Received: 21 September 2022 | Revised: 21 June 2022 | Accepted: 23 September 2022

DOI: 10.1002/pbc.30055

Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

WILEY

LETTER TO THE EDITOR

Prolonged remission in multiple relapsed MLL-rearranged infant B-ALL with inotuzumab ozogamicin

To the Editor:

Mixed lineage leukemia (MLL)-rearranged (MLL-r) infant acute lymphoblastic leukemia (ALL) is an aggressive leukemia with poor prognosis. The 4-year event-free survival is 47%.[1] Inotuzumab ozogamicin (InO) is a CD22-targeted antibody-drug conjugate approved to treat relapsed ALL. There is limited data on InO in infant leukemia.[2,3] Here, we present a case of MLL-rearranged pre-B infant ALL with multiple relapses and eventual long-term response to InO.

Our patient was diagnosed at 9-month-old of age with MLL-rearranged pre-B ALL. He was presented with leukemia cutis, leukocytosis, and CNS2. He was enrolled in Children's Oncology Group (COG) study AALL15P1.[4] He had an isolated bone marrow relapse 5 months into the treatment. He was then enrolled on the COG relapse protocol AALL1331 and randomized to receive chemotherapy with plans for bone marrow transplant. However, he had a second marrow relapse before he could receive a transplant.

Blinatumomab was then given as a bridging therapy while awaiting chimeric antigen receptor-T cell (Car-T) therapy. Ironically, on the day of admission for CAR-T therapy, he was found to have central nervous system (CNS) relapse and extra medullary disease. Thus, CAR-T therapy was postponed and at this time he was given InO along with triple intrathecal chemotherapy for CNS3 disease.

Our patient had an excellent response to InO. After two cycles of InO, he was able to receive Car-T therapy. Unfortunately, while his marrow remained minimal residual disease (MRD) negative, his 28-day post-Car-T evaluation showed CNS and extramedullary relapse.

After having so many treatment failures within a span of 15 months, his family chose to prioritize quality of life over the unlikelihood of cure. InO was then resumed for palliative purposes. He was also treated with triple intrathecal therapy followed by cranial radiation (1200 Gy) for his CNS disease. Surprisingly, our patient tolerated the InO well and received nine total cycles over the following year, his longest treatment-related remission, maintaining negative MRD. Dosing of InO was given weekly for 3 weeks/month for the first five cycles, then spaced bi-weekly and then monthly for the remainder of the treatment.

Complications during InO treatment included moderate but persistent pancytopenia, mucocutaneous bleeding, and one admission for localized pseudomonas cellulitis.

As his mucocutaneous bleeding seemed out of proportion to the level of thrombocytopenia (platelet count 40,000–50,000), investigations were done to identify other potential causes of bleeding. Coagulation studies, which were normal at diagnosis, showed prolongation of partial thromboplastin time (PTT) (45 s, range: 25–35), with no correction of mixing studies (42 s). Factors VIII, IX, XI levels and vitamin C and K levels were normal. Workup for Von Willebrand disease was negative. Dental evaluation was also normal. Aminocaproic acid for persistent episodes of gingival bleeding was given with some improvement, but the bleeding and bruising ultimately resolved as InO dosing was spaced out.

Aside from thrombocytopenia, there are no previous reports of coagulation abnormalities associated with InO.[5,6] Due to our patient's mucocutaneous bleeding, we suspect InO may have precipitated some degree of platelet dysfunction. Platelet aggregation studies were not done during this time period but would have been helpful to better delineate this cause. Additionally, we did not test for inhibitors that may have caused the prolonged PTT.

Due to the risk for vaso occlusive disease with InO, his hepatic function was monitored closely. Bilirubin levels remained normal, and aspartate transaminase, alanine transaminase, and gamma glutamyl transferase were only mildly elevated (grade 1). He was treated with prophylactic Actigall (10 mg/kg) two times a day for liver protection.

Our patient had an excellent quality of life with few complications during prolonged InO treatment. Because of his unexpected and prolonged remission, after 1 year of therapy, his parents elected to pursue a curative stem cell transplant with a haploidentical paternal donor. His conditioning regimen for transplant included fludarabine and cyclophosphamide with post-transplant cyclophosphamide. Unfortunately, 1 month after transplant, his bone marrow was found to have complete autologous reconstitution. He remains in complete remission and MRD negative with a detection level of 10^{-6} (done by CloneSeq), with recent bone marrow surveillance done 14 months after stopping InO therapy.

After four prior relapses on conventional treatment protocols, our patient has achieved a prolonged and ongoing remission with inotuzumab. His disease control can be attributed primarily to the prolonged treatment of InO, as he has had disease recurrence after every other agent. Although he was treated with cytoxan and fludarabine as a part of the conditioning regimen for transplant, it is unlikely this chemotherapy had an impact on his disease as he was already in remission. Because he had 100% autologous reconstitution after transplant, there is no graft versus leukemia to explain this prolonged response. Since InO has poor CNS concentration, as it does not cross the blood–brain barrier[7]; intrathecal therapy as well as cranial radiation was instrumental in maintaining our patient's excellent response.

This is the first reported case of prolonged MRD negative remission using Inotuzumab in a patient with heavily treated, multiple relapsed, MLL-r infant ALL. InO was effective in maintaining disease control and was well tolerated. Surprisingly, disease control has persisted even after the cessation of InO. InO could be considered as an alternative therapy for relapsed/refractory $CD22^{+}$ infant ALL, either as a bridge to curative therapy or as an option for life prolongation therapies.

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Previously presented as a case report at ASPHO 2021, April 20–April 23 2021; abstract published in the *Pediatric Blood & Cancer* online.

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