Title Page

Title: Adverse Effects of Pegaspargase in Pediatric Patients Receiving Doses Greater Than 3,750 Units

Authors:

Rachel Lebovic, PharmD, BCOP

Clinical Pharmacist, Ambulatory Oncology

University of Michigan Comprehensive Cancer Center

Natalie Pearce, PharmD

Clinical Research and Drug Development Fellow

UNC Eshelman School of Pharmacy/United Therapeutics

Laura Lacey, PharmD

PGY-1 Pharmacy Resident, Ambulatory Care

Carolinas Healthcare System NorthEast

James Xenakis, PhD Candidate

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University of North Carolina Department of Biostatistics and Gillings School of Public Health

Cassidy B. Faircloth, PharmD, BCPS, BCOP, CPP

Pediatric Oncology Clinical Pharmacist

University of North Carolina Medical Center, Department of Pharmacy

Patrick Thompson, MD

Pediatric Oncologist

University of North Carolina Lineberger Comprehensive Cancer Center

Corresponding Author Information:

Cassidy B. Faircloth, PharmD, BCOP, BCPS, CPP

101 Manning Drive, CB 7600

Chapel Hill, NC 27514

Email: Cassidy.faircloth@unchealth.unc.edu

Phone: 984-974-8307

Fax: 984-974-8579

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Abbreviations table:

ALL	Acute Lymphocytic Leukemia
CALGB	Cancer and Leukemia Group B
IU	International Units
PEG-ASP	Pegaspargase
COG	Children's Oncology Group
VTE	Venous thromboembolism
IM	Intramuscular
IV	Intravenous
UNC	University of North Carolina
BSA	Body surface area
AST	Aspartate transaminase
ALT	Alanine transaminase
ALP	Alkaline phosphatase
PE	Pulmonary embolism

Abstract

Background: Increased toxicities have been identified with higher doses of pegaspargase (PEG-ASP) in adults. This has led to routine use of a 3,750 IU dose cap for adult acute lymphocytic leukemia (ALL) patients in most institutions. In pediatric ALL, PEG-ASP is not capped. There is concern at our institution that larger doses may result in increased rates of adverse effects and that increased monitoring may be warranted in pediatric patients receiving doses greater than 3,750 IU. The objective of this study is to quantify the difference in rates of PEG-ASP-associated adverse events between pediatric patients who received doses greater than 3,750 IU and 3,750 IU or less.

Methods: Retrospective chart review of patients 1-21 years old with pre-B cell ALL who received PEG-ASP between 2007 and 2014 at an academic medical center.

Results: Of 183 patients included in the analysis, 24 patients received PEG-ASP doses >3,750 IU and 159 patients received doses ≤3,750 IU. The incidence of VTE was significantly higher for patients in the >3,750 IU group compared to those who received ≤3,750 IU, 20.8% vs. 1.89% respectively, p=0.0011. The incidence of pancreatitis (p=0.0306) and hyperglycemia (p=0.0089) were also higher in the >3,750 IU group.

Conclusions: PEG-ASP doses >3,750 IU are associated with higher rates of VTE, pancreatitis, and hyperglycemia in pediatric patients with pre-B cell ALL. Patients receiving

>3,750 IU should have increased monitoring, and larger, multicenter trials are needed to determine if monitoring, VTE prophylaxis, and potential dose capping recommendations should be added to clinical trial protocols.

Introduction

Asparaginase formulations are a critical aspect of acute lymphoblastic leukemia (ALL) remission-induction treatment in both pediatric and adult populations. As part of an intensive, multi-agent chemotherapy regimen, asparaginase prolongs event- and disease-free survival.[1,2] Pegaspargase (Oncaspar®) is the current formulation of choice in most pediatric oncology clinical trials and protocols, as it was shown to be as effective as *Escherichia coli* asparaginase but with a prolonged duration of action.[3] However, there are concerns regarding the toxicity profile of asparaginase formulations at higher doses. In 2007, the Cancer and Leukemia Group B (CALGB) study 9511 demonstrated that adult patients with ALL receiving pegaspargase (PEG-ASP) 2,000 IU/m^2 with max dose 3,750 IU resulted in achieving effective asparagine depletion with improved disease free and overall survival.[3,4] Subsequent studies, including COG AALL0232 and CALGB 10403, used a dose of 2,500 IU/m^2 without a max dose and saw an increase in adverse events, specifically hepatotoxicity, during induction therapy.[4,5] Therefore, many institutions, including our own, will cap PEG-ASP dose at the single vial size, 3,750 IU, for adult patients.

