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DRUG INDUCED HEPATOTOXICITY AFTER INDUCTION PHASE OF CHEMOTHERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIC PATIENTS.

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ABSTRACT

The present study includes 20 prediagnosed Acute lymphoblastic Leukemic (ALL) and 20 normal control children. The Biochemical parameters (Bilirubin, Alanine amino transferase, Alkaline phosphatase and gamma glutamyl transferase) and complete blood count were investigated in control and leukemic patients. It was found that there was no significant difference between serum level of Bilirubin, Alanine aminotransferase, Alkaline phosphatase in leukemic patients as compared to control normal subjects. The serum Gamma glutamyl transferase of leukemic patients was high as compared to control subjects. There was significant increase in the blood level of Bilirubin, Alanine aminotransferase, Alkaline phosphatase and γ – Glutamyl transferase in patients after chemotherapy (Vincristine, L – asparaginase, Daunomycin, and Methotrexate) as compared to patients before Therapy. There was significant decrease in the number of blast cells and an increase in the level of hemoglobin, RBC, PCV, MCV, and neutrophil in leukemic patients after chemotherapy as compared to patients before chemotherapy. **Conclusion:** The chemotherapy induced hepatotoxicity, is present in ALL patients.

KEYWORD: Acute Lymphoblastic Leukemia (ALL), Chemotherapy, Induction phase, Hepatotoxicity, Hematological disorder.

INTRODUCTION

Leukemia is a neoplastic disorder involving blood forming cells. Uncontrolled proliferation of these cells results in overcrowding of the bone marrow with the exclusion of red cells and platelet production with the expression of extreme leukocytosis, anemia, and thrombocytopenia, in the peripheral blood. About 80% of childhood leukemia is the type in which bone marrow makes too many lymphocytes these may be called acute lymphoblastic leukemia[1] (ALL).

Acute lymphoblastic leukemia is the most common childhood malignancy, accounting for 25% of all childhood cancer in United States approximately 3000 children aged 1-19 years are diagnosed with ALL annually.[2] There is also high incidence of Leukemia in Pakistan. About 25% patients died before completing induction phase therapy[3].

The rationale use of multi agent systemic chemotherapy over a prolonged duration with antibiotics and blood products support were responsible for early improvements.[4] There are four phases of treatment of ALL. These phases of therapy include Induction phase, consolidation, late intensification and maintenance therapy. These phases of therapy span 2 – 3 years[5]. In the induction phase of therapy the chemotherapeutic agents which are usually used are vincristine, Prednisolone, Daunamycine and L – asparaginase. The intense chemotherapeutic treatments of ALL, can have serious short and long side effects. Most of the patients develop hematological and hepatic complications, which may be due to cytotoxic agents used in chemotherapy or due to disease process involving the important vital organs. In the present study we will try to explore some of the insights by observing different stages of toxicities during the treatment in the induction phase.

MATERIAL AND METHOD

Newly diagnosed patients below the age of 15 years with Acute Lymphoblastic leukemia in induction phase of chemotherapy were selected from children cancer institute and National Institute of Blood disease and Bone marrow Transplantation. Karachi, Pakistan. The study was approved by Ethical Committee of Biochemistry Department Karachi University and the study is in accordance to the principles set forth in the Helsinki declaration. Before the start of the study the patients filled the consent form for the participation in the research study. The blood samples were collected before and after the chemotherapy of induction phase that is after one month of therapy. The control subjects

were selected having no signs or symptoms of any disease clinically, and the blood counts of control subjects was also normal.

The leukemic patients received vincristine, dose 1.5gm/m^2 once a week. Daunamycin dose 25mg/m^2 once a week, L - asparaginase 6000 IU/m^2 three times per week (9 dose) along with methotrexate 10 mg / week intrathecally. The duration of chemotherapy is one month.

The blood of patients and control was analyzed for the hematological parameters such as total Leuckocyte counts, differential cell counts, packed cell volume (PCV), Mean corpuscular volume (MCV), by hematological analyzer (model. CA – 620 balder Sweden) Hemoglobin was estimated by DrabKins Method.

Liver function Tests were also performed serum Bilirubin by Randox kit method (cal. FR 4/2). Serum Gamma Glutamyl transferase (γ G T) by Randox kit (GT523). Serum alanine amino transferase by Randox kit Method (Al 1205). Serum alkaline phosphatase by Randox kit method (AP. 307)

For statistical analysis the data was analyzed by student's t – test by SPSS-16.

