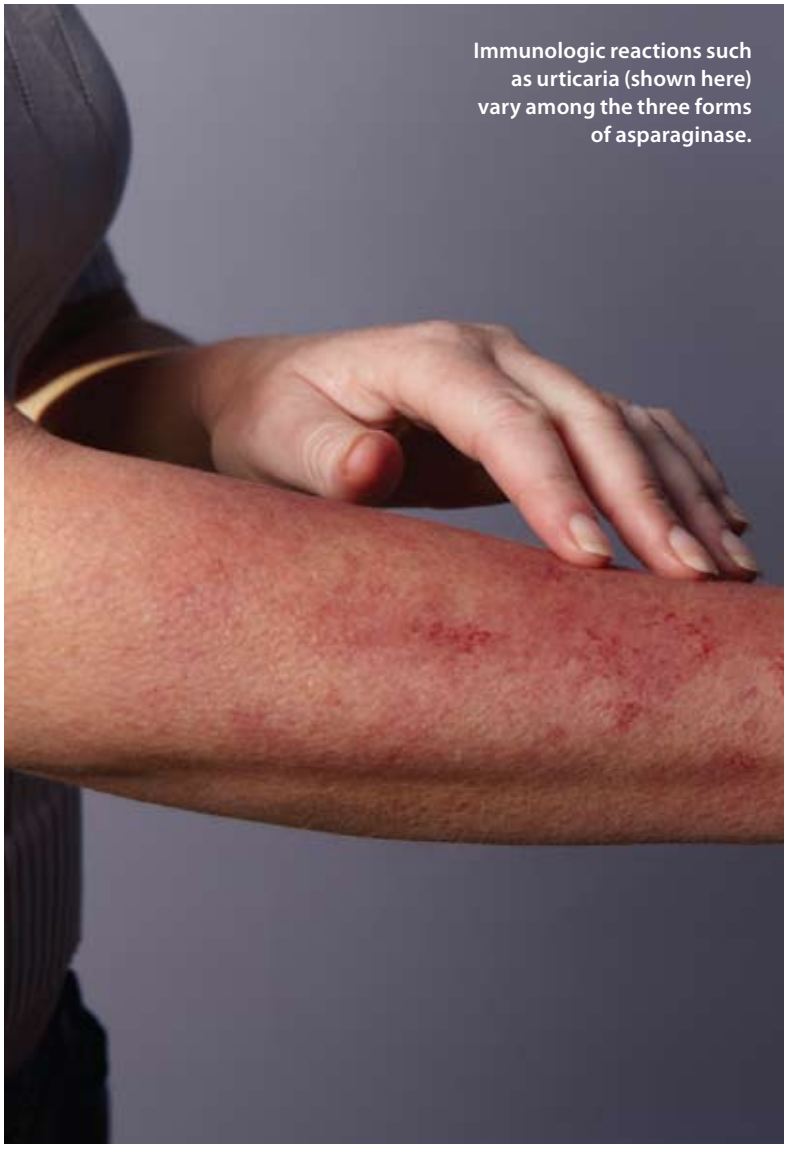
Managing asparaginase-related toxicity in adult patients

Recognition and prompt management of symptoms is key to minimizing risk to the patient and maximizing tolerance of this antineoplastic agent.



Immunologic reactions such as urticaria (shown here) vary among the three forms of asparaginase.

BARBARA TRIPP, MSN, CNS, AOCN

An increasing number of antineoplastic agents and complex treatment regimens challenge oncology nurses to stay well-versed on the specifics of drug administration and patient care management issues. One such agent is asparaginase (Elspar), which has the potential for life-threatening infusion-related reactions. In addition, serious adverse reactions can occur days to weeks after administration. However, asparaginase is an important component of many multidrug regimens used to treat acute lymphoblastic leukemia (ALL). This article focuses on what the oncology nurse needs to know to safely administer asparaginase in the adult oncology patient.

Asparaginase is an enzyme isolated from a number of natural sources. Two sources used in clinical practice are *Escherichia coli* (also called *native asparaginase*) and *Erwinia carotovora* (currently available in the United States through the National Cancer Institute [NCI] for compassionate use only). Asparaginase hydrolyzes the amino acid L-asparagine to aspartic acid and ammonia, eliminating the exogenous availability of asparagine needed for DNA and RNA synthesis during the G1 phase of cell division.[1] This unique mechanism of action capitalizes on the defect in leukemia cells, which lack the ability to synthesize asparagine. Thus, asparagine becomes an essential amino acid for the leukemic cell, and depleting its exogenous availability results in cell death.[2]

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A version with a molecular modification created with monomethoxypolyethylene glycol (mPEG) was developed because the immune system recognizes the foreign proteins *E coli* and *E carotovora*. Furthermore, the *E coli* and *E carotovora* preparations have a short half-life and require frequent dosing (**Table 1**). The pegylated version (pegaspargase [Oncaspar, PEG-l-asparaginase]) reduces hypersensitivity and prolongs interval dosing yet preserves clinical efficacy. One dose of pegaspargase can replace six to nine doses of native asparaginase. **Table 2** lists frequently used dosages of the three asparaginase preparations.

