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Original Article

L-Asparaginase Related Thrombotic Complications in Acute Lymphoblastic Leukemia Patients – An Experience from a Tertiary Care Centre

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Abstract
Background: *L- Asparaginase is commonly used chemotherapeutic agent in the treatment of acute lymphoblastic leukemia patients. The overall incidence of symptomatic venous thrombosis in acute lymphoblastic leukemia (ALL) varies from 1.5-11%. The risk of thrombotic complications in acute lymphoblastic leukemia (ALL) in children ranges from 1 to 37%. Most of the patients develop thrombosis related to L-asparaginase in the induction phase of chemotherapy.*
Purpose: *To highlight the incidence of life threatening thrombotic complications related to L –Asparginase in acute lymphoblastic leukemia patients.*
Materials and Methods: *This study was carried out retrospectively over a period of ten years. The data was taken from regional cancer registry and was compiled.*
Conclusions: *Early identification and management of life threatening thrombotic complications associated with L-asparaginaseis necessary to improve survival outcome in Acute lymphoblastic leukemia patients.*
Keywords: *Thrombosis, Acute lymphoblastic leukemia, L-Asparaginase.*

Introduction

Asparaginase is an enzyme that converts asparagine to aspartic acid in the extracellular fluid.[1] Leukemic cells express low levels of asparaginase synthetase[2-4] and are unable to produce more when exposed to asparaginase.[5,6] Whereas normal cells contain high levels of asparaginase synthetase and are able to produce asparagine, leukemic cells have a heightened sensitivity to the depletion of extracellular asparagine disrupting asparagine-dependent protein synthesis and leading to cell death.[7] Asparaginase levels serve as a surrogate marker for asparagine concentration demonstrating an inverse relationship, and as such, have often been

used in the pediatric population to determine asparagine depletion.[8-10.]

There are three formulations of L-Asparaginase with fourth under development. Two are derived from bacterium Escherichia coli (E.Coli) and third from Erwinia chrysanthemi. Native L-Asparginase has been initially derived from bacteria (E.Coli and Erwinia) and lately E.Coli asparaginase was modified by conjugation to polyethylene glycol toyieldpegasparginase. L-Asparaginase is an important component of therapy for acute lymphoblastic leukemia (ALL). L-Asparaginase exhibits its toxicity via mechanism of inhibition of proteins normally essential for various body functions and from its antigenicity as a foreign protein in the body. Notable side effects include Anaphylaxis, pancreatitis, Hepatotoxicity, immune dysfunction, Encephalopathy, Hyper-glycemia, myelosuppression and coagulation abnormalities (Thrombosis). The pathogenesis of thrombosis related to L-asparaginase is complex. Profound asparagine depletion by L-asparaginase generate a multiplicity of effects on the coagulation cascade, anticoagulants, fibrinogen, fibrinolysis, platelets, and vascular endothelium. The result isa net shift in the hemostatic balance toward thrombosis.[11] The protocol used for therapy is also important since the doses of steroids and L-asparaginase as well as their timing vary by protocols.[12]Early diagnosis of cerebral venous thrombosis demands low threshold for imaging and MRI with venography which is preferred over computed tomographic scanning (CT) for same.[13,14]The reported incidence of thrombosis is between 1.7%to 36.7%depending on the individual study protocol and whether asymptomatic events areincluded.[15,16]

Materials and Methods

This study was carried out retrospectively over a period of ten years. The data was taken from regional cancer registry and was compiled. Ethical clearance was obtained from SKIMS ethical committee. All acute lymphoblastic leukemia patients were included in the study. The details taken included Age, Sex, Hematological parameters and biochemical parameters at presentation, diagnostic work up done, treatment protocols initiated with detailed study of thrombotic complications related to L-Asparaginase. The details considered related to complications included time of onset of thrombotic complications, phase of chemotherapy in which the complication was commonly seen, management of thrombotic complications and outcome.

Results

Table 1: Patient characteristics at presentation

Total no of patients	669
Median age in years	15 years
M:F ratio	1.3:1
B-Cell ALL	540
T-Cell ALL	129
High Risk ALL	234
Intermediate and Low Risk ALL	435

Table: 2 Age and sex distribution in children

Age group (in years)	No of cases(n)	Percentage (%)
<1	7	1.04
1-9	289	43.1
10-19	117	17.4
20-39	132	19.73
40-59	117	17.4
>= 60	7	1.04

Table 3: Treatments Protocols Received

Protocol	No of cases (% age)
UK-ALL XII	329 (49.1%)
Modified BFM-90	185 (27.6%)
Pediatric BFM (Intermediate Risk)	88 (13.1%)
Pediatric BFM (Standard Risk)	66 (9.8%)
PCI received	432 (64.5%)

