Pegaspargase Dose Capping in Obese Pediatric/Adolescent Patients with Acute Lymphoblastic Leukemia and Lymphoma: A Single Institution Study

Erin Kneeskern, MS4; Dillon McKinley, MS4; Kelly Faulk, MD; Vida Alami, BA; Dexiang Gao, PhD, MS
University of Colorado Anschutz Medical Campus, Children's Hospital Colorado Center for Cancer and Blood Disorders, Aurora, CO
Authors have no financial relationships to disclose

Background and Aim

Asparaginase in pediatric acute lymphoblastic leukemia (ALL)/lymphoblastic lymphoma (LLy):

- Pediatric ALL/LLy survival rates have dramatically improved over the past several decades and now exceed 90%[1]
- Asparaginase is a cornerstone of therapy that improves remission and survival rates[2]. Acts via depletion of asparagine, inducing apoptosis in leukemia cells[3,4]. Associated with significant toxicities including hypersensitivity, pancreatitis, thrombosis, encephalopathy, and metabolic disturbances[2,5-8]
- Toxicity is dose-dependent, with a higher risk in older and obese patients[6,11]

Dosing considerations:

- Adult protocols cap asparaginase dose at 3750 IU to limit toxicity[12]
- Historically, pediatric protocols dose by body surface area at 2500 IU/m², often exceeding doses in adult counterparts[13]

Dose-Capping Protocol:

- In October 2022, Children's Hospital Colorado instituted a dose capping protocol in which patients ≥ 10 years old and with body mass index (BMI) ≥ 30 at diagnosis were capped at 3750 IU
- Serum asparaginase activity (SAA) levels were obtained per institutional standard at days 0 (peak), 7 (when able) and 14

Project Aim: Assess feasibility and evaluate the impact of an asparaginase dose capping protocol at a pediatric oncology institution

Methods

Study Design

- Retrospective Cohort
  - Diagnosed with ALL/LLy between 2011-2021
  - BMI ≥ 30, Age ≥ 10 years at diagnosis
  - Asparaginase dosing at 2500 IU/m²
- Prospective Cohort
  - Diagnosed with ALL/LLy after October 2022
  - BMI ≥ 30, Age ≥ 10 years at diagnosis
  - Asparaginase dosing capped at 3750 IU

Data Collection

- Patient demographics, diagnosis, asparaginase doses, toxicities (start of induction to start of maintenance), unscheduled admissions, treatment delays (>2 weeks) and outcomes
- Asparaginase-Associated Adverse Events (AEs, per CTCAE v5)
  - Allergic reaction/anaphylaxis
  - Thrombosis, coagulopathy
  - Hyperglycemia, hypertriglyceridemia, hyperbilirubinemia, transaminitis, pancreatitis
  - Infections
  - Seizures, encephalopathy

Patient Characteristics

Patient Characteristic	Retrospective Cohort (n=25)	Prospective Dose Capped Cohort (n=3)
Age at Diagnosis (median, years)	15 (range 11-21)	13 (range 13-17)
Gender	Male- 14(56%) Female- 11 (44%)	Male- 3 (100%) Female- 0 (0%)
Absolute BMI at Diagnosis (median, kg/m2)	34.3 (range 29.9-51.0)	33.77 (range 33.36-35.85)
Race and Ethnicity	Hispanic, Any Race- 10 (40%) White and Not Hispanic -10 (40%) Black or African American, Not Hispanic or Unknown Ethnicity- 3 (12%) Multiple and Not Hispanic- 1 (4%) Unknown and Not Hispanic- 1 (4%)	Hispanic, Any Race- 2 (67%) White and Not Hispanic -1(33%)
Primary Diagnosis	B-Cell Acute Lymphoblastic Leukemia (B-ALL)- 20 (80%) T-ALL or T-LLy- 3 (12%) Philadelphia Positive B-cell Acute Lymphoblastic Leukemia (Ph+ B-ALL)- 2 (8%)	B-Cell Acute Lymphoblastic Leukemia (B-ALL)- 3 (100%)
Number of Doses of Asparaginase Per Patient (median)	4 (range 1-8)	4.5 (range 2-7)
Asparaginase Dose (median, IU)	5,225 (range 2,790-6,675)	3750

Table 1: Baseline characteristics of retrospective and prospective cohorts

Results

Asparaginase-Associated Toxicities

Adverse Event Category	Total Events in Retrospective Cohort	Total Events in Prospective Cohort
Allergic Reaction	8	1
Coagulopathy	1	0
Infectious	34	2
Liver/GI	26	9
Neruologic	2	0
Thrombotic	5	1

Table 2: Total asparaginase-related toxicities by category in each cohort.

