

Incidence and Management of Asparaginase-associated Adverse Events in Patients With Acute Lymphoblastic Leukemia

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Abstract: Asparaginase is an enzyme that breaks down extracellular asparagine into aspartic acid and ammonia. Depletion of extracellular asparagine inhibits the growth of lymphocytic leukemic cells. Unlike normal cells, lymphoblasts lack the enzyme to synthesize asparagine and therefore rely on an exogenous source of this amino acid to maintain cellular protein synthesis. Asparagine depletion results in nutritional deprivation, inhibition of protein synthesis, and subsequent apoptotic cell death in lymphoblasts. Asparaginase therapy is an essential component of the treatment protocol for acute lymphoblastic leukemia. The effect of asparaginase on protein synthesis may result in a number of toxicities, including thrombosis, pancreatitis, hyperglycemia, and hepatotoxicity. This review discusses the incidence of asparaginase-related adverse events, compares available asparaginase formulations with respect to the emergence of certain toxicities, and considers management strategies for these toxicities in patients with acute lymphoblastic leukemia.

Introduction

Asparaginase is an enzyme that causes rapid depletion of extracellular asparagine by hydrolyzing it to aspartic acid and ammonia.¹⁻³ Human lymphoblasts characteristically have low asparagine synthetase activity and rely upon exogenous asparagine for protein synthesis. Asparagine deficiency therefore leads to the death of lymphoblasts.⁴

L-asparaginase is an essential component of regimens used to treat patients with acute lymphoblastic leukemia (ALL).⁵⁻⁸ Three formulations of asparaginase are available: native L-asparaginase derived from *Escherichia coli* (native L-asparaginase, Elspar, Merck), *E. coli* L-asparaginase conjugated with polyethylene glycol (PEG) (pegaspargase, Oncaspar, Enzon) and L-asparaginase derived from the plant bacteria *Erwinia chrysanthemi* (*Erwinia* L-asparaginase, Erwinase), approved in Europe but available in the United States with compassionate use protocol through the manufacturer EUSA Pharma.

Keywords

Acute lymphoblastic leukemia, asparaginase, adverse events

Table 1. Evaluation of Injection Site and Hypersensitivity Reactions¹⁰

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Injection site reaction/ extravasation changes	Pain, itching, erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe, operative intervention indicated	—	—
Allergic reaction/ hypersensitivity	Transient flushing or rash, drug fever <100.4°F	Rash, urticaria, dyspnea, drug fever >100.4°F and/or asymptom- atic bronchospasm	Symptomatic broncho- spasm with or without urticaria, parenteral medication(s) indicated, allergy-related edema/angioedema	Anaphylaxis	Death

Asparaginase treatment is associated with several adverse events, including hypersensitivity reactions, coagulation disorders, pancreatitis, hyperglycemia, and hepatotoxicity.⁹ This review discusses the adverse events associated with the use of asparaginase, differences between formulations, and strategies for managing these side effects in patients with ALL.

Mechanisms of Toxicity

Hypersensitivity

Immunologic reactions caused by exposure to bacterial proteins can be quite common and may range in severity from localized, transient erythema and rash at the site of injection to urticaria, respiratory distress, and acute life-threatening anaphylaxis. Hypersensitivity reactions are graded according to the Cancer Therapy Evaluation Program's Common Terminology for Clinical Adverse Events (Table 1).¹⁰

Coagulation Disorders

The adverse events related to coagulation disorders are a product of the drug's effect on protein synthesis. The most consistent findings are reductions in plasminogen, fibrinogen, antithrombin, and factors IX and X with prolongation of activated partial thromboplastin time.^{11,12} Deficiencies of protein C and S have also been reported.¹³⁻¹⁷ These deficiencies in anticoagulant proteins impair thrombin inhibition or result in excess thrombin levels. These results may increase the risk for bleeding or thrombosis. Hypofibrinogenemia has been reported to occur anywhere from 15–65%. Asparaginase therapy may affect the hemostatic system indirectly through the effect of supportive care.¹³ For example, central venous line catheters used during treatment may cause thrombotic complications.¹⁸ These complications are believed to be due to several mechanisms, including vessel wall

damage by the catheter itself, as well as the chemotherapeutic agent. Table 2 presents the diagnosis and clinical presentation of thromboembolisms.

