Impact of Clinical and Subclinical Hypersensitivity to Asparaginase in Acute Lymphoblastic Leukemia

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Asparaginase is an essential element of acute lymphoblastic leukemia treatment. It depletes serum asparagine (an amino acid necessary for synthesis of cellular proteins), deprives leukemic blast cells of asparagine, and eventually results in cell death. To gain benefit from asparaginase, asparagine depletion must be ensured by giving intensive therapy and completing the full course of treatment. Three formulations of asparaginase exist; two are derived from Escherichia coli, a native form and pegylated form, and one is derived from Erwinia chrysanthemi (Erwinia asparaginase). Like many large proteins, asparaginases are immunogenic, and some patients develop antibodies to asparaginase. Antibodies may result in clinical hypersensitivity or subclinical hypersensitivity without symptoms, and both can result in a reduction in asparaginase activity and may affect therapeutic benefit. Clinical hypersensitivity is the most common reason for patients to stop asparaginase treatment. Subclinical hypersensitivity can only be identified by laboratory testing; therapeutic monitoring of asparaginase activity is used as a surrogate measure for asparagine depletion.

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease, and treatment is selected on the basis of risk of relapse. Pediatric study groups classify patients into standard-, high-, and very high-risk groups, whereas adult study groups generally classify patients as standard or high risk (Pui & Evans, 2006). The risk of relapse is graded according to a number of factors including clinical features, cytogenetics, and initial response to therapy. Age at diagnosis and presenting leukocyte count are strong prognostic indicators. In pediatrics, standard-risk disease is usually defined as patients aged 1–9 years with a presenting leukocyte count of less than 50 x 10⁹/L. In adults, prognosis worsens as age and leukocyte count increase (Pui & Evans, 2006).

Response to treatment has the greatest prognostic strength. Newer technological advances have made the measurement of minimal residual disease (MRD) to assess the proportion of leukemic cells remaining after induction therapy, a strong determining factor for treatment stratification; MRD of less than 0.01% identifies patients with an excellent outcome, whereas MRD of more than 1% after induction or more than 0.1% later in treatment identifies patients with an extremely high risk of relapse (Pui & Evans, 2006). The use of MRD in terms of methodology, time points of testing, and appropriate cutoffs to identify different groups is an area of active investigation among all cooperative groups and continues to evolve.

Asparaginase is a cornerstone of treatment for ALL and is used in all treatment protocols (Pieters et al., 2011). To gain clinical benefit from asparaginase, patients must receive intensive therapy and complete the full course of treatment. A number of studies have shown significant benefit in terms of event-free survival (EFS), disease-free survival, and continuous complete remission rate with intensive asparaginase therapy (Rizzari et al., 2013).

Asparaginase Products

Mode of Action

Asparaginase is a naturally occurring enzyme in animals, plants, and microorganisms. It hydrolyzes asparagine to aspartic acid and ammonia, removing asparagine from the serum. Leukemic blast cells are unable to synthesize asparagine and, therefore,
must rely on extracellular sources. Depletion of plasma asparagine by asparaginase results in inadequate extracellular sources, and the leukemic cell is effectively starved of asparagine. The lack of asparagine leads to impairment of cellular function and cell death. However, normal cells are unaffected because they are able to synthesize asparaginase and are not dependent on extracellular asparagine (Müller & Boos, 1998).

Two formulations of asparaginase are available in the United States: pegylated asparaginase (polyethylene glycol [PEG]-asparaginase) derived from Escherichia coli (*E. coli*) and asparaginase *Erwinia chrysanthemi* or *Erwinia* asparaginase derived from *Erwinia chrysanthemi* (Pieters et al., 2011). Un pegylated asparaginase (native *E. coli* asparaginase) remains available in most countries outside of the United States. In the United States, PEG-asparaginase has replaced native *E. coli* asparaginase in all frontline ALL treatment protocols. *Erwinia* asparaginase is licensed by the U.S. Food and Drug Administration for use in patients who experience hypersensitivity to *E. coli*-derived asparaginases (U.S. Food and Drug Administration, 2011).

### Pharmacology

All three asparaginases share the same mode of action (Müller & Boos, 1998); however, they have different pharmacologic profiles (Asselin, 1999). Covalent binding of PEG to *E. coli* asparaginase to form PEG-asparaginase extends the half-life of the product and reduces immunogenicity (Asselin, 1999; Earl, 2009).

Duration of asparagine depletion is dependent on the half-life of asparaginase. PEG-asparaginase has the longest half-life (5.73 days, SD = 3.24), and *Erwinia* asparaginase and native *E. coli* asparaginase have shorter half-lives (0.65 days, SD = 0.13; 1.28 days, SD = 0.35, respectively). PEG-asparaginase has the longest duration of asparagine depletion (26–34 days), whereas *Erwinia* asparaginase and native *E. coli* asparaginase have shorter durations of asparagine depletion (7–15 days and 14–23 days, respectively) (Asselin, 1999) (see Table 1). The differences in half-life and duration of asparagine depletion are reflected in the doses used in clinical practice, meaning that the asparaginases are not interchangeable at the same dose and frequency (Asselin, 1999; Pieters et al., 2011).

