Chapter

Acute Pancreatitis in Children with Acute Lymphoblastic Leukemia Using L-Asparaginase: A Review of the Literature

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Abstract

L-asparaginase (L-Aspa) is utilized as a part of the therapy in children with acute lymphoblastic leukemia (ALL), achieving remission in 83–95% of the younger patients. Hypersensitivity reactions, as well as liver and pancreatic cytotoxicity, are severe documented side effects. L-Aspa-induced acute pancreatitis (AP) has been observed in 2.5–16% of treated patients. Patients with mild pancreatitis may be retreated with L-Aspa if they have no clinical symptoms within 48 hours, amylase and lipase levels are less than three times the normal's upper limit, and there is no evidence of pseudocysts or necrosis on imaging. It is crucial to monitor patients under L-Aspa therapy, through careful observation of clinical signs and laboratory follow-up, as well as a continuous checkup for associated medications.

Keywords: acute lymphoblastic leukemia, L-Asparaginase, acute pancreatitis

1. Introduction

L-Asparaginase (L-Aspa) is a keystone therapy of acute lymphoblastic leukemia (ALL) [1]. Its mechanism of action is complex, depleting the body of the non-essential amino acid asparagine through deamidation of asparagine into aspartic acid and ammonia [2]. The proportion of cured patients under L-Aspa increases by targeting malignant lymphoblasts, which lost the ability to asparagine synthesis [3, 4]. In fact, asparaginase therapy leads to the complete depletion of serum asparagine concentrations, depriving leukemic blasts of this amino acid, resulting in reduced protein synthesis and ultimately leukemic cell death [5]. L-Aspa is administered in combination with other anti-neoplastic drugs intramuscularly or intravenously. However, with a high incidence of cumulative dose of asparaginase ranging from 2 to 10%, L-Aspa-associated pancreatitis is the main cause of substantial morbidity in patients receiving this drug [6]. Despite low mortality, asparaginase-associated pancreatitis (AAP) often results in a switch of asparaginase therapy, which might be associated with an increased risk of leukemia relapse [3, 4].

This review explores the definition, treatment, complications, and possible risk factors for AAP in children.

2. L-Asparaginase (L-Aspa)

2.1 Mechanism of action

Asparagine is a non-essential amino acid, provided from food or produced by asparagine synthetase (ASNS). Normal cells may manufacture L-asparagine for growth using the transaminase enzyme, which converts oxaloacetate into the intermediate aspartate, which then transfers an amino group from glutamate to oxaloacetate, producing ketoglutarate and aspartate. Finally, the enzyme asparagine synthetase transforms aspartate to asparagine in healthy cells [7].

ASNS is very low expressed or even absent in ALL cells, rendering them reliant on extracellular asparagine for growth and survival, L-Aspa lowers plasma asparagine concentrations by catalyzing asparagine deamination into aspartic acid and ammonia [2]. Asparaginase therapy results in the entire depletion of blood asparagine concentrations, depriving leukemic blasts of this amino acid, resulting in decreased protein synthesis and, eventually, leukemic cell death at optimal enzyme activity levels [5].

Circulating asparagine concentrations range between 40 and 80 μm in normal physiological conditions [8]. Researchers defined complete asparagine depletion as less than 0.1–0.2 μm based on the limit of detection of the high-performance liquid chromatography assay used [8, 9]. However, the critical level of serum asparagine depletion for in vivo leukemic cell death is unknown.

2.2 Asparaginase formulations

Three distinct formulations of L-Aspa are available. The native-Asparaginase modified pegylated version (PEG-Asparaginase), are both generated from *Escherichia coli* (*E. coli*). The third is Erwinase, which is derived from *Erwinia Chrysanthemi*. The three formulations vary in terms of pharmacokinetics, pharmacodynamics, and immunogenic propreties [10, 11]. The glutamine pharmacokinetics differs in these current formulations. While both *Erwinia Chrysanthemi* and *E. coli*–derived asparaginase formulations show similar binding affinities for glutamine, the maximal conversion rate at saturation is greater with *Erwinia Chrysanthemi* [12, 13].

First-line treatment in ALL was based on native *E. coli* asparaginase. However, in the United States, this formulation was replaced with PEG-asparaginase [5].

