PEER PERSPECTIVES
IN THE TREATMENT OF ALL

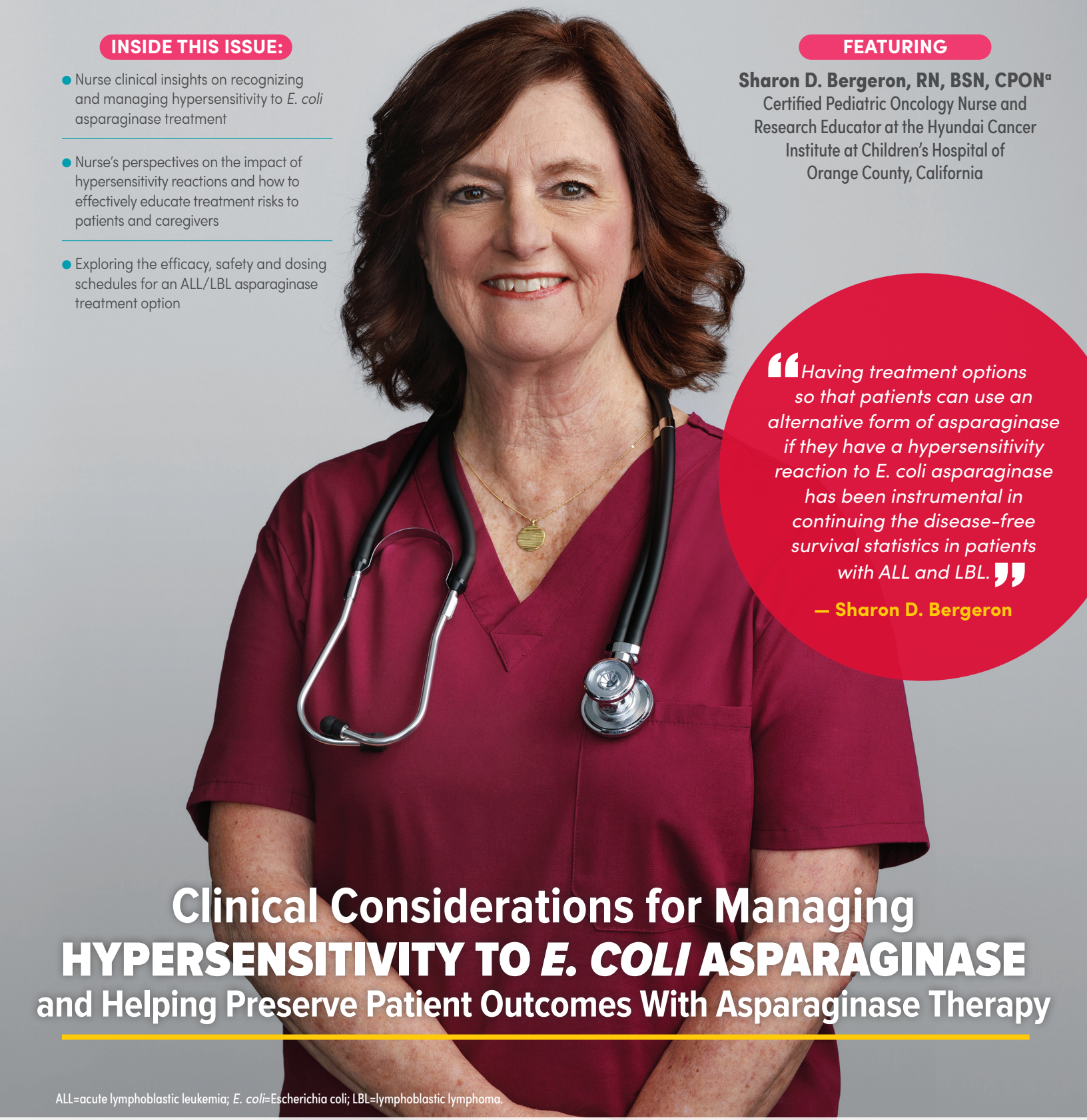
ISSUE 2 ALL

INSIDE THIS ISSUE:

- Nurse clinical insights on recognizing and managing hypersensitivity to *E. coli* asparaginase treatment
- Nurse's perspectives on the impact of hypersensitivity reactions and how to effectively educate treatment risks to patients and caregivers
- Exploring the efficacy, safety and dosing schedules for an ALL/LBL asparaginase treatment option

FEATURING

Sharon D. Bergeron, RN, BSN, CPON[a]
Certified Pediatric Oncology Nurse and Research Educator at the Hyundai Cancer Institute at Children's Hospital of Orange County, California



> *"Having treatment options so that patients can use an alternative form of asparaginase if they have a hypersensitivity reaction to E. coli asparaginase has been instrumental in continuing the disease-free survival statistics in patients with ALL and LBL."*
>
> — Sharon D. Bergeron

Clinical Considerations for Managing HYPERSENSITIVITY TO *E. COLI* ASPARAGINASE and Helping Preserve Patient Outcomes With Asparaginase Therapy

ALL=acute lymphoblastic leukemia; *E. coli*=Escherichia coli; LBL=lymphoblastic lymphoma.

[a]Sharon D. Bergeron is a paid consultant of Jazz Pharmaceuticals. This content is intended for informational purposes only and is not a substitute for your clinical knowledge or professional judgment. The views and opinions expressed in this article are those of the author and Jazz Pharmaceuticals and do not necessarily reflect the opinions of the Hyundai Cancer Institute at the Children's Hospital of Orange County.

PEER PERSPECTIVES IN THE TREATMENT OF ALL

WITH **SHARON D. BERGERON, RN, BSN, CPON**

Q. On average, how many patients with ALL/LBL do you manage a year?

A. On average, we get about 50 newly diagnosed patients in a year's time, and their length of treatment with asparaginase and other chemotherapy agents spans a couple of years. In our clinic, we can treat patients up to 26 years of age.

Q. What role does asparaginase play in the treatment plan for your patients with ALL/LBL?

A. As a certified pediatric oncology nurse who takes care of patients with ALL and LBL, I believe that asparaginase is a key component of a multiagent chemotherapy regimen.[1] Asparaginase is a very important part of the puzzle. Research over the years has shown that introduction of asparaginase in ALL treatment protocols has resulted in improvements in survival estimates over time.[1,2] Not receiving all of the required doses of asparaginase can result in compromised outcomes, including higher risk of relapse and lower disease-free survival in high-risk B-ALL patients.[3] I think asparaginase has made such an impact for so many pediatric patients.[4]

> *"Education is really important, not only to our nurses but also to our physician team. That's why my role was created. I believe that further educating the multidisciplinary team of healthcare providers and proactively discussing with patients both the value of asparaginase and the risk of developing hypersensitivity to asparaginase is of great importance."*
>
> **— Sharon D. Bergeron**

Q. In your opinion as a nurse, what are the biggest challenges in managing patients with ALL/LBL who are receiving asparaginase therapy?

A. Hypersensitivity to asparaginase is one of the biggest challenges we face as healthcare professionals who treat patients with ALL/LBL.[5,6] This can be very scary for the patient as well as the patient's loved ones. Hypersensitivity to *E. coli* asparaginase warrants a change in asparaginase therapy because we know once hypersensitivity occurs, a patient is at increased risk for another reaction when treated with asparaginase derived from the same source.[5,7] We also know that disease-free survival is affected when a patient does not fully complete a course of asparaginase, based on outcomes data in high-risk B-ALL patients.[3] Because we know the importance of completing asparaginase therapy, having alternative forms of therapy we can switch to is increasingly important for optimal patient outcomes.[5]

SYMPTOMS OF HYPERSENSITIVITY REACTIONS CAN COMPROMISE THE SAFETY OF PATIENTS AND THEIR TREATMENT[8]