### Hypersensitivity

Like most large proteins, asparaginase can elicit an immunologic response; the body recognizes asparaginase as a foreign protein or antigen and produces anti-asparaginase antibodies. Antibodies produced against asparaginase may neutralize enzyme activity by blocking the active site or accelerating enzyme clearance, reducing the effectiveness of subsequent doses. Not all anti-asparaginase antibodies are neutralizing.

In some patients, the presence of anti-asparaginase antibodies leads to an overt clinical reaction (clinical hypersensitivity); in others, no clinical signs and symptoms occur, which is known as subclinical hypersensitivity and is sometimes called silent inactivation (Asselin, 1999; Pieters et al., 2011). The presence of antibodies, whether clinical signs and symptoms of hypersensitivity occur or not, may result in a reduction in asparaginase activity (Avramis et al., 2002; Panosyan et al., 2004; Zaleswska-Szewczyk et al., 2007) and poorer clinical outcomes (Panosyan et al., 2004).

#### Clinical Hypersensitivity

Clinical hypersensitivity reactions are the most commonly reported adverse events in patients receiving asparaginase, occurring in about 10%–30% of patients (Earl, 2009; Vrooman et al., 2013). Incidence rates vary according to the preparation of asparaginase used, frequency of administration, number of doses given, and concurrent chemotherapy (Woo et al., 2000). Because of this, comparing rates across the asparaginases is difficult; however, rates appear highest with native *E. coli* asparaginase (Earl, 2009). Hypersensitivity reactions can manifest as a local injection-site reaction or as a more generalized reaction with varying symptoms (see Figure 1). Some patients experience a localized and generalized reaction (Woo et al., 2000). Hypersensitivity reactions can be very unpleasant for the patient and may even be life threatening (Earl, 2009). Any symptoms suggestive of hypersensitivity should be carefully evaluated to identify whether a true immune reaction occurred and to assess the severity (see Table 2).

Anaphylaxis is characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with shortness of breath, larynged breathing, wheezing, headache, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death (U.S. Department of Health and Human Services [USDHHS], 2010). Asparaginase should only be administered in settings where close observation is possible and measures for treating an anaphylactic reaction are readily available. Clinical hypersensitivity is the most common reason for patients to discontinue treatment with asparaginase (Earl, 2009; Müller & Boos, 1998; Pieters, 2011; Shinnick, Browning, & Koontz, 2013; Vrooman et al., 2010). Patients who discontinue treatment early do not gain the full benefit of treatment and may have significantly poorer clinical outcomes than those who continue treatment (Silverman et al., 2001).

#### Subclinical Hypersensitivity

Given that subclinical hypersensitivity is asymptomatic, the incidence rate is more difficult to determine, and identification is by laboratory testing. Antibody testing is not generally used because tests are not commercially available and antibodies can form against different components of asparaginase, making it

### TABLE 1. Asparaginase Half-Life and Duration of Asparagine Depletion

<table>
<thead>
<tr>
<th>Type of Asparaginase</th>
<th>Dose</th>
<th>Half-Life (Days)</th>
<th>Duration of Depletion of Asparagine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native <em>E. coli</em> asparaginase</td>
<td>Single dose of 25,000 IU/m² IM</td>
<td>1.28 ± 0.35</td>
<td>14–23 days</td>
</tr>
<tr>
<td>PEG-asparaginase</td>
<td>Single dose of 2,500 IU/m² IM</td>
<td>5.73 ± 3.24</td>
<td>26–34 days</td>
</tr>
<tr>
<td><em>Erwinia</em> asparaginase</td>
<td>Single dose of 25,000 IU/m² IM</td>
<td>0.65 ± 0.13</td>
<td>7–15 days</td>
</tr>
<tr>
<td><em>E. coli—Escherichia coli; Erwinia asparaginase—asparaginase Erwinia chrysanthemi</em> IM—intramuscularly; PEG—polyethylene glycol</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. Based on information from Asselin, 1999.
The use of a standard scale ensures that adverse events are reported objectively and consistently across clinical trials and within clinical practice. In clinical trials, CTCAE grading is used to determine patient eligibility; define dose-limiting toxicity; and determine maximum tolerated dose, dose modifications, and patient safety monitoring.

Management of Asparaginase Hypersensitivity

Patients should be observed for one hour after administration of asparaginase for signs of hypersensitivity. Parents and patients should be aware that hypersensitivity may occur hours after administration and should be able to recognize signs of hypersensitivity at home (Shinnick et al., 2013).

