Changes in asparaginase exposure and toxicity profiles in obese pediatric acute lymphoblastic leukemia patients

Pegaspargase is an important component in the treatment of acute lymphoblastic leukemia (ALL) but is associated with several toxicities including pancreatitis, hepatotoxicity, and thrombosis which can lead to discontinuation and delays in other chemotherapy.[1] In pediatric and adult patients, obesity has been identified as a risk factor for pegaspargase-associated toxicity.[2,3] In addition to obesity, age >10 years was also identified as a risk factor for toxicity in pediatric patients.[2] To mitigate concerns over toxicity, studies have capped pegaspargase doses at 3,750 IU.[4] In the St. Jude Children's Research Hospital Total XVI trial, a randomized study of pegaspargase doses 2,500 IU/m^2 *versus* 3,500 IU/m^2, higher doses did not increase rates of missed doses or frequency of pancreatitis, thrombosis, osteonecrosis, or hepatotoxicity.[5] This suggested that higher asparaginase doses can be given to pediatric patients without increasing risk of toxicity. To explore the rationale behind capping doses, we retrospectively evaluated whether obesity impacted pegaspargase pharmacokinetics, probability of asparaginase-related toxicities, or treatment efficacy (measured by minimal residual disease [MRD] at day 15, MRD at the end of induction [EOI], and event-free survival [EFS]) within the Total XVI study population during induction and continuation. Our findings demonstrate that pegaspargase clearance was significantly decreased in obese individuals relative to non-obese individuals (5.3%; *P*=0.006). However, pegaspargase exposure, frequency of toxicities, and treatment efficacy were not different between obese and non-obese individuals.

Children (N=598) with newly diagnosed ALL were enrolled in St Jude Children's Research Hospital Total XVI protocol study from September 2007 to March 2017 (ClinicalTrials.gov identifier: NCT00549848). Approved by the institutional review board, consent was obtained from patients and parents/guardians in accordance with the Declaration of Helsinki. Details of this trial have been previously described.[6] Patients less than 2 years old were excluded from this retrospective analysis. Chi-square and exact tests were used to compare the frequency of obese patients by toxicity. Simple and multiple logistic regression models controlling for body mass index (BMI), final risk, age at diagnosis, randomization arm, and immunophenotype were estimated to determine the odds of toxicity given BMI at the beginning of induction or continuation. Toxicities were prospectively graded based on Common Terminology Criteria for Adverse Events, version 3. We subdivided age at 9 years old when evaluating osteonecrosis because individuals 9 years old and older were prospectively screened with magnetic resonance imaging.

Pegaspargase activity data from 564 of 598 patients enrolled in the Total XVI study were available and used to determine individual asparaginase pharmacokinetic parameter estimates.[5] The population pharmacokinetics were summarized previously.[5]

A summary of patients' characteristics stratified by obesity status is shown in Table 1. There were significant differences in age and final risk classification, with a higher percentage of overweight and obese individuals among the older patients (≥10 years old) and those classified as standard or high risk. During induction therapy, clearance of the first pegaspargase dose did not differ based on obesity status (309.4 *vs*. 303.1 *vs*. 299.6 *vs*. 307.1 mL/day/m^2 in normal weight, obese, overweight, and underweight individuals, respectively; *P*>0.1). Additionally, the estimated day 14 asparaginase activity did not differ based on obesity status (1.06 *vs*. 1.1 *vs*. 1.1 *vs*. 1.1 IU/mL in normal weight, obese, overweight, and underweight individuals, respectively; *P*>0.1).

During re-induction therapy asparaginase pharmacokinetics were determined at weeks 7 and 17 of continuation. After controlling for various covariates (therapy timepoint, asparaginase dosage, age, antibody status, adverse events to asparaginase, randomization arm, and final risk) pegaspargase clearance was significantly lower in obese (220.7 *vs*. 233.8 mL/day/m^2 or 5.3%; *P*=0.006) and overweight (222.5 *vs*. 233.8 ml/day/m^2 or 4.5%; *P*=0.005) patients compared to the normal weight group (Table 2). However, pegaspargase exposure was not significantly different in either obese or overweight groups compared to the normal weight group (asparaginase day 14 activity: 1.08 *vs*. 1.12 *vs*. 1.13 IU/mL in normal weight, obese, and overweight individuals, respectively; *P*>0.1 and asparaginase area under the curve: 23.5 *vs*. 23.8 *vs*. 24.4 IU day/mL in normal weight, obese, and overweight individuals, respectively; *P*>0.08).

