EFFECT OF CHEMOTHERAPY ON LIVER FUNCTION DURING INDUCTION OF REMISSION IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA RECEIVING STANDARD PROTOCOL

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Abstract

Objective: *The present study was undertaken to assess liver function (using markers like SGPT, serum bilirubin, prothrombin time, serum albumin) in children suffering from Acute Lymphoblastic Leukemia.*

Materials & Methods: *This study was carried out in the Department of Pediatric Hematology & Oncology, Dhaka Medical College Hospital, Dhaka, over a period 12 months from the day of approval of the protocol. All acute lymphoblastic leukaemia children admitted in Pediatric Hematology & Oncology Department in Dhaka Medical College Hospital and receiving chemotherapy of standard protocol for induction of remission were the study population. A total of outcome variable was hepatotoxicity resulting from chemotherapy given for induction of remission.*

Result: *The mean age of the children was 4.4 years (range 2- 8 years). Males were a bit higher in the series with male to female ratio being 11:9. Liver function tests before therapy revealed that none of the children exhibited raised serum billirubin and only 2(4.5%) children had increased SGPT. However, 50% of the children had raised prothrombin and 43.2% had reduced serum . albumin. Liver function tests after therapy after induction of remission shows that 9(20.5%) children exhibited raised serum billirubin, the proportion of children with raised prothrombin remained almost same as before but the status of serum billirubin improved to some extent. However, proportion of children with raised SGPT was increased to 25%. Comparison of liver function in children after therapy during induction of remission with that before induction did not show any significant difference, except that the serum SGPT was significantly raised during induction of remission ($p < 0.001$).*

Conclusion: *The study concluded that the current therapy for induction of remission of ALL cases does not produce any toxic effect on liver. Although, enzymes like SGPT take a sharp rise during induction of remission, it is transient and does produce any deleterious effect on liver.*

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Introduction

Leukemia is the most common childhood malignancy, accounting for about 41% of all childhood malignancies.[1,2] It can be broadly divided into two types: Acute Leukemia and Chronic Leukemia. Acute Leukemia accounts for about 97% of all childhood leukemias.[3] Among them Acute Lymphoblastic Leukemia (ALL) is 80% and Acute Non Lymphocytic Leukemia (ANLL) is 20%.[3] Acute lymphoblastic leukaemia occurs in both children and adults but its incidence peaks between 2 and 5 years of age. [4] There are about 13000 new cases of childhood cancer among them near about 2600 ALL in the Bangladesh each year.[5]

Diagnosing ALL begins with a medical history, physical examination, complete blood count, and blood smears. A bone marrow biopsy is conclusive proof of ALL. A lumbar puncture (also

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known as a spinal tap) will tell if the spinal column and brain have been invaded. For a patient with ALL, the treatment plan includes multidrug chemotherapy, radiation therapy and bone marrow transplantation. Now a days risk-based protocol is used for ALL patient. The stages of chemotherapy are induction of remission, consolidation, interim maintenance, delayed intensification and maintenance. [6,7] The drugs used during induction of remission are Methotrexate, Cytarabin, Vincristin, Asperginase, Dexamethasonede and 6-mercaptopurine. The total duration of treatment is 2 to 2.5 years. [7] The duration of induction of remission is 28 days. In case of relapse the standard treatment is allogenic hematopoietic cell transplantation (HCT) after induction and consolidation.[8] The prognosis of Acute Lymphoblastic Leukemia is excellent at initial presentation with complete remission with multidrug induction chemotherapy of up to 98%.[9] The current 5 year event free survival rate is 90% .[10]

Liver is the largest gland in the body. Hepatomegaly is common in leukemia (30-40%), have clinical and biochemical abnormalities in liver function tests sometimes during the illness.[1] It is due leukemic liver infiltration. Although hepatic involvement is usually mild and silent at the time of diagnosis, a postmortem study showed liver infiltration in > 95% of Acute Lymphoblastic Leukemia cases.[11,12] Massive leukemic cell infiltration of the liver may present as fulminant hepatic failure.[11,13]

The most important cause of liver involvement in leukemic patient is chemotherapy. Drugs used in the treatment of Acute Leukemia are Methotrexate, Asparginase, Vincristin, Cytarabin, 6-Mercaptopurine and steroid. These drugs have a wide range of hepatotoxicity. Cytotoxic drugs cause rise of transaminases if large amounts are given and serum bilirubin concentration become significantly higher than before intervention as anticancer drugs decrease metabolic activity of liver .[14] Liver function test is an important indicator for showing adverse effect of chemotherapy on liver. Commonly available liver function tests are SGPT, serum bilirubin, prothrombin time and serum albumin.[15] A study was conducted in Japan among 27 children of ALL. Liver function test was done at baseline and 3 months apart. SGPT was elevated three times of normal in all reports but it became normal after completion of chemotherapy. Serum bilirubin, prothrombin time and serum albumin were normal from starting of chemotherapy up to completion.[16] The Cochrane Review database shows liver complications to be common during and soon after treatment for childhood cancer. However, about 8-53% of the childhood cancer survivors developed hepatic late adverse effect after treatment.[17] The present study will show liver function abnormalities in leukemic patient receiving induction of remission chemotherapy.

