Title

Clinical utilization of blinatumomab and inotuzumab immunotherapy in children with relapsed or refractory B-acute lymphoblastic leukemia

Journal

Pediatric Blood & Cancer, 68(1)

ISSN

1545-5009

Authors

Contreras, Cristina F
Higham, Christine S
Behnert, Astrid
et al.

Publication Date

2021

DOI

10.1002/pbc.28718

Peer reviewed

HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

Pediatr Blood Cancer. 2021 January ; 68(1): e28718. doi:10.1002/pbc.28718.

Clinical Utilization of Blinatumomab and Inotuzumab Immunotherapy in Children with Relapsed or Refractory B-Acute Lymphoblastic Leukemia

Cristina F Contreras[1], **Christine S Higham**[2], **Astrid Behnert**[3], **Kailyn Kim**[4], **Elliot Stieglitz**[3], **Sarah K Tasian**[1,5]

[1]Children's Hospital of Philadelphia, Division of Oncology and Center for Childhood Cancer Research; Philadelphia, Pennsylvania

[2]University of California, San Francisco Benioff Children's Hospital and School of Medicine, Pediatrics, Division of Pediatric Bone Marrow Transplantation; San Francisco, California

[3]University of California, San Francisco Benioff Children's Hospital and School of Medicine, Pediatrics, Division of Hematology-Oncology; San Francisco, California

[4]Sidney Kimmel Medical College at Thomas Jefferson University; Philadelphia, Pennsylvania

[5]University of Pennsylvania Perelman School of Medicine, Department of Pediatrics and Abramson Cancer Center; Philadelphia, Pennsylvania

Abstract

Background: The treatment paradigm for patients with relapsed/refractory B-cell acute lymphoblastic leukemia (rrALL) has been revolutionized given recent clinical trials demonstrating remarkable success of immunotherapies and leading to drug approvals by United States and European agencies. We report experience with commercial blinatumomab and inotuzumab use at two North American pediatric oncology centers in children and adolescents/young adults with B-ALL.

Procedure: Patients 0–25 years-old treated with the CD19xCD3 bispecific T cell-engaging antibody blinatumomab and/or the CD22 antibody-drug conjugate inotuzumab from 1 January 2010 to 1 June 2018 were eligible. Disease status included relapsed B-ALL in second or greater relapse, primary chemotherapy-refractory B-ALL, or B-ALL complicated by severe infection precluding delivery of conventional chemotherapy.

Correspondence to: Elliot Stieglitz, MD, University of California, San Francisco Benioff Children's Hospital, 1450 3rd Street, Room 230, San Francisco, California 94158, Phone: 415.502.2649, Fax: 415.502.5127, elliot.stieglitz@ucsf.edu, Sarah K Tasian, MD, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, 3501 Civic Center Boulevard, CTRB 3010, Philadelphia, Pennsylvania 19104, Phone: 215.590.5476, Fax: 215.590.3770, tasians@email.chop.edu.
CFC, CSH, and AB contributed equally as first authors.
ES and SKT contributed equally as senior authors.

Author contributions: CFC, CSH, and AB collected and analyzed primary data and contributed to manuscript writing. KK analyzed data and assisted with figure preparation. ES and SKT designed and oversaw the study and wrote the manuscript. All authors approved the final manuscript submission.

Data availability: Data is available on request due to privacy/ethical restrictions.

Conflicts of Interest: The authors declare no relevant conflicts of interest.

Results: We identified 27 patients who received blinatumomab and/or inotuzumab outside of clinical trials during the study period. Four of the 13 patients (31%) with relapsed disease achieved MRD-negative remission, and 5 patients (39%) underwent HSCT. In the 12 patients with primary chemorefractory B-ALL treated with immunotherapy, 11 (92%) achieved minimal residual disease (MRD)-negative remission as assessed by flow cytometry; 10 patients (83%) underwent subsequent hematopoietic stem cell transplant (HSCT). Two patients with B-ALL in MRD-negative remission received blinatumomab due to severe infection and remained in remission after chemotherapy continuation.

Conclusions: Blinatumomab and inotuzumab can induce deep remissions in patients with rrALL and facilitate subsequent HSCT or other cellular therapies. Blinatumomab can also serve as an effective bridging therapy during severe infection. The optimal timing, choice of immunotherapeutic agent(s), and duration of responses require further investigation via larger-scale clinical trials.

Keywords

acute lymphoblastic leukemia; blinatumomab; immunotherapy; inotuzumab; hematopoietic stem cell transplantation

INTRODUCTION

B-acute lymphoblastic leukemia (B-ALL) is the most common malignancy of childhood with approximately 3500 new patients diagnosed annually in North America. While the majority of children and adolescents and young adults (AYAs) with B-ALL are cured with modern risk-stratified chemotherapy regimens, resulting in event-free survival (EFS) >85%,[1] outcomes for those patients who relapse or are refractory to frontline chemotherapy remain suboptimal. At first relapse, the most predictive prognostic variables for outcomes include duration of first remission and site of relapse. Early medullary relapse, defined by the Children's Oncology Group (COG) as <36 months from initial leukemia diagnosis and by the Berlin-Frankfurt-Münster (BFM) group as <18 months, is associated with worse outcomes.[2,3] Children with primary chemotherapy-refractory disease (particularly those with induction failure)[4] may benefit from allogeneic hematopoietic stem cell transplantation (HSCT) in first remission, although achievement of sufficiently low or negative minimal residual disease (MRD) with conventional cytotoxic chemotherapy to proceed to HSCT can be challenging. As expected, EFS and overall survival (OS) rates have been historically lower with subsequent relapse.[5] Intensive salvage therapies for patients with relapsed/refractory B-ALL (rrALL) are associated with appreciable infectious and end-organ sequelae,[6] emphasizing need for alternative therapeutic approaches to overcome chemoresistance and/or decrease toxicity.

