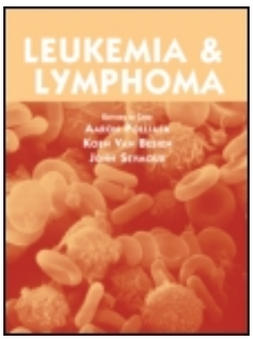

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REVIEW

Asparaginase-associated toxicity in children with acute lymphoblastic leukemia

Nobuko Hijiya[a] and Inge M. van der Sluis[b]

[a]Division of Hematology/Oncology/Stem Cell Transplant, Ann & Robert H. Lurie Children's Hospital of Chicago and Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; [b]Department of Pediatric Oncology/Hematology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands

ABSTRACT

Asparaginase is an integral component of multiagent chemotherapy regimens for the treatment of children with acute lymphoblastic leukemia. Positive outcomes are seen in patients who are able to complete their entire prescribed course of asparaginase therapy. Toxicities associated with asparaginase use include hypersensitivity (clinical and subclinical), pancreatitis, thrombosis, encephalopathy, and liver dysfunction. Depending on the nature and severity of the toxicity, asparaginase therapy may be altered or discontinued in some patients. Clinical hypersensitivity is the most common asparaginase-associated toxicity requiring treatment discontinuation, occurring in up to 30% of patients receiving *Escherichia coli*–derived asparaginase. The ability to rapidly identify and manage asparaginase-associated toxicity will help ensure patients receive the maximal benefit from asparaginase therapy. This review will provide an overview of the common toxicities associated with asparaginase use and recommendations for treatment management.

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Introduction

With current multiagent chemotherapy regimens, long-term outcomes for children with acute lymphoblastic leukemia (ALL) have greatly improved, with reported overall survival rates >90% compared with <30% in the 1960s [1,2]. These substantial gains in survival are due, at least in part, to the increased use of intense and prolonged asparaginase therapy [3–5]. However, asparaginase use is associated with a number of toxicities. Failure to receive the full course of asparaginase therapy due to treatment-emergent toxicity has been associated with poor outcomes in children with ALL [3,6–8]. This review provides a concise overview of common toxicities associated with asparaginase therapy and recommendations for management.

Mechanism of action of asparaginase

The administration of asparaginase reduces plasma asparagine concentrations by catalyzing the deamination of asparagine into aspartic acid and ammonia [8]. At sufficient enzyme activity levels, asparaginase therapy results in the complete depletion of serum asparagine concentrations, depriving leukemic blasts of this amino acid [9], resulting in reduced protein synthesis and ultimately leukemic cell death.

Three different asparaginase preparations are currently used for the treatment of patients with ALL. Two preparations, native *Escherichia coli* (*E. coli*) asparaginase and polyethylene glycolated (PEG)-asparaginase, are derived from the bacterium *E. coli* [10]. Native *E. coli* asparaginase has been widely used as a first-line treatment in ALL; however, the supply of this preparation has recently ceased in the United States and has largely been replaced with PEG-asparaginase [11]. The third preparation, *Erwinia* asparaginase, is derived from the bacterium *Erwinia chrysanthemi* [12]. The distinct bacterial origins of *Erwinia* asparaginase give it a unique immunogenic profile, showing no cross-reactivity with native *E. coli* asparaginase or PEG-asparaginase [13]. *Erwinia* asparaginase is indicated as a component of a multiagent chemotherapy regimen for the treatment of

CONTACT Nobuko Hijiya, MD nhijiya@luriechildrens.org Division of Hematology/Oncology/Stem Cell Transplant, Ann & Robert H. Lurie Children's Hospital of Chicago, Box #30, 225 E. Chicago Avenue, Chicago, IL 60611, USA or
Inge M. van der Sluis, MD, PhD i.vandersluis@erasmusmc.nl Department of Pediatric Oncology/Hematology, Erasmus MC-Sophia Children's Hospital, Na 1607 Wytemaweg, 3015 CN, Rotterdam, The Netherlands

patients with ALL who have developed hypersensitivity to *E. coli*–derived asparaginases [14]. Each of the three asparaginase preparations displays markedly different pharmacokinetics that must be accounted for when determining dosing schedules [15]. The half-life of PEG-asparaginase has been estimated at 4.8–7.0 days and is longer than that reported with native *E. coli* asparaginase and *Erwinia* asparaginase [16–19]. In comparison, the half-life of native *E. coli* asparaginase and *Erwinia* asparaginase are 1.28 days and 15.6 hours, respectively [14,19]. Due to the shorter half-life of *Erwinia* asparaginase, patients who switch to this formulation should receive a higher dose at a greater frequency in order to maintain therapeutic levels of asparagine depletion [20].

