bjh short report

Blinatumomab and inotuzumab for B cell precursor acute lymphoblastic leukaemia in children: a retrospective study from the Leukemia Working Group of the Spanish Society of Pediatric Hematology and Oncology (SEHOP)

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Summary

Blinatumomab and inotuzumab ozogamycin represent promising alternatives to conventional chemotherapy in acute lymphoblastic leukaemia (ALL). We analysed data from 29 children with ALL treated under compassionate use with blinatumomab, inotuzumab or both. The complete remission (CR) rate in a heavily pretreated population with overt relapse was 47·6%. At earlier stages (first/second CR), both antibodies represented a useful tool to reduce minimal residual disease, and/or avoid further toxic chemotherapy until stem cell transplantation. Six patients developed grade 3 reversible non-haematological toxicity. The 12-month overall survival and event-free survival rates were 50·8 ± 26·4% and 38·9 ± 25·3% with blinatumomab, 45·8 ± 26% and 27·5 ± 25% with inotuzumab.

Keywords: acute lymphoblastic leukaemia, relapse, children, blinatumomab, inotuzumab.

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Relapse is the main cause of treatment failure in children with acute lymphoblastic leukaemia (ALL), affecting about 15% of cases.[1] Long-term survival rates after relapse remains below 50%,[2] and prognosis of relapse after allogeneic haematopoietic stem cell transplantation (HSCT), second or subsequent relapse, or failure of second-line salvage chemotherapy is dismal, with 2- to 3-year survival rates of ≤20%,[3,4] 13–27%,[5] and below 10%,[6] respectively. Monoclonal antibodies (MoAb) and chimeric-antigen receptor (CAR)-T cells are among the most appealing alternative approaches. Blinatumomab is a bispecific MoAb, able to target CD19 on leukaemic blasts and the CD3 subunit of the T cell receptor, triggering the activation of T cells.[7]

Blinatumomab was effective in adults and children with refractory/relapsed (R/R) ALL;[7,8] it was superior to standard chemotherapy as post-reinduction consolidation in children and adolescents/young adults with high- or intermediate-risk first relapse;[9] and it is still under clinical investigation in children with first high-risk relapse (NCT02393859) and as first-line treatment for ALL (NCT03117751).[7]

Inotuzumab ozogamicin (InO) is another MoAb targeting CD22, which is conjugated to calicheamicin, a potent cytotoxic agent.[10] InO, as monotherapy and in combination with low-intensity chemotherapy, was effective in adults with R/R ALL[10] and is being explored in children (EudraCT Number 2016-000227-71), but clinical experience is still quite limited.[11,12]

Methods

This was a retrospective study of children with B cell precursor ALL (preB-ALL) who received blinatumomab or InO under a compassionate use program in Spain (see Data [S1] for inclusion criteria, data collection and response evaluation criteria). The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee from University Hospital "Virgen de la Arrixaca" (Murcia, Spain).

Response evaluation was performed after each cycle by cytological examination of bone marrow (BM) smears and flow cytometry for minimal residual disease (MRD), and as appropriate for extramedullary disease. A negative MRD response was defined as <0·01% (10^{-4}) leukaemic cells in the BM.

Overall survival (OS) was defined as the time from the start of treatment to death from any cause or last contact, and event-free survival (EFS) as the time to relapse, progression, second malignant neoplasm, death or last contact. For refractory patients, the first day of treatment was censored as an event. The Kaplan-Meier method was used to generate survival curves.

Results and discussion

Fifteen patients treated with blinatumomab and 16 with InO were notified from 11 institutions. Four patients received InO after failing to respond to blinatumomab (2), or because of subsequent relapse (2). Two patients are included in both groups, rendering a total of 31 administrations in 29 patients. Median age at diagnosis and at time of treatment was 4 (0·5–15) and 7 (0·5–18) years, respectively. Seven patients had high-risk cytogenetics: four *KMT2A*-, one *BCR*-

ABL1−, one *TCF3-PBX1*-rearrangement and one hypodiploid ALL.

Indication for treatment

One patient (6·6%) received blinatumomab as part of first line treatment and 14 (93·3%) at the time of R/R; median number of previous lines was 2 (1–3), and eight patients (53·3%) had undergone HSCT, including three receiving haploidentical transplantation (haplo-SCT). One patient (6·2%) received InO as part of first line treatment and 15 (93·7%) at the time of R/R; median number of previous lines was 2 (1–4), and seven patients (43·7%) had undergone HSCT (2 haplo-SCT). Overall, most patients were heavily pre-treated high-risk patients, 14 (45%) with ≥2 previous relapses; 12 (38·7%) were refractory to the previous line and 15 (48·4%) had relapsed after HSCT (Table I; Table SI).

