Case Report

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Athanasios Tragiannidis [1,*], Vassiliki Antari [1], Eleni Tsotridou [1], Theodoros Sidiropoulos [1], Aikaterini Kaisari [2], Maria Palabougiouki [1], Timoleon-Achilleas Vyzantiadis [3], Emmanuel Hatzipantelis [1], Assimina-Galli Tsinopoulou [1] and Evgenios Goussetis [2]

[1] Children & Adolescent Hematology-Oncology Unit, Second Department of Pediatrics, School of Medicine, Aristotle University of Thessaloniki, Greece
[2] Stem Cell Transplant Unit, "Agia Sofia Children's Hospital", Athens, Greece
[3] Department of Microbiology, School of Medicine, Aristotle University of Thessaloniki, Greece.
* Correspondence: atragian@auth.gr or atragian@hotmail.com

Abstract: Despite the progress achieved regarding survival rates in childhood acute lymphoblastic leukemia, relapsed and/or refractory disease still poses a therapeutic challenge. Inotuzumab ozogamicin is a CD22-directed monoclonal antibody conjugated to calicheamicin, which has been approved by the Food and Drug Administration for adults and pediatric patients 1 year and older with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia. Herein, we present the case of a 23-month-old girl with high-risk B-acute lymphoblastic leukemia, who experienced very early isolated medullary relapse. She underwent conventional chemotherapy according to the ALL-IC REL 2016 protocol but due to unresponsiveness she was administered the bispecific T-cell engager (BiTE) blinatumomab. While on blinatumomab therapy the patient developed a probable invasive pulmonary aspergillosis and was put on combined antifungal treatment with voriconazole and liposomal amphotericin B. Due to refractory disease during blinatumomab therapy, the patient underwent treatment with the combination of fludarabine, cytarabine and the proteasome inhibitor bortezomib without remission. Given the high CD22 expression by the lymphoblasts, off-label use of inotuzumab ozogamicin (InO) was decided to be administrated in a 28-day cycle as salvage treatment. The MRD was 0.08% on day 28, which led to the decision to proceed to another cycle of InO. Following its completion, MRD was negative, and the patient underwent successfully an allogenic stem cell transplantation from a matched family donor.

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1. Introduction

Acute lymphoblastic leukemia (ALL) constitutes the most common malignancy in childhood. 5-year survival rates have increased significantly exceeding 90% but relapsed or refractory (r/r) disease still poses a therapeutic challenge [1,2]. According to literature, about 10-15% of patients experience relapse [3]. In cases of early medullary relapse, the probability of 10-year event-free-survival (EFS) remains very low [4]. Furthermore, achieving remission in order to proceed to hematopoietic stem cell transplantation (HSCT) can be challenging.

Recently novel treatments including monoclonal antibodies, small molecule drugs and chimeric antigen receptor T-cell (CAR-T) therapy have been added to clinicians' armamentarium. Inotuzumab ozogamicin (InO) is an antibody-drug conjugate comprising of a monoclonal antibody targeting CD22 and the cytotoxic agent calicheamicin. The proposed mechanism of action includes binding to CD22 on the surface of leukemic cells, internalization of the complex, fusion of the endosome containing the complex with a lysosome, release of calicheamicin, induction of double-stranded DNA

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breaks and ultimately of cell apoptosis due to irreversible DNA damage [5]. On March 6, 2024, the Food and Drug Administration approved inotuzumab ozogamicin (Besponsa, Pfizer) for pediatric patients 1 year and older with relapsed or refractory CD22-positive B-cell precursor ALL [6].

Herein, we report the case of a patient with high-risk disease, very early medullary relapse and invasive pulmonary aspergillosis during relapse therapy, who achieved complete remission with MRD negativity using InO following failure of salvage conventional chemotherapy, blinatumomab and bortezomib plus fludarabine and cytarabine and successfully underwent HSCT.

2. Detailed case description

A 23-month-old girl was admitted to our department due to fever, leukocytosis, anemia and thrombocytopenia. The patient's blood cell count revealed a total white blood cell count of 21.6x10^9/L, platelet count of 50x10^9/L and hemoglobin of 71.00g/L. Notably, bone marrow cytology analysis demonstrated that abnormal lymphocytes comprised 94% of nucleated cells, suggesting a new diagnosis of acute lymphoblastic leukemia. Flow cytometry analysis also confirmed the presence of abnormal lymphocytes expressing CD10, CD19, CD22, CD24, CD34 CD79a, CD105, CD123 and HLA-DR. Karyotype analysis revealed a female hyperdiploid clone with 56 chromosomes (56,XX,+X,+4,+6,+8,+14,+17,+18,+21,+22,+mar [18]/46,XX[2]). Translocations t(4;11), t(9;22), t(1;19) and t(12;21) were not detected. The patient also presented with central nervous system (CNS) disease at diagnosis (CNS 3 disease). She started induction therapy according to the ALLIC-BFM 2009 and was assigned to the HR group due to MRD positivity on day 33 (0.95%). Following reinduction completion the patient underwent cranial radiotherapy and subsequently started maintenance therapy.

