CASE SERIES

Unraveling L-asparaginase adverse reactions in paediatric acute lymphocytic leukaemia – A comprehensive case series from a paediatric oncology unit at a tertiary care center

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Abstract

This case series explores adverse reactions to *E coli* L-Asparaginase in paediatric Acute Lymphoblastic Leukemia (ALL). Five cases illustrate several complications, including hyperbilirubinemia, pancreatitis, and hypersensitivity reactions. Asparaginase is integral to paediatric ALL chemotherapy, but its use introduces potential toxicities, including hypersensitivity, pancreatitis, and liver dysfunction. The synthesis of the case series and review contributes to understanding challenges and strategies associated with L-asparaginase therapy in paediatric ALL, emphasizing the need for precision in managing adverse reactions for maximized treatment benefits.

Keywords: L - asparaginase, hypersensitivity reactions, acute lymphocytic leukaemia.

Introduction

L-asparaginase stands as a vital element in paediatric Acute Lymphoblastic Leukemia (ALL) chemotherapy, pivotal in depleting asparagine and impeding leukemic cell proliferation, and operates as a cornerstone in paediatric ALL therapy, enhancing survival rates and emerging as an indispensable therapeutic agent. Incomplete administration of L-asparaginase, attributable to its substantial toxicity, correlates with unfavorable outcomes in pediatric ALL patients [1].

The mechanism of action involves depleting asparagine in plasma and cerebrospinal fluid, thereby depriving tumor cells of essential nutrients for protein synthesis. As lymphoblasts are highly dependent on external asparagine due to low asparagine synthetase levels, the efficacy of L-asparaginase in ALL therapy becomes evident [2]. L-asparaginase exists in three forms, including two native preparations obtained from bacterial sources (*E. coli* or Erwinia chrysanthemi) and one modified variant derived from a native source. The third variant, known as PEG-asparaginase, is derived from *E. coli* and is chemically linked to monomethoxy Polyethylene Glycol (PEG), enhancing the pharmacokinetics of asparaginase. This PEGylated form demonstrates improved tolerance [3]. Its administration entails a unique toxicity profile encompassing allergic reactions, hepatotoxicity, hyperglycemia, diabetes, pancreatitis, thrombosis, encephalopathy, and hypertriglyceridemia.

Recognizing the spectrum of adverse reactions and employing tailored management approaches are imperative for balancing treatment efficacy with reduced morbidity and mortality. This case series unveils the myriad adverse reactions encountered with *E. coli* L-asparaginase therapy in pediatric

ALL patients, emphasizing the critical role of personalized management strategies.

Material and Methods

Newly diagnosed paediatric B-Acute Lymphoblastic Leukemia (B-ALL) cases being treated at our hospital Chacha Nehru Bal Chikitsalaya (CNBC) were included in this case series during the period from March to December 2023. A facility for measuring L-asparaginase activity levels was not available and the hospital only procures *E. coli*-derived asparaginase at our center. We followed the ICICLE-ALL-014 protocol, which involved administering 10,000 units/m^2 of L-asparaginase intravenously for 4–8 doses, along with other drugs depending on the risk category of the patients [4]. Three generic formulations of L-asparaginase were available at the center and administered as an intra-venous infusion. The adverse reactions ranged from hypersensitivity and pancreatitis to hyperbilirubinemia. In this case series, we present five patients with newly diagnosed B-ALL; three of these patients developed Grade 3 hypersensitivity following L-asparaginase and were treated with pre-medications and temporary withholding of the drug, one patient with Grade 3 hyperbilirubinemia was given l-carnitine and N-acetylcysteine infusion, while one patient developed Grade 3 pancreatitis. In this case series, we have summarized patients' clinical characteristics, and course and review the literature regarding asparaginase-associated toxicities. However, we obtained consent from the patient's parents (LAR) to use Case-Record-Form (CRF) data for the study.

Case Presentations

L-asparaginase hypersensitivity reactions

Case 1: A 16-year-old female presented with an initial leucocyte count of 99,200/microlitre, non-bulky disease, and TCF3-PBX1 cytogenetics, demonstrating high hyperdiploid. On initiating the Indian Collaborative Childhood Leukaemia (ICiCle) Intermediate Risk (IR) Induction chemotherapy, the patient exhibited a favorable response to prednisolone, with a negative CNS status on day 8 assessment. L-asparaginase was administered at 10,000 units/m^2 on days 9, 12, 15, 18, 21, 24, and 27. However, a Grade 2 Common Terminology Criteria for Adverse Events (CTCAE) reaction occurred on day 30, necessitating discontinuation of L-asparaginase infusion. End of induction Minimal Residual Disease (MRD) response was < 0.01%. Plans for L- asparaginase re-challenge during delayed intensification are in place.

