Blinatumomab as maintenance therapy for pediatric acute B-lymphoblastic leukemia in the setting of asparaginase-associated pancreatitis

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Abstract

Modern chemotherapy for pediatric acute B-lymphoblastic leukemia (B-ALL), including a maintenance phase on the backbone of oral antimetabolite administration, has resulted in a generally excellent prognosis for newly diagnosed disease. However, therapy-related toxicities may preclude a patient’s ability to safely receive traditional chemotherapy. We report the case of a child with B-ALL unable to tolerate oral antimetabolite therapy due to recurring necrotizing pancreatitis secondary to asparaginase. She received a modified maintenance therapy with blinatumomab, a CD3- and CD19-directed bispecific T-cell engager antibody, which was well tolerated and allowed for resolution of her pancreatitis while maintaining a durable remission.

Introduction:

Modern chemotherapy for children and young adults with acute B-lymphoblastic leukemia (B-ALL) has yielded remission rates of over 90%.¹⁻³ The maintenance phase of ALL therapy is critical to mitigate relapse risk and is composed of oral antimetabolite administration along with corticosteroid bursts and intermittent vincristine and intrathecal (IT) methotrexate (MTX).⁴⁻⁶ While the overall duration of maintenance varies per patient, the current standard in the United States is generally around 1.5 years. However, a patient’s comorbidities, therapy-related toxicities, or critical illness may require deviations from typical treatment protocols. There is no standard of care for patients who are unable to safely tolerate maintenance therapy.

Blinatumomab is a CD3- and CD19-directed bispecific T-cell engager (BiTE) antibody approved by the U.S. Food and Drug Administration (FDA) for children and adults with relapsed or refractory B-ALL, and adults with newly diagnosed B-ALL with detectable minimal residual disease (MRD) following induction.⁷ Its efficacy and tolerability in the relapsed and refractory settings⁸⁻¹³ have led to trials in the upfront settings in infant, pediatric, and adult B-ALL, as well as maintenance therapy for adults after hematopoietic stem cell transplant (HSCT).¹⁴⁻²¹ Herein we describe a pediatric patient unable to tolerate oral antimetabolite therapy due to severe necrotizing pancreatitis secondary to asparaginase administration. She received three cycles of adjusted maintenance therapy on a blinatumomab-based backbone. Blinatumomab was well tolerated and allowed for resolution of her pancreatitis while maintaining a longer durable remission.

Case Description:

A 12-year-old female was diagnosed with B-ALL after presenting to the emergency department with acute appendicitis; coincidentally she was found to be pancytopenic with B-lymphoblasts on peripheral blood flow cytometry. She was diagnosed with NCI high risk B-ALL with neutral cytogenetics and CNS 1 status. She enrolled on the Children’s Oncology Group (COG) AALL1732 study and received four-drug induction, after which she achieved an MRD-negative remission. The patient underwent pharmacogenomic testing and
was confirmed to have normal metabolism mediated by thiopurine S-methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15).

During consolidation therapy the patient developed anaphylaxis to pegylated (PEG)-asparaginase. Desensitization was unsuccessful, as serum asparaginase activity levels were subtherapeutic. Subsequent PEG-asparaginase doses were substituted for asparaginase erwinia chrysantheni recombinant-rwyn (Rylaze®) with dosing and frequency of administration according to the FDA package insert.22 However, during the second block of interim maintenance, the patient was admitted with abdominal pain and vomiting. Lipase was elevated to 900 U/L, eventually peaking at 2,500 U/L. She was diagnosed with acute pancreatitis, a known adverse event associated with asparaginase products, two weeks after starting her most recent Rylaze® sequence. Magnetic resonance cholangiopancreatography (MRCP) confirmed acute hemorrhagic necrotizing pancreatitis with a peripancreatic fluid collection (4.6 x 8.7 x 11.3 cm). The patient’s course was complicated by occlusive splenic vein thrombosis, shock requiring vasoactive support, and acute hypoxemic respiratory failure requiring intubation and mechanical ventilation. She fully recovered after a prolonged hospitalization.

