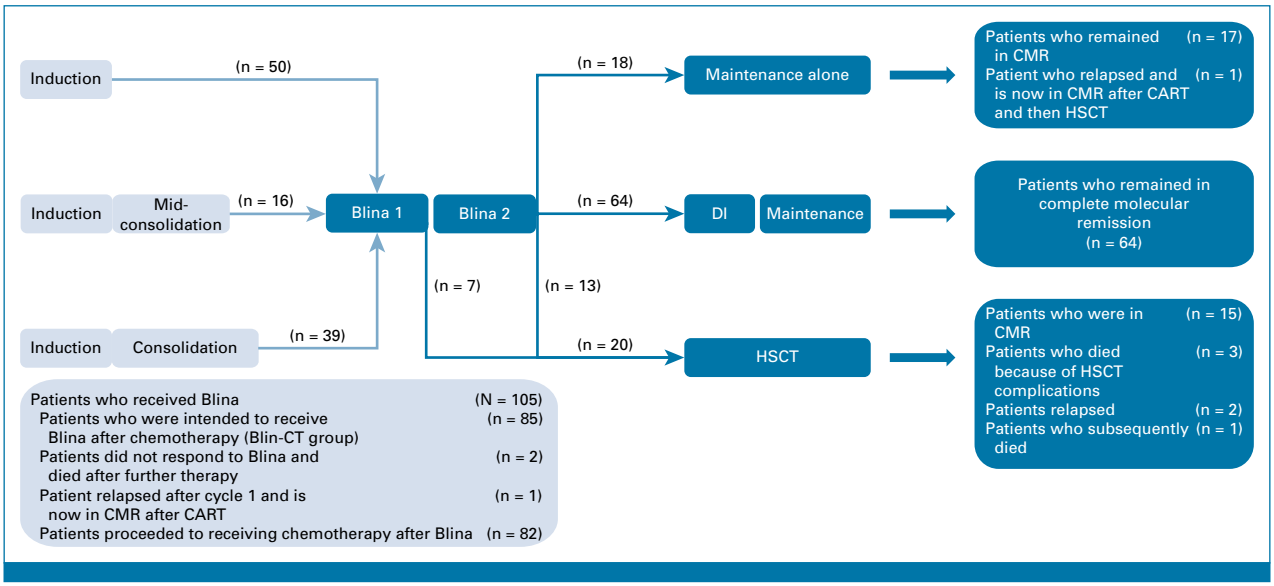

FIG 1. CONSORT diagram: patients started Blina at the end of induction, mid-consolidation, or the end of consolidation and as bridge to HSCT or continuing chemotherapy. Blina, blinatumomab; Blin-CT, blinatumomab chemotherapy; CART, chimeric antigen receptor T-cell therapy; CMR, complete molecular remission; DI, delayed intensification; HSCT, hematopoietic stem-cell transplant.

Republic of Ireland were treated with Blina as part of frontline treatment according to the consensus guideline. As shown in Figure 1 and Table 1, the majority (n = 85) were planned for further chemotherapy (Blin-CT group), whereas 20 patients proceeded to a CR1 HSCT (Blin-HSCT group).

In the Blin-CT group, 50 of 85 (59%) received Blina post-induction and 35 of 85 (41%) received Blina mid-/post-consolidation (Fig 1). The indications for treatment are shown in Table 1, with the majority of the Blin-CT group being treated for toxicity or comorbidities (70 of 85, 82%). Of the eight patients with DS, all had intermediate cytogenetic risk (6 of 8 had either an *IKZF1* or *PAX5* deletion), three had additional significant comorbidities (cardiac disease, Binder's syndrome, and a tracheostomy), and one was age 21 years at the time of diagnosis.

Blina was well tolerated, with only one case of G3/G4 neurotoxicity and no cases of G4 cytokine release syndrome (CRS). The neurotoxicity event was in a patient with DS who did not receive prophylactic anticonvulsants before the guideline was amended. Of the patients who were MRD-positive pre-Blina, 58 of 60 (97%) responded, with the remaining 25 remaining MRD-negative. A total of 55 of 58 (95%) MRD responses were observed at the end of cycle 1. Both patients who did not respond to Blina died, one because of progressive disease and the other because of transplant-related toxicity.

In the Blin-CT group, two patients have relapsed after an initial response to Blina. Both were CD19-positive isolated marrow relapses. One occurred at 9 months after diagnosis and is in ongoing second remission 13 months after successful CART. The second relapse occurred at 24 months, having received only 2 weeks of prednisolone as induction followed by two cycles of Blina and maintenance because of presentation with severe life-threatening sepsis at diagnosis requiring four limb amputation. This patient is currently in CR2 after CART followed by HSCT for early loss of B-cell aplasia.