New antibody-based immunotherapies targeting B-cell surface markers have demonstrated remarkable clinical activity in patients with rrALL, leading to United States FDA and EMA approval of several agents in recent years. Blinatumomab, a bispecific CD19 x CD3 T-cell engager (BiTE) antibody, links and directs endogenous CD3+ effector T-cells against CD19+ B-cells (malignant and non-malignant) to induce apoptosis.[7] Phase 1, 2, and 3 clinical trials of blinatumomab have demonstrated remission induction rates of >30% in

patients with rrALL.[8–12] Particular efficacy was demonstrated in patients with MRD-level disease as a bridge to HSCT with a recent study reporting achievement of MRD negativity in >78% of adults with rrALL and markedly improved relapse-free survival (RFS) and OS.[13] A retrospective study in pediatrics also demonstrated efficacy in eliminating MRD-level disease prior to HSCT.[14] A COG randomized phase 3 trial AALL1331 (NCT02101853) assessed potential non-inferiority of blinatumomab intercalation versus standard salvage chemotherapy upon RFS and OS in children and AYAs with first relapse of B-ALL,[15] as well as potential for decreasing salvage therapy-associated toxicity. Preliminary outcomes suggest an advantage for blinatumomab both in terms of higher rates of MRD-negative responses and decreased toxicity compared to conventional chemotherapy as post-reinduction consolidation prior to HSCT.[16]

The antibody-drug conjugate (ADC) inotuzumab ozogamicin is comprised of an anti-CD22 monoclonal antibody bound to the anti-tumor antibiotic calicheamicin. Inotuzumab was recently approved by the FDA and EMA for use in adults with rrALL based upon phase 2 and randomized phase 3 clinical trial data demonstrating 80.7% versus 29.7% remission re-induction rates in patients treated with inotuzumab or standard chemotherapy, respectively.[17,18] One study of 12 children with rrALL treated with compassionate-access inotuzumab in France reported complete or partial remission in 8 patients, although nine patients subsequently died of relapsed/progressive disease.[19] A more recent retrospective review of 51 pediatric patients with rrALL treated with inotuzumab via compassionate or commercial access reported a 67% CR rate. However, 11 of 21 (52%) of these heavily-pretreated patients who underwent subsequent HSCT developed sinusoidal obstructive syndrome (SOS), a higher than expected rate than was previously observed in adults with rrALL (11%).[18,20] The recent COG AALL1621 phase 2 trial (NCT02981628) studied the efficacy of inotuzumab in 48 uniformly-treated children and AYAs in second or greater relapse of B-ALL; preliminary outcomes show CR rates >50%, nearly two-thirds of whom achieved MRD negativity.[21] Preliminary results of the Dutch ITCC-059 study also showed remarkable efficacy of inotuzumab in pediatric patients with rrALL with an 80% overall response rate and 79% of responding patients achieving an MRD-negative CR.[22]

In the current retrospective study, we sought to determine (1) the rates of commercial blinatumomab and inotuzumab usage in children and AYAs with rrALL at two large academic North American pediatric oncology centers and (2) the ability to bridge patients successfully to subsequent allogeneic HSCT or other cellular immunotherapies.

METHODS

Patients

Patients aged 0–25 years treated with blinatumomab and/or inotuzumab from January 1, 2010 to June 1, 2018 at our institutions with clinical follow-up until June 1, 2019 were eligible for inclusion. Patients who received blinatumomab or inotuzumab on clinical trials (*e.g.*, COG AALL1331 or AALL1621) were excluded from this study. Subjects were classified as having primary chemotherapy-refractory ALL (MRD ≥0.01% after two or more induction attempts as assessed by flow cytometry), relapsed B-ALL in second or greater relapse, or ALL complicated by an acute infection precluding delivery of standard

myelosuppressive chemotherapy. Patients were coded with unique study identifiers (USIs). Medical records were reviewed to abstract clinical data, including age at initial leukemia diagnosis, sex, National Cancer Institute ALL risk status,[23] frontline chemotherapy regimen(s), age at leukemia diagnosis and/or relapse, salvage therapy regimens (chemotherapy, immunotherapy), bone marrow MRD quantification by flow cytometry (FC), MRD quantification by high-throughput sequencing of immunoglobulin rearrangements (HTS), and receipt of allogeneic HSCT. This study was approved by the Institutional Review Boards at the Children's Hospital of Philadelphia (CHOP) and the University of California, San Francisco (UCSF) Benioff Children's Hospital and conducted in accordance with the Declaration of Helsinki.

Evaluation of response

Patients' treatment responses to blinatumomab and inotuzumab were classified as CR if marrow demonstrated <5% blasts morphologically (M1). An additional category of MRD-negative CR (<0.01% by FC) was included. Some patients who were MRD-negative by FC were also assessed for MRD negativity by HTS of immunoglobulin heavy chain gene rearrangements.[24] Partial response (PR) was defined as a reduction in blasts from M3 (>25%) to M2 (5–25%). Progressive disease (PD) was defined as an increase of at least 25% blasts by absolute number of blasts. Stable disease (SD) was defined as patients who did not satisfy requirements for CR or PR.

Evaluation of toxicity

Adverse events of interest including neurotoxicity, cytokine release syndrome, sinusoidal obstructive syndrome and tumor lysis syndrome were graded using the Common Terminology Criteria for Adverse Events, version 4.

RESULTS

We identified 27 patients who received commercial blinatumomab and/or inotuzumab during the study period from 2010 to 2018 (Figure 1). Five patients received both agents at different points in their care. At the time of initial *de novo* B-ALL diagnosis, patients were a median age of 9.2 years (0.4–29.2). Seventeen of the 27 (63%) were male, 10 were NCI standard risk (SR; 37%), 17 were NCI high risk (HR; 63%), and 21/27 (78%) were CNS 1 at diagnosis (Table 1).

