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Clinical Characteristics of Intravenous PEG-Asparaginase Hypersensitivity Reactions in Patients Undergoing Treatment for Acute Lymphoblastic Leukemia CE

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Abstract

Background: Asparaginase poses a substantial risk for hypersensitivity reactions during and after administration; however, these reactions vary by asparaginase formulation and administration route. It is imperative that nurses be knowledgeable of clinical symptoms associated with intravenous (IV) monomethoxypolyethylene glycol (PEG)-asparaginase reactions, as well as potential reaction timing. **Purpose:** This single institution retrospective study describes the clinical factors among patients with IV PEG-asparaginase hypersensitivity reactions. **Methods:** Reaction frequency and severity, dose, phase of treatment, and time between infusion initiation and reaction were collected on patients identified as having an IV PEG-asparaginase hypersensitivity reaction while undergoing acute lymphoblastic leukemia treatment. **Results:** Sixty-three patients (12.8%) developed a hypersensitivity reaction to IV PEG-asparaginase, with the reaction occurring during a median of 3 doses in both risk arms. Reactions were noted ≤60 minutes after infusion initiation in 98% of patients, and no reactions were fatal. **Conclusion:** Nurses should carefully observe patients throughout the infusion and anticipate adverse reactions, particularly during the first 3 doses and first 10 minutes of each infusion. Patient and family education should include the rare risk of delayed reactions.

Keywords

PEG-asparaginase, hypersensitivity, reaction, allergy, nursing

Introduction

Treatment for acute lymphoblastic leukemia (ALL) includes multiple chemotherapy drugs delivered in a rotational schedule. Asparaginase is an essential agent in the treatment for pediatric ALL, and is unique in its ability to deplete plasma asparagine into aspartic acid and ammonia (Muller & Boos, 1998). Without serum asparagine, lymphoblasts are deprived of the essential amino acid for the synthesis of proteins and DNA, resulting in lymphoblast death (Riccardi, Holcenberg, Glaubiger, Wood, & Poplack, 1981). Several forms of asparaginase have been produced: native or L-asparaginase is derived from *Escherichia coli* and *Erwinia* asparaginase is derived from *Erwinia chrysanthemi. E coli* asparaginase, however, is no longer produced in the United States (Bechwith, Wheeler, & Jensen, 2013). The third form, pegylated asparaginase (PEG-asparaginase), is formulated by covalently conjugating monomethoxypolyethylene glycol (PEG) to *E coli* asparaginase (Abuchowski et al., 1984). In modern pediatric ALL treatment, PEG-asparaginase is the most commonly used formulation because of its longer half-life and intravenous (IV) administration option (Hijiya & van der Sluis, 2016).

As a result of its bacterial derivation, exposure to any asparaginase formulation may potentiate an immune response and anti-asparaginase antibody development (Muller & Boos, 1998). The presence of antibodies increases the hypersensitivity risk on asparaginase reexposure and

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Table 1. PEG-Asparaginase Treatment Schedule.[a]

Treatment Phase	All Patients	Standard/High Risk Only
Induction (~6 weeks' duration)	Day 3; [b]Day 15-21	
Consolidation (~8 weeks' duration)		
Continuation weeks 1-6		Weeks 1, 3, and 5
Reinduction I (weeks 7-9)	Weeks 7 and 9	
Continuation weeks 10-16		Weeks 11, 13, 15
Reinduction II (weeks 17-19)	Weeks 17 and 19	
Continuation weeks 20-29		Weeks 21, 23, 25, 27, 29

[a]PEG-asparaginase doses: induction dose(s) = 3000 IU/m^2. Patients were randomized to receive either 2500 IU/m^2 or 3500 IU/m^2 during continuation.
[b]Single dose for patients with ≥1% minimal residual disease on induction day 15 bone marrow evaluation.

may jeopardize the continuation and effectiveness of treatment. Hypersensitivity reactions can range from mild rashes and flushing to life-threatening airway compromise and cardiovascular collapse. Rates of clinical hypersensitivity to *E coli* asparaginase generally range from 10% to 30%, and with PEG-asparaginase rates range from 3% to 24% Vrooman et al., 2010). Children receiving PEG-asparaginase IV have been found to have a greater risk of hypersensitivity than intramuscular (IM) administration (Hasan, Shaikh, Rassekh, Howard, & Goddard, 2017), but the time to IV PEG-asparaginase reaction onset has not been extensively studied. This lack of evidence creates challenges for nurses caring for patients receiving IV PEG-asparaginase as the ideal postinfusion monitoring time has not been established (Woods et al., 2017).

