Journal of Hematology & Oncology

CORRESPONDENCE

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Reduced-dose chemotherapy and blinatumomab as induction treatment for newly diagnosed Ph-negative B-cell precursor acute lymphoblastic leukemia: a phase 2 trial

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Abstract

Blinatumomab has emerged as a promising component of first-line therapy for acute B-cell precursor lymphoblastic leukemia (BCP-ALL), bolstering treatment efficacy. To mitigate CD19 selection pressure and reduce the incidence of blinatumomab-associated toxicities, pre-treatment chemotherapy is recommended before administering blinatumomab. From September 2022 to December 2023, we conducted a single-arm, multicenter, phase 2 trial (NCT05557110) in newly diagnosed Philadelphia chromosome-negative BCP-ALL (Ph-negative BCP-ALL) patients. Participants received induction treatment with reduced-dose chemotherapy (RDC), comprising idarubicin, vindesine, and dexamethasone over 7 days, followed by 2 weeks of blinatumomab. Those failing to achieve composite complete remission (CRc) received an additional 2 weeks of blinatumomab. The primary endpoint was the CRc rate post initial induction treatment. Of the 35 enrolled patients, 33 (94%) achieved CRc after 2 weeks of blinatumomab, with 30 (86%) achieving measurable residual disease (MRD) negativity. Two patients extended blinatumomab to 4 weeks. With either 2 or 4 weeks of blinatumomab treatment, all patients achieved CR (35/35) and 89% (31/35) were MRD negativity. The median time to CR was 22 days. Immune effector cell-associated neurotoxicity syndrome was limited (14%, all grade 1). Non-hematological adverse events of grade 3 or higher included pneumonia (17%), sepsis (6%), and cytokine release syndrome (9%). With a median follow-up

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of 11.5 months, estimated 1-year overall survival and 1-year progression-free survival rates were 97.1% and 82.2%, respectively. These findings affirm that RDC followed by blinatumomab is an effective and well-tolerated induction regimen for newly diagnosed Ph-negative BCP-ALL, supporting a shift towards less intensive and more targeted therapeutic approaches.

Trial registration: https://www.clinicaltrials.Gov. Identifier NCT05557110.

Keywords Blinatumomab, Reduced-dose chemotherapy, Induction treatment, B-cell precursor acute lymphoblastic leukemia, Philadelphia chromosome-negative

To the editor: Patients with Philadelphia chromosome-negative acute B-cell precursor lymphoblastic leukemia (Ph-negative BCP-ALL) typically achieve a high complete remission (CR) rate of 70–80% with conventional multi-drug introduction chemotherapy. However, 30–50% remain measurable residual disease (MRD) positive, often leading to relapse [1, 2]. Blinatumomab, approved for relapsed/refractory BCP-ALL or consolidation therapy for BCP-ALL, shows promising efficacy with ponatinib as a chemo-free strategy in Ph-positive ALL [3]. It is also being investigated for early induction in Ph-negative BCP-ALL. Given the high tumor burden in newly diagnosed BCP-ALL patients, bridging chemotherapy before blinatumomab may reduce CD19 selective pressure and associated toxicities [4, 5]. Intensive chemotherapy may impair immune cells, potentially affecting the effectiveness of blinatumomab [6]. Therefore, optimization of the dosage and duration of blinatumomab and chemotherapy in warranted.

From September 2022 to December 2023, we conducted a prospective, multicenter, single-arm, phase 2 study to assess the efficacy and safety of reduced-dose chemotherapy (RDC) combined with two weeks of blinatumomab (RDC-Blinatumomab-2 W) as first-line induction treatment for Ph-negative BCP-ALL patients (aged 15–65). The regimen included idarubicin 8 mg/m^2 intravenously injection (IV), day 1, vindesine 3 mg/m^2, up to 4 mg, IV, day 1, dexamethasone 9 mg/m^2/day, IV, days 1–7 and blinatumomab 9 μg/day, days 8–14 and 28 μg/day, days 15–21. If CR/CR with incomplete recovery of blood cell counts (CRi) was not achieved at day 22, blinatumomab (28 μg/day) was extended for another 2 weeks (RDC-Blinatumomab-4 W). The primary endpoint was composite complete remission (CRc, including CR+CRi) rate after one cycle of induction treatment. Secondary endpoints included MRD detection by multi-flow cytometry (MFC) after one cycle of induction treatment, adverse events during the induction therapy and survival. This trial is registered at clinicaltrials.gov (NCT05557110), and the last follow-up was on April 15, 2024. The protocol and detailed scheme of the study are shown in supplemental material (Protocol, Additional file 1: Figure S1).