Response

Median number of treatment cycles of blinatumomab was 2 (1–4). Median follow up was 9 months (1–38). Complete and partial response (PR) after the first cycle was reported in four (40%) and one (10%) out of 10 (66·6%) patients with overt relapse, respectively. All complete remissions (CR) were MRD-negative after the first cycle. Five patients failed to respond. This yielded an overall response rate (ORR) of 50%. Five patients received blinatumomab in remission: one first CR (CR1) and four second CR (CR2); four out of these five cases achieved a sustained MRD-negative CR before HSCT, and one patient progressed after blinatumomab. Overall, seven patients proceeded to HSCT after blinatumomab (Table I).

Median number of cycles of InO was 1·5 (1–6). Median follow up was 3·5 months (1–30). Complete and PR after the first cycle was reported in six (54·5%) and one (9%) out of 11 (68·7%) patients with overt relapse, respectively. All CRs were MRD-negative after the second cycle (four after the first cycle). Three patients failed to respond and one patient was not evaluated because of early death. This yielded an ORR of 63·6%. Five patients received InO in remission (2 CR1 and 3 CR2); all these five cases achieved and/or maintained a sustained MRD-negative CR before HSCT. Overall, eight patients proceeded to HSCT after InO.

Two of four patients receiving InO after failing to respond (2) or relapsing after blinatumomab (2) achieved MRD-negative CR Table I.

CR rate was 47·6% among patients with overt disease (42·8% of patients relapsing after HSCT); all CRs occurred after one single cycle of MoAb (Table SII) and across almost all biological preB-ALL subtypes and age groups. These results are comparable with those previously reported.[4,8,11,13]

MRD response after re-induction is an important prognostic factor for sustained CR after relapse, able to predict EFS.[4,14] In our series, all patients achieving CR were also MRD-negative. Among 12 survivors in CR, 11 cases achieved an MRD-negative CR after one single cycle. Contrarily, among 12 patients not having an MRD-negative CR, only one was alive in remission.

Toxicity

One patient developed grade 3 neurotoxicity which rapidly recovered after transient discontinuation of blinatumomab infusion, and another grade 4 hypokaliemia. Two patients developed grade 3 hepatic sinusoidal obstruction syndrome after InO, which was successfully managed with defibrotide: one after conditioning for haplo-SCT, and the other without subsequent transplantation but 3 months after a myeloablative conditioning for HSCT (patient 26).

Outcome

Among 10 patients achieving a new CR, five suffered a subsequent relapse (6–22 months after MoAb) and died of disease (DOD); two underwent HSCT and were alive in remission 8 and 12 months later; one underwent consolidation with CAR-T cell therapy, then developed a myelodysplastic syndrome, underwent haplo-SCT and is alive in remission 30 months after starting InO; one was rescued with CAR-T after subsequent relapse and is alive in remission 13 months after InO; and one died of systemic *adenovirus* infection. Two patients achieving a PR (one in each group) progressed and died. Among eight non-responders (five in the blinatumomab group, three in the InO group), five DOD 1–7 months after treatment; one was alive with disease; 1 was lost to follow up; and one achieved CR with fludarabine, cytarabine and liposomal daunorubicin, underwent HSCT, relapsed again, was rescued with CAR-T cell therapy followed by HSCT (because short CAR-T persistence) and was alive in CR 38 months after blinatumomab (patient 7). One patient died from pulmonary unspecified infection before evaluation of response 1 month after starting InO (Table I).

Ten patients (five in each group) received the MoAb in remission in order to reduce MRD before transplantation (seven patients), to avoid further chemotherapy after overwhelming toxicity during re-induction (two patients in the InO group), and in CR2 with negative MRD after high-risk relapse (one patient in the blinatumomab group). Seven out of theses 10 patients underwent HSCT and were in CR 2–22 months later; one in each group died of treatment-related complications after haplo-SCT, and one progressed and died 4 months after blinatumomab. Thus, both MoAb might represent useful alternatives for the management of MRD before transplantation and for certain fragile patients with low disease burden.[7,15]

The 12-month EFS and OS rates were 38·9 ± 25·3% and 50·8 ± 26·4% in the blinatumomab group, 27·5 ± 25% and 45·8 ± 26% in the InO group (Fig 1). Median OS and EFS were 22 (3–41) and 8·5 (0–17) months with blinatumomab,