Case 2: A 3-year-old boy, initially presenting with leucocyte count of 16,000/microlitre, demonstrated bulky disease. Following ICiCle induction, which he tolerated well, MRD remained positive at the end of induction. Escalating treatment risk to high risk, the patient was commenced on high-risk consolidation with L-asparaginase doses on days 15, 18, 21, 24, 43, 46, 49, 52, and 58. A CTCAE Grade 3 allergic reaction occurred on day 46, leading to the discontinuation of subsequent doses on days 49, 52, and 58. Re-challenging L-asparaginase on day 49 resulted in a similar episode despite pre-medications.

Case 3: A 3.5-year-old boy, presenting with IR B-ALL, bulky disease, and White Blood Cell (WBC) counts of 11,300/ microlitre with high hyperdiploid exhibited a good response to prednisolone. Tolerating L-aspara-ginase on days 9, 12, 15, 18, an episode of fever associated with infusion on day 21 prompted withdrawal of L-asparaginase. Severe allergic reactions (CTCAE Grade 3) occurred on day 24, necessitating hydrocortisone intervention.

The day 30 dose was skipped, and MRD levels were detectable (0.01%), leading to treatment risk escalation to high risk. Subsequent doses during consolidation were not administered due to similar reactions. Recognizing the pivotal role of L-Asparaginase in ALL therapy and considering the non-availability of alternate preparations, L-Asparaginase was re-challenged in the delayed intensification phase with pre-medications, and this approach was well-tolerated.

Case 4: Asparaginase related liver injury

This case details the clinical course of a 5-year-old male child diagnosed with IR B-ALL who experienced severe hyperbilirubinemia and transaminitis post-induction chemotherapy at the beginning of the consolidation phase. Baseline laboratory values revealed total bilirubin of 1.08 mg/dL, ALT 10 units/L, and AST 26 units/L, with normal PT/INR. The patient received 8 doses of L-asparaginase during the induction phase at 10,000 units/m^2. Fourteen days after the last L-asparaginase dose, the patient presented with scleral icterus, jaundice with hepatomegaly of 5 cm below the right costal margin on examination. Total bilirubin of 5.6 mg/dl with a conjugated component of 4.5 mg/dl and elevated liver enzymes (AST-907 units/L, ALT-663 units/L), consistent with Grade 3 hyperbilirubinemia and transaminitis. Due to these complications, consolidation therapy was delayed. L-carnitine and N-acetyl cysteine infusions were initiated, presuming drug-related liver injury. After 6 days of treatment, total bilirubin decreased from 17 mg/dL to 10 mg/dL, ALT from 663 to 118, and AST from 907 to 175. N-acetylcysteine infusion was discontinued after 10 days, while L-carnitine was continued. A vincristine-dexamethasone pulse was administered, adjusting the vincristine dose according to bilirubin levels. Consolidation therapy commenced 40 days after induction completion, with total bilirubin decreasing to below 2 mg/dL by day 15 of consolidation. Cytarabine and 6-mercap-topurine doses were adjusted due to hepatotoxicity, but 100% of doses were resumed by day 16 of consolidation. End of consolidation MRD results were negative (< 0.01%) The patient was continued on oral L-carnitine supplementation, and L-asparaginase, and re-challenge during delayed intensification resulted in a CTCAE Grade 3 hypersensitivity reaction, leading to subsequent dose withholding. L-carnitine supplementation was discontinued a week later. This case highlights the successful management of severe drug-related hepatotoxicity emphasizing the importance of close monitoring, prompt intervention, and adjustment of chemotherapy regimens to ensure optimal patient outcomes.

Case 5: Asparaginase related pancreatitis

A 13-year-old female child diagnosed with IR B-ALL encountered significant complications during induction chemotherapy. The patient, concurrently on anti-tubercular treatment for four months, commenced induction chemotherapy with a steroid prophase. Initial assessments unveiled WBC count of 2300 with 60% and 80% blasts in peripheral smear and bone marrow aspirate, respectively. On day 8 of induction, the patient exhibited a favorable response, with only 2% blasts in the peripheral smear, signifying a robust prednisolone response and a CNS1 status.

However, during L-asparaginase administration on day 15, a CTCAE Grade 2 allergic reaction occurred. Subsequent doses on days 18, 21, and 24 were successfully administered with pre-medications.

On day 26, the patient developed fever and neutropenia, prompting the initiation of piperacillin-tazobactam and amikacin. Despite escalating antibiotics to meropenem due to persistent fever, the patient presented severe abdominal pain on day 27. Clinical examination revealed low-volume pulses, blood pressure below the 50th percentile, a tender abdomen, irritability, and a normal respiratory system. She was administered oxygen via a face mask and underwent fluid resuscitation but continued to exhibit low-volume pulses with blood pressure below the 50th percentile, prompting the initiation of inotropic support with adrenaline.