The purpose of this study was to determine the clinical factors among patients with IV PEG-asparaginase hypersensitivity reactions, including reaction frequency and severity, asparaginase dose, treatment phase of the event, and the duration of time between infusion initiation and reaction. This data will inform evidence-based nursing guidelines for IV PEG-asparaginase monitoring and patient and family education.

Methods

Patients

This retrospective study identified 492 patients from March 21, 2008 to March 23, 2016 enrolled on the institutional ALL treatment protocol (Total XVI) and eligible for review after completing their asparaginase therapy. Sixty-three of the eligible patients were identified as developing a clinical hypersensitivity reaction to IV PEG-asparaginase during ALL treatment. Electronic medical records were reviewed for demographic information, including gender, age, and risk group. Medication administration records were reviewed to determine the amount of time between initiation of PEG-asparaginase infusion and reaction onset, as well as the dose of asparaginase administered. Protocol roadmaps were reviewed to determine the chemotherapeutic phase in which the reaction occurred. The description of the reaction was collected, and the severity of the reaction was graded according to the Common Terminology Criteria for Adverse Events version 3 (CTCAE) (National Cancer Institute [NCI], 2006), as this was the version used to grade toxicity for the entire protocol. CTCAE grade 1 represents transient flushing, rash, or drug fever; grade 2 involves a rash, flushing, urticaria, dyspnea, or drug fever; grade 3 includes symptomatic bronchospasm with or without urticaria, allergy-related edema/angioedema, hypotension, or parenteral medication(s) indicated for symptom control; anaphylaxis is required for grade 4; and death is considered a grade 5 reaction (NCI, 2006).

Treatment

Patients were classified as low-, standard-, or high-risk for relapse based on demographics, leukemia disease features, and response to therapy. Table 1 outlines the PEG-asparaginase treatment schedule. All patients received IV PEG-asparaginase (3000 international units [IU]/m^2) on day 3 of induction, and a second dose was given between induction days 15 to 21 for patients with ≥1% minimal residual disease on their day 15 bone marrow examination. Patients were randomized in the continuation phase of treatment to receive higher than recommended dose (3500 IU/m^2) or conventional dose (2,500 IU/m^2) PEG-asparaginase in order to compare pharmacokinetic and pharmacodynamic properties and clinical benefit. Standard-risk/high-risk (SR/HR) patients received IV PEG-asparaginase every 2 weeks over the first 29 weeks of continuation for a total of 15 doses. Low-risk (LR) patients received 2 IV PEG-asparaginase doses in each of the 2 reinduction phases, for a total of 4 doses over the first 19 weeks of continuation. According to research protocol guidelines, patients occasionally received a reduced

dose (1000 IU/m^2) due to treatment toxicity. Patients with persistent minimal residual disease received 1 course of reintensification prior to hematopoietic cell transplant that included a single dose of IV PEG-asparaginase (3000 IU /m^2). All PEG-asparaginase doses were administered via 60-minute IV infusion unless a patient-specific prolonged infusion was indicated. Premedication was not standard practice; however, reactions during the induction or reintensification phases occurred despite patients receiving steroids per ALL protocol at doses of 40 mg/m^2/d prednisone or 20 mg/m^2/d dexamethasone, respectively.

Statistical Analysis

Patient characteristics and clinical parameters of hypersensitivity reactions to PEG-asparaginase were summarized by descriptive statistics. Mantel-Haenszel chi-square tests (exact *P* values reported) were performed to examine differences for ordinal categorical variables between risk groups and dose levels of PEG-asparaginase. Wilcoxon rank sum tests were performed to determine differences in continuous variables between risk groups and dose levels of PEG-asparaginase. Statistical analyses were conducted with SAS 9.4 (SAS Institute, Cary, NC). A 2-sided significance level of $P < .05$ was used for all statistical tests.

Results

Of the 492 eligible patients, 63 patients (12.8%) developed a hypersensitivity reaction to IV PEG-asparaginase. Patients experiencing a reaction were a mean age of 7.1 years (range 1.4-17.7 years). Fifty-five percent of patients were in the SR/HR treatment arm and 60% were male.

