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L-ASPARGINASE TOXICITY PROFILE AT A TERTIARY CARE HEMATOLOGY CENTRE IN KASHMIR – 10 YEAR EXPERIENCE.

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ABSTRACT

Purpose: To study overall incidence of adverse effects, highlight incidence of life threatening complications, identify unusual complication if any and possible measures to prevent them.
Materials and methods: This was a ten year retrospective study where in data related to patients at presentation and data related to complications was taken from regional cancer registry and was compiled.
Conclusion: Asparaginase is an essential component of acute leukemia protocols . The ability to rapidly identify and manage asparaginase-associated toxicity will help ensure patients receive the maximal benefit from asparaginase therapy.

Key words:L-Asparginase, Complications, Life-threatening.

INTRODUCTION

Antileukemic effect of guinea pig serum and identification of l-asparginase was for the first time reported by Kidd[1] in 1953 and later this enzyme was introduced into cancer chemo-therapy by Broome[2] in 1981. Most of the normal cells synthesize l-aspargine in amounts sufficient for protein synthesis but certain neoplastic cells including those in acute lymphoblastic leukemia(ALL) require an exogenous source of this amino acid.

L-Asparginasecatalyses the hydrolysis of circulatingaspargine to aspartic acid and ammonia and deprives cancer cells of aspargine necessary for protein synthesis, leading to cell death. L-Asparginase is commonly used in the treatment of ALL in combination with steroids, vincristine and anthracyclines. L-Asparginasecauses cell death through activation of apoptosis as well.[3]

L-Asparginase has been initially derived from bacteria vizE.Coli and Erwinia and lately E.Coliasparginase was modified by conjugation to polyethylene glycol toyieldpegasparginase. L-Asparginase 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.Ho and Keating[4] in 1986 demonstrated safety of pegasparginase and relative cautious use of Erwiniaasparginasein comparison to E.Coliasparginasein their studies.

Notable side effects due to protein synthesis inhibition include coagulation system abnormalities, albumin deficiency, insulin deficiency leading to diabetes, inhibition of immune system related globulins and deficiency of hormones.[3,6,7]

In addition to these side effects, coma may result due to ammonia production and pancreatitis of uncertain etiology[3] and very rarely pancreatic pseudocyst[18] may occur.

The coagulation related abnormalities like cortical venous thrombosis have been shown especially to occur in patients having underlying inherited disorders of coagulation such as Factor V Leiden mutation, elevated homocysteine levels, protein C or S deficiency, AT III deficiency, or 620210 variant of prothrombin.[5]

Cavernous sinus thrombosis is well known with patients of ALL on induction chemotherapy.[8,9] The etiology for thrombosis relates to disease process, use of L-Asparginase and steroids in induction chemotherapy, presence of central venous catheters and associated co-morbidities.[9,10]The role of steroids in cavernous sinus thrombosis is unclear but these act in synergism with L-Asparginase to increase the risk by 6-8 fold.[9,10]

The overall incidence of symptomatic venous thrombosis in ALL varies from 1.5-11%.[11,12,13,14,15].This percentage is much higher if asymptomatic thrombosis is also taken into account.[9] The incidence of central venous thrombosis is approximately 2%.[8]The protocol used for therapy is also important since the doses of steroids and L-asparaginase as well as their timing vary by protocols.[10] Early diagnosis of CVT demands low threshold for imaging and MRI with venography is preferred over CT for same.[16,17]

Materials and methods: This was a ten year retrospective study where in data related to patients at presentation and data related to complicationsoccuring after administering L-asparaginase was taken from regional cancer registry and was compiled. Ethical clearance was obtained from the instutional ethics committee. We recorded data about all ALL patients entertained in this hospital during the said period. The details recorded included age, sex, baseline haematologic and biochemical parameters, diagnostic workup, treatment protocol used and complications related to L-Asparginaseusage.The details about the complications were recorded extensively and included time of onset, nature of complication, remedial measures taken and response to these measures.

RESULTS

Table 1a-Patient characteristics

Total No of patients	688
Median Age in years	15
Age Range in years	1-63
Male:Female	397:291
Diagnosis	100% ALL
B-Cell ALL	540(78.48%)
T-Cell ALL	129(18.75%)
Mixed& Bi- Phenotype Acute Leukemia	19(2.76)
High risk ALL	234(34.01%)
Low &intermediate risk ALL	454(65.98)

Table 1b-Age distribution of patients.

Age group.(years)	Patients (%)
<1	7 (1.01)
1-9	289 (42)
10-19	117(17)
20-39	151(21.94)
40-59	117(17)
>=60	7(1.01)

Table 1c-Age and sex distribution in children.

Age group	N(%)	M:F
<1	7(1.69)	4:3
1-9	289(69.97)	161:128
10-19	117(28.32)	65:52
Total	413(100)	230:183

Table 1d-Age and sex distribution in adults.

Age group	N(%)	M:F
20-39	151(54.9)	90:61
40-59	117(42.54)	71:46
>=60	7(2.54)	4:3
Total	275(100)	165:110

Table 3 Toxicity profile of L asparaginase

Adverse drug reaction	Number of patients	Percentage of patients
Allergy and anaphylaxis	36	5.23
Hyperglycemia	28	4.06
DKA	5	0.72
Cerebral venous thrombosis	8	1.16
Pancreatitis	20	2.90
Seizures	3	0.43
Hyperammonemic encephalopathy	2	0.29

Table 4: Treatments Protocols Received

Protocol Received	No.	%age
UKALL-XII	348	50.6
Modified BFM 90	185	26.9
Pediatric BFM (intermediate risk)	88	12.8
Pediatric BFM (Standard risk)	66	9.6
PCI Received	432	62.8

Table 5-Presenting counts on hemogram.