Asparaginase toxicity

Hypersensitivity

The asparaginases used in ALL treatment protocols are large molecules of bacterial origin, and thus have the ability to elicit an immune response in patients [8]. Immune reactions to asparaginase are classified as either clinical or subclinical hypersensitivity (also referred to as "silent inactivation"). Clinical hypersensitivity is one of the most common reasons for the discontinuation of asparaginase therapy.

Rates of clinical hypersensitivity reactions in the literature vary. Clinical hypersensitivity to native *E. coli* asparaginase has been reported in up to 75% of patients with ALL [21], although rates generally range from 10–30% [7,22–26]. Clinical hypersensitivity reactions appear to be less prevalent with PEG-asparaginase, with rates from 3–24% reported in clinical trials [3,7,24,26]. Hypersensitivity reactions to PEG-asparaginase are more common when patients have been previously exposed to native *E. coli* asparaginase, owing to their common bacterial source [27].

Rates of clinical hypersensitivity in patients receiving *Erwinia* asparaginase, which is derived from an alternative bacterial source, have been reported in 3–37% of patients in clinical trials [7,14,20,26,28–34]. Patients who develop clinical hypersensitivity to asparaginase have shown increased antibody formation and decreased asparaginase activity levels compared with patients who do not develop hypersensitivity [32,35,36]. Tong and colleagues [32] reported clinical hypersensitivity (grades 1–4) in 20 of 89 patients (22%) administered PEG-asparaginase during the intensification phase after receiving native *E. coli* asparaginase during the induction phase of the Dutch Childhood Oncology Group (DCOG) ALL-10 protocol. All 20 patients with hypersensitivity showed PEG-asparaginase activity levels of 0 IU/L, and *E. coli* antibodies were found in all patients with hypersensitivity during intensification.

The likelihood of asparaginase eliciting an immune response in patients may be influenced by a number of factors, including the asparaginase preparation, treatment intensity, and use of concomitant medications [23,24,29,36,48]. The risk of antibody formation for patients increases with repeated exposure to asparaginase; consolidation and reinduction phases of treatment show the greatest incidence of hypersensitivity reactions and antibody formation [30,49]. However, prolonged exposure to asparaginase, without gaps in treatment, has been associated with decreased antibody levels [36,50]. Due to this, hypersensitivity reactions are most common within the first few doses of asparaginase after a break in treatment [32]. Additionally, the concomitant administration of corticosteroids has been associated with reduced signs of clinical hypersensitivity [24,25]. However, as clinical hypersensitivity is often the only observable symptom of antibody formation, suppression of these symptoms may only mask signs of hypersensitivity and result in prolonged periods of suboptimal asparaginase activity levels in patients. Whenever possible, therapeutic dose monitoring of asparaginase activity levels should be utilized to identify patients with suboptimal activity levels to adjust treatment in these patients accordingly [32].

Patients who display a hypersensitivity reaction to an *E. coli*–derived asparaginase should immediately discontinue their current therapy and be switched to *Erwinia* asparaginase (Table I) [33, 37]. Patients with hypersensitivity switched to *Erwinia* asparaginase show therapeutic levels of asparaginase activity, and the majority of patients with hypersensitivity are able to complete their prescribed course of treatment [33]. The FDA-approved dose substitution of *Erwinia* asparaginase for each planned dose of PEG-asparaginase is 25,000 IU/m^2 administered intramuscularly (IM) or intravenously (IV) 3 times a week (Monday/Wednesday/Friday) for six doses [14]. No established guidelines exist for when treatment with the new preparation should be initiated in patients who switch asparaginase preparations because of clinical hypersensitivity. In practice, many patients with hypersensitivity begin treatment with the new preparation at the time of their next scheduled dose. Given the strong association between clinical hypersensitivity and reduced asparaginase activity [32], this practice may result in suboptimal asparagine depletion in the patients between doses. To avoid a prolonged gap in asparagine depletion, patients with hypersensitivity to asparaginase should begin treatment with an alternative asparaginase as early as possible, preferably within 48–72 hours after the hypersensitivity

Table I. Asparaginase-associated toxicities and recommendations for management of asparaginase therapy [33,37–47].