• Symptoms of hypersensitivity reactions may be localized or systemic, and common symptoms include[9,10]:

Anaphylaxis

Respiratory
Wheezing, Dyspnea, Bronchospasm, Respiratory distress

Gastrointestinal
Nausea/vomiting, Abdominal pain, Diarrhea

Dermatologic
Urticaria, Pruritus, Erythema, Angioedema

Cardiovascular
Hypotension, Bradycardia

General
Headache, Lethargy, Malaise

▶ **Once hypersensitivity occurs, a patient is at increased risk for another reaction when treated with asparaginase derived from the same source.[5]**

Q. How do you recognize and monitor patients for signs and symptoms of hypersensitivity?

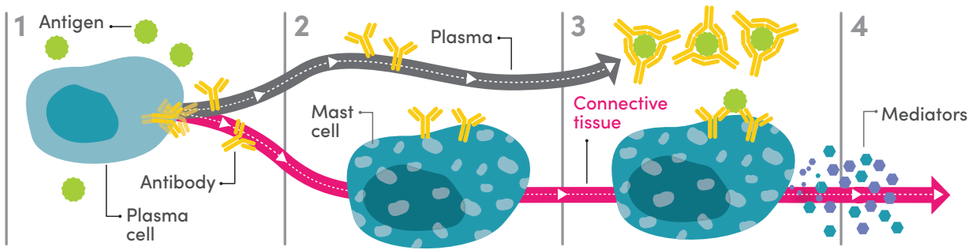
A. Over time we have learned that the more doses a patient gets, their risk of experiencing a hypersensitivity reaction is higher.[5,11] That is why monitoring is so important when the patient comes in.[5] Nurses evaluate the patient to make sure they don't have a fever or any symptoms that might mask a potential situation like respiratory issues or complications that could become exacerbated if we administer an asparaginase product. If a hypersensitivity reaction does occur, our facility has created what we call a "Red Box." Our nurses and pharmacists developed order sets that contain the protocol for emergency drugs as well as the appropriate doses so that if we need to cross that bridge, the drugs are right there and we can pull them to administer immediately. By doing this, we have all the tools to help or mitigate hypersensitivity reactions before they even occur or soon after.[12] We also monitor the patient routinely during the treatment. One thing we have identified is that a noticeable dip on the pulse-ox could signify the occurrence of possible hypersensitivity reactions or a telltale sign that the reaction is evolving.[9,10,12,13]

Q. How do you educate your patients and caregivers about hypersensitivity reactions and how do you recognize the symptoms?

A. Education is essential. Patients can have symptoms like nausea, vomiting, headache and minor skin reactions, which can be due to infusion reaction or hypersensitivity.[14] Where they have to be watched more closely is on those second and subsequent doses of asparaginase,

PEER PERSPECTIVES IN THE TREATMENT OF ALL

PATIENTS WHO HAVE EXPERIENCED A HYPERSENSITIVITY REACTION ARE AT INCREASED RISK OF ANOTHER REACTION WHEN TREATED WITH ASPARAGINASE FROM THE SAME SOURCE[5]



Native *E. coli* asparaginase, a bacterial protein, may trigger an immune response, resulting in proliferation and release of antibodies from plasma B cells[12]

Antibodies may directly bind to the surface of the mast cell, thereby activating it. Antibodies are also present in the plasma[12]

Upon reexposure, the antigen may bind to:

- Antibodies that are present on the surface of the mast cell (characterized by an IgE response or Type 1 reaction)[12]
- Free antibodies (mainly IgG or IgM) may neutralize or clear the antigen[12]

Adapted from Shinnick et al, 2013.[12]

Antigens bound to antibodies on mast cells trigger the release of histamine and other mediators that can cause clinical symptoms, including hypersensitivity reactions[8,12]

IgE=immunoglobulin E; IgG=immunoglobulin G; IgM=immunoglobulin M.

when a hypersensitivity reaction is more likely to occur.[5,7] Reactions that would warrant us to stop treatment and intervene are respiratory symptoms, the emergence of dry cough or severe rash, and a major dip in blood pressure.[9,10,12] Hypersensitivity reactions can be scary and both patients and caregivers can be affected. Patient education is integral to successful therapy. So, it is important to explain what is happening and how we plan to address and manage it. It is essential to communicate that we have an alternative asparaginase therapy that can replace their current regimen and allow for uninterrupted asparaginase therapy.[15] I don't think we've ever had issues where an appropriate patient or their family refused to continue with an alternative asparaginase. That can mostly be attributed to how we educate both the staff and the patient support system.