For pediatric patients, PEG-ASP 2,500 IU/m^2 is typically used and there is no dose capping at 3,750 IU. Additionally, in some treatment regimens pediatric patients receive PEG-ASP as frequently as every 14 days, as opposed to adults who only receive PEG-ASP every 28 days.[6] At our center, pediatric oncology practitioners have noted that patients

receiving doses greater than 3,750 IU experience increased rates of adverse drug events. To date there are currently no studies in the literature that illustrate a difference in the rates of adverse effects in children who receive PEG-ASP doses above or below 3,750 IU.

Adverse effects associated with PEG-ASP include venous thromboembolism (VTE), coagulation disorders, pancreatitis, hypertriglyceridemia, hypersensitivity reactions, hyperglycemia, and increases in bilirubin and liver function tests.[7,8,9] Given the known efficacy of PEG-ASP, this study aims to retrospectively compare the rates of adverse drug events in pediatric patients with B-cell ALL who receive >3,750 IU of PEG-ASP and ≤3,750 IU of PEG-ASP in order to further elucidate the safety profile of PEG-ASP in a pediatric population. The primary objective is to evaluate the hypothesis that use of doses greater than 3,750 units of PEG-ASP in pediatric oncology patients results in increased rates of adverse drug events. The secondary objective of this study is to assess the effect of doses >3,750 IU of PEG-ASP on treatment delays.

Methods

We performed a retrospective cohort study of pediatric patients with ALL who received intramuscular (IM) or intravenous (IV) PEG-ASP at University of North Carolina (UNC) Medical Center in Chapel Hill, North Carolina. The Biomedical Institutional Review Board at UNC Medical Center approved this study.

Patients were identified via the electronic medical record and were eligible for inclusion if they had pre-B-cell ALL and received PEG-ASP between January 1, 2007 and December 31, 2014. We identified 266 patients with ALL who received a total of 1,248 PEG-ASP doses during this timeframe.

Demographics collected included patient's sex, age, weight, body surface area (BSA), primary cancer diagnosis, comorbid conditions at time of PEG-ASP administration, along with date of disease relapse. Obesity and hyperglycemia were determined by diagnosis code and problem list. Parameters for PEG-ASP included dose(s), route and date(s) of administration, number of doses received, and adverse events potentially contributable to PEG-ASP occurring within 4 weeks of administration. The adverse effects reviewed were pancreatitis, hypertriglyceridemia, VTE, coagulation disorder, hyperglycemia, hypersensitivity, and elevated bilirubin and liver function tests. To assess the occurrence of these adverse events, the highest values of each of the following laboratory tests were collected: amylase, lipase, triglycerides, prothrombin time, D-dimer, total bilirubin, direct bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP). The lowest fibrinogen level within 4 weeks of PEG-ASP administration was also collected. Additionally, diagnosis codes and physician notes were utilized to identify adverse events not evident in the laboratory values.

Statistical Analysis

Laboratory value analyses involved reducing the data to the most extreme recorded value for each category (i.e., the lowest for fibrinogen, and the highest for all others). Treatment delays were treated as binary variables (i.e., presence or absence of delays), and when analyzing treatment delays we included all observed doses and treated them as independent observations. All continuous variables were analyzed using the Wilcoxon rank sum test. Fisher's exact test was employed for binary variables. All reported p-values are two-sided.

Results

Patients

In total, 266 pediatric patients with ALL were identified to have received a total of 1,248 orders for PEG-ASP doses over the 8 year study period. We excluded 704 doses of PEG-ASP due to duplicate medication orders and diagnoses of NK-cell and T-cell ALL, thus leaving 544 doses from 189 patients for analysis. Among the 189 patients, 24 patients received PEG-ASP doses greater than 3,750 IU, 159 patients received doses less than or equal to 3,750 IU, and 6 patients were excluded from analyses because they received doses both above and below 3,750 IU. Therefore, the final analysis included 183 patients who received 523 PEG-ASP doses.

Full details regarding the patient demographics are described in Table 1. Some variation was noted in baseline characteristics between groups. Patients who received PEG-ASP doses >3,750 IU were significantly older, had a significantly higher BSA and an increased presence of obesity than patients who received doses ≤3,750 IU.

