Received: 14 April 2019 | Revised: 2 June 2019 | Accepted: 9 June 2019

DOI: 10.1002/pbc.27898

Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

WILEY

BRIEF REPORT

Blinatumomab as a bridge to further therapy in cases of overwhelming toxicity in pediatric B-cell precursor acute lymphoblastic leukemia: Report from the Israeli Study Group of Childhood Leukemia

Sarah Elitzur[1,2] | Nira Arad-Cohen[3] | Shlomit Barzilai-Birenboim[1,2] | Miriam Ben-Harush[4] | Bella Bielorai[2,5] | Ronit Elhasid[2,6] | Tamar Feuerstein[1] | Gil Gilad[1,2] | Alexander Gural[7] | Mira Kharit[8] | Naomi Litichever[1] | Ronit Nirel[9] | Sigal Weinreb[10] | Ofir Wolach[2,11] | Amos Toren[2,5] | Shai Izraeli[1,2] | Elad Jacoby[2,5]

[1]The Rina Zaizov Division of Pediatric Hematology-Oncology, Schneider Children's Medical Center, Petah Tikva, Israel

[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[3]Pediatric Hematology-Oncology Department, Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

[4]Department of Pediatric Hematology-Oncology, Soroka Medical Center, Ben Gurion University, Beer Sheva, Israel

[5]Division of Pediatric Hematology, Oncology and BMT, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan, Israel

[6]Pediatric Hemato-Oncology, Sourasky Medical Center, Tel Aviv, Israel

[7]Department of Hematology, Hadassah Hebrew University Medical Center, Jerusalem, Israel

[8]Department of Hematology, Shaare Zedek Medical Center, Jerusalem, Israel

[9]Department of Statistics, Hebrew University, Jerusalem, Israel

[10]Pediatric Hematology-Oncology, Hadassah Hebrew University Medical Center, Jerusalem, Israel

[11]Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel

Correspondence
Sarah Elitzur, The Rina Zaizov Division of Pediatric Hematology-Oncology, Schneider Children's Medical Center, 14 Kaplan St., Petah Tikva 4920235, Israel.
Email: sarhae@clalit.org.il

Funding information
This work was supported by the Israel Cancer Association and Amutat Chaim.

Abstract

Tremendous progress in the therapy of pediatric acute lymphoblastic leukemia (ALL) has been achieved through combination cytotoxic chemotherapy, leading to high cure rates, at the cost of significant life-threatening toxicity. The bispecific T-cell engager blinatumomab, recently approved for relapsed/refractory ALL, has a unique nonmyelotoxic toxicity profile. As blinatumomab causes B-cell depletion, the safety of its use during severe chemotherapy-induced toxicity is unclear. We report 11 pediatric patients with ALL, treated with blinatumomab following overwhelming chemotherapy-associated toxicity, with recovery of all patients and successful bridging to further antileukemia therapy. Blinatumomab can be considered for rare patients who cannot tolerate cytotoxic therapy.

KEYWORDS

blinatumomab, childhood acute lymphoblastic leukemia, immunotherapy, treatment-related toxicity

1 | INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, with cure rates currently approaching 90%.[1,2] Despite the great progress in curing childhood ALL, significant challenges still

Abbreviations: ALL, acute lymphoblastic leukemia; B-ALL, B-cell precursor acute lymphoblastic leukemia; DS, Down syndrome; MRD, minimal residual disease; R/R, relapsed/refractory.