Side effects associated with asparaginase are divided into two categories: hypersensitivity or immunologic reactions to *E coli* or *E carotovora* and protein synthesis inhibition resulting from asparagine depletion (**Table 3**). Asparaginase has little to no effect on bone marrow and is not cytotoxic to oral or intestinal mucosa, allowing for its use in combination therapy regimens. It also does not cause hair loss.

HYPERSENSITIVITY/IMMUNOLOGIC REACTIONS

Immune reactions vary from mild erythema at the injection site to generalized urticaria, bronchospasm, laryngeal edema, hypotension, hypoxia, and full-blown anaphylaxis (rare). Acute lymphoblastic leukemia is uncommon in adults; therefore, the adult oncology nurse may be unfamiliar with administering asparaginase. Information on asparaginase hypersensitivity in this patient population is limited. For example, some reviews of management and preparedness for infusion and hypersensitivity reactions do not include asparaginase.[3] In addition, the resources of a protocol and research staff usually are available only in clinical trials. Thus, even the most experienced oncology nurse may be uncomfortable administering asparaginase. An unfamiliarity of the risks of infusion-related reactions, including life-threatening anaphylaxis, is intimidating.

TABLE 1. Half-life of asparaginase preparations[2]

Asparaginase preparation	Elimination half-life
Escherichia coli	26-30 h
Erwinia carotovora	16 h
Pegylated	5.5-7 d

TABLE 2. Frequently administered dosages of asparaginase[2]

Asparaginase preparation	Dosage
Escherichia coli	6,000 IU/m^2 three times per wk
Erwinia carotovora	6,000 IU/m^2 daily for 10 d, then three doses per wk
Pegylated	2,000-2,500 IU/m^2 every 2-4 wk

Hypersensitivity rates vary among the three forms of asparaginase. Severe (grade 3 or 4) acute allergic reactions were seen in an average of 24% and 29% of pediatric and adult patients, respectively, treated with native asparaginase,[4] but in 3% to 14% of all patients treated with pegaspargase.[4,5] The potential for a reaction increases with each dose because of the type 1 hypersensitivity mechanism of action of the immune response. Patients should be monitored frequently to ensure prompt recognition of a reaction and instructed to report any change in how they feel during and immediately following administration of the agent.

> Unlike for a hypersensitivity reaction, switching to another asparaginase preparation if protein synthesis inhibition occurs is not beneficial.

Patients should be observed for 1 hour following asparaginase administration in a setting with resuscitation equipment available.[6] When administering intravenously, standing orders to stop the infusion and initiate corticosteroids, antihistamine, epinephrine, oxygen, and IV fluids as symptoms dictate can limit the severity of the reaction. Attempts to predict a significant immunologic reaction via an intradermal test dose are unreliable, producing both false-positive and false-negative results.[7] The efficacy of premedication with a corticosteroid and/or antihistamine has not been studied. However, concomitant administration of high-dose corticosteroids during a treatment cycle has been anecdotally associated with lower rates of hypersensitivity, prompting some clinicians to include premedication when a patient is not taking high-dose corticosteroids.

The route of administration may play a role. Hypersensitivity was lower when native asparaginase was administered intramuscularly (IM) compared with intravenous administration.[7] Increased rates of injection site reaction, notably induration and erythema, are seen when asparaginase is given subcutaneously. However, IV administration of pegaspargase is associated with comparable or lower rates of hypersensitivity compared with IM administration of pegaspargase.[8,9] In cases of grade 3 or 4 hypersensitivity, asparaginase should be discontinued. Native asparaginase may be switched to

pegaspargase. Approximately two-thirds of patients are able to tolerate pegaspargase. If hypersensitivity occurs, *E carotovora* asparaginase may be tolerated if available.

INHIBITION OF PROTEIN SYNTHESIS

Other significant side effects associated with asparaginase are related to the drug's inhibitory effect on protein synthesis. The incidence of this effect is similar among the three types of asparaginase; therefore, unlike for a hypersensitivity reaction, switching to another type of asparaginase preparation if protein synthesis inhibition occurs is not beneficial. Although these effects are normally transient and without clinical significance, symptoms may be severe enough to warrant discontinuation of therapy, and further dosing during future cycles of the current regimen or in the event of relapse is prohibited.

Bleeding and/or thrombosis may occur as a result of a decrease in or imbalance of coagulation factors such as fibrinogen; factors II, VI, VII, and VIII; antithrombin III; and protein-C. Although routine laboratory values such as prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, antithrombin III, and/or protein-C are often monitored, there are no standard or reliable parameters for predicting or preventing complications related to coagulatory alterations. In an effort to address thromboembolic complications, a study was conducted to evaluate the role of fresh frozen plasma.[10] Findings did not support improved plasma levels of coagulation proteins.[10] Treating low fibrinogen levels with cryoprecipitate is controversial. In the absence of bleeding, there is no documented clinical benefit.

