The Practical Oncologist

The Nurses' Role in Differentiating and Treating Infusion and Hypersensitivity Reactions

Sharon Bergeron, RN, BSN, CPON
Pediatric Hematology/Oncology Nurse Specialist
Research Nurse Educator
Hyundai Cancer Institute
Children's Hospital of Orange County
Orange, California

The Practical Oncologist continues our interview with Sharon Bergeron, RN, BSN, CPON a certified pediatric hematology/oncology nurse specialist caring for pediatric, adolescent and young adult patients living with acute lymphocytic leukemia (ALL) and lymphoblastic lymphoma (LBL). Additionally, Sharon is a research nurse educator for the Hyundai Cancer Institute, Children's Hospital of Orange County (CHOC).

Mary McGorray, MD, talked with Sharon about her experience treating patients with asparaginase in multi-agent chemotherapeutic regimens for patients living with ALL and LBL. This interview will be in three parts: Part I describes the role and utility of asparaginase in treating ALL and LBL. Part II reviews how hematology/oncology nurses are key in observing, identifying, and negotiating hypersensitivity reactions from infusion reactions. Finally, Part III will assist nurses in recognizing silent inactivation and how, through astute nursing observation and collaboration with healthcare providers, nurses can facilitate appropriate therapy choices and enhance clinical outcomes for people living with ALL and LBL.

Mary: ***Sharon, in our last interview, you explained how asparaginase can be used in multi-agent chemotherapeutic regimens to treat ALL and LBL. Now, I'd like to discuss some of the major adverse events (AEs) that can occur with asparaginase therapy and how nurses can prevent and mitigate these AEs to facilitate better clinical outcomes for their patients. Let's start with hypersensitivity reaction. What is hypersensitivity reaction and how does this AE interfere with therapy?***

Sharon Bergeron, RN, BSN, CPON: Asparaginase is a protein of bacterial origin; specifically, Escherichia coli or Erwinia chrysanthemi. Because this treatment involves enzymes that are foreign to humans, it confers the potential to induce an immune response. When asparaginase is administered, exposure to these large, foreign, protein-based bodies induces a primary immune response and development of low-affinity anti-asparaginase immunoglobulin M (IgM) antibodies. Re-exposure to

asparaginase activates memory B cells and plasma cells to secrete anti-drug antibodies more rapidly than during the primary immune response.

So, these antibodies bind to the asparaginase molecule, reducing the activity of the drug. In addition, antibody inactivation of asparaginase can occur in the absence of clinical manifestations of hypersensitivity reaction; an event termed 'silent inactivation.'

In all, about 40% of asparaginase-treated individuals will develop hypersensitivity reactions, and between 8% and 44% will have silent inactivation.1,2 These reactions can happen at any time when a patient is re-exposed to asparaginase therapy, so healthcare professionals must always be on the look-out for signs of an immune response in their asparaginase-treated patients.

Mary: ***These reactions sound very similar to infusion reactions. What is the difference between hypersensitivity reactions and infusion reactions?***

Sharon: The very short answer is that a hypersensitivity reaction is antibody-mediated, whereas an infusion reaction is not. So, for a reaction to be a hypersensitivity reaction, the patient must have been exposed to the drug first. Unlike an infusion reaction, which will happen fairly soon after first treatment initiation, a hypersensitivity reaction is unlikely to occur the first time you give the drug; instead, it typically occurs during the second or subsequent treatments.

The clinical manifestations of hypersensitivity reactions and infusion reactions can overlap considerably, but the timing of the events can help to distinguish between these two AEs. Hypersensitivity reactions tend to occur rapidly, often in the first few minutes of the infusion. These reactions tend to be dramatic, for lack of a better word. They can present with urticaria, hypotension, dizziness, shortness of breath, wheezing, or lip swelling. Alternately, infusion reactions have a slower rate of onset – as much as an hour or so after the infusion starts. The infusion reaction is likely a result of the asparaginase breaking down asparagine into aspartic acid and ammonia and a rapid increase in ammonia, which can cause nausea, vomiting, headache, flushing, rash, and anxiety. These symptoms are usually short-lived.

