How Nursing Intervention Can Facilitate Clinical Outcomes

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In Part 3 of our newsletter series on asparaginase therapy, ***The Practical Oncologist*** interviewed Sharon Bergeron, RN, BSN, CPON, about how nurses can identify silent inactivation of asparaginase therapy, as well as other adverse events (AEs) such as hyperammonemia, pancreatitis, thrombosis/hemorrhage, and hepatotoxicity. Finally, she touches on the role of the hematology/oncology nurse in facilitating optimal asparaginase treatment.

Mary: *Sharon, what is silent inactivation and how does it differ from an acute hypersensitivity reaction?*

Sharon Bergeron, RN, BSN, CPON: In part 2 of this series, we discussed how asparaginase therapy can cause the production of anti-drug antibodies that limit the clinical efficacy of asparaginase as part of a hypersensitivity reaction. Silent inactivation describes a scenario where anti-asparaginase antibodies are released without clinical manifestations of hypersensitivity reaction. Silent inactivation is recognized only by measuring trough serum asparaginase activity (SAA); it is defined by SAA <0.1 IU/mL across two independent samples in the absence of clinical symptoms of hypersensitivity reaction.[1]

We don't fully know the rates of silent inactivation in patients receiving asparaginase, but reports suggest that between 8% and 44% of patients receiving *E. coli*-derived asparaginase will experience this adverse event (AE).[2] Because silent inactivation is not accompanied by clinical symptoms, it can be difficult to identify. Therefore, guidelines recommend that all patients receiving asparaginase treatment undergo therapeutic drug monitoring (TDM) for silent inactivation, especially when first starting treatment.[1] TDM has been a real 'game-changer,' allowing us to mitigate AEs with premedication while still ensuring adequate drug activity such that asparaginase confers a therapeutic benefit.

Mary: *Sharon, can you clarify why premedication might have been avoided in patients being treated with asparaginase? Isn't premedication supposed to be beneficial in these individuals?*

Sharon: Premedication is indeed beneficial in increasing the tolerability of asparaginase therapy. However, concerns were raised that premedication might mask a hypersensitivity reaction in some

people. If this were the case, then we would have no way of knowing that the efficacy of the asparaginase therapy was being diminished.

This is why TDM has been so pivotal to asparaginase administration. This approach allows us to maximize the tolerability of asparaginase therapy all the while being able to determine if anti-asparaginase antibodies are interfering with treatment. The effectiveness of premedication combined with SAA testing was presented in a published paper by Dr. Brown and his colleagues at Johns Hopkins, who confirmed that this approach reduced asparaginase substitutions and acute AEs, while simultaneously signaling instances of silent inactivation.[3]

In short, TDM allows us to premedicate patients and achieve uninterrupted asparaginase treatment. In the event that a patient develops a hypersensitivity reaction or a silent inactivation, we can quickly pivot to an alternative therapy without significant treatment interruption, which has been established as a cornerstone of effective asparaginase therapy.

Mary: ***Let's move on to another common AE of asparaginase therapy: hyperammonemia. How is this condition recognized and managed in your institution?***

Sharon: One of the challenges of asparaginase therapy is that all forms of asparaginase catabolize asparagine to aspartic acid and ammonia. Additionally, intrinsic glutaminase activity converts glutamine to glutamate and ammonia. Both of these effects can cause hyperammonemia. In early studies of asparaginase therapy, ammonia levels have been as high as 700 umol/L in some patients.[4] Symptoms of hyperammonemia, which include nausea, vomiting, dizziness, and lethargy, can be hard to distinguish from other AEs. Alternately, some patients remain asymptomatic despite hyperammonemia. There are a lot of unanswered questions regarding this side effect. We don't currently understand why some patients develop symptomatic hyperammonemia and some do not. Moreover, the severity of symptoms do not always correlate with ammonia levels, which further complicates therapy.