Asparaginase hypersensitivity is managed according to the type of reaction and guidelines outlined in the treatment protocol. In most cases the current asparaginase is discontinued if the patient develops a grade 2 or higher systemic allergic reaction as defined by CTCAE. Asparaginase should be discontinued in patients who develop an anaphylactic reaction of any grade (Shinnick et al., 2013).

Like clinical hypersensitivity rates, subclinical hypersensitivity rates vary according to the preparation of asparaginase used, dose, and number of doses given as well as other variables. However, studies in children with ALL have shown rates ranging from 9%–29% (Panosyan et al., 2004; Vrooman et al., 2013; Woo et al., 2000).

Grading Clinical Hypersensitivity

The Common Terminology Criteria for Adverse Events (CTCAE) is used to grade severity of clinical hypersensitivity events in real time at the time of the reaction (USDHHS, 2010). The CTCAE is widely accepted in the oncology and hematology communities and is used as the standard scale to grade adverse events in oncology and hematology clinical trials.

The CTCAE grading is used to grade severity of clinical hypersensitivity events in real time at the time of the reaction (USDHHS, 2010).

### TABLE 2. CTCAE Grading for Allergic Reaction and Anaphylaxis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Transient flushing or rash, drug fever of less than 38°C (100.4°F); intervention not indicated</td>
</tr>
<tr>
<td>2</td>
<td>Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics); prophylactic medications indicated for less than or equal to 24 hours</td>
</tr>
<tr>
<td>3</td>
<td>Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

### Anaphylaxis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angiodyema; hypotension</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

CTCAE—Common Terminology Criteria for Adverse Events; NSAIDs—nonsteroidal anti-inflammatory drugs

Note: Based on information from U.S. Department of Health and Human Services, 2010.
The use of prophylaxis (i.e., steroids or antihistamines) masks the symptoms of hypersensitivity, and patients still may have severe allergy or anaphylactic reaction may receive emergency and supportive care medications, such as antihistamines, IV steroids, oxygen, and epinephrine (Shinnick et al., 2013). In these situations, an alternative noncrossreactive preparation of asparaginase can be substituted. Patients with severe allergy or anaphylactic reaction may receive emergency and supportive care medications, such as antihistamines, IV steroids, oxygen, and epinephrine (Shinnick et al., 2013).

After a clinical or subclinical hypersensitivity reaction, a decision is made regarding the next scheduled dose of asparaginase and whether to make the change to Erwinia asparaginase. The decision is protocol or clinician driven.

Potential Options After Hypersensitivity to Asparaginase

A number of potential options exist once a patient has experienced hypersensitivity. Stopping treatment with asparaginase in patients experiencing hypersensitivity is not a viable option (Rizzari et al., 2013) because significantly poorer clinical outcomes have been demonstrated for patients who do not complete the full course of treatment compared with those who do complete the planned course (Silverman et al., 2001). Erwinia asparaginase is an alternative asparaginase to PEG-asparaginase and provides an option for patients to continue treatment.

The use of prophylaxis (i.e., steroids or antihistamines) masks the symptoms of hypersensitivity, and patients still may have reduced asparaginase activity and will not benefit from additional asparaginase (Rizzari et al., 2013). Asparaginase activity is significantly reduced after a clinical hypersensitivity reaction to below the activity required for complete asparagine depletion (Zalewska-Szewczyk et al., 2007). Asparaginase activity may be undetectable in patients treated with native E. coli asparaginase who continue treatment after a hypersensitivity reaction, even after a relatively mild reaction such as urticaria or a minor injection-site reaction (Asselin et al., 1993).

In addition, patients who continue treatment with asparaginase after a clinical hypersensitivity reaction are likely to experience another reaction (González, Saez, Rodilla, Yges, & Toledano, 2000). Subsequent clinical hypersensitivity reactions were seen in 85% of patients who continued treatment with native E. coli asparaginase after an initial hypersensitivity reaction, even with premedication (Woo et al., 1998).

Immunologic crossreactivity exists between native E. coli asparaginase and PEG-asparaginase (Hak et al., 2004); therefore, administration of native E. coli asparaginase after a reaction to PEG-asparaginase is not recommended because the presence of antibodies may result in a significant reduction in asparaginase activity (Avramis et al., 2002; Panosyan et al., 2004; Zalewska-Szewczyk et al., 2007).

Erwinia asparaginase is immunologically distinct from E. coli–derived asparaginases; it has a significantly different amino acid composition (Zalewska-Szewczyk et al., 2009). Studies have demonstrated that no crossreactivity exists between antibodies to E. coli–derived asparaginases and Erwinia asparaginase (Hak et al., 2004; Wang et al., 2003; Zalewska-Szewczyk et al., 2009).