Materials & methods

This prospective analytical study was carried out in the department of Pediatric Hematology & Oncology, Dhaka Medical College Hospital, Dhaka. Total 44 children with acute lymphoblastic leukaemia patients from 2-10 years receiving chemotherapy for induction of remission in Pediatric Hematology & Oncology Department in Dhaka Medical College Hospital were included in this study. Children suffering from liver disease and parents/guardians were unwilling to allow their children to participate in the study were excluded. After enrollment physical examination was done. With all aseptic precaution 10 ml venous blood were collected from medial cubital vein of patient and was sent for liver function test. Serum albumin was done by Spectrophometer or colorimeter measuring at 630 nm (SPAIN) and general laboratory equipment. SGPT was done by Autoanalyzer Spintech 240 (SPAIN). Serum bilirubin was done by the TBIL Flex reagent cartridge, Cat. No. DF 67 A. Prothrombin time was done by NEOPLASTNE CL PLUS (5) Kits. All tests were done by chief technician of clinical pathology department of Dhaka Medical College Hospital. Second sample was taken after completion of Induction remission phase of treatment of Acute Lymphoblastic Leukemia. Informed written consent was taken from guardian and protocol was passed by ethical board of Dhaka Medical College.

Using computer software SPSS (Statistical Package for Social Sciences) data were processed and analysed. The test statistics used to analyse the data were descriptive statistics, Chi-square ($\div^2$) Probability Test (for comparison of data presented on categorical scale). Level of significance was set at 5% and $p < 0.05$ was considered significant.

Result

The mean age of the patients was 4.4 years and the youngest and the oldest children were 2 and 8 years old respectively About 55% of the respondents were male and the rest female giving a male to female ratio of roughly being 1.1:1 .

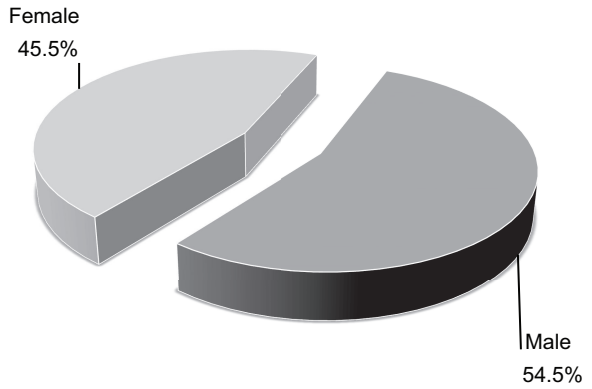

Fig.-1: *Distribution of patients by their sex (n = 44)*

Table-I

Distribution of patients by their symptoms (n = 44)

Symptoms	Frequency	Percentage
Fever	44	100.0
Progressive pallor	40	90.9
Bleeding Purpura/ Petechiae	30	68.2
Bone pain	16	36.4
Mucosal bleeding	12	27.3
Gum bleeding	8	18.2
Joint pain	6	13.6

Almost all children presented with fever with mean temperature being 100^0C. In 50% cases single and in 50% cases multiple lymph nodes LN were involved. Approximately 64% had hepatomegaly and 45.5% splenomegaly

Table-II

Distribution of patients by their physical findings (n = 44)

Physical findings	Mean	SD
Temperature (°C)	100	0.7
Pulse (beats/min)	98.4	12.4
Systolic BP (mmHg)	91.4	7.3
Diastolic BP(mmHg)	59.1	6.4
LN group involved		
Single	22	50
Multiple	22	50
Hepatomegaly	28	63.6
Splenomegaly	20	45.5

Investigation findings show that the mean Hb level was 7.2 ± 1.3 gm/dl. The mean TC of WBC, differential count and mean platelet count are illustrated in table IV. While lymphocyte count was drastically increased, neutrophil count was reduced to great extent. A sizable portion of blast cell were also found (13.2%). Platelet count was not was within normal range.