> *"If hypersensitivity to E. coli asparaginase occurs, it warrants an alternative treatment... We recognize the importance of continuing asparaginase therapy. What we would do is utilize an alternative form of asparaginase, which is RYLAZE. By switching our patients to RYLAZE, they can continue to get all their required doses, which we know is essential to successful outcomes."*
>
> **— Sharon D. Bergeron**

Q. How does hypersensitivity to *E. coli* asparaginase impact the overall treatment process for patients with ALL/LBL?

A. In order to mitigate the risk of having another hypersensitivity reaction, patients should be switched to an alternative form of asparaginase. Replacement therapy should begin as soon as clinically possible, ideally within 48 to 72 hours following a hypersensitivity reaction.[5] The alternative form of therapy would be RYLAZE. Based on what we've seen, the safety profile of RYLAZE has been consistent with other asparaginase therapies.[15,16] Switching to an asparaginase from a different source allows patients to continue necessary asparaginase treatment.[5] Since RYLAZE is an *Erwinia*-derived asparaginase, it is expected to have minimal immunologic cross-reactivity with *E. coli* asparaginase.[17]

Q. What factors are taken into consideration when deciding whether to switch a patient with ALL/LBL to RYLAZE? How is RYLAZE administered?

A. When a healthcare provider has determined that a patient has experienced hypersensitivity to *E. coli* asparaginase and defined it as such, then we switch. Once the hypersensitivity reaction is documented, we initiate RYLAZE treatment within 48 to 72 hours.[5,15] Our facility will administer the first dose closer to the 48-hour mark. The first step is to ensure that our pharmacy has RYLAZE. If we do not have RYLAZE on hand, we are able to order and quickly receive it so that we can schedule the patient to come in to our outpatient facility as soon as possible.

Our staff utilizes the 25/25/50 mg/m^2 intramuscular dosing regimen Monday morning, Wednesday morning, and Friday afternoon, respectively.[15] This is beneficial because we can dose Monday-Wednesday-Friday and avoid instances of weekend injections. Initiating the dose replacement regimen within 48 to 72 hours is achievable because the first dose can be started on Monday, Wednesday, or Friday. Starting on another asparaginase treatment can sometimes cause unease, but after educating the patient and family, it's clear to all that it's better to get it done as soon as clinically possible, ideally within 48 to 72 hours, than to wait a week to avoid the development of anti-asparaginase antibodies.[5]

OPTIMIZED DOSING PROVIDES SUSTAINED ASPARAGINASE ACTIVITY THROUGHOUT THE ENTIRE COURSE OF TREATMENT[15]

Proportion of patients with NSAA ≥0.1 U/mL by simulation[15]

RYLAZE IM Dosing Options	Trough Sampling Time	Proportion With NSAA ≥0.1 U/mL (95% CI)[a]
Q48 25 mg/m^2	48 hours	96.0% (94.4%-97.2%)
Monday morning, Wednesday morning, and Friday afternoon 25/25/50 mg/m^2	**Friday afternoon:** 58 hours after 25 mg/m^2 Wednesday morning dose[b]	91.6% (90.4%-92.8%)
	Monday morning: 67 hours after 50 mg/m^2 Friday afternoon dose[c]	91.4% (90.1%-92.6%)

[a]Based on 2,000 virtual subjects.[15]
[b]Based on maximum interval of 58 hours between the Wednesday morning and Friday afternoon doses.[15]
[c]Based on maximum interval of 67 hours between the Friday afternoon and Monday morning doses.[15]

Activity of ≥0.1 U/mL has been demonstrated to correlate with asparagine depletion and serum levels that predict clinical efficacy.[1,18]

CI=confidence interval; IM=intramuscular; NSAA=nadir serum asparaginase activity; Q48=every 48; U=unit.