RESULT

The study was performed on 20 pre diagnosed (16 male, 4 female) leukemic patients with mean age 8.8 ± 1.4 years and 20 healthy normal control subjects (18 male, 2 female) having age 7.8 ± 0.79 years.

The symptoms of leukemia patients were taken before starting the drug which shows that most of the patients were suffering from fever and Fatigue and weight loss and patechia. Fewer patients complained for headache, vomiting, Bone pain and loss of appetite (Table -1). The Leukemic patients had low level of Hemoglobin, RBC count and platelet and high levels of total leukocytes counts and lymphocytes as compared to normal control children (Table – 2) The γ – Glutamyl transferase level was also high in leukemic children at the time of initial presentation as compared to control children (Table – 3).

The patients after the induction phase of chemotherapy had improved their hematological parameters, that is increased in Hb level, RBc count, PCV and MCV and Nutrophil counts as compared to the level before chemotherapy, where as the percentage of blast cells also have been decreased (Table – 2) after chemotherapy.

The ALL Patients after induction phase of chemotherapy had shown liver toxicity. The total bilirubin, direct bilirubin, Alanine amino transferase, Alkaline phosphatase and γ-Glutamyl levels were increased as compared to controls level and the level before chemotherapy (Table – 3).

Table – 1 Symptoms of Acute Lymphoblastic Leukemic Patients The symptoms of Leukemic patients are shown as the percentage

SYMPTOMS	PERCENTAGE (%)
Fever	80
Fatigue	50
Headache	30
Vomiting	10
Patechiae	75
Weight loss	100
Bone Pain	25
Loss of Appetite	25

Table – 2

Variation of hematological parameters in control and Acute Lymphoblastic leukemic patients

	Control	Patients Before chemotherapy	Patients after Induction phase of chemotherapy
Hb gm/dl	12.26 ± 0.37 (20)	* 8.24± 0.56 (20)	• 9.72± 0.39 (20)
RBC Per cubic millimeter	4.21± 0.13 (20)	* 2.78± 0.22 (20)	• 3.55± 0.15 (20)
PCV %	28.2± 1.47 (20)	* 23.8± 2.13 (20)	• 31.03± 1.58 (20)
MCV Femtoliter	86.0 ± 1.02 (20)	* 81.33± 1.59 (20)	• 84.89 ± 1.16 (20)
MCH Pg/cell	28.3± 1.35 (20)	26.69± 0.79 (20)	27.97± 0.57 (20)
TLC Per cubic millimeter	6.87± 4.33 (20)	* 16.57± 4.91 (20)	7.84 ± 3.52 (20)
Neutrophil (%)	64.5± 0.74 (20)	* 27.81± 4.73 (20)	• 46.1 ± 5.21 (20)
Lymphocytes (%)	31.4± 0.46 (20)	* 54.0± 4.71 (20)	50.8 ± 5.88 (20)

Eosinophil (%)	2.4 ± 0.24 (20)	* 1.65± 0.35 (20)	2.5 ± 0.25 (20)
Monocytes (%)	1.7± 0.27 (20)	* 3.95± 0.57 (20)	4.25 m± 0.48 (20)
Blast (%)	- - -	67.5± 5.33 (20)	• 2.65 ± 0.28 (20)
Platelets x 10^9/L	191.600± 49.7 (20)	* 129.7± 2.9 (20)	181.10 ± 3.3 (20)

* = ***P< 0.05 as compared to control subjects***

• = ***p< 0.05 as compared to Leukemic Patients before therapy***

Table – 3

Variation of serum Bilirubin and Hepatic Enzymes in control and Acute Lymphoblastic Leukemic Patients

	Control	**Patients Before chemotherapy**	**Patients after induction phase of chemotherapy**
Total Bilirubin mg%	0.67 ± 0.06 (20)	0.61 ± 0.08 (20)	• 1.55 ± 0.32 (20)
Direct Bilirubin mg%	0.23 ± 0.02 (20)	0.21 ± 0.05 (20)	• 0.61 ± 0.15 (20)
Alanine Aminotransferase u/l	27.05 ± 2.26 (20)	33.95 ± 5.20 (20)	• 61.92 ± 4.63 (20)
Alkaline Phosphatase u/l	320.36 ± 24.29 (20)	333.70 ± 26.18 (20)	• 536.56 ± 56.44 (20)
γ-Glutamyltransferase u/l	30.25 ± 3.31 (20)	* 47.59 ± 1.98 (20)	• 63.24 ± 2.79 (20)

* = ***p<0.05 statistically significant as compared to control***

• = ***p<0.05 statistically significant as compared to before therapy.***

DISCUSSION

Acute lymphoblastic leukemia is the most common childhood malignancy, which accounts for about 75 percent of pediatric acute leukemias. In the present study the sign and symptoms of Leukemic patients include fever, fatigue, headache, vomiting patechiae, weight loss, bone pain and loss of appetite. Among these symptoms weight loss was found in all patients (100%) and fever was present in 80 percent patients (Table – 1) Margolin etal[6] also had reported these symptoms in his studies.