remain. Acute adverse effects of chemotherapy may be life threatening, and long-term side effects often impair survivors' quality of life. As cure rates improve, treatment-related complications account for a higher percentage of deaths, and currently the rates of treatment-related deaths are approaching those of relapse-associated mortality.[3] Treatment-related toxicity remains unacceptably high especially for specific subgroups, such as adolescents and young adults, high-risk patients receiving more intensive chemotherapeutic regimens, and patients with certain genetic predisposition syndromes.[4–6] Blinatumomab is a bispecific construct designed to engage T cells towards CD19, an antigen expressed on a majority of B-cell precursor ALL (B-ALL) blasts,[7,8] leading to cytotoxic killing of leukemic cells. Blinatumomab therapy has induced remissions in relapsed/refractory (R/R) leukemia[9,10] and eradication of minimal residual disease (MRD) in adults with ALL,[11] ultimately leading to improved survival. In the R/R setting, adults receiving blinatumomab experienced less cytopenia and a lower rate of infections than that of those treated with standard of care chemotherapy.[12] Administration of noncytotoxic therapies, such as blinatumomab, during life-threatening chemotherapy-associated adverse events has not been previously assessed, but may potentially aggravate toxicity due to B-cell depletion. Here we present a retrospective multicenter report of pediatric patients who received blinatumomab due to overwhelming chemotherapy-associated toxicity.

2 | RESULTS

The medical records of all children and young adults diagnosed with frontline or relapsed B-ALL in six hematology centers in Israel between May 1, 2015 and December 1, 2018 (n = 352) were retrospectively reviewed. Thirty-six patients were treated with blinatumomab. In 11 of these (30%), the indication for blinatumomab treatment was overwhelming chemotherapy-associated toxicity, causing prolonged delay of leukemia therapy. In these patients, blinatumomab was administered as a bridge to further therapy (Table 1). The median age was 6 years (range 2.5-17). Four patients had underlying genetic syndromes, including Down syndrome (DS) (n = 2), neurofibromatosis (n = 1), and psychomotor retardation with dysmorphic features (n = 1). In eight patients, toxicity occurred during frontline therapy of leukemia, and in three during treatment of late (n = 2) or early (n = 1) bone-marrow relapse. Toxicity occurred mainly during induction (n = 6), but also during delayed intensification (n = 2), high-risk Berlin Frankfurt Munster (BFM) consolidation (n = 1), FLAG-Ida salvage (n = 1), and high-dose methotrexate (n = 1, patient with DS). Five events were caused by gram-negative bacteria (three with extensive necrotizing fasciitis), in four events the main pathogen was fungal, and two patients had severe noninfectious gastrointestinal and pulmonary toxicity. Seven of 11 patients (64%) required prolonged intensive care unit admission with mechanical ventilation or vasopressor therapy, and 7/11 patients (64%) required several surgical interventions. The median time from toxicity presentation to blinatumomab was 50 days (range 15-90). The median interval without chemotherapy was 122 days (range 75-210 days). Several patients received

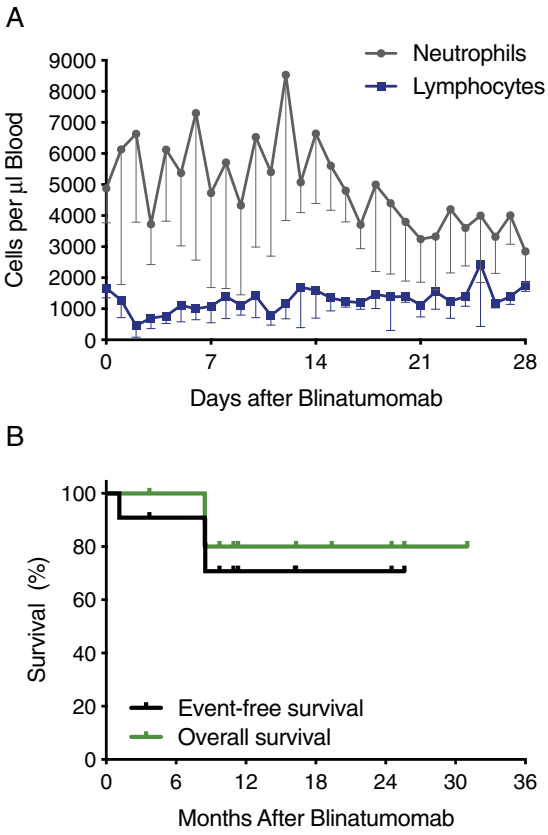

FIGURE 1 (A) The absolute neutrophil count (grey) and lymphocyte count (blue) in 11 patients during their first blinatumomab cycle; dots represent the median values, and whiskers the interquartile range. (B) Event-free survival (black line) and overall survival (green line) as measured from initiation of the first blinatumomab cycle in 11 patients treated for toxicity