Treatment Impact Category	Affected Patients in Retrospective Cohort	Affected Patients in Prospective Cohort
Unscheduled Admissions	23/25 (92%)	3/3 (100%)
PICU Admissions	4/25 (16%)	0/3 (0%)
Treatment Delay > 2 weeks	9/25 (36%)	2/3 (67%)

Table 3: Proportion of patients enduring treatment delays due to asparaginase-associated toxicities

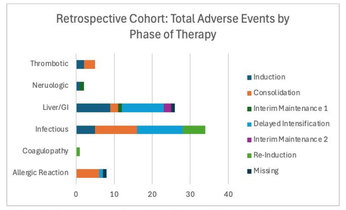

Figure 1. Total Adverse Events by Phase of Therapy in the Retrospective Cohort

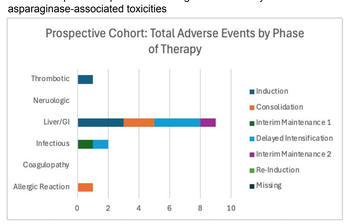

Figure 2. Total Adverse Events by Phase of Therapy in the Prospective Cohort

Event-Free Survival (EFS) and Overall Survival (OS) of Retrospective Cohort

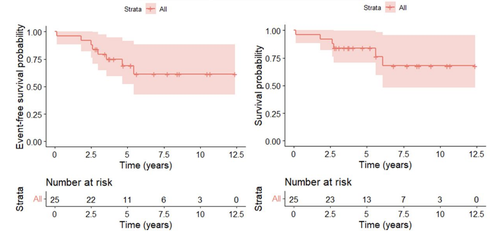

Figure 3. With a median follow-up time of 5.6 years, 5-year EFS is 69.14% (95% CI, 52.17% to 91.61%) and the 5-year OS is 84% (95% CI, 70.79% to 99.67%)

Serum Asparaginase Activity (SAA)

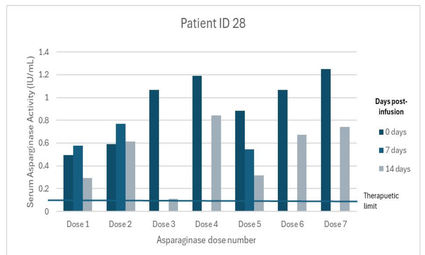

Figure 4. SAA Levels of patient ID 28 per pegaspargase infusion.

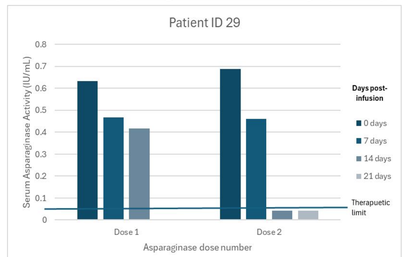

Figure 5. SAA levels of patient ID 29 per pegaspargase infusion.

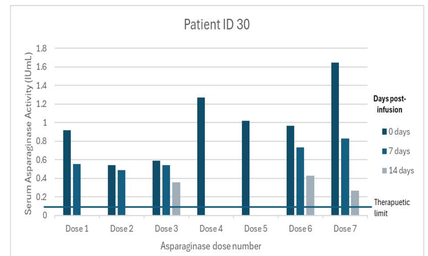

Figure 6. SAA levels of patient ID 30 per pegaspargase infusion. Day 7 and 14 SAA levels not resulted for Doses 4 and 5 due to presence of persistent lipemia.

Discussion and Impact

Asparaginase-Associated Toxicities

- Retrospective Cohort
  - N=24/25 (96%) patients experienced *at least* one asparaginase-associated toxicity with infectious (n=34 AE's), liver/GI (n=26 AE's), and hypersensitivity reaction (n=8 AE's) events as the most common; 76 total toxicities were identified.
  - N=23/25 (92%) patients experienced *at least* one unscheduled admission, with N=4 (16%) requiring PICU admission at least once, and N=9 (36%) requiring treatment delay > 2 weeks due to their toxicities
- Prospective Cohort
  - N = 3/3 (100%) patients experienced *at least* one asparaginase-associated toxicity with Liver/GI (n=9 AE's) and Infectious (n=2 AE's) events as the most common; 13 total toxicities were identified.
  - N=3/3 (100%) patients experience *at least* one unscheduled admission, with N = 0 (0%) requiring PICU admission, and N=2/3 (67%) requiring treatment delay > 2 weeks due to their toxicities

EFS and OS of Retrospective Cohort[1]

- 5-year EFS of 69.14% is less than reported EFS rates of ~85%, however this cohort is comprised entirely of high-risk patients that may explain this difference
- 5-year OS of 84% is consistent with reported OS rates of ~90%

Serum Asparaginase Activity (SAA)

- SAA levels at day 7 and/or 14 achieved therapeutic levels in n=15/16 doses across 3 dose-capped patients
- Patient ID 29 was found to have undetectable SAA levels on day 7 and 14 following dose 2 and was un-capped for their third dose. The patient experienced a hypersensitivity reaction with Dose 3, suggesting the development of neutralizing antibodies with Dose 2 leading to the rapid clearance that was seen with the associated SAA draws.

