# Blinatumomab for Infant Acute Lymphoblastic Leukemia

## Authors

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## Running title: Blinatumomab for Infant ALL

## To the editor

Unlike older children with acute lymphoblastic leukemia (ALL), there has been limited improvement in outcome for infants in the last two decades, with a similar 6-year event-free survival (EFS) and overall survival (OS) of 46.1% and 58.2% in two successive international studies [1] [2]. 'High risk' patients in the latter study had a 6-year EFS and OS of 20.9% and 29.9% despite hemopoietic stem cell transplantation (HSCT) in first remission (CR1). Outcome after relapse is dismal with a 3-year OS of 20.9% [3].

Among novel approaches, immune therapies such as chimeric antigen receptor (CAR)-T cells and blinatumomab offer the greatest potential for improving cure rates. The bi-specific CD3/CD19 engaging antibody, blinatumomab, was found to achieve complete, often minimal residual disease (MRD) negative, remission in children with relapsed/refractory B cell acute lymphoblastic leukemia (B-ALL). Higher responses were observed in patients with less than 50% bone marrow blasts (55.6% vs 32.7% (95% CI 30.8-78.5 and 20.3-47.1 respectively)[4], and an adult study showed complete MRD response rates of 78% when blinatumomab was used to treat MRD-positive ALL in haematological remission [5]. As the risk of relapse after HSCT is predicted by MRD status prior to transplant, deeper molecular remissions achieved by blinatumomab might improve post-transplant outcomes.

Here we report the outcome of 11 infants who received blinatumomab for persistent MRD prior to HSCT. To our knowledge this is the largest experience reported to date in this rare sub-group of patients.

This retrospective analysis included patients from the U.K and Republic of Ireland with B-lineage ALL whose initial diagnosis was before the first birthday. Patients were identified from the minutes of a national tumour board supplemented by a survey of pediatric hematologists in the 2 countries. All children were initially treated according to the Interfant 06 protocol [2]. Patients in first remission or after relapse received blinatumomab between 2016-2019 for MRD reduction prior to HSCT. None of the patients had received a prior HSCT. MRD was measured by standardised real-time quantitative polymerase chain reaction (PCR) of immunoglobulin gene rearrangements, pre- and post-blinatumomab. EFS was defined as time

from diagnosis to relapse, secondary tumor, or death, and OS was defined as time to death. OS and EFS were reported using the Kaplan-Meier function. Analysis was performed using GraphPad Prism version 7.00 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com

Eleven patients were identified and met the eligibility criteria for analysis which was treatment with Blinatumomab of MLL-rearranged infant ALL in first remission or relapse regardless of age at which it was administered. The median age at the time of blinatumomab administration was 0.5 years (range, 0.2-2.9 years). One patient had a late relapse of MLL rearranged infant ALL (2.9 years) and was included in the analysis as the aim. All patients had *KMT2A* (MLL)-rearrangement. Seven patients received blinatumomab after relapse and 4 as first line therapy for resistant or refractory disease. Of the 8 patients who were in first or second MRD positive complete remission, the median was MRD was 0.2%, range 0.06-1% (Table 1).

Nine patients received a single 28-day cycle of blinatumomab and the other two received a second cycle pending transplant being arranged. Nine became MRD negative and 2 had a >1 log reduction in MRD prior to HSCT giving a partial or complete MRD response rate of 100%. There was no obvious differences in the presenting features or previous treatment/responses of the 2 patients that didn't achieve MRD negativity. All patients proceeded to HSCT without intervening therapy. The median time from commencing blinatumomab to HSCT was 51 days (range, 34-119). The median follow up following HSCT was 267 days (range, 58-1163). Pre-treatment lymphocyte count did not predict response to blinatumomab with even severely lymphopenic patients obtaining a complete MRD response (data not shown).

Three patients had grade 1-2 CRS; one patient had short interruption of blinatumomab and a short course of steroids and the treatment restarted at the lower dose; the remaining two resolved spontaneously without steroid or Tociluzimab. One patient had neurotoxicity manifesting as confusion and somnolence which resolved on interrupting the infusion and did not recur on restarting at a lower dose. This patient also received steroid for grade 2 CRS. Eight of the patients were able to be discharged from hospital after the first week of therapy and they received the remaining infusion whilst an outpatient. The low toxicity and out-patient delivery of therapy concords with the reports of better health-related quality of life in adults treated with blinatumomab compared with standard chemotherapy[6] .

