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CASE REPORT

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Blinatumomab therapy for B cell acute lymphoblastic leukemia accompanied by persistent or relapsed low-level MRD prior to hematopoietic stem cell transplantation in Chinese children: a case series

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Abstract

Background Blinatumomab could be successfully used to reduce minimal residual disease (MRD) prior to hematopoietic stem cell transplantation (HSCT) in pediatric B cell precursor acute lymphoblastic leukemia (BCP-ALL), but sound evidence is lacking in China.

Case presentation This retrospective study assessed the application of blinatumomab in B-ALL accompanied by persistent or relapsed low-level MRD before HSCT from April 2019 to July 2021. Two cases (Cases 1 and 2) initially achieved remission with MRD < 0.01% upon conventional therapy but had MRD relapse with MRD ≥ 0.01% but < 1% during maintenance treatment. Case 3 had no response to routine treatment, with high MRD (9.88% and 1.23% at days 19 and 46, respectively). Nevertheless, all patients had undetectable MRD. Cases 2 and 3 had undetectable fusion gene following blinatumomab therapy. By bone marrow monitoring (bone marrow morphology, bone marrow MRD and fusion gene) post-HSCT, the patients were persistently negative until May 15, 2022. No patient had serious adverse events before or during blinatumomab treatment.

Conclusions Blinatumomab therapy showed a good performance for three pediatric cases with detectable but low MRD before HSCT in China. However, further prospective studies with large sample sizes are still needed for further clarification.

Keywords Acute B lymphoblastic leukemia, Blinatumomab, Minimal residual disease, Hematopoietic stem cell transplantation, China

Background

Acute lymphoblastic leukemia (ALL) is a critical hematological cancer, making up 75–80% of all pediatric acute leukemia cases (Alvarnas et al. 2012). Although advanced chemotherapy regimens are highly efficient in pediatric ALL, approximately 15–20% of cases eventually relapse, while 8–10% die from disease progression or treatment-related complications (Nguyen et al. 2008). ALL is common in children with hematological

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cancers in China. Although China has made substantial progress treating pediatric ALL(Chen et al. 2021), more effective and less toxic approaches to treat young patients with relapsed/refractory ALL (R/R ALL) are still urgently needed (Sun et al. 2022; Wang et al. 2022).

Minimal residual disease (MRD), reflected by the presence of leukemic cells undetectable microscopically and that may be evaluated by standardized methods with 0.01% sensitivity, is an biomarker for evaluating disease remission and also the strongest factor predicting relapse in B cell precursor acute lymphoblastic leukemia (BCP-ALL) (Modvig et al. 2021; Dongen et al. 2015). Additionally, R/R ALL cases still have an extremely poor prognosis with MRD that persists or recurs (Shen et al. 2021; Gokbuget et al. 2018). The best treatment with curative potential in MRD cases still showing poor response to chemotherapy alone is allogeneic hematopoietic stem cell transplantation (HSCT). Nevertheless, patients undergoing HSCT with MRD remain at a significant risk of overall survival and disease relapse (Shen et al. 2021; Klyuchnikov et al. 2021). Furthermore, detectable pre-HSCT MRD is associated with poor outcome, and low-level MRD (quantifiable/non-quantifiable MRD < 0.1% determined by qPCR) negatively affects cases transplanted in second- or further complete remission (CR) (Lovisa et al. 2018). Thus, an MRD-guided treatment prior to HSCT is required, including low-level MRD.

Blinatumomab is a US Food and Drug Administration-approved bispecific T cell engager designed to redirect $CD3^+$ T cells for the inhibition of $CD19^+$ target cells in relapsed/refractory B-ALL patients or individuals showing persistent MRD ≥ 0.1% (Locatelli et al. 2022; Queudeville and Ebinger 2021). Despite potential neurotoxicity, cytokine release syndrome (CRS) and tumor lysis, blinatumomab could be used, thanks to its safety and efficacy profiles, to address some unmet needs by introducing the current status and treatment outcomes for children with ALL in China based on data reported by an international single-arm clinical trial (Locatelli et al. 2022). Substantial evidence indicates blinatumomab can be successfully used as a bridge treatment for HSCT in relapsed/refractory B-ALL (R/R B-ALL) cases (Locatelli et al. 2022; Dombret et al. 2019); however, children in China have been rarely evaluated, especially for the choice of MRD elimination methods prior to transplantation in ALL cases with low tumor load (MRD of 0.01%-1%).