A total of 192 controls were identified for 80 of 85 (94%) patients in the Blin-CT group. Patient characteristics of cases and controls were not significantly different (Table 2). Compared with unselected UKALL 2003 trial patients, the Blin-CT patients were more likely to have higher-risk prognostic features including older age, NCI high risk, poor cytogenetic risk, and MRD ≥0.01% (Table 2).

At 2 years, the EFS (95%; [95% CI, 85 to 98] *v* 90% [95% CI, 65 to 93]) and OS (97% [95% CI, 86 to 99] *v* 94% [95% CI, 89 to 96]) of the 80 matched Blin-CT patients were similar to those of the 192 controls (Fig 2). There have been no events among the five patients for whom we could not identify a matched control.

Subgroup analysis showed that there have been no events among the Blin-CT cases who were cytogenetic high risk (n = 21), NCI standard risk (n = 42), EOC MRD >0.05% (n = 10, not fit for HSCT), or had significant comorbidities such as DS (n = 8) in contrast to an event rate as shown in Figure 3 among the equivalent controls.

In the Blin-HSCT group, all patients responded to Blina and there were no significant G3/G4 neurotoxicity or CRS events. All proceeded to HSCT, but three died in ongoing remission because of HSCT complications, and two have relapsed, both of whom were CD19-positive (Table 3).

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TABLE 2. Characteristics of Matched Blin-CT Cases, UKALL 2003 Controls, and the Overall Trial Population

Characteristic	Cases, %	UKALL 2003 Controls, %	*P*	UKALL 2003 Trial Population, %
Age at Dx, years				
1-9	65	61	.82	77
10-15	30	33		15
≥15	5	6		8
Sex				
Male	54	55	.89	54
Female	46	45		46
NCI risk				
High	51	49	.98	37
Standard	49	51		63
Cytogenetic risk			.73	
Good	25	30		61
Intermediate	49	46		33
High	26	24		6
MRD EOI				
≥0.01%	80	73	.22	47
<0.01%	20	27		54
MRD EOI				
≥0.1%	64	57	.37	NA
0.01%-0.1%	16	17		NA
<0.01%	20	27		NA
Down syndrome			.26	
No	93	96		NA
Yes	7	4		NA

NOTE. *P* value calculated using the chi-squared test. Cytogenetic high-risk patients defined as those with *BCR::ABL1*, *KMT2A* fusions, near haploidy, low hypodiploidy (<40 chromosomes), iAMP21, *TCF3::HLF*, and ABL-class fusions (fusions involving *ABL1*, *ABL2*, *PDGFRB*, *CSF1R*).
Abbreviations: Blin-CT, blinatumomab-chemotherapy; Dx, diagnosis; EOI, end of induction; MRD, minimal residual disease; NA, not available; NCI, National Cancer Institute.

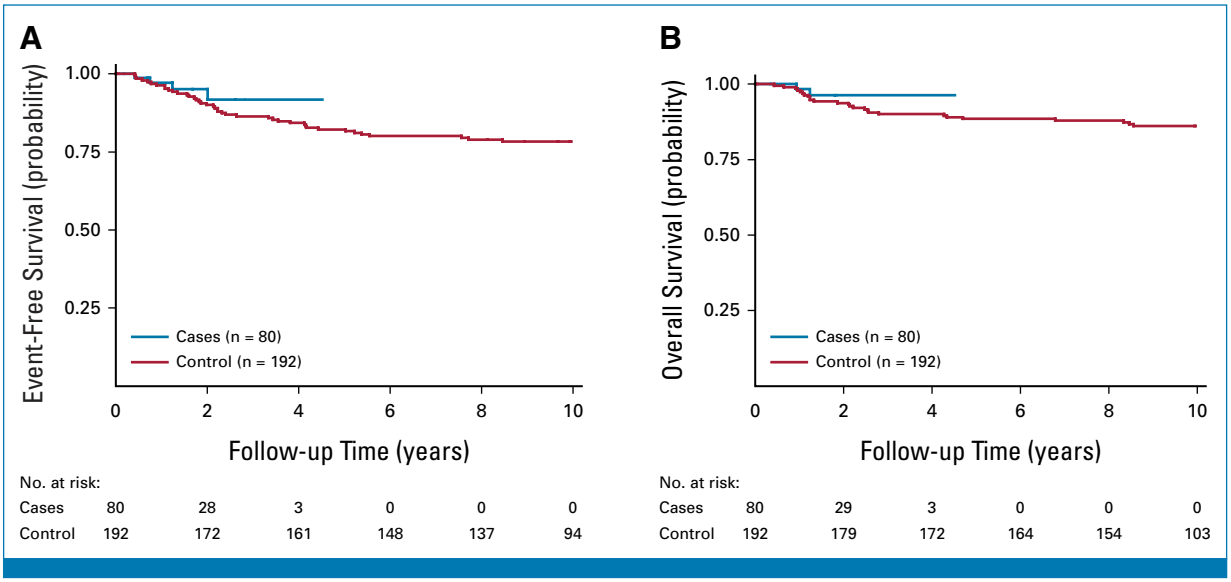

FIG 2. (A) Event-free survival and (B) overall survival of the matched Blin-CT cohort compared with UKALL 2003 controls. Blin-CT, blinatumomab-chemotherapy.

