VIA MEDICA

REVIEW ARTICLE

Acta Haematologica Polonica 2023
Number 5, Volume 54, pages 295–301
DOI: 10.5603/ahp.95319
ISSN 0001–5814
e-ISSN 2300–7117

Acute pancreatitis in children with acute lymphoblastic leukemia

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Abstract

One of the most common causes of acute pancreatitis in children are medications. These include L-asparaginase, glucocorticoids and 6-mercaptopurine, which are widely used in the therapy of acute lymphoblastic leukemia (ALL). When L-asparaginase and glucocorticoids are administered together, blood triglyceride levels increase, which consequently further enhances the risk of pancreatitis. Therefore, acute pancreatitis is a common adverse effect of ALL treatment, present in 2.3–11% of pediatric patients.

The aim of this paper was to assess potential risk factors, treatment outcomes and recurrence of acute pancreatitis in children with ALL. Based on the studies conducted, we found potential risk factors, other than the drugs mentioned above, to be the patient's age at diagnosis, obesity, the type of L-asparaginase administered, and the cumulative or peak dose of L-asparaginase or other drug used. The course of pancreatitis is usually mild to moderate, and the treatment is mainly symptomatic. Moreover, a successful treatment option may be octreotide. As children who have received less than 25 weeks of L-asparaginase therapy have presented with inferior outcomes, it seems reasonable to reintroduce this drug into ALL treatment after an episode of pancreatitis. The incidence of recurrent pancreatitis after re-treatment with L-asparaginase varies depending on the study. The outcomes for children who develop acute pancreatitis during ALL treatment are usually worse compared to children without an acute pancreatitis history, but the results remain inconclusive. In conclusion, acute pancreatitis remains a serious adverse effect of ALL therapy in children, which may result in worsening patients' outcomes.

Key words: acute lymphoblastic leukemia, acute pancreatitis, L-asparaginase, glucocorticoids, children

Acta Haematologica Polonica 2023; 54, 5: 295–301

Introduction

Acute pancreatitis (AP) is the presence of histological features of inflammation in the parenchyma of this organ associated with premature activation of proteolytic enzymes. Among pediatric patients, the etiology is more diverse than among adults. Research suggests the most common causes to be, in order, causes related to trauma, systemic diseases, infections, and drugs [1].

Etiology associated with the use of drugs is responsible for less than a quarter of cases of pancreatitis in children. The most common drugs are valproic acid,

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Received: 26.04.2023 Accepted: 03.08.2023 Early publication date: 03.10.2023

Table I. Classification of drugs according to risk of pancreatitis and possibility of recurrence (source [3])

Group of drugs	The association between drugs and pancreatitis	Examples
Group 1	Drugs, among which recurrence of pancreatitis after re-administration of drug has been proven in at least one study	Dexamethasone, enalapril, furosemide, hydrocortisone, isoniazide, metronidazole
Group 2	Drugs in which a constant latency period between supply of drug and onset of pancreatitis has been proven in at least 75% of cases	Acetaminophen, azathioprine, clozapine, erythromycin, L-asparaginase, tamoxifen
Group 3	Drugs with weaker evidence of pancreatitis than drugs from Groups 1 and 2	Captopril, ceftriaxone, clarithromycin, gold, hydrocholorothiazide, interferon
Group 4	All other drugs where an association with induction of acute pancreatitis is unclear, or where data is underdeveloped	Ampicillin, colchicines, ketoprofen, octreotide, risperidone

6-mercaptopurine, L-asparaginase and prednisone [2]. Based on the available scientific research, medicines can be divided into four groups according to the risk of pancreatitis and the possibility of recurrence, as set out in Table I [3].

Although the prognosis for children treated for acute lymphoblastic leukemia (ALL) has improved thanks to the development of various therapies [4], there are still serious complications of these treatment protocols, including those involving the pancreas.

Drugs potentially harmful to the pancreas in the treatment of ALL in pediatric patients include L-asparaginase (listed in Group 2) and prednisone/dexamethasone (Group 1).

Glucocorticoids

Glucocorticoids are one of the most popular groups of drugs, used by about 1% of the general population. Although they have many well-known adverse effects such as osteoporosis, weakening of immunity, carbohydrate metabolism disorder, diabetes and hyperlipidemia, a damaging effect on the pancreas should also be mentioned [5, 6]. Despite not being a common adverse effect (2.6% of cases of AP in the adult population [5]), it significantly affects the deterioration of the patient's condition and worsens the effects of treatment. The use of glucocorticoids, especially high doses, has a confirmed, although unclear, relationship with the development of AP [6]. According to current guidelines, oral steroids such as prednisone are used as part of the first stage of treatment — induction [7]. Therefore, pediatric patients may be additionally at risk.