Approved dosing is based on the RYLAZE AALL1931 Study.[15,17] In collaboration with Children's Oncology Group, the AALL1931 study was an open-label, multicohort, multicenter trial that evaluated the efficacy and safety of RYLAZE administered intramuscularly as part of a multiagent chemotherapeutic regimen for 167 ALL and LBL patients aged 1-25 years with hypersensitivity to *E. coli* asparaginase, to demonstrate that at least 90% of patients could achieve and maintain NSAA ≥0.1 U/mL.[15,17]

Indication

RYLAZE is indicated as a component of a multi-agent chemotherapeutic regimen given by intramuscular injection for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adult and pediatric patients 1 month or older who have developed hypersensitivity to *E. coli*-derived asparaginase.[15]

IMPORTANT SAFETY INFORMATION

Contraindications

RYLAZE is contraindicated in patients with: history of serious hypersensitivity reactions to *Erwinia asparaginase*, including anaphylaxis; history of serious pancreatitis during previous asparaginase therapy; history of serious thrombosis during previous asparaginase therapy; history of serious hemorrhagic events during previous asparaginase therapy; or severe hepatic impairment.

RYLAZE®
asparaginase erwinia chrysanthemi (recombinant)-rywn for injection 10mg/0.5mL per vial

Please see additional Important Safety Information on page 7. Please see full Prescribing Information.

RECOMMENDED DURATION OF RYLAZE DOSING TO REPLACE ONE LONG-ACTING ASPARAGINASE DOSE[15]

When RYLAZE is Administered	Recommended Duration of RYLAZE to Replace 3 Weeks of Asparaginase Coverage (Calaspargase Products)	Recommended Duration of RYLAZE to Replace 2 Weeks of Asparaginase Coverage (Pegaspargase Products)
25 mg/m^2 intramuscular every 48 hours	Replace 1 dose of calaspargase pegol products with 11 doses of RYLAZE	Replace 1 dose of pegaspargase products with 7 doses of RYLAZE
25 mg/m^2 intramuscular on Monday morning and Wednesday morning, and 50 mg/m^2 intramuscular on Friday afternoon*	Replace 1 dose of calaspargase pegol products with 9 doses of RYLAZE	Replace 1 dose of pegaspargase products with 6 doses of RYLAZE

*Administer the Friday afternoon dose 53 to 58 hours after the Wednesday morning dose.[15]

The table above shows the number of RYLAZE dosages recommended for the intended duration of treatment for replacement of:

-3 weeks of asparaginase coverage (1 dose of calaspargase pegol products) or

-2 weeks of asparaginase coverage (1 dose of pegaspargase products)

See the full Prescribing Information for the long-acting asparaginase product to determine the total duration of administration of RYLAZE as replacement therapy[15]

Q. How do you and your peers feel about the safety profile of RYLAZE?

A. As a certified pediatric hematology/oncology nurse, I think that healthcare providers feel comfortable with RYLAZE. It is essential that we do our due diligence and educate our families before and after patients receive their dose of RYLAZE. Our facility ensures that caregivers know that if their child is having any type of reaction, such as respiratory complications or they just "seem off," they should seek medical advice immediately so that we can assess and manage their symptoms.[12,15]

> *"When we are switching to RYLAZE, we use the number of doses needed for the intended duration of asparaginase treatment according to the protocol we are following."*
>
> **— Sharon D. Bergeron**

IMPORTANT DOSING INFORMATION

Recommended Premedication

Premedicate patients with acetaminophen, an H-1 receptor blocker (such as diphenhydramine), and an H-2 receptor blocker (such as famotidine) 30-60 minutes prior to administration of RYLAZE to decrease the risk and severity of hypersensitivity reactions.

