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Original Research Article

Assessing the Incidence and Spectrum of L-Asparaginase-Induced Adverse Events in Young Patients with Acute Lymphoblastic Leukemia at A Tertiary Care Center

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Abstract:
This retrospective observational study conducted at a tertiary care center in Odisha, India, assessed the incidence and spectrum of adverse events induced by L-asparaginase in 109 young patients treated for acute lymphoblastic leukemia (ALL) over six months. The study found that 34% of patients experienced adverse effects, with hyperglycemia (35%) and hypersensitivity (30%) being the most common, followed by pancreatitis, hypoglycemia, thrombosis, and other effects. Age-specific analysis revealed a higher incidence of hyperglycemia in patients older than 14, underscoring the need for age-tailored monitoring and management strategies. The findings emphasize the importance of vigilant surveillance and proactive management of adverse events to optimize treatment outcomes for ALL patients.

Keywords: L-asparaginase, Acute Lymphoblastic Leukemia, Hyperglycemia, Chemotherapy Toxicity.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, characterized by the overproduction of immature white blood cells in the bone marrow. The management of ALL often involves a multimodal approach, with chemotherapy being the cornerstone of treatment [1,2]. Among the chemotherapeutic agents, L-asparaginase plays a pivotal role due to its unique mechanism of starving leukemic cells of essential nutrients, particularly asparagine. However, the therapeutic success of L-asparaginase is often tempered by its toxicity profile, which can significantly affect patient outcomes and quality of life [3,4].

The enzyme L-asparaginase, derived from *Escherichia coli* or *Erwinia chrysanthemi*, has been a mainstay in pediatric ALL treatment protocols for decades. While effective, its administration is frequently associated with a range of adverse events ranging from mild allergic reactions to severe life-threatening conditions such as pancreatitis, thrombosis, and neurotoxic effects [5,6]. Understanding these adverse events is crucial for improving patient management strategies and therapy outcomes [7].

This study aimed to comprehensively analyze the toxicity profile associated with the administration of native E. coli-derived L-asparaginase in the treatment of young patients diagnosed with acute lymphoblastic leukemia (ALL) at a tertiary care center in Odisha, India. Specifically, the study sought to quantify the incidence of adverse events, identify the most prevalent toxicities, and explore their distribution across different age groups and risk categories. By elucidating these aspects, the research intends to contribute to the optimization of ALL treatment protocols, enhancing both the safety and efficacy of L-asparaginase use in clinical practice.

Methodology

This retrospective, hospital-based observational study was conducted in the Department of Clinical Hematology at SCB Medical College and Hospital, a prominent tertiary care government hospital in Cuttack, Odisha. The study was carried out over six months from January 2023 to June 2023, focusing on patients receiving first-line chemotherapy for acute lymphoblastic leukemia (ALL).

Participants included in the study were diagnosed with ALL based on the World Health Organization (WHO) criteria. The inclusion criteria targeted patients aged below 50 years who were undergoing the ALL-BFM (Berlin-Frankfurt-Münster) protocol. Exclusion criteria were set to omit

patients over the age of 50 and those with pre-existing conditions or prior adverse events that could confound the assessment of L-asparaginase-induced toxicity. Additionally, cases where adverse events could overlap with those induced by other drugs used in the treatment protocol were carefully evaluated and excluded if another causative drug could not be ruled out.

Data were collected from medical records including patient demographics, specific chemotherapy protocols followed, dosage and duration of L-asparaginase administration, and documented adverse events. Adverse events were classified and graded according to the Common Toxicity Criteria for Adverse Events (CTCAE), Version 5.0. Specific attention was paid to the onset, severity, and duration of each adverse event. The primary outcome measure was the incidence of adverse events associated with L-asparaginase. These events were further analyzed to identify patterns related to age, gender, and risk category (standard, moderate, high) of leukemia. Secondary outcomes included the severity of these events and the need for medical intervention or modification of the chemotherapy regimen. Statistical analysis was performed using chi-square tests for categorical data and t-tests for continuous variables. The significance level was set at $p < 0.05$. Data were analyzed using statistical software, which facilitated the handling of complex variables and allowed for multivariate analysis to adjust for potential confounders.