L-asparaginase

L-asparaginase is an enzyme, of which the mechanism of action is hydrolyzing L-asparagine into L-aspartic acid and ammonia. As a result, it reduces the L-asparagine concentration in the cells. Because leukemic cells, unlike normal cells, do not have the ability to upregulate the synthesis of L-asparagine and are fully dependent on its exogenous concentration, the administration of L-asparaginase results in leukemic cell apoptosis [8, 9].

There are currently few different types of this drug used in the treatment of ALL [10]. Three of them are the most commonly used: two of these are derived from the bacterium *Escherichia coli* (*E.coli*) — native and polyethylene glycolated L-asparaginase, while the third is derived from the bacterium *Erwinia chrysanthemi* and is used in patients with hypersensitivity to L-asparaginase derived from *E.coli* [11]. The study by Knoderer et al. on 254 pediatric patients reported a higher incidence of AP in a group of patients receiving polyethylene glycol (PEG)-asparaginase than *E. coli* L-asparaginase [12]. However, other studies have found no correlation between the type of L-asparaginase and the incidence of AP [13, 14]. L-asparaginase is present in all pediatric protocols for ALL treatment [15]. Apart from hypersensitivity reactions, the most common adverse effects include thrombosis, encephalopathy, myelosuppression, hepatotoxicity, hyperglycemia, hypertriglyceridemia, and pancreatitis, which is among the most common reasons for the discontinuation of treatment [11, 16]. A possible mechanism of asparaginase-associated pancreatitis is L-asparagine deficiency, which results in reduced protein synthesis [16]. Moreover, it is suggested that the glutaminase activity of asparaginase is linked with liver and pancreas toxicity. Most asparaginases show glutaminase activity, which is dependent on asparaginase efficacy. If the asparaginase is highly efficacious and asparagine depletion is achieved rapidly, more glutaminase activity is noted after achieving asparaginase depletion, so the drug may show more adverse effects [10].

The incidence of AP in children with ALL varies in different studies, and has been estimated as being between 2.3% and 11% [13, 20–25]. The severity of the AP is assessed based on the Common Terminology Criteria for Adverse Events, as described in Table II [12].

The aim of this study was to review reports on AP in children with ALL, and to analyze the incidence, potential risk factors, treatment outcomes and recurrence of acute pancreatitis.

Risk factors

There are many drugs which contribute to increase in the risk of the acute pancreatitis [18, 19]. Of these, in this work we will focus on both glucocorticoids and

Table II. Classification of acute pancreatitis according to the severity of the course of the disease (source [12])

Grade 1	Asymptomatic enzyme elevation greater than 1.5 times upper limit of normal or radiographic findings of pancreatic edema, necrosis, or pseudocyst
Grade 2	Symptomatic pancreatitis with indication for medical intervention
Grade 3	Pancreatitis requiring interventional radiology or surgery
Grade 4	Pancreatitis leading to life-threatening consequences
Grade 5	Death due to pancreatitis

L-asparaginase, which are associated with the risk of developing AP, although the pathomechanisms are diverse. When administered together, the possibility of hypertriglyceridemia increases, which consequently enhances the risk of AP even more [17]. Therefore, these drugs are well-known risk factors for AP in children with ALL. Many studies have been conducted on how to predict this condition in pediatric ALL patients, and some of these results are presented below.

Liu et al. [20] conducted a cohort study on 5,185 children and young adults (age 0–30 years) with newly diagnosed ALL, treated with different protocols (Total XIIIB, Total XV, COG P9904, P9905, P9906, AALL0232 and AALL0331). 117 (2.3%) of these patients developed at least one episode of AP during treatment. The analysis of potential risk factors for AP showed that older age, Native American ancestry, and a higher cumulative dose of L-asparaginase are associated with a higher risk of this disease [20].

However, Chen et al. [21] examined 353 children with ALL, treated with the Taiwan Pediatric Oncology Group 2002 and 2013 protocols, of whom 14 (4.0%) patients had AP. As the incidence of AP was significantly higher in the group treated with the 2013 protocol than with the 2002 protocol (9.5% vs. 1.3%), this study suggested that the risk of AP depends more strongly on the peak dose intensity than on the cumulative dose of L-asparaginase, which contradicts the previous result. Similarly, older age (>6.8 years) at diagnosis was an independent risk factor [21].

Similar conclusions were drawn from a study by Abbott et al. [22] on 186 pediatric patients with ALL treated with PEG-asparaginase, of whom eight (4.3%) experienced AP. Older age at diagnosis was associated with a higher risk of this disease [22].

Dharia et al. [23] examined 548 patients with ALL (age 1–22 years) treated with PEG-asparaginase. 29 (5.3%) of these patients developed AP. This study confirmed that older age at diagnosis (>10 years) is an independent risk factor for AP [23].