Table I. Characteristic of patients treated with blinatumoman (patients 1-15) and inotuzumab (patients 16-31)

Pt.	Age (years)	Biology	Previous lines of treatment	Indication	No of cycles	Response	MRD	Grade 3/4 haematological toxicity (grade)	Grade 3/4 non haematological toxicity (grade)	Outcome	Current status (months)
1	9	"B-other"	2	2nd relapse after HSCT	1	Progression		Neutropenia (3)	No	DOD	Dead (1)
2	6	High hyperdiploidy	3	2nd refractory relapse after haplo-SCT	1	Progression		Anaemia (3); leukopenia (4); thrombocytopenia (4)	GGT (3)	DOD	Dead (1)
3	15	*KMT2A*-rearranged	3	2nd refractory relapse after HSCT	2	PR (M2 bone marrow)	0,21%	Anaemia (4); neutropenia (4); thrombocytopenia (4)	No	Progression; DOD	Dead (3)
4	17	*BCR-ABL1*	2	2nd relapse after HSCT[†]	2	CR	Negative	Anaemia (3); neutropenia (4); thrombocytopenia (2)	No	2nd HSCT; subsequent relapse; DOD	Dead (26)
5*	7	Hypodiploidy	2	2nd relapse after HSCT	4	CR	Negative	Anaemia (3); neutropenia (4); thrombocytopenia (4)	No	DLI; subsequent relapse ($CD19^{-}$); inotuzumab; remission; DLI; new relapse; DOD	Dead (21)
6	1	*KMT2A*-rearranged	2	1st refractoy relapse	2	CR	Negative	Anaemia (2); neutropenia (3)	Hypokalemia (4)	HSCT	CR (12)
7	4	High-hyperdiploidy	2	1st refractory relapse	1	Progression		Neutropenia (3)	No	CR2 with FLA-DNX; HSCT; subsequent relapse; CR3 with CAR-T; 2nd HSCT	CR (38)
8	10	*ETV6-RUNX1*	3	3rd relapse after haplo-SCT	2	CR	Negative	Neutropenia (3)	ALT (3); AST (3); GGT (3)	2nd haplo-SCT; subsequent relapse; DOD	Dead (10)
9[‡]	4	High-hyperdiploidy	2	2nd relapse after HSCT	1	Progression		Anaemia (3); neutropenia (3); thrombocytopenia (4)	No	Inotuzumab[‡]; PR; DOD	Dead (4)
10	0·5	High-hyperdiploidy	1	Primary refractoy disease	1	Progression		Anaemia (3); neutropenia (4); thrombocytopenia (4)	No	CR after 3rd line	LFU (7)
11	9	"B-other"	1	CR1 high-risk ALL with emergent MRD (MRD 0·12%)	1	CR	Negative	No	Dysarthria (3); Paresthesia (3); Somnolence (3)	Haplo-SCT (CD3αβ-depletion)	CR (22)
12	12	"B-other"	2	CR2 (MRD 0·15%)	2	CR	Negative	Anaemia (2); neutropenia (4)	No	HSCT	CR (9)
13	15	"B-other"	2	CR2 (MRD 0·1%); Down syndrome	2	CR	Negative	No	No	HSCT	CR (17)

Table I. (*Continued*)