Herein, we retrospectively report the outcomes of 3 B cell acute lymphoblastic leukemia (B-ALL) patients with low MRD after front-line induction or consolidation chemotherapy (persistent MRD) or subsequently showing MRD positivity upon prior MRD negativity (relapsed MRD) that were administered blinatumomab as a bridging therapy before planned transplantation in our hospital between April 2019 and July 2021.

The study was approved by the ethics committee of Shenzhen Children's Hospital (No. 2021090). Each patient provided informed consent.

Case presentation

Case 1 was a 5 year, 7 month-old boy diagnosed with B-ALL according to bone marrow morphology, immunophenotyping of bone marrow leukemia, fusion genes, and comprehensive chromosome examination (Table 1). He was first treated in a different hospital using the CCCG-ALL-2015 (Yang et al. 2021) procedure with a MRD < 0.01% at both 19 and 46 days (assessed by multicolor flow cytometry). However, he showed relapse 30 months later; about 1 month after the maintenance, chemotherapy was stopped, with a bone marrow MRD of 1.5% and the cerebrospinal fluid being still negative. The boy was administered reinduction treatment with dexamethasone, cytarabine, etoposide and L-asparaginase (DEAL), alongside reconsolidation treatment with cyclophosphamide, cytarabine and mercaptopurine (CAT); however, MRD remained at 0.03%. Following continuous blinatumomab treatment (15 μg/m^2/day) between 2022.02.14 and 2022.02.29 in our department, MRD became negative again (Fig. 1A). The case underwent HSCT on 2022.03.22, with donation by his mother matched with HLA 5/10 (Fig. 2). Based on CTCAE (v5.0), there were no adverse reactions, and only a mild fever was recorded (grade of adverse event was evaluated by CTCAE v5.0).

Case 2 was a 13-month-old girl diagnosed with B-ALL (cytogenetics: KMT2A-AFF1; t (4; 11) (q21; q23)) (Table 1) and treated by the CCCG-ALL-2020 protocol. MRD values were 0.45% and < 0.01% on days 19 and 46, respectively. The MLL/AF4 fusion gene remained negative until subsequent intensive chemotherapy with cyclophosphamide, cytarabine, mercaptopurine, vincristine and L-asparaginase (CAT +). Regrettably, MRD (0.4%) and fusion gene (1.53%) tests were positive again on day 323 of the maintenance treatment. One week later, bone marrow re-evaluation showed an increasing MRD of 0.72% and a fusion gene rate of 2.31%. Both MRD and fusion gene levels were undetectable at 28 days of therapy with blinatumomab at 15 mg/m^2 daily (Fig. 1B). The case underwent HSCT on 2022.03.21 after 1 cycle of blinatumomab treatment (Fig. 2). Only a mild fever was recorded in case 2.

Case 3 was a 5 year and 1 month-old girl with B-ALL responding poorly to routine induction treatment with prednisolone, vincristine, daunorubicin and L-asparaginase (PVDL), who was considered a high-risk case (cytogenetics: ETV6-RUNX1) based on the