Table 4- Haemogram at presentation

Leucocyte count (x 10^9/L)	**No of cases(%)**
<10	299(44.6%)
10-49	192 (27.3%)
50-99	76 (11.3%)
>100	111 (16.5%)
Hemoglobin concentration (g/dL)	
<8	390(58.2%)
8-10	151 (22.5%)
>10	128 (19.1%)
Platelet count (x 10^9/L)	
<50	325 (48.5%)
50-100	150 (22.4%)
>100	194 (28.9%

Table 5: Toxicity profile of L -Asparaginase

Adverse drug reaction	Number of patients /percentage
Allergy and Anaphylaxis	36 /5.3%
Hyperglycemia	28/4.1%
Pancreatitis	20/2.9%
Thrombotic complications	8 /1.1%
Diabetic ketoacidosis	5 /0.7%
Seizures	3 / 0.4%
Hyperammonemic encephalopathy	2 /0.2%

Table 6: Thrombotic complications associated with L-Asparaginase

Thrombotic complications	Number of patients /percentage
Cavernous sinus thrombosis	2 /0.2%
Cerebral vein thrombosis	6/0.8%

Discussion

L-Asparaginase is a potent chemotherapeutic agent that has been a component of the treatment of acute lymphoblastic leukemia. Increasing dose intensity of L-Asparaginase and other improvements in therapy have now achieved cure rates of nearly 80%in children. Teenagers and young adults with ALL have recently started to receive pediatric treatment regimens containing higher dose L- Asparaginase with evidence that this improves their outcome. However, unfortunately, toxicity limits dose escalation of, L-Asparaginase particularly in adults, for whom cure is achievable in less than half of the cases. One of the mostproblematic side effects of L-Asparaginase treatment is thrombosis, [15,18] which remains an important source of avoidable morbidity and mortality, particularly during remission induction.[17,18] Venous thrombosis is more common than arterial thrombosis, with upper central venous thrombosis being the most common.[20] However, arterial and central nervous system (CNS) thrombotic events have been observed

This study was conducted to analyse the toxicity profile of L-Asparaginase in acute lymphoblastic leukemia (ALL) patients with special emphasis on thrombotic complications. Over a period of ten years we analyzed 669 ALL cases treated with L-Asparaginase. Out of 669cases 102 patients developed L-Asparaginase related complications with 8 patients showing thrombotic complications. Among 8 cases 6patients developed cerebral vein thrombosis presenting with sudden onset seizures with neurological deficits of focal nature in the induction phase of chemotherapy. Computed tomographic scanning of brain was done showing multiple venous infarcts and 2 cases developed cavernous sinus thrombosis presenting with sudden onset severe headache and vomiting during induction phase.

Alterations in hemostasis have been well documented in children receiving Asparaginase as a single agent or in combination with prednisolone [19]. Cerebral thrombotic events are mostly seen in induction phase of chemotherapy. The mechanism of induction of thrombosis by L-asparaginase is believed to be due to disruption of physiologic balance between the hemostatic and anticoagulation pathways, along with activation of platelets and endothelial [21-23]Although L-asparaginase appears to decrease the synthesis of both procoagulant and anticoagulant proteins by the liver, the decline in the levels of anticoagulant proteins C, S and antithrombin III contributes to an increased risk of thrombosis.[22-24]Coagulation profile in these patients show prolongation of PT and APTT in association with reduced levels of haemostatic proteins and fibrinogen.

Thrombotic complications were managed by intravenous anticonvulsants viz phenytoin loading doses of 15-20 mg/kg as infusion followed by maintenance dose of 5mg/kg in two divided doses. Leveteracetam was also used as add on drug where ever needed. Patients were also started on mannitol infusions of 60 grams daily and adjusted as per clinical response. The patients with renal impairment were treated with hypertonic saline infusions. These patients were also started on therapeutic low molecular heparin with subsequent overlap with warfarin and then on warfarin alone for nearly six months. All the patients were closely monitored for cell counts, INR (target INR 2-3), features of raised ICP and other routine clinical parameters. After stabilization these patients were continued on

treatment for ALL except that L-Asparaginase was omitted from the treatment protocols. We lost one patient during the treatment and another patient relapsed immediately after completion of treatment.

Conclusion

Venous thrombosis is rare and well known complication of L-Asparaginase use in ALL. Diagnosis is made on clinical suspicion followed by neuroimaging. Timely treatment and omission of L-Asparaginase from treatment regime helps saving patients life and use of peg-Asparaginase where ever available is associated with very rare such instances.

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