However, two months after the initiation of maintenance therapy the patient presented with leukopenia, neutropenia and thrombocytopenia. Bone marrow flow cytometric analysis showed 78% of abnormal lymphocytes expressing CD19, CD 10, CD22, CD9, CD38+partial and CD58 (Figure 1). She underwent chemotherapy according to the ALL-IC REL 2016 protocol. After the completion of the second consolidation block she underwent a routine minimal residual disease (MRD) measurement that was highly positive (88%). Conventional chemotherapy was discontinued and subsequently the patient was administered the bispecific T-cell engager (BiTE) blinatumomab as continuous intravenous infusion (15mg/m^2). During blinatumomab administration she developed a grade 2 cytokine release syndrome (CRS). Her symptoms were mild and were resolved with low doses of dexamethasone and low-flow oxygen supplementation for less than one week. During the third week of blinatumomab infusion the patient was still agranulocytopenic and due to low fever, persistent cough and malaise a thorax computer tomography scan (CT) and serum galactomannan test were performed. Due to the presence of nodules on CT scan and positive galactomannan in two consecutive serum samples (>0.5ng/ml) the patient was diagnosed with probable pulmonary aspergillosis (IPA). While on therapy with blinatumomab the patient was put on combined antifungal treatment with liposomal amphotericin B (3mg/kg/day iv) and voriconazole (9 mg/kg/bid iv). Due to the infectious complication and to the persistence of neutropenia an MRD measurement was performed that was highly positive (92%). Due to refractoriness of disease, the patient continued combined antifungal treatment for 2 weeks and without discontinuation of antifungals she underwent salvage treatment with the combination of fludarabine, cytarabine (FLA) and the proteasome inhibitor bortezomib. However, MRD after completion of the cycle raised to 98% and patient showed sevopositivity for varicella zoster virus (VZV) due to bortezomib therapy although was on prophylactic treatment with acyclovir (Figure 1).

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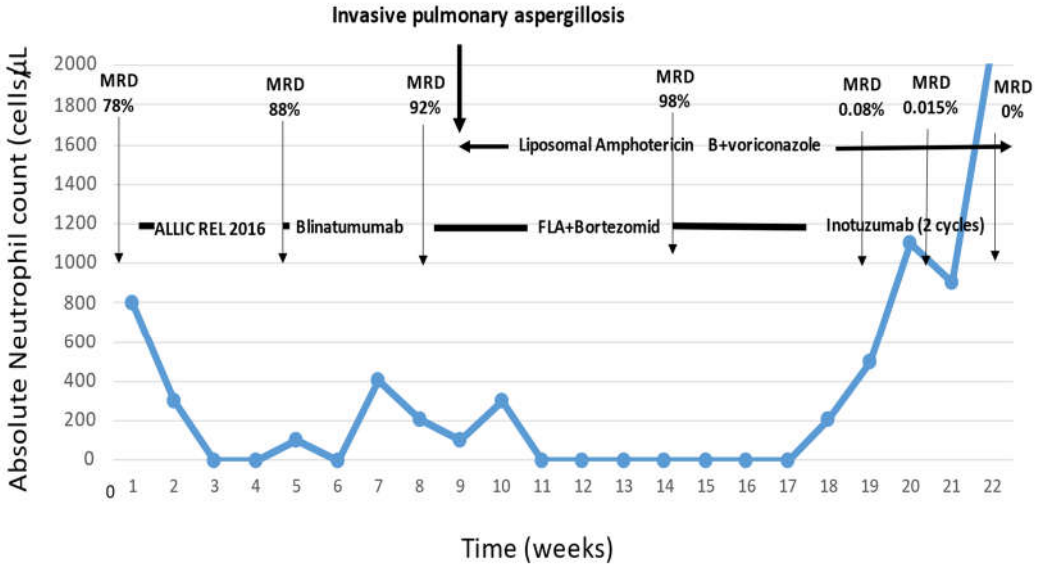

Figure 1. Clinical course of the patients. MRD: minimal residual disease, FLA: fludarabine+cytarabine