Erwinia asparaginase, which is produced from a distinct bacterial origin, has a unique immunogenic profile, with no cross-reactivity with native *E. coli* asparaginase or PEG-asparaginase [14]. Consequently, *Erwinia* asparaginase is indicated as a component of a multiagent chemotherapy regimen in patients with ALL and a history of hypersensitivity to *E. coli*-derived asparaginases [5].

Intravenously or intramuscularly routes are possible for the three asparaginase formulations. However, the intramuscular route is associated with lower plasma peak values, local bleeding in cases of thrombocytopenia, and local pain, which can be alleviated by co-administration of lidocaine [15]. However, intramuscular injections have the advantage to reduce the risk of anaphylactic reactions [16].

2.3 L-Asparaginase side effects

L-Aspa-induced adverse effects may be minor or severe and fatal. Some common adverse effects are related to the L-glutaminase coactivity including a decrease in the production of various essential proteins such as albumin, insulin, fibrinogen, and protein-C [17]. So, L-Aspa may induce fever, hepatic dysfunction, hyperglycemia and diabetes, leucopenia, pancreatitis, neurological convulsions, and coagulation abnormalities such as thrombosis and hemorrhage [17].

Hypersensitivity life-threatening reactions may occur on asparaginase-based medications, causing edema, skin eruption, serum sickness, bronchospasm, urticaria, and anaphylactic shock [17].

3. Asparaginase-associated pancreatitis (AAP)

3.1 Definition

AAP is defined as acute pancreatitis occurring in patients receiving L-Aspa treatment at the time of onset of symptoms [18]. Pancreatitis is defined as the histological presence of inflammation within the pancreatic parenchyma. Acute pancreatitis is a reversible process characterized by the presence of interstitial edema, infiltration by acute inflammatory cells, and varying degrees of apoptosis, necrosis, and hemorrhage [19].

In various clinical trials, pancreatitis has been reported in 2–18% of patients undergoing L-Aspa therapy for ALL, with grade 3/4 pancreatitis occurring in 5–10% of patients [20, 21].

3.2 Pathophysiology

The exact pathogenesis of AAP is still unclear, but it may be related to the reduction in protein synthesis resulting from asparaginase-induced depletion of asparagine [18, 21].

Moreover, genetic predispositions are likely to play an important role. AAP occurs even after one or a few administrations of the drug with a high likelihood of recurrence upon re-exposure [21].

3.3 Diagnosis

Diagnosis of pancreatitis is based on a combination of clinical, biological (amylase, lipase), and radiological evidence.

3.3.1 Clinical presentation

In children, abdominal pain has many characteristics but is still the most common symptom of acute pancreatitis, occurring in 87% of cases. Abdominal pain in acute pancreatitis is of acute onset, especially in the epigastric region accompanied by nausea and vomiting [22].

3.3.2 Biochemical markers

Generally, amylasemia and lipasemia exceeding three times the upper normal level confirm the diagnosis. In pediatric patients, the simultaneous elevation of both

pancreatic enzymes increases the sensitivity of the test to 94%. Thus, the analysis of both enzymes is recommended, especially in very young children [23].

3.3.3 Imaging methods

Imaging methods in AAP are based on ultrasonography and computerized tomography (CT). The main sonographic signs are increased pancreatic size and decreased pancreatic echogenicity. While, in mild cases, a normal gland can be observed, increased pancreatic size and decreased echogenicity may be reported in severe cases [24, 25]. When performed days or weeks after the onset of AAP, contrast-enhanced CT is used to identify pancreatic necrosis. Concerning the usage of magnetic resonance imaging (MRI), there are currently no recommendations.

Adult studies demonstrate that MRI provides roughly the same information as CT, although the evidence in children is limited [26].

3.3.4 Diagnostic criteria

In a child presenting with abdominal pain during cancer treatment, acute pancreatitis should always be considered and ruled out. The diagnosis of AP requires at least 2 of 3 criteria according to the INSPPIRE Project (International Study Group of Pediatric Pancreatitis: In Search for a Cure) [27]:

a. Abdominal pain caused by AP is frequently of sudden onset, especially in the epigastric region, and may radiate to the shoulder, accompanied by nausea or vomiting.

b. Serum amylase and/or lipase activity at least three times higher than normal (in international units/liter).

c. Imaging findings suggestive of AP (e.g., transabdominal ultrasonography, contrast-enhanced computerized tomography).

