Blinatumomab in pediatric patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia

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Abstract
Objective: Pediatric patients with relapsed or refractory acute lymphoblastic leukemia have a poor prognosis. We here assess the response rates, adverse events, and long-term follow-up of pediatric patients with relapsed/refractory acute lymphoblastic leukemia receiving blinatumomab.

Methods: Retrospective analysis of a single-center experience with blinatumomab in 38 patients over a period of 10 years.

Results: The median age at onset of therapy was 10 years (1-21 years). Seventy-one percent of patients had undergone at least one hematopoietic stem cell transplantation (HSCT) prior to treatment with blinatumomab. We observed a response to blinatumomab in 13/38 patients (34%). The predominant side effect was febrile reactions, nearly half of the patients developed a cytokine release syndrome. Eight events of neurotoxicity were registered over the 78 cycles (15%). To date, nine patients (24%) are alive and in complete molecular remission. All survivors underwent haploidentical HSCT after treatment with blinatumomab.

Conclusions: Despite heavy pretreatment of most of our patients, severe adverse events were rare and response rates encouraging. Blinatumomab is a valuable bridging salvage therapy for relapsed or refractory patients to a second or even third HSCT.

1 | INTRODUCTION

Children with relapsed or refractory acute lymphoblastic leukemia (R/R ALL) have a dismal prognosis.\(^1,2\) Remission induction for these patients is challenging due to cumulative chemotherapeutic toxicities, a subsequent hematopoietic stem cell transplantation (HSCT) remaining the most promising curative treatment.

Immunologic approaches help to circumvent the problems of chemo-resistance and previous toxic organ damage. Especially, T-cell-based therapeutic strategies display strong efficacy.

Bispecific T-cell engager (BiTE) monoclonal antibody components bind T cells with close proximity to a specific surface expressed antigen and thereby lead to T-cell activation. Blinatumomab is a BiTE construct with dual specificity for CD19 and CD20.
and CD3-positive to CD19-positive cells leading to T cell–mediated lysis of CD19 expressing normal and malignant B cells. It exhibits high activity in the therapy of adult CD19-positive ALL.3–5

Blinatumomab also demonstrated efficacy in a phase I/II trial in a pediatric population.6 Twenty-seven of 70 patients (39%) achieved complete remission (CR) after one to two cycles, thereof 14 patients showed complete minimal residual disease response.

The recently published follow-up study of these patients described the final results at 24 months. Twenty-two of 70 (31%) patients were alive at last follow-up visit.7

We here report a retrospective analysis of our single-center experience with blinatumomab in R/R pediatric B-cell precursor (BCP)-ALL patients on a compassionate use basis.

2 | METHODS

Retrospective evaluation of all patients with R/R BCP-ALL receiving blinatumomab at the University Children’s Hospital Tübingen over a period of 10 years (2008-2017). The analysis was performed in accordance with the local ethics institutional review board and with the Declaration of Helsinki of 1975, revised in 2008. CR was defined as <5% leukemic blasts in bone marrow. Minimal residual disease (MRD) response was defined as a drop of at least one log-fold in MRD signal. MRD was assessed using real-time quantitative polymerase chain reaction detecting clonally rearranged immune gene rearrangements according to the EuroMRD guidelines.8 Molecular remission was defined as no target amplification with a minimum sensitivity of 1E-04. The statistical analysis was performed using SPSS software version 27, Armonk, New York, USA; the flow cytometric analysis was performed using FlowJo v10 software, Ashland, USA. Antibodies used for flow cytometry are listed in the supplement. Toxicity was assessed using CTCAEv4 criteria.

3 | RESULTS

3.1 | Patient characteristics

We treated 38 patients over 10 years (2008-2017) and administered a total of 78 cycles. Sixteen of the patients were part of the phase I/II trial NCT01471782.5,6 The median age at onset of blinatumomab therapy was 10 years, ranging from 1 to 21 years (Table 1).