Pancreatitis, Hyperglycemia, and Hepatotoxicity

Causes for pancreatitis, hyperglycemia, and hepatotoxicity causes are less well defined but may be a result of the effect on protein synthesis. Hepatotoxicity has been theorized to involve glutamine deficiency, decreased hepatic protein synthesis, oxidative stress, and consequent impairment of mitochondrial b-oxidation.¹⁹⁻²¹ Histologic results are rarely reported in patients who develop liver abnormalities while being treated with asparaginase; however, instances of macro- and microvesicular liver steatosis have been described.^{19,22} Microvesicular steatosis can lead to liver failure and coma and may be fatal in certain instances.

Incidence of Adverse Reactions

Hypersensitivity reactions are the most commonly reported adverse reaction. Early studies report these reactions in up to 30% of patients.²³⁻²⁵ More recent data suggest that the incidence may be closer to 5–15%.²⁶⁻²⁸ Coagulation disorders can occur in up to one third of patients while pancreatitis (2–16%) and hyperglycemia (up to 10%) occur less often.²⁹⁻³⁷ Hepatotoxicity, while rare in children, has been reported in one third of adults.¹⁹

Incidence of Adverse Reactions in Adults versus Children

Hypersensitivity

A study by Advani and colleagues reported that a proportionately greater number of pediatric patients with ALL had hypersensitivity/allergic reactions in response to asparaginase therapy compared with adult ALL patients

(10 vs 1%).³⁸ These differences may be related to the use of different asparaginase formulations; the earlier studies used native L-asparaginase, whereas this study used pegaspargase. The lower rate of hypersensitivity reactions in adults reported by Advani and colleagues may also be due to the lower number of doses administered in adults (average, 2.5 per patient in adults vs 5.2 in children).³⁸ A recent update of this study reported that 5% of adults exhibited allergic reactions.³⁹ Douer and associates reported that there were no allergic reactions in 25 adult patients treated with intravenous (IV) pegaspargase.²⁶

Coagulation Disorders

Hemostatic complications are less well defined in adult ALL patients. Therefore, the majority of data are based upon studies in pediatric populations. In adults with ALL who are receiving asparaginase therapy, the reported overall incidence of thromboembolisms varies from 4.2–9.6%.^{11,40–42} The wide variation in incidence reported in both pediatric and adult ALL patients may be due to differences in the definition of pathology, diagnostic methods, study design, and the protocols used to treat these patients.^{30,31} A significant majority of thromboembolisms occur during early (induction) versus later (consolidation, intensification) phases of treatment. For example, in a large-scale retrospective survey of pediatric patients with ALL, 90% of thromboembolisms that were reported occurred during the induction phase of treatment.⁴³

Hepatotoxicity

Recent data suggest that a greater number of adult patients with ALL have hepatotoxicity reactions in response to asparaginase therapy compared with pediatric populations (elevated liver enzymes, 36% vs 20%; hyperbilirubinemia, 14% vs 3%; hypofibrinogenemia, 16% vs 2%). Overall, results of this study showed that IV pegaspargase is hepatotoxic in approximately one third of adult patients.³⁸ A follow-up to this study reported elevated liver enzymes in 51% of adult patients treated with IV pegaspargase.³⁹ Of note, pegaspargase-associated hepatotoxicity reactions have generally been reported to be mild and transient.^{26,38,39}

Adverse Reactions by Asparaginase Formulation

Hypersensitivity

Pegaspargase Versus Native L-asparaginase Covalent linkage to PEG blocks potentially immunogenic epitopes without obstructing the substrate-interaction site, and may thereby reduce the propensity for dose-limiting hypersensitivity without functional compromise.⁴⁴ In the Dana-Farber Cancer Institute (DFCI) Childhood ALL