4. Early assessment of severity of APP

AAP is usually mild, not life-threatening, and responds favorably to intensive medical treatment. Several scores have been developed to assess the severity of AP. (For example, Ranson, Balthazar, SOFA, APACHE II, and Marshall scores). Outside of clinical trials, none of these indicators are commonly used in clinical practice [28].

The Harmless Acute Pancreatitis Score (HAPS) is a German-developed score that may reliably identify mild types of pancreatitis at the time of admission [29].

This score was created by combining three parameters that best predicted a non-severe course (no signs of peritonitis (rebound tenderness, guarding), normal hematocrit level, and normal serum creatinine level $\leq$ 2 mg/dl).

To identify patients at high risk of severe pancreatitis, the Bedside Index for Severity in Acute Pancreatitis (BISAP) score can be used [30]. This score has five parameters:

B unconjugated Bilirubin level > 25 mg/dl.
I Impaired mental status (Glasgow Coma Scale score < 15).

S Development of systemic inflammatory response syndrome (SIRS).
A Age > 60 years.
P Presence of pleural effusion.

With an 83% sensitivity, a BISAP score of three or above can indicate a severe course of AP.

The Pancreatitis Activity Scoring System (PASS) recently expanded its severity criteria to include organ failure, pain, intolerance to a solid diet, systemic inflammatory response syndrome, and morphine equivalent dosage by relative weight [31].

However, these grading methods have not been verified in the pediatric population. On admission, different clinical and laboratory criteria may suggest moderate or severe AP, although variable threshold levels frequently complicate matters. However, in children, a high C-reactive protein (>150 mg/l), hypocalcemia, an elevated hematocrit, or hyperglycemia are more likely to suggest a severe course of pancreatitis [32].

According to the 2012 Atlanta criteria, pancreatitis is classified as mild, moderate, or severe [33]. Mild acute pancreatitis was defined by the absence of organ failure and local complications. Moderately severe acute pancreatitis was defined by local complications and/or transitory organ failure (<48 h) and severe acute pancreatitis was defined by persistent organ failure >48 h. Organ failure often includes respiratory, renal, or cardiovascular failure, requiring admission to an intermediate or intensive care unit. The revised Atlanta criteria are widely used by pediatricians in the classification of pancreatitis severity although not validated in this population. Until a consensus on the classification of AAP is reached among pediatric oncologists, we recommend that the Atlanta criteria are applied. L-Asparaginase is among the most trigger causes of severe acute pancreatitis [34].

5. Risk factors for AAP

5.1 Genetic predisposition

Genetic predisposition is suggested to play an important role in the occurrence of AAP. Although nucleotide sequence variants in several genes (e.g., CFTR, CTRC, PRSS1, and PRSS2) have been associated with the risk of pancreatitis in general [35], no specific genetic polymorphisms have been associated with AAP.

In 2016, Liu et al. identified a nonsense variant of the CPA2 gene, which encodes carboxypeptidase A2, associated with a higher predisposition risk of AAP [36].

5.2 Age

Higher age is associated with a higher risk of AAP. When compared to younger children, children above the age of 10 at the time of diagnosis had an increased risk of developing AAP [37].

5.3 Severe hypertriglyceridemia

In the presence of severe hypertriglyceridemia (i.e., levels above 11.3 mmol/l), the risk of acute pancreatitis is increased even in patients not receiving L-Aspa [38].

Hypertriglyceridemia is frequently observed in patients treated with L-Aspa, especially when given in combination with steroids [39].

5.4 Formulations of L-asparaginase

Alvarez and Zimmerman investigated the prevalence of pancreatitis in patients given different formulations of L-Aspa: PEG-asparaginase versus L-Aspa. The authors reported that the PEG asparaginase group had a statistically significant increase in pancreatitis when compared to the control group. (18% PEG-asparaginase vs. 1.9% L-Aspa, $p = 0.007$) [40]. This effect was explained by a longer half-life of PEG-asparaginase resulting in prolonged asparagine depletion.