Toxicity	Management of asparaginase therapy	References
Asparaginase hypersensitivity	Discontinue native *E. coli*–derived asparaginase or PEG-asparaginase in the case of hypersensitivity and switch patient to *Erwinia* asparaginase	Salzer *et al.* [33]
Clinical hypersensitivity	In the case of clinical hypersensitivity to an *E. coli*–derived asparaginase and *Erwinia* asparaginase, discontinue asparaginase therapy	Vrooman *et al.* [37]
Subclinical hypersensitivity	In the case of subclinical hypersensitivity to an *E. coli*–derived asparaginase, switch patient to *Erwinia* asparaginase	
Hyperglycemia	Asparaginase therapy should continue if patient shows normal glucose levels with insulin	Howard and Pui [38]
Pancreatitis	Discontinue asparaginase if amylase/lipase levels are $\geq 3 \times$ ULN and/or imaging/clinical signs are compatible with pancreatitis	Raja *et al.* [39]
	May rechallenge in patients with mild pancreatitis if within 48 hours the patient displays no symptoms, amylase/lipase levels $<3 \times$ ULN, and no pseudocysts or necrosis	Stock *et al.* [40]*
Thrombosis	Withhold asparaginase in the case of clinically significant thrombosis	Payne and Vora [41]
	Restart asparaginase under anticoagulation therapy once symptoms resolve	Truelove *et al.* [42]*
		Grace *et al.* [43]
Encephalopathy	Treat symptoms of encephalopathy and normalize serum ammonia levels if elevated	Panis *et al.* [44]
	Asparaginase treatment may continue if symptoms are not life-threatening	
Myelosuppression	Continue asparaginase treatment	Merryman *et al.* [45]
	Reduce dose of other myelosuppressive agents (not recommended during induction)	
Hypertriglyceridemia	Maintain asparaginase therapy and monitor the patient closely for signs of pancreatitis	Tong *et al.* [46]
		Bhojwani *et al.* [47]
Hepatic toxicity	In adults, withhold asparaginase for clinical symptoms and alanine/glutamine aminotransferase >5.0–$20.0 \times$ ULN	Stock *et al.* [40]*
	No clear pediatric guidelines; asparaginase management varies across treatment protocols	

E. coli, *Escherichia coli*; PEG, pegylated; ULN, upper limit of normal.
*Focused on adult patients with acute lymphoblastic leukemia.

event if symptoms are fully resolved [51,52]. Patients who develop hypersensitivity to both *E. coli*– and *Erwinia chrysanthemi*–derived formulations are forced to discontinue asparaginase treatment [32].

Subclinical hypersensitivity is characterized by the development of antiasparaginase antibodies and significantly reduced asparaginase activity levels [19,37]. Although difficult to identify because of the lack of clinical symptoms, subclinical hypersensitivity has been reported in 8–29% of patients receiving *E. coli*–derived asparaginases [25,32,37]. Subclinical hypersensitivity is strongly associated with poor clinical outcomes if not readily identified and addressed [25,37]. The ability to prospectively identify patients with subclinical hypersensitivity and switch these patients to an alternate asparaginase formulation has been associated with improved outcomes in a clinical trial [37].

Following the IV administration of asparaginase, localized non-antibody-mediated infusion reactions may occur in patients [53]. Unlike true clinical hypersensitivity reactions, patients who display an infusion reaction to asparaginase do not show antiasparaginase antibodies and infusion reactions are not associated with a decrease in asparaginase activity levels. Patients with a non-antibody-mediated infusion reaction to asparaginase may be rechallenged with a longer infusion duration and appropriate premedication. Differentiating between clinical hypersensitivity, subclinical hypersensitivity, and non-antibody-mediated infusion reactions can be difficult in practice. But measurement of asparaginase activity levels might help to differentiate between these reactions.