blinatumomab while still in the intensive care unit, two patients while receiving mechanical ventilation, and five received blinatumomab while undergoing recurrent surgical interventions, such as abscess drainages, debridement procedures, complex facial reconstruction procedures, or gastrointestinal surgical interventions.

Since neutropenia was previously reported following blinatumomab in the R/R-ALL settings,[10,12] we reviewed complete blood count parameters during blinatumomab infusion. We noted an initial drop in lymphocytes occurring on the first day of treatment, as reported previously,[8] related to immune engagement and T-cell activation seen in these patients. We observed no events of significant neutropenia, defined as an absolute neutrophil count <500/μL (Figure 1A). Adverse events during blinatumomab included grade 2 (Common Terminology Criteria for Adverse Events version 4.0) seizures (n = 3), grade 2 encephalopathy (n = 1), and one event of *Staphylococcus aureus* bacteremia, treated with intravenous antibiotics only.

The goal of bridging to further therapy was achieved in all 11 patients, with resolution of toxic events. Four patients were able to resume standard chemotherapy protocols, four were unable to tolerate standard chemotherapy due to residual comorbidities and were therefore bridged to maintenance therapy, and three high-risk patients received allogeneic hematopoietic stem cell transplantation. Nine

TABLE 1 Patient characteristics, toxic events, and outcome

	Sex	Age (years)	Underlying syndrome	Frontline/ relapse	Treatment protocol	Timing of toxicity	Toxicity description	Treatment	Time to blinatumomab (days)	Blinatumomab cycles	Interval without chemotherapy (days)	Postblinatumomab treatment	Status	Follow-up (months)
1	F	2.5	None	Frontline	ALL-IC BFM 2009	Induction	*Pseudomonas aeruginosa*: sepsis and extensive facial necrotizing fasciitis	ICU, debridement procedures, facial reconstruction with skin grafts	30	2	120	Chemotherapy: AIEOP BFM ALL 2009	Alive CR1	26+
2	M	2	None	First early relapse	IntreALL HR	Relapse HR blocks	*P. aeruginosa*: extensive necrotizing fasciitis of perianal area	ICU, debridement procedures	15	1	75	alloSCT	Alive CR2	25+
3	M	3	None	Frontline	AIEOP BFM ALL 2009	Induction	*Acinetobacter baumannii* sepsis and ARDS with extensive perianal necrotizing fasciitis	ICU, ventilation, tracheostomy, surgical debridement procedures	65	1	100	Chemotherapy: AIEOP BFM ALL 2009	Alive CR1	10+
4	F	15	None	Frontline	AIEOP BFM ALL 2009	Delayed intensification	*Escherichia coli* septic shock with multiple soft tissue abscesses	ICU, ventilation, vasopressors, prolonged hemodialysis, surgical drainage	90	2	180	Maintenance	Alive CR1	11+
5	M	3	DS	Frontline	AIEOP BFM ALL 2009	High-dose MTX	*Klebsiella oxytoca* sepsis, severe mucositis, *Clostridium difficile* colitis	Prolonged IV antibiotics	30	2	122	Maintenance	Alive CR1	12+
6	M	6	None	Frontline	AIEOP BFM ALL 2009	After FLAG-Ida	*Candida tropicalis*, disseminated	Prolonged antifungal treatment	55	1	110	alloSCT	Alive CR1	4+

(Continues)

TABLE 1 (Continued)

