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

Purpose/Objectives: Asparaginase is an essential component of therapy for acute lymphoblastic leukemia (ALL) and lymphoma (LLy), though it carries significant toxicity risk. Older and/or obese children have demonstrated an increased risk of asparaginase-associated toxicities[1]. While asparaginase dosing is capped in adults to limit toxicities, this approach is not routinely utilized in pediatric patients, where doses are based on body surface area[2]. A single institution prospective quality improvement study assessed the feasibility of asparaginase dose capping in obese pediatric and adolescent patients. Further, a retrospective cohort study was performed to provide historic estimates for the incidence of asparaginase-associated adverse events (AEs), therapeutic impact (unscheduled admissions and treatment delays), and outcomes. (109 words)

Design/Methods: In October 2022, Children's Hospital Colorado implemented a protocol to cap asparaginase doses at 3750 IU for ALL/LLy patients aged ≥ 10 years with BMI ≥30 at diagnosis. A retrospective cohort included 25 patients meeting these criteria, diagnosed between 2011 and 2021. Data on demographics, treatment, toxicity, and outcomes were analyzed to establish a historic control. The prospective cohort included three patients diagnosed after October 2022, all of whom received the dose cap. Therapeutic drug monitoring using serum asparaginase activity (SAA) levels was obtained in the prospective cohort. The incidence of asparaginase-associated AEs and rates of unscheduled admissions and pediatric intensive care unit (PICU) admissions were described in each cohort. (110 words)

Results: 24/25 patients in the retrospective cohort experienced at least one asparaginase-associated AE. The most common toxicities included infectious (n=34 AEs), liver/gastrointestinal (n=26 AEs) and anaphylaxis/hypersensitivity (n=8 AEs). 23/25 patients had unscheduled admissions; four were admitted to the PICU at least once. Nine patients experienced a treatment delay >2 weeks. In the prospective cohort, all three patients had unscheduled admissions, though no patients required PICU admission. Liver/GI toxicity was most common (n=9 AEs), followed by infectious (n=2 AEs), anaphylaxis/hypersensitivity (n=1 AE) and thrombotic event (n=1 AE). Two patients experienced treatment delay >2 weeks. SAA levels achieved the therapeutic threshold (≥0.1 at 14 days post-dose) in n=15/16 doses across the three patients. With a median follow-up of 5.6 years, the 5-year event-free survival was 69% (95% CI, 52.17-91.61%) and overall survival was 84% (95% CI, 70.79%-99.67%) for the retrospective cohort; survival analysis is not feasible for the prospective cohort due to small sample size and short follow-up. (177 words)

Discussion/Conclusions: 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. One dose failed to reach therapeutic levels likely due to neutralizing antibodies from a hypersensitivity reaction. Further enrollment is needed to assess toxicity rates and outcomes between cohorts. (54 words)

[1] Meenan, Chelsea K., et al. "Obesity in pediatric patients with acute lymphoblastic leukemia increases the risk of adverse events during pre-maintenance chemotherapy." Pediatric blood & cancer 66.2 (2019): e27515.

[2] 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