Results

A total of 109 patients were included in the analysis, with a predominant male representation (62%). The age distribution highlighted a significant skew towards younger patients, with 81% being under 14 years of age. Most patients were categorized into three risk groups based on their prognosis: moderate risk (40.5%), standard risk (35.2%), and high risk (24.3%). Out of the 109 patients treated with L-asparaginase, 37 patients (34%) experienced one or more adverse events. The study revealed that younger patients, particularly those under 14, were more prone to experiencing adverse effects, although the difference was not statistically significant ($p > 0.05$).

The most commonly reported adverse event was hyperglycemia, affecting 35% of the patients who experienced side effects, followed closely by hypersensitivity reactions in 30%. Other notable adverse effects included:

- Pancreatitis: 19%
- Hypoglycemia: 13.5%
- Thrombosis: 8%
- Intestinal dysmotility: 8%
- Hepatopathy: 5.5%
- Encephalopathy: 5.5%

A deeper analysis into the age-wise distribution of adverse effects showed that hyperglycemia was significantly higher in patients above 14 years old ($p = 0.00032$). In cases involving pancreatitis, this condition presented independently in 8% of the affected patients. Interestingly, 11% of the patients exhibited both hyperglycemia and pancreatitis concurrently. Statistical analysis using chi-square tests demonstrated the variability in risk with no significant statistical correlation in most comparisons, indicating that the adverse effects could be predominantly attributed to the pharmacological action of L-asparaginase rather than patient-specific factors like age or risk category.

Among the complications, two deaths were reported, accounting for a 5.5% mortality rate among those who experienced adverse effects. These deaths were directly attributed to the severe manifestations of drug-induced toxicities. Charts and tables included in the study provided a clear visual representation of the spectrum of adverse effects, enhancing the understanding of their impact on the patient cohort.

Table 1: Patient Demographics and Risk Category

Risk Category	Number of Patients	Percentage
Moderate Risk	44	40.5%
Standard Risk	38	35.2%
High Risk	27	24.3%

Table 2: Incidence of Adverse Events

Adverse Event	Patients Affected	Percentage
Hyperglycemia	13	35%
Hypersensitivity	11	30%
Pancreatitis	7	19%
Hypoglycemia	5	13.5%
Thrombosis	3	8%
Intestinal Dysmotility	3	8%
Hepatopathy	2	5.5%
Encephalopathy	2	5.5%

Table 3: Age-wise Distribution of Adverse Effects

Age Group	Hyperglycemia	Pancreatitis	Hyperglycemia with Pancreatitis
<14 years	9	3	2
≥14 years	4	5	2

Table 4: Statistical Significance of Findings

Comparison	p-value	Significant at p < 0.05
Age-wise risk of hyperglycemia	0.00032	Yes
Hyperglycemia vs. Pancreatitis	0.0012	Yes
Overall adverse effects by age	>0.05	No

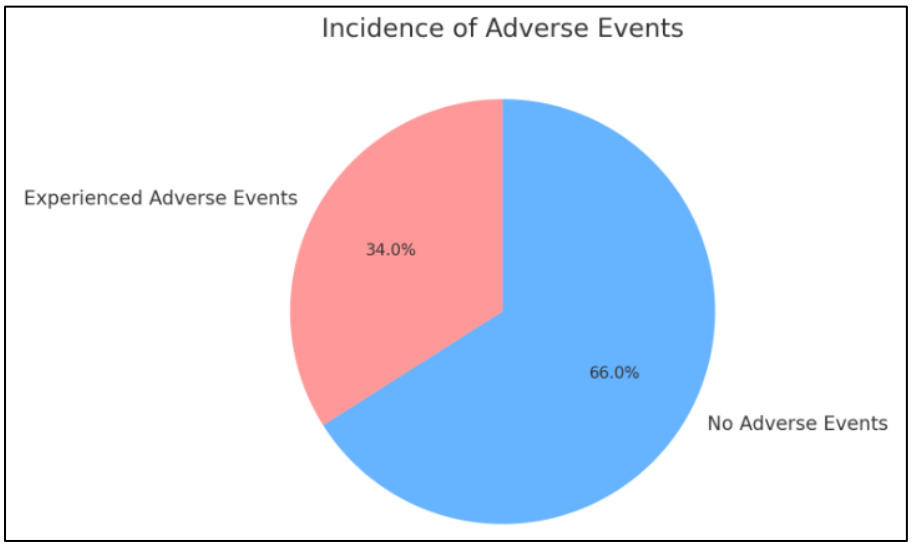

Figure 1: The pie chart shows the incidence of adverse events, where 34% of the patients experienced adverse events, and 66% did not.