At the time of blinatumomab and/or inotuzumab administration, 13 (48%) were in first or greater relapse, 12 (44%) patients were classified as refractory (MRD ≥0.01% after two or more induction attempts), and two (7%) patients had B-ALL complicated by an acute infection that precluded administration of standard-of-care cytotoxic chemotherapy (Table 2, Supplemental Table 1). The median number of cycles for each immunotherapy agent was one (range 1–4). Individual clinical courses and outcomes are shown in Figure 2. Representative patients from each of the three disease classifications are presented below as illustrative teaching cases prior to summary data for this case series.

(1) Immunotherapy treatment of a patient with relapsed B-ALL

Patient CHOP26 was diagnosed with HR B-ALL in 2014 at 6 years of age after presenting with fatigue, hepatomegaly, and a white blood cell (WBC) count of 5,270 cells/mm^3 with 7% peripheral blasts. She had no extramedullary disease (CNS1), and leukemia cytogenetics and FISH analysis of her bone marrow showed trisomy 5. She received a three-drug induction on COG study AALL0932, had EOI FC MRD of 1.1%, was reclassified as very high risk, and was treated with post-induction therapy as per COG study AALL1131. She had persistent low-level MRD at end of consolidation (0.09%) and mid-interim maintenance (0.013%) that was below institutional standard-of-care recommendations at the time for HSCT in CR1 in a patient with initially SR B-ALL,[25] and she completed chemotherapy as per AALL1131. She subsequently experienced a late medullary relapse in 2017 at 12 months off therapy (39 months from initial diagnosis) and was re-induced with UKALLR3 therapy on COG study AALL1331.[16,26] She had end-reinduction FC MRD of 2.5% and was removed from study to pursue definitive immunotherapy given concerns for chemoresistant disease. She achieved MRD 0% after one cycle of inotuzumab and was recommended to undergo 10/10 HLA-matched allogeneic HSCT. Family declined allogeneic HSCT due to toxicity concerns, and the patient subsequently received CD19-redirected chimeric antigen receptor T cells (CD19CART) in an MRD-negative state in lieu of transplant. She had early B cell recovery at 4.5 months after CD19CART, received a second infusion of CD19CART in an MRD-negative remission without re-induction of normal B cell aplasia, and remains in continued MRD-negative remission at 16 months post-inotuzumab (13 months after initial dosing of CD19CART).

(2) Immunotherapy treatment of a patient with primary chemotherapy-refractory B-ALL

Patient UCSF2 was diagnosed with HR B-ALL in 2016 at 11 years of age after presenting with a WBC count of 200,000. He had no extramedullary disease (CNS1). Leukemia cytogenetics, FISH, and molecular analyses showed a normal male karyotype without detected fusions or other pathogenic mutations. He received a four-drug induction as per COG AALL1131 and had flow cytometric EOI MRD of 15.9%. MRD by FC at the end of consolidation, interim maintenance, and delayed intensification chemotherapy were 0.5%, 0.78% and 0.14%, respectively. Given his persistent MRD positivity, he was treated with blinatumomab with goal of subsequent HSCT. He achieved MRD negativity (0%) after one cycle of blinatumomab without appreciable side effects and then underwent haploidentical transplantation from his mother. He remains in continued clinical CR at 26 months post-HSCT.

(3) Immunotherapy ‘bridging’ treatment of a patient with de novo B-ALL and systemic fungal infection

Patient UCSF4 was diagnosed with SR B-ALL in 2017 at 23 months old after presenting with pancytopenia with a WBC count of 2.6 and 7% peripheral blasts. He had microscopic evidence of CNS leukemia involvement (CNS2b) and no other sites of extramedullary disease. He received a three-drug induction therapy as per AALL0932 and cleared his CSF with intrathecal chemotherapy. Day 8 peripheral blood and day 29 marrow FC MRD were 0.044% and 0%, respectively. His post-induction course was complicated by invasive

mucormycosis of the sinuses, requiring prolonged anti-fungal therapy with liposomal amphotericin and caspofungin and extensive surgical debridement with anterior skull base resection for graft reconstruction. Given this infectious severity and risk of prolonged neutropenia with usual post-induction cytotoxic chemotherapy, he received one cycle of blinatumomab during active medical and surgical management of his *Mucor* infection. He tolerated blinatumomab well without toxicity, and his marrow remained MRD-negative prior to resumption of post-induction therapy as per AALL0932. He is currently in maintenance and in continued clinical remission at 22 months from diagnosis.

Relapsed disease—Among the 13 patients with multiply-relapsed disease, the median percent of bone marrow blasts by FC prior to therapy was 51.8% (0.08–98) and 21.0% (0.0–97.9) post-therapy. Best response was categorized as MRD-negative CR for 4 patients (31%, 1 following blinatumomab, 3 following inotuzumab), morphologic CR for 1 patient (8%) who received both blinatumomab and inotuzumab, PR for 1 patient (8%) following inotuzumab, SD for 2 patients (15%) after inotuzumab, and PD for 5 patients (39%, 1 following blinatumomab, 2 after inotuzumab, and 2 after both blinatumomab and inotuzumab). Four of the 13 patients (31%) underwent HSCT after inotuzumab (n=3 patients) or blinatumomab (n=1) therapy. Five of the 13 patients also received CD19CART and/or CD22CART following inotuzumab or blinatumomab, four of them intended as definitive therapy without planned subsequent HSCT (Table 2, Figure 1). Two of the 5 patients who achieved CR were alive and in continued remission with a median of 21.9 months at the time of last follow-up (Table 2, Figure 2).

Refractory disease—In the 12 patients with refractory B-ALL, the median percent blasts by FC pre- and post-therapy was 3.35% (range 0.0–53%) and 0% (0.0–50%), respectively. Eleven patients (92%) achieved MRD-negative CR as best response, while one patient (8%) experienced progressive disease on blinatumomab and then achieved a morphologic CR with inotuzumab with negative FC MRD in a hypocellular marrow. Four patients with negative MRD by FC were assessed by HTS after treatment with blinatumomab, and two (50%) were also MRD-negative by HTS. Ten of the 12 patients (83%; 9 of whom received blinatumomab, one of whom received blinatumomab and then inotuzumab prior to transplant) underwent subsequent HSCT. One patient received CD19CART after receipt of both blinatumomab and inotuzumab (Figure 1). Eleven of the 12 patients (92%) are alive and in continuous CR with a median of 25.3 months at the time of last follow-up (Table 2, Figure 2).

