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TO THE EDITOR:

Blinatumomab for infant acute lymphoblastic leukemia

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Unlike older children with acute lymphoblastic leukemia (ALL), there has been almost no improvement in outcome for infants in the last 2 decades. Six-year event-free survival (EFS) and overall survival (OS) in successive international infant trials, Interfant99[1] and Interfant06,[2] were 46.4% and 53.8%, and 46.1% and 58.2%, respectively. High risk patients in Interfant06 had a 6-year EFS and OS of 20.9% and 29.9%, respectively, despite hematopoietic stem cell transplantation (HSCT) in first complete 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 bispecific CD3/CD19-engaging antibody, blinatumomab, was found to result in complete and often minimal residual disease (MRD)-negative remission in children with relapsed/refractory B-cell ALL (B-ALL). Better responses were observed in patients with <50% bone marrow blasts (55.6% vs 32.7%; 95% confidence interval, 30.8-78.5 and 20.3-47.1, respectively),[4] and an adult study showed a complete MRD response rate of 78% when blinatumomab was used to treat MRD-positive ALL in hematological remission.[5] Because the risk of relapse after HSCT is predicted by MRD status prior to transplant, deeper molecular remissions achieved by using blinatumomab might improve posttransplant 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 in this rare subgroup of patients.

This retrospective analysis included patients from the United Kingdom and the Republic of Ireland with B-ALL, whose initial diagnosis was before the first birthday. Patients were identified from the minutes of a national tumor board, supplemented by a survey of pediatric hematologists in the 2 countries. All children were initially treated according to the Interfant 06 protocol.[2] Between 2016 and 2019, patients in first remission or after relapse received blinatumomab for MRD reduction prior to HSCT. None of the patients had received a prior HSCT. Individual patient MRD at all time points was measured in the same laboratory using a Euro-MRD Consortium–accredited and standardized technique for real-time quantitative polymerase chain reaction of immunoglobulin gene rearrangements. 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, CA).

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

Nine patients received a single 28-day cycle of blinatumomab, and the other 2 patients received a second cycle, pending

Table 1. Patient characteristics

Patient/disease characteristics		Blinatumomab treatments							Outcomes		
Age at blinatumomab administration, y/sex	Disease status	Pre-CNS status	Pre-MRD, %	Lymphocyte count pre-blinatumomab (×10⁹/mL)	Cycles, n	CRS	Neurotoxicity	Post-MRD, %	HSCT conditioning	Donor source	Status
0.75/M	CR2	CNS 1	0.1	0.94	1	No	No	<0.005	FBT	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	First 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¶	CY/TBI/Alem	MSD	CR
0.2/F	Primary refractory	CNS 1	9	N/A	2	No	No	<0.005¶	FTT/ATG	MUD	Relapse→CR‖

Alem, alemtuzumab; ATG, anti-thymocyte globulin; CNS, central nervous system; CRS, cytokine release syndrome; CY, cyclophosphamide; F, female; FBT, fludarabine, busulfan, thiotepa; FTT, fludarabine, treosulfan, thiotepa; M, male; MMSD, mismatched sibling donor; MSD, matched sibling donor; MMUD, mismatched unrelated donor; MUD, matched unrelated donor; N/A, not available; TBI, total body irradiation.

*Relapse with acute myeloid leukemia posttransplant.

†B-ALL relapse posttransplant, remission following CAR T-cell therapy.

‡B-ALL relapse posttransplant, planned CAR T-cell therapy.

§Died from posttransplant pneumonitis.

¶Results after 2 cycles.

‖B-ALL relapse posttransplant, remission following CAR T-cell therapy.

