# Nursing Considerations Regarding the Role of Asparaginase within Multi-Agent Chemotherapeutic Regimens for Pediatric, Adolescent and Young Adult, and Adult Patients Living with ALL and LBL

**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*** welcomes 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).

Today, our contributor, 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:** ***Welcome, Sharon.***

**Sharon Bergeron, RN, BSN, CPON:** Thank you! It's a pleasure to be here and share my expertise. I've been a pediatric hematology-oncology nurse for over 40 years. During this time, I've observed many changes in the drugs available to us to treat acute lymphocytic leukemia (ALL) and lymphoblastic lymphoma (LBL) – all for the good. We know from experience, especially with pediatric and adolescent and young adult (AYA) patients, that one drug isn't going to do it—it takes a multi-agent approach. But asparaginase has really made a difference for patients living with ALL and LBL.

**Mary:** ***Sharon, can you explain how asparaginase helps patients with ALL and LBL?***

**Sharon:** Essentially, asparaginase deprives the leukemia cells of asparagine, a vital amino acid that helps the leukemia cell, as well as normal cells, thrive. It achieves this by converting serum asparagine into aspartic acid and ammonia thereby depriving the leukemia cells of asparagine. This depletion of asparagine leads to leukemia cell apoptosis. Interestingly, leukemia cells are not able to synthesize asparagine on their own, in contrast to normal cells. Thus, when a cellular environment contains low levels of asparagine, the normal healthy cells remain unaffected, but the leukemia cells cannot thrive.

**Mary:** ***Sharon, what was the mortality for ALL in the 1960s, before these multi-agent regimens incorporating asparaginase?***

**Sharon:** Prior to the use of modern therapeutics, survival for ALL was abysmal. In the 1960s, the 5-year survival rate for ALL was less than 10%.[1] Fortunately, development of anti-leukemia and anti-lymphoma therapies – including asparaginase – has dramatically improved outcomes for these individuals. The 5-year survival rate for children and adolescents with ALL increased from 83.7% (between 1990 and 1994) to 90.4% (between 2000 and 2005).[1] Today, survival in pediatric patients has reached 92%.[1,2] Unfortunately, the survival rate for adults remains low, at about 20-40%.[2] However, these rates can vary significantly depending on the presence or absence of prognostic indicators. With our current advanced technology, we can look at certain genetic findings and clinical markers that can be associated with an increased risk of relapse. So, we've been able to think ahead and develop therapy that's even more targeted—with this new information, we are in the process of developing other drugs to help improve overall disease-free survival.

**Mary:** ***Sharon, building on what you just explained, what are the FDA-approved formulations of asparaginase, why are there so many formulations, and for whom are they therapeutic?***

**Sharon:** Well, to answer that correctly, I will give you a little history about the development of asparaginase. The first asparaginase product – L-asparaginase derived from *Escherichia coli* – was approved in 1978. Although this product was highly effective, it was limited by its short half-life, which required frequent intramuscular (IM) doses, as well as a high rate of immunogenicity. In the 1990s, pegylated asparaginase (pegaspargase) was developed with an extended half-life, allowing for a less frequent dosing schedule of every two weeks rather than multiple times per week. The incorporation of the PEG moiety also decreased immunogenicity, although clinical allergic reactions to pegaspargase can still occur. The plasma half-life of asparaginase therapy was further expanded with the approval of calasparagase pegol in 2018.

The continued persistence of allergic reactions to *E. coli*-based asparaginase products prompted the development of an alternative asparaginase therapy. In 2011, an *Erwinia chrysanthemi*-based asparaginase was approved by the FDA. *Erwinia* asparaginase does not share cross-reactivity with the

*Escherichia* enzyme, making it an ideal alternative to traditional asparaginase products in patients with hypersensitivity reactions. Unfortunately, this particular agent was limited by manufacturing delays and drug shortages. This obstacle was addressed in 2021 with the development of a recombinant *Erwinia* L-asparaginase; a bioengineered version manufactured using a *Pseudomonas fluorescens* expression platform for more rapid and consistent manufacturing.