In contrast, other studies have found no difference in pancreatitis frequency between PEG-asparaginase and L-Aspa patients [41, 42].

5.5 ALL risk stratification and L-Aspa dosing

In two studies, patients in the high-risk ALL stratification group had a higher incidence of AAP, receiving the highest doses of asparaginase [21, 43]. In Raja and colleagues' study, the high-risk stratification group received lower doses of asparaginase and had a lower rate of AAP [20]. These findings suggest that a higher cumulative dose of asparaginase may be associated with a higher incidence of AAP.

6. Treatment

Actually, there is no pharmacological treatment for acute pancreatitis whether it is primary or secondary. The therapeutic approach of AAP is identical to that of the pancreatitis of other etiologies. Treatment of AAP is primarily supportive and aims to reduce symptoms and monitor potential complications after immediate discontinuation of L-Aspa [21, 40, 44].

Patients with acute pancreatitis should be clinically examined for symptoms of organ failure to be appropriately treated immediately.

6.1 Fluid resuscitation

Circulatory anomalies are frequent in patients with severe sepsis or septic shock and must be managed in an intensive care unit. Early administration of adequate fluid resuscitation to avoid hypovolemia and organ hypoperfusion is a major pillar of management [45].

Numerous studies have investigated the type and amount of intravenous fluid resuscitation in severe AP. Keystones in fluid resuscitation are the followings:

a. Appropriate intravenous fluid resuscitation should be done within the first 24–48 hours; postponed or deficient fluids decrease the survival rate [45, 46].

b. High-volume fluid treatment (1000 mL/h) may increase the mortality rate and should be prevented [47].

c. Ringer's lactate is the optimum fluid to use. During the first 24 hours, the infusion rate should be assessed on a frequent basis and adjusted based on urine

excretion (target: 0.5–1 mL/kg/h) and vital parameters. The recommended infusion rate is 250–500 ml/h unless there are cardiovascular, renal, or other related comorbidities [48, 49].

Goal-directed therapy typically focuses on heart rate, mean arterial pressure, central venous pressure, urine output, blood urea nitrogen concentration, and hematocrit [2].

6.2 Analgesia

Opioid (e.g., pethidine) and non-opioid (e.g., metamizole) analgesics are indicated. In fact, pain is a distress condition that must be managed with adequate intravenous analgesia. If intravenous analgesia fails to provide sufficient relief or enhances bowel paralysis, the use of thoracic epidural analgesia may be considered. This pain-relieving technique was associated with improved survival in a multicenter retrospective trial [50]. A recent study showed a beneficial trend but no significant improvement in organ dysfunction or mortality upon thoracic epidural analgesia [51].

6.3 Enteral feeding

Based on several randomized clinical trials of non-asparaginase-related pancreatitis in adults, early enteral feeding seems to reduce the incidence of complications [44, 52]. Nutrition most likely protects the mucosal barrier and reduces bacterial translocation in the gut, decreasing the risk of infection and necrosis [52]. This is contrary to earlier beliefs. However, studies on children are lacking.

6.4 Prophylactic antibiotics/protease inhibitors

There is no clear evidence of the benefits of routine use of antibiotics in the early course of severe acute pancreatitis [53]. A recent study including more than 800 patients showed that antibiotic prophylaxis in patients with severe AP may lead to the development of invasive candidiasis of the pancreas [54]. Further studies must clarify the benefice of antimicrobial prophylaxis in certain subgroups of severe AP. Intravenous antibiotics are recommended in the case of cholangitis or other local infections, for example, infected walled-off necrosis.

More rarely applied treatments in case of severe pancreatitis are the administration of the synthetic somatostatin analog Octreotide or continuous regional arterial infusion of protease inhibitors and antibiotics [55, 56]. In fact, Somatostatin (Octreotide) inhibits secretions of the pancreatic digestive enzymes leading to a decrease in pancreatic inflammation [55].

There are no large studies of Octreotide treatment in children with AAP or other children with AP. In addition, there is no consensus on doses, duration, and the pattern of side effects. In the case reports, patients were treated with doses that ranged from 2.5 to 7.2 μg/kg per day [56].