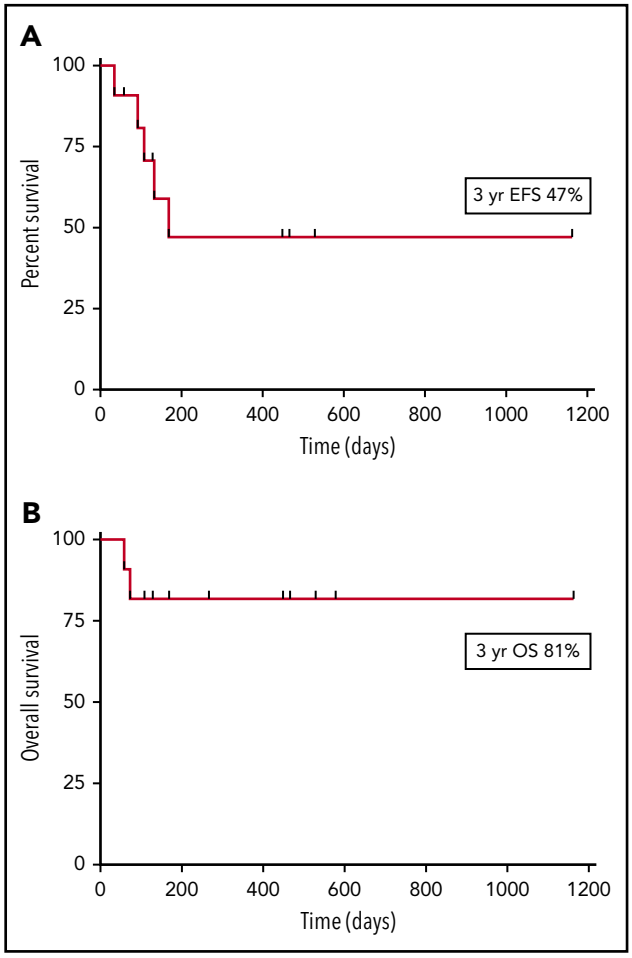

Figure 1. EFS and OS post-HSCT. (A) EFS, (B) OS.

transplant being arranged. Nine patients became MRD negative, and 2 patients had a >1-log reduction in MRD prior to HSCT, resulting in a partial or complete MRD response rate of 100%. There were no obvious differences in the presenting features or previous treatment/responses of the 2 patients who did not 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). Pretreatment lymphocyte count did not predict response to blinatumomab, with even severely lymphopenic patients achieving a complete MRD response (Table 1).

Three patients had grade 1-2 cytokine release syndrome; 1 patient had a short interruption of blinatumomab and a short course of steroids, and the treatment restarted at the lower dose; the remaining 2 cases resolved spontaneously without steroid or tocilizumab. 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 steroids for grade 2 cytokine release syndrome. Data were available for 5 patients who received intrathecal methotrexate on days 15 and 29 of the blinatumomab cycle without neurotoxicity. Eight of the patients were able to be discharged from the hospital after the first week of therapy, and they received the remaining infusion as an outpatient. The low toxicity and outpatient delivery of therapy concords with reports of better health-related quality of life in adults treated with blinatumomab compared with standard chemotherapy.[6]

Three-year EFS and OS posttransplant were 47% and 81%, respectively (Figure 1), and were similar when measured from the point of blinatumomab administration (51% and 79%, respectively). Following transplantation, 1 patient died of parainfluenza pneumonitis (day 57), and 4 patients relapsed (at 35, 92, 108, and 133 days), 1 of whom was MRD positive (0.05%) and 3 were MRD negative pretransplant. Three had CD19-positive relapse and subsequently achieved a remission with CD19-directed CAR T-cell therapy. The remaining patient relapsed with lineage-switch monoblastic acute myeloid leukemia at day 35 posttransplant and died of progressive leukemia shortly thereafter. This patient had expression of myeloid antigen (CD15) at presentation and relapse. Patients with *KMT2A*-rearranged B-ALL have been reported to be at an increased risk for relapse with a myeloid phenotype.[7] Relapse with a myeloid lineage switch has been reported following treatment with CD19-directed CAR T cells[8] and blinatumomab[9] in *KMT2A*-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 an aberrant response to inflammatory cytokines (notably interleukin-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 focused on using blinatumomab in a relatively large series of infant ALL. A previous case series reported the use of blinatumomab for children with MRD-positive ALL as a "bridge" to transplant and included 2 infants with ALL who achieved a complete MRD response but relapsed posttransplant.[11] Additional experience was gained in the phase 1-2 study[4] that included 3 infants (A.V., unpublished data). In our multicenter 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 about long-term outcomes, but a 12-month EFS of 50% compares favorably with historical outcomes in chemotherapy-treated patients.

Authorship

Contribution: K.C. and A.V. wrote the first and subsequent drafts of the manuscript; and all authors contributed to the acquisition or analysis of data, critically revised the manuscript, approved the final version for publication, and agreed to be accountable for the results published.

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