Pt.	Age (years)	Biology	Previous lines of treatment	Indication	No of cycles	Response	MRD	Grade 3/4 haematological toxicity (grade)	Grade 3/4 non haematological toxicity (grade)	Outcome	Current status (months)
14	7	"B-other"	2	CR2 with emergent MRD after haplo-SCT (MRD 10·6%)	3	CR	Negative	No	No	Haplo-SCT; grade 5 steroid refractory GVHD; dead (septic shock)	Dead (8)
15	4	"B-other"	2	CR2 (MRD < 0·01%)	1	Progression		No	No	CAR-T; progression; DOD	Dead (4)
16[§]	7	"B-other"	3	3rd relapse after haplo-SCT, blinatumomab and DLI	2	CR	Negative	Neutropenia (4); thrombocytopenia (3)	No	Dead (ADV)	Dead (2)
17 [§]	14	"B-other"	2	1st relapse after HSCT without response to blinatumomab	1	Progression		Anaemia (3); nutropenia (4); thrombocytopenia (4)	No	DOD	Dead (1)
18	5	"B-other"	3	2nd refractory relapse	2	CR	Negative	Neutropenia (3); thrombocytopenia (3)	No	Haplo-SCT	CR (8)
19	2	High-hyperdiploidy	2	1st refractoy relapse after HSCT	2	CR	Negative	Neutropenia (3); thrombocytopenia (2)	No	Haplo-SCT; subsequent relapse; CR3 with CAR-T	CR (13)
20	18	"B-other"	3	2nd refractory relapse after haplo-SCT	1	Not evaluated (early death)		Anaemia (3); neutropenia (4); thrombocytopenia (4)	No	Dead (lung infection)	Dead (1)
21	6	*TCF3-PBX1*	2	2nd relapse	2	CR	Negative	Anaemia (3); neutropenia (4); thrombocytopenia (4)	No	CAR-T; MDS; haplo-SCT	CR (30)
22*	8	Hypodiploidy	3	3rd relapse after blinatumomab (2nd relapse after HSCT)	6	CR	Negative	Neutropenia (4)	No	DLI; subsequent relapse ($CD22^{+}$); DOD	Dead (12)
23	7	*KMT2A*-rearranged	2	1st refractory relapse	1	Progression		No	No	DOD	Dead (1)
24	10	"B-other"	2	2nd relapse after HSCT	1	Progression		Anaemia (3); neutropenia (4); thrombocytopenia (4)	No	DOD	Dead (1)
25	15	"B-other"	1	Primary refractory disease	2	CR	Negative	Neutropenia (4); thrombocytopenia (3)	No	HSCT; subsequent relapse; DOD	Dead (7)
26 [‡]	4	High-hyperdiploidy	4	2nd relapse after HSCT, refractory to re-induction and blinatumomab	1	PR (M0 bone marrow)	Negative	Anaemia (3); thrombocytopenia (4)	SOS (3)	DOD	Dead (3)

Table I. (*Continued*)

Pt.	Age (years)	Biology	Previous lines of treatment	Indication	No of cycles	Response	MRD	Grade 3/4 haematological toxicity (grade)	Grade 3/4 non haematological toxicity (grade)	Outcome	Current status (months)
27	14	"B-other"	1	CR1 high-risk ALL with emergent MRD (MRD 0·4%)	1	CR	Negative	No	No	HSCT	CR (2)
28	0,5	*KMT2A*-rearranged	2	CR1 (MRD 0·46) after 1st-line failure and FLA-doxo rescue with severe toxiciity	1	CR	Negative	Anaemia (3)	No	Haplo-SCT	CR (22)
29	9	"B-other"	2	CR2 (MRD < 0·01%); severe toxicity after re-induction	2	CR	Negative	Anaemia (2)	No	HSCT	CR (20)
30	10	"B-other"	2	CR2 (MRD 0·27%)	1	CR	Negative	Anaemia (1)	SOS (3)	HSCT	CR (2)
31	6	High-hyperdiploidy	3	CR2 (MRD < 0·01%) after refractory relapse; clofarabine, VP16, cyclophosphamide rescue with severe toxicity	2	CR	Negative	Anaemia (2)	No	Haplo-SCT; dead (ADV)	Dead (4)

ADV, adenovirus; ALL, acute lymphoblastic leukaemia; ALT, alanine aminotransferase increase; AST, aspartate aminotransferase increase; CAR-T, chymeric antigen receptor T cell therapy; CR, complete remission; CR1, first CR; CR2, second CR; CR3, third CR; DLI, donor lymphocyte infusions; DNX, lyposomal daunorubicin; DOD, dead of disease; doxo, liposomal doxorubicin; FLA, fludarabine, cytarabine; GGT, gamma-glutamyltransferase increased; GVHD, graft versus host disease; haplo-SCT, haploidentical transplantation; HSCT, allogeneic haematopoietic stem cell transplantation; LFU, lost to follow up; MDS, myelodysplactic syndrome; MRD, minimal residual disease; M0, empty bone marrow without blasts; M2, ≥ 5% to < 25% blasts; PR, partial response; Pt, patient; SOS, sinusoidal obstruction syndrome.

*Cases 5 and 22 correspond to the same patient.

†This patient received blinatumomab without concomitant tyrosine kinase inhibitor treatment (previous treatment with imatinib, dasatinib and nilotinib).

‡Cases 9 and 26 correspond to the same patient.

§Previous treatment with blinatumomab not included in this study.