Table 2 summarizes the severity and timing of PEG-asparaginase hypersensitivity reactions for all patients and by risk group. The majority of patients (80.9%) developed a hypersensitivity reaction in the first 6 weeks of continuation (SR/HR) or during the first reinduction phase (LR). PEG-asparaginase hypersensitivity reactions developed during a median of 3 IV infusions (range, 2-16) and were primarily grade 3 in severity (71.4%). The majority of patients (76.2%) developed a hypersensitivity reaction by the third dose of PEG-asparaginase and nearly all patients (93.7%) developed a hypersensitivity reaction by the fifth dose. Figure 1 demonstrates the percentages of patients that experienced a hypersensitivity reaction and the reaction grade by the number of PEG-asparaginase doses administered; the single grade 4 reaction occurred during the fourth dose. All patients except one developed the hypersensitivity reaction while actively receiving the PEG-asparaginase infusion over 60 minutes. The one exception developed a grade 3 reaction 199 minutes after infusion initiation. There was no difference in the median number of PEG-asparaginase doses administered prior to reaction between risk groups, as LR patient reactions occurred during a median of 3 doses (range, 2-5) and SR/HR patient reactions occurred during a median of 3 doses (range, 2-16) ($P = .119$, Table 2). There was no difference in the severity of hypersensitivity reactions between risk groups, with 67.9% grade 3 reactions occurring in the LR and 74.3% grade 3 reactions in the SR/HR group ($P = 1.000$, Table 2). There was no significant difference in the timing of hypersensitivity reactions between LR and SR/HR patients (median of 5 vs 7 minutes into infusion, respectively; $P = .361$, Table 2).

The severity and timing of hypersensitivity reactions by randomized dose (2500 IU/m^2 vs. 3500 IU/m^2) of PEG-asparaginase is summarized in Table 3. There was no significant difference in the severity of reactions ($P = .401$) or in time from initiation of infusion to reaction onset ($P = .692$). The majority of hypersensitivity reactions were grade 3 in both dose levels (2500 IU/m^2 [75.9%]; 3500 IU/m^2 [69%]). A median of 9 (range, 1-199) versus 7 (range, 1-60) minutes into the infusion elapsed before reaction onset in 2500 IU/m^2 and 3500 IU/m^2 dose recipients, respectively.

Discussion

The mean and median age of patients who developed a hypersensitivity reaction to IV PEG-asparaginase was typical of the age of patients enrolled on study, and there were noticeably more males (n = 38) than females (n = 25). This slight disproportion is to be expected considering the increased prevalence of ALL among the male population. Among patients with hypersensitivity reactions, we did not find SR/HR patients who receive more intensive ALL therapy to have higher rates of hypersensitivity reactions than LR patients. However, SR/HR patients did experience hypersensitivity reactions earlier in treatment than LR patients. This finding is likely a result of SR/HR patients receiving PEG-asparaginase earlier in continuation treatment, as well as more frequently. The higher dose of PEG-asparaginase was not found to increase the hypersensitivity reaction within this cohort, as there was no significant difference in randomized dose (2500 IU/m^2 or 3500 IU/m^2) of PEG-asparaginase among patients with grades 2 and 3 hypersensitivity reactions.

The vast majority of reactions occurred during the second and third doses of PEG-asparaginase, while only one patient developed a reaction prior to the beginning of

Table 2. Description of PEG-Asparaginase Hypersensitivity Reactions by Risk Group.

	All (N = 63)		Risk				
			Low (n = 28)		Standard/High (n = 35)		
	n	%	n	%	n	%	*P*
Age at enrollment, years							
Mean (SD)	7.1 (4.8)						
Median (range)	6.3 (1.4-17.7)						
Sex							
Female	25	39.7					
Male	38	60.3					
Severity of hypersensitivity reaction							
Grade 2	17	27.0	8	28.6	9	25.7	1.000
Grade 3	45	71.4	19	67.9	26	74.3	
Grade 4	1	1.6	1	3.6	0	0	
Treatment phase of hypersensitivity reaction							
Induction day 15	1	1.6	1	3.6	0	0	
Continuation weeks 1-6	28	44.4	0	0	28	80.0	
Reinduction I	23	36.5	22	78.6	1	2.9	
Continuation weeks 10-16	1	1.6	0	0	1	2.9	
Reinduction II	4	6.3	4	14.3	0	0	
Continuation weeks 20-29	3	4.8	1	3.6	2	5.7	
Reintensification I–day 6	3	4.8	0	0	3	8.6	
Continuation phase dose number at time of hypersensitivity reaction (n = 59)[a]							
1	31	52.5	12	44.4	19	59.4	
2	17	28.8	10	37.0	7	21.9	
3	5	8.5	3	11.1	2	6.3	
4	3	5.1	2	7.4	1	3.1	
6	1	1.7	0	0	1	3.1	
12	1	1.7	0	0	1	3.1	
14	1	1.7	0	0	1	3.1	
Dose of PEG-asparaginase given at time of hypersensitivity reaction (IU/m^2)							
1000	1	1.6	0	0	1	2.9	
2500[b]	29	46.0	14	50.0	15	42.9	
3000	4	6.3	1	3.6	3	8.6	
3500	29	46.0	13	46.4	16	45.7	
Total number of PEG-asparaginase doses given prior to hypersensitivity reaction[c]							
2	23	36.5	13	46.4	10	28.6	
3	25	39.7	10	35.7	15	42.9	
4	8	12.7	3	10.7	5	14.3	
5	3	4.8	2	7.1	1	2.9	
6	1	1.6	0	0	1	2.9	
8	1	1.6	0	0	1	2.9	
14	1	1.6	0	0	1	2.9	
16	1	1.6	0	0	1	2.9	
Median (range)	3 (2-16)		3 (2-5)		3 (2-16)		
Minutes from PEG-asparaginase administration to hypersensitivity reaction							
≤60	62	98.4	27	96.4	35	100.0	0.361
>60	1	1.6	1	3.6	0	0	
Median (range)	7.5 (1-199)		5 (1-199)		7 (2-60)		