Table 2. Diagnosis and Clinical Presentation of Thromboembolisms⁵⁷

Site	Clinical signs	Incidence
Central venous line	Swelling, pain, tenderness, erythema or discoloration of affected limbs, dilated vessels, CVL malfunction, headache, swelling of face	5% (symptomatic) ^{33,63} 29–37% (asymptomatic) ^{*33,63}
Central nervous system	Headache, vomiting, visual problems, neurological deficits, seizure, drowsiness, or any unexplained change in status	2.9% ³²
Cardiac	CVL malfunction, sepsis, congestive heart failure	2% (symptomatic) ³⁰ 5% (asymptomatic) ^{*33}
Deep venous	Swelling, pain, tenderness, erythema, or discoloration of affected limb	5–10% (symptomatic) ^{30,64}
Pulmonary embolism	Breathing problems, chest pain, hypoxia, cyanosis, syncope, pneumonia	2% (symptomatic) ³⁰

*Prophylactic Antithrombin Replacement in Kids with ALL (PARKAA) study; native L-asparaginase.

CVL = central venous line.

Consortium protocol 91-01, pegaspargase was associated with a significantly lower incidence of mild allergic reactions versus native L-asparaginase. No difference was observed in the rates of severe allergic reaction between the 2 treatment arms.⁴⁵ In the Children's Cancer Group CCG-1962 protocol, 3% of patients receiving pegaspargase experienced acute allergic reactions while no reactions occurred in the L-asparaginase group. One of the patients experienced a grade 1 allergic reaction, and the other grade 3 hives.²³ Among patients treated on the intensified post-induction intensification arms of the CCG-1961 protocol, 54% experienced an allergic reaction to pegaspargase; however, these patients had prior exposure to asparaginase. Severe allergic reactions were exhibited by patients initially receiving native L-asparaginase and later exposed to pegaspargase. The authors therefore suggested using pegaspargase during induction and all subsequent phases of induction therapy.⁴⁶

Types of Thromboembolisms	Management Strategies
Central venous line-related thromboembolisms	<p>Acute and symptomatic</p> <ul style="list-style-type: none"> • Remove line if no longer required • Consider anticoagulant therapy 3–5 days before line removal • LMWH anticoagulant therapy with line in place if access is still required and properly functioning <p>Asymptomatic (radiographically detected)</p> <ul style="list-style-type: none"> • Ensure patency of line • LMWH anticoagulation therapy in the absence of contraindications
Central nervous system thromboembolisms	<p>Supportive care</p> <ul style="list-style-type: none"> • Anticoagulation therapy unless major central nervous system hemorrhage (3–6 months) • Unfractionated heparin or low molecular weight heparin 1 week, followed by oral anticoagulant • Consider antithrombin in cases with no response to anticoagulation • Re-exposure to asparaginase under cover of anti-coagulant prophylaxis
Cardiac thromboembolisms	<ul style="list-style-type: none"> • Chronic anticoagulation for 6 months

Table 3. Management Strategies for Thromboembolisms^{54,55}

Erwinia* L-asparaginase Versus Native *E. L-asparaginase In the DFCI 95-01 protocol, native L-asparaginase was associated with more allergic reactions than *Erwinia* L-asparaginase (14% vs 6% respectively, $P=.03$).²⁸

Hepatotoxicity

Pegaspargase Versus Native L-asparaginase In the CCG-1962 trial, no patients receiving pegaspargase exhibited abnormal liver function, compared with 7% of patients receiving native L-asparaginase (eg, aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase >1.5 times the normal value, or total bilirubin >1.5 times the normal value).²³ Dinndorf and colleagues reported abnormal liver function in 5% of patients receiving pegaspargase and in 8% of patients receiving native L-asparaginase.⁴⁷ Reversible elevations in liver enzymes (76%) and bilirubin (72%) levels were also recently reported with IV pegaspargase.²⁶