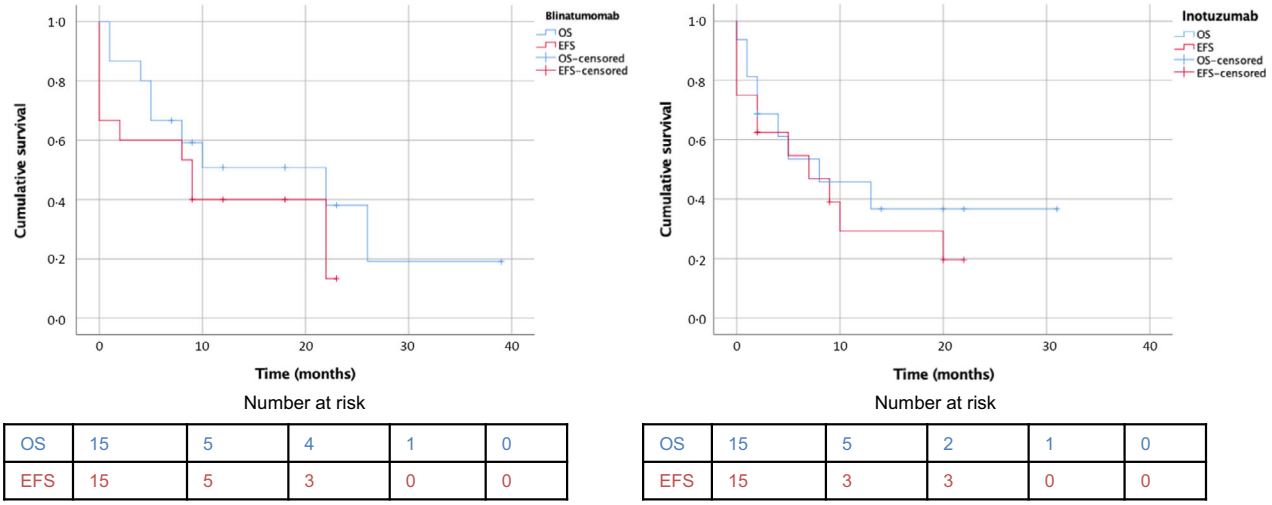

Fig 1. Twelve months overall (OS) and event free survival (EFS) of patients treated with blinatumomab and inotuzumab ozogamicin: OS 50·8 ± 26·4% and 45·8 ± 26%, EFS 38·9 ± 25·3% and 27·5 ± 25%, respectively.

7·5 (0–14) and 7 (0–14) months with InO. Patients starting treatment in remission did better than those who started with overt disease (Fig S1). These results are similar to those previously reported in children.[8,11]

In our series, all survivors in remission had undergone HSCT or CAR-T cell therapy, supporting the notion that, for patients in advanced stage, MoAb should be considered as a bridge to consolidation. However, this represents a heavily pretreated population, and administration of blinatumab or InO, or even sequential administration of both MoAbs, might improve outcome at earlier stages.

In summary, although no definite conclusions can be extracted from this small retrospective study, we found that both blinatumomab and InO were able to induce MRD-negative remission in advanced-stage ALL in children, and may be considered for the improvement of MRD before HSCT, or under situations where further chemotherapy is not warranted. Their different target antigens, mechanism of action and different toxicity profile deserve individualised indication considering leukaemia phenotype, previous toxicity and further consolidation therapy delineated.

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Conflict of Interest

J.L.F. is a consultant/advisory member for Amgen, Jazz Pharmaceuticals and Novartis; receives honoraria for speaking at symposia from Amgen, Servier, Jazz Pharmaceuticals and Pfizer; and receives support for attending symposia from Servier and Jazz Pharmaceuticals. F.B. is a consultant/advisory member for Bayer, Amgen and Eusa Pharma; receives honoraria for speaking at symposia from Amgen and Jazz Pharmaceuticals; and receives support for attending symposia from Takeda, EusaPharma and Jazz Pharmaceuticals. M.R. receives support for attending symposia from Jazz Pharmaceuticals. Other authors' competing interests: none.

Author Contributions

All authors contributed to the acquisition, analysis and interpretation of the data; revised the manuscript critically; approved the final version for publication and agreed to be accountable for the results presented. J.L.F. generated first and subsequent drafts of the manuscript.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Indication for treatment.

Table SII. Response to blinatumomab and inotuzumab.

Fig S1. Event-free survival (A and C) and overall survival (B and D) of patients starting treatment with blinatumomab and inotuzumab ozogamicin in remission *versus* those starting treatment with overt disease.

Data S1. Supplemental methods.

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