Continuous regional arterial infusion of protease inhibitors and antibiotics are shown to be effective in preventing complications and in reducing mortality rates in severe acute pancreatitis in a large adult trial [57].

Pediatric data is still insufficient. Five pediatric patients with severe AAP were treated with continuous regional arterial infusion within 48 hours of diagnosis in one trial [58]. After 22 days, all five patients had satisfactory clinical results and could continue chemotherapy, despite the fact that none received further L-Aspa treatment [58].

7. Complications of AAP

Acute severe complications following AP include systemic inflammatory response syndrome and multiorgan failure affecting most frequently lungs and kidneys. Patients may develop pleural effusions, toxic pneumonia, acute respiratory distress syndrome, and renal failure [59].

7.1 Short-term complications

Short-term complications, usually appearing after the first week, include the development of life-threatening systemic inflammatory response syndrome and multiorgan failure. Other complications include necrosis and infection [18].

Pseudocysts can emerge as a complication to AAP. Such cysts contain pancreatic juice enclosed by a non-epithelialized wall [60]. Although most pseudocysts have been observed to arise within 4 weeks after acute pancreatitis [60], there are no significant studies that document this in detail for AAP patients. In general, pseudocysts should be treated conservatively, as the majority of instances diminish after a few weeks or months [22].

Intervention is indicated in patients that have persistent symptoms, such as severe pain, despite supportive care, or in case of infection or bleeding [61].

7.2 Long-term complications

Long-term consequences include diabetes mellitus, persistent abdominal discomfort, and chronic pancreatitis [15, 21, 22, 40]. It was demonstrated that the risk of the enduring requirement for insulin medication and recurring abdominal pain was related to having had pseudocysts [14].

8. Re-introduction of L-asparaginase

In children with ALL, suspending asparaginase therapy after toxicity is associated with significantly decreased event-free survival [4]. It is, therefore, crucial that ALL protocols include recommendations regarding the re-introduction of L-Aspa treatment after AAP.

Five studies have described the re-administration of L-Aspa after the occurrence of AAP [20, 43, 60–63]. The rate of AAP when L-Aspa was re-introduced was reported to be 0% (0 out of one patient) [62], 7, 7% (two out of 26 patients) [63], 25% (1 out of 4 patients) [43], 63% (10 out 16 patients) [64] and 17% (2 out 12 patients) [20]. The difference in the incidence of AAP after reintroduction of L-Aspa in the two larger studies primarily reflects the criteria for reintroduction, being mild AAP and complete resolution of symptoms in one study [63], whereas the other study only required resolution of symptoms within 72 h [64].

Currently, there are no established guidelines for the reintroduction of asparaginase following an episode of pancreatitis.

Based on the current literature and the Atlanta criteria, Raja et al. [18] suggested that in cases where patients with AAP had a rapid resolution of clinical symptoms and a reduction in serum amylase and lipase to levels less than three times the upper limit of normal within 48 hours of being diagnosed with pancreatitis and did not have signs of severity such as a pancreatic pseudocyst or necrosis, reintroduction of L-Aspa

could be attempted. If a second episode of pancreatitis occurs after reintroducing L-Aspa, asparaginase medication should be avoided completely. These findings suggest that clinicians should be conscious of the relatively high risk of recurrent pancreatitis with asparaginase reexposure following a first episode of AAP.

9. Conclusion

AAP is a life-threatening complication of ALL therapy and there is a need for consensus on its definition in all L-Aspa-containing protocols. Monitoring the patients treated with L-Aspa, through careful observation of clinical signs and laboratory follow-up is crucial to early detect asparaginase-associated toxicity to enable effective and appropriate management and recognize cases where re-exposure is possible.

Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

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Abbreviations

L-Aspa	L-Asparaginase
ALL	Acute lymphoblastic leukemia
AP	Acute pancreatitis
AAP	Asparaginase-associated pancreatitis
ASNS	Asparagine synthetase
CT	Computerized tomography
MRI	Magnetic resonance imaging
HAPS	The harmless acute pancreatitis score
BISAP	The bedside index for severity in acute pancreatitis
PASS	The pancreatitis activity scoring system

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