Leucocyte count (x 10^9/L)	No	%
<10	309	44.91
10-49	192	27.90
50-99	76	11.04
>100	111	16.13
Hemoglobin concentration (g/dL)		
<8	399	57.99
8-10	151	21.94
>10	138	20.05
Platelet count (x 10^9/L)		
<50	330	47.96
50-100	158	22.96
>100	200	29.06

DISCUSSION:

The first goal of therapy for patients with leukemia is inducing a complete remission and restoring normal hematopoiesis. The induction regimen typically includes a glucocorticoid (prednisone, prednisolone, or dexamethasone), vincristine, and L-asparaginase for children or an anthracycline for adults.[19,20,21.]

Asparaginase acts by reducing plasma asparagine concentrations by catalyzing the deamination of asparagine into aspartic acid and ammonia [22]. At sufficient enzyme activity levels, asparaginase therapy results in the complete depletion of serum asparagine concentrations, depriving leukemic blasts of this amino acid [23], resulting in reduced protein synthesis and ultimately leukemic cell death.

The induction mortality ranges between 2 percent and 11 percent in adult ALL, with increasing age associated with higher death rate.[19,20,.] Toxicities associated with asparaginase use include hypersensitivity (clinical and subclinical), pancreatitis, thrombosis, encephalopathy, and liver dysfunction. Depending on the nature and severity of the toxicity, asparaginase therapy may be altered or discontinued in some patients. Most deaths are caused by bacterial or fungal infections. The death rate among elderly patients receiving remission induction therapy can be as high as 30 percent because of increased hematologic and nonhematologic toxicities (e.g., hepatotoxicity and cardiotoxicity).[24] This poor tolerance of chemotherapy and consequent reduction of dose intensity largely account for the generally poor clinical outcome in elderly patients.

This study was conducted to see the adverse effect profile of L-asparaginase in ALL patients. Over a period of ten years, 688 patients had been treated with L-Asparaginase. There were 102 adverse drug reactions in these patients. The most common adverse drug reaction recorded in our patients was allergy and anaphylaxis. Thirty six patients (5.23%) had some allergic/anaphylactic reactions to L-Asparaginase. Amongst these, one patient developed anaphylactic shock. L-Asparaginase was discontinued in this patient. The other thirty five patients had mild allergic reactions to the drug and were managed conservatively. Anaphylaxis due to L-Asparaginase is a known complication L-Asparaginase carries the potential to elicit an immune response when administered to patients as it is a large protein of bacterial origin and the immune responses are characterized by the development of anti-asparaginase antibodies which bind to the asparaginase molecule, potentially reducing its enzymatic activity, and initiate a number of downstream effects. The formation of IgG and IgE antibodies have been associated with the development

of clinical allergy following asparaginase administration in patients [25,26]

Pancreatitis was the third common adverse drug reaction seen in 20(2.90%) of cases.Majority of the patients were given supportive treatment in the form of fliud resuscitation and antibiotics. somatostatin analogue was added in 5 patients.

Asparaginase-associated Pancreatitis associated with is defined as acute pancreatitis in patients receiving L-Asparaginase treatment at the time of onset of acute pancreatitis. The pathophysiology behind Asparginase induced pancreatitis is regarded to reflect systemic depletion of asparagine with a subsequent reduction of protein synthesis, especially in organs with high protein turnover, such as the liver and pancreas.[27]

In our study hyperglycemia was reported in28(4.06%) of patients with DKA in 5(0.72%) patients.These patients were started on iv fluids 1L of 0.95 Nacl over 1 hr along with iv insulin 0.1 u/kgBW as bolus f/b 0.1u/kg/hr as continuous infusion . Blood monitoring was done every 2–4 h, for serum electrolytes, renal function, CO2 content and pH .Accordingly correction of electrolyte imbalance was done.

Hyperglycemia is a well-documented complication of L- asparaginase therapy for ALL [28,29.] The reported incidence of hyperglycemia ranges from 2.5-23% [30.]

One of the fatal complication seen in our study was cerebral vein thrombosis seen in 8(1.16%) of cases. 6 patients presented with sudden onset seizures with focal neurological deficits during induction phase of chemotherapy. CT brain showed multifocal hemorrhagic infarcts involving frontal lobe.. T1-weighted MRI brain showed isointense thrombus in superior sagittal . 4 patients presented with severe headache of sudden onset during induction therapy. All patients were anticoagulation in the form of low molecular weight heparin in addition to supportive care.

Alterations in hemostasis have been well documented in children receiving Asparaginase as a single agent or in combination with prednisolone [31]. Cerebral venous sinuses thrombosis is a unique feature of Asparaginase-related thrombosis and is reported to occur in 1%–3% of patients [31.]Other less common adverse drug reaction seen in our patients was seizures and hyperammonemic encephalopathy seen in 0.43 and 0.29% of the cases respectively.

Conclusions:: Asparaginase is an essential component of acute leukemia protocols . The ability to rapidly identify and manage asparaginase-associated toxicity will help ensure patients receive the maximal benefit from asparaginase therapy.

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