There are several methods available to manage severe hyperammonemia. Sodium benzoate can modify glycine to produce hippurate, which is excreted through the urine; sodium benzoate can be administered orally or intravenously. Phenylbutyrate, which is converted to phenylacetate in the liver, combines with glutamine to form phenylacetylglutamine, which is also excreted through the urine. Lactulose limits absorption of ammonia through the gut, while rifaximin (an antibiotic derivative of rifamycin) depresses bacteria growth and subsequent ammonia production in the gut. Other approaches include protein restriction, high dextrose fluids, and dialysis.

Mary: ***What are some other potential AEs of asparaginase therapy that healthcare providers should be monitoring for?***

Sharon: Pancreatitis is an asparaginase toxicity that is associated with an estimated mortality rate of 2% in those receiving asparaginase therapy.[5] Pancreatitis is the result of asparaginase inhibition of protein synthesis and the effects on calcium and adenosine triphosphate (ATP). Pancreatitis can be recognized through clinical symptoms, which include abdominal pain, emesis, nausea, back pain, and fever. It can also be identified through laboratory studies and radiological imaging. Although pancreatitis has

historically been managed with asparaginase discontinuation, the growing importance of asparaginase therapy for treatment outcomes has led to some success in asparaginase rechallenge.

Asparaginase also modifies the proteins involved in the coagulation cascade and fibrinolysis, increasing the risk for thrombosis or hemorrhage. Thrombosis occurs in 2% to 8% of all pediatric ALL patients, most commonly in the extremities but also in the cerebral sinuses.[5] Asparaginase should be withheld in cases of hemorrhage or thrombosis, but can typically be resumed, depending on the severity of the thrombosis or hemorrhage. The exception would be cerebral sinus thrombosis, which increases risk for morbidity and mortality and therefore precludes additional asparaginase therapy.

Finally, we must watch for hepatotoxicity in our asparaginase-treated patients, which can present with either non-cholestatic (elevated transaminases) or cholestatic (elevated bilirubin) abnormalities. Differentiating between asparaginase-associated transaminase elevation and chemotherapy-associated transaminase elevation can be difficult. There are currently no recommendations for modifying asparaginase therapy in response to hepatotoxicity, although prophylactic administration of levocarnitine has been piloted with good results.[6]

Mary: ***Sharon, what would be your key takeaways regarding management of patients receiving asparaginase?***

Sharon: Well, some of the key takeaways, I think for everyone would be:

- Asparaginase has been a core component of a multi-agent treatment regimen for more than 40 years.
- We have learned from clinical trials that maintaining uninterrupted therapy over the course of treatment is essential to therapeutic success of patients with ALL and LBL.
    - Significantly inferior disease-free survival was observed in patients who did not receive all their prescribed asparaginase doses—it is extremely important that patients receive timely dosing throughout their regimen.
- TDM has greatly facilitated asparaginase administration, allowing us to premedicate patients and maintain uninterrupted asparaginase treatment.
- TDM also eliminates the fear of masking silent inactivation reactions with necessary premedication

It's also important to acknowledge the important role that nurses play in recognizing and distinguishing between different potential AEs and adjusting therapy as necessary. We are on the front lines of care for these patients and are highly trained to spot early signs of trouble and react quickly and effectively to arising problems.

Nurses can target education to inform patients/caregivers and manage their expectations about therapy. We can assure them that, while AEs may occur, we are well prepared to recognize and manage these events, and in most cases, patients can continue asparaginase therapy and achieve optimal outcomes.

Mary: ***Sharon, I want to thank you for your expertise. I sense your deep commitment to and love for your patients living with ALL and LBL. Thank you for sharing your vast knowledge about administering asparaginase to patients in multi-agent chemotherapeutic regimens.***

Sharon: Well, thank you, Mary. My profession, including nursing practice and the research that supports it, is dear to my heart. As we gain more knowledge, I hope I can add my perspective and experience to support other hematology/oncology nurses facing the same daily challenges in asparaginase treatment.

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