A study by Kearney et al. [24] on 403 children with ALL treated with DFCI ALL Consortium protocols (protocols 87-01, 91-01, 95-01, 00-01), of whom 28 (7.0%) patients developed AP, confirmed again that older age (>10 years) at diagnosis was associated with a higher risk of this condition.

Silverman et al. [13] conducted a study on 377 children with ALL treated with the Dana-Farber Consortium Protocol 91-01. 26 (7.0%) of these patients experienced an episode of pancreatitis. Similarly, older age (>9 years) was shown to be associated with the risk of AP [13].

Denton et al. [25] analyzed 262 patients (age 1–21 years) diagnosed with ALL. 28 (11%) of these patients developed AP during treatment. Again, older age (>10 years) was a predictor of AP. Obesity was identified as another independent risk factor [25].

Based on a large cohort study, Orgel et al. [26] confirmed that obesity is related to pancreatic toxicities in pediatric ALL patients.

Regarding the relationship between asparaginase-associated pancreatitis and other drugs, a study by Knoderer et al. [12] on 254 patients reported a higher incidence of AP in a group of patients receiving L-asparaginase with prednisone and daunorubicin, and a lower incidence of AP in a group receiving it with dexamethasone.

To sum up, L-asparaginase and glucocorticoids are well-known risk factors for AP among pediatric patients with ALL. Other risk factors for this toxicity are older age (the age threshold depends on the study, and varies from 6.8 to 10 years [13, 21, 23–25]) and obesity. The correlation between the cumulative dose of L-asparaginase, the peak L-asparaginase dose intensity, and other drugs administered requires further research. Table III illustrates the incidence of AP among various ALL protocols, as well as potential risk factors of this condition [13, 20–25, 27, 28].

Treatment

The management of AP is based on disease severity and associated complications [29]. Treatment of pancreatitis is mainly symptomatic and is based on the administration of fluids [30]. Regarding nutritional treatment, for mild AP, early oral nutrition in the form of a low-fat solid diet is recommended. For severe AP, enteral rather than parenteral nutrition should be provided, reducing the risk of infection. Specific antibiotic regimens are recommended for infectious complications. In cases of persistent fluid collections or infected necrosis, intervention is required if significant symptoms are observed. Various minimally

Table III. Incidence and risk factors of acute pancreatitis (AP) in children with acute lymphoblastic leukemia (ALL) (based on [13, 20–25, 27, 28])

Study	Number of patients	Dose of L-asparaginase used	Number of cases of AP (% of all patients)	Risk factors of AP	Source
Liu et al. 2016	5,185	2,500–25,000 U/m^2	117 (2.3%)	Older age at diagnosis, Native American ancestry, high dose asparaginase regimens (>240,000 U/m^2)	[20]
Kearney et al. 2009	403	2,500–25,000 U/m^2	28 (6.9%)	Older age at diagnosis (>10 years)	[24]
Silverman et al. 2012	377	25,000 IU/m^2/dose	26 (7.0%)	Older age at diagnosis (>9 years)	[13]
Denton et al. 2018	262	–	28 (10.6%)	Older age at diagnosis (>10 years), obesity	[25]
Chen et al. 2022	353	–	14 (4.0%)	High peak L-asparaginase dose intensity (>45,000 U/m^2/month), older age at diagnosis (>6.8 years)	[21]
Dharia et al. 2022	548	Pegaspargase 2,500 mg/m^2/ /dose (AALL0031 also included two doses of L-asparaginase 6,000 IU/m^2/dose)	29 (5,3%)	Older age at diagnosis (>10 years), overweight, treatment intensity	[23]
Abbott et al. 2023	186	2,500 units/m^2/dose	8 (4.3%)	Older age at diagnosis	[22]
Min et al. 2019	421	–	14 (3.3%)	Prolonged aPTT, fresh frozen blood transfusion	[27]
Raja et al. 2014	786	1,000 IU/m^2/dose	45 (5.7%)	None	[28]

aPTT – activated partial thromboplastin time

invasive techniques such as percutaneous drainage, laparoscopy and endoscopy can be used. In patients with acute biliary pancreatitis, it is recommended that early cholecystectomy is performed to prevent recurrence [29].

A successful medication for drug-induced AP in children with ALL may be octreotide, which works as a synthetic somatostatin analog [31]. Therefore, it inhibits the secretion of pancreatic enzymes, insulin and glucagon [31]. The efficacy of octreotide in the treatment of AP and in the prevention of recurrence of AP has been presented in several clinical case reports, which include severe cases of necrotizing and hemorrhagic pancreatitis during ALL therapy [30–36]. However, randomized clinical trials are still needed in order to assess its efficacy and safety on larger groups of patients. Another study was recently conducted by Tsai et al. to determine the relevance of retinoids in asparaginase-associated pancreatitis. This showed that decreased dietary vitamin A intake was associated with a greater risk of experiencing the onset of AP. Therefore, dietary vitamin A supplementation may play an important role in preventing or treating AP during ALL treatment [37].