Two thirds of patients suffered from second or subsequent relapse. Seventy-one percent of the patients had undergone at least one HSCT. At initiation of treatment, eight of the total 38 patients were in morphological CR with persisting or reemerging MRD, all other 30 patients displayed high blast percentages in bone marrow. But also the patients with mere MRD positivity in morphological remission at initiation of blinatumomab treatment were patients with relapsed and refractory disease (three patients displayed refractory disease during 1st relapse, two patients suffered 2nd relapse, one patient 3rd and one patient 4th relapse, one patient had never achieved molecular remission of his primary disease).

Eighteen patients received a single cycle of blinatumomab, 20 patients received 2 to 5 cycles. According to the recommended maximum tolerated dose evaluated in the phase I trial,6 blinatumomab was administered by continuous intravenous infusion over 28 days, at a dose of 5 µg/m²/d, escalating the dose to 15 µg/m²/d, with the exception of 2 patients receiving 30 µg/m²/d due to highly refractory disease. Ten cycles were discontinued: two due to fatal adverse events, two due to neurotoxicity, and six due to leukemia progression under treatment.

In order to mitigate possible side effects such as cytokine release syndrome (CRS) and neurotoxicity, it is advised to administer steroid premedication. In our patients, we administered at least one dose of dexamethasone to 68% of patients. In twelve patients with highly resistant disease, we omitted steroid prophylaxis completely for fear of impairing T-cell function and thereby attenuating the effect of blinatumomab.

3.2 | Response and outcome

The majority of patients received blinatumomab infusion in a relapse situation with excessive blast infiltration of bone marrow (71% of patients with a bone marrow infiltration above 25%). Despite the high tumor load, blinatumomab induced CR (<5% leukemic blasts in bone marrow) in eight patients after the first cycle and three further patients achieved CR after a second cycle (CR after overt leukemia 8/30 patients after 1st cycle, and 3/10 patients after 2nd cycle). Two additional patients with overt leukemia at initiation of blinatumomab achieved CR in bone marrow while still displaying an extramedullary manifestation of the leukemia other than the central nervous system (CNS).

For patients in morphological CR but newly detectable or persisting MRD, we observed an MRD reduction in at least one log-fold for two patients during the 1st cycle (2/8 pts) and three patients after the 2nd cycle (3/10 pts), one of which had already responded
TABLE 1  Patient characteristics

| Sex            | No. (%) |
|----------------|---------|
| Male           | 24 (63) |
| Female         | 14 (37) |

| Age at initial diagnosis, median (range) in years | 4.6 (0.2-19) |
| Age at onset of therapy with blinatumomab, median (range) in years | 9.8 (1.1-20.7) |

| Genetic aberrations | No. (%) |
|---------------------|---------|
| ETV6/RUNX1<sup>a</sup> | 5 (13.2) |
| MLL-AF4             | 5 (13.2) |
| BCR/ABL             | 2 (5.3)  |
| PBX1/TCF3           | 1 (2.6)  |
| No known genetic aberrations | 25 (65.7) |

| Constitutional trisomy 21 (CRLF2-positive) | 1 (2.6) |

| Status prior to blinatumomab therapy | |
|--------------------------------------|---------|
| Refractory disease                   | 3 (8)   |
| 1st relapse                          | 11 (29) |
| 2nd relapse                          | 18 (47) |
| 3rd relapse                          | 3 (8)   |
| 4th relapse                          | 3 (8)   |

| Previous HSCT | |
|---------------|---------|
| None<sup>b</sup> | 10 (26) |
| MSD            | 3 (8)   |
| MUD            | 12 (32) |
| Haploidentical | 8 (21)  |
| 1x MSD, 1x MUD | 1 (2.6) |
| 1x MUD, 1x haploidentical | 1 (2.6) |
| 1x MUD, 1x haploidentical | 1 (2.6) |
| 1x MSD, 1x MUD, 1x haploidentical | 1 (2.6) |
| 1x MUD, 1x UCB, 1x haploidentical | 1 (2.6) |