Upon recovery the patient started maintenance therapy including oral chemotherapy: 6-mercaptopurine (6-MP), MTX, and prednisone bursts. However, over the subsequent three months, she had three prolonged hospital admissions for recurrent pancreatitis, resulting in frequent and prolonged gaps in her therapy. The patient developed walled-off pancreatic necrosis and required cyst-gastrostomy, stent placement, and necrosectomy. There were multiple attempts to resume oral chemotherapy, including at significantly reduced dosing, all of which were unsuccessful. 6MP and MTX were suspected to be the triggers of the patient’s acute pancreatitis exacerbations as per consultation with pancreatic disease experts and reported literature.23-30

Due to its efficacy and favorable safety profile, blinatumomab was selected as the backbone for a modified maintenance therapy. This modified maintenance therapy consisted of three cycles, each with continuous infusion of blinatumomab 15 mcg/m²/day (maximum dose 28 mcg/day) for 28 days. For CNS prophylaxis the patient received seven additional doses of IT MTX given at least four weeks apart to achieve the total number of doses given during typical maintenance therapy. Additionally, vincristine was given at the beginning of each cycle as it was previously tolerated without issue. The patient was admitted for approximately 48 hours of observation with the start of each blinatumomab infusion as per institutional standard of care. She was monitored for cytokine release syndrome (CRS) and neurotoxicity, neither of which she developed. Immunoglobulin was repleted to maintain normal IgG level for age. Blinatumomab cycles were well tolerated except for an episode of bacteremia with Enterobacter cloacae and Stenotrophomonas maltophilia, which was treated with antibiotics and required central line removal. The patient is now eight months off therapy and remains in remission. She experienced one additional episode of pancreatitis four months off-therapy, which required hospital admission but was milder than prior episodes. Her most recent MCRP showed near resolution of her pancreatitis, and she is scheduled to have her cyst-gastrostomy stent removed.

Discussion:

Although the overall prognosis for newly diagnosed pediatric B-ALL is excellent, chemotherapy carries potential toxicities that may preclude administration of conventional therapy.1-3 In the described case the patient was unable to tolerate standard maintenance oral chemotherapy due to pancreatitis suspected to be related to Rylaze® administration. The risk of pancreatitis associated with asparaginase products is well established,31-34 and antimetabolites and corticosteroids, comprising the backbone of maintenance therapy, have also been implicated.23-30,35-37 Additionally, certain genetic polymorphisms in TPMT and NUDT15 can affect both the efficacy and safety of 6-MP, potentially increasing the risk of drug toxicity.38-41 However, our patient was found to have normal phenotypes for both.

While maintenance therapy, including CNS prophylaxis, is vital in preventing disease relapse, there is no standard of care for patients unable to safely receive this phase of therapy.4-6 Blinatumomab is a CD3- and CD19-directed BiTE immunotherapy that is FDA-approved in children and adults with relapsed or refractory B-ALL, as well as adults with newly diagnosed B-ALL with detectable MRD following induction. Its efficacy and tolerability in the relapsed setting were demonstrated in the COG AALL1331 trial, in which
blinatumomab was associated with fewer grade 3-5 adverse events than cytotoxic chemotherapy and resulted in fewer treatment delays.\textsuperscript{11} Due to its favorable safety profile, blinatumomab has been used as temporizing therapy for patients who are too ill to receive traditional chemotherapy, allowing for clinical recovery before resuming cytotoxic chemotherapy, while maintaining a remission.\textsuperscript{42,43}

Here we report the use of blinatumomab as substitute for traditional maintenance therapy in a pediatric patient whose treatment-related toxicity precluded continuation of oral chemotherapy. In this setting blinatumomab was safe and well tolerated with no evidence of CRS or neurotoxicity, though the risk of such events was presumed to be low in this patient with no leukemic burden. Of note, the patient continued to receive IT chemotherapy to mitigate risk of CNS relapse, as the CNS activity of blinatumomab is not significant or widely agreed upon.\textsuperscript{44-48} As immunotherapeutic and other novel agents demonstrate success, the challenge is to determine the settings in which they will be most effective and the optimal patients to receive them. The role of blinatumomab in upfront pediatric and infant B-ALL therapy is currently being investigated in cooperative group trials, including COG AALL1731 and Interfant-21, respectively.\textsuperscript{15,16} Though successful in our patient, with the caveat of short follow up duration, the feasibility and efficacy of blinatumomab as maintenance therapy for the broader pediatric population requires much further investigation, ultimately in a multicenter randomized control trial.

**Conflict of Interest:** The authors declare no competing financial interests.

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Legends: None