Thirty-five eligible patients were enrolled across five study sites (Additional file 1: Table S2). Both were included in the efficacy and safety analyses (Additional file 1: Figure S2). The clinical characteristics of patients are shown in Additional file 1: Table S1. The median age was 42 (15–65) years, with 9 (26%) patients having a white blood cell count over 30×10^9/L. Seventeen (49%) patients had poor-risk genetic aberrations.

Following RDC-Blinatumomab-2 W therapy, 33/35 patients (94%, 95% CI 81–98) achieved CRc. Moreover, 30/35 patients (86%, 95% CI: 71–94) achieved MRD negativity (Table 1). The results were comparable to the early findings of the GMALL-BOLD study [7]. Two patients extended blinatumomab to 4 weeks. With up to 4 weeks of blinatumomab treatment, the CR rate reached 100% (35/35) and the MRD-negative CR rate reached 89% (31/35). Notably, bone marrow (BM) evaluations of 33 patients after RDC showed no CRc or MRD negativity. Subgroup analyses revealed no significant differences in treatment responses based on traditional prognostic factors (sex, age, WBC counts and genetic risk stratification at diagnosis) or BM blasts percentage prior to blinatumomab (Additional file 1: Figure S3). Subgroup results aligns with that of a randomized controlled blinatumomab study in pediatric patients with high-risk first-relapse BCP-ALL [8].

The median follow-up time was 11.5 (IQR: 7.4–13.1) months. The estimated one-year overall survival rate was 97.1% (95% CI: 91.8–100) and one-year progression-free survival rate was 82.2% (95% CI: 69.0–98.0) (Fig. 1). One patient died of thrombocytopenia-related intracranial hemorrhage after the first consolidation chemotherapy. All patients received hyper-CVAD-based consolidation therapy and underwent standard central nervous system prophylaxis with 8–12 intrathecal injections. 13 patients underwent allogenic transplantation based on their MRD levels or patients' preference. Four patients relapsed: one isolated CNS relapse, one hematologic relapse, and two MRD-positive relapses. Among these, three were CD19-positive and one was CD19-negative.

During induction therapy, no deaths occurred within 4 weeks, significantly lower than the 2–10% mortality rate observed with intensified chemotherapy [9]. Grade 3–4 neutropenia occurred in 24 (69%) patients and grade 3–4 thrombocytopenia in 8 (23%) patients (Table 1). The median time to neutrophil recovery was only 7 days (IQR: 4–13), much shorter than the 16–20 days for

Table 1 Overview of reduced-dose chemotherapy followed by blinatumomab as induction therapy

Efficacy outcomes for RDC-Blinatumomab-2 W regimen		
After RDC	*N* = 33	
BM blasts < 5%	11 (33%) [20–50]	
BM blasts ≥ 5%	22 (67%) [50–80]	
0·01% < MFC MRD < 1%	11 (33%) [20–50]	
MFC MRD ≥ 1%	22 (67%) [50–80]	
After RDC-Blinatumomab-2 W	*N* = 35	
Composite complete remission	33 (94%) [81–98]	
CR	28 (80%) [64–90]	
CRi	5 (14%) [6–29]	
MFC MRD < 0.01%	30 (86%) [71–94]	
Treatment related adverse events for RDC-Blinatumomab-2 W regimen		
	Grade 1–2	Grade 3–4
Hematologic AEs		
Leukopenia	0	26 (74%)
Neutropenia	0	24 (69%)
Febrile neutropenia	0	9 (26%)
Anemia	3 (9%)	8 (23%)
Thrombocytopenia	9 (26%)	8 (23%)
Blinatumomab related AEs		
Cytokine release syndrome	16 (45%)	3 (9%)
ICANS	5 (14%)	0
Other non-hematologic AEs		
Pneumonia	0	6 (17%)
Sepsis	0	2 (6%)
Other infections	6 (17%)	0
Fatigue	13 (37%)	0
Alanine aminotransferase elevation	12 (34%)	1 (3%)
Fever	10 (29%)	1 (3%)
Nausea or vomiting	9 (26%)	0
Rash	6 (17%)	0
Edema	6 (17%)	0
Purpura	4 (11%)	0
Mucositis	3 (9%)	0
Diarrhea	2 (6%)	0

Data are n (%) or n (%) [95% CI].