Severe infection precluding systemic chemotherapy—Two patients with B-ALL received blinatumomab as bridging therapy due to severe infection in this study. One patient had *de novo* disease and developed an invasive systemic fungal infection as described above in the third vignette. The other patient had relapsed disease and achieved an MRD-negative response with UKALL R3 reinduction chemotherapy as per AALL1331,[26] but developed an intercurrent *severe Pseudomonas* peri-rectal abscess requiring multiple surgical debridements and diverting colostomy. The patient then received one cycle of blinatumomab while recovering from her infection before proceeding to allogeneic HSCT. Both patients were in MRD-negative remission before and after blinatumomab and remain alive in

continued clinical CR at the time of final study follow-up at 20.7 and 16.6 months, respectively (Table 2, Figure 2).

Adverse effects of immunotherapy—Ten of the 27 patients (37%) had adverse events during immunotherapy (summarized in Table 3). Of those 18 patients who received blinatumomab, six developed CRS (grade 1, n=2; grade 2, n=1, grade 3, n=2; grade 4, n=1). Four patients experienced neurologic complications, one of which was classified as grade 4. One patient treated with blinatumomab and one patient with inotuzumab experienced moderate SOS treated with defibrotide, both occurring post-HSCT. No patients experienced TLS as a result of blinatumomab or inotuzumab immunotherapy.

DISCUSSION

In this two-institution case series, we highlight the short- and long-term therapeutic potential of two now FDA-approved CD19 or CD22 antibody-based immunotherapies in a variety of clinical scenarios for children with B-ALL: (1) relapsed disease, (2) primary chemotherapy-refractory disease, and (3) non-myeloablative bridging therapy in the setting of severe infection. The alternative mechanisms of action of immunotherapies that can successfully overcome chemoresistance in patients with leukemia has shifted the therapeutic paradigm and facilitated MRD negativity prior to HSCT that is essential to maximize long-term cure.[24] A relatively new dilemma for pediatric hematologist/oncologists is how to prioritize available commercial or investigational immunotherapies for patients with rrALL, including blinatumomab, inotuzumab, and cellular therapies to achieve deep and durable remission, maximize EFS and OS, and potentially minimize treatment-associated toxicity.

Currently-approved immunotherapies for patients with B-ALL target B cell antigens CD19 and CD22. CD19 is near-universally expressed at high level in childhood B-ALL, while CD22 surface expression can be more variable, particularly in specific genetic subtypes of B-ALL.[27,28] In comparison to CAR T cell immunotherapy, blinatumomab and inotuzumab are ‘off-the-shelf’ products that are immediately available for use and have been associated with a lower incidence of CRS. While blinatumomab or inotuzumab monotherapy has not generally been used as definitive therapy without subsequent allogeneic HSCT,[10,20] our results demonstrate that these agents can be effectively used to induce often-deep MRD negativity and facilitate prompt HSCT, which has been shown to improve outcomes for many patients.[24,29,30]

While often well-tolerated, blinatumomab and inotuzumab can be associated with serious side effects. CNS toxicity has been reported in up to 10% of patients treated with blinatumomab.[10] Neurotoxicity symptoms range from headache and disorientation to seizure, encephalopathy, and aphasia. Symptoms usually resolve shortly after interruption of treatment. In our cohort, we observed blinatumomab-associated neurotoxicity in 22% of treated patients, the majority of which were <= grade 3 and resolved spontaneously or with supportive care. Only one patient experienced grade 4 neurotoxicity (encephalopathy) that fully resolved with temporary pausing of blinatumomab infusion. High-grade CRS was rare in our population (three patients with grade 3 or 4 CRS) and generally did not require dose modifications to blinatumomab or inotuzumab.

Hepatotoxicity with SOS is a known adverse effect of inotuzumab ozogamicin that can be life-threatening, particularly when administered in close proximity to HSCT.[18,20,21] SOS is caused by damage to the hepatic endothelium that causes blood extravasation through the space of Disse with consequent downstream obstruction and hemorrhagic necrosis.[31] The precise mechanism for inotuzumab-associated SOS remains unknown, but is thought likely due to its conjugation with calicheamicin that has been linked to SOS in patients with AML treated with gemtuzumab.[32] SOS occurrence can be delayed and has been reported up to two years after HSCT, most frequently following dual-alkylator conditioning regimens.[31,33,34] Current strategies to prevent SOS include limiting number of inotuzumab cycles, avoiding concomitant hepatotoxic medications and dual-alkylator HSCT conditioning, and prophylactic use ursodiol and/or defibrotide.[35] In our study, we observed SOS in one patient treated with inotuzumab and one patient treated with blinatumomab, both occurring post-transplant and treated successfully with defibrotide and supportive care. While one patient (UCSF21; treated with inotuzumab) did not receive a dual-alkylator conditioning regimen, the other patient (UCSF22; treated with blinatumomab) received both total body irradiation and cyclophosphamide, which may have contributed to SOS pathology.

