Acta Haematologica Polonica 2023
Number 4, Volume 54, pages 248–251
DOI: 10.5603/AHP.a2023.0041
ISSN 0001–5814
e-ISSN 2300–7117

SHORT COMMUNICATION

VIA MEDICA

Impact of CAR-T therapy for outcomes in primary refractory acute lymphoblastic leukemia

Joanna Stankiewicz*, Ewa Demidowicz, Natalia Bartoszewicz, Andrzej Kołtan, Monika Richert-Przygońska, Jan Styczyński

Department of Pediatric Hematology and Oncology, *Collegium Medicum*, Nicolaus Copernicus University in Toruń, Jurasz University Hospital 1, Bydgoszcz, Poland

Introduction

Acute lymphoblastic leukemia (ALL) is the most common type of malignancy in children. Improvements in ALL therapy have led to significant progress in outcomes, so that currently more than 85% of children with ALL survive for five years or longer after diagnosis [1]. Unfortunately, relapses or refractory disease remain one of the main reasons for therapy failure. Patients who do not achieve remission after the induction phase are considered a very high-risk group, with an unfavorable prognosis [2]. Since the early 2010s, patients not responding to initial treatment have been treated with intensified chemotherapy, with allogeneic hematopoietic stem cells transplantation (allo-HSCT) as the treatment of choice [2]. However, this treatment is associated with severe toxicity and potentially life-threatening complications [1, 2].

During the last decade, several new therapeutic options for children with high-risk ALL have been developed, such as monoclonal antibodies, drug-antibody conjugates, and chimeric antigen receptor T-cells (CAR-T) [3].

We describe below two children with refractory ALL treated with modern therapeutic options in the pre-CAR-T era, as well as after the introduction of CAR-T therapy in Poland.

Methods

Anonymized data of two patients treated in the Department of Pediatric Hematology and Oncology, Antoni Jurasz University Hospital No. 1 in Bydgoszcz, Poland was collected. The diagnosis was established based on a bone marrow biopsy including cell morphology with French–American–British (FAB) classification and immunophenotyping. Analyzed data included clinical observations, laboratory test results and therapy outcomes. Analysis of blast cells in peripheral blood (PB) and bone marrow (BM) was performed in the Laboratory of Clinical and Experimental Oncology at Antoni Jurasz University Hospital No. 1; molecular analysis of blast cells was performed in the Medical Laboratory of Pediatric Oncology and Hematology at the Central Clinical Hospital of the Medical University of Lodz; flow cytometry monitoring of minimal residual disease (MRD) was performed in the Department of Pediatric Hematology and Oncology in the Central Clinical Hospital of the Medical University of Silesia; and polymerase chain reactions (PCR) MRD were also performed in the Medical Laboratory of Pediatric Oncology and Hematology in the Central Clinical Hospital of the Medical University of Lodz. This study was approved (KB 577/2021) by the Bioethics Committee of the Nicolaus Copernicus University in Toruń.

Results

Patient 1

A 4-month-old boy, previously healthy, was referred to the Department of Pediatric Hematology and Oncology due to hyperleukocytosis (112 G/L), severe anemia (3.9 g/dL) and thrombocytopenia (7 G/L). The child was diagnosed with pro-B ALL with MLL/KMT mutation, without central nervous system (CNS) involvement. Therapy according to the AIEOP-BFM ALL 2017 protocol was initiated. On day 8 of his treatment, the response was assessed as satisfying without blast cells in PB (no prednisone poor response). MRD on day 15 measured by flow cytometry was 9.9%. Bone marrow biopsy performed on day 33 showed 0.6% of

*Address for correspondence: Joanna Stankiewicz, Department of Pediatric Hematology and Oncology, *Collegium Medicum*, Nicolaus Copernicus University in Toruń, Skłodowskiej-Curie 9, 85–094 Bydgoszcz, Poland, e-mail: joanna.konieczek@cm.umk.pl

Received: 19.03.2023 Accepted: 27.04.2023 Early publication date: 04.08.2023

blast cells in myelogram and PCR MRD 3×10^{-2}. The boy was subsequently stratified to a high risk (HR) group with therapy intensification.