Table-III

Distribution of patients by their investigations (n = 44)

Investigations	Mean	SD	Range
Hb (gm/dl)	7.2	1.3	3.7-9.5
TC (/mm^3)	17452.5	12043.5	3470 – 40000
DC			
Neutrophil (%)	15	8	6 – 36
Lymphocyte (%)	50	20	10 – 90
Eosinophil (%)	2	1.6	0 – 7
Monocyte (%)	2	1.9	0 – 7
Blast cell (%)	31	25	0 – 80
Total platelet count (/mm^3)	28613.6	23798.7	5000 – 90000

Liver function tests before therapy showed that none of the children exhibited raised serum billirubin and only 2(4.5%) children had increased SGPT. However, 50% of the children had risen prothrombin time and 43.2% had

Table-IV

Comparison of liver function in children before therapy and after induction of remission (n = 44)

Biochemical variables	Groups		p-value
	Before therapy	During remission	
S. bilirubin (mg/dl)	0.8 ± 0.2	1.2 ± 0.6	0.921
SGPT (IU/L)	33.0 ± 2.0	95.4 ± 17.9	< 0.001
Prothombin time (sec)	12.9 ± 0.2	12.7 ± 0.9	0.549
S. albumin (g/dl)	4.1 ± 0.02	4.2 ± 0.02	0.602

reduced a. albumin. Liver function tests after induction of remission therapy showed that 9(20.5%) children exhibited raised serum billirubin, the proportion of children with raised prothrombin time remained almost same as before but the status of serum billirubin improved to some extent. However, proportion of children with raised SGPT was increased to 25%. There was no significant difference in children before therapy and after therapy during induction of remission with respect to liver function test, except that the serum SGPT was significantly raised during induction of remission ($p < 0.001$).

Discussion

The present study demonstrated that antileukemic therapy given for induction of remission did not induce hepatotoxicity except that the serum SGPT was transiently increased during induction of remission. An ALT level of more than three times the upper limit of normal values and a total bilirubin concentration of more than twice the upper limit are used to define clinically significant abnormalities on liver test. Elevation in serum enzyme levels is taken as indicator of liver injury, whereas increases in bilirrubin levels, albumin concentration and the prothrombin time are measures of overall liver function.[18] In the present study only three patients had SGPT more than three times the upper limit of the normal range. The serum billirubin, serum albumin and prothrombin time were not altered to significant proportion

However, studies show that despite progress in the treatment of childhood acute lymphoblastic leukaemia, current therapy is not free from its toxic effect on liver, which is a serious concern for the paediatricians engaged in the management of the ALL cases. The true incidence of subclinical hepatic pathology undoubtedly is higher. This is because the presence of subclinical cirrhosis is seldom detected by abnormal liver function tests. Transaminasemia may be asymptomatic and liver biopsies or liver scans are not routinely done after therapy.[19]

Methotrexate has been implicated as a cause of chronic hepatopathy. Chemotherapy-induced hepatotoxicity is a common cause of abnormal liver function test in patients with ALL.

Hepatotoxicity usually begins with vague clinical symptoms such as fatigue, anorexia, nausea, dark urine, right upper quadrant discomfort and jaundice.

However, the latent period is highly variable and enzyme levels may take weeks to increase. Before attributing these symptoms to a chemotherapy drug, other causes of liver injury must be ruled out.[18]

Abnormal liver function may be due to multiple causes in patients with ALL. Leukemic infiltration usually causes mild to moderate hepatomegaly with limited impact on serum transaminase levels. Transfusions increase the likelihood of viral hepatitis. Other circumstances such as sepsis, hypotension or malnutrition may contribute to liver damage.[20].

ALL patients are treated with combination chemotherapy, making it difficult to identify the precise agent involved in the hepatic injury. Moreover, diagnosis becomes more challenging by the large number of non-chemotherapeutic drugs commonly used in those patients, some of them holding the potential of being hepatoxic, e.g. allopurinol, ondansetron and different antifungal agents.[21]

Pre-existing liver disease can alter the metabolism and excretion of chemotherapy

causing increased and persistent drug levels and hence systemic toxicity. On the other hand, chemotherapy may worsen liver disease, such as occurs with hepatitis. Severe liver dysfunction and fatal fulminant hepatitis through virus reactivation have been described in patients with viral hepatitis. Prophylactic therapy with nucleoside analogues, typically lamivudine, has been recommended for HBs Ag positive patients. This strategy has been reported to allow optimal administration of chemotherapy.[22]

Summarizing the findings of the present study, it is evident that antileukaemic therapy for induction of remission can safely be given without any major alteration in liver function. However, the enzymes like SGPT rises during induction of remission is transient and not injurious to liver.

Conclusion

From the findings of the present study, it can be concluded that the current therapy for induction of remission of ALL cases does not produce any toxic effect on liver. Although, enzymes like SGPT take a sharp rise during induction of remission, it is transient and does not produce any deleterious effect on liver. However, as the sample size was small, a large-scale study is recommended to validate findings of the present study.

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