Primary Outcomes – Effect of Dosing on Asparaginase Related Toxicities

Table 2 describes the primary outcome showing the incidence of treatment-related toxicities for the two dosing groups. As shown in the table, the incidence of VTE was significantly higher for patients in the >3,750 IU group compared to those who received ≤3,750 IU, 20.8% vs. 1.9% respectively, p=0.001. Additionally, patients receiving >3,750 IU PEG-ASP developed pancreatitis more frequently (p=0.031). No difference was noted between groups regarding pulmonary embolism (PE) occurrences or the incidence of hypersensitivity reactions. Of the patients who experienced a VTE, only one patient in each group had a line-associated VTE. Detailed information about the patients who experienced VTE are shown in Table 3.

The majority of laboratory values did not differ significantly between the groups. Those labs that were statistically different included amylase, lipase, total and direct bilirubin, as well as ALT (Table 4).

Secondary Outcomes – Effect of Dosing on Treatment Delays

Table 5 summarizes the secondary outcome analysis. In the >3,750 IU group, patients experienced an increased incidence of treatment delays, however, this difference was not statistically significant (p=0.06).

Discussion

PEG-ASP has been shown to be effective in the treatment of pediatric ALL, as asparaginase formulations prolong event- and disease-free survival when added to intensive, multi-agent chemotherapy regimens.[1,2] While CALGB caps adult doses of PEG-ASP at 3,750 IU, the Children's Oncology Group protocols currently do not dose cap for pediatric patients receiving PEG-ASP. To our knowledge, no studies have assessed the rates of PEG-ASP-associated adverse effects in pediatric patients receiving doses above 3,750 IU.

The results of this study demonstrate that PEG-ASP doses greater than 3,750 IU are associated with a higher incidence of adverse effects including VTE, pancreatitis, and hyperglycemia. Notably, over 20% of patients that received >3,750 IU PEG-ASP experienced VTE compared to <2% of patients that received ≤3,750 IU PEG-ASP. Also, patients who experienced a VTE did not have severe hypertriglyceridemia (>1,000 mg/dL) which has been previously reported as a potential risk factor for VTE.[8] Furthermore, it is standard practice for our group to a place single lumen port-a-cath in all patients upon

diagnosis. Previous reports suggest that ports or internal lines are preferred as the risk of VTE is lesser than external central lines.[10,11] Differences in the incidence of pancreatitis and hyperglycemia between the groups were also clinically relevant. The rate of pancreatitis in the >3,750 IU PEG-ASP group was over 6 times that of the ≤3,750 IU PEG-ASP group, and the rate of hyperglycemia was nearly 4 times as high in the >3,750 IU PEG-ASP group. The difference in hyperglycemia incidence is difficult to explain, as all patients will receive either dexamethasone or prednisone during ALL remission-induction therapy. However, there have been previous reports of increased hyperglycemia incidence in patients who are greater than 10 years old or overweight and these characteristics are more likely to be present in patients receiving PEG-ASP doses >3,750 IU.[12]

There were many lab parameters that were significantly different between groups, including amylase, lipase, total bilirubin, and direct bilirubin. These differences are difficult to interpret as less than half of the patients in the study had a value obtained within four weeks of a PEG-ASP dose, which limits the external validity of the laboratory analysis. These results suggest the need for further evaluation of increased monitoring of specific lab parameters in pediatric patients receiving PEG-ASP.

Limitations of the study include the retrospective single-institution design, which does not allow for causality to be determined. However, the results outlined earlier identify a need for larger trials analyzing adverse effects of PEG-ASP doses greater than 3,750 IU in pediatric patients. Additionally, this study had a small number of patients who received doses greater than 3,750 IU and 95% (23/24) were greater than 10 years old. Older age may be a confounder given that in B-cell ALL, age greater than 10 years at diagnosis is associated with poorer disease outcomes. Given the small number of patients identified, outliers in the sample population also may skew results.

