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

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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 3750 IU.[4] In the St. Jude Children's Research Hospital Total XVI trial, a randomized study of pegaspargase doses 2500 IU/m^2 versus 3500 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 in 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 two years old were excluded in this retrospective analysis. Chi-square and exact test were used to compare the frequency of obese patients by toxicity. Simple and multiple logistic regression models controlling for 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 CTCAE version 3. We subdivided age at 9 years old when evaluating osteonecrosis because individuals 9 years old and older were prospectively screened with MRI.

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 patient 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 ($p>0.1$; 309.4 vs 303.1 vs 299.6 vs 307.1 ml/day/m^2 in normal weight, obese, overweight, and underweight individuals). Additionally, the estimated day 14 asparaginase activity did not differ based on obesity status ($p>0.1$; 1.06 vs 1.1 vs 1.1 vs 1.1 IU/mL in normal weight, obese, overweight, and underweight individuals).

During re-induction therapy asparaginase pharmacokinetics were determined at weeks 7 and 17 of continuation. After controlling for various covariates (therapy time point, asparaginase dosage, age, antibody status, adverse events to asparaginase, randomization arm, and final risk) pegaspargase clearance was significantly lower in obese (p=0.006; 220.7 vs 233.8 ml/day/m^2 or 5.3%) and overweight (p=0.005; 222.5 vs 233.8 ml/day/m^2 or 4.5%) 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; p>0.1 and asparaginase AUC: 23.5 vs 23.8 vs 24.4 IU day/mL; p>0.08 in normal weight, obese, and overweight individuals).

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 showed significantly higher odds of pancreatitis (SHR vs LR 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 ALT (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 hyperbilirubinemia or high ALT 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%) (p=0.93; **Table 3**). The odds of osteonecrosis (grade ≥ 2) were higher in SHR vs LR individuals (OR=4.971, p=0.0011) and individuals ≥9 vs <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 significantly differ by obesity status during either remission induction or continuation therapy (**Table 3**). Instead, thrombosis (grade ≥ 3) occurrence was higher in T-cell ALL compared to B-cell ALL during remission induction (OR=3.438, p=0.0239) and in individuals ≥10 vs. <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 older than 10 years old were 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 less than 10 years old. Controlling for age, obesity status was not associated with differences in either day 15 or EOI MRD.

Event-free survival (EFS) was higher in individuals younger than 10 years old (10-year EFS: 92.8% [95% CI: 89.6%, 95.1%] vs 79.1% [95% CI: 71.9%, 84.7%]; p<0.0001) and in LR vs SHR individuals (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.[1,7] Our previous analysis demonstrated no disparity in the number of pegaspargase doses or treatment outcomes between those receiving 2500 vs 3500 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 (CR).[3, 9] Additionally, in adults, there has been a dose-dependent relationship between pegaspargase dose and rates of grade ≥3 toxicities, particularly in individuals with BMI ≥ 25 kg/m^2 receiving pegaspargase doses > 1000 IU/m^2 compared to those receiving doses < 1000 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 3750 IU of pegaspargase (with 16.7% being obese) had higher incidences of venous thromboembolism, pancreatitis, and hyperglycemia.[13] However, Kloos et al. observed no statistically significant correlation 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, though this was not statistically significant, aligning with our results.[15]

Based on results of this study in patients receiving treatment on Total XVI protocol, we do not recommend capping pegaspargase dose. Instead, we advocate monitoring both asparaginase activity and related toxicities and consider adjusting 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 2500 and 3500 IU/m^2 and 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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Tables

Table 1: Patient Characteristics, n (%), subdivided by obesity classification.

Clinical feature	Underweight	Normal	Overweight	Obese	P-value
Age at time of first PEG					0.0786
<10 years	19(4.7)	274(67.8)	53(13.1)	58(14.4)	
>=10 year	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 year	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
2500 units/m^2	6(3.1)	127(65.1)	31(15.9)	31(15.9)	
3500 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 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)	
EOI MRD					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 pre 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: chi-square test except for * exact chi-square test (Fisher's Exact Test)

Abbreviations: PEG, polyethylene glycol; NOS, not specified; MRD, minimal residual disease; PEG-ASP. pegaspargase

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-value
Intercept	(ml/day/m^2)	233.18 (225.33, 241.02)	**<.0001**
BMI	Obese	-12.44 (-21.25, -3.64)	**0.0062**
	Overweight	-10.64 (-17.87, -3.41)	**0.0045**
	Underweight	1.55 (-9.80, 12.91)	0.7860
	Normal	REF	
Gender	Female	-0.22 (-5.65, 5.22)	0.9381
	Male	REF	
Time point	Week 17	20.02 (15.54, 24.50)	**<.0001**
	Week 7	REF	
Actual dose	Actual dose (IU/m^2)	0.01 (0.00, 0.01)	**0.0066**
Age	Age (years)	-1.84 (-3.53, -0.14)	**0.0338**
Random Arm / Final risk	Low 3500 IU/m^2	54.56 (44.78, 64.34)	**<.0001**
	Std/High 2500 IU/m^2	108.84 (101.54, 116.15)	**<.0001**
	Std/High 3500 IU/m^2	207.95 (197.11, 218.79)	**<.0001**
	Low 2500 IU/m^2	REF	
Antibody status pre PEG	Positive	24.05 (13.70, 34.39)	**<.0001**
	Negative	REF	
Adverse event	Yes	56.46 (-29.89, 142.81)	0.1065
	No	REF	

Abbreviations: BMI, body mass index; PEG, polyethylene glycol; Std, standard

Table 3: Asparaginase Toxicities by Body Mass Index Category, n (%). P-value: exact test

	Yes	No	P-value*
Pancreatitis (Grade ≥ 2) Toxicity 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) Toxicity 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 ALT (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 ALT (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) Toxicity 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 CTCAE version 3.0; Abbreviation: ALT, alanine transaminase