In summary, we report a ‘real-world’ experience at two large academic pediatric centers using blinatumomab and inotuzumab for several indications in children and adolescents with B-ALL. While our study is limited by its retrospective nature, small patient numbers, and shorter-term follow-up, it highlights the remarkable potential of pediatric oncologists’ new armamentarium of immunotherapeutic options that can now be commercially accessed. Patients with NCI high-risk B-ALL MRD positivity after two induction attempts (EOC timepoint) are known to have higher rates of relapse and poor survival compared to their MRD-negative counterparts and are thus often allocated to HSCT,[36] but historically have unable to achieve deep MRD-negative remissions with additional cytotoxic chemotherapy. Similarly, patients who are MRD-negative prior to HSCT have superior outcomes compared to those who are transplanted with disease.[24,36] The conversion to MRD negativity by FC in patients with primary refractory B-ALL in 11 of 12 patients using primarily blinatumomab is a particularly promising finding in our series. We further show that blinatumomab can convert patients from FC-MRD positivity to HTS-MRD negativity, which may be associated with improved outcomes.[37] In this study, children with multiply-relapsed B-ALL also benefited from blinatumomab or inotuzumab therapy; conversion to MRD negativity was less frequent, but still allowed for definitive treatment with HSCT or CAR T cell immunotherapy in certain patients. We predict that these off-the-shelf immunotherapies may be particularly useful in heavily-pretreated patients in whom T cell pheresis for cellular immunotherapy is unsuccessful. Lastly, blinatumomab also offered a non-myelosuppressive alternative for patients with B-ALL and severe opportunistic infections, which allowed delivery of effective anti-fungal therapy while not compromising continued delivery of effective anti-leukemia therapy. In summary, immunotherapy with the FDA- and EMA-approved agents blinatumomab and inotuzumab offer novel treatment options for rrALL patients who have not adequately benefited from conventional chemotherapy. The optimal timing and sequence of antibody-based and cellular immunotherapies in children and AYAs with relapsed/refractory or newly-diagnosed B-ALL remains incompletely elucidated, and

ongoing or soon-to-open clinical trials investigating these agents will likely yield new insights in the coming years.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

This study was supported by institutional funding at the Children's Hospital of Philadelphia (CFC), German Cancer Aid (AB), an Alex's Lemonade Stand Foundation Center of Excellence award to UCSF (ES), the Frank A Campini Foundation (ES), and NIH/NCI K08CA184418 and 1U01CA232486 (SKT). This study is dedicated in honor of Adelaide Kanton.

ABBREVIATIONS LIST

ADC	antibody-drug conjugate
AYAs	adolescents and young adults
B-ALL	B-acute lymphoblastic leukemia
BFM	Berlin-Frankfurt-Münster
BiTE	bispecific T-cell engager
CAR	chimeric antigen receptor
CD19CART	CD19-redirected chimeric antigen receptor T cell immunotherapy
CD22CART	CD22-redirected chimeric antigen receptor T cell immunotherapy
CHOP	Children's Hospital of Philadelphia
CNS	central nervous system
COG	Children's Oncology Group
CR	complete remission
CRS	cytokine release syndrome
EFS	event-free survival
EMA	European Medicines Agency
EOI	end of induction
FC	flow cytometry
FDA	Food and Drug Administration
HSCT	hematopoietic stem cell transplant
HTS	high-throughput sequencing (next-generation sequencing)

MRD	minimal residual disease
OS	overall survival
PD	progressive disease
PR	partial response
RFS	relapse-free survival
rrALL	relapsed/refractory acute lymphoblastic leukemia
SD	stable disease
SOS	sinusoidal obstructive syndrome
TLS	tumor lysis syndrome
UCSF	University of California, San Francisco
USI	unique study identifier

REFERENCES

1. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. N Engl J Med. 2015;373(16):1541–1552. [PubMed: 26465987]
2. Nguyen K, Devidas M, Cheng SC, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. Leukemia. 2008;22(12):2142–2150. [PubMed: 18818707]
3. Tallen G, Ratei R, Mann G, et al. Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: results of trial ALL-REZ BFM 90. J Clin Oncol. 2010;28(14):2339–2347. [PubMed: 20385996]
4. Schrappe M, Hunger SP, Pui CH, et al. Outcomes after induction failure in childhood acute lymphoblastic leukemia. N Engl J Med. 2012;366(15):1371–1381. [PubMed: 22494120]
5. Sun W, Malvar J, Sposto R, et al. Outcome of children with multiply relapsed B-cell acute lymphoblastic leukemia: a therapeutic advances in childhood leukemia & lymphoma study. Leukemia. 2018.
6. Salzer WL, Burke MJ, Devidas M, et al. Toxicity associated with intensive postinduction therapy incorporating clofarabine in the very high-risk stratum of patients with newly diagnosed high-risk B-lymphoblastic leukemia: A report from the Children's Oncology Group study AALL1131. Cancer. 2018;124(6):1150–1159. [PubMed: 29266189]
7. Loffler A, Gruen M, Wuchter C, et al. Efficient elimination of chronic lymphocytic leukaemia B cells by autologous T cells with a bispecific anti-CD19/anti-CD3 single-chain antibody construct. Leukemia. 2003;17(5):900–909. [PubMed: 12750704]
8. Topp MS, Kufer P, Gokbuget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol. 2011;29(18):2493–2498. [PubMed: 21576633]
9. Topp MS, Gokbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol. 2015;16(1):57–66. [PubMed: 25524800]
10. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med. 2017;376(9):836–847. [PubMed: 28249141]