Hyperglycemia

The use of asparaginase is associated with reduced insulin production and possibly a decrease in the expression of insulin receptors [38,54]. Corticosteroid use is associated with greater insulin resistance and an increase in hepatic gluconeogenesis [55,56]. Hyperglycemia is more common during phases of therapy when asparaginase and corticosteroids are administered together and in relatively higher doses [38,57].

Asparaginase-associated hyperglycemia has been reported in 4–20% of pediatric patients receiving *E. coli* asparaginase for ALL [57–60] and in 4–17% of patients receiving *Erwinia* asparaginase [14,33,34]. The asparaginase preparation and the type of corticosteroid (prednisone or dexamethasone) used in treatment do not seem to influence the risk of hyperglycemia [24,58,60]. Insulin therapy may be required in severe

cases; however, asparaginase therapy can continue if the patient shows normal glucose levels (< 200 mg/dL or 11 mmol/L) with insulin [Table I] [8,38,40]. The final decision regarding the continuation of asparagainse should be made by the treating physician based on the patient's general status.

Pancreatitis

While the precise pathogenesis of pancreatitis is unknown, the reduction in protein synthesis resulting from asparaginase-induced depletion of asparagine has been implicated [61]. In clinical trials, pancreatitis has been reported in 2–18% of patients undergoing asparaginase therapy for ALL, with grade 3/4 pancreatitis occurring in 5–10% of patients [39,61–65]. The formulation of asparaginase does not influence the incidence of pancreatitis in patients [61].

Diagnosis of pancreatitis is based on a combination of clinical, biochemical (amylase, lipase), and radiological evidence. Asparaginase therapy can be continued with mildly elevated amylase or lipase levels if clinical signs are absent; however, asparaginase treatment is generally discontinued in the case of severe pancreatitis [Table I] [39,40]. Patients with mild pancreatitis may be rechallenged with asparaginase if within 48 hours the patient displays no clinical symptoms, amylase and lipase levels are below 3 times the upper limit of normal (ULN), and there are no signs of pseudocysts or necrosis on imaging [61]. Caution should be exercised, as recurrence of pancreatitis has been reported in up to 63% of patients following re-exposure to asparaginase [62].

Thrombosis

Asparaginase is associated with a decrease in the production of a number of proteins involved in coagulation and fibrinolysis, and may increase the risk of thrombosis or bleeding [66–70]. The majority of asparaginase-associated thrombotic events occur during induction and are likely attributable to multiple factors, including indwelling central venous catheter, treatment with corticosteroids, treatment with asparaginase, and leukemia itself [41,71]. The incidence of symptomatic thrombosis ranges from 2–7% in clinical trials and has been reported with both *E. coli*– and *Erwinia*-derived asparaginase [14,33,34,41,71–73]. A meta-analysis of 17 studies focused on thrombotic complications in children with ALL found that the overall incidence of thrombosis is 5.2% [71]. The authors report that the majority of events (53.8%) occurred in the central nervous system (CNS), and 28.6% of the total events were classified as central venous thrombosis. Of the non-CNS events, the greatest incidence was seen in the upper limbs and was categorized as deep venous thrombosis and central venous catheter–related [71].

Patients with deep venous thrombosis should be managed with anticoagulation therapy, preferably with low-molecular-weight heparin (LMWH) [42]. Asparaginase use should be temporarily discontinued in the case of clinically significant bleeding or thrombotic events; however, reports suggest that re-exposure to asparaginase with LMWH is safe and feasible in patients who develop thrombosis once clinical symptoms have resolved [Table I] [43,73]. Screening patients for prothrombotic risk factors has been suggested in some reports [71]; however, the evidence linking thrombophilia and other risk factors to the incidence of thrombotic events is mixed [74–78].