On day 64 of therapy, PCR MRD was still positive ($1 \times \times 10^{-3}$) and increased to 2×10^{-2} on day 118 of treatment. According to the therapy protocol, the boy was eligible for allo-HSCT. Subsequently, he received the IDA-FLAG [fludarabine, high-dose cytarabine (HD-Ara-C), idarubicin, granulocyte colony-stimulating factor (G-CSF)] chemotherapy cycle, which was complicated by sepsis and cardiorespiratory failure. He was treated with broad-spectrum antibiotics and catecholamines, and he responded well to the treatment. Afterwards, he received one cycle (of 28 days) of blinatumomab therapy administered through continuous infusion with a dose of 2 µg/day during the first seven days, followed by a dose of 6 µg/day for the next 21 days. However, after the cycle, PCR MRD increased to 8×10^{-1}. The therapy was switched to HIB chemotherapy according to the ALL IntReALL2010 HR protocol. After three weeks of the next line treatment, there were 79.8% blast cells in the bone marrow. Due to the failure of classical chemotherapy, the patient received two cycles of immunotherapy treatment with monoclonal antibody-drug conjugate anti-CD22 (inotuzumab ozogamicin) at a dose of 0.5 mg in a single infusion, as part of mini-Hyper-CVD [cyclophosphamide, dexamethasone, methotrexate and cytarabine in reduced doses] chemotherapy. The blast cell load in the bone marrow was 40% after the first cycle of inotuzumab and 28% after the second one. However, after the third cycle of immunotherapy, there was another increase of blast cells in the bone marrow, with the percentage reaching 30%. The patient then received another cycle of chemotherapy with clofarabine, cyclophosphamide, etoposide and vincristine. Treatment was complicated with *Candida* sepsis, pneumonia and cardiorespiratory failure, which required treatment in the intensive care unit. Over the next few days, continuous clinical progression of leukemia was observed (progressive hepatosplenomegaly, increased blast cells count in PB). He was qualified for palliative care treatment. He died 14 months after the beginning of the ALL treatment.

Patient 2

A 13-month-old girl, previously healthy, was referred the Department of Pediatric Hematology and Oncology with hyperleukocytosis (268 G/L), severe anemia (3.9 g/dL), and thrombocytopenia (16 G/L). The girl was subsequently diagnosed with pro-B ALL with MLL mutation without CNS involvement. She was treated according to the AIEOP-BFM ALL 2017 protocol. During the induction phase, a poor response to initial treatment was observed (poor prednisone response on 8th day, 74% of blast cells in PB by flow cytometry (FC) MRD on 15th day, 6.6% of blast cells in BM on 33rd day). At the end of the consolidation phase, there were 0.4% of blast cells in BM. Due to an unsatisfactory response, the girl began the first of two scheduled cycles of blinatumomab administered through continuous infusion with a dose of 2 µg/day. The first cycle was interrupted after only two days because of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, but it was resumed immediately with a dose of 3 µg/day after the patient recovered from the infection. After the first cycle of blinatumomab, which lasted a total of 28 days, MRD PCR was 2×10^{-4}. During the second cycle of blinatumomab therapy, she received the drug at a dose of 12.5 µg/day via continuous infusion for 28 days.

However, despite the higher dose of blinatumomab, the MRD PCR increased to 7×10^{-4} after the second cycle. Furthermore, there were no matched related or unrelated donors for allo-HSCT. The patient was eligible for CAR-T therapy. As a bridge therapy during CAR-T preparation, she received immunotherapy with a single infusion of inotuzumab ozogamicin at a dose of 0.4 mg, followed by another infusion at a dose of 0.5 mg one week later. Unfortunately, there was a poor response, as demonstrated by a bone marrow biopsy that showed 47% blast cells. The therapy was switched to HIB cycle according to the IntReALL HR 2010 protocol. The next step was CAR-T infusion which was complicated by grade I cytokine release syndrome (CRS) and autoimmune hypothyroidism. Another complication of the treatment was secondary hypogammaglobulinemia, which has required IVIG substitution continuing up to date. The girl has been in remission since CAR-T infusion (for 19 months now), in a good general condition, and with adequate psychomotor development.