3-year EFS and OS post-transplant were 47% and 81%, respectively (Figure 1) and were similar when measured from the point of blinatumomab administration (51% and 79%). Following transplantation, one patient died of parainfluenza pneumonitis (day 57) and four patients relapsed (35, 92, 108 and 133 days respectively), one of whom was MRD positive (0.05%) and 3 MRD negative pre-transplant. Three had CD19 positive relapse and have subsequently achieved a remission with CD19 directed CAR-T therapy. The remaining patient relapsed with lineage-switch monoblastic acute myeloid leukaemia (AML) at day 35 post-transplant and died of progressive leukemia shortly afterwards. This patient had expression of myeloid antigen (CD15) at presentation and relapse. Patients with *MLL*-rearranged B-ALL have been reported to be at increased risk of relapse with a myeloid phenotype [7] . Relapse with a myeloid lineage switch has been reported following treatment with CD19 directed CAR-T [8] and blinatumomab [9] in *MLL*-rearranged B-ALL. In these cases, the 'switch' occurred early following CD19-directed therapy which was not consolidated with HSCT. Different mechanisms for this have been proposed including aberrant response to inflammatory cytokines (notably IL-6), and selection of clones by targeted treatment in combination with different oncogenic drivers [9] [10]. Taken together, these mechanisms demonstrate the inherent plasticity of these primitive cells when exposed to different selection pressures.

This is the first report focussed on using blinatumomab in a relatively large series of infant ALL. A previous case series reported the use blinatumomab for children with MRD positive ALL as a 'bridge' to transplant and included 2 infant ALLs who achieved a complete MRD response but relapsed post-transplant [11]. Additional experience was gained in the phase 1-2 study [4] which included 3 infants (unpublished data, A Vora). In our multicentre experience we have demonstrated that blinatumomab can be safely and effectively delivered to infants with relapsed or refractory B-ALL with MRD positive disease to achieve molecular remission. Complete MRD responses were seen in the majority of cases and this led to HSCT being undertaken in all patients. The numbers in our series are too small to make definitive conclusions on the long-term outcome but a 12 month EFS of 50% compares favorably with historical outcomes in chemotherapy treated patients.

## Authorship

All authors contributed to the acquisition or analysis of the data. All authors revised the manuscript critically, approved the final version for publication, and agreed to be accountable for the results printed. K.C wrote the first and subsequent drafts of the manuscript.

## Conflict of interest disclosure.

Nothing to disclose

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Table 1. Patient Characteristics

| Patient and disease characteristics | | Blinatumomab treatments | | | | | | | Outcomes | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age/Sex | Disease Status | Pre-CNS status | Pre-MRD (%) | Lymphocyte-pre($x10^9$/ml) | Cycles | CRS (grade) | Neurotoxicity | Post-MRD (%) | HSCT conditioning | Donor source | Status |
| 0.75/M | CR2 | CNS 1 | 0.1 | 0.94 | 1 | No | No | <0.005 | Flu/Bu/Thiotepa | MUD | CR |
| 0.75/F | CR2 | CNS 3 | 0.6 | 0.22 | 1 | No | No | <0.005 | FTT | MSD | CR |
| 0.5/M | CR2 | CNS 1 | 1 | 0.55 | 1 | Grade 1 | No | <0.005 | FTT + ATG | MMUD | CR |
| 0.41/F | CR2 | CNS 1 | 1 | N/A | 1 | No | No | <0.005 | FTT | MSD | Relapse →Died * |
| 0.5/M | Primary Refractory | CNS 1 | 9 | 0.28 | 1 | No | No | 0.06 | FTT + ATG | MUD | CR |
| 0.5/M | CR2 | CNS 1 | 0.3 | 0.35 | 1 | No | No | 0.05 | N/A | | Relapse →CR ** |
| 0.5/F | CR1 | CNS 1 | 0.06 | 0.41 | 1 | Grade 2 | Yes | <0.005 | FTT + ATG | MMSD | CR |
| 0.2/F | CR1 | CNS 1 | 0.06 | 2.43 | 1 | No | No | <0.005 | FTT | MSD | Relapse →*** |
| 0.2/M | 1st Relapse | CNS 3 | 40 | N/A | 1 | Grade 1 | No | <0.005 | FTT + ATG | MUD | Died **** |
| 2.9/M | CR2 | CNS 1 | 0.01 | 0.95 | 2 | No | No | <0.005 [a] | CY/TBI/alemtuzumab | MSD | CR |
| 0.2/F | Primary Refractory | CNS 1 | 9 | N/A | 2 | No | No | <0.005 [a] | FTT/ATG | MUD | Relapse→CR ***** |