| Drug | Route of administration | Half-life | Indication |
|---|---|---|---|
| *E. coli* Asparaginase (Native) | IM/IV | IM: 34-39 hr<br>IV: 8-30 hr | Indicated as part of multi-agent chemotherapy to treat ALL |
| Pegaspargase | IM/IV | IM: 5.8 days<br>IV: 5.3 days | Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of pediatric and adult patients with 1) first-line ALL or 2) ALL and hypersensitivity to native forms of L-asparaginase |
| Calaspargase pegol | IV | 16.1 days | Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL in pediatric and young adult patients aged 1 month to 21 years |
| *Erwinia* Asparaginase (Native) | IM/IV | IM: 16 hr<br>IV: 7.5 days | Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL who have developed hypersensitivity to E. coli-derived asparaginase |
| *Erwinia* Asparaginase (recombinant) | IM | 18.2 hr | Indicated for the treatment of ALL and LBL in adult and pediatric patients aged 1 month or older who have developed hypersensitivity to E. coli-derived asparaginase |

**Mary:** ***How do you utilize asparaginase products in young adults living with ALL and LBL in your clinic?***

**Sharon:** The efficacy of asparaginase has been well established in pediatric patients. In adults, pediatric or 'pediatric-inspired' regimens involving asparaginase therapy are being increasingly utilized, even in adults in their fifth or sixth decade of life. While the benefits of asparaginase-containing regimens are not as well studied in adults compared with children, available data support the use of asparaginase in this patient population. However, even with asparaginase therapy, overall survival declines with increasing age, from as high as 75% in adolescents and young adults to only 10-20% in those aged 55 years and older.[3]

When I encounter a new patient being treated with asparaginase-containing regimens, the biggest priority is to ensure that the current regimen is not interrupted, as we have data indicating that premature discontinuation leads to inferior disease-free survival.[4]

To prevent potential drug shortages and interruptions in asparaginase therapy, pegasparagase is currently reserved in our clinic for ALL and LBL patients aged 22 years and older. For our younger patients aged from one month to 21 years, treatment is typically administered with calaspargase pegol, which is similar to pegasparagase in terms of both safety and efficacy.

If the patient has already been receiving pegaspargase when they present for treatment, then they will continue this therapy. However, since we now have calasparagase pegol, this agent is typically used in newly diagnosed patients. Whenever possible, we have replaced pegasparagase with calaspargase pegol due to its greater shelf life and longer half-life.

In all instances, asparaginase therapy should be optimized to prevent early discontinuation. In a recent publication from Dr. Gupta et al through the Childrens' Oncology Group (COG) in 2020, high-risk and very high-risk inpatients who failed to receive all asparaginase doses had significantly inferior disease-free survival.[5] Of the patients who failed to receive all prescribed asparaginase doses, 21.3% experienced relapse—a significant amount. This study demonstrated why the development of an alternative *Erwinia*-based asparaginase product was so important in terms of treatment persistence. Because recombinant *Erwinia*-based asparaginase has an efficacy and safety profile similar to other asparaginases, it is now considered an essential alternative to ensure the optimal delivery of asparaginase in all patients.

**Mary:** ***Sharon, what is the length of time that a patient needs to receive asparaginase? And what is the evidence that supports that length of time needed for treatment leading a patient towards event-free survival in the context of a multi-agent chemotherapeutic regimen?***

**Sharon:** ALL therapy is a long and intense process that can extend for a duration of two to three years. Provided as a multi-agent regimen, ALL treatment is delivered in phases: induction, consolidation, and maintenance. Asparaginase is a crucial part of this multi-agent regimen that plays an essential role in treatment success through asparagine depletion. From clinical trials we know that sufficient and sustained asparagine depletion is believed to be important in obtaining cell apoptosis and favorable patient outcomes. So, maintaining periods of asparaginase activity over the course of treatment is essential.

Treatment is based on risk factors that were identified by the National Cancer Institute.[6] Standard risk patients are under the age of 10 years at diagnosis and have a white blood cell (WBC) count $<50 \times 10^9$/L, while high risk patients are aged 10 or older at diagnosis and have a WBC count $\geq 50 \times 10^9$/L. Very high-risk patients are 13 years old or older. For these patients, asparaginase is given in multiple phases: induction, consolidation, interim maintenance, delayed intensification, and maintenance. In the earlier phases of treatment, asparaginase is a very important component within a multi-agent chemotherapeutic regimen. However, while all patients will receive at least one dose of asparaginase at

induction, individuals stratified as high risk or very high-risk will receive more doses of asparaginase over time.