Discussion

Primary refractory childhood ALL occurs in a small subsequent group of patients, and represents 2–3% of all cases. Ten-year overall survival in this group is 32 ± 1%, with a particularly unfavorable survival rate among infants with an *MLL* gene rearrangement [2]. Previously, children with primary refractory ALL have received an intensification of conventional chemotherapy, but the results of this approach have proved unsuccessful due to the high toxicity of the treatment [4]. New therapeutic options based on immunotherapy have significantly improved prognosis in this high-risk group, with particular success demonstrated by CAR-T, which has proved to be a breakthrough in the treatment of patients with primary refractory or relapsed disease.

Blinatumomab has become the first approved bispecific monoclonal antibody for the treatment of pediatric relapsed or refractory B-cell ALL (B-ALL) [4]. Blinatumomab is a monoclonal antibody that simultaneously targets CD3+ of endogenous T-cells and CD19+ B-ALL cells. In phase I/II studies, it has demonstrated complete response (CR) rates of 30% in patients with refractory ALL, and of 48% in those with relapsed disease [5]. In phase III clinical trials in

high-risk relapsed childhood ALL, the incidence of events in the blinatumomab versus chemotherapy groups was 31% versus 57% (p <0.001) [6]. The most severe adverse effects include infections, anemia, thrombocytopenia, febrile neutropenia and CRS [5].

Another approach to immunotherapy in ALL is represented by drug-antibody conjugates such as inotuzumab ozogamicin, which is a CD22-directed monoclonal antibody conjugated to the cytotoxin calicheamicin. In the Children Oncology Group study, inotuzumab proved to be effective in children with relapsed ALL, with a response rate of 58% [CR or CR with incomplete bone marrow recovery (CRi)] [7]. Similar promising effects were shown in a study in an infant and young child population, where 50% of patients achieved CR [8]. The most severe and life-threatening complication of inotuzumab treatment is sinusoidal obstruction syndrome which can occur in as many as 50% of patients who have received allo-HSCT as part of their ALL treatment [8].

CAR-T has recently emerged as a breakthrough therapy for patients with refractory or relapsed B-ALL. CAR-T are T-cells engineered from the patient to express a chimeric antigen receptor for targeted receptor on B-ALL cells. Currently, only CD-19 targeted CAR-T are approved for childhood B-ALL treatment [4, 9]. CR after CAR-T infusion has reached 70–90% in clinical trials, depending on the CAR-T type and CR definition [9]. However, it is still unclear whether CAR-T should be considered as a final treatment, or whether it should be followed by allo-HSCT [9, 10]. On the other hand, CAR-T manufacturing can be challenging and the treatment is related to manageable, albeit life-threatening, complications such as CRS or neurotoxicity [9, 11, 12].

In this report we have described two cases of primary refractory childhood ALL. In both patients, a lack of remission at the end of induction was combined with other risk factors such as MLL rearrangements and high hyperleukocytosis at diagnosis [1]. Because of the failure of standard therapy, both children were qualified to second line therapy with immunotherapy as one of the available options. In both cases, monoclonal antibodies as well as intensification of classical chemotherapy have been shown to be only partially effective. Unfortunately, CAR-T therapy was unavailable in the first case, but it proved highly effective in the second patient, being a curative option. Since September 2021, CAR-T therapy has been reimbursed in Poland for children and adults up to the age of 25 with refractory or relapsed B-ALL.

We hope that innovative therapies will improve outcomes in patients with primary refractory disease, as until now the prognosis in these patients has been highly unfavorable.