Distinguishing between hypersensitivity reactions and infusion reactions is important, because in the past, we used to classify hypersensitivity reactions as a type of infusion reaction and respond by switching to an alternative asparaginase product. However, when we started having drug shortages, that limited the availability of alternative forms of asparaginase to be utilized for our patients experiencing a hypersensitivity reaction to the front-line asparaginase product. Now, we know that these different AEs require separate techniques for prevention and management.

Mary: Sharon, as an expert in chemotherapy infusion, what are the different management strategies for a hypersensitivity reaction versus an infusion reaction?

Sharon: Infusion reactions are typically managed by slowing the rate of infusion or discontinuing if necessary. At my institution, the Children's Hospital of Orange County (CHOC), we provide asparaginase infusion over a two-hour period, which helps to curtail the infusion-like symptoms. Patients can also be supported with saline, which seems to be helpful in optimizing health during the infusion period. But

infusion reactions can often be managed without discontinuation. Importantly, patients who experience an infusion reaction can usually be rechallenged with the same asparaginase therapy and are often able to successfully complete further treatment. We give pre-medications and utilize therapeutic drug monitoring for the second and subsequent doses of asparaginase.

Hypersensitivity reactions are a bit of a different story. There are a number of potential consequences of hypersensitivity reactions, including loss of asparaginase activity, decreased asparaginase half-life, and poorer outcomes including shorter disease-free survival and overall survival.3-5 Prevention and appropriate management of hypersensitivity reactions are therefore an essential aspect of asparaginase administration.

Pre-medication with either antihistamines and/or corticosteroids can stabilize mast cells and prevent the release of some pro-inflammatory mediators. This pre-medication often includes an 'H1' (Histamine-1 receptor) blocker like diphenhydramine, and an 'H2' (Histamine-2 receptor) blocker such as famotidine. At CHOC, we provide these medications about 30 to 60 minutes prior to the asparaginase infusion. We then put patients in a room that has oxygen available and monitor them by pulse oximeter.

Our nurses and pharmacists have also developed an anaphylaxis treatment box—we call it the 'Red Box'—that is individualized to each patient and kept at the bedside. If a hypersensitivity reaction is identified, the box contains everything we need to treat this AE. The medications we have on hand include intramuscular (IM) epinephrine, which is our first-line therapy when encountering a severe reaction. We may then go on to use diphenhydramine, hydrocortisone, and normal saline, as needed, which can help manage hypotension.

We also developed a critical care sheet that includes the patient's weight for easier and faster administration of medications that are dosed based on weight. Additionally, we schedule the patient earlier in the day and ensure that there are healthcare providers on stand-by in case of emergencies.

It's also important to remember that, at certain institutions, including my own, children may be getting their asparaginase on the same day in which they get a lumbar puncture (LP) with concomitant administration of methotrexate. In this case, the child may have been sedated and may have not had food or water prior to the LP, so dehydration is a potential contributor to asparaginase-related problems. At CHOC, we often reduce the dosage of asparagine if this is the case to mitigate the increased risk for hypersensitivity reactions post-LP.

Mary: Once the hypersensitivity reaction is treated, what are the next steps? How can healthcare providers prevent hypersensitivity reactions from occurring again?

Sharon: In the setting of a true antibody-mediated hypersensitivity reaction, switching to an alternative asparaginase formulation derived from a different bacterial protein is recommended, particularly for reactions that are grade 2 or greater according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading system.6 For example, if the patient is taking an E. coli-based asparaginase, they should be switched to a non-E. coli¬-derived product. This recommendation is based on evidence showing that switching to an alternate formulation does not impact treatment

success. That's why it is so important that we have the two forms of asparaginase at our disposal, although cross-reactivity can and does occur in some patients. Asparaginase has significantly improved outcomes in ALL and LBL, and we don't want to be forced to discontinue therapy early due to lack of an alternative product.

Mary: ***Thank you, Sharon*** ***for your input on identifying hypersensitivity reactions in asparaginase-treated patients, as well as sharing CHOC's excellent protocol for the preparation and treatment of AEs that can occur when administering asparaginase therapy as part of a multi-agent chemotherapeutic regimen.***

In Part III, ***The Practical Oncologist*** **will review with Sharon Bergeron, RN, BSN, CPON, the concept of silent inactivation in asparaginase therapy, and how nursing intervention can uncover this phenomenon and positively influence clinical outcomes for patients living with ALL and LBL. Many thanks to Sharon Bergeron for her generosity and expertise.**

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