| Leukemia load at start of first cycle (% blasts in BM) | |
|------------------------------------------------------|---------|
| >50                                                  | 22 (58) |
| 25-50                                                | 5 (13)  |
| 5-25                                                 | 3 (8)   |
| <5                                                   | 8 (21)  |

| Extramedullary manifestations before first cycle | |
|-------------------------------------------------|---------|
| CNS positivity<sup>c</sup>                      | 6 (15.7) |
| Bones                                            | 2 (5.3)  |
| Kidney                                           | 1 (2.6)  |

Note: Data are presented as no. (%) unless otherwise indicated.

Abbreviations: BCR-ABL, breakpoint cluster region-Abelson murine leukemia viral oncogene homolog 1 gene; BM, bone marrow; CNS, central nervous system; ETV6-RUNX1, ETS-variant gene 6-run-related transcription factor; HSCT, hematopoietic stem cell transplantation; MLL, mixed-lineage leukemia; MSD, matched sibling donor; MUD, matched unrelated donor; UCB, unrelated cord blood.

<sup>a</sup>One patient with additional t(4;11) (MLL not affected).

<sup>b</sup>One patient had not undergone SCT before 1st, but SCT from an MUD before 2nd cycle.

<sup>c</sup>In all patients, leukemic cells in cerebrospinal fluid were cleared by intrathecal chemotherapy or irradiation before administration of blinatumomab.

During 1st cycle. Eight of 38 patients achieved complete MRD negativity (21%), of which six patients had high blast counts at initiation of blinatumomab and two patients only displayed a molecular relapse. In total, we observed a response to blinatumomab in 13 of 38 patients (34%), excluding patients with bone marrow response but persisting extramedullary manifestations (Table 2).

Median follow-up time for the surviving patients is 54 months (minimum 8.9 to maximum 113 months). Median overall survival for all patients was 11.1 months (min. 0.2 to max. 113 months) with a trend toward increased overall survival for patients responding to the first cycle of blinatumomab (Figure 1A). Relapse-free survival within responders was 6.17 months (CI, 0-18 months). Of the 13 patients responding to the first and or second cycle of blinatumomab, eleven had undergone HSCT before administration of blinatumomab and ten patients received HSCT after treatment with blinatumomab. HSCT after application of blinatumomab was crucial for better overall survival (Figure 1B). Of all the patients responding to blinatumomab, only those survived who received a haploidentical HSCT after the treatment with blinatumomab (Figure 1C).

Patients in morphological CR with molecular relapse before first cycle did not seem to achieve better response rates in our cohort, compared to those with overt leukemia. Also, the response was not better in 12 patients who did not receive steroids up front compared with patients receiving dexamethasone pretreatment.

Of the six patients who received blinatumomab after 3rd or 4th relapse, none responded. Also, none of the three patients with primary refractory disease responded to blinatumomab. Patients aged 2-10 years when starting blinatumomab seemed to have better response rates than older patients and infants, albeit not reaching statistical significance (7/10 patients aged 2-10 years responded while only 3/14 patients older than ten and only 1/4 patients under the age of two showed a response to blinatumomab). Two patients with highly refractory disease received an augmented dose of blinatumomab with 30 µg/m²/d, and this did not lead to a better response in these two cases. Lymphocyte subset counts were available for 28 patients. There was no difference observed in initial absolute count or percentage of T-cell subsets between the responding and non-responding patients.

To date, nine patients (24%) are alive and in continuous molecular remission. Eighteen patients died due to relapse of ALL, three patients died of severe infections in non-remission, and six patients suffered transplant-related complications in remission, such as multi-organ failure, infections, or graft-vs-host disease. Two patients were lost to follow-up.