11. Martinelli G, Boissel N, Chevallier P, et al. Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome-Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study. J Clin Oncol. 2017;35(16):1795–1802. [PubMed: 28355115]
12. 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. [PubMed: 27998223]
13. Gokbuget 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. [PubMed: 29358182]
14. Keating AK, Gossai N, Phillips CL, et al. Reducing minimal residual disease with blinatumomab prior to HCT for pediatric patients with acute lymphoblastic leukemia. Blood Adv. 2019;3(13):1926–1929. [PubMed: 31243002]
15. Hogan LB, Bhatla T, Rheingold S, et al. Induction Toxicities Are More Frequent in Young Adults Compared to Children Treated on the Children's Oncology Group (COG) First Relapse B-Lymphoblastic Leukemia Clinical Trial AALL1331. Blood. 2018;132. [PubMed: 29866817]
16. Brown PA, Ji L, Xu X, et al. A Randomized Phase 3 Trial of Blinatumomab Vs. Chemotherapy As Post-Reinduction Therapy in High and Intermediate Risk (HR/IR) First Relapse of B-Acute Lymphoblastic Leukemia (B-ALL) in Children and Adolescents/Young Adults (AYAs) Demonstrates Superior Efficacy and Tolerability of Blinatumomab: A Report from Children's Oncology Group Study AALL1331. Blood. 2019;134(Supplement_2):LBA-1-LBA-1.
17. Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. Lancet Oncol. 2012;13(4):403–411. [PubMed: 22357140]
18. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. N Engl J Med. 2016;375(8):740–753. [PubMed: 27292104]
19. Calvo C, Cabannes-Hamy A, Adjaoud D, et al. Inotuzumab ozogamicin compassionate use for French paediatric patients with relapsed or refractory CD22-positive B-cell acute lymphoblastic leukaemia. Br J Haematol. 2020;190(1):e53–e56. [PubMed: 32424837]
20. Bhojwani D, Sposto R, Shah NN, et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. Leukemia. 2018.
21. O'Brien MM, Ji L, Shah NN, et al. A Phase 2 Trial of Inotuzumab Ozogamicin (InO) in Children and Young Adults with Relapsed or Refractory (R/R) CD22+ B-Acute Lymphoblastic Leukemia (B-ALL): Results from Children's Oncology Group Protocol AALL1621. Blood. 2019;134(Supplement_1):741–741. [PubMed: 31243041]
22. Brivio E, Lopez-Yurda M, Ownes C, et al. A Phase I Study of Single-Agent Inotuzumab Ozogamicin in Pediatric CD22-Positive Relapsed/Refractory Acute Lymphoblastic Leukemia: Preliminary Results of the ITCC-059 Study. Blood. 2019;134(Supplement_1):2629–2629.
23. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. J Clin Oncol. 1996;14(1):18–24. [PubMed: 8558195]
24. Wood B, Wu D, Crossley B, et al. Measurable residual disease detection by high-throughput sequencing improves risk stratification for pediatric B-ALL. Blood. 2018;131(12):1350–1359. [PubMed: 29284596]
25. Rachel Rau YD, Meenakshi Devidas, Karen Rabin, Patrick Zweidler-McKay, Anne Angiolillo, Reuven Schore, Michael Burke, Wanda Salzer, Nyla Heerema, Andrew Carroll, Naomi Winick, Steven Hunger, Elizabeth Raetz, Mignon Loh, Brent Wood, Michael Borowitz. IMPACT OF MINIMAL RESIDUAL DISEASE AT END CONSOLIDATION IN STANDARD RISK B-LYMPHOBLASTIC LEUKEMIA. Pediatric blood & cancer. 2019;66(S2):e27713. [PubMed: 30950178]
26. Parker C, Krishnan S, Hamadeh L, et al. Outcomes of patients with childhood B-cell precursor acute lymphoblastic leukaemia with late bone marrow relapses: long-term follow-up of the ALLR3 open-label randomised trial. Lancet Haematol. 2019;6(4):e204–e216. [PubMed: 30826273]

27. Fry TJ, Shah NN, Orentas RJ, et al. CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. Nat Med. 2018;24(1):20–28. [PubMed: 29155426]

28. Ramakrishna S, Highfill SL, Walsh Z, et al. Modulation of Target Antigen Density Improves CAR T-cell Functionality and Persistence. Clin Cancer Res. 2019;25(17):5329–5341. [PubMed: 31110075]

29. Brown P, Zugmaier G, Gore L, Tuglus CA, von Stackelberg A. Day 15 bone marrow minimal residual disease predicts response to blinatumomab in relapsed/refractory paediatric B-ALL. Br J Haematol. 2020;188(4):e36–e39. [PubMed: 31797346]

30. Gore L, Locatelli F, Zugmaier G, et al. Survival after blinatumomab treatment in pediatric patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia. Blood Cancer J. 2018;8(9):80. [PubMed: 30190453]

31. Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives-a position statement from the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2015;50(6):781–789. [PubMed: 25798682]

32. Wadleigh M, Richardson PG, Zahrieh D, et al. Prior gemtuzumab ozogamicin exposure significantly increases the risk of veno-occlusive disease in patients who undergo myeloablative allogeneic stem cell transplantation. Blood. 2003;102(5):1578–1582. [PubMed: 12738663]

33. Bonifazi F, Barbato F, Ravaioli F, et al. Diagnosis and Treatment of VOD/SOS After Allogeneic Hematopoietic Stem Cell Transplantation. Front Immunol. 2020;11:489. [PubMed: 32318059]

34. Dalle JH, Giralt SA. Hepatic Veno-Occlusive Disease after Hematopoietic Stem Cell Transplantation: Risk Factors and Stratification, Prophylaxis, and Treatment. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2016;22(3):400–409.

35. Kebriaei P, Cutler C, de Lima M, et al. Management of important adverse events associated with inotuzumab ozogamicin: expert panel review. Bone Marrow Transplant. 2018;53(4):449–456. [PubMed: 29330398]

36. Campana D, Pui C-H. Minimal residual disease–guided therapy in childhood acute lymphoblastic leukemia. Blood. 2017;129(14):1913–1918. [PubMed: 28167658]