	Sex	Age (years)	Underlying syndrome	Frontline/ relapse	Treatment protocol	Timing of toxicity	Toxicity description	Treatment	Time to blinatumomab (days)	Blinatumomab cycles	Interval without chemotherapy (days)	Postblinatumomab treatment	Status	Follow-up (months)
7	M	17	NF1	Frontline	AIEOP BFM ALL 2009 and then NOPHO AML 2012	Induction	Rhinocerebral mucormycosis and pulmonary aspergillosis	Debridement procedures, resection of right lung cavitation.	60	1	210	alloSCT	Death of TRM (GVHD)	8.5
8	F	13.5	None	Frontline	EsPhALL	Induction	Disseminated mucormycosis	ICU, vasopressors, mechanical ventilation, surgical procedures	40	4	135	Chemotherapy trial, and then maintenance	Alive CR1	20+
9	F	2.5	Psychomotor retardation and dysmorphism	Frontline	AIEOP BFM ALL 2009	Induction	Candida sepsis, hepatosplenic and pulmonary candidiasis, *Enterobacter cloacae* sepsis, cardiac failure, prolonged myelosuppression	Prolonged antibiotics, diuretics, beta blockers, ACE inhibitors	60	2	165	Maintenance	Death of pneumococcal sepsis during maintenance	8.5
10	F	9	DS	First late relapse	IntreALL SR	Delayed intensification	Severe prolonged pneumonitis with hemodynamic instability	ICU, ventilation, and vasopressors	50	1	140	Chemotherapy: IntreALL SR	Alive CR2	16+
11	F	8	None	First late relapse	IntreALL SR	Induction	Intestinal perforation and intra-abdominal abscess	ICU, laparotomy: resection of cecum with ileostomy, drainage procedures	40	1	90	Chemotherapy; after relapse 2 treated with CAR-T and alloSCT	Alive CR3	31+

Abbreviations: ACE, angiotensin converting enzyme; ALL, acute lymphoblastic leukemia; alloSCT, allogeneic stem cell transplantation BFM, Berlin Frankfurt Munster; CAR-T, chimeric antigen receptor T-cells; CR, complete remission; DS, Down syndrome; GVHD, graft versus host disease; ICU, intensive care unit; MTX, methotrexate; NF1, neurofibromatosis type 1; TRM, treatment-related mortality.
Note. Treatment protocols: ALL-IC BFM 2002 (NCT00764907), AIEOP BFM ALL 2009 (NCT01117441), EsPhALL2010 (NCT00287105), NOPHO DBH AML 2012 (NCT01828489), IntreALL SR (NCT01802814), and FLAG-Ida (NCT00487448).

patients with MRD-negative disease prior to blinatumomab retained this status. Of two treated with measurable MRD, one had an MRD-negative response and one patient had no MRD response and developed active extramedullary disease at the end of the first blinatumomab cycle, further treated with chemotherapy and CD19 chimeric antigen receptor T cells.[13] Two patients eventually died of toxicities following subsequent treatment phases—one of septic shock during maintenance and one of transplant-related toxicity. Beside the aforementioned patient with extramedullary progression, no disease relapse occurred. With a median follow-up of 12 months, the 1-year event-free and overall survival for these 11 patients were 71% and 80%, respectively (Figure 1B).

3 | DISCUSSION

In this retrospective multicenter national study, we report 11 pediatric patients with B-ALL who received blinatumomab due to overwhelming chemotherapy-induced toxicity, causing prolonged therapy delay. In six of 11 patients (55%), this exceptional toxicity occurred during the first month of leukemia treatment. All 11 patients were successfully bridged to further therapy, with toxicity resolution.