Recommended Monitoring and Dosage Modifications for Adverse Reactions

Monitor patient's bilirubin, transaminases, glucose, and clinical examinations prior to treatment every 2-3 weeks and as indicated clinically. If results are abnormal, monitor patients until recovery from the cycle of therapy. If an adverse reaction occurs, modify treatment according to Table 2 in the accompanying full Prescribing Information.

Indication

RYLAZE is indicated as a component of a multi-agent chemotherapeutic regimen given by intramuscular injection for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adult and pediatric patients 1 month or older who have developed hypersensitivity to *E. coli*-derived asparaginase.

IMPORTANT SAFETY INFORMATION

Contraindications

RYLAZE is contraindicated in patients with: history of serious hypersensitivity reactions to *Erwinia asparaginase*, including anaphylaxis; history of serious pancreatitis during previous asparaginase therapy; history of serious thrombosis during previous asparaginase therapy; history of serious hemorrhagic events during previous asparaginase therapy; or severe hepatic impairment.

Warnings and Precautions

Hypersensitivity Reactions

Hypersensitivity reactions after the use of RYLAZE occurred in 29% of patients in clinical trials, and it was severe in 6% of patients. Anaphylaxis was observed in 2% of patients after intramuscular administration. Discontinuation of RYLAZE due to hypersensitivity reactions occurred in 5% of patients. Hypersensitivity reactions were higher in patients who received intravenous asparaginase erwinia chrysanthemi (recombinant)-rywn. The intravenous route of administration is not approved.

In patients administered RYLAZE intramuscularly in clinical trials, the median number of doses of RYLAZE that patients received prior to the onset of the first hypersensitivity reaction was 12 doses (range: 1-64 doses). The most commonly observed reaction was rash (19%), and 1 patient (1%) experienced a severe rash.

Hypersensitivity reactions observed with L-asparaginase class products include angioedema, urticaria, lip swelling, eye swelling, rash or erythema, blood pressure decreased, bronchospasm, dyspnea, and pruritus.

Premedicate patients prior to administration of RYLAZE as recommended. Because of the risk of serious allergic reactions (e.g., life-threatening anaphylaxis), administer RYLAZE in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, oxygen, intravenous steroids, antihistamines). Discontinue RYLAZE in patients with serious hypersensitivity reactions.

Pancreatitis

Pancreatitis, including elevated amylase or lipase, was reported in 20% of patients in clinical trials of RYLAZE and was severe in 8%. Symptomatic pancreatitis occurred in 7% of patients, and it was severe in 6% of patients. Elevated amylase or lipase without symptomatic pancreatitis was observed in 13% of patients treated with RYLAZE. Hemorrhagic or necrotizing pancreatitis have been reported with L-asparaginase class products.

Inform patients of the signs and symptoms of pancreatitis, which, if left untreated, could be fatal. Evaluate patients with symptoms compatible with pancreatitis to establish a diagnosis. Assess serum amylase and lipase levels in patients with any signs or symptoms of pancreatitis. Discontinue RYLAZE in patients with severe or hemorrhagic pancreatitis. In the case of mild pancreatitis, withhold RYLAZE until the signs and symptoms subside and amylase and/or lipase levels return to 1.5 times the ULN. After resolution of mild pancreatitis, treatment with RYLAZE may be resumed.

Thrombosis

Serious thrombotic events, including sagittal sinus thrombosis and pulmonary embolism, have been reported in 1% of patients following treatment with RYLAZE. Discontinue RYLAZE for a thrombotic event, and administer appropriate antithrombotic therapy. Consider resumption of treatment with RYLAZE only if the patient had an uncomplicated thrombosis.

Hemorrhage

Bleeding was reported in 25% of patients treated with RYLAZE, and it was severe in 2%. Most commonly observed reactions were bruising (12%) and nose bleed (9%).