The level of leukemia infiltration of our surviving nine patients prior to initiation of blinatumomab ranged between 1% and 97% in the bone marrow. Blinatumomab led to MRD negativity in five of the long-term survivors, enabling transition to haploidentical HSCT. The remaining four patients required additional cytotoxic treatments after blinatumomab before undergoing HSCT. All nine of our patients currently alive and in remission received HSCT before and after blinatumomab administration.
3.3  |  Adverse events

3.3.1  |  Cytokine release syndrome

Febrile reactions during blinatumomab infusion were frequent (84% of patients had temperatures between 38°C and 39°C, 76% experienced fever above 39°C). Half of the patients experienced a CRS (20/38 during first cycle, 52%; 40/78 over all cycles, 51%). Seven patients (18% of all patients) developed grade 3 or 4 CRS during 1st cycle. In 16 of all 78 cycles, patients developed grade 3 or 4 CRS (21% of all cycles) (Table 3).

Two patients needed intensive care treatment due to systemic inflammatory response syndrome requiring vasoressors and oxygen supplementation. An interleukin-6 receptor antagonist was administered in one patient.

The patients with CRS grade 3 or 4 all developed symptoms during the first 24 to 48 hours. Blinatumomab was then reduced or paused and reintroduced/elevated stepwise in most patients.

Leukemia load prior to blinatumomab infusion is associated with the level of CRS: All patients with high-grade CRS started blinatumomab therapy with excessive leukemic bone marrow infiltration (Figure 2A). Also, there is a trend between absolute CD3-cell count and development of CRS (Figure 2B).

Highest C-reactive protein (CrP) levels measured during the first cycle ranged from 0.085 to 285.3 mg/L (median 127.8 mg/L). CrP levels during the first cycle of blinatumomab were available for 36 patients. There was no clear association between CrP and development of CRS. Both patients with CRS grade 4 displayed relatively high CrP levels (122.4 and 285.3 mg/L) but there were also eight patients with no clinical evidence of CRS who had high CrP levels above 150 mg/L.

| TABLE 2  | Response |
| --- | --- |
| Prior to 1st cycle | After 1st cycle | Prior to 2nd cycle | After 2nd cycle |
| Leukemia load | N = 38 (100) | N = 38 (100) | N = 20 (100) | N = 20 (100) |
| ≥5% | 30 (79) | 21 (55) | 10 (50) | 6 (30) |
| <5% (CR) | 8 (21) | 16 (42) | 10 (50) | 12 (60) |
| CR BM but EM | 1 (2.6) | | 1 (5) | |
| MRD neg. but EM | 1 (2.6) | | | |
| Not evaluable | | | 1 (5) | |
| Change from open leukemia to CR | N = 30 (100) | N = 10 (100) |
| No | 22 (73.3)b | 6 (60)c |
| Yes | 8 (26.6) | 3 (30) |
| MRD neg. | 3 (10) | 5 (50)d |
| Not evaluable | 1 (10) |
| "MRD only" | N = 8 (100) | N = 8 (100) | N = 10 (100) | N = 10 (100) |
| >1x 10⁻³ | 4 (50) | 4 (50) | 6 (60) | 3 (30) |
| 1x 10⁻⁴ to 1x 10⁻³ | – | 1 (12.5) | 1 (10) | 1 (10) |
| <1x 10⁻⁴ | 4 (50) | 3 (37.5) | 3 (30) | 5 (50) |
| MRD neg. but EM | | | 1 (10) | |
| "MRD only" | N = 8 (100) | N = 10 (100) |
| MRD neg. | 1 (12.5) | 1 (10) |
| MRD reduction | 2 (25) | 3 (30) |
| No change | 4 (50) | 6 (60) |
| Rise in MRD-level | 2 (25) | – |
| MRD neg. but EM | | | 1 (10) |

Note: Data are presented as no. (%) unless otherwise indicated. MRD reduction defined as drop of at least one log-fold.

