ORIGINAL RESEARCH

A Retrospective Study Of Pegaspargase In Pediatric Patients With Acute Lymphoblastic Leukemia

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is a heterogeneous hematological disease, constituting 75-80% of leukemia in children. L-asparaginase is a key component of the standard induction therapy for pediatric ALL. The present study aimed to evaluate the clinical profile of pegylated *Escherichia coli* asparaginase (pegaspargase) in terms of treatment-related side effects in pediatric patients with ALL.

Methods: This retrospective study included pediatric patients with ALL who were treated at the Pediatric Hemato-Oncology Center in Hyderabad from Jan 2019 to Dec 2022. The medical records of patients aged 18 years and below, with a diagnosis and treatment for ALL, were accessed. Patients treated with intramuscular/intravenous pegaspargase (2,500 IU/m^2) for ALL were included in the study. Patient demographic characteristics and disease status were documented. The adverse events with the use of pegaspargase were also noted.

Results: A total of 300 patients with ALL were included in the study. The majority of patients were aged <10 years (65.7%). Most of the patients were male (58%). B-cell ALL was the predominant immunophenotype in 253 patients. As per the National Cancer Institute (NCI) criteria, 192 patients had standard-risk ALL. Bacterial/fungal infection was the most common manifestation in 25.7% of patients. Allergic reactions were observed in 15% of patients. Thrombosis was noted in 19 patients, while 18 patients experienced fatigue. Other side effects included hypertension (n=13), hyperglycemia (n=11), and pancreatitis (n=8).

Conclusion: Pegaspargase holds promise as a vital therapeutic agent in the treatment of pediatric ALL, with most adverse events being manageable and reversible.

Keywords: acute lymphoblastic leukemia, pediatric ALL, pegaspargase, side effects.

Introduction

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematological disease, constituting 75-80% of leukemia in children [1]. It accounts for approximately 25% of cancer diagnoses in children below 15 years of age [2]. This common pediatric malignancy is developed by the rapidly growing lymphoid progenitor cells in the bone marrow, peripheral blood, and other organs [3]. In India, the age-adjusted incidence rates of ALL for boys and girls have been reported to be 101.4 per million and 62.3 per million, respectively [4]. L-asparaginase is a key component of the standard induction therapy for pediatric ALL [5]. Because leukemic cells rely solely on the exogenous asparagine for survival, L-asparaginase hydrolyzes asparagine, depleting the circulating pool of serum asparagine and starving the leukemic cells to death [6]. L-asparaginase preparations approved for treating ALL include *Escherichia coli*-derived native *E. coli* asparaginase, PEGylated *E. coli* asparaginase, and *Erwinia chrysanthemi*-derived *Erwinia* asparaginase [7]. The covalent linking of polyethylene glycol (PEG) to *E. coli* L-asparaginase produces pegylated *E. coli* asparaginase (pegaspargase) [5]. In recent times, pegaspargase has gained importance in the treatment of pediatric ALL. Pegylation of *E. coli* L-asparaginase aids by prolonging the circulation of a period of enzyme and reducing immunogenicity. Pegaspargase has a favorable pharmacokinetic and immunogenicity profile that lowers the incidence of allergic reactions, the production of neutralizing antibodies, and the frequency of administration while preserving its anti-leukemic activity [8]. The virtue of pegaspargase to be

administered in patients hypersensitive to *E. coli* L-asparaginase makes it valuable for re-induction therapy in selected patients with ALL [9]. The present study aimed to evaluate the clinical profile of pegaspargase regarding treatment-related side effects in pediatric patients with ALL.

Materials and methods

Study design: This retrospective study was conducted in pediatric patients with ALL, who were treated at the Pediatric Hemato-Oncology Center in Hyderabad.

Study population: The medical records of patients aged 18 years and below, with a diagnosis and treatment for ALL were accessed. Patients treated with pegaspargase for ALL were retrieved from the medical records and included in the study. These patients received an intramuscular/intravenous dose of pegaspargase 2,500 IU/m^2 once in 14 days.