37. IgH-V(D)J NGS-MRD measurement pre- and early post- allo-transplant defines very low and very high risk ALL patients.

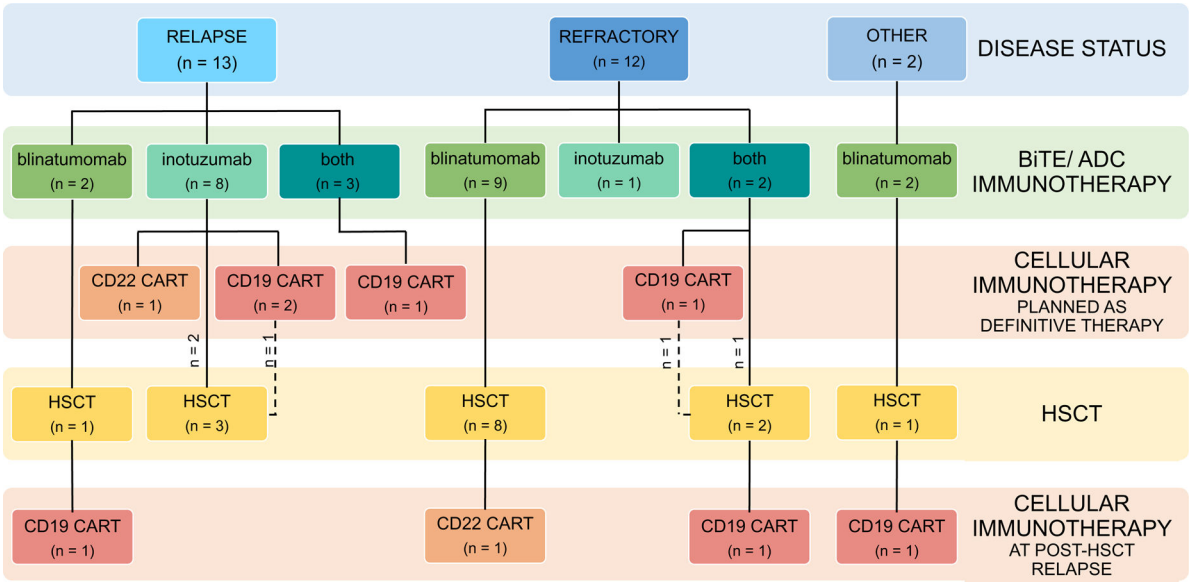

Figure 1.
Schema of administered immunotherapy to pediatric patients with B-ALL.

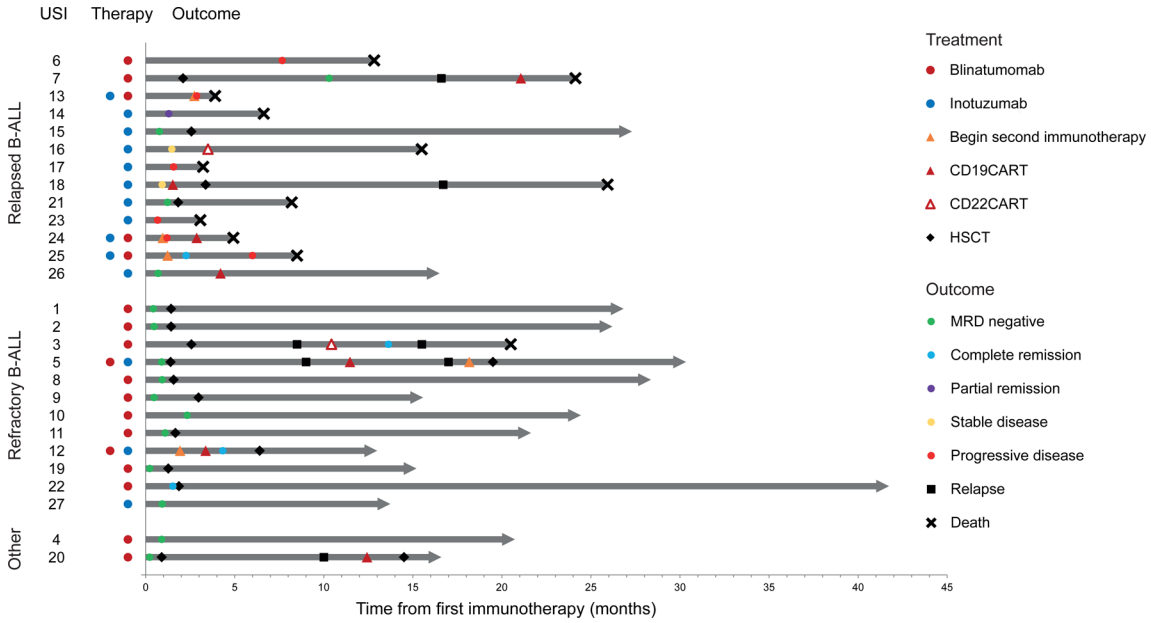

Figure 2. Swimmer plot of patients' responses to immunotherapy.

The clinical course of each patient is shown over time; each bar represents one patient. Therapeutic agents, disease status, and clinical outcomes are illustrated by symbols shown on the right.

Table 1.

Demographic characteristics and initial risk status at B-ALL diagnosis.

	Study USI	Age at diagnosis (years)	Sex	CNS status at diagnosis	NCI risk status	Cytogenetic alterations	Age at relapse (years)	Relapse type*
Relapse	CHOP6	9.2	F	CNS 1	SR	*JAZF1-TAX1BP1* fusion	14.3	Late medullary
	CHOP7	3.9	M	CNS 2c	SR	*CDKN2A* deletion	9.8	Late medullary
	CHOP13	13.8	M	CNS 1	HR	*TCF3-HLF* fusion	15	Early medullary
	CHOP14	3.4	F	CNS 1	HR	*P2RY8-CRLF2* fusion *IKZF1, PAX5, CDKN2A,* and *TP53* deletions	5.9	Early medullary
	CHOP15	6	M	CNS 1	SR	*CDKN2A* deletion	7	Early medullary
	CHOP16	6	M	CNS 1	SR	Partial iAMP21 *RUNX1* amplification	12.5	Late medullary
	CHOP17	14.3	M	CNS 1	HR	Low hypodiploidy	15.4	Early medullary
	CHOP18	11	M	CNS 1	HR	Low hypodiploidy	11.8	Very early medullary
	UCSF21	8.5	F	CNS 1	SR	*ETV6-RUNX1* fusion	10.4	Early medullary
	UCSF23	1.9	M	CNS 1	HR	None detected	6.1	Early medullary
	UCSF24	14.3	M	CNS 1	HR	iAMP1 and *RUNX1* amplification *CDKN2A* deletion	15.2	Early medullary
	CHOP25	3.3	M	CNS 1	SR	Hypodiploidy	12	Late medullary
	CHOP26	6.9	F	CNS 1	SR	Trisomy 5	10.2	Late medullary
Refractory	UCSF1	19.4	F	CNS 1	HR	Hypodiploidy	-	-
	UCSF2	11	M	CNS 1	HR	None detected	-	-
	UCSF3	18.8	M	CNS 2	HR	*IGH-CRLF2* fusion	-	-
	UCSF5	5.3	M	CNS 1	SR	Hyperdiploidy	-	-
	CHOP8	0.4	M	CNS 2a	HR	*KMT2A* rearrangement	-	-
	CHOP9	17	M	CNS 1	HR	*JAZF1-TAX1BP1* fusion	-	-
	UCSF10	29.2	M	CNS 2c	HR	*IGH-CRLF2* fusion *JAK2* mutation *FLT3*-ITD	-	-
	UCSF11	4.3	F	CNS 2	SR	*RUNX1-ETV6* fusion	-	-
	CHOP12	18.5	M	CNS 1	HR	*KRAS* mutation CDKN2A deletion	-	-
	UCSF19	26	F	CNS 1	HR	*BCR-ABL1* fusion	-	-
	UCSF22	12.8	F	CNS 1	HR	None detected	-	-
	CHOP27	10.4	F	CNS 1	HR	*PAX5-JAK2* fusion	-	-