Abbreviations: BM, bone marrow; CR, complete remission; EM, extramedullary manifestation (with neg. MRD in bone marrow); MRD, minimal residual disease.

bNot evaluable as the second cycle was stopped after 3 days due to an adverse event.

One patient had a complete response in bone marrow after first cycle but displayed an extramedullary bone manifestation.

cOne patient had a complete response in bone marrow after second cycle but displayed an extramedullary bone manifestation.

dTwo of five patients were already MRD negative after the first cycle of blinatumomab.
Dexamethasone was administered at 10 mg/m² 12 hours before start of blinatumomab and at 5 mg/m² immediately before blinatumomab infusion. At least one dose of dexamethasone was administered to 26 patients during the first cycle. Of the twelve patients who did not receive any steroid premedication, seven developed CRS (58%), two of which suffered severe CRS grade 4. Of the 26 patients with dexamethasone pretreatment, half did not display CRS, and the other 13 patients had CRS grade 2 or 3.

3.3.2 | Neurotoxicity

Neurotoxicity was seen in 7 patients (18%), and there were 8 events of neurotoxicity over the 78 cycles (15%). One patient displayed neurotoxicity grade 1 (tremor) during 1st cycle and grade 2 (tremor and seizure) during 2nd cycle. Two patients had to discontinue therapy with blinatumomab because of generalized seizures. Three patients...
received further cycles of blinatumomab without evidence of neurotoxicity, two of which had only displayed mild neurotoxicity such as tremor, slurred speech, or loss of sense of vibration. One patient had experienced two generalized seizures during the second cycle and did not suffer further episodes of neurotoxicity during two further cycles under antiepileptic medication with levetiracetam.

Of the eight neurotoxic events, prophylactic dexamethasone had been administered in six cases. Two patients had not received any prophylactic steroids, one of which displayed tremor and slurred speech during the first cycle and the other suffering a seizure during the fourth cycle. The same patient had not had any neurologic side effects during the first three cycles, which had also been administered without steroid prophylaxis. There had been a pause of several months between the third and fourth cycles due to therapy with inotuzumab in between. Five patients with neurotoxic events were treated with dexamethasone. CNS disease had always been cleared through intrathecal administration of chemotherapy or radiotherapy prior to administration of blinatumomab. Of all six patients with previous CNS manifestation of the leukemia, only one developed neurotoxicity under blinatumomab and it merely occurred during the second cycle.

### 3.3.3 | Cytopenias

Hematological toxicity was the most common adverse event. In most cases, the condition was preexisting. Anemia grades 3 and 4 were seen in 24 patients during the first cycle (63%) with a median drop of hemoglobin level of 2.2 g/dL (0-6.9). Thrombocytopenia grades 3 and 4 were also seen in 24 patients during the first cycle (63%) with a median drop of platelets of 44 000/µL (0-258 000/µL).

Neutropenia grades 3 and 4 occurred in 20 patients (52%) during the first blinatumomab cycle.

### 3.3.4 | Infections and fatal adverse events

Seven patients encountered septic events above grade 3. Systemic mycotic infections occurred in 4 patients (15%): 3 patients suffered from pneumonia due to aspergillus, two of which led to an aspergillus sepsis, one patient succumbed to a systemic mycotic infection with *Rhizomucor pusillus*. Another patient died due to acute respiratory distress syndrome and evidence of *Pseudomonas aeruginosa* in the sputum.

### 3.3.5 | Other adverse events

Hypotension was observed in 7 patients (18%) during the first cycle and in 8 patients over all cycles (10%). Both patients with grade 4 hypotension had CRS and evidence of pneumonia.

Hepatic toxicity in form of elevated liver enzymes alanine transaminase and/or aspartate transaminase, regarding all cycles, was seen in nine patients (12%): Three patients showed hepatotoxicity grades 1 and 2, four showed patients grade 3, and two showed patients grade four.
Further adverse events included pain in the head, back, or limbs in 19% of patients. Moreover, we observed individual cases of mild tumor lysis syndrome, prolonged aplasia/refractory cytopenia, skin toxicities, and renal insufficiency.