L-asparaginase reintroduction

As L-asparaginase is an integral part of the treatment of ALL, it seems relevant to reintroduce it into treatment following AP while minimizing the risk of pancreatitis recurrence. In the study by Knoderer et al. [12], out of 26 patients who experienced AP, only two developed AP recurrence after reintroduction of L-asparaginase. One of these patients had the onset of AP three times – after each course of L-asparaginase, while the other one tolerated the second reintroduction of L-asparaginase without developing AP. On this basis, the authors suggested that treatment with L-asparaginase should be attempted again after AP [12]. However, in another study by Kearney et al. [24], 10/16 patients who were re-administered L-asparaginase following AP developed the disease a second time. In nine of these patients, the pancreatitis self-healed; the tenth patient developed a pseudocyst requiring surgical intervention [24].

Based on these studies, the recurrence of AP following L-asparaginase reintroduction varies widely depending on which study you look at. As AP cases in children with ALL are mostly mild to moderate [12], it seems reasonable to

Table IV. Treatment of acute pancreatitis (AP) and impact of AP on acute lymphoblastic leukemia (ALL) treatment and patient outcomes (based on [13, 24, 25, 27, 28])

Study	Treatment of AP	Number of patients re-exposed to ASP treatment	Number of patients with AP recurrence following ASP re-exposure	Number of patients deceased/ /surviving with AP	Source
Kearney et al. 2009	28 patients → intravenous narcotics 5 patients developed pseudocysts	16	10	0/28	[24]
Silverman et al. 2012	–	–	–	0/26	[13]
Denton et al. 2018	–	3	1	0/28	[25]
Min et al. 2019	–	11	1	0/14	[27]
Raja et al. 2014	35 patients → antibiotics 31 patients → analgesic therapy 19 patients developed complications (i.e. pseudocysts and/ /or necrotizing/hemorrhagic pancreatitis)	12	2	1/44	[28]

ASP — L-asparaginase

try to reintroduce L-asparaginase into treatment following AP, as the benefits seem to outweigh the risks.

Outcomes

As AP is among the most frequent adverse effects leading to discontinuation of the ALL therapy, it represents a significant concern in the treatment of ALL. Unfortunately, children who have received less than 25 weeks of L-asparaginase therapy (due to e.g. AP) have been shown to be associated with worse 5-year event-free survival compared to those who received at least 26 weeks of L-asparaginase (73% vs. 90%). This is based on a study by Silverman et al. [13] on 377 pediatric patients with ALL. In another study by Kearney et al. [24] on 403 children, patients who experienced AP during ALL therapy relapsed more frequently that did those without an AP history (29% vs. 14%). Another retrospective cohort study, by Treepongkaruna et al. [38] on 192 pediatric ALL patients, showed that the mortality rate was significantly higher among children with an AP history than among those without one (43.8% vs. 19.3%). However, an analysis conducted on 1,180 patients did not show any significant difference between patients with and patients without a history of AP when comparing their event-free survival and their leukemia-free survival [24]. Therefore, the impact of AP on patient outcomes remains unclear. Table IV presents the treatment of AP in different studies and the impact of AP on ALL therapy and patients' outcomes [13, 24, 25, 27, 28].

Conclusions

Acute pancreatitis is a significant clinical concern in the treatment of children with ALL, which occurs in 2.3–11% of patients.

Drugs such as steroids and L-asparaginase administered during therapy are recognized risk factors for pancreatitis. When they are administered together, as is the case in ALL treatment protocols, blood triglyceride levels increase, which consequently further enhances the risk of pancreatitis. According to the studies we have analyzed, the two proven independent risk factors for this condition are older age at diagnosis and obesity. However, it remains unclear whether the type of L-asparaginase administered and other drugs used affect the risk of pancreatitis.

As L-asparaginase is a crucial drug in the treatment of ALL, it is reasonable to try to reintroduce it into therapy following an episode of pancreatitis. The incidence of recurrent pancreatitis after re-treatment with L-asparaginase varies depending on the study analyzed. The outcomes for children who develop AP during ALL treatment are usually worse compared to children without an AP history, taking into account their 5-year survival rate, recurrence and mortality rates.

Further research is required to refine the management of acute pancreatitis and to minimize the worsening of ALL outcomes among these patients.

Authors' contributions

Conceptualization — JZ, ML. Methodology — JZ, AM, MLa, PK. Writing: original draft preparation — AM, MLa. PK, ML. Review and editing — JZ, ML. All authors read and agreed published version of manuscript.

Conflict of interest

The authors declare no conflict of interest.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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