Finally, given the high CD22 expression by the lymphoblasts, off-label use of inotuzumab ozogamicin (InO) was decided to be administrated in a 28-day cycle with a dosing of 1.8mg/m^2 divided on days 1 (1mg/m^2), 8 (0.5mg/m^2) and 15 (0.5mg/m^2). InO was administered in combination with liposomal amphotericin B and voriconazole. The MRD was 0.08% on day 28, which led to the decision to proceed to another cycle of InO. InO was well tolerated, and the patient did not experience CRS, VOD (veno-occlusive disease), SOS (sinusoidal obstruction syndrome) and/or any other adverse events related to its administration. Although galactomannan values were negative while on InO therapy the patients continued combined antifungal treatment. Following the completion of the second InO cycle the MRD was negative. Thorax CT scan showed amelioration of nodular lesions with decrease in size and number. Liposomal amphotericin B was interrupted and monotherapy with voriconazole was continued. While on remission the patient underwent allogenic stem cell transplantation (SCT) from a matched family donor after a conditioning regimen with treosulfan, fludarabine and thiotepa.

3. Discussion

Inotuzumab ozogamicin has been proven to be both efficacious and safe for pediatric patients with r/r disease and is indicated as monotherapy for CD19 B precursor r/r ALL in pediatric patients aged one year or older. On March 6, 2024, the Food and Drug Administration approved inotuzumab ozogamicin (Besponsa, Pfizer) for pediatric patients 1 year and older with relapsed or refractory CD22-positive B-cell precursor ALL [6]. Locatelli et al. demonstrated that blinatumomab is superior to a third chemotherapy consolidation block before allogeneic HSCT (alloHSCT) in patients with high-risk first relapse in terms of event free survival (EFS) and MRD remission (90% versus 54%), as well as incidence of serious adverse events (24.1 versus 43.1%), but eligible patients had M1 or M2 bone marrow status at randomization [7]. Additionally, in the final analysis of the open-label, single-arm RIALTO study of blinatumomab administration in patients with r/r B-ALL only 21% were refractory to reinduction [8]. Furthermore, in a phase 3 randomized controlled trial by the Childrens' Oncology Group (COG), which compared the administration of blinatumomab with consolidation chemotherapy earlier on, i.e., post reinduction in cases of intermediate or high risk relapse, the results were also very encouraging with increased overall survival (71% versus 58%) and MRD remission (75% versus 32%), but a small subset of patients who received blinatumomab (17%) had experienced very early medullary relapse (<18 months from initial diagnosis) [9]. In our case of very early medullary relapse and a rising MRD despite reinduction and one consolidation block of

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chemotherapy there was no response to blinatumomab. Likewise, the use of bortezomib in combination with chemotherapy has rendered very promising results in r/r ALL [10,11]. FLAG (FLA+G-CSF) with bortezomib is particularly appealing due to both high remission rates (morphological remission of 92% and negative MRD of 61%) and minimal gut toxicity in a heavily pretreated patient population, thus minimizing the risk of bacterial translocation and subsequent sepsis. Of interest, post bortezomib seropositivity for varicella-zoster virus was detected in our case, as described in literature [12].

CD22 is a B-lineage differentiation antigen that has emerged as an appealing therapeutic target in cases of r/r ALL, as it is expressed on more than 90% of leukemic cells in pediatric patients with relapsed B-ALL with the exception of the presence of MLL-rearrangements [13,14]. InO has been approved in adults with r/r B-ALL based on the results of the INO-VATE trial, but data in the pediatric population remains limited [15]. In two retrospective studies of small patient cohorts who received InO on compassionate grounds very high complete remission (CR) rates were reported (approximately 67% in both studies) with high percentages of MRD negativity among responders [16,17]. It is noteworthy that in the study by Bhojwani et al. the patient population included cases of prior CD22-directed therapy and that the majority of responders achieved CR after only one cycle of InO, similarly to our case [16]. Objective response rate (ORR) ranged between 58.3% and 83% in phase 1 and 2 clinical trials of InO as single agent in patients with r/r B-ALL with MRD negativity being achieved in the vast majority of responders [18–21]. Regarding its safety profile, InO was generally well-tolerated with hematological toxicity, infections, hepatotoxicity, and particularly sinusoidal obstruction syndrome (SOS) being the most common and alarming adverse events [18–21]. SOS in the pediatric population mainly occurs after HSCT. Previous HSCT, conditioning with busulfan or clofarabine, shorter time interval between the last dose of InO and HSCT have all been associated with increased risk of SOS, but there is contradicting data between studies [18–21]. In our case hematologic toxicities could not be precisely assessed, as the patient was already experiencing cytopenias, but no hepatic or other toxicity before or after HSCT was observed.

Our case highlights the efficacy and safety of InO as salvage treatment in the setting of relapsed B-ALL refractory not only to conventional chemotherapy, but also to novel treatments, such as blinatumomab and bortezomib.

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