We did not encounter any allergic reactions to blinatumomab. There were also no signs of graft-vs-host disease in the 28 patients who received blinatumomab after HSCT (Table 3).

### 3.4 | CD19 expression

None of the patients displayed a CD19-negative subclone detectable by flow cytometry before receiving a first cycle of blinatumomab. The leukemic cells of seven patients (18%) showed reduced expression of the target antigen CD19 during or after blinatumomab. Two of these patients had additionally received a CD19-targeting monoclonal antibody, used in our center on a compassionate use basis. One patient experienced a CD19-negative relapse after the second cycle was completed, and one patient’s leukemia lacked CD19 expression between the second cycle and third cycle. Interestingly, these blasts quickly regained normal CD19 levels. For details, please see the flow cytometry data in the supplementary figure.

One patient with MLL-translocation showed myeloid differentiation along with disappearance of CD19 under treatment with blinatumomab and spontaneous conversion back to a CD19-positive immunophenotype after discontinuation of blinatumomab.

Sixteen patients had CD19-positive relapses, and the other patients remained in remission or died from complications other than relapse (please see Supplement S1).

### 4 | DISCUSSION

This retrospective single-center analysis is the cohort of pediatric patients with the longest observation time after treatment with blinatumomab. Together with the pediatric phase I/II trial and the two very recent reports on eleven cases of infant ALL as well as 15 patients retrospectively analyzed in Spain, these are the only case series evaluating this immunotherapeutic approach for R/R BCP-ALL in children.6,7,10-13
The response rate of 34% in our analysis is identical to the rates previously reported.\textsuperscript{4,7} The TOWER trial is the largest trial comparing blinatumomab treatment in 271 adult patients with R/R ALL randomized with “standard of care” cytotoxic therapy.\textsuperscript{4} It reports a CR rate of 44%. A recent study showed that for adult patients with ALL, overall survival was higher both in first salvage and in later salvage for blinatumomab compared with chemotherapy.\textsuperscript{14}

Median overall survival in our series was 11 months (median follow-up of 54 months) compared with 7.5 months (median follow-up of 23.8 months; n = 70) in the von Stackelberg trial and 7.7 months (median follow-up of 11.7 months) in the TOWER trial.\textsuperscript{4,6}

The rate of survivors in our series to date is 9/38 patients (24%). Their median survival is of 51 months (8.9-113 months). These figures are similar to those reported for children with 20% survivors (median follow-up of 23.8 months) and higher than the rate reported for adult patients.\textsuperscript{6} The TOWER data described 9% survivors for the blinatumomab group with a median follow-up of 11.7 months, similar to the international multicenter trial NCT01466179.\textsuperscript{15} Twenty-four percent of the patients of the TOWER trial proceeded to HSCT, whereas 44% of our patients and 34% of the von Stackelberg cohort underwent HSCT.\textsuperscript{4,6}

Blinatumomab demonstrated antileukemic efficacy in heavily pretreated patients over all age groups, but patients between 2 and 10 years of age appear to have higher response rates. The performance of blinatumomab is dependent on the activation of the patient’s T cells. Immunosuppressive therapies such as HSCT might therefore impair its efficacy. But in fact, the pediatric study shows that prior HSCT was associated with prolonged survival after blinatumomab treatment.\textsuperscript{7} Adult ALL patients receiving blinatumomab after allogeneic HSCT also show CR rates of 45% within the first two cycles, the incidence of adverse events being similar in patients with and without previous allogeneic SCT.\textsuperscript{16}