This study illustrates the safety concerns for pediatric patients receiving PEG-ASP >3,750 IU. In order to decrease the risks associated with PEG-ASP in pediatric patients,

increased monitoring for patients receiving doses >3,750 IU is an important first step. Additionally, with the vast majority of pediatric ALL patients treated on national clinical trial protocols, data on adverse effects related to PEG-ASP from large multi-center clinical trials should be collated to determine if increased monitoring, VTE prophylaxis, or dose capping at 3,750 IU should be incorporated into these national protocols. Furthermore, recent data published on the use of asparaginase activity levels for therapeutic drug monitoring and PEG-ASP dose adjustments suggests that incorporation of asparaginase activity levels into upcoming treatment protocols might be one strategy available for reducing PEG-ASP dose-related toxicities in the future.[13,14]

Overall, our study suggests pediatric patients experience serious adverse effects associated with PEG-ASP doses >3,750 IU. The most remarkable toxicity associated with higher doses of PEG-ASP was VTE, which occurred at an alarming rate of greater than 20% in the patients receiving >3,750 IU of PEG-ASP. This data suggests the need for increased monitoring in patients receiving PEG-ASP doses above 3,750 IU, and we hope that it prompts a larger analysis on this issue. Larger multicenter trials are needed to confirm the increased rates of PEG-ASP toxicities that were identified here. Subsequently, clinical trial protocols could be updated with increased monitoring, VTE prophylaxis, and potential dose capping recommendations.

Conflicts of Interest Statement: the authors have no conflicts of interest to disclose

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References

1. Linker CA, Levitt LG, O'Donnell M, Forman SJ, Ries CA. Treatment of adult acute

lymphoblastic leukemia with intensive cyclical chemotherapy: a follow-up report. Blood. 1991;78(11):2814-2822.

2. Clavell LA, Gelber RD, Cohen HJ, et al. Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. N Engl J Med. 1986;315(11):657-663.

3. Wetzler M, Sanford BL, Larson RA. Effective asparagine depletion with pegylated asparaginase results in improved outcomes in adult acute lymphoblastic leukemia: Cancer and Leukemia Group B Study 9511. Blood. 2007;109(10):4164-4167.

4. Curran E, Stock W. How I treat acute lymphoblastic leukemia in older adolescents and young adults. Blood 2015;124(24):3702-3710.

5. Advani AS, Sanford B, Luger S, et al. Frontline treatment of acute lymphoblastic leukemia (ALL) in older adolescents and young adults (AYA) using a pediatric regimen is feasible: toxicity results of the prospective US Intergroup Trial C10403 (Alliance) [abstract]. Blood 2013;122(21). Abstract 3903.

6. Douer D, Aldoss, I, Lunning, A, et al. Pharmacokinetics-based integration of multiple doses of intravenous pegaspargase in a pediatric regimen for adults with newly diagnosed acute lymphocytic leukemia. J Clin Oncol 2014;32(9):905-911.

7. Caruso, V, Lacoviello, L, Castelnuovo, A, et al. Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients. Blood 2006;108(7):2216-2222.

8. Bhojwani, D, Darbandi, R, Pei, D, et al. Severe hypertriglyceridaemia during therapy for childhood acute lymphoblastic leukaemia. Euro J of Cancer 2014;50(15):2685-2694.

9. Pegaspargase package insert. Enzon Pharmaceuticals, Inc. 23 June 2003

10. McLen T, Fisher C, Snively B, et al. Central Venous Lines in Children With lesser Risk Acute Lymphoblastic Leukemia: Optimal Type and Timing of Placement. J Clin Oncol 2005;23(13):3024-3029.

11. Farinasso L, Bertorello N, Garbarini L, et al. Risk factors of central venous lines-related thrombosis in children with acute lymphoblastic leukemia during induction therapy: a prospective study. Leukemia 2007;21:522-556.

12. Lowas, S, Marks, D, Malempati S. Prevalence of transient hyperglycemia during induction chemotherapy for pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer 2009;52(7):814-818.

13. Bleyer A, Asselin B, Koontz S, et al. Clinical application of asparaginase activity levels following treatment with pegasparagase. Pediatr Blood Cancer 2014;62(6):1102-1105.

14. Benitez L, Perissinotti A, Santarossa M, et al. Pharmacokinetic and clinical considerations for monitoring asparaginase activity levels during pegaspargase therapy. Pediatr Blood Cancer 2015;62(6):1115.