Age when blinatumomab administered, M, Male; F, female; FTT, Fludarabine, Treosulphan, Thiotepa; FBT, Fludarabine, Busulphan, Thiotepa; ATG, Anti-thymocyte globulin; MSD, matched sibling donor; MUD, mathced unrelated donor; MMUD, mis-matched unrelated donor; MMSD, mis-matched sibling donor; N/A, not available; [a], results after 2 cycles. *Relapse with AML post-transplant. ** B-ALL relapse post-transplant, remission following CAR-T. ***B-ALL relapse post-transplant, planned CAR-T therapy, **** Died post transplant pneumonitis, *****B-ALL relapse post-transplant, remission following CAR-T.

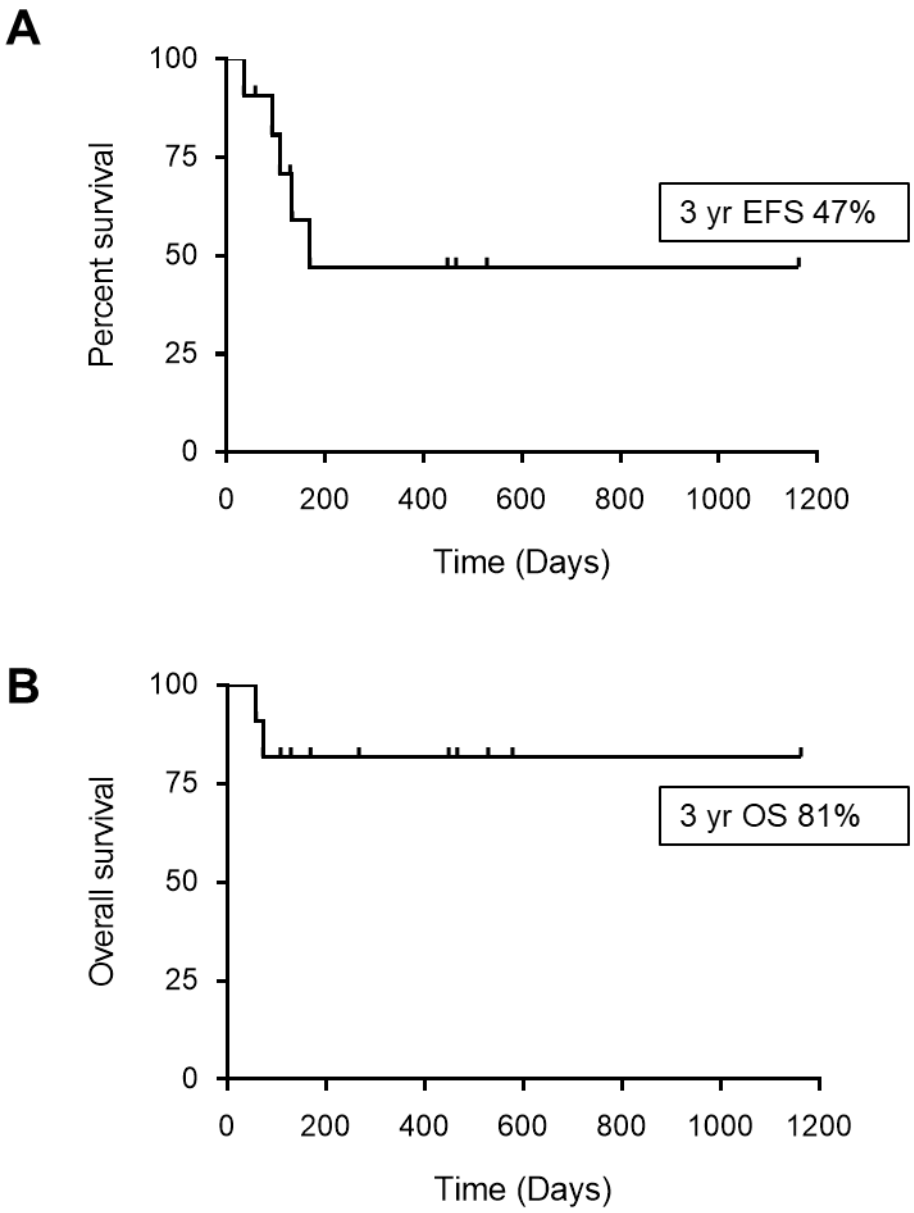


Figure 1: Event-free (A) and Overall Survival (OS) post HSCT

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