In patients treated with L-asparaginase class products, hemorrhage may be associated with increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenemia. Consider appropriate replacement therapy in patients with severe or symptomatic coagulopathy.

Hepatotoxicity, including Hepatic Veno-Occlusive Disease

Elevated bilirubin and/or transaminases occurred in 75% of patients treated with RYLAZE in clinical trials, and 26% had Grade ≥3 elevations. Elevated bilirubin occurred in 28% of patients treated with RYLAZE in clinical trials, and 2% had Grade ≥3 elevations. Elevated transaminases occurred in 73% of patients treated with RYLAZE in clinical trials, and 25% had Grade ≥3 elevations.

Hepatotoxicity, including severe, life-threatening, and potential fatal cases of hepatic veno-occlusive disease (VOD), have been observed in patients treated with asparaginase class products in combination with standard chemotherapy, including during the induction phase of multiphase chemotherapy. Do not administer RYLAZE to patients with severe hepatic impairment. Inform patients of the signs and symptoms of hepatotoxicity.

Evaluate bilirubin and transaminases prior to each cycle of RYLAZE and at least weekly during cycles of treatment that include RYLAZE, through four weeks after the last dose of RYLAZE. Monitor frequently for signs and symptoms of hepatic VOD, which may include rapid weight gain, fluid retention with ascites, hepatomegaly (which may be painful), and rapid increase of bilirubin. For patients who develop abnormal liver tests after RYLAZE, more frequent monitoring for liver test abnormalities and clinical signs and symptoms of VOD is recommended. In the event of serious liver toxicity, including VOD, discontinue treatment with RYLAZE and provide supportive care.

Adverse Reactions

The most common adverse reactions (incidence >20%) with RYLAZE are abnormal liver test, nausea, musculoskeletal pain, infection, fatigue, headache, febrile neutropenia, pyrexia, hemorrhage, stomatitis, abdominal pain, decreased appetite, drug hypersensitivity, hyperglycemia, diarrhea, pancreatitis, and hypokalemia.

Use in Specific Populations

Pregnancy and Lactation

RYLAZE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective non-hormonal contraceptive methods during treatment with RYLAZE and for 3 months after the last dose. Advise women not to breastfeed during treatment with RYLAZE and for 1 week after the last dose.

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Please see full Prescribing Information.

"Putting in the effort to know your patient and understanding how they process information or how they react to things is key to making them feel comfortable receiving the drug. The nurses are comfortable with how they're giving the drug and our physician teams are good at being able to assess the patient for particular side effects. RYLAZE has had a favorable impact on our ALL and LBL patients who experience hypersensitivity reactions to E. coli asparaginase by providing an alternative asparaginase."

— Sharon D. Bergeron

LEARN MORE ABOUT AN ALTERNATIVE ASPARAGINASE TREATMENT OPTION WHEN HYPERSENSITIVITY TO *E. COLI* ASPARAGINASE THREATENS YOUR PATIENT'S ALL/LBL TREATMENT COURSE AT

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Sharon D. Bergeron is a leading research expert in treating patients with ALL and LBL.

Sharon D. Bergeron, RN, BSN, CPON is a certified pediatric oncology nurse and research educator at the Hyundai Cancer Institute at the Children's Hospital of Orange County in Orange, California. She received her Bachelor of Science in Nursing degree at the California State University Long Beach School of Nursing. She is a Board Member Director-at-Large of the Association of Pediatric Hematology Oncology Nurses and past Nursing Nominating Committee Chair of the Children's Oncology Group/Nursing Committee. She is currently a Children's Oncology Group DVL Protocol Core Group Nurse and member of the Children's Oncology Group Nursing Committee. She is also a board member of the Southern California Association of Pediatric Hematology and Oncology Nurses and serves on the Oncology Nursing Society and Oncology Nursing Certification Corporation Clinical Trials Advisory Board.

Please see Important Safety Information on page 7. Please see full Prescribing Information.

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