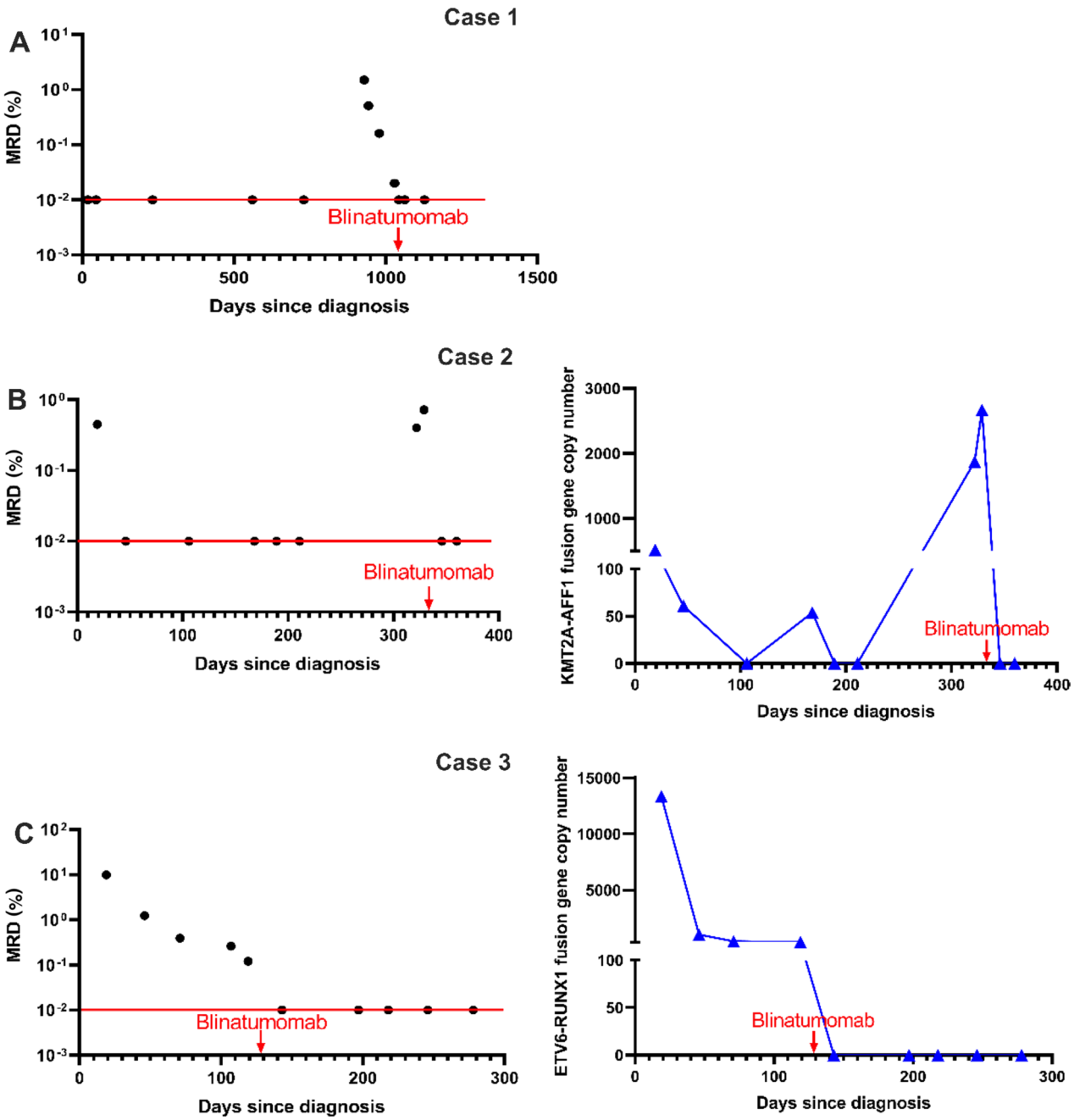

Fig. 1 Variations of MRD and fusion gene copy number in the three patients. MRD, minimal residual disease

CCCG-ALL-2020 protocol (Table 1). MRD values were 9.88% on day 19, 1.23% on day 46 following intensive therapy with cyclophosphamide, cytarabine and mercaptopurine (CAT), and 0.39% upon intensive therapy with CAT +. After two cycles of high-dose methotrexate, MRD remained at 0.12%. Therefore, blinatumomab was administered as monotherapy by continuous intravenous infusion via a central line catheter between 2021.12.08 and 2021.12.23. Then, bone marrow analysis showed molecular-level remission with an MRD below 0.01% (Fig. 1C); the girl received HSCT with allele/antigen mismatch (5/10) from her brother on 2022.01.11 (Fig. 2). Besides a mild fever, no adverse reactions were detected.

Up to 2022.05.15, bone marrow monitoring (bone marrow morphology, bone marrow MRD and fusion gene) was persistently negative in the above cases.

