Guidance for Keeping Appropriate Patients on ONCASPAR®

Premedication, Therapeutic Drug Monitoring, and Treatment Modification

oncaspar®
pegaspargase

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Studies show a significant drop in acute lymphoblastic leukemia (ALL) survival when asparaginase is discontinued[1,2]

- Among 8000 patients in Children's Oncology Group studies AALL0331 and AALL0232, there was a 50% decrease in the likelihood of disease-free survival in patients who discontinued asparaginase treatment[1]

- In Dana-Farber Cancer Institute study 91-01, the 5-year event-free survival (EFS) rate was 90% in patients who received asparaginase for at least 26 weeks compared with a 73% 5-year EFS rate in those who received fewer than 25 weeks of asparaginase[2]

A proven asparaginase therapy. A safer way to administer with premedication

The National Comprehensive Cancer Network® (NCCN®) recommends premedication with anti-allergy agents ahead of a dose of asparaginase.[3] This has been shown to reduce reactions by more than 65.8% along with zero grade 4 adverse events or intensive care unit admissions. It also allowed more patients to remain on ONCASPAR® (pegaspargase) treatment, reducing the rate of patients switching to another asparaginase formulation by 57%.[4]

Using premedication and therapeutic drug monitoring (TDM) to control adverse events

TDM measures serum asparaginase activity level and is used as a diagnostic tool to help clinicians distinguish among true allergic reactions, silent inactivation, and non–antibody-mediated infusion reactions, and to determine when switching asparaginase formulations is warranted.[5,6]

Some patients treated with asparaginase may have the following responses:

Nonallergic Reaction (Infusion Reaction)	Allergic Reactions (Hypersensitivity)	Silent Inactivation (Subclinical Hypersensitivity)
Non–antibody mediated[7]	Antibody-mediated; antibodies inactivate asparaginase, reducing asparaginase activity[5,7]	Patients develop anti-asparaginase antibodies without clinical signs of hypersensitivity[5]
When misdiagnosed as an allergic reaction, can lead to unnecessary contraindication to and discontinuation of asparaginase treatment[5,8]	Nonallergic reactions cannot be distinguished from allergic reactions based on clinical symptoms or grade[3,5,9]	If unrecognized, patients are often continued on the same asparaginase formulation with no therapeutic benefit[5]
Premedication with anti-allergy agents (eg, hydrocortisone, diphenhydramine, ranitidine, and acetaminophen) and slowing the rate of infusion by 50%, with concurrent infusion of saline, can reduce the risk of nonallergic reactions[3]	**TDM can help distinguish between allergic and nonallergic reactions[5]**	**TDM will help to establish whether a patient has silent inactivation[5]**

Implementation of universal premedication and TDM is recommended by the NCCN to reduce the incidence and severity of adverse events and the need for substitution of pegaspargase (ONCASPAR) with another asparaginase formulation.[3]

Avoiding premedication due to concerns about masking allergic reactions? You are not alone. But when premedication is used in combination with TDM, you can help patients potentially avoid interruption or discontinuation of ONCASPAR.[3,5,6]

Although ONCASPAR is associated with unique toxicities, the majority are manageable and reversible

Mitigate adverse reactions with treatment modifications

Monitor patients at least weekly, with bilirubin, transaminases, glucose, and clinical examinations, until recovery from the cycle of therapy. If an adverse reaction should occur, modify treatment according to the table below[10]:

Adverse Reaction	Severity*	Action
Infusion Reaction/ Hypersensitivity Reaction	**Grade 1**	• Reduce the infusion rate by 50%
	Grade 2	• Interrupt the infusion of ONCASPAR • Treat the symptoms • When symptoms resolve, resume the infusion and reduce the infusion rate by 50%
	Grade 3 to 4	• Discontinue ONCASPAR permanently
Hemorrhage	**Grade 3 to 4**	• Hold ONCASPAR • Evaluate for coagulopathy and consider clotting factor replacement as needed • Resume ONCASPAR with the next scheduled dose if bleeding is controlled
Pancreatitis	**Grade 3 to 4**	• Hold ONCASPAR for elevations in lipase or amylase >3 times the upper limit of normal (ULN) until enzyme levels stabilize or are declining • Discontinue ONCASPAR permanently if clinical pancreatitis is confirmed
Thromboembolism	**Uncomplicated deep vein thrombosis**	• Hold ONCASPAR • Treat with appropriate antithrombotic therapy • Upon resolution of symptoms, consider resuming ONCASPAR, while continuing antithrombotic therapy
	Severe or life-threatening thrombosis	• Discontinue ONCASPAR permanently • Treat with appropriate antithrombotic therapy
Hepatotoxicity	**Total bilirubin more than 3 times to no more than 10 times the ULN**	• Hold ONCASPAR until total bilirubin is ≤1.5 times the ULN
	Total bilirubin more than 10 times the ULN	• Discontinue ONCASPAR and do not make up for missed doses

*Grade 1 is mild, grade 2 is moderate, grade 3 is severe, and grade 4 is life-threatening.

