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Original Article

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Evaluating Asparaginase Toxicity in Hispanic Patients With Acute Lymphoblastic Leukemia in a Large Safety-Net Hospital

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is relatively rare in adults with poor rates of long-term remission. Chemotherapy protocols for adults have been adapted from pediatric protocols, including asparaginase. While asparaginase has shown significant efficacy in pediatric patients, its use in adults is limited due to hepatotoxicity, pancreatitis, and thrombosis. This study seeks to review the toxicity profile in Hispanic adults at a large safety-net hospital.

Methods: We performed a chart review of patients over the age of 18 with ALL treated with asparaginase. Data were collected between the years of 2015 and 2021 and included demographics, laboratory parameters on diagnosis, treatment details, and information on complications related to treatment.

Results: A total of 14 Hispanic patients diagnosed with ALL and treated with asparaginase from January 2016 to November 2021 were included in this study. Our patient population had an average body mass index (BMI) of 34 (standard deviation (SD) 8.7), with the majority (64%) classified as obese (BMI ≥ 30). Twelve patients (86%) were Philadelphia chromosome negative. The incidence of grade 3 to 4 hyperbilirubinemia (> 3 times the upper limit of normal (ULN) for serum bilirubin) was six out of 14 patients (43%). The incidence of grade 3 to 4 transaminitis (> 5 times the ULN for alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels) was 13 out of 14 patients (93%). Thrombosis occurred in six out of 14 patients (43%), with one patient experiencing disseminated intravascular coagulation (DIC).

Conclusions: Our cohort of Hispanic adults experienced transaminitis and hyperbilirubinemia at a high rate (93%). The higher incidence noted in our patients with class III obesity is in line with recent expert recommendations for dose reduction of asparaginase in patients with severe obesity. Our study suggests that our Hispanic population is at higher risk for developing hepatotoxicity after asparaginase use, though this could also be related to the high prevalence of obesity in our population. This is important for future care in selecting candidates for asparaginase therapy including those who may be at higher risk for adverse events.

Keywords: Asparaginase; Toxicity; Acute lymphoblastic leukemia; Hispanic; Safety-net

Introduction

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy of lymphoid progenitor cells. ALL is the most common childhood malignancy [1], with over 80% of ALL cases occurring in children [2]. In contrast, ALL is relatively rare in adults, accounting for less than 1% of adult cancer diagnoses in the USA [3]. Whereas ALL cases have a favorable cure rate of over 80% among children [4], only about 30-40% of adult ALL patients achieve long-term remission [2]. This age-related discrepancy has inspired a decades-long shift toward incorporating high-intensity pediatric ALL protocols into the management of adult patients, with studies demonstrating subsequent improvements in adult ALL outcomes [5, 6].

Asparaginase has been a staple component of induction therapy in pediatric ALL patients since the 1960s [7]. Asparaginase catalyzes the hydrolysis of asparagine. Since ALL cells rely on serum asparagine to sustain proliferation, depletion of extracellular asparagine leads to inhibition of cancer cell growth and eventual apoptosis [8]. Although asparaginase has shown significant efficacy when used in combination with chemotherapy in children, this medication is not used ubiquitously in the adult ALL population. This can be attributed to its unique toxicity profile in adults, with serious adverse effects including hepatotoxicity, thrombosis, pancreatitis, and hypersensitivity reactions [9]. Still, a number of prospective studies have demonstrated improved clinical outcomes with the use of asparaginase in adults with ALL [10-12], especially when utilizing long-acting pegylated asparaginase (PEG-asparaginase) over its native form. These findings have prompted further investigation and adoption of the practice.

Our study aims to review the toxicity profile of asparaginase in Hispanic patients at a large safety-net hospital. Children, adolescents and young adults (AYA) of Hispanic ethnicity have the highest incidence of ALL [13], and Hispanic adults have higher rates of B-ALL compared with non-Hispanic White adults [14].

