Received: 4 March 2024 | Revised: 11 April 2024 | Accepted: 30 April 2024

DOI: 10.1002/jha2.927

eJHaem

British Society for Haematology

CASE REPORT

Case report: Sequential inotuzumab, blinatumomab, and chemotherapy with concurrent donor lymphocyte infusions induce complete remission in relapsed pre-B acute lymphoblastic leukemia

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Abstract

This case report presents the successful management of relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia in a 54-year-old male post-allogeneic hematopoietic cell transplantation. The combinatorial approach of sequential antibody treatment (Inotuzumab [InO] and Blinatumomab [Blina]) combined with three donor lymphocyte infusions (DLI) applications and cytoreductive chemotherapy-induced sustained complete molecular remission as documented at the last follow-up 30 months later. This case highlights the feasibility and potential synergistic efficacy of a Blina/DLI regimen and supports the hypothesis that T-cell engagers could enhance the DLI effect. Furthermore, the co-administration of InO, Blina, DLI, and cytoreductive chemotherapy was proven to be feasible without severe adverse events.

KEYWORDS
B-ALL, case report, DLI, immunotherapy, monoclonal antibodies

1 | INTRODUCTION

The prognosis of relapsed or refractory (r/r) acute lymphoblastic leukemia (ALL) remains dismal to date and worsens with age [1]. 20%–40% of patients relapse after allogeneic hematopoietic cell transplantation (alloHCT), with a median overall survival (OS) of only 5.5 months [2]. Donor lymphocyte infusions (DLI) after alloHCT can boost the graft-versus-leukemia (GvL)-effect of the allograft. However, DLI showed limited efficacy in r/r ALL [3]. Explanatory hypotheses focus on immune-escape mechanisms with T-cell-anergy [4] or reduced expression of co-stimulatory molecules [5]. Recently, antibody-based therapeutics like Blinatumumab (Blina), a CD3/CD19 bispecific T-cell engager, and Inotuzumab-ozogamicin (InO), a CD22 antibody-drug conjugate, have demonstrated promising efficacy in adult r/r B-ALL, with a median OS of 7.7 months [6, 7]. Using Blina/Ino in sequence has not yet been investigated in prospective, randomized trials. But case series show a benefit of the combination [8, 9]. Adding low-intensity chemotherapy was successful in avoiding full-dose antibody therapy and accompanying side effects [10]. Inspired by the idea of the superiority of combinatorial antibody-based regimes and presuming that additional DLI may increase anti-leukemic effects, the following case was reviewed academically.