***Erwinia* L-asparaginase Versus Native L-asparaginase Versus Pegaspargase** In a recent report presented at the annual meeting of the American Society of Clinical Oncology, *Erwinia* L-asparaginase had a statistically significantly lower incidence of liver dysfunction (24%) compared with native L-asparaginase (50%) and pegaspargase (58%; $P<.0001$).⁴⁸

***Erwinia* L-asparaginase Versus Native L-asparaginase** Duval and coauthors reported hepatotoxicity (World

Health Organization grade 3–4) in 4.5% of pediatric patients receiving native L-asparaginase versus 3.8% of patients receiving *Erwinia* L-asparaginase ($P=NS$).⁴⁹

Management Strategies

Hypersensitivity

Antihistamines can be used to prevent or treat urticaria. However, more severe reactions often require discontinuation of the specific drug formulation and switching to an alternative asparaginase formulation. Anaphylactic reactions can be managed by epinephrine and steroids.³ Combination chemotherapy with vincristine and glucocorticoid may also help avoid allergic reactions, through immunosuppression.^{50,51}

Coagulation Disorders

Managing a thromboembolism presents unique challenges in terms of balancing the risks versus benefits of therapy. Conservative therapy may lead to clot extension and increased morbidity related to the thromboembolism. Aggressive therapy may result in bleeding complications due to thrombocytopenia and coagulopathy from concurrent chemotherapy.^{52,53} Several management strategies based upon the site of pathology are given in Table 3.

When acute and symptomatic thromboembolisms are related to the central venous line, management depends on the need to keep the line in place. If the line is no longer required, it should be removed.⁵⁴ If central

venous line access is required, the line may be removed and another line inserted into another vein. If the line must remain in place, anticoagulation therapy should be given.⁵⁵ Treatment with anticoagulation should also be considered for significant venous thrombosis. This treatment decision should take into account the elevated risk of bleeding complications due to thrombocytopenia from concurrent chemotherapy.

The recommended therapy for CNS thromboembolisms includes anticoagulation therapy with/without antithrombin concentrates for the initial treatment phases and, in some cases, antithrombin concentrates for secondary prophylaxis.⁵⁴ Patients can be re-exposed to asparaginase with concurrent anticoagulant prophylaxis. The use of unfractionated heparin versus low molecular weight heparin must be determined on a case-by-case basis.

The clinician should also be aware of bleeding risks during treatment. Hypofibrinogenemia is common during therapy and should be handled cautiously with the thrombosis concerns. Current data are lacking as to whether or not fibrinogen levels should be monitored and cryoprecipitate given when low. The risk of thrombosis should be considered before administration of any blood products that may further increase this risk.

Future management/prevention strategies incorporating evidence-based risk stratification may help identify groups at high risk for thromboembolisms or bleeding who may be candidates for intensified therapy, and low-risk groups that may benefit from treatment reduction.

Pancreatitis

Pancreatitis associated with asparaginase therapy is usually not life-threatening and shows a favorable response to nasogastric decompression and IV hyperalimentation.⁵⁶ A recent study suggested that severe L-asparaginase-associated pancreatitis may be effectively managed through continuous regional arterial infusion of a protease inhibitor with concomitant antibiotic administration.⁵⁷ Octreotide, a synthetic somatostatin analog with a prolonged half-life, has been demonstrated as safe and effective for use in the management of pancreatitis in both adults and children.^{34,35,58,59} It has no effect on asparaginase metabolism and may be useful for preventing pancreatitis in recovering patients.³⁵ Doses varied from 3.5–7.2 $\mu\text{g}/\text{kg}/\text{day}$ as a continuous infusion and were tapered over a period of 1–2 weeks.^{60,61} In rare instances, asparaginase-induced pancreatitis may be life-threatening, and asparaginase must be terminated. However, since asparaginase therapy remains a key component of effective ALL treatment, rechallenge with asparaginase may be considered after recovery from acute pancreatitis.³⁵

Although asparaginase-associated pancreatitis has been reported for more than 30 years, the mechanism of this toxicity remains unclear.⁶² Knowledge of potential predisposing factors would enable the effective modification of currently available treatment and management regimens.