Data collection: Patient demographic characteristics and disease status were documented. Patients were classified as per the National Cancer Institute (NCI) criteria into standard- and high-risk groups according to age, immunophenotype and white blood cell (WBC) count [10]. An absolute blast count of cells <1000/mm^3 defined a good response to steroids. Remission status was assessed by minimal residual disease (MRD) in patients. The adverse events of pegaspargase treatment in patients were also noted.

Statistical analysis: Data was entered into excel sheet and analyzed. Descriptive statistics was used to describe categorical variables (frequency and percentages). Quantitative variables were described with mean and standard deviation (SD).

Results

A total of 300 patients with ALL were included in the study. Table 1 depicts the demographic and disease characteristics of patients. The majority of patients were aged <10 years (65.7%). Most of the patients were male (58%). B-cell ALL was the predominant immunophenotype in 253 patients. The total WBC count was <50,000/mm^3 in 71.7% of patients. Eighty-six percent of patients received treatment for the first time, whereas 7.7% of patients seeking treatment had the disease relapsed. Moreover, 6.3% of patients were refractory to treatment. As per the NCI criteria, 192 patients had standard-risk ALL. A good response to steroids was observed in 92% of patients. The pegaspargase-related adverse events are presented in Table 2. Bacterial/fungal infection was the most common manifestation in 25.7% of patients. Allergic reactions were observed in 15% of patients, of which nine percent had grade 1 and 2 reactions, whereas six percent had grade 3 and 4 reactions. Thrombosis was noted in 19 patients, while 18 patients experienced fatigue. Other side effects included hypertension (n=13), hyperglycemia (n=11), and pancreatitis (n=8).

Table 1: Demographic and disease characteristics of patients

Parameters	Number of patients(N=300)
Age (years)<10≥10	197 (65.7)103 (34.3)
Sex Male Female	174 (58.0)126 (42.0)
ImmunophenotypeB-cellT-cell	253 (84.3)47 (15.7)
WBC count (cells/mm^3)<50,000>50,000	215 (71.7)85 (28.3)
Disease status First-line therapyRelapsedRefractory	258 (86.0)23 (7.7)19 (6.3)
NCI risk group StandardHigh	192 (64.0)108 (36.0)
Steroid response GoodPoor	276 (92.0)24 (8.0)
MRDPositiveNegative	29 (9.6)271 (90.3)
Duration of treatment (months), mean (SD)	24.43 (28.01)
Data presented as n (%), unless otherwise specified. MRD, minimal residual disease; NCI, National Cancer Institute; WBC, white blood cell.	

Table 2: Treatment-related adverse events

Parameters	Number of patients (N=300)
Fatigue	18 (6.0)
Allergy	45 (15.0)
Grade 1 and 2	27 (9.0)
Grade 3 and 4	18 (6.0)
Pancreatitis	8 (2.7)
Hypertension	13 (4.3)
Hyperglycemia	11 (3.6)
Hyperbilirubinemia	3 (1.0)
Thrombosis	19 (6.3)
CNS	7 (2.3)
Non-CNS	12 (4.0)

Infection (bacterial/fungal)	77 (25.7)
Data presented as n (%). CNS, central nervous system.	