We could not demonstrate a positive effect for HSCT prior to administration of blinatumomab, but HSCT after blinatumomab was essential for better overall survival. All nine of our patients currently alive and in remission received HSCT before and after blinatumomab administration. Especially, a second haploidentical HSCT was associated with better relapse-free survival in our cohort. Haploidentical HSCT has proven to be a highly efficient therapy especially for refractory malignant diseases.\textsuperscript{17-20} However, the small number of patients receiving a matched HSCT after blinatumomab does not enable a valid comparison between both HSCT subtypes. The results of the RIALTO trial also show a trend toward improved OS and RFS for patients who received HSCT after blinatumomab as compared with those who did not.\textsuperscript{21} Moreover, durable remissions in TCF3-HLF-positive ALL with blinatumomab and subsequent HSCT have recently been reported, a rare subtype of leukemia characterized by a high rate of treatment failure.\textsuperscript{22} In line with previous works, we did not observe exacerbations of graft-vs-host disease.\textsuperscript{23,24}

All pediatric patients in the phase I/II study received prophylactic dexamethasone. Until now, there is no evidence for the premedication with dexamethasone to hamper efficacy of blinatumomab treatment. Yet, it is unlikely that two doses of dexamethasone are not impairing T-cell function at all. Preclinical data suggest dexamethasone-mediated T-cell suppression\textsuperscript{23,25} and a dose-dependent reduction of different T-cell subtypes.\textsuperscript{26} We therefore omitted the preemptive steroids completely in 12 of our patients with highly refractory disease and high leukemic burden. Patients without steroid pretreatment did not achieve better response rates, but two of the patients experienced grade 4 CRS.

The rate of adverse events in this study was comparable to previously published data with respect to frequency and severity.

Potentially life-threatening infectious adverse events occurred in 7 patients (26%), presumably due to the severely impaired general condition of some patients prior to blinatumomab. Two patients had fatal AEs (2/38, 5%), which is comparable to published data with six of 70 patients suffering fatal AEs (8%).\textsuperscript{5}

Other adverse events observed were cytopenias which were mostly preexisting due to overt leukemia and heavy cytotoxic chemotherapy. Nonetheless, most patients could be treated on an outpatient basis with cessation of the initial fever.

The rate of CRS in the first treatment seems to be higher in trials with patients displaying high blast counts during relapse compared with patients in morphological CR with mere increase in MRD load. Two larger trials reported rates of CRS of 14% in patients >5% blasts,\textsuperscript{4} compared to 4% in a MRD situation.\textsuperscript{5} In our analysis, we found a significant association between the leukemia load and the grade of CRS with patients displaying a high blast count in bone marrow at start of blinatumomab suffering higher grades of CRS. It is therefore important to expect this most common adverse event in patients with high tumor burden at start of treatment.

For patients with a high leukemia burden, the event of neurotoxicity under blinatumomab has been reported from 10% for grade 3 and higher\textsuperscript{4} to 50% overall\textsuperscript{27} in adults and 24% in children\textsuperscript{6} whereas the adult MRD trial describes neurotoxic events in over 50% of the patients.\textsuperscript{7} This inverse correlation supports the hypothesis that a low leukemic burden increases the risk of off-target effects of blinatumomab in terms of an enhanced non-specific T-cell activation.\textsuperscript{15,28} We do not see a correlation between low leukemia burden and neurotoxicity, possibly due to the low number of patients being treated in morphological CR. Importantly, we did not see more neurotoxic events in the 12 patients who did not receive prophylactic dexamethasone or in the patients with prior CNS leukemia.

Adult trials report that lower leukemic burden enhances the chances for CR.\textsuperscript{28,29} Our data cannot corroborate these findings, as only two of the eight patients in morphological remission at start of blinatumomab are in continuous molecular remission. But the number of patients with molecular relapse in our cohort is too low to draw a conclusion.