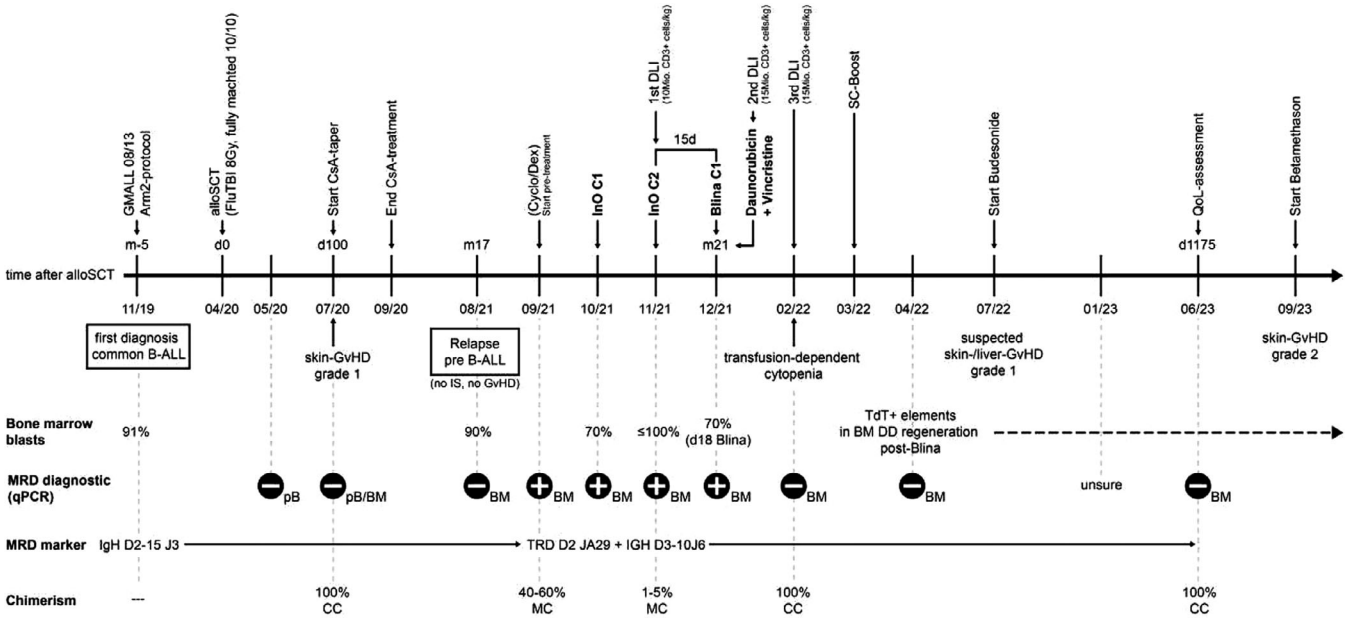

FIGURE 1 Disease history over time. Allogenic stem-cell transplantation (alloSCT), fludarabin with total body irradiation (FluTBI), complete chimerism (CC), mixed chimerism (MC), cyclosporine A (CsA), graft versus host disease (GvHD), immunosuppressive therapy (IS), inotuzumab ozogamicin (InO), blinatumomab (Blina), donor-lymphocyte infusion (DLI), stem-cell (SC) boost, and quality of life (QoL).

TABLE 1 Patient and treatment characteristics. Allogenic stem-cell transplantation (alloSCT), fludarabin with total body irradiation (FluTBI), matched unrelated donor (MUD), graft versus host disease (GvHD), rabbit anti-thymocyte globulin (ATG), cyclosporine (CsA), methotrexate (MTX), mixed chimerism (MC), bone marrow (BM), inotuzumab ozogamicin (InO), blinatumomab (Blina), donor-lymphocyte infusion (DLI), progressive disease (PD), complete response (CR), and quality of life (QoL).

Age at alloSCT	Cytogenetics	Remission at alloSCT	Conditioning	Donor	GvHD prophylaxis	Time to relapse	Chimerism and blast count at relapse
52	Complex karyotype	CR (MRD negative)	FluTBI 8 Gy	MUD 10/10	ATG, CsA, MTx	510 days	40-60 % MC 90% (BM)
DLI dose per infusion (CD3+ cells/kg)	**DLI timepoints**	**Best responses**	**Time from Ino to Blina (days)**	**Start Blina to best response**	**Follow-up time from relapse**	**Outcome**	**QoL (GHS in %)**
1st 10 Mio	C2 Ino	PD	15	90 days	30 months	Mol.CR	83.3
2nd 15 Mio	C1 Blina, Dauno + Vincristine	CR					
3rd 15 Mio	Unrelated	CR					

2 | CASE REPORT

Sequential Ino, Blina, and chemotherapy with concurrent DLI application were explored in a 54-year-old male with common-B-ALL, who relapsed 17 months after alloHCT from a fully matched unrelated donor. Figure 1 and Table 1 provide an overview of the disease history and therapy course. The initial disease presented anemia, thrombocytopenia, and 12% blasts in peripheral blood. Bone marrow (BM) analysis showed 91% leukemic infiltration with CD19+, CD20+, CD10+, TdT+ phenotype and a hypodiploid karyotype (36 < 2n >, X,-Y,−2,−3,−4,−12,−13,−15,−16,−17 [2]. 72 < 4n > [2] and 46, XY [21]). The medical history included hypertension and suspicion of primary hyperaldosteronism, without any long-term medication. Minimal residual disease (MRD) diagnostic by real-time polymerase chain reaction was established for two markers related to clonal IGH-gene rearrangements. 1st line treatment followed the GMALL08/13 study protocol. After consolidation, I, a molecular CR (mol.CR) was reached. A 25-year-old male was selected as a fully matched, unrelated donor (MUD 10/10, matched A rh^- blood type, CMV negative). Myeloablative conditioning was performed with Flu-TBI (Fludarabin 30 mg/m^2, day −6 to −3; TBI 8 Gy abs., day −2 to −1), and rabbit anti-thymocyte globulin (ATG, day −4 to −1), cyclosporine (CsA, started day −2) and methotrexate (MTX 10 mg/m^2, day +1, +3, +6, +11). 4.45 Mio. CD34+ cells/kg were transplanted. Delayed blood count regeneration and a