	Study USI	Age at diagnosis (years)	Sex	CNS status at diagnosis	NCI risk status	Cytogenetic alterations	Age at relapse (years)	Relapse type*
Other	UCSF4	1.8	M	CNS 2b	SR	Hyperdiploidy	-	-
	UCSF20	0.8	F	CNS 1	HR	*KMT2A-MLLT3* fusion	-	Early medullary

*very early = medullary relapse <18 months, early = medullary relapse >= 18 months and <36 months, late = medullary relapse > 36 months from initial B-ALL diagnosis, - = not applicable.

Table 2.

Treatment and outcome characteristics for patients who received blinatumomab and/or inotuzumab.

Patients with B-ALL	**27**
Patients with refractory disease, n (%)	12 (44.4)
Patients with relapsed disease, n (%)	13 (48.2)
Patients with “other” disease status, n (%)	2 (7.4)
Treatment	
Blinatumomab, n (%)	13 (48.2)
refractory disease, n (%)	9 (75.0)
relapsed disease, n (%)	2 (15.4)
“other,“ n (%)	2 (100)
Inotuzumab, n (%)	9 (33.3)
refractory disease, n (%)	1 (8.3)
relapsed disease, n (%)	8 (61.5)
“other,“ n (%)	
Both, n (%)	5 (18.5)
refractory disease, n (%)	2 (16.7)
relapsed disease, n (%)	3 (23.1)
“other,“ n (%)	
Median MRD by FC prior to immunotherapy	
refractory disease, %	3.4
relapsed disease, %	51.8
“other,“ %	0
Median MRD by FC post immunotherapy	
refractory disease, %	0
relapsed disease, %	21
“other,“ %	0
Best response to immunotherapy	
Complete remission	4 (14.8)
refractory disease, n (%)	3 (25.0)
relapsed disease, n (%)	1 (7.7)
“other,” n (%)	
MRD-negative complete remission	13 (48.2)
refractory disease, n (%)	9 (75.0)
relapsed disease, n(%)	4 (30.8)
“other,“ n (%)	
Partial remission	1 (3.7)
refractory disease, n (%)	
relapsed disease, n (%)	1 (7.7)
“other,“ n (%)	

Patients with B-ALL	**27**
Stable disease	2 (7.4)
refractory disease, n (%)	
relapsed disease, n (%)	2 (15.4)
“other,“ n (%)	
Progressive disease	5 (18.5)
refractory disease, n (%)	
relapsed disease, n (%)	5 (38.5)
“other,“ n (%)	
Additional therapy	
Allogeneic HSCT	15 (55.6)
refractory disease, n (%)	10 (83.3)
relapsed disease, n (%)	4 (30.8)
“other,“ n (%)	1 (50.0)
CAR T cells	9 (33.3)
refractory disease, n (%)	3 (25.0)
relapsed disease, n (%)	5 (38.5)
“other,“ n (%)	1 (50.0)
Treatment outcome	
Median last follow-up, months	16.6
refractory disease, months	25.3
relapsed disease, months	8.5
“other,“ months	18.6
Alive at last follow-up, n (%)	17 (63.0)
refractory disease, n (%)	11 (91.7)
relapsed disease, n (%)	2 (15.4)
“other,“ n (%)	2 (100)
If alive, CR at last follow-up, n (%)	15 (55.6)
refractory disease, n (%)	11 (91.7)
relapsed disease, n (%)	2 (15.4)
“other,“ n (%)	2 (100)

Table 3.

Adverse effects of immunotherapy in study subjects.

Variable	Blinatumomab cohort (n=18)	Inotuzumab cohort (n=14)
Mean number of cycles (range)	1.47 (0.5–4)	1.62 (1–3)
Total complications, n (%)	9 (50.0%)	1 (7.1%)
CRS, n (%)	6 (33.3%)	0
grade 1, n (%)	2 (33.3%)	n/a
grade 2, n (%)	1 (16.7%)	n/a
grade 3, n (%)	2 (33.3%)	n/a
grade 4, n (%)	1 (16.7%)	n/a
Neurotoxicity, n (%)	4 (22.2%)	0
grade 2, n (%)	3 (75.0%)	n/a
grade 4, n (%)	1 (25.0%)	n/a
HSCT following immunotherapy, n (%)	13 (72.2%)	5 (35.7%)
SOS post-HSCT, n (%)	1 (7.7%)	1 (20.0%)

Note bene: This table contains 5 patients who received both blinatumomab and inotuzumab. Percentage of SOS post-HSCT refers to total number of patients who underwent HSCT in each cohort.