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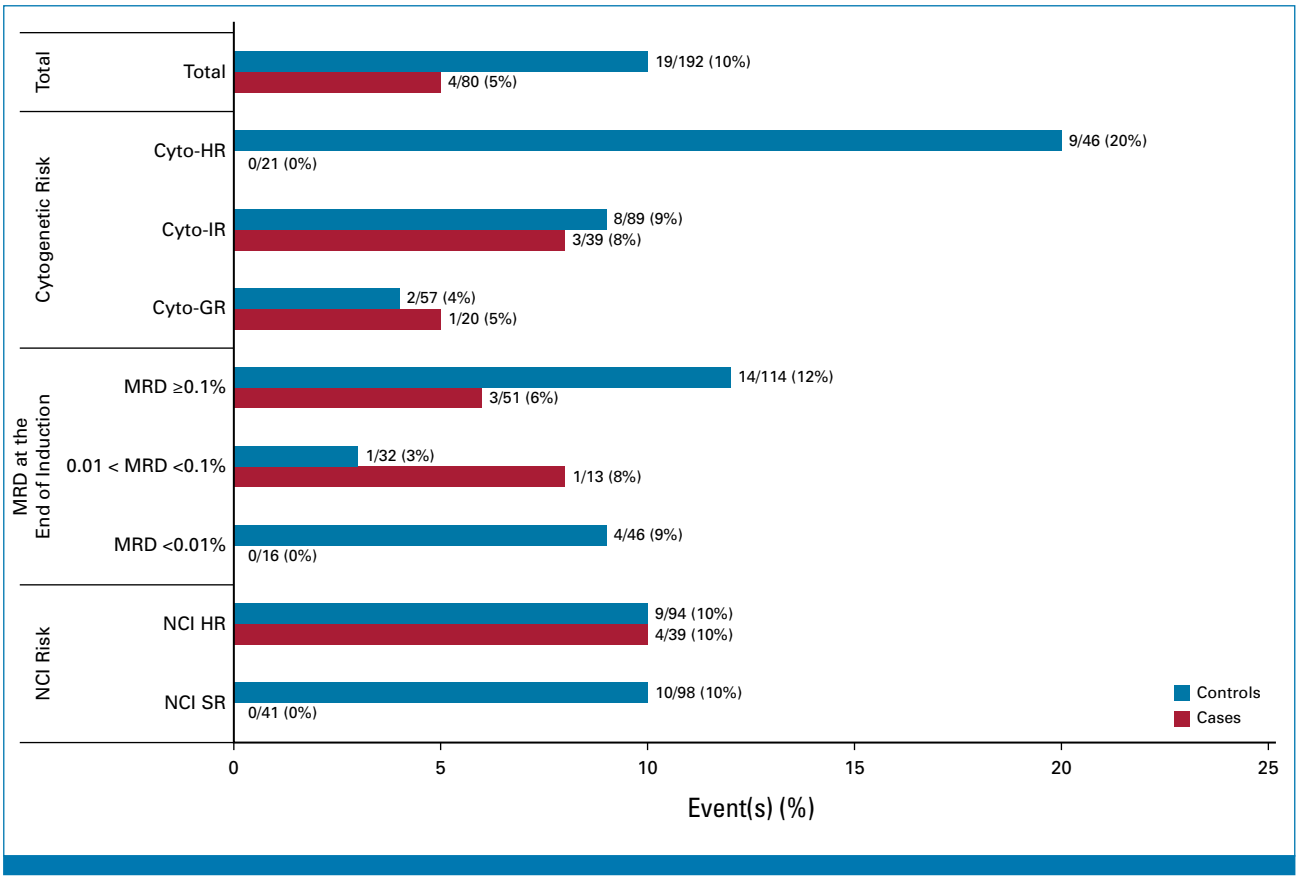

FIG 3. Number of events (%) by prognostic subgroups in controls versus matched Blin-CT cases at 2 years. Blin-CT, blinatumomab-chemotherapy; Cyto, cytogenetics; GR, good risk; HR, high risk; IR, intermediate risk; MRD, minimal residual disease; NCI, National Cancer Institute; SR, standard risk.