N, number; BM, bone marrow; CR, complete remission; CRi, complete response with incomplete count recovery; ICANS: immune effector cell-associated neurotoxicity syndrome; MFC, multiparameter flow cytometry; MRD, measurable residual disease; RDC, reduced-dose chemotherapy; RDC-Blinatumomab-2 W, reduced-dose chemotherapy followed by blinatumomab for 2 weeks

conventional chemotherapy [10]. Grade 3–4 infections were observed in 23% (8/35) of patients, significantly lower than 37% reported in the MDACC study [11]. Cytokine release syndrome (CRS) occurred in 19 (54%) patients, with 3 (9%) patients experiencing grade 3 CRS. Patients with BM blasts ≥ 5% had a higher incidence of CRS compared to those with BM blasts < 5% before blinatumomab treatment (73% vs. 18%, $P = 0.0094$). Immune effector cell-associated neurotoxicity syndrome (ICANS) was observed in 14% (5/35) patients, all grade 1. The incidences of CRS and ICANS were similar to previously reported results at comparably low levels [12].

In conclusion, our study provides compelling evidence for efficacy and safety of the RDC-Blinatumomab regimen as first-line induction therapy. These findings support a shift towards less intensive, more targeted therapeutic approaches for young patients with Ph-negative BCP-ALL. Due to the single-arm design and small sample size, further investigation in larger, randomized controlled trials with longer follow-ups is warranted.