Hyperglycemia

Improving glycemic control through diet and exercise, monitoring urine glucose, and controlling blood glucose with insulin therapy in severe cases have been suggested to improve the outcomes of hyperglycemia in patients with ALL treated with asparaginase.³⁷

Hepatotoxicity

All patients receiving chemotherapy require careful assessment of liver function before treatment to determine which drugs may not be appropriate and which drug doses should be modified. It is important to distinguish between liver abnormalities resulting from malignancy and those that are treatment-emergent. Additionally, other comorbid conditions, such as hepatitis, should be taken into consideration.²² In patients treated with asparaginase, liver-related blood tests should be routinely assessed before and during the course of therapy, as other drugs (vincristine, anthracyclines) used concomitantly in the treatment of ALL may need to be adjusted to avert/reduce toxicity.

Conclusions and Future Directions

Asparaginase therapy remains a cornerstone of ALL treatment. Although asparaginase-associated adverse events are an important consideration, severe adverse events rarely occur. Further, the toxicity profile is generally comparable among commercially available preparations, with hypersensitivity reactions being the most commonly reported side effect. The effective management of asparaginase-associated toxicities is crucial, as adverse events can lead to a reduction of the dose or the discontinuation of treatment, increasing the risk of a poor outcome. For example, in adults the historical association between asparaginase treatment and severe toxicities has led to the exclusion of asparaginase from the treatment regimen or the use of lower doses of the enzyme. However, in recent clinical trials, asparaginase was well tolerated and toxicities were easily managed in adults with ALL. These data underscore the importance of addressing the management of asparaginase-associated adverse events, thereby helping patients and their healthcare team effectively manage the anticipated side effects of chemotherapy. Regular assessment and the early reporting of symptoms may avoid potentially serious consequences. A proactive, integrative

approach involving both the healthcare team and the patient may help alleviate patient anxiety and assist in the selection of appropriate interventions.

Therefore, a greater awareness of the range and severity of asparaginase-associated adverse events, and how they differ among available formulations, can aid the early detection and monitoring of treatment-related side effects and facilitate the development of more effective, standardized management strategies. Recognizing adverse events through consistent patient and caregiver communication may improve the management of adverse events and allow most patients to continue their asparaginase treatment.