We observed a decreased expression of CD19 in 7/38 (18%) patients, which is similar to the level published initially for pediatric patients with evaluable data in the phase I/II study with 4/18 (22%),\textsuperscript{30} but much higher than the numbers described in the follow-up publication pediatric phase II study where only 4/70 (5%) of patients showed a CD19-negative relapse.\textsuperscript{7} In adult patients with
R/R ALL after failure of blinatumomab therapy, only 8% (5/61) had CD19-negative disease. Interestingly, one of the infants in our study with MLL-rearranged leukemia lost CD19 expression during treatment with blinatumomab with outgrowth of a myeloid clone. The immunophenotype quickly switched back to CD19 positive after discontinuation of blinatumomab. This phenomenon of lineage switch in MLL-rearranged leukemias has previously been described by others. To overcome the target antigen-induced resistance, an approach directed against multiple antigens seems promising. Anti-CD20 rituximab and anti-CD22 inotuzumab ozogamicin and others have shown efficacy. Recent reports showed similar effectiveness for inotuzumab and blinatumomab in two retrospective studies with children and adults as a bridging therapy to HSCT.

An alternative approach is the direct genetic manipulation of patient’s T cells. Two FDA-approved substances are currently available: Tisagenlecleucel and Axicabtagene-Ciloleucel, both targeting CD19. The main difficulty with this therapeutic option is the necessity to draw enough T cells from the patient. Especially in patients with refractory disease or relapse shortly after HSCT, it can be impossible to collect sufficient numbers of T cells for transfection. The high costs and the availability of only few clinical trials open to pediatric patients are additional hurdles.

Blinatumomab is an “off the shelf” immunotherapeutic option in the treatment of R/R pediatric ALL with satisfactory response rates and favorable safety profile compared with cytotoxic chemotherapy. The results of the expanded access study (RIALTO) showed a median OS of 13.1 months for patients with >5% blasts at baseline, and the median RFS for patients reaching CR after first two cycles was 8.5 months. These data are comparable to ours. Furthermore, the interim analysis of a randomized controlled clinical trial of the Children’s Oncology Group AALL1331 comparing standard of care chemotherapy to blinatumomab for patients with ALL in first relapse revealed improved disease-free survival, superior overall survival, lower toxicity, and superior MRD clearance for the experimental arm with blinatumomab.

There is still considerable paucity of pediatric data for the use of blinatumomab, and the results of a preponderance of adult trials cannot simply be transferred to the pediatric setting. It is widely accepted that pediatric and adult ALL are biologically different with distinct underlying genetic alterations. The relapse rate and prognosis is markedly worse in adults, and co-morbidities in adult patients might lead to a different profile of adverse events.

In our heavily pretreated patients, only those survived who received a second allogeneic HSCT after the bridging therapy with blinatumomab. This could only hold true for the very aggressive refractory leukemias treated in our cohort as a very recent publication in adult ALL shows that although they also see best cure rates for patients undergoing HSCT after blinatumomab a cure seems possible after blinatumomab only.

Blinatumomab is currently under investigation in pediatric randomized controlled clinical trials not only for relapsed patients but also as frontline therapy in medium and high-risk patients. The excellent response rates in MRD-positive adult patients and a recent report on eleven cases of infants with MRD-positive ALL showing a 3-year overall survival of 81% confer big hopes to a high effectiveness of blinatumomab as first salvage therapy in pediatric patients.

5 | STATEMENT OF SIGNIFICANCE

Our work shows that in children with relapsed or refractory acute lymphoblastic leukemia successfully treated with blinatumomab, only those have a long-term survival who underwent a second HSCT after the bridging therapy with blinatumomab.

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CONFLICT OF INTEREST

GZ is an Amgen employee and Amgen stock holder.

AUTHOR CONTRIBUTIONS

MQ collected and analyzed data and wrote the manuscript. PS, ATH, and TL collected and analyzed data. HK performed MRD analysis. MD, UH, AVS, MS, GZ, and TF collected data. RH, PL, and ME involved in conception of analysis and interpretation of results.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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