When do treatment delays compromise outcome? Progress in ALL has been achieved through collaborative randomized clinical trials,[1] and adherence to treatment protocols is of paramount importance. Yet, delays in treatment occur almost universally,[14,15] and the risk of developing at least one serious adverse event during childhood ALL therapy has been reported to be between 35% and 50%.[16,17] Modest delays caused by myelosuppression are expected, and guidelines are provided by protocols to delay further therapy until resolution. There is limited information regarding the impact of therapy delays on the risk of leukemia relapse. Several studies did not find a higher risk of relapse in patients with longer cumulative therapy delays throughout treatment,[14,18,19] but treatment interruptions were primarily due to expected toxicity, mostly hematological, which may may have been due to general germline sensitivity to the regimen. During maintenance therapy, interruptions due to myelosuppression have been found to predict superior event-free survival.[20] Conversely, significant unexpected delays were associated with worse outcome in several studies from developed[15] and developing countries.[21] Therefore, very rare cases of overwhelming toxicity causing months of therapy delay, such as the cases reported in this study, are a cause for consternation. Only in these rare cases should alternative therapies be considered.

Blinatumomab was administered to patients at the time of recovery from overwhelming toxicity. Lack of significant neutropenia in patients treated for toxicity may be related to the baseline higher neutrophil count, prolonged gap since last cytotoxic chemotherapy, and low overall disease burden in these patients, most being MRD negative, leading to less immune activation and cytokine-release-syndrome-associated cytopenia.[22] Despite infectious complications reported in R/R patients treated with blinatumomab,[9,10,12] no new fatal or life-threatening infections were reported during the treatment course of these 11 patients, notwithstanding their debilitated condition. Treatment with blinatumomab enabled recovery from chemotherapy-induced toxicity and bridging to further treatment.

Prospective clinical studies in both relapsed and newly diagnosed patients with B-ALL will help define the optimal role of blinatumomab in the cure of high-burden leukemia and in decreasing treatment-related toxicity. Meanwhile, data concerning blinatumomab administration in children are still limited.[9] In this first report of blinatumomab therapy during profound chemotherapy-associated toxicity, we show that blinatumomab is safe for pediatric patients, even in the presence of overwhelming infectious complications, and can be considered as a bridging therapy for rare patients who cannot tolerate cytotoxic therapy.

ACKNOWLEDGMENTS

This work was supported by the Israeli Society of Pediatric Hematology-Oncology, the Israel Cancer Association, and Amutat Chaim. We thank Dina Kugel for the data collection. We wish to acknowledge all pediatric hematology-oncology departments in Israel for their devoted care of these patients.

AUTHOR CONTRIBUTIONS

Study conception and design: Elitzur and Jacoby. Collection and assembly of data: Elitzur, Arad-Cohen, Barzilai-Birenboim, Ben-Harush, Bielorai, Elhasid, Feuerstein, Gilad, Gural, Kharit, Litichever, Weinreb, Wolach, Toren, Izraeli, and Jacoby. Data analysis and interpretation: Elitzur, Nirel, and Jacoby. Manuscript writing: Elitzur and Jacoby. Final approval of manuscript: all authors.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

ORCID

Sarah Elitzur https://orcid.org/0000-0002-3495-7578
Bella Bielorai https://orcid.org/0000-0003-3066-6439
Ronit Elhasid https://orcid.org/0000-0002-5663-6919
Elad Jacoby https://orcid.org/0000-0003-1411-8942

REFERENCES

1. Pui C-H, Yang JJ, Hunger SP, et al. Childhood acute lymphoblastic leukemia: progress through collaboration. *J Clin Oncol*. 2015;33(27):2938-2948.
2. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med*. 2015;373(16):1541-1552.
3. Hough R, Vora A. Crisis management in the treatment of childhood acute lymphoblastic leukemia: putting right what can go wrong (emergency complications of disease and treatment). *Hematol Am Soc Hematol Educ Program*. 2017;2017(1):251-258.
4. Boissel N, Baruchel A. Acute lymphoblastic leukemia in adolescent and young adults: treat as adults or as children? *Blood*. 2018;132(4):351-361.
5. Izraeli S, Vora A, Zwaan CM, Whitlock J. How I treat ALL in Down' s syndrome: pathobiology and management. *Blood*. 2014;123(1):35-40.