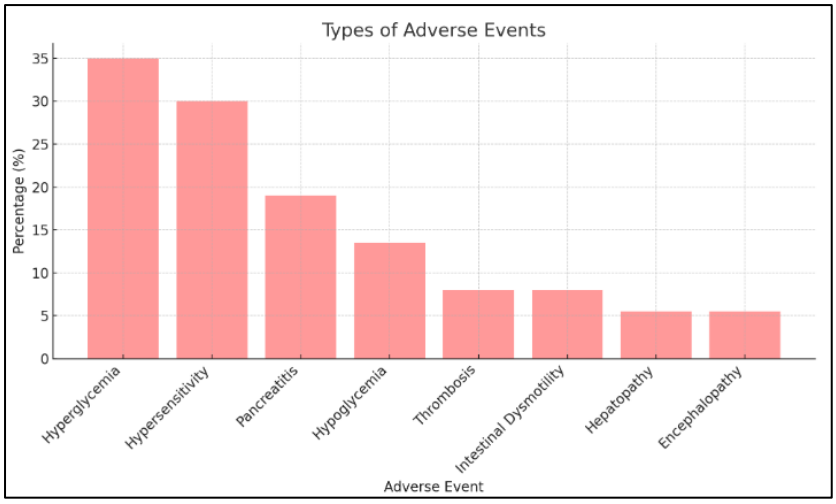

Figure 2: The bar chart detailing the types of adverse events experienced by patients undergoing treatment with L-asparaginase. It clearly shows hyperglycemia and hypersensitivity as the most frequent adverse events, among others like pancreatitis and hypoglycemia.

Discussion

The results of this retrospective study at a tertiary care center in Odisha, assessing the incidence and spectrum of L-asparaginase-induced adverse events in young patients with acute lymphoblastic leukemia (ALL), highlight significant clinical considerations [8,9]. The incidence of adverse events was notable at 34%, with hyperglycemia and hypersensitivity being the most prevalent, underscoring the need for vigilant monitoring during L-asparaginase therapy [10]. Notably, the higher incidence of hyperglycemia in patients older than 14 suggests a possible age-related differential response to L-asparaginase, which warrants further investigation to tailor treatment protocols more effectively [11].

The findings also bring attention to the severe complications such as pancreatitis and thrombosis, albeit less frequent, but significant due to their potential to influence morbidity and treatment outcomes [12]. The co-occurrence of hyperglycemia and pancreatitis in a small subset of patients suggests a complex interplay of treatment-induced metabolic disturbances, which could guide more personalized monitoring and management strategies [13].

Statistical analysis indicated that the overall risk distribution did not significantly influence the occurrence of adverse events, which might imply that the toxicities are more inherently linked to the pharmacologic properties of L-asparaginase rather than patient-specific risk categories. This aspect challenges the current risk stratification methods in predicting adverse events and suggests a potential area for further research [14,15].

Moreover, the study's implications extend to the clinical setting where routine monitoring of glucose levels and pancreatic enzymes could be integrated into treatment protocols, especially for those identified at higher risk for these specific adverse events [16,17]. The two fatalities reported underscore the importance of these findings and the necessity of developing strategies to mitigate these risks. While L-asparaginase remains a cornerstone in the treatment of ALL due to its effectiveness, this study reinforces the critical need for comprehensive adverse effect management and highlights areas for improvement in clinical practices and future research. As L-asparaginase continues to be integral in ALL therapy, these insights are invaluable in refining treatment approaches to maximize efficacy while minimizing adverse outcomes [18,19,20].

Conclusion

This study conclusively demonstrates that while L-asparaginase is an effective component of acute lymphoblastic leukemia (ALL) treatment, its administration is associated with a considerable incidence of adverse events, affecting approximately 34% of the young patient cohort at a tertiary care center in Odisha. The spectrum of adverse effects, led by hyperglycemia and hypersensitivity, emphasizes the necessity for meticulous monitoring and preemptive management strategies to mitigate these risks. The findings highlight the need for personalized treatment adjustments, especially for those over 14 years of age who are more susceptible to hyperglycemia, and underscore the importance of a multidisciplinary approach in managing the complex side effects of chemotherapy in ALL. This study not only sheds light on the common and severe toxicities associated with L-asparaginase but also calls for ongoing research to refine therapeutic protocols and enhance patient outcomes in pediatric oncology.

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