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These disparities persist in the incidence of treatment-related toxicity; Hispanic ALL patients have been found to develop hepatotoxicity at an increased rate compared to other ethnicities [15]. Established risk factors for asparaginase toxicity include increased age, obesity, and higher treatment dosages [16]. We suspect that our cohort will have a higher incidence of various toxicities due to a higher prevalence of obesity and liver disease in this patient population.

Materials and Methods

Patient data

Harbor-UCLA Medical Center Institutional Review Board (IRB) approval was obtained (IRB number 18CR-32572-01), and the study was performed in accordance with the ethical standards described in the 1964 Declaration of Helsinki and subsequent amendments.

We performed a retrospective chart review of all patients over 18 years of age who presented to Harbor-UCLA Medical Center between 2015 and 2021, were diagnosed with ALL, and received a treatment regimen that included asparaginase. Patient demographic data (including biologic sex, age at diagnosis, ethnicity, body mass index (BMI) at diagnosis), laboratory parameters on diagnosis (including Philadelphia chromosome status, white blood cells (WBCs), creatinine, and liver function tests), treatment details (including dosages), and information on treatment-related complications were collected from the electronic health record (EHR). Data for treatment-related complications were collected during the induction phase of treatment for all but one patient, for which complications were recorded during the consolidation phase. Complications were further categorized by the type of adverse event, namely hepatotoxicity, thrombosis, pancreatitis, hypertriglyceridemia, or allergic reaction.

Statistical analysis

Patient characteristics for continuous values were reported as medians with first and third interquartile ranges. Toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, which describes the grading criteria for all adverse events reported. If a grade is not applicable to a particular adverse event, it is reported as "-" in our data. The maximum grades per patient of adverse events after initiating treatment were reported.

Results

Study population

A total of 14 Hispanic patients diagnosed with ALL and treated with PEG-asparaginase at Harbor-UCLA Medical Center from January 2016 to November 2021 were included in this study. Table 1 describes the demographics of the cohort and Philadelphia chromosome status. Our cohort consists of 53% males and 46% females, with an average age of 31 (standard deviation (SD) 9.4). Our patient population had an average BMI of 34 (SD 8.7), with the majority (64%) classified as obese (BMI ≥ 30). Twelve patients (86%) were Philadelphia chromosome negative. Patients received PEG-asparaginase as part of AALL 1131 (64%), AALL 0232 (14%), AALL 0622 (7%), CALGB 8811 (7%), or CCG-188221 (7%) treatment protocols. Ten patients (71%) received doses above the typical cap of 3,750 units.

Table 1. Summary of Cohort Characteristics

Cohort characteristic (n = 14)	N (%)
Age at diagnosis	
Median	28.5
Range	21 - 57
21 - 39 (young adults)	12 (85.7)
40 - 57 (adult)	2 (14.3)
Biologic sex	
Male	5 (35.7)
Female	9 (64.3)
BMI	
Median	31.4
Range	21.8 - 49.0
18.5 - 24.9	1 (7.1)
25 - 29.9	4 (28.6)
30 - 39.9	5 (5.7)
≥ 40	4 (28.6)
Ethnicity	
Hispanic	14 (100)
Philadelphia chromosome	
Positive	2 (14.3)
Negative	12 (85.7)

BMI: body mass index.

Lab parameters were recorded at the time of diagnosis and at their peak values and are listed in Table 2. At diagnosis, alanine aminotransferase (ALT) levels ranged from 15 to 191, with a median of 54 (interquartile range (IQR): 32, 107). Peak ALT values rose to a median of 453 (IQR: 218, 643) and a range of 43 - 3491. At diagnosis, aspartate aminotransferase (AST) levels ranged from 22 to 175, with a median of 48 (IQR: 38, 63). Peak AST values rose to a median of 325 (IQR: 216, 468) and a range of 51 - 3137. At the time of diagnosis, 10 patients (71%) already had transaminitis of grade 1 or higher. Total bilirubin levels at diagnosis ranged from 0.4 to 11.4, with a median of 0.9 (0.7, 1.2). Five patients (36%) had grade 1 or higher hyperbilirubinemia at diagnosis.