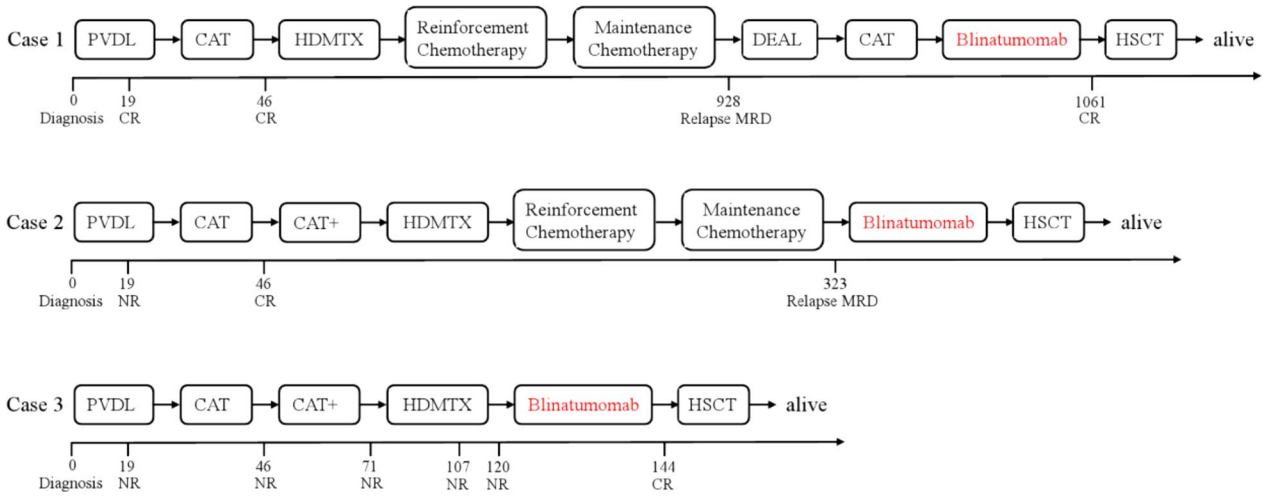

Fig. 2 Flowchart of the treatment protocol used in the three cases. PVDL, prednisolone, vincristine, daunorubicin and L-asparaginase; CAT, cyclophosphamide, cytarabine and mercaptopurine; HDMTX, high-dose methotrexate; DEAL, dexamethasone, cytarabine, etoposide and L-asparaginase; HSCT, hematopoietic stem cell transplantation; CAT+, cyclophosphamide, cytarabine, mercaptopurine, vincristine and L-asparaginase, with or without bortezomib

Discussion

B-ALL has a high prevalence in China, including R/R B-ALL; however, current response to routine treatments remains unsatisfactory. Blinatumomab could be successfully utilized to reduce MRD prior to HSCT in pediatric ALL (Keating et al. 2019; Pawinska-Wasikowska et al. 2022), but associated studies in China are scarce. Here, three B-ALL children achieved a complete remission at the molecular level after blinatumomab administration prior to HSCT even with primary resistance or relapse, suggesting a beneficial effect of blinatumomab in MRD clearance in Chinese B-ALL children pre-HSCT.

In the international multicenter ALL-REZ BFM 2002 trial, MRD after induction treatment and MRD persistence $\geq 0.1\%$ pre-HSCT, reflecting high resistance to routine intensive chemotherapy for this pathology, was demonstrated to independently predict prognosis in high-risk ALL relapse (Eckert et al. 2015). Furthermore, persistently high MRD right before HSCT independently predicts poor prognosis in high-risk relapsed ALL patients with complete remission (Eckert et al. 2015). Patients with high MRD levels require more intensive chemotherapy (Inaba and Pui 2019). However, the intensity of conventional chemotherapy has reached the limit of tolerance for children with ALL (Inaba and Pui 2019). Therefore, new treatment strategies are required to improve patient outcome and the quality of life in pediatric ALL.

The efficacy of blinatumomab in children has been broadly shown in clinic (Locatelli et al. 2022; Locatelli et al. 2020; Brown et al. 2021). Blinatumomab has received conditional approval from the National Medical Products Administration (NMPA) for adult R/R CD19+B-ALL; however, more data are required for blinatumomab's use in pediatric ALL cases in China. Previous evidence suggests MRD reduction before blinatumomab treatment has a tight association with response and outcome improvement (Locatelli et al. 2022; Pawinska-Wasikowska et al. 2022; Gore et al. 2018; Ampatzidou et al. 2020). In the above cases, a complete remission at the molecular level (MRD-negative) was achieved following use of blinatumomab in patients with low MRD load, suggesting a good prognosis and the feasibility of using blinatumomab for eliminating low-level MRD prior to HSCT.