Encephalopathy

Encephalopathy has been reported in patients receiving asparaginase treatment for ALL, although the precise relationship between asparaginase and neurotoxicity is unclear [40,44,79,80]. Posterior reversible encephalopathy is one of the encephalopathies sometimes seen in patients with ALL. The majority of reported cases of posterior reversible encephalopathy in patients with ALL occur during induction treatment, which could also be related to hypertension caused by glucocorticoids, and resolve without serious complications in most cases. [80–83].

Elevated plasma ammonia levels, due to the asparaginase-driven breakdown of asparagine into aspartic acid and ammonia, are sometimes associated with encephalopathy in patients undergoing asparaginase therapy [79,80,84]; however, hyperammonemia alone does not typically result in symptoms, and reduced expression of the glutamine transporter proteins may also play a role [85]. Patients with existing liver disease may be at an increased risk for developing symptoms of hyperammonemia. There is no standard therapy for patients with asparaginase-induced hyperammonemia. Treatments with decreased protein intake, lactulose treatment, benzoic acid, and arginine and sodium phenylbutyrate have been reported; however, there is sparse evidence for these treatments and their efficacy is unclear [84,86,87].

Myelosuppression

Although a number of early studies described an association between asparaginase use and myelosuppression [88,89], asparaginase itself is not typically considered a myelosuppressive agent. Asparaginase

may cause myelosuppression directly or indirectly by altering the myelosuppressive effects of other agents, such as methotrexate (MTX) or 6-mercaptopurine (6-MP) [45,90,91]. A recent report of pediatric patients (<10 years of age) with ALL treated on the Dana-Farber Cancer Institute ALL Consortium Protocol 05-01 found increased myelosuppression during prolonged asparaginase therapy in consolidation [45]. Patients received 30 weeks of asparaginase treatment during consolidation, but no asparaginase was administered during continuation. A greater percentage of patients required dose reductions of MTX and/or 6-MP during consolidation compared with continuation (24% vs. 9%, respectively), suggesting a myelosuppressive role of asparaginase. Dose reduction of concurrently administered myelosuppressive agents may be used to manage asparaginase-associated myelosuppression during consolidation (Table I)[45].

Hypertriglyceridemia

Asparaginase use is associated with a number of abnormalities in lipid metabolism, including hypertriglyceridemia [8,92]. Corticosteroids are adipokinetic agents that alter lipid synthesis, clearance, and metabolism, and thus contribute to a transient elevation of triglyceride levels [92,93]. Transient elevations in triglyceride levels are most often seen when patients receive high doses of asparaginase and corticosteroids [94]. Combined treatment with asparaginase and corticosteroids leads to hypertriglyceridemia in up to 67% of patients receiving asparaginase treatment for ALL [95].

Data from patients treated on the DCOG ALL-10 protocol showed a significant positive relationship between asparaginase activity levels and triglyceride levels [46]. This study prospectively evaluated the incidence and clinical course of hypertriglyceridemia and hypercholesterolemia in 89 pediatric patients undergoing prolonged asparaginase therapy. Hypertriglyceridemia (grade 3/4) was more prevalent in patients receiving PEG-asparaginase compared with patients administered *Erwinia* asparaginase (47% vs. 0%, respectively) [46]. Additionally, hypercholesterolemia (grade 3/4) was reported in 25% of patients receiving PEG-asparaginase compared with no patients administered *Erwinia* asparaginase. In this study, asparaginase activity levels were consistently higher in patients receiving PEG-asparaginase compared with patients receiving *Erwinia* asparaginase, possibly contributing to the greater incidence of hypertriglyceridemia and hypercholesterolemia.

Hypertriglyceridemia is often transient and asymptomatic in patients. Adjustments in asparaginase therapy are generally not required; however, patients with elevated triglyceride levels should be closely monitored for signs of pancreatitis [Table I] [46,93,95,96]. Several treatment approaches have been reported for patients with hypertriglyceridemia, including short-term fasting or low-fat diet, oral fibrates, omega-3, and plasmapheresis [47,97–101]. Strong evidence for any specific option is lacking, and there is currently no standard treatment for hypertriglyceridemia. Tong and colleagues [102] reported the successful resolution of severe hypertriglyceridemia in a pediatric patient by temporarily omitting dexamethasone courses without any further changes to therapy.