Discussion

L-asparaginase is critical in the combination chemotherapy protocols for ALL. In recent times, pegaspargase has gained preference over the traditional L-asparaginase due to its lower incidence of allergies and longer half-life. As a result, it has become the primary drug of choice worldwide for the initial treatment of pediatric ALL [3]. The present study was conducted to evaluate the clinical profile of pegaspargase in terms of treatment-related side effects in pediatric patients with ALL. This observational study included 300 pediatric patients with ALL who were treated with pegaspargase. The incidence of ALL was higher among patients <10 years of age (65.7%). Moreover, the incidence was considerably more common in males (58%) than in females (42%). These findings were backed up by the National Comprehensive Cancer Network (NCCN), which stated that ALL is slightly more common in boys, with a peak incidence in 2-5 years [4]. Similar trends of ALL incidence were reported in the DFCI 11-001 trial [11] and other studies [5,12]. A review summarizing the outcomes of childhood ALL and acute myeloid leukemia (AML) from India reported that 23 to 37% of children with ALL had a baseline WBC count of >50,000/mm^3 and that 21 to 50% of children with ALL had T-cell lymphoblastic leukemia [13]. In the study by Jayaraman et al., 25.7% of children with ALL had a WBC count of >50,000/mm^3, and 18.3% had T-cell lymphoblastic leukemia. Likewise, the current study exhibited 28.3% of patients having a WBC count of >50,000/mm^3 and reported T-cell lymphoblastic leukemia in 15.7% of patients. Additionally, the proportion of patients with T-cell leukemia reported in this study was on agreeing terms that T-cell ALL constitutes about 15-20% of pediatric ALL [4]. The study patients were stratified as per the NCI criteria of risk classification for children with ALL [10]. According to this criteria, the standard-risk category (4-year event-free survival [EFS] rate, ~80%) would include patients with B-precursor, aged 1 to 9 years, with a WBC count at diagnosis of <50,000/µL. The remaining patients would be classified as having high-risk ALL (4-year EFS rate, ~65%). Owing to this criteria, the present study included 64% of patients in the standard-risk ALL group and 36% of patients in the high-risk ALL group.Despite the use of pegaspargase in pediatric ALL protocols as a global therapeutic standard, its safety profile still remains a challenge. The bacterial origin of L-asparaginase could confer either a clinical or subclinical immune response in the pediatric population. A clinical hypersensitivity rate of up to 75% has been reported in children treated with *E. coli* asparaginase. However, pegaspargase is associated with lesser clinical hypersensitivity than native asparaginase, with rates from 3–24% [14]. On parallel lines, the present study exhibited overall allergic reactions in 15% of patients. Other side effects associated with the use of asparaginase are pancreatitis, thrombosis, hyperglycemia, and liver dysfunction. The incidence of hyperglycemia is more common when the combination of asparaginase and corticosteroids are administered at relatively higher doses while on therapy [14]. Hyperglycemia was identified in 3.6% of patients; these findings were twice the incidence of hyperglycemia (1.8%) reported by Jayaraman et al. [5]. Asparaginase-associated pancreatitis is a cause of substantial morbidity, with an incidence between 2% and 10% [15]. The present study reported patients with pancreatitis falling between these ranges, with an incidence of 2.7%. On the contrary, the frequency of intravenous pegaspargase-associated pancreatitis (grade ≥2) was 12% in the DFCI 05-001 trial [16], whereas the post-induction asparaginase pancreatitis (grade ≥2) of 15% was reported by the DFCI 11-001 trial [11]. Asparaginase use is more commonly associated with abnormalities in liver function and elevations in bilirubin levels [14]. The FDA drug approval summary of pegaspargase for the first-line treatment of children with ALL reported hyperbilirubinemia in 2% of patients receiving native *E. coli* asparaginase and pegaspargase, each [17]. The present study findings were comparable, with hyperbilirubinemia in only 1% of patients. The overall thrombosis incidence of 5.2% was reported by a meta-analysis of 17 studies that highlighted thrombotic complications in children with ALL [18]. In this study, the overall thrombosis was 6.3%, comparable to the intravenous pegaspargase thrombosis of 7% in the DFCI 05-001 trial [16].

Conclusion

The results indicate that pegaspargase is well-tolerated and has a favorable toxicity profile, with most adverse events being manageable and reversible. In conclusion, the present study provides valuable insights into the clinical profile of pegaspargase in pediatric ALL. Overall, this study contributes to the growing body of evidence supporting the use of pegaspargase in pediatric ALL.

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