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DARATUMUMAB IN T-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA: A CASE REPORT AND REVIEW OF THE LITERATURE

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Abstract

Relapsed/refractory paediatric T-ALL carries a dismal prognosis and newer therapy options are urgently needed. Daratumumab, an antibody to transmembrane protein CD38 expressed on T-cells, is currently under investigation as a targeted immunotherapy approach to T-ALL. A 2-year-old male with refractory T-ALL received off-label, monotherapy with daratumumab, resulting in a rapid partial response with minimal toxicity. This is the first documentation of daratumumab administered to a child with this indication, and supports its potential benefit in T-ALL.

INTRODUCTION

Relapsed/refractory paediatric T-cell acute lymphoblastic leukaemia (T-ALL) is an aggressive, often chemo-resistant, malignancy associated with survival rates of less than 25%.[1] There are few options for salvage therapy with significant short and long-term toxicities.[2] In striking contrast to B-cell malignancies, there are yet to be well-established immunotherapy agents developed for the treatment of T-ALL. The challenges of developing such targeted agents lie in the heterogeneity of T-ALL blast cells on a molecular level.[3,4] First identified in 1980, the transmembrane glycoprotein CD38, expressed on the surface of thymocytes and activated T-cells, has more recently emerged as a promising target.[5,6] The stability of this glycoprotein's expression despite exposure to cytotoxic chemotherapy, favours its profile as a potential target in T-ALL.[7] Here we describe our experience of a patient with refractory T-ALL who received daratumumab, an anti-CD38 antibody.

CASE DESCRIPTION

A previously healthy 2-year-old male presented with lethargy, pallor, and bruising whilst visiting family in Iran. He had marked hepatosplenomegaly, and his full blood picture demonstrated anaemia (5.6g/L), thrombocytopaenia (58 x 10^9/L), and marked leucocytosis (540 x 10^9/L). Immunophenotyping of peripheral blood confirmed a diagnosis of T-ALL. Bone marrow cytogenetic analysis revealed a normal karyotype with no chromosomal abnormalities.

He first received chemotherapy as per the Berlin-Frankfurt-Muenster 2009 study (Protocols IA and IB). He tolerated these cycles with minimal toxicity and was subsequently transferred to our unit for ongoing treatment. Day 15 and day 33 bone marrow flow cytometry minimal residual disease (FCM-MRD) results were documented as high at 16.48% and 0.38% respectively. Bone marrow examination following completion of BFM Protocol IB had FCM-MRD level of 0.887%. In view of this result, he received three high-risk intensification chemotherapy blocks as per the Children's Oncology Group AALL1231 protocol. Bone marrow

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assessment following these cycles demonstrated morphological remission, with an improved MRD level of 0.062%.

At this juncture, he was considered for an allogeneic haematopoeitic stem cell transplant (HSCT) with his 5-year-old sibling identified as an optimal donor. With the aim of achieving MRD remission priot to HSCT, he went on to receive a further cycle of chemotherapy including nelarabine (to which he was naïve). Unfortunately, despite this, his leukaemia burden worsened with bone marrow examination confirming morphological relapse. The immunophenotype indicated additional new clonal evolution with preservation of normal cytogenetics. MRD of the initial clone was 0.043%, with its persistence indicative of treatment-refractory leukaemia.

Soon after, the child developed a vesicular rash to his upper limb confirmed to be varicella zoster infection, and he was commenced on anti-viral therapy. He was noted to have increasing hepatosplenomegaly with a rising white cell count (WCC) and peripheral blast count. Multiple discussions were had with his parents who understood the dismal prognosis but were keen to explore further therapies, still with the aim of receiving HSCT. He was not fit to receive further intensive myelosuppressive chemotherapy given the risk of varicella dissemination. Daratumumab was offered as a bridging agent with the aim of reducing tumour burden and providing recovery time from his acute infection.