6. Schmiegelow K. Treatment-related toxicities in children with acute lymphoblastic leukaemia predisposition syndromes. *Eur J Med Genet*. 2016;59(12):654-660.
7. Dreier T, Baeuerle PA, Fichtner I, et al. T cell costimulus-independent and very efficacious inhibition of tumor growth in mice bearing subcutaneous or leukemic human B cell lymphoma xenografts by a CD19-/CD3-bispecific single-chain antibody construct. *J Immunol*. 2003;170(8):4397-4402.
8. Bargou R, Leo E, Zugmaier G, et al. Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. *Science*. 2008;321(5891):974-977.
9. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med*. 2017;376(9):836-847.
10. Von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *J Clin Oncol*. 2016;34(36):4381-4389.
11. Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood*. 2018;131(14):1522-1531.
12. Stein AS, Larson RA, Schuh AC, et al. Exposure-adjusted adverse events comparing blinatumomab with chemotherapy in advanced acute lymphoblastic leukemia. *Blood Adv*. 2018;2(13):1522-1531.
13. Jacoby E, Bielorai B, Avigdor A, et al. Locally produced CD19 CAR T cells leading to clinical remissions in medullary and extramedullary relapsed acute lymphoblastic leukemia. *Am J Hematol*. 2018;93(12):1485-1492.
14. Yeoh A, Collins A, Fox K, et al. Treatment delay and the risk of relapse in pediatric acute lymphoblastic leukemia. *Pediatr Hematol Oncol*. 2017;34(1):38-42.
15. Kumar AJ, Gimotty PA, Gelfand JM, et al. Delays in postremission chemotherapy for Philadelphia chromosome negative acute lymphoblastic leukemia are associated with inferior outcomes in patients who undergo allogeneic transplant: an analysis from ECOG 2993/MRC UK ALLXII. *Am J Hematol*. 2016;91(11):1107-1112.
16. Toft N, Birgens H, Abrahamsson J, et al. Toxicity profile and treatment delays in NOPHO ALL2008—comparing adults and children with Philadelphia chromosome-negative acute lymphoblastic leukemia. *Eur J Haematol*. 2016;96(2):160-169.
17. Hough R, Rowntree C, Goulden N, et al. Efficacy and toxicity of a paediatric protocol in teenagers and young adults with Philadelphia chromosome negative acute lymphoblastic leukaemia: results from UKALL 2003. *Br J Haematol*. 2016;172(3):439-451.
18. Koka A, Saygin C, Uzunaslan D, Ozdemir N, Apak H, Celkan T. A 17-year experience with ALL-BFM protocol in acute lymphoblastic leukemia: prognostic predictors and interruptions during protocol. *Leuk Res*. 2014;38(6):699-705.
19. Stock W, La M, Sanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. *Blood*. 2008;112(5):1646-1654.
20. Chessells JM, Harrison G, Lilleyman JS, Bailey CC, Richards SM. Continuing (maintenance) therapy in lymphoblastic leukaemia: lessons from MRC UKALL X. *Br J Haematol*. 1997;98(4):945-951.
21. Suarez A, Piña M, Nichols-Vinueza DX, et al. A strategy to improve treatment-related mortality and abandonment of therapy for childhood ALL in a developing country reveals the impact of treatment delays. *Pediatr Blood Cancer*. 2015;62(8):1395-1402.
22. Teachey DT, Rheingold S, Maude SL, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. *Blood*. 2013;121(26):5154-5158.

How to cite this article: Elitzur S, Arad-Cohen N, Barzilai-Birenboim S, et al. Blinatumomab as a bridge to further therapy in cases of overwhelming toxicity in pediatric B-cell precursor acute lymphoblastic leukemia: Report from the Israeli Study Group of Childhood Leukemia. *Pediatr Blood Cancer*. 2019;e27898. https://doi.org/10.1002/pbc.27898