Hepatic toxicity

Hepatic toxicity associated with asparaginase use is rarely associated with fatal complications; however, clinical outcomes may be negatively affected if significant delays in treatment are required due to asparaginase-associated dysfunction. Asparaginase use is more commonly associated with abnormalities in liver function and hepatic transaminases as well as elevations in bilirubin and alkaline phosphates [7]. The mechanism of action by which asparaginase causes hepatic dysfunction is unknown; however, the reduction in protein synthesis associated with asparaginase therapy is believed to play a role [40]. The degree to which hepatic dysfunction in patients undergoing treatment for ALL can be attributed to asparaginase use is unclear, as many regimens include the use of several potentially hepatotoxic drugs (e.g. corticosteroids, vinca alkaloids, anthracyclines, and antimetabolites). Elevated levels of hepatic transaminase, alkaline phosphatase, and bilirubin have been reported in 30–60% of patients receiving asparaginase as part of multiagent therapy for ALL [40,95]. In a study of 118 children receiving native *E. coli* asparaginase or PEG-asparaginase, abnormal liver function (grade 3/4), including elevated transaminases and hyperbilirubinemia, was found in 8% of patients receiving native *E. coli* asparaginase and in 5% of patients receiving PEG-asparaginase [24,103,104]. In children and adults receiving *Erwinia* asparaginase, grade 3/4 liver toxicity has been reported in approximately 4% of patients [14,33,34,105]. There are no clear pediatric guidelines for the management of asparaginase in patients with hepatic toxicity, and treatment recommendations vary across protocols. In the DCOG ALL-11 pediatric protocol, patients are required to display aspartate aminotransferase/alanine aminotransferase $< 10 \times$ ULN and no signs of jaundice with bilirubin $< 3 \times$ ULN prior to starting asparaginase treatment [106]. Recommendations for adolescent and young adults

(AYA) call for witholding asparaginase in patients with grade 3/4 hepatotoxicity (alanine or glutamine aminotransferase elevation $>5 \times$ ULN) with the option to rechallenge patients with careful monitoring if complications resolve [Table I] [40].

Toxicity in AYA patients

The treatment of AYA patients (16–39 years of age) diagnosed with ALL represents a unique challenge. Older patients are believed to be at a greater risk for asparaginase-associated toxicities, and therefore, many adult protocols limit asparaginase use [107]. However, a number of retrospective studies have reported significantly greater long-term survival when AYA patients are included in pediatric protocols, which use high-intensity asparaginase therapy [108–112]. A large prospective study, C10403, evaluated the feasibility of using a pediatric regimen in 318 AYA patients (16–39 years of age) treated by adult hematologists and oncologists [113]. Safety and toxicity results were compared with data from AYA patients (16–21 years of age) treated on the pediatric Children's Oncology Group AALL0232 trial. The rates of adverse events were relatively similar in the two study populations, and overall treatment-related mortality was low (3%) in the C10403 study. Investigators concluded that treatment with a pediatric regimen was feasible in AYA patients up to 40 years of age [113]. Differences in toxicities between age groups were not evaluated in C10403; however, results from another recent trial suggest a similar safety profile in pediatric and AYA patients. In this compassionate-use trial, 147 AYA patients (16 to <40 years of age) were switched to *Erwinia* asparaginase following hypersensitivity to an *E. coli*–derived asparaginase [34]. Rates of asparaginase-related toxicity were reportedly similar in AYA patients and in patients <16 years of age. Hypersensitivity to *Erwinia* asparaginase was reported in 10.9% of patients $\geq$16 years of age compared with 15.1% in patients $\leq$10 years of age. Overall, toxicities were manageable, and the majority of AYA patients (73%) were able to complete their planned course of asparaginase therapy with *Erwinia* asparaginase [34].

Conclusions

Asparaginase is a critical component of all pediatric ALL protocols and is increasingly used to treat AYA patients. With many protocols incorporating prolonged and high-intensity asparaginase treatment, it is important that practitioners be aware of all potential treatment-related toxicities. Effective management of asparaginase toxicity will help ensure patients receive their complete course of asparaginase therapy and obtain optimal treatment outcomes.

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