DISCUSSION

In this multicenter study of consecutive CYP treated according to a CCLG-approved consensus guideline, Blina was found to be safe and effective in chemotherapy-intolerant or chemotherapy-resistant patients. With a median follow-up of 22 months, the Blin-CT group had similar 2-year EFS (95%) and OS (97%) to matched controls treated on a legacy trial with excellent outcomes.[19,20] Given their chemotherapy intolerance, this group would be expected to have a higher relapse risk because of delays and omissions of postremission therapy. The results are even more remarkable considering that our study was enriched in patients at higher risk of relapse because of high-risk cytogenetics and persistent MRD at the end of induction or consolidation.

Eighteen patients in the Blin-CT group received only maintenance chemotherapy after Blina, of whom seven had received minimal chemotherapy before Blina because of serious comorbidities. Only one of these seven patients had relapsed at the 2-year follow-up. Such patients have a high risk of relapse because of their inability to tolerate curative chemotherapy. In view of the relatively short follow-up, we cannot be certain that they will not relapse but have an opportunity for cure without significant compromise of HRQOL.

Patients with DS have a high risk of death because of toxicity and a similar risk of relapse to non-DS patients,[7] precluding radical de-escalation of the chemotherapy backbone. Our experience suggests that this should be possible by replacing the early intensive chemotherapy phases with Blina as there have been no toxic deaths or relapses among the eight patients with DS in our study. We are testing this formally within a larger study (ClinicalTrials.gov identifier: NCT03911128).

Ph+ patients have until recently been treated with very intensive chemotherapy schedules, and a significant

TABLE 3. Outcome of Patients With an Indication for HSCT by Intervention

Intervention	No. of Patients	Events	Median Follow-up
HSCT	20	Five (three died because of TRM and two relapsed, of whom one died)	26 months
Chemotherapy	10 (EOC MRD >0.05%)	0	22 months

Abbreviations: EOC, end of consolidation; HSCT, hematopoietic stem-cell transplant; MRD, minimal residual disease; TRM, treatment-related mortality.

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proportion earmarked for first remission transplant, both of which are associated with a high treatment-related mortality.[22] There is an ongoing trial testing whether continuous TKI given from week 1 or 2 of induction allows de-escalation of the chemotherapy backbone and can reduce the proportion requiring first remission transplant (ClinicalTrials.gov identifier: NCT03007147). However, on the basis of previous pediatric trials of imatinib in combination with intensive chemotherapy,[22] this approach is unlikely to reduce the current relapse risk of 30%-40%, even if the EFS is improved because of a lower treatment-related mortality. Recent studies in elderly Ph+ patients of a chemotherapy-free approach using second- or third-generation TKIs in combination with Blina point the way toward dramatically improving outcomes with much lower toxicity.[15-17] Our study lends indirect support to this approach as none of our eight Ph+ patients have relapsed despite receiving a reduced intensity chemotherapy backbone.

The main limitation of our study is a relatively short median follow-up of 22 months, but the rate of events for the CT group can be estimated by examining the long-term outcome of the controls in the matched analysis where nearly half of the 10-year events (19 of 43) had occurred within 2 years. Hence, if the same is applied to the CT group, their 10-year EFS would be nearly 90%. However, we cannot exclude the possibility that Blina has merely delayed relapses to beyond 2 years.

Another limitation is the restriction on reimbursed use of Blina in the United Kingdom to patients with MRD ≥0.1%, which explains the skewing toward higher-risk cases in our study. Blina for chemotherapy-intolerant patients with MRD below that level had to be funded by local institutions, and this was not always successful. Hence, there might have been some patients who were eligible for Blina because of serious chemotherapy intolerance but were unable to receive it, and we do not have data to compare their outcome with the Blina-treated patients. However, the matched control analysis should have accounted for any selection bias within the Blin-CT group.

The small HSCT group was effectively bridged to transplant but has suffered several transplant-related deaths, highlighting the need to reduce toxicity in this group, especially as there have been no events in the 10 patients with EOC MRD >0.05% who could not be transplanted because of poor performance status or lack of donor availability (Table 3).

Although our study did not include infants, we have previously reported that Blina is safe and effective at relapse[23] and this has recently also been shown to be the case in the first-line setting.[24] We are currently piloting the use of Blina to reduce toxicity and improve outcomes in infant B-ALL.

Trials are underway testing the benefit of Blina in first-line treatment of CYP with B-ALL (ClinicalTrials.gov identifiers: NCT03643276, NCT03914625), but as an addition rather than a replacement for intensive phases of chemotherapy backbones. Our results and those of other small case series[25-28] in patients with chemotherapy intolerance provide a strong argument for testing the latter strategy for all CYP with B-ALL.

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EQUAL CONTRIBUTION

A.V. and S.S. contributed equally to this work as joint senior authors.

PRIOR PRESENTATION

Presented in part at the American Society of Hematology annual meeting, New Orleans, LA, December 9-12, 2022; and at the European Society for Paediatric Oncology meeting, Valencia, Spain, August 5, 2023.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.23.01392.

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Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Blinatumomab for First-Line Treatment of Children and Young Persons With B-ALL

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