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References

- Asselin BL, Ryan D, Frantz CN, et al. In vitro and in vivo killing of acute lymphoblastic leukemia cells by L-asparaginase. *Cancer Res.* 1989;49:4363-4368.
- Asselin BL, Lorenson MY, Whittin JC, et al. Measurement of serum L-asparaginase in the presence of L-asparaginase requires the presence of an L-asparaginase inhibitor. *Cancer Res.* 1991;51:6568-6573.
- Capizzi RL, Bertino JR, Handschumacher RE. L-asparaginase. *Annu Rev Med.* 1970;21:433-444.
- Kafkewitz D, Bendich A. Enzyme-induced asparagine and glutamine depletion and immune system function. *Am J Clin Nutr.* 1983;37:1025-1030.
- Tallal L, Tan C, Oetting H, et al. *E. coli* L-asparaginase in the treatment of leukemia and solid tumors in 131 children. *Cancer.* 1970;25:306-320.
- Jones B, Holland JF, Glidewell O, et al. Optimal use of L-asparaginase (NSC-109229) in acute lymphocytic leukemia. *Med Pediatr Oncol.* 1977;3:387-400.
- Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med.* 2006;354:166-178.
- Zakarija A, Kwaan HC. Adverse effects on hemostatic function of drugs used in hematologic malignancies. *Semin Thromb Hemost.* 2007;33:355-364.
- Cairo MS. Adverse reactions of L-asparaginase. *Am J Pediatr Hematol Oncol.* 1982;4:335-339.
- Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0. National Cancer Institute. March 31, 2003 (<http://ctep.cancer.gov>). August 9, 2006. Accessed February 20, 2009.
- Mitchell LG, Halton JM, Vegh PA, et al. Effect of disease and chemotherapy on hemostasis in children with acute lymphoid leukemia. *Am J Pediatr Hematol Oncol.* 1994;16:120-126.
- Miniero R, Pastore G, Saracco P, et al. Hemostatic changes in children with acute lymphoblastic leukemia treated according to two different L-asparaginase schedules. *Am J Pediatr Hematol Oncol.* 1986;8:116-120.
- Athale UH, Chan AKC. Thrombosis in children with acute lymphoblastic leukemia: part II. Pathogenesis of thrombosis in children with acute lymphoblastic leukemia: effects of the disease and therapy. *Thromb Res.* 2003;111:199-212.
- Athale UH, Chan AKC. Thrombosis in children with acute lymphoblastic leukemia: part III. Pathogenesis of thrombosis in children with acute lymphoblastic leukemia: effects of host environment. *Thromb Res.* 2003;111:321-327.
- Nowak-Gottl U, Heinecke A, von Kries R, Nurnberger W, Munchow N, Junker R. Thrombotic events revisited in children with acute lymphoblastic leukemia: impact of concomitant *Escherichia coli*/prednisone administration. *Thromb Res.* 2001;103:165-172.
- Payne JH, Vora AJ. Thrombosis and acute lymphoblastic leukaemia. *Br J Haematol.* 2007;138:430-435.
- Mitchell LG, Sutor AN, Andrew M. Hemostasis in childhood acute lymphoblastic leukemia: coagulopathy induced by disease and treatment. *Semin Thromb Hemost.* 1995;21:390-401.
- Revel-Vilk S. Central venous line-related thrombosis in children. *Acta Haematol.* 2006;115:201-206.
- Bodmer M, Sulz M, Stadlmann S, Droll A, Terracciano L, Krahenbuhl S. Fatal liver failure in an adult patient with acute lymphoblastic leukemia following treatment with L-asparaginase. *Digestion.* 2006;74:28-32.
- Fromenty B, Pessayre D. Inhibition of mitochondrial beta-oxidation as a mechanism of hepatotoxicity. *Pharmacol Ther.* 1995;67:101-154.
- Fromenty B, Pessayre D. Impaired mitochondrial function in microvesicular steatosis. Effects of drugs, ethanol, hormones and cytokines. *J Hepatol.* 1997;26(suppl 2):43-53.
- Sahoo S, Hart J. Histopathological features of L-asparaginase-induced liver disease. *Semin Liver Dis.* 2003;23:295-299.
- Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native *Escherichia coli* asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. *Blood.* 2002;99:1986-1994.
- Killander D, Dohlwitz A, Engstedt L, et al. Hypersensitive reactions and antibody formation during L-asparaginase treatment of children and adults with acute leukemia. *Cancer.* 1976;37:220-228.
- Oetting HF, Stephenson PA, Schwartz MK, et al. Toxicity of *E. coli* asparaginase in man. *Cancer.* 1970;25:253-278.
- Douer D, Yampolsky H, Cohen LJ, et al. Pharmacodynamics and safety of intravenous pegaspargase during remission induction in adults aged 55 years or younger with newly diagnosed acute lymphoblastic leukemia. *Blood.* 2007;109:2744-2750.
- Schorin MA, Blattner S, Gelber RD, et al. Treatment of childhood acute lymphoblastic leukemia: results of Dana-Farber Cancer Institute/Children's Hospital Acute Lymphoblastic Leukemia Consortium Protocol 85-01. *J Clin Oncol.* 1994;12:740-747.
- Moghribi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. *Blood.* 2007;109:896-904.
- Priest JR, Ramsay NK, Steinherz PG, et al. A syndrome of thrombosis and hemorrhage complicating L-asparaginase therapy for childhood acute lymphoblastic leukemia. *J Pediatr.* 1982;100:984-89.
- Athale UH, Chan AKC. Thrombosis in children with acute lymphoblastic leukemia: part I. Epidemiology of thrombosis in children with acute lymphoblastic leukemia. *Thromb Res.* 2003;111:125-131.
- Beinart G, Damon L. Thrombosis associated with L-asparaginase therapy and low fibrinogen levels in adult acute lymphoblastic leukemia. *Am J Hematol.* 2004;77:331-335.
- Caruso V, Iacoviello L, Di Castelnuovo A, et al. Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients. *Blood.* 2006;108:2216-2222.
- Mitchell LG, Andrew M, Hanna K, Abshire T, Anderson R, Cherrick I. A prospective cohort study determining the prevalence of thrombotic events in children with acute lymphoblastic leukemia and a central venous line who are treated with L-asparaginase. Results of the prophylactic antithrombin replacement in kids with acute lymphoblastic leukemia treated with asparaginase (PARKAA) study. *Cancer.* 2003;97:508-516.
- Garrington T, Bensard D, Ingram JD, Silliman CC. Successful management with octreotide of a child with L-asparaginase induced hemorrhagic pancreatitis. *Med Pediatr Oncol.* 1998;30:106-109.
- Suzuki M, Takata O, Sakaguchi S, Fujimura J, Saito M, Shimizu T. Rethrapy using L-asparaginase with octreotide in a patient recovering from L-asparaginase-induced pancreatitis. *Exp Hematol.* 2008;36:253-254.
- Cetin M, Yetgin S, Kara A, et al. Hyperglycemia, ketoacidosis and other complications of L-asparaginase in children with acute lymphoblastic leukemia. *J Med.* 1994;25:219-229.
- Howard SC, Pui CH. Endocrine complications in pediatric patients with acute lymphoblastic leukemia. *Blood Rev.* 2002;16:225-243.
- Advani A, Earl M, Douer D, Rytting M, Bleyer A. Toxicities of intravenous (IV) pegaspargase (ONCASPAR) in adults with acute lymphoblastic leukemia (ALL). *Blood (ASH Annual Meeting Abstracts).* 2007; Abstract 2811.
- Rytting M, Earl M, Douer D, Muriera B, Advani A, Bleyer A. MD5 toxicities in adults with acute lymphoblastic leukemia (ALL) treated with regimens using pegaspargase. *Blood (ASH Annual Meeting Abstracts).* 2008;112:1924.
- Gugliotta L, Massuccconi MG, Leone G, et al. Incidence of thrombotic complications in adult patients with lymphoblastic leukemia receiving L-asparaginase during induction therapy: a retrospective study. The GIMEMA Group. *Eur J Haematol.* 1992;49:63-66.