Ultrasonography of the abdomen displayed no significant abnormalities, and a CT scan revealed fat stranding around the mesentery in the right iliac fossa. Antibiotic therapy was escalated to meropenem, colistin, and tigecycline due to life-threatening septic shock and suspicion of neutropenic enterocolitis, leading to the temporary withholding of induction chemotherapy.

Laboratory findings on day 27 indicated a WBC count of 500, Absolute Neutrophil Count (ANC) of 100, and electrolyte imbalance with hypokalemia (3 meq/L). Liver function tests revealed hypoalbuminemia (2.8 mg/dL), and serum amylase and lipase levels were 500U/L and 1060 U/L, respectively. Although imaging was unremarkable, clinical and biochemical parameters strongly favored acute pancreatitis. Symptomatic management, nutritional support, and inotropic support were provided in the paediatric intensive care unit from day 27 to day 33, leading to gradual improvement in ANC and a decreasing trend in amylase and lipase levels. Induction chemotherapy was withheld for 10 days, and subsequent doses of L-asparaginase were not re-challenged. Despite these complications, the patient responded to treatment with subsequent vincristine administration on day 36 of induction. She was discharged until the ANC was >1000/ microlitre. However, end-of-induction response assessments revealed MRD levels of 16%, and bone marrow aspirate demonstrated 55% blasts, leading to an escalation to the high-risk category according to the treatment protocol.

Discussion

We performed a retrospective case series study that included 5 patients diagnosed with acute lymphoblastic leukaemia admitted at CNBC from March - December 2023, who were treated according to the chemotherapy protocol ICiCle-ALL-014 and received L-asparaginase. According to Leukaemia and Lymphoma Society 2015, ALL is the most common cancer in children aged 1 to 16 years of age. The use of intense asparaginase therapy is essential in improving outcomes in paediatric patients with ALL. To ensure this, it is necessary that patients receive continuous asparaginase treatment and complete their entire scheduled therapy to get an optimal anti-leukemic effect. Adverse Drug Events (ADEs), such as hypersensitivity, pancreatitis, Venous Thromboembolic Events (VTEs), hyperbilirubinemia, and hyperglycemia, are common reasons for treatment interruption or the discontinuation of asparaginase therapy. Prompt identification and management of these common asparaginase-associated ADEs are of paramount importance to patients' response to therapy. Because of the bacterial origin, all asparaginases can elicit an immune response in patients.

Clinical hypersensitivity reactions are a commonly reported reason for the discontinuation of aspara-

ginase, and can negatively affect survival. We also noticed this spectrum of hypersensitivity reactions that ranged from rash to severe allergic reactions in three of our patients. However considering the crucial role of asparaginase, we had to rechallenge it, taking utmost care, using premedications. The likelihood of these reactions depends on many factors, including the type and route (IM or IV) of asparaginase, prior exposure, genetics of the patient, and corticosteroid use [5-6].

In patients treated with native *E. coli* asparaginase, studies report 30%–60% of patients experiencing a reaction [5, 7]. Patients treated with PEG-asparaginase generally show a lower incidence of hypersensitivity, ranging from 3%–24% among studies. Erwinia asparaginase is indicated for patients who have a previous experience of hypersensitivity to *E.coli* derived asparaginase, and hypersensitivity reactions have been reported in 3–37% of these patients [8]. Retrospective data suggests that hypersensitivity is more common following IV infusions compared to IM injections of asparaginase. In one patient, we observed hyperbilirubinemia and transaminitis who received 8 doses of L-asparaginase during the induction phase. L-carnitine and N-acetylcysteine infusions were given to manage this drug induced liver injury along with prompt dose adjustments with the dose of other anticancer drugs.

Schmidt *et al*. [9] also reported hepatotoxicity as the second-most-observed side effect [32 (19.4%)] associated with asparaginase. They found 20 patients (62.5%) had CTCAE Grade $\geqslant$ 3 hepatotoxicity and 12 patients out of 17 (37.5%) had Grade < 3. Three patients (12.5%) had Grade 5 hepatotoxicity with fulminant liver failure and death. We reported a case of acute pancreatitis which was managed symptomatically with nutritional and inotropic support in the paediatric intensive care unit. Previous studies also found 3% (5/165) cases with asparaginase associated pancreatitis in their study [10]. Literature search revealed that the incidence of pancreatitis in children with ALL treated with asparaginase is about 7% and grade 2–4 pancreatitis has been reported in 9% of adults.

Conclusion

This case series underscores the diverse adverse reactions to L-asparaginase in paediatric ALL patients and emphasizes the significance of thoughtful management, including the strategic rechallenge of L-asparaginase, to optimize treatment outcomes.

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