Indications and Usage

ONCASPAR (pegaspargase) is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of pediatric and adult patients with:

- First-line acute lymphoblastic leukemia (ALL)
- ALL and hypersensitivity to native forms of L-asparaginase

Detailed Important Safety Information

CONTRAINDICATIONS

- History of serious hypersensitivity reactions, including anaphylaxis, to ONCASPAR or to any of the excipients.
- History of serious thrombosis with prior L-asparaginase therapy.
- History of pancreatitis, including pancreatitis related to prior L-asparaginase therapy.
- History of serious hemorrhagic events with prior L-asparaginase therapy.
- Severe hepatic impairment.

WARNINGS and PRECAUTIONS

Anaphylaxis and Serious Hypersensitivity Reactions: Anaphylaxis and serious hypersensitivity reactions can occur. The risk of serious hypersensitivity reactions is higher in patients with known hypersensitivity to *E. coli* derived L-asparaginase formulations. Observe patients for 1 hour after administration in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. Discontinue ONCASPAR in patients with serious hypersensitivity reactions.

Thrombosis: Serious thrombotic events, including sagittal sinus thrombosis, can occur. Discontinue ONCASPAR in patients with serious thrombotic events.

Pancreatitis: Pancreatitis can occur. Fatal outcomes have been reported. Inform patients of the signs and symptoms of pancreatitis. Discontinue ONCASPAR in patients where pancreatitis is suspected. If pancreatitis is confirmed, do not resume ONCASPAR.

Glucose Intolerance: Glucose intolerance can occur. In some cases, glucose intolerance is irreversible. Monitor serum glucose.

Hemorrhage: Increased prothrombin time, increased partial thromboplastin time, and hypofibrinogenemia can occur. Evaluate patients with signs and symptoms of hemorrhage with coagulation parameters including PT, PTT, and fibrinogen. Consider appropriate replacement therapy in patients with severe or symptomatic coagulopathy.

Hepatotoxicity: Hepatotoxicity and abnormal liver function can occur. Evaluate bilirubin and transaminases at least weekly during cycles of treatment through at least 6 weeks after the last dose. In the event of serious liver toxicity, discontinue ONCASPAR.

ADVERSE REACTIONS

The most common grade 3 and 4 adverse reactions with ONCASPAR (>5%) included hypoalbuminemia, elevated transaminase, febrile neutropenia, hypertriglyceridemia, hyperglycemia, bilirubin increased, pancreatitis, abnormal clotting studies, embolic and thrombotic events, and hypersensitivity.

oncaspar®
pegaspargase

Please see Full Prescribing Information.

References: 1. 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. *J Clin Oncol*. 2020;38(17):1897-1905. **2.** Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. *Blood*. 2001;97(5):1211-1218. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Acute Lymphoblastic Leukemia V.2.2021. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed March 24, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. **4.** Cooper SL, Young DJ, Bowen CJ, Arwood NM, Poggi SG, Brown PA. Universal premedication and therapeutic drug monitoring for asparaginase-based therapy prevents infusion-associated acute adverse events and drug substitutions. *Pediatr Blood Cancer*. 2019;66(8):e27797. **5.** Burke MJ, Rheingold SR. Differentiating hypersensitivity versus infusion-related reactions in pediatric patients receiving intravenous asparaginase therapy for acute lymphoblastic leukemia. *Leuk Lymphoma*. 2017;58(3):540-551. **6.** Marini BL, Perissinotti AJ, Bixby DL, Brown J, Burke PW. Catalyzing improvements in ALL therapy with asparaginase. *Blood Rev*. 2017;31(5):328-338. **7.** Asselin B. Immunology of infusion reactions in the treatment of patients with acute lymphoblastic leukemia. *Future Oncol*. 2016;12(13):1609-1621. **8.** Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. *Allergy*. 2014;69(4):420-437. **9.** Kloos RQH, Pieters R, Escherich G, van der Sluis IM. Allergic-like reactions to asparaginase: atypical allergies without asparaginase inactivation. *Pediatr Blood Cancer*. 2016;63(11):1928-1934. **10.** ONCASPAR [package insert]. Boston, MA: Servier Pharmaceuticals LLC; 2020.

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