It is obvious HSCT alleviates R/R BCP-ALL cases previously treated with blinatumomab (Locatelli et al. 2022). For individuals still MRD^+ before HSCT, 1–2 blinatumomab cycles with subsequent HSCT was proposed (Hunger and Raetz 2020). In a nutshell, patients administered blinatumomab have markedly reduced risk of infection and sepsis, elevated rates of MRD negativity, and improved disease-free survival (DFS) and overall survival (OS), with higher odds of proceeding to HSCT than cases administered standard chemotherapy. Besides, it was confirmed by the Children's Oncology Group (Brown et al. 2021) and IntReALL Consortium (Locatelli et al. 2022) that blinatumomab is superior to routine chemotherapy in preparing pediatric cases for HSCT. Here, among the three cases, one (Case 3) did not show remission by induction and consolidation treatment, but had molecular remission after blinatumomab treatment. Although case 1 initially achieved remission, chemotherapy had no efficacy upon relapse; however,

Table 1 Clinical features of the three cases

Case	Age	Sex	Disease status	Cytogenetics	Pre-MRD %MNC	Post-MRD %MNC	Fever	Grade 3/4 toxicities	Days to HSCT*	Graft source	Post-HSCT days
1	5Y7M	M	CR1	46, XY	0.03	< 0.01	Yes	None	21	Haplo sib, PBSC + UCB	54
2	1Y1M	F	CR1	KMT2A-AFF1; t (4;11) (q21;q23)	0.72	< 0.01	Yes	None	22	Haplo sib, PBSC + BM + UCB	80
3	5Y1M	F	CR1	ETV6-RUNX1	0.12	< 0.01	Yes	None	19	Haplo sib, PBSC + UCB	124

Y year, *M* month, *BM* bone marrow, *MNC* mononuclear cell, *PBSC* peripheral blood stem cell, *UCB* umbilical cord blood, *UCB* umbilical cord blood

* Days to HSCT represents the time from the end of blinatumomab treatment to the day of stem cell infusion

* Post-HSCT days represents the time from the day of stem cell infusion to May 15, 2022

blinatumomab administration induced complete remission prior to HSCT. Furthermore, all three patients had persistent undetectable MRD and fusion gene levels (< 1%) following HSCT, suggesting a good outcome.

It was reported cytokine release syndrome and neurologic toxicity can result from blinatumomab (Jain and Litzow 2020). A systematic review and meta-analysis of children with ALL indicated blinatumomab decreases the risk of serious adverse events, febrile neutropenia and infection in comparison with chemotherapy (Marrapodi et al. 2022). In a randomized phase 3 clinical trial of pediatric high-risk first-relapse B-ALL cases, the incidence rates of serious adverse events in the blinatumomab and consolidation chemotherapy groups were 24.1% and 43.1%, respectively, with the incidence rates of grade ≥ 3 adverse events of 57.4% and 82.4%, respectively (Locatelli et al. 2021). In the current study, no children had serious adverse events before or during blinatumomab administration, and only a mild fever was detected.

Conclusions

Although this study was limited by the small sample size (3 cases) and had a retrospective design, our therapeutic regimen including blinatumomab was effective in children with MRD + B-ALL. The cases achieved cytomorphologic and cytometric remission before HSCT. These data are promising, indicating a management option for individuals with detectable but low MRD and revealing the optimal timing of administration prior to HSCT. However, further prospective studies with large sample sizes will be performed to confirm the effectiveness and safety of blinatumomab therapy in Chinese children with B-ALL by persistent or relapsed low-level MRD before HSCT. Additionally, it would be of high interest to predict patients who may benefit from blinatumomab treatment, to detect the optimal time to introduce HSCT following immunotherapeutic elimination of MRD and to identify cases in whom such treatment would only delay further HSCT without tangible benefit. Overall, blinatumomab treatment was carried out in 3 Chinese cases with MRD^+ B-ALL pre-HSCT. Children with MRD^+ B-ALL may obtain a deep remission following use of blinatumomab with a good safety profile, providing a pre-HSCT management option.

Abbreviations

ALL	Acute lymphoblastic leukemia
B-ALL	B cell acute lymphoblastic leukemia
BCP-ALL	B cell precursor acute lymphoblastic leukemia
CAT	Cytarabine and mercaptopurine
CRS	Cytokine release syndrome
HSCT	Hematopoietic stem cell transplantation
MRD	Minimal residual disease
NMPA	National Medical Products Administration
PVDL	Prednisolone, vincristine, daunorubicin and L-asparaginase
R/R ALL	Refractory or relapsed ALL

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Author contributions

WY was involved in study conception and design, experiments, data analysis and manuscript revision. ZGC and WLL performed data collection and analysis, and wrote the manuscript. All authors reviewed the data and approved the final version of the manuscript.

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Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate

The present trial had approval from the ethics committee of Shenzhen Children's Hospital (No. 2021090). Each patient provided signed informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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