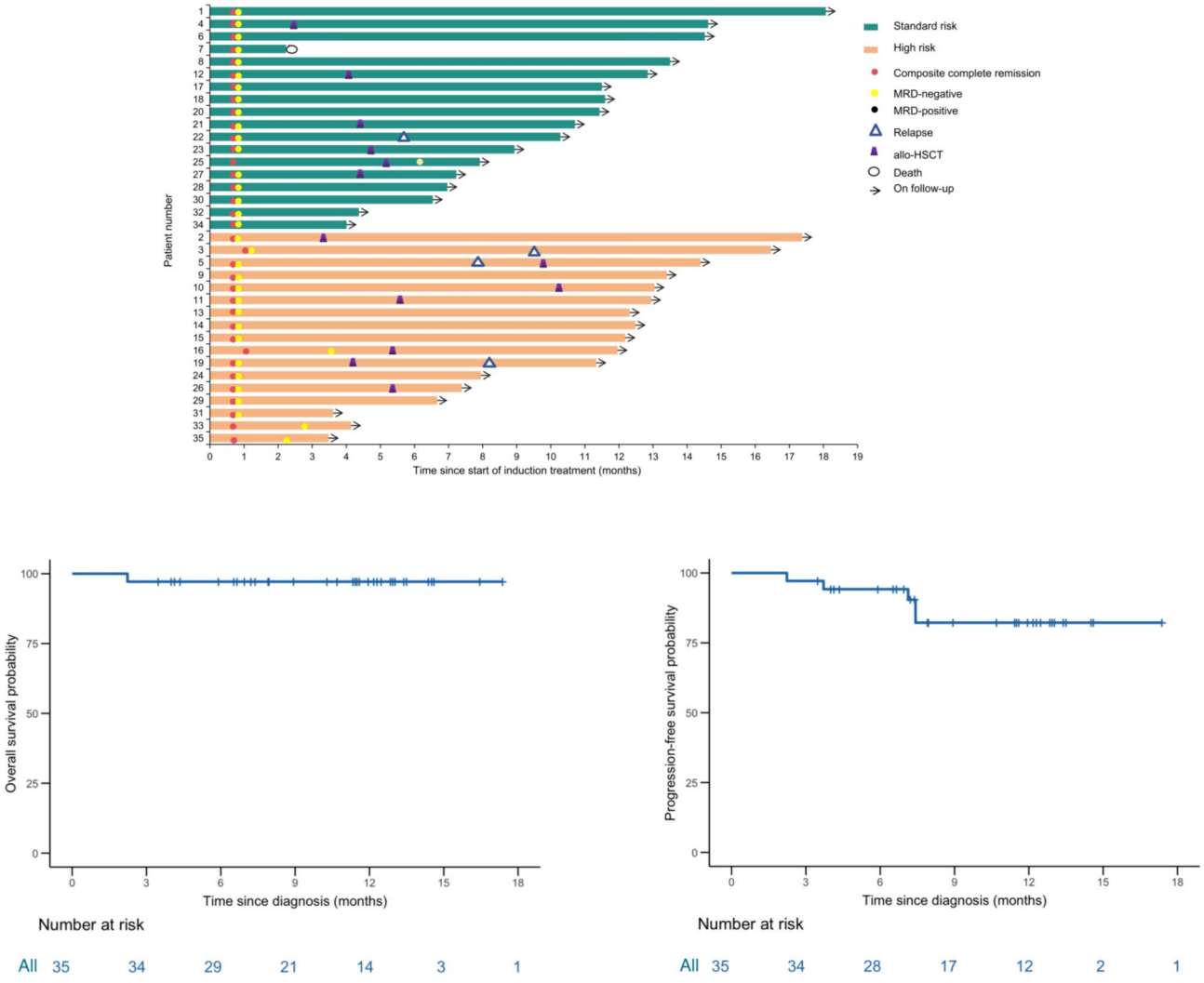

Fig. 1 Swimmer plot and survival analysis
(**a**) Swimmer plot of patients after induction therapy. (**b**) Overall survival analysis. (**c**) Progression-free survival analysis
MRD: measurable residual disease; allo-HSCT, allogeneic hematopoietic stem cell transplantation

Abbreviations

BCP-ALL	acute B-cell precursor lymphoblastic leukemia
BM	bone marrow
CR	complete remission
CRc	composite complete remission rate
CRi	complete remission with incomplete blood cell count recovery
CRS	cytokine release syndrome
ICANS	immune effector cell-associated neurotoxicity syndrome
IV	intravenous
MFC	multiparameter flow cytometry
MRD	measurable residual disease
Ph-negative	Philadelphia chromosome-negative
RDC	reduced-dose chemotherapy
RDC-Blinatumomab	reduced-dose chemotherapy combined with blinatumomab
RDC-Blinatumomab-2W	RDC combined with 2 weeks of blinatumomab
RDC-Blinatumomab-4W	RDC combined with 4 weeks of blinatumomab
TKI	Tyrosine kinase inhibitor
WBC	white blood cell

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13045-024-01597-8.

Supplementary Material 1

Supplementary Material 2

Acknowledgements
We would like to express our gratitude to all the patients and their families for participating in this study. We appreciate the efforts of the clinical staff at all participating centers for their dedication and hard work. Special thanks to our research team for their invaluable contributions to the study design, data collection, and analysis.

Author contributions
Contribution: concept and design: CSN, WDP, LJ. Provision or treatment of research patients: LJ, QHY, WY, ZX, LXZ, YXF, GB, HM, MM, LRN, WJ, WQ, XMX, WY, DAL, SYY, LY, DXQ, WDP, ZY, CSN. Data collection and assembly: LJ, LYT. Data analysis and interpretation: LJ, DHP, CSN. Draft of the manuscript: LJ and

DHP wrote the first draft of the manuscript. CSN and ZY read and revised the manuscript. All authors gave final approval for submission of the manuscript.

Funding
Funders are not involved in any aspect of the research process. This includes research design, data collection, data analysis and interpretation, or report writing.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Studies were conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the First Affiliated Hospital of Soochow University (Approval number: 2022235).

Consent for publication
Written informed consent was obtained from all patients or their guardians.

Competing interests
The authors declare no competing interests.

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Received: 8 July 2024 / Accepted: 12 August 2024
Published online: 02 September 2024

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