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Adverse effects of pegaspargase in pediatric patients receiving doses greater than 3,750 IU

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Abstract

Background: Increased toxicities have been identified with higher doses of pegaspargase (PEG-ASP) in adults. This has led to routine use of a dose cap of 3,750 IU for adult acute lymphoblastic leukemia (ALL) patients in most institutions. In pediatric ALL patients, 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 the rates of PEG-ASP-associated adverse events between pediatric patients who received doses greater than 3,750 IU and less than or equal to 3,750 IU.

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 received PEG-ASP doses higher than 3,750 IU and 159 received doses less than or equal to 3,750 IU. The incidence of venous thromboembolism (VTE) was significantly higher for patients in the group that received more than 3,750 IU compared with those who received 3,750 IU or less (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 group that received more than 3,750 IU.

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

KEYWORDS
oncology, pegaspargase, pediatric

1 | 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, multiagent 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 Children's Oncology Group (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

Abbreviations: ALL, acute lymphocytic leukemia; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BSA, body surface area; CALGB, Cancer and Leukemia Group B; COG, Children's Oncology Group; IM, intramuscular; IU, International Units; IV, intravenous; PEG-ASP, pegaspargase; UNC, University of North Carolina; VTE, venous thromboembolism

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.[7–9] 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 more than 3,750 IU of PEG-ASP and 3,750 IU or less 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 the use of doses greater than 3,750 IU 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 more than 3,750 IU of PEG-ASP on treatment delays.

2 | METHODS

We performed a retrospective cohort study of pediatric patients with ALL who received intramuscular (IM) or intravenous (IV) PEG-ASP at the 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 the time of PEG-ASP administration, and date of disease relapse. Obesity and hyperglycemia were determined by the 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.

2.1 | 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 exact test was employed for binary variables. All reported *P* values are two-sided.

3 | RESULTS

3.1 | 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 natural killer cell and T-cell ALL, thus leaving 544 doses from 189 patients for analysis. Among the 189 patients, 24 received PEG-ASP doses greater than 3,750 IU, 159 received doses less than or equal to 3,750 IU, and 6 were excluded from the 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 of more than 3,750 IU were significantly older, had a significantly higher BSA, and had an increased presence of obesity than patients who received doses of less than or equal to 3,750 IU.

3.2 | 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 who received more than 3,750 IU compared with those who received 3,750 IU or less (20.8 vs. 1.9%, respectively; $P = 0.001$). Additionally, patients receiving more than 3,750 IU of PEG-ASP developed pancreatitis more frequently ($P = 0.031$). No difference was noted between groups regarding pulmonary embolism occurrences or the incidence of hypersensitivity reactions. Of the patients who experienced a VTE, only one in each group had a line-associated VTE. Detailed information about the patients who experienced VTE is shown in Table 3.

TABLE 1 Demographics

	≤3,750 IU PEG-ASP n = 159	>3,750 IU PEG-ASP n = 24	*P* value
Age at the time of PEG-ASP dose (years)	5.5 (3.5)	15.9 (3.2)	<0.0001
Mean (SD)			
BSA at the time of PEG-ASP dose (m^2)	0.8 (0.3)	2.0 (0.4)	<0.0001
Mean (SD)			
Sex	89 (56.0)	15 (62.5)	0.66
Male count (%)			
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	1 (0.6)	1 (4.2)	0.25
N (%)			
VTE	3 (1.9)	5 (20.8)	0.001
N (%)			
Pancreatitis	3 (1.9)	3 (12.5)	0.03
N (%)			
Hypersensitivity	12 (7.6)	1 (4.2)	1.00
N (%)			
Hyperglycemia	10 (6.3)	6 (25.0)	0.009
N (%)			

PE, pulmonary embolism.

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

3.3 | Secondary outcomes—effect of dosing on treatment delays

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

4 | 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, multiagent chemotherapy regimens.[1,2] While CALGB caps adult doses of PEG-ASP at 3,750 IU, the COG protocols currently do not cap doses 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

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	Line-associated VTE
17	5,700	10/27/2014	5	Venous superior sagittal sinus thrombosis	No
47	2,500	5/3/2013	12	Venous superior sagittal sinus thrombosis	No
68	4,000	6/24/2013	18	Left branch portal vein thrombosis	No
69	4,600	10/02/2007	35	Left basilic vein	Yes
	4,775	2/25/2008	25	Right basilic vein	
111	4,050	6/10/2008	17	Parietal venous thrombus	No
140	4,250	1/27/2010	19	Transverse venous sinus thrombosis	No
176	2,850	10/30/2009	18	Intracardiac superior vena cava thrombus	Yes
186	2,800	12/14/2011	12	Cavernous sinus thrombosis	No

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* value
Amylase (U/l)	N Mean (SD) Median (min, max)	56 72.5 (110.3) 38 (30, 639)	13 91.9 (69.0) 67 (30, 267)	0.013
Lipase (U/l)	N Mean (SD) Median (min, max)	61 272.2 (823.1) 72 (18, 6312)	17 686.4 (1383.2) 171 (13, 5307)	0.049
Triglycerides (mg/dl) Median (min, max)	N Mean (SD) Median (min, max)	8 1,004.8 (1,413.7) 270 (70, 3,900)	5 639.2 (830.2) 179 (0, 1,911)	0.510
Platelets (10^9 per l)	N Mean (SD) Median (min, max)	40 23.1 (45.5) 13.8 (8, 300)	17 14.6 (2.8) 14.1 (10.5, 19.1)	0.937
Fibrinogen (mg/dl)	N Mean (SD) Median (min, max)	27 178.7 (132.6) 136 (40, 565)	14 131.4 (107.3) 114 (40, 429)	0.196
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)	0.429
Bilirubin - total (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)	<0.0001
Bilirubin - direct (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)	<0.0001
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)	0.169
ALT (U/l)	N Mean (SD) Median (min, max)	156 181.3 (260.6) 117.5 (29, 2712)	24 310.7 (347.3) 180.5 (25, 1517)	0.018
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)	0.690

the patients who received more than 3,750 IU of PEG-ASP experienced VTE compared with less than 2% of the patients who received 3,750 IU or less of 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 group receiving more than 3,750 IU of PEG-ASP was over six times that of the group receiving 3,750 IU or less of PEG-ASP, and the rate of hyperglycemia was nearly four times as high in the group receiving more than 3,750 IU of PEG-ASP. 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 older than 10 years or overweight, and these characteristics are more likely to be present in patients receiving PEG-ASP doses of more than 3,750 IU.[12]

TABLE 5 Treatment delays

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

There were many laboratory parameters that were significantly different between the 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 4 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 laboratory 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 the 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 older than 10 years. Older age may be a confounder given that in B-cell ALL, age older 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 more than 3,750 IU of PEG-ASP. In order to decrease the risks associated with PEG-ASP in pediatric patients, increased monitoring for patients receiving doses higher than 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 multicenter 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 suggest 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 that pediatric patients experience serious adverse effects associated with PEG-ASP doses higher than 3,750 IU. The most remarkable toxicity associated with higher doses of PEG-ASP was VTE, which occurred at an alarming rate of more than 20% in the patients receiving more than 3,750 IU of PEG-ASP. These data suggest 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.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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