We did not observe differences in pancreatitis (grade ≥2) relative to BMI classification (Table 3). Specifically, in multivariable analysis, when controlling for risk classification, randomization arm, age and BMI classification, only risk classification was associated with significantly higher odds of pancreatitis (standard/high risk *vs*. low risk odds ratio [OR]=5.55; *P*=0.0088). No differences were observed in hyperbilirubinemia rates (grade ≥3 or ≥4) during remission induction or continuation therapy relative to BMI classification (Table 3). Additionally, there were no significant differences in rates of high alanine aminotransferase (grade ≥3) in remission induction while there was a significantly higher rate in overweight and obese individuals (*P*=0.042) (Table 3) during continuation. In multivariable analysis, only age ≥10 years was significantly associated with grade ≥4 hyperbilirubinemia during continuation (OR=46.6; *P*=0.0049). BMI classification was not significantly associated with increased odds of

Table 1. Patients' characteristics, subdivided by body mass index classification.

Clinical feature, N (%)	Underweight	Normal	Overweight	Obese	*P*
Age at time of first PEG					0.0786
<10 years	19 (4.7)	274 (67.8)	53 (13.1)	58 (14.4)	
≥10 years	8 (5.0)	91 (56.9)	32 (20.0)	29 (18.1)	
Age at diagnosis					0.0471
<10 years	19 (4.7)	277 (68.1)	53 (13.0)	58 (14.3)	
≥10 years	8 (5.1)	88 (56.1)	32 (20.4)	29 (18.5)	
Sex					0.5852
Male	14 (4.2)	210 (63.4)	51 (15.4)	56 (16.9)	
Female	13 (5.6)	155 (66.5)	34 (14.6)	31 (13.3)	
Race					0.342*
White	20 (4.5)	290 (65.8)	71 (16.1)	60 (13.6)	
Black	6 (7.1)	46 (54.8)	9 (10.7)	23 (27.4)	
Other	0 (0.0)	13 (81.3)	2 (12.5)	1 (6.3)	
Ethnicity					0.0630*
Non-Spanish speaking/non-Hispanic	23 (4.6)	334 (66.4)	72 (14.3)	74 (14.7)	
NOS Spanish/Hispanic/Latino	3 (8.3)	15 (41.7)	8 (22.2)	10 (27.8)	
Other	1 (4.5)	13 (59.1)	5 (22.7)	3 (13.6)	
Randomization arm					0.6644
2,500 units/m^2	6 (3.1)	127 (65.1)	31 (15.9)	31 (15.9)	
3,500 units/m^2	14 (7.1)	125 (63.8)	27 (13.8)	30 (15.3)	
Not randomized	7 (4.0)	113 (65.3)	27 (15.6)	26 (15.0)	
Final risk					0.0063
Low	15 (6.0)	177 (70.5)	33 (13.1)	26 (10.4)	
Standard/high	12 (3.8)	188 (60.1)	52 (16.6)	61 (19.5)	
MRD day 15/19					0.2280
<5%	25 (5.2)	317 (65.5)	74 (15.3)	68 (14.0)	
≥5%	2 (2.7)	45 (60.0)	11 (14.7)	17 (22.7)	
MRD end of induction					0.3711
<0.01%	25 (5.1)	314 (64.2)	77 (15.7)	73 (14.9)	
≥0.01%	2 (2.8)	48 (67.6)	7 (9.9)	14 (19.7)	
Allergic reaction to PEG-ASP					1.0*
No	27 (4.8)	362 (64.5)	85 (15.2)	87 (15.5)	
Yes	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	
Antibody status before PEG-ASP					0.6657
Negative	25 (4.8)	336 (64.5)	77 (14.8)	83 (15.9)	
Positive	2 (4.7)	29 (67.4)	8 (18.6)	4 (9.3)	

P value: χ^2 test except for *exact χ^2 test (Fisher exact test). PEG: polyethylene glycol; NOS: not specified; MRD: minimal residual disease; PEG-ASP: pegaspargase.

hyperbilirubinemia or high alanine aminotransferase levels when controlling for risk group, randomization arm, and age. During continuation therapy, the rate of osteonecrosis did not differ significantly between overweight or obese individuals and normal individuals: 13 of 202 (6.4%) *versus* 21 of 336 (6.3%), respectively (*P*=0.93) (Table 3). The odds of osteonecrosis (grade ≥2) were higher in standard/high-risk individuals than in low-risk ones (OR=4.971; *P*=0.0011) and individuals ≥9 years old compared to those <9 years old (OR=16.5; *P*<0.0001). However, controlling for these factors, BMI classification was not significantly associated with osteonecrosis.