Hyperglycemia may be noted following the asparaginase administration due to a decreased serum concentration of insulin. Because concomitant use of high-dose corticosteroids is common, determining the exact etiology of elevated glucose levels may be difficult. Monitoring blood glucose levels along with careful dosing of insulin is necessary to avoid hypoglycemia upon recovery of the synthesis of endogenous insulin.

Hypoalbuminemia, caused by a decrease in albumin production, may result in third spacing of fluid with mild peripheral edema to massive anasarca (in rare instances). Cholesterol-carrying proteins may also be depressed, resulting in hyperlipidemia. This may be evidenced by a milky white substance noted when drawing a blood sample, and the elevated lipids may hinder laboratory evaluation.

Hepatic toxicities usually resolve spontaneously, allowing the patient to continue chemotherapy.[5] Elevated AST, ALT, and bilirubin levels are common during treatment with asparaginase, especially when administered in combination with other antineoplastic agents. Other supportive therapies such as antibiotics also increase the risk of hepatic toxicity. However, severe hepatic dysfunction is rare.

TABLE 3. Indications of asparaginase toxicity

Hypersensitivity/allergic reaction
Erythema/induration at injection site
Urticaria, at injection site or systemic
Dyspnea/bronchospasm/laryngeal edema, including anaphylaxis[a]
Hypotension[a]
Inhibition of protein synthesis
Decreased coagulation factors leading to bleeding and/or thrombosis
Decreased insulin resulting in hyperglycemia
Decreased albumin resulting in edema
Alteration in liver function
Elevated liver enzymes
Hyperbilirubinemia
Fatty liver/hyperlipidemia
Pancreatitis
Neurologic dysfunction
Lethargy/somnolence

[a] Symptoms may be mild to severe.

Acute pancreatitis occurs in 2% to 5% of patients.[11] Symptoms may be mild and noted only as some nausea, anorexia, and/or vomiting. Abdominal pain may be mild to severe. In rare instances, pancreatitis may progress to hemorrhagic pancreatitis and pseudocyst formation. Lipase and amylase levels may not be elevated due to decreased protein synthesis; therefore, routine monitoring of lipase and amylase levels may have little to no benefit. The actual etiology has not been identified. The hemorrhagic component may implicate an association with coagulopathy issues. Any patient who develops symptomatic pancreatitis should not receive further doses of asparaginase. Treatment is the same as pancreatitis from any cause; it is based on the severity of symptoms and consists of bowel rest, IV fluids, nutrition support, and pain management.

Neurologic symptoms such as headache, lethargy, and somnolence were reported in patients receiving asparaginase. These symptoms are more common in adult patients. Although many patients receiving asparaginase may have

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elevated ammonia levels, a correlation between ammonia levels and degree of toxicity has not been made.[11]

CONCLUSION

Asparaginase therapy presents a challenge for the oncology nurse both during and after administration. Comprehensive patient education and astute clinical assessment are imperative when managing treatment of patients with ALL who are receiving complicated and intensive chemotherapy regimens. These components provide the patient with the best opportunity to survive treatment, allow for the possibility of achieving remission, and ultimately, hope for cure. ■

Barbara Tripp works at the Cleveland Clinic, Cleveland, Ohio.

REFERENCES

1. Avramis VI, Panosyan EH. Pharmacokinetic/pharmacodynamic relationships of asparaginase formulations: the past, the present and recommendations for the future. *Clin Pharmacokinet.* 2005;44(4):367-393.
2. Ueno T, Ohtawa K, Mitsui K, et al. Cell cycle arrest and apoptosis of leukemia cells induced by L-asparaginase. *Leukemia.* 1997;11(11):1858-1861.
3. Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist.* 2007;12(5):601-609.
4. 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(6):1986-1994.
5. Rytting M, Earl M, Douer D, et al. Toxicities in adults with acute lymphoblastic leukemia (ALL) treated with regimens using pegasparaginase [poster session]. ASH Annual Meeting Abstracts. *Blood.* 2008;112:1924.
6. Oncaspar [package insert]. Bridgewater, NJ: Enzon Pharmaceuticals Inc; 2006.
7. Capizzi RL, Holcenberg JS. Asparaginase. In: Holland JF, Frei E, Bast RC, Morton DL, eds. *Cancer Medicine.* 3rd ed. Philadelphia, PA: Williams & Wilkins; 1993:796-805.
8. Müller HJ, Löning L, Horn A, et al. Pegylated asparaginase (Oncaspar) in children with ALL: drug monitoring in reinduction according to the ALL/NHL-BFM 95 protocols. *Br J Haematol.* 2000;110(2):379-384.
9. Douer D. L-asparaginase in adult lymphoblastic leukemia. Presented at: Cleveland Clinic Taussig Cancer Center Grand Rounds; April 21, 2005.
10. Halton JM, Mitchell LG, Vegh P, et al. Fresh frozen plasma has no beneficial effect on the hemostatic system in children receiving L-asparaginase. *Am J Hematol.* 1994;47(3):157-161.
11. Graham ML. Pegaspargase: A review of clinical studies. *Adv Drug Deliv Rev.* 2003;55(10):1293-1302.