The Practical Oncologist

Asparaginase hypersensitivity and silent inactivation in pediatric and AYA patients with ALL

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What is basis for asparaginase therapy in pediatric ALL?

The premise of asparaginase therapy is centered around the dependence of cancer cells on L-asparagine (Asn). Asn is an amino acid that is necessary for protein production and cell replication in leukemia cells. Because lymphoblastic leukemia cells cannot manufacture Asn, they are dependent on extracellular Asn for replication; reduced availability of extracellular asparagine ultimately causes leukemia cell death.

Asparaginase is an enzyme that catalyzes the conversion of Asn to aspartic acid and ammonia, thereby depleting the serum Asn that leukemic cells rely on for survival and proliferation. Asparaginase was first identified as an anti-cancer agent in the 1960s, when guinea pig serum was found to have anti-lymphomic effects.[1,2] Advancing research has now established the utility of asparaginase in pediatric regimens. Asparaginase therapy has been shown to significantly increase complete remission (CR), disease-free survival (DFS), and event-free survival (EFS) rates in children and some adults with acute lymphoblastic leukemia (ALL).[3,4]

What are the administration considerations for asparaginase therapy?

Since the 1960s, two bacterial sources of asparaginase have been utilized: *Escherichia coli* and *Erwinia chrysanthemi*. Until December 2012, native *E. coli* asparaginase was used in the United States, at which point it was withdrawn by the manufacturer. Native *E. coli* asparaginase was used in the United States through 2012. Today, available formulations of asparaginase include pegylated *E. coli* asparaginase (pegaspargase), calaspargase-pegol, asparaginase *Erwinia chrysanthemi* (recombinant)-rywn. Pegaspargase is intended for intramuscular (IM) or intravenous (IV) injection no more frequently than every 14 days,[5] while calaspargase should be delivered via IV injection no more frequently than every 21 days. Of note, calaspargase is only approved for pediatric and young adult patients aged 1 month to 21 years.[6]

More recently, asparaginase *Erwinia chrysanthemi* (recombinant)-rywn was approved for adult and pediatric ALL patients age 1 month or older who have developed hypersensitivity to *E. coli*-derived asparaginase.[7] When replacing a long-acting asparaginase product, this drug is intended to be administered via IM injection every 48 hours.

Common toxicities of asparaginase include hypertriglyceridemia, liver toxicity, and infusion-related reactions, while severe toxicities include anaphylaxis, thrombosis or increased bleeding risk, and pancreatitis.[5-7] Depending on the nature and severity of the toxicity, asparaginase therapy may require alteration or discontinuation in some patients.

What are asparaginase hypersensitivity and silent inactivation?

Asparaginase hypersensitivity and silent inactivation affect up to 30% of patients who receive asparaginase therapy.[8] These events result from the development of anti-asparaginase antibodies, which bind to the asparaginase molecule to reduce the activity of the drug. While both hypersensitivity and silent inactivation are antibody-mediated responses, hypersensitivity reactions are accompanied by clinical symptoms that appear during or shortly after asparaginase administration, while silent inactivation is only detectable through assessment of antibody presence and asparaginase activity; in these cases, low asparaginase activity is a key feature.

Silent inactivation can be difficult to identify, and monitoring of asparaginase-treated patients is essential for recognizing this phenomenon. Patients who experience unrecognized silent inactivation are at risk for continued asparaginase therapy with no therapeutic benefit. Risk factors for silent inactivation include 1) pre-medication with steroids, which can reduce the likelihood of observing low-grade reactions, and 2) inconsistent dosing or extended intervals between asparaginase doses.

Alternately, hypersensitivity reactions are associated with characteristic symptoms of allergic reactions, including bronchospasm, urticaria, angioedema, and anaphylaxis. These reactions can be graded according to severity (see **Table**). Medical intervention is indicated at grade 2 for allergic reactions, while all grade 3 or higher reactions require emergent intervention.[9]

Table: Grading Asparaginase Levels

Modified Pegasparaginase Reaction Grading Scale Modified from Common Terminology Criteria for Adverse Events (CTCAE) V5.0 Consider use of below definitions when classifying pegasparaginase infusion reactions	
Grade 1	– Transient flushing or rash during the infusion that resolves without intervention – Fever <38.4°C
Grade 2	– Persistent symptoms that require interruption of infusion – Flushing – Rash with urticaria – Dyspnea – Fever ≥38.5°C
Grade 3	– Persistent symptoms that require discontinuation of infusion – Cough, shortness of breath, bronchospasm, or other significant respiratory symptoms – Edema or angioedema – Hypotension
Grade 4	– Life-threatening reaction necessitating urgent intervention
Grade 5	– Death

It is important to differentiate true allergic reactions from infusion reactions, which are the result of either the infusion itself or from hyperammonemia from asparaginase metabolism. Symptoms of hyperammonemia could include anxiety/confusion, malaise, weakness, nausea, vomiting, dyspnea, hypertension, and abdominal cramping.[10] These symptoms may be mistaken for asparaginase hypersensitivity. Clinicians should note that allergic manifestations could occur within a few minutes of IV infusion and can include urticarial rashes, flushing, nausea and vomiting, bronchospasm, hypotension, and respiratory distress syndrome.[10]

How can asparaginase hypersensitivity and silent inactivation be prevented and managed?

Use of pre-medication can reduce the risk of mild allergic reactions.[8,11] Pre-medications are administered to minimize the risk for non-inactivating reactions to asparaginase, as this approach does not appear to affect asparaginase activity. In the past, pre-medications were avoided over the concern that they would mask potential allergies. With the advent of activity monitoring, pre-medication is becoming more common in practice, as laboratory analysis can provide an accurate picture of true allergic reactions regardless of the presence (or absence) of symptoms. Today, commonly used pre-medications include diphenhydramine, acetaminophen, steroids, and famotidine.[8]

Protocols have been developed for the management of reactions to asparaginase.[12] For severe allergic reactions, pegylated asparaginase formulations should be discontinued and substituted with an asparaginase *Erwinia*-based formulation, ideally within 72 hours of the reaction. Mild-to-moderate reversible reactions should be managed based on infusion completion versus discontinuation. In patients in whom the infusion was completed, consider ordering a laboratory asparaginase activity level and switch to *Erwinia*-based formulations if activity levels are not within goal range. Of note, an asparaginase activity level of at least 0.1 IU/mL or greater at 14 days after administration is generally considered to represent therapeutic activity for patients receiving pegaspargase, although different thresholds have been proposed for switching to *Erwinia*-based formulations. If the infusion was discontinued prematurely, but symptoms were not severe or didn't include angioedema, consider re-challenging with pegaspargase after premedication and order asparaginase activity level testing to determine therapeutic efficacy post-infusion.[11]

The ability of pediatric ALL patients to continue asparaginase therapy is essential for achieving treatment success. Unfortunately, asparaginase hypersensitivity/silent inactivation represents a direct threat to effective and durable asparaginase treatment. Fortunately, healthcare providers can take steps to prevent and manage these events, thereby setting patients up for therapeutic success and, ultimately, improved ALL outcomes.

For more information on acute lymphoblastic leukemia, **click here**.

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