Rate of grade ≥3 thrombosis did not differ significantly by obesity status during either remission induction or continuation therapy (Table 3). Instead, thrombosis (grade ≥3) was more common in T-cell ALL than in B-cell ALL during remission induction (OR=3.438; *P*=0.0239) and in individuals ≥10 years old than in those <10 years old during continuation therapy (OR=6.461; *P*<0.0001). However, controlling for these factors, BMI classification was not significantly associated with thrombosis.

We observed that the cumulative frequency of pegaspargase doses and the percentage of protocol-defined pegaspargase doses given were not significantly different between obese and normal weight individuals (*P*=0.11 and *P*=0.59, respectively). A higher percentage of individuals ≥10 years old were

Table 2. Mixed effects model of the effect of body mass index on asparaginase clearance (mL/day/m^2) during re-induction therapy, accounting for covariates.

Main effect	Estimate (95% CI)	*P*
Intercept, mL/day/m^2	233.18 (225.33 to 241.02)	<0.0001
BMI classification		
Obese	-12.44 (-21.25 to -3.64)	0.0062
Overweight	-10.64 (-17.87 to -3.41)	0.0045
Underweight	1.55 (-9.80 to 12.91)	0.7860
Normal	Reference	
Gender		
Female	-0.22 (-5.65 to 5.22)	0.9381
Male	Reference	
Timepoint		
Week 17	20.02 (15.54 to 24.50)	<0.0001
Week 7	Reference	
Actual dose, IU/m^2	0.01 (0.00 to 0.01)	0.0066
Age	-1.84 (-3.53 to -0.14)	0.0338
Final risk/dose randomization arm		
Low 3,500 IU/m^2	54.56 (44.78 to 64.34)	<0.0001
Standard/high 2,500 IU/m^2	108.84 (101.54 to 116.15)	<0.0001
Standard/high 3,500 IU/m^2	207.95 (197.11 to 218.79)	<0.0001
Low 2,500 IU/m^2	Reference	
Antibody status before PEG-ASP		
Positive	24.05 (13.70 to 34.39)	<0.0001
Negative	Reference	
Adverse events		
Yes	56.46 (-29.89 to 142.81)	0.1065
No	Reference	

95% CI: 95% confidence interval; BMI: body mass index; PEG-ASP: pegaspargase.

MRD positive at day 15 (25.8% *vs*. 8.9%; *P*=0.022) and at the EOI (17.6% *vs*. 10.4%; *P*=0.022) as compared to those <10 years old. Controlling for age, obesity status was not associated with differences in either day 15 or EOI MRD status.

The 10-year EFS rate was higher in individuals <10 years old than in those older (10-year EFS: 92.8%, 95% confidence interval [95% CI]: 89.6%-95.1% *vs*. 79.1% [95% CI: 71.9%-84.7%], respectively; *P*<0.0001) and in low-risk individuals compared to standard/high-risk ones (10-year EFS: 96.7% [95% CI: 93.4%-98.3%] *vs*. 82.7% [95% CI: 77.8%-86.6%]; *P*<0.0001). However, EFS was not significantly different based on obesity status when controlling for age and risk status.

This study revealed a significant decrease in pegaspargase clearance in obese individuals compared to non-obese individuals (5.3%). We are unable to determine a reason to explain this difference in clearance for obese individuals. This alteration in pharmacokinetics did not result in a clinically significant increase in pegaspargase exposure, efficacy or toxicity, as evidenced by the similar activity and absence of a rise in pegaspargase-related toxicities in the obese group. Additionally, obesity status was not associated with a difference in day 15 MRD, EOI MRD, or EFS.

Asparaginase-related toxicities can potentially delay or truncate asparaginase therapy, which has been linked to lower EFS rates.[1,7] Our previous analysis demonstrated no disparity in the number of pegaspargase doses or treatment outcomes between those receiving 2,500 *vs*. 3,500 IU/m^2.[5,6] In our current analysis we have also shown no decline in cumulative asparaginase dosing or EFS in obese individuals compared to their normal weight counterparts.

Several adult studies have shown a higher BMI associated with hyperbilirubinemia, more missed treatment, and lower rates of complete remission.[3,9] Additionally, in adults, a dose-dependent relationship has been found between pegaspargase dose and rates of grade ≥3 toxicities, particularly in individuals with a BMI ≥25 kg/m^2 receiving pegaspargase doses >1,000 IU/m^2 compared to those receiving doses <1,000 IU/m^2.[10]

Several pediatric studies have also reported higher rates of hyperbilirubinemia, pancreatitis, and thrombosis in obese compared to non-obese pediatric patients, although in most cases, this observation was based on the overall rates of toxicities rather than specifically related to asparaginase treatment.[2,8,11,12] It has also been shown that pediatric patients who received more than 3,750 IU of pegaspargase (with 16.7% being obese) had higher incidences of venous thromboembolism, pancreatitis, and hyperglycemia.[13] However, Kloos *et al*. found no statistically significant correlation

Table 3. Asparaginase toxicities by body mass index category.