grade I skin graft-versus-host-disease (GvHD) was monitored. GvHD was self-limiting over the course of time. At month +4, the patient was MRD negative with 100% donor chimerism, allowing tapering of immunosuppression until month +7. However, at month +17, a fulminant hematologic relapse as pre-B-ALL was detected. No signs of cGvHD were evident at this time. The BM showed 94.5% blasts (CD19low CD10+ CD34+, TdT+, cyIgM+, and CD20+) and 40–60% mixed chimerism. Due to clonal evolution, MRD assessment of the initially determined markers remained negative until two new markers were identified 3 months later. Relapse treatment started with a preliminary phase (dexamethasone, 5 days 10 mg/m^2; cyclophosphamide, 3 days 200 mg/m^2) and two cycles of InO with a 1st DLI-application (10 Mio CD3+ cells/kg, InO-Cycle 2 day 22). After the 1st cycle of InO, the leukemic MRD clone persisted at a level of 70%. After the 2nd cycle InO including DLI, the BM was entirely replaced by infiltrates of the pre-B-ALL. Again, a preliminary phase with additional intrathecal MTX application (15 mg abs.) was applied. Intravenous Blina was started 15 days after the end of InO and 8 days after 1st DLIs with the following side effects: deterioration in fine motor skills, psychomotor slowing, edema, fever, and cytopenia (grade IV). Remission control at day 18 of Blina-Cycle 1 revealed 70% marrow disease with an unchanged high MRD. Subsequently, cytoreductive chemotherapy with Daunorubicin (2 × 45 mg/m^2) and Vincristine (2 mg abs.) was parallelly administered to Blina-days 20 and 21 as well as a 2nd DLI-application (15 Mio CD3+ cells/kg) on Blina-day 25. Blina was discontinued on day 26 of 28 at the patient's request. 40 days after the last therapy and 90 days after starting Blina, a mol. CR with complete chimerism was seen. A 3rd DLI application (15 Mio CD3+ cells/kg) in month +6 and a stem-cell boost in month +7, due to persistent transfusion-dependent pancytopenia, were given. At month +11, a skin and liver GvHD grade 1 was suspected, why budesonide was started. At month +13, the skin GvHD progressed to a grade 2, and treatment was switched to betamethasone. At the last follow-up (month +30 after relapse, day +1419 after alloHCT), the patient is off-treatment and shows an ongoing hematologic and mol.CR. A mild cytopenia persists. The last histological BM evaluation in month +20 after relapse revealed a normocellular, reactively altered hematopoiesis. Increased PAX5- (20%–30%) and TdT-positive cells (10%) were interpreted as part of hematologic regeneration as MRD evaluation was negative. A quality-of-life assessment (EORTC QLQ30, FACT-BMT), showed a good global health status of 83.3%. Functional subscales revealed deficits in role functioning (66.6/100%) and family well-being (23.3/28 points). Symptom scales showed minor complaints related to insomnia and fatigue.

3 | DISCUSSION

Our case illustrates the synergistic potential of Blina/DLI application with cytoreductive chemotherapy in r/r B-ALL treatment. Given the multiple therapeutic components, it is difficult to ascertain the specific contribution of each component to the observed leukemia response. But the combination of different mechanisms of action all demonstrated superiority in recent trials, compared to monotherapy concepts [11]. In our case, the facts indicate InO refractoriness, even with simultaneous DLI application. Rather, we assume that the subsequent use of Blina may significantly augment DLI activity and vice-versa. Additionally, the chemotherapy likely provides temporary support, allowing the Blina/DLI regimen to be fully effective. Nevertheless, seeing high levels of persistent disease after Blina initially, both DLIs and Blina neither seem solely responsible for the far better disease-free survival of 30 months seen so far. More likely, we interpret the durability of response as a sign of the treatment sequence with repetitive DLI administrations. Concurrent Blina/DLI therapy showed already good response rates in the case series [12], but the patient cohorts were in a more favorable position than our patient [13]. Therefore, a synergistic effect of Blina in combination with DLI must be discussed. Another explanation could be the DLI dose escalation at the 2nd and 3rd administrations. However, existing data tend to contradict this explanation. Solely pre-DLI chemotherapy did not reliably impact survival [3] and OS with DLI-monotherapy is limited to 9.8 months [2]. The absence of problematic GvHD despite moderate DLI doses is also unusual, as many cases reported high rates of severe GvHD using a chemo-DLI approach [3, 11]. Lastly, our timeline was tight, choosing a 15-day InO-Blina interval (compared to, e.g., 99 days [8]). Likewise, DLI applications mostly took place in Blina-Cycle 3, while we applied them in Cycle 1. In sum, our case indicates Blina to be a good host conditioning regimen for r/r ALL patients receiving DLI. The hypothesis that T-cell engagers enhance the DLI effect is supported. Co-administration of InO, Blina, DLI, and cytoreductive chemotherapy was feasible without severe adverse events.

AUTHOR CONTRIBUTIONS

Conceptualization, Wichard Vogel and Sina Beer; Data curation, Sina Beer; Investigation, Sina Beer; Resources, Sina Beer; Supervision, Claudia Lengerke, Wolfgang Bethge, and Wichard Vogel; Visualization, Sina Beer; Writing – original draft, Sina Beer; Writing – review & editing, Wichard Vogel, Wolfgang Bethge, Christoph Faul, and Claudia Lengerke. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGMENTS

We acknowledge support from the Open Access Publication Fund of the University of Tübingen.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

For original data, please contact sina.beer@med.uni-tuebingen.de.

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

PATIENT CONSENT STATEMENT

Informed consent was obtained from the patient described in the case report.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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How to cite this article: Beer SA, Bethge W, Faul C, Lengerke C, Vogel W. Case report: Sequential inotuzumab, blinatumomab, and chemotherapy with concurrent donor lymphocyte infusions induce complete remission in relapsed pre-B acute lymphoblastic leukemia. eJHaem. 2024;5:620–23. https://doi.org/10.1002/jha2.927