Toxicities

Table 3 shows the adverse events in our cohort. The incidence

Table 2. Lab Values Obtained at Diagnosis Compared to Their Peak Values

Lab parameter	At diagnosis	At peak value
ALT		
Median (IQR)	54 (32, 107)	453 (218, 643)
Range	15 - 191	43 - 3491
AST		
Median (IQR)	48 (38, 63)	325 (216, 468)
Range	22 - 175	51 - 3137
Total bilirubin		
Median (IQR)	0.9 (0.7, 1.2)	3.3 (2.8, 13.7)
Range	0.4 - 11.4	1.2 - 32.3

ALT: alanine aminotransferase; AST: aspartate aminotransferase; IQR: interquartile range.

of grade 3 to 4 hyperbilirubinemia (> 3 times the upper limit of normal (ULN) for serum bilirubin) was six out of 14 patients (43%). Half of our patients who suffered from hyperbilirubinemia also suffered from class III obesity, which is defined as a BMI ≥ 40.

The incidence of grade 3 to 4 transaminitis (> 5 times the ULN for ALT or AST levels) was 13 out of 14 patients (93%). Four patients (29%) had no transaminitis at diagnosis, but only one of them remained without transaminitis by the end of the study; the rest were found to have high-grade 3 or 4 transaminitis after treatment with asparaginase. Five patients (36%) with transaminitis experienced a dose reduction in their treatment regimens, and two patients (14%) were given reversal agents.

Thrombosis occurred in six out of 14 patients (43%), with one patient experiencing disseminated intravascular coagulation (DIC); the rest were thromboembolic events that required medical intervention, though none were considered life-threatening.

Hypertriglyceridemia occurred in four out of 14 patients (29%), two of which were started on gemfibrozil.

Pancreatitis occurred in one patient (7%), and only one patient (7%) experienced an allergic reaction in the form of a mild rash.

Discussion

To the best of our knowledge, this study represents the only report focusing on adult Hispanic ALL patients and the adverse effects of asparaginase. Much of the existing literature either describes pediatric ALL patients or adult ALL patients but not specific to the Hispanic ethnicity. In either case, data limited to Hispanic patients demonstrate increased rates of toxicity, including hepatotoxicity.

The results of this study support other evidence of Hispanic ALL patients experiencing higher rates of transaminitis as an adverse effect of asparaginase. Approximately 93% of our cohort of Hispanic patients experienced grade 3 or higher transaminitis, often considered high grade. This encompassed 85% patients with ALT elevation and 78% with AST elevation. These rates are similar, if not slightly higher than a similar study of ALL pediatric patients that reported 83% ALT and 47% AST high grade transaminitis in Hispanic patients [15]. When not delineating by ethnicity, grade 3 or higher transaminitis as a toxicity occurs in roughly 50% of patients [17, 18].

The patients in our study experienced high-grade hyperbilirubinemia at a rate of 43%. AYA and adult studies have reported rates ranging from 14% to 24% [12, 19]. A pediatric study reported that Hispanic patients experience higher rates of hepatotoxic bilirubin levels at rates of 12% compared to 4% in non-Hispanics [15]. The discrepancy between adult and pediatric rates of hyperbilirubinemia toxicity is not clearly understood. However, in both pediatric and adult populations, Hispanic patients experience higher rates of hyperbilirubinemia from asparaginase toxicity.