Examples of different regimens include those being utilized by the Children's Oncology Group (COG), Dana Farber Cancer Institute (DFCI) and St Jude Children's Research Hospital (SJCRH). These groups each apply, evaluate, and further refine different asparaginase strategies in the context of their ALL/LBL protocols. The COG ALL protocols for standard-risk B-cell ALL include only one dose of pegaspargase in induction and one in the post-induction phase.[7] Alternately, the DFCI employs continuous asparagine depletion for the majority of the post-induction and pre-maintenance phase, equaling approximately 30 weeks of asparaginase therapy.[8] Finally, the SJCRH Consortium uses a risk-adapted approach, with low-risk patients receiving intermittent post-induction dosing and higher-risk patients receiving continuous dosing.[9]

While the outcomes of these regimens are overall very good and generally comparable, more in-depth comparison of these approaches has been difficult. Recently, the Nordic Society of Pediatric Hematology and Oncology NOPHO ALL2008 study compared these dosing strategies in a randomized fashion for non-high-risk pediatric ALL patients.[10] While the 5-year disease-free survival rate was not statistically significant between treatment arms, the risk of toxicity was higher in the standard, continuous dosing group.

To achieve ideal asparaginase depletion without risking toxicity, asparaginase drug monitoring is being explored. Surrogate assays have been designed to quantify the serum asparaginase activity (SAA), and research has demonstrated a strong inverse correlation between SAA levels and serum asparagine. The literature has also established a nadir SAA of ≥0.1 IU/mL as the target level necessary to ensure adequate asparagine depletion. However, we must continue to refine the therapeutic SAA level and create a better picture of the pharmacokinetic and pharmacodynamic properties of asparaginase activity in leukemia and lymphoma cells.

In all, it is an exciting time for ALL/LBL treatment, and I look forward to seeing how we can better optimize asparaginase therapy to further improve outcomes in these patients.

**Mary:** ***Thank you, Sharon!***

---

**In Part II of this series, *The Practical Oncologist* spent additional time with Sharon Bergeron, RN, BSN, CPON, reviewing the 4 types of adverse reactions nurses can expect when administering asparaginase to their patients living with ALL and LBL. In Part III, Sharon explains how nursing observations during infusions, and utilizing therapeutic drug monitoring is key in facilitating ALL and LBL disease-response and clinical outcomes. Watch our website for Part II of this learning experience with expert Sharon Bergeron.**

---

## *References:*


1. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncol. 2012 May 10;30(14):1663-9.
2. Leukemia and Lymphoma Society. ALL Treatment Outcomes. https://www.lls.org/leukemia/acute-lymphoblastic-leukemia/treatment/treatment-outcomes. Accessed October 11, 2023.
3. Douer D, Gökbuget N, Stock W, Boissel N. Optimizing use of L-asparaginase-based treatment of adults with acute lymphoblastic leukemia. Blood Rev. 2022 May;53:100908.
4. Aldoss I, Douer D. How I treat the toxicities of pegasparaginase in adults with acute lymphoblastic leukemia. *Blood*. 2020;135(13):987-995. doi:10.1182/blood.2019002477
5. Gupta S, Wang C, Raetz EA, et al. Impact of Asparaginase Discontinuation on Outcome in Childhood Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group. *Journal of Clinical Oncology*. 2020;38(17):1897-1905. doi:10.1200/JCO.19.03024
6. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. J Clin Oncol. 1996 Jan;14(1):18-24.
7. Angiolillo AL, Schore RJ, Kairalla JA, et al. Excellent Outcomes With Reduced Frequency of Vincristine and Dexamethasone Pulses in Standard-Risk B-Lymphoblastic Leukemia: Results From Children's Oncology Group AALL0932. J Clin Oncol. 2021 May 1;39(13):1437-1447.
8. Place AE, Stevenson KE, Vrooman LM, et al. Intravenous pegylated asparaginase versus intramuscular native Escherichia coli L-asparaginase in newly diagnosed childhood acute lymphoblastic leukaemia (DFCI 05-001): a randomised, open-label phase 3 trial. Lancet Oncol. 2015 Dec;16(16):1677-90.
9. Jeha S, Pei D, Choi J, et al. Improved CNS Control of Childhood Acute Lymphoblastic Leukemia Without Cranial Irradiation: St Jude Total Therapy Study 16. J Clin Oncol. 2019 Dec 10;37(35):3377-3391.
10. Albertsen BK, Grell K, Abrahamsson J, et al. Intermittent Versus Continuous PEG-Asparaginase to Reduce Asparaginase-Associated Toxicities: A NOPHO ALL2008 Randomized Study. J Clin Oncol. 2019 Jul 1;37(19):1638-1646.


Provided by MediCom Worldwide, Inc.
Supported by an independent medical education grant from Jazz Pharmaceuticals.