[a]Only applicable to patients who had a hypersensitivity reaction during the continuation phase of treatment.
[b]Food and Drug Administration–approved dose, as stated in the package insert.
[c]Including the dose that triggered the hypersensitivity reaction.

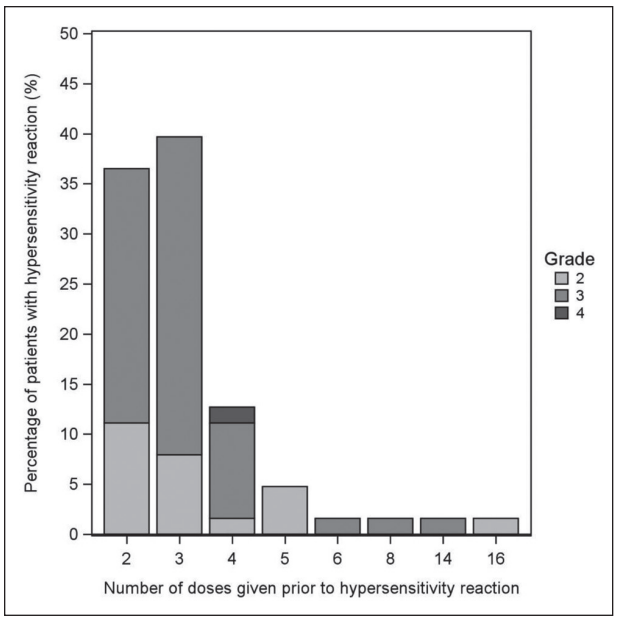

Figure 1. Distribution of reaction grade by number of PEG-asparaginase doses administered.
Number of doses includes the dose that triggered the hypersensitivity reaction.

continuation. This result is consistent with other studies noting that prolonged periods between asparaginase exposures may increase the risk of the patient experiencing clinical hypersensitivity on reexposure (Tong et al., 2014). The majority of patients in our study experienced a reaction at the start of continuation, several months after their exposure to PEG-asparaginase in induction. Nurses should be aware that patients are at increased risk following any prolonged break in asparaginase administration, and may need to be monitored more closely during the infusion.

While there was no major difference in incidence of clinical hypersensitivity between IV administration (12.8%) in our study and an earlier study of IM PEG-asparaginase (13.2%) (Henriksen et al., 2015), there was a noteworthy difference in the timing of these reactions. Fifty-eight percent of patients who experienced a hypersensitivity reaction did so within 2 hours of IM administration and 29% of patients experienced a reaction between 2 and 6 hours (Henriksen et al., 2015). While IV PEG-asparaginase administration may not decrease the hypersensitivity reaction risk, it is more likely that reactions will occur during the 60-minute infusion (98.4% in our sample), while the patient has access to nurses and other health care professionals who can assess and manage the reaction immediately.

The majority of reactions were grade 3 (71.4%), equating with a severe reaction that required immediate intervention in order to control symptoms. Common symptoms of patients included dyspnea, pruritus, edema, rash, cough, and vomiting. Considering the observed time to hypersensitivity reaction onset (98.4% in <60 minutes), patients should be observed throughout the entire hour-long infusion and most closely monitored during the first 10 minutes of the infusion. It is imperative for nurses to educate children and their families about the rare possibility of a delayed reaction, as one was noted as late as 199 minutes after the initiation of IV PEG-asparaginase.