Multiple risk factors, such as obesity, low albumin, low platelet count and older age, are associated with higher risk of asparaginase-induced hepatotoxicity. Obesity is associated with both poorer outcomes in ALL and hepatotoxicity from asparaginase [12, 18, 20, 21]. In our cohort of Hispanic patients, 64% were in the BMI range of obesity. This rate is higher than the national average obesity rates for Hispanics (45%), as well as non-Hispanic Whites (41%) [22]. The relationship between obesity and hepatotoxicity is not clearly understood, and there is a paucity of evidence to connect underlying liver disease (e.g., cirrhosis or metabolic dysfunc-

Table 3. Frequency of Adverse Events in Our Cohort

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	N (%)	N (%)	N (%)	N (%)	N (%)
Allergic reaction/hypersensitivity	1 (7%)	0	0	0	0
Hyperbilirubinemia	2 (14%)	5 (36%)	1 (7%)	5 (36%)	0
Hypertriglyceridemia	1 (7%)	2 (14%)	1 (7%)	0	0
Pancreatitis	-	1 (7%)	0	0	0
Thrombosis	0	6 (43%)	0	0	0
Transaminitis (ALT)	1 (7%)	1 (7%)	10 (71%)	2 (14%)	0
Transaminitis (AST)	1 (7%)	2 (14%)	9 (64%)	2 (14%)	0

All grades were assessed using CTCAE version 5.0 definitions. If a grade is not applicable to a particular adverse event, it is reported as "-". CTCAE: Common Terminology Criteria for Adverse Events.

tion-associated fatty liver disease) to toxicity. Notably, of the four patients who did not have transaminitis on diagnosis, three were found to have grade 3 or 4 hepatotoxicity after asparaginase therapy.

Even after controlling for BMI, the rates of hepatotoxicity in Hispanics are still higher than in non-Hispanics [15]. To investigate a genetic component to asparaginase-associated hepatotoxicity, the superoxide dismutase 2 (*SOD2*) gene has been identified in mitochondrial enzyme protection against liver injury. Specifically, the rs4880-CC phenotype is associated with asparaginase hepatotoxicity. This variant has been shown to be more prevalent in Hispanic pediatric and adult patients [15, 19]. To date, no guidance or recommendations have been published that discuss changing agents or asparaginase dose based on SOD2 phenotype.

Though the cohort size of our study is modest, the marked incidence of hepatotoxicity raises the question of whether mitigation strategies like dose capping could be of particular benefit to high-risk populations like ours. Notably, 71% of our cohort received asparaginase doses above the typical capped value of 3,750 units. Emerging research demonstrate that dose capping can lead to significant reductions in grade 3 and 4 toxicities in adult ALL populations [23], with some studies suggesting particular benefit in mitigating hepatotoxicity [24]. While promising, data on the efficacy of dose capping remain limited, particularly for high-risk subgroups like obese patients [21]. Our data add to the body of evidence that ongoing research in mitigating hepatotoxicity risk is well warranted in Hispanic ALL populations.

Conclusions

This study demonstrates how adult ALL patients of Hispanic ethnicity experience high-grade transaminitis and hyperbilirubinemia more frequently than reported rates in the general ALL population undergoing asparaginase therapy. While this has been well studied in pediatric populations, our results suggest a similar trend in adult ALL patients. Our cohort experienced obesity at a higher rate than average, a condition known to affect the Hispanic population disproportionately. Our results support the association between obesity and hepatotoxicity in asparaginase therapy, but we recognize there are still unknown factors that are responsible for higher rates of asparaginase adverse effects in Hispanic patients. This warrants further investigation into alternative etiologies, including genetic, which can explain and potentially mitigate this considerable risk in Hispanic patients with ALL. These results highlight the importance of considering the elevated toxicity risk that Hispanic patients have in asparaginase therapy.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Harbor-UCLA Medical Center Institutional Review Board (IRB) approval was obtained (IRB number 18CR-32572-01). Informed consent was waived due to the retrospective nature of the study. Identifiable patient information was removed at the time of data analysis.

Author Contributions

ST is the principal investigator who provided the study concept, initial study design, and patient recruitment. ST aided in data analysis, manuscript revision, and overall supervision of project. MD performed the initial data collection and analysis. DZ completed the remainder of the data collection and analysis, generated all study tables, and completed the initial draft of the manuscript. JJ contributed to literature review and writing of the Discussion. All authors have read and agreed to the published version of the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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