With provision made on compassionate grounds, the child received 2 doses of daratumumab 1 week apart. The prescribed dose was 16mg/kg based on an ongoing phase II clinical trial. Both doses were well tolerated, except for the development of a grade I rash during the first infusion which resolved with anti-histamine therapy. There were no other features of cytokine toxicity. Over the next 48 hours, he showed signs of improvement with a steep drop in his WCC from 34.33 (x 10^9/L) to 3.31 (x 10^9/L) and peripheral blast count from 82% to 7% pre and post daratumumb respectively (Fig. 1). Concurrently, his lactate dehydrogenase level rose from 3510 U/L pre-daratumumab to 7030 U/L 24 hours later, and fell progressively to 944 U/L on day 8 indicating initial tumour lysis and subsequent reduced tumour burden. On serial examination, he demonstrated significant reduction in the degree of hepatosplenomegaly and improvement in his overall clinical condition. His WCC remained low until 4 days after the second dose of daratumumab after which he was found to have an increase in his peripheral blast count and increasing hepatosplenomegaly. By this time, the zoster infection was under control and he proceeded to receive a course of fludarabine, high-dose cytarabine, idarubicin chemotherapy (FLA-Ida). Unfortunately, 3 weeks later his bone marrow showed persistent disease and he died at home the following week.

DISCUSSION

Daratumumab is a human monoclonal antibody that specifically binds a unique isotope on the CD38 molecule, and exerts its anti-tumour activity through various complement- and antibody-dependent cytotoxic mechanisms.[8] It has demonstrated a favourable toxicity profile, and is currently U.S. Food and Drug Adminisration (FDA) approved for the treatment of adults with relapsed or refractory multiple myeloma.[8,9] Daratumumab has now emerged as a potential agent to be used in the treatment of T-ALL given its efficacy demonstrated in mouse models.[7,10] In a preclinical study it was tested in a large panel of paediatric T-ALL patient-derived xenografts (PDX) where it was found to be efficacious in 14 of 15 the different PDXs as measured by reduction in leukaemia burden in blood and spleen.[7] The single PDX that failed to respond had low expression of CD38. In another study in mice, daratumumab was found to eradicate MRD in 7 of the 8 T-ALL PDX mice who had been treated.[10] There is also evidence that daratumumab can be combined with conventional cytotoxic chemotherapy with minimal toxicity in adults with multiple myeloma giving hope for its translation to leukaemia therapy. Off-label use has been reported in three adult patients from a single centre, all heavily pre-treated, one with relapsed high-risk B-ALL and two with relapsed T-ALL who achieved MRD remission for at least 10 months by using daratumumab in combination with vincristine or nelarabine with minimal toxicity.[11,12]

This unprecedented case documents the use of daratumumab in paediatric T-ALL and suggests its potential benefit for the treatment of this disease. For our patient, daratumumab was used as monotherapy to tide over

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the crisis in the setting of an active varicella infection and a high tumour burden. Although complete remission was not achieved, there was a significant response as demonstrated by a rapid reduction in the patient's WCC and peripheral blast counts, as well as clinical improvement. It may be inferred that his reponse was only partial due to the inherently aggressive nature and late stage of his disease with failure to respond to FLA-Ida chemotherapy. However, notwithstanding his refractory leukaemia, it could also be hypothesised that a partial and less sustained response was achieved as daratumumab was used as monotherapy. Based on our patient's leukaemia resurgence 2 weeks later and prior case reports,[11,12] daratumumab will likely to be more effective when used in combination with other chemotherapy agents.

It is clear that larger clinical studies are required to further investigate daratumumab in paediatric T-ALL. Currently there is an open phase II clinical study (NCT03384654) evaluating daratumumab in combination with chemotherapy in children and young adults (less than 30 years) with relapsed and/or refractory T- or B-ALL.[13]Hopefully, further studies will be able to answer some of these questions surounding daratumumab's role in paediatric T-ALL, and in turn bring a novel approach to what is ordinarily a devastating disease in the relapse/refractory setting.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to disclose.

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LEGENDS

FIGURE 1 Effect of daratumumab on the patient's total white cell count (x 10^9/L) and absolute (peripheral) blast count (x 10^9/L) over time in days: 2 doses of daratumumab administered on day 1 and day 8, with an initial reduction in WCC and ABC between day 3 and day 10. WCC and ABC rose from day 11 until FLA-Ida commenced at day 14. See Supplemental table 1 for further laboratory values. WCC, white cell count; ABC, absolute blast count; Dara, daratumumab; FLA-Ida, fludarabine, high-dose cytarabine, idarubicin