Impact: This study demonstrates that dose-capping asparaginase in higher risk ALL/LLy patients (age > 10, BMI > 30) is feasible, with 15/16 doses achieving therapeutic SAA levels and characterized frequency and types of asparaginase-associated adverse events in a historic cohort of higher risk pediatric and adolescent ALL/LLy patients.

Limitations and Future Directions

Limitations:

- Small sample size, with only 3 patients treated on the prospective dose-capped cohort thus far
- Limited to patients treated at Children's Hospital Colorado, with demographic limitations
  - 80% of patients were White or Hispanic
- Heterogeneity in the cohort (e.g., Ph+ vs. Ph- ALL) may have influenced treatment regimens and toxicity outcomes
- Observational nature of the study may introduce confounding variables, such as institution-specific protocols (e.g., central line exchanges), affecting toxicity rates (e.g., catheter-related infections)
- Asparaginase-associated toxicities are likely multifactorial and not solely due to asparaginase (e.g., hyperglycemia likely a result of corticosteroids and asparaginase)

Future Directions:

- Enrollment is ongoing for the prospective dose-capping protocol
- Will analyze differences in asparaginase associated toxicities and long term outcomes between cohorts as more patients complete therapy with dose-capped protocol
- Consideration to include patients from other pediatric institutions to increase the power and generalizability of the study

References

[1] Pui CH, Evans WE. A 50-year journey to cure childhood acute lymphoblastic leukemia. *Semin Hematol*. 2013;50(3):185-196. doi:10.1053/j.seminhematol.2013.06.007
[2] Buhtoiarov IN, Zembillas AS. Excessive toxicities of pegylated asparaginase in pediatric acute lymphoblastic leukemia patients with high body surface area: A call for action. *Pediatr Blood Cancer*. 2021;68(3):e28743. doi:10.1002/pbc.28743
[3] Müller, H. J., and J. Boos. "Use of L-asparaginase in childhood ALL." Critical reviews in oncology/hematology 28.2 (1998): 97-113
[4] Juluri KR, Siu C, Cassaday RD. Asparaginase in the Treatment of Acute Lymphoblastic Leukemia in Adults: Current Evidence and Place in Therapy. *Blood Lymphat Cancer*. 2022;12:55-79. Published 2022 May 30. doi:10.2147/BLCTT.S342052
[5] Hijiya N, van der Sluis IM. Asparaginase-associated toxicity in children with acute lymphoblastic leukemia. Leuk Lymphoma. 2016;57(4):748-757. doi:10.3109/10428194.2015.1101098
[6] Bender C, Maese L, Carter-Febres M, Verma A. Clinical Utility of Pegaspargase in Children, Adolescents and Young Adult Patients with Acute Lymphoblastic Leukemia: A Review. Blood Lymphat Cancer. 2021;11:25-40. Published 2021 Apr 19. doi:10.2147/BLCTT.S245210
[7] Henriksen, Louise Tram, et al. "PEG-asparaginase allergy in children with acute lymphoblastic leukemia in the NOPHO ALL2008 protocol." Pediatric blood & cancer 62.3 (2015): 427-433.
[8] Alvarez, Ofelia A., and Grenith Zimmerman. "Pegaspargase–induced pancreatitis." Medical and Pediatric Oncology: The Official Journal of SIOP—International Society of Pediatric Oncology (Société Internationale d'Oncologie Pédiatrique 34.3 (2000): 200-205.
[9] Gupta S, Wang C, Raetz EA, et al. Impact of Asparaginase Discontinuation on Outcome in Childhood Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group. J Clin Oncol. 2020;38(17):1897-1905. doi:10.1200/JCO.19.03024
[10] Gottschalk Højfeldt S, Grell K, Abrahamsson J, et al. Relapse risk following truncation of pegylated asparaginase in childhood acute lymphoblastic leukemia. Blood. 2021;137(17):2373-2382. doi:10.1182/blood.2020006583
[11] Lynggaard, Line Stensig, et al. "Asparaginase enzyme activity levels and toxicity in childhood acute lymphoblastic leukemia: a NOPHO ALL2008 study." Blood advances 6.1 (2022): 138-147.
[12] Cassaday RD. Asparaginase dosing for obese patients with acute lymphoblastic leukemia and factors that contribute to outcomes. Best Pract Res Clin Haematol. 2023;36(4):101519. doi:10.1016/j.beha.2023.101519
[13] Lebovic, Rachel, et al. "Adverse effects of pegaspargase in pediatric patients receiving doses greater than 3,750 IU." Pediatric Blood & Cancer 64.10 (2017): e26555.