The study relied on the diligence of nurses and clinicians to give accurate and descriptive documentation of medication administration and patient reactions; however, the possibility of inaccurate records is a potential study limitation. As this was a review of a single treatment protocol, differences in risk classification, treatment schedules, and PEG-asparaginase doses may prevent the generalizability to other ALL protocols. Additionally, we did not compare the clinical characteristics with patients who did not experience a grade 2 or 3 hypersensitivity reaction and cannot describe findings as being predictive of a reaction. Patients may have developed anti-asparaginase antibodies by experiencing subclinical hypersensitivity or mild reactions that may have gone unreported, and thus they were not included in this study. Glucocorticoids may mitigate hypersensitivity reaction severity, but may also decrease serum asparaginase activity (Fernandez et al., 2015). Thus, patients receiving glucocorticoids concomitantly or as premedication should be closely monitored for symptoms of milder reactions.

Conclusions

This retrospective review describes the clinical characteristics among patients with IV PEG-asparaginase hypersensitivity reactions, and builds evidence for time points in therapy that patients are at the greatest risk for reaction. This study reveals that both LR and SR/HR patients were more likely to have a reaction at the time of their second or third dose. For SR/HR patients, this is typically within weeks 1 to 6 of continuation treatment, and during reinduction I for LR patients. We also found that IV PEG-asparaginase typically results in a reaction during the infusion, as opposed to IM PEG-asparaginase which yielded a higher frequency of delayed reactions (Henriksen et al., 2015). It is a common practice for nurses to monitor patients during their infusion and for an additional hour post completion of the 60-minute infusion. This study provides preliminary data to support the modification of nurse monitoring guidelines to eliminate the additional postinfusion monitoring, as 98.4% of patients experienced the reaction during the infusion, and the single postinfusion reaction was beyond the 120-minute observation time. Further prospective study is warranted to validate our study findings.

Table 3. Description of PEG-Asparaginase Hypersensitivity Reactions by Randomized Dose.

	All (N = 58)[a]		Dose (IU/m^2)				
			2500 (n = 29)		3500 (n = 29)		
	n	%	n	%	n	%	*P*
Age at enrollment, years							
Mean (SD)	6.9 (4.7)		7.8 (5.2)		6.0 (4.2)		
Median (range)	5.1 (1.4-17.7)		6.8 (1.4-17.7)		4.3 (1.6-15.6)		
Sex							
Female	23	39.7	12	41.4	11	37.9	
Male	35	60.3	17	58.6	18	62.1	
Risk							
Low	27	46.6	14	48.3	13	44.8	
Standard/High	31	53.4	15	51.7	16	55.2	
Severity of hypersensitivity reaction							
Grade 2	15	25.9	6	20.7	9	31.0	.401
Grade 3	42	72.4	22	75.9	20	69.0	
Grade 4	1	1.7	1	3.4	0	0	
Treatment phase of hypersensitivity reaction							
Continuation weeks 1-6	28	48.3	15	51.7	13	44.8	
Reinduction I	23	39.7	10	34.5	13	44.8	
Continuation weeks 10-16	1	1.7	0	0	1	3.4	
Reinduction II	4	6.9	3	10.3	1	3.4	
Continuation weeks 20-29	2	3.4	1	3.4	1	3.4	
Total number of PEG-asparaginase doses given prior to hypersensitivity reaction[b]							
2	22	37.9	8	27.6	14	48.3	
3	22	37.9	12	41.4	10	34.5	
4	8	13.8	7	24.1	1	3.4	
5	3	5.2	2	6.9	1	3.4	
6	1	1.7	0	0	1	3.4	
8	1	1.7	0	0	1	3.4	
14	1	1.7	0	0	1	3.4	
Median (range)	3 (2-5)		3 (2-14)				
Dose number in continuation phase at time of hypersensitivity reaction							
1	31	53.4	12	41.4	19	65.5	
2	17	29.3	11	37.9	6	20.7	
3	5	8.6	5	17.2	0	0	
4	3	5.2	1	3.4	2	6.9	
6	1	1.7	0	0	1	3.4	
12	1	1.7	0	0	1	3.4	
Minutes from PEG-asparaginase administration to hypersensitivity reaction							
≤60	57	98.3	28	96.6	29	100.0	
>60	1	1.7	1	3.4	0	0	
Median (range)	9 (1-199)				7 (1-60)		.692

[a]Only those patients who had not developed a hypersensitivity reaction before the start of the continuation phase of treatment were randomized. Note 1 patient was excluded because he/she did not receive the required dose of 2500 or 3500 (patient received 1000 IU/m^2).
[b]Including the dose that triggered the hypersensitivity reaction.

Declaration of Conflicting Interests

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