TABLE 1 Demographics

	≤3,750 IU PEG-ASP n=159	**>3,750 IU PEG-ASP n=24**	**P-value**
Age at Time of PEG-ASP Dose (years) Mean (SD)	5.5 (3.5)	15.9 (3.2)	<0.0001
BSA at Time of PEG-ASP Dose (m^2) Mean (SD)	0.8 (0.3)	2.0 (0.4)	<0.0001
Sex Male count (%)	89 (56.0)	15 (62.5)	0.66
Obesity at baseline count (%)	1 (0.6)	4 (16.7)	0.001

TABLE 2 PEG-ASP Treatment Related Toxicities

	≤3,750 IU PEG-ASP N=159	**>3,750 IU PEG-ASP N=24**	**P-value**
PE N (%)	1 (0.6)	1 (4.2)	0.25
VTE N (%)	3 (1.9)	5 (20.8)	0.001
Pancreatitis N (%)	3 (1.9)	3 (12.5)	0.03
Hypersensitivity N (%)	12 (7.6)	1 (4.2)	1.00
Hyperglycemia N (%)	10 (6.3)	6 (25.0)	0.009

PE= pulmonary embolism, VTE=venous thromboembolism

TABLE 3 Types of VTE

Patient Identification Number	PEG-ASP Dose (IU)	Date of PEG-ASP Dose Immediately Preceding VTE	Number of Days from PEG-ASP Dose to VTE	Location of VTE
17	5,700	10/27/2014	5	Venous superior sagittal sinus thrombosis
47	2,500	5/3/2013	12	Venous superior sagittal sinus thrombosis
68	4,000	6/24/2013	18	Left branch portal vein thrombosis
69	4,600; 4,775	10/02/2007; 2/25/2008	35; 25	Left basilic vein; Right basilic vein
111	4,050	6/10/2008	17	Parietal venous thrombus
140	4,250	1/27/2010	19	Transverse venous sinus thrombos
176	2,850	10/30/2009	18	Intracardiac superior vena cava thrombus
186	2,800	12/14/2011	12	Cavernous sinus thrombosis

TABLE 4 Effect of PEG-ASP Dosing on Routine Laboratory Values

		≤3,750 IU PEG-ASP (N = 159)	>3,750 IU PEG-ASP (N = 24)	P-va
Amylase (U/L)	N	56	13	0.0
	Mean (sd)	72.5 (110.3)	91.9 (69.0)	
	Median (Min, Max)	38 (30, 639)	67 (30, 267)	
Lipase (U/L)	N	61	17	0.0
	Mean (sd)	272.2 (823.1)	686.4 (1383.2)	
	Median (Min, Max)	72 (18, 6312)	171 (13, 5307)	
Triglycerides (mg/dL)	N	8	5	0.5
	Mean (sd)	1,004.8 (1,413.7)	639.2 (830.2)	
	Median (Min, Max)	270 (70, 3,900)	179 (0, 1,911)	
Platelets (10^9/L)	N	40	17	0.9
	Mean (sd)	23.1 (45.5)	14.6 (2.8)	
	Median (Min, Max)	13.8 (8, 300)	14.1 (10.5, 19.1)	
Fibrinogen	N	27	14	0.1

(mg/dL)	Mean (sd) Median (Min, Max)	178.7 (132.6) 136 (40, 565)	131.4 (107.3) 114 (40, 429)	
D-Dimer (ng/mL)	N Mean (sd) Median (Min, Max)	26 2,012.4 (3276.2) 523.5(150, 14696)	16 1,658.8 (1978.0) 733 (305, 7704)	0.4
T-Bili (g/dL)	N Mean (sd) Median (Min, Max)	156 1.1 (1.5) 0.8 (0.10, 15.1)	24 2.8 (2.5) 2.15 (0.5, 9.8)	<0.0
D-Bili (g/dL)	N Mean (sd) Median (Min, Max)	111 0.4 (1.3) 0.2 (0.1, 11.3)	17 1.9 (2.8) 0.6 (0.1, 9.0)	<0.0
AST (U/L)	N Mean (sd) Median (Min, Max)	149 144.0 (509.7) 67 (20, 6228)	24 162.3 (207.8) 108.5 (12, 889)	0.1
ALT	N	156	24	0.0

(U/L)	Mean (sd) Median (Min, Max)	181.3 (260.6) 117.5 (29, 2712)	310.7 (347.3) 180.5 (25, 1517)	
ALP (U/L)	N Mean (sd) Median (Min, Max)	146 240.0 (108.2) 217.5 (13.0, 680)	24 240.6 (134.7) 216.5 (88, 714)	0.6

TABLE 5 Treatment Delays

Dose	**Treatment Delay (n)**		**Proportion**	**P-value**
	No	**Yes**		
≤ 3,750 IU PEG-ASP	321	124	0.28	0.06
> 3,750 IU PEG-ASP	68	41	0.38	