Asparaginase depletion is maintained in patients switched to Erwinia asparaginase after the development of antibodies or hypersensitivity to native E. coli asparaginase, whereas depletion may not be maintained in patients with antibodies if switched to PEG-asparaginase (Hak et al., 2004).

The continuation of asparagine depletion is reflected in clinical outcomes. In a study of 215 children with newly diagnosed ALL, patients received native E. coli asparaginase and were switched to Erwinia asparaginase if they experienced any form of clinical hypersensitivity (Vrooman et al., 2010). Clinical hypersensitivity to native E. coli asparaginase developed in 21% of patients (n = 45), 42 of whom were switched to Erwinia asparaginase. NSAA was measured in 38 of these patients; 89%

### TABLE 3. Interim Analysis of the Impact of Subclinical Hypersensitivity or Hypersensitivity on Outcome (N = 280)

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>n</th>
<th>%</th>
<th>Switched to Erwinia asparaginase</th>
<th>Event Rate at 30 Months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hypersensitivity or antibody present</td>
<td>57</td>
<td>20</td>
<td>No</td>
<td>5.2</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>142</td>
<td>51</td>
<td>Yes</td>
<td>3.5</td>
</tr>
<tr>
<td>Subclinical hypersensitivity</td>
<td>81</td>
<td>29</td>
<td>No</td>
<td>16</td>
</tr>
</tbody>
</table>

Erwinia asparaginase—asparaginase Erwinia chrysanthemi

had adequate asparaginase activity (NSAA at or above 100 IU/L). At the median follow-up of 5.4 years, EFS was not significantly different between patients switched to Erwinia asparaginase and patients remaining on native E. coli asparaginase (86%, SD = 5% versus 81%, SD = 5%, respectively; p = 0.55) (see Figure 2).

A study comparing fixed-dose and individualized dosing of asparaginase revealed that fixed-dose patients with low NSAA (maximum of 100 IU/L) who never switched preparations had a five-year EFS of 76% compared with 95% for the individualized-dose patients who switched preparations when subclinical hypersensitivity was identified (Vrooman et al., 2013).

A study of 280 high-risk children followed for at least 30 months after induction revealed that patients with subclinical hypersensitivity remaining on E. coli-derived asparaginase had higher relapse rates compared with those with hypersensitivity switched to Erwinia asparaginase (16% versus 3.5%, respectively) (Panosyan et al., 2004) (see Table 3). The clinical value of a switch to Erwinia asparaginase in cases of hypersensitivity is recognized in study protocols. However, identification of subclinical hypersensitivity with the implementation of a switch in such cases is less well recognized.

In the Children’s Oncology Group (COG) ALL protocols, PEG-asparaginase is used for frontline care and discontinued if the patient develops clinical allergy grade 2 or higher, defined by CTCAE, version 4 (USDHHS, 2010). Erwinia asparaginase is substituted at a dose of 25,000 IU/m² intramuscularly on a Monday/Wednesday/Friday schedule for six doses for each dose of PEG-asparaginase (Hunger & COG Pharmacy Committee, 2010; Shinnick et al., 2013). Other protocols also recommend switching to Erwinia asparaginase in cases of clinical hypersensitivity (Shinnick et al., 2013).

Conclusion

Hypersensitivity, whether clinical or subclinical, may have a negative impact on outcomes regardless of clinical symptoms. The presence of antibodies may result in a reduction in asparaginase activity and decreased clinical efficacy.

Patients with clinical hypersensitivity experience unpleasant symptoms and often discontinue asparaginase. Ensuring that patients are observed for at least one hour after administration of asparaginase and that symptoms are managed appropriately is important. In most cases, the current asparaginase should be discontinued if an allergic reaction is rated as grade 2 or higher or if anaphylaxis of any grade occurs and substitution of an alternate asparaginase has been considered.

Because no crossreactivity exists, switching to Erwinia asparaginase allows patients with hypersensitivity to continue with treatment and maintain outcomes. Given that subclinical hypersensitivity is asymptomatic, therapeutic monitoring of asparaginase activity may help to identify patients who may be hypersensitive and facilitate a switch to Erwinia asparaginase. Therapeutic monitoring also provides reassurance that the 100 IU/L target for asparaginase activity considered effective for adequate asparagine depletion is being met.

References


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Implications for Practice

- Monitor patients for the development of antibodies to asparaginase; antibodies may be symptomatic (overt clinical hypersensitivity reaction) or asymptomatic (subclinical hypersensitivity), both of which may reduce the therapeutic benefit of asparaginase.

- Observe patients for at least one hour after administration of asparaginase; measures for treating anaphylaxis should be readily available.

- Perform therapeutic monitoring of asparaginase activity to help identify patients with subclinical hypersensitivity, determine the best choice of treatment, and facilitate a switch to Erwinia asparaginase.