41. Melillo L, Grandone E, Colazzo D, Cappucci F, Valvano MR, Cascavilla N. Symptomatic venous thromboembolism and thrombophilic status in adult acute leukemia: a single-center experience of 114 patients at diagnosis. *Acta Haematol.* 2007;117:215-220.
42. Hunault-Berger M, Chevallier P, Delain M, et al. Changes in antithrombin and fibrinogen levels during induction chemotherapy with L-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Use of supportive coagulation therapy and clinical outcome: the CAPELAL study. *Haematologica.* 2008;93:1488-1494.
43. Sutor AH, Mall V, Thomas KB. Bleeding and thrombosis in children with acute lymphoblastic leukaemia, treated according to the ALL-BFM-90 protocol. *Klin Padiatr.* 1999;211:201-204.
44. Abuchowski A, Kazo GM, Verhoest CR Jr, et al. Cancer therapy with chemically modified enzymes. I. Antitumor properties of polyethylene glycol-asparaginase conjugates. *Cancer Biochem Biophys.* 1984;7:175-186. Wiernikowski JT, Athale UH. Thromboembolic complications in children with cancer. *Thromb Res.* 2006;118:137-152.
45. Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana Farber Consortium Protocol 91-01. *Blood.* 2001;97:1211-1218.
46. Seibel NL, Steinherz PG, Sather HN, et al. Early postinduction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood.* 2008;111:2548-2555.
47. Dinndorf PA, Gootenberg J, Cohen MH, Keegan P, Pazdur R. FDA drug approval summary: pegaspargase (Oncaspar) for the first-line treatment of children with acute lymphoblastic leukemia (ALL). *Oncologist.* 2007;12:991-998.
48. Dhall G, Robison NJ, Rubin JJ, et al. Incidence of adverse reactions to post-induction asparaginase (ASP) therapy in children and adolescents with high-risk acute lymphoblastic leukemia (ALL): a report from the Children's Oncology Group Study CCG-1961. *J Clin Oncol (ASCO Annual Meeting Abstracts).* 2008;26:110021.
49. Duval M, Suci S, Ferster A, et al. Comparison of *Escherichia coli*-asparaginase with *Erwinia*-asparaginase in the treatment of childhood lymphoid malignancies: results of a randomized European Organization for Research and Treatment of Cancer-Children's Leukemia Group phase 3 trial. *Blood.* 2002;99:2734-2739.
50. Narta UK, Kanwar SS, Azmi W. Pharmacological and clinical evaluation of L-asparaginase in the treatment of leukemia. *Crit Rev Oncol Hematol.* 2007;61:208-221.
51. Evans WE, Tsiatis A, Rivera G, et al. Anaphylactoid reactions to *Escherichia coli* and *Erwinia* ASNase in children with leukemia and lymphoma. *Cancer.* 1982;49:1378-1383.
52. Wiernikowski JT, Athale UH. Thromboembolic complications in children with cancer. *Thromb Res.* 2006;118:137-152.
53. Monagle P, Chan A, Massicotte P, Chalmers E, Michelson AD. Antithrombotic therapy in children. *Chest.* 2004;126:645S-687S.
54. Payne JH, Vora AJ. Thrombosis and acute lymphoblastic leukaemia. *Br J Haematol.* 2007;138:430-435.
55. Banks PA, Freeman ML, and the Practice Parameters Committee of the American College of Gastroenterology. Practice Guidelines in Acute Pancreatitis. *Am J Gastroenterol.* 2006;101:2379-2400.
56. Top PC, Tissing WJ, Kuiper JW, Pieters R, van Eijck CH. L-asparaginase-induced severe necrotizing pancreatitis successfully treated with percutaneous drainage. *Pediatr Blood Cancer.* 2005;44:95-97.
57. Morimoto A, Imamura T, Ishii R, et al. Successful management of severe L-asparaginase-associated pancreatitis by continuous regional arterial infusion of protease inhibitor and antibiotic. *Cancer.* 2008;113:1362-1369.
58. Paran H, Neufeld D, Mayo A, et al. Preliminary report of a prospective randomized study of octreotide in the treatment of severe acute pancreatitis. *J Am Coll Surg.* 1995;181:121-124.
59. Tauber MT, Harris AG, Rochiccioli P. Clinical use of the long acting somatostatin analogue octreotide in pediatrics. *Eur J Pediatr.* 1994;153:304-310.
60. Wu S, Chen A, Peng C, et al. Octreotide therapy in asparaginase-associated pancreatitis in childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2008;51:824-825.
61. Suzuki M. Retherapy using L-asparaginase with octreotide in a patient recovering from L-asparaginase-induced pancreatitis. *Exper Hematol.* 2008;36:253-254.
62. Knoderer HM, Robarge J, Flockhart DA. Predicting asparaginase-associated pancreatitis. *Pediatr Blood Cancer.* 2007;49:634-639.