Acknowledgements

We thank the physicians and nurses from the Department of Pediatric Hematology and Oncology and the Bone Marrow Transplantation Unit in the Antoni Jurasz University Hospital No. 1 in Bydgoszcz and the Clinical Department of Immunology, Bone Marrow Transplantation and Gene Therapy at the Jan Mikulicz-Radecki University Clinical Hospital in Wrocław for performing CAR-T therapy for Patient 2.

Authors' contributions

JS — data collection and interpretation, description of results, manuscript preparation. NB, ED, AK, MRP — data collection and interpretation. JS — thesis draft, critical review and important intellectual content, acceptance of final version for publication.

Conflict of interest

The authors declare no conflict of interest.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

References

1. Ceppi F, Cazzaniga G, Colombini A, et al. Risk factors for relapse in childhood acute lymphoblastic leukemia: prediction and prevention. Expert Rev Hematol. 2015; 8(1): 57–70, doi: 10.1586/17474086.2015.978281, indexed in Pubmed: 25367188.
2. Schrappe M, Hunger SP, Pui CH, et al. Outcomes after induction failure in childhood acute lymphoblastic leukemia. N Engl J Med. 2012; 366(15): 1371–1381, doi: 10.1056/NEJMoa1110169, indexed in Pubmed: 22494120.
3. Firczuk M. Old and new targets for immunotherapy of B cell acute lymphoblastic leukemia. Acta Haematol Pol. 2021; 52(4): 291–299, doi: 10.5603/AHP.2021.0056.
4. Asare JM, Rabik CA, Muller B, et al. Investigational treatment options in phase I and phase II trials for relapsed or refractory acute lymphoblastic leukemia in pediatric patients. Expert Opin Investig Drugs. 2021; 30(6): 611–620, doi: 10.1080/13543784.2021.1916466, indexed in Pubmed: 33896328.
5. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol. 2016; 34(36): 4381–4389, doi: 10.1200/JCO.2016.67.3301, indexed in Pubmed: 27998223.
6. Locatelli F, Zugmaier G, Rizzari C, et al. Effect of blinatumomab vs chemotherapy on event-free survival among children with high-risk first-relapse B-cell acute lymphoblastic leukemia: a randomized clinical trial. JAMA. 2021; 325(9): 843–854, doi: 10.1001/jama.2021.0987, indexed in Pubmed: 33651091.
7. O'Brien MM, Ji L, Shah NN, et al. A phase 2 trial of inotuzumab ozogamicin (InO) in children and young adults with relapsed or refractory (R/R) CD22+ B-acute lymphoblastic leukemia (B-ALL): results from Children's Oncology Group Protocol AALL1621. Blood. 2019; 134(Suppl_1): 741–741, doi: 10.1182/blood-2019-128977.

8. Brivio E, Hoogendijk R, Chantrain C, et al. A retrospective study on inotuzumab ozogamicin in infants and young children with relapsed or refractory acute lymphoblastic leukemia (ALL). Blood. 2019; 134(Suppl_1): 3890–3890, doi: 10.1182/blood-2019-126472.
9. Pulsipher MA. Are CAR T cells better than antibody or HCT therapy in B-ALL? Hematology Am Soc Hematol Educ Program. 2018; 2018(1): 16–24, doi: 10.1182/asheducation-2018.1.16, indexed in Pubmed: 30504287.
10. Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med. 2018; 378(5): 449–459, doi: 10.1056/NEJMoa1709919, indexed in Pubmed: 29385376.
11. Curran KJ, Margossian SP, Kernan NA, et al. Toxicity and response after CD19-specific CAR T-cell therapy in pediatric/young adult relapsed/refractory B-ALL. Blood. 2019; 134(26): 2361–2368, doi: 10.1182/blood.2019001641.
12. Strzelec A, Klima A, Gawlik-Rzemieniewska N, et al. A living drug: application of CAR-T therapy for lymphoid malignancies and beyond. Acta Haematol Pol. 2022; 53(4): 241–248, doi: 10.5603/ahp.a2022.0032.