Toxicity	Yes, N (%)	No, N (%)	*P**
Pancreatitis (grade ≥2) during induction			
Underweight	0 (0.0)	29 (100.0)	0.168
Normal	8 (2.3)	346 (97.7)	
Overweight	5 (6.3)	74 (93.7)	
Obese	1 (1.2)	85 (98.8)	
Pancreatitis (grade ≥2) during continuation			
Underweight	2 (11.8)	15 (88.2)	0.6402
Normal	22 (6.7)	307 (93.3)	
Overweight	10 (9.1)	100 (90.9)	
Obese	9 (9.8)	83 (90.2)	
Hyperbilirubinemia (grade ≥3) during induction			
Underweight	0 (0.0)	29 (100.0)	0.2599
Normal	10 (2.8)	344 (97.2)	
Overweight	3 (3.8)	76 (96.2)	
Obese	6 (7.0)	80 (93.0)	
Hyperbilirubinemia (grade ≥3) during continuation			
Underweight	0 (0.0)	17 (100.0)	0.5188
Normal	8 (2.4)	321 (97.6)	
Overweight	5 (4.5)	105 (95.5)	
Obese	4 (4.3)	88 (95.7)	
Hyperbilirubinemia (grade ≥4) during continuation			
Underweight	0 (0.0)	17 (100.0)	0.5253
Normal	2 (0.6)	327 (99.4)	
Overweight	2 (1.8)	108 (98.2)	
Obese	1 (1.1)	91 (98.9)	
High alanine transaminase (grade ≥3) during induction			
Underweight	1 (3.5)	28 (96.5)	0.4826
Normal	16 (4.5)	338 (95.5)	
Overweight	1 (1.3)	78 (98.7)	
Obese	5 (5.8)	81 (94.2)	
High alanine transaminase (grade ≥3) during continuation			
Underweight	0 (0.0)	17 (100.0)	0.0422
Normal	11 (3.3)	318 (96.7)	
Overweight	11 (10.0)	99 (90.0)	
Obese	6 (6.5)	86 (93.5)	
Osteonecrosis (grade ≥2) during continuation			
Underweight	1 (5.9)	16 (94.1)	0.9340
Normal	20 (6.1)	309 (93.9)	
Overweight	6 (5.5)	104 (94.5)	
Obese	7 (7.6)	85 (92.4)	
Thrombosis (grade ≥3) toxicity during induction			
Underweight	2 (6.9)	27 (93.1)	0.4346
Normal	10 (2.8)	344 (97.2)	
Overweight	1 (1.3)	78 (98.7)	
Obese	2 (2.3)	84 (97.7)	
Thrombosis (grade ≥3) toxicity during continuation			
Underweight	1 (5.9)	16 (94.1)	0.3930
Normal	13 (4.0)	316 (96.0)	
Overweight	6 (5.5)	104 (94.5)	
Obese	7 (7.6)	85 (92.4)	

Toxicity was prospectively graded based on Common Terminology Criteria for Adverse Events, version 3.0. **P* value determined by the exact test.

between pancreatitis, central neurotoxicity, thrombosis, triglyceride levels and asparaginase levels.[14] Dharia *et al.* reported a higher odds ratio of pancreatitis, thrombosis and hyperbilirubinemia with pegaspargase in overweight or obese patients, although this was not statistically significant, aligning with our results.[15]

Based on results of this study in patients receiving treatment on the Total XVI protocol, we do not recommend capping pegaspargase dose. Instead, we advocate monitoring both asparaginase activity and related toxicities and considering adjustments of dose and/or schedule if either the predicted activity at day 14 falls outside a predefined range (e.g., 0.1-1 IU/mL) or if toxicities are observed.

In conclusion, our previous study showed no difference in toxicity between pegaspargase doses of 2,500 and 3,500 IU/m^2 and the current study showed no difference in toxicity or efficacy based on obesity status. Therefore, our study does not support capping asparaginase doses in treatment regimens similar to our Total XVI protocol.

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Contributions

JCP, EA and CC organized and analyzed the data. SJ, C-HP, HI, SEK and CC developed the protocol. SJ, CHP, HI and SEK recruited patients. JCP and HDS interpreted the data and wrote the manuscript.

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Data-sharing statement

No data will be shared.

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