The mean value of hemoglobin of Leukemic patients was significantly ($p<0.05$) less than normal subjects (Table – 2). The ALL patients after induction phase of treatment showed increased level of hemoglobin and red blood cell, yasmin etal also showed early hematopoietic recovery in remission induction phase of ALL children.[7]

The mean value of neutophil count of Leukemic patients was significantly low ($p<0.05$) as compared to control subjects (Table – 2). In majority of patients the neutropenia is due to the infiltration of Leukemic cells in the marrow which decreases the production of these cells.[8] The total leukocytes Lymphocytes and monocytes of leukemia patients are greater ($p<0.05$) than the normal control subjects. Hyperleukocytosis occurs in the patients of acute lymphoblastic Leukemia.[9]

In ALL the bone marrow makes a lot of unformed cells called blasts that normally would develop into Lymphocytes. However in ALL the blasts are abnormal and they do not develop and cannot fight infection. These abnormal cells grow quickly[6] and are found in the blood of ALL patients. Blast cells is an identification of Leukemia. But after chemotherapy of induction phase the number of Blast cells decreased (Table – 2). In the present studies less platelet counts was found in leukemic patients as compared to normal subjects. Thrombocytopenia is a common complaint of leukemia.[8]

The serum γ – Glutamyl transferase level in leukemic children was higher as compared to control normal children. The level of ALT was also high but not significant in leukemic patients as compared to controls. Seqal etal[10] had found elevated transaminases in leukemic patients at initial presentation which may be due to hepatic injury from leukemic infiltrates.

The ALL patients were given induction chemotherapy. The goal of the induction therapy is to bring the disease into remission. Remission is, when the patients' blood counts return to normal and bone marrow samples show no sign of disease. Induction therapy achieves a remission in more than 95% of children.[11] Induction therapy is very intense and last for about one month. In the present study the number of blast cell decreased significantly after induction phase of chemotherapy Rana

also reported a decreased level of blast cells in 74% patients after the end of induction chemotherapy.

In the present study the ALL patient's blood sample were taken before chemotherapy and the second blood sample was taken after one moth of induction phase of therapy. Chemotherapy includes vincristine, L – Asparaginase, Daunomycin and Methotrexate drugs, which effects all rapidly dividing cells whether it is cancerous or normal which is the basis of many side effects of drugs used in leukemia treatment.[12]

Anemia may arise as a potential complication for the leukemia therapy[13]. Thrombocytopenea occur in cancer patients Daunamycine may cause a mild reduction in platelet count. Vincristine is often used to increase the platelets from marrow and results in thrombocytosis. Thrombosis is the main complication of asparaginase therapy due to the decrease of antithrombin[14].

In the present study an increase in hemoglobin concentration, RBC count, Packed cell volume and neutrophil count was found in patient's blood after chemotherapy as compared to before treatment. This increase in values may be due to blood transfusion during treatment.

In this study a moderate increase of ALT & AST and a significant increase of γ-Glutamyl transferase was observed at initial presentation of ALL, which may be due to hepatic injury[10] from Leukemic infiltrates. Chemotherapy also cause liver damage and the level of LFT enzymes increased significantly after chemotherapy. Alanine amino transferase is mainly found in liver but due to the damage of liver by chemotherapy ALT levels are increased in the blood. Gama glutamyl transferase (γ GT) is also a liver enzyme, and is a sensitive indicator of hepatobiliary condition. Drugs used in chemotherapy may also cause high γ GT level in the blood. Bilirubin increased level in the blood also is an indicator of liver dysfunction[15]. The earlier studies reported gastrointestinal (GI), hepatic & Neurological abnormalities during remission induction phase.[16]

The present study shows a significant increased blood level of Bilirubin, ALT, Alkaline phosphatase and γ – Glutamyl Transferase of ALL patients after chemotherapy as compared to before chemotherapy. So these elevated biochemical parameters were due to hepatotoxicity induced by chemotherapy after induction phase of treatment with drugs. It is concluded that vincristine. L – Asparagnase, Daunamycine and Methotrexate cause hepatotoxicity and also produce hematological complications.

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