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Impairment of liver function in pediatric acute leukemia before and after induction chemotherapy

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Abstract

Background: Patients of acute leukemia require careful assessment of liver function prior to start chemotherapy to determine which drugs may be appropriate or to be modified. Post chemotherapy abnormalities of liver function tests may be due to drugs or due to disease itself.

Objective: To evaluate the status of liver function in Pediatric acute leukemia patients before and after induction chemotherapy.

Methodology: This was a prospective cross-sectional study conducted in the Department of Pediatric Hematology & Oncology Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh from January 2022 to December 2023 on sixty (60) newly diagnosed patients of acute leukemia who fulfilled the selection criteria. Blood samples for serum total bilirubin, alanine transaminase (ALT) and aspartate transaminase (AST) were collected before chemotherapy (Day 1) and after induction chemotherapy on 14th day and 30th day. Serum ALT and AST were measured by kinetic method and serum total bilirubin was measured by DMSO method. Data were analyzed and compared by statistical tests.

Result: In this study, the mean level of serum total bilirubin before chemotherapy at day 1 was 0.78 ± 0.72 mg/dl. It was significantly ($p < 0.001$) raised to 1.32 ± 0.95 mg/dl at day 14 of chemotherapy, and again significantly ($p < 0.002$) reduced to 0.71 ± 0.45 mg/dl at day 30 of chemotherapy as compared to day 1. Similarly the mean serum ALT at day 1 was 43.55 ± 12.23 U/L which significantly ($p < 0.001$) raised to 89.04 ± 58.22 U/L at day 14 of chemotherapy and significantly ($p < 0.001$) reduced at day 30 of chemotherapy to 35.44 ± 9.23 U/L as compared to day 1. The mean serum aspartate transaminase (AST) before chemotherapy at day 1 was 37.12 ± 6.22 U/L that significantly ($p < 0.001$) increased to 45.43 ± 6.21 U/L at day 14 of chemotherapy and significantly ($p < 0.001$) decreased to 34.21 ± 4.33 U/L at day 30 of chemotherapy compared to baseline value at day 1.

Conclusion: It is concluded that serum total bilirubin, ALT and AST increase in response to chemotherapeutic drugs during treatment of acute leukemia.

Keywords: Acute leukaemia, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, chemotherapy

Introduction

Hematological malignancy originates from hematopoietic cells in the bone marrow and lymphatic system^[1]. Acute leukemia is a heterogeneous group of diseases characterized by uncontrolled and clonal neoplastic proliferation of hematopoietic precursor cells with impairment of normal hematopoiesis leading to neutropenia, anemia and thrombocytopenia^[2]. Acute myeloid leukemia (AML) involves myeloid precursors in the bone marrow and acute lymphoblastic leukaemia (ALL) involves lymphoid precursor cells at bone marrow and other lymphoid organs. AML represents 15% to 20% of acute leukemia cases in children and 80% in adults^[2]. In the United States, the number of new cases of acute myeloid leukemia is 4.3 per 100,000 people per year^[3]. ALL affects both children and adults, with peak prevalence between the ages of 2 and 5 years reported in up to 68% of ALL pediatric patients at diagnosis^[4]. Bilirubin is the breakdown product of the hem moiety of hemoglobin and other hemoproteins. Because of internal hydrogen bonding, bilirubin is water-insoluble and requires enzyme-mediated glucuronidation in the liver for biliary excretion. In normal circumstances plasma bilirubin is mostly unconjugated and is tightly bound to circulating albumin. It is taken up by hepatocytes by facilitated diffusion, stored in hepatocytes bound to glutathione-S-transferases and conjugated to glucuronides by microsomal UGT1A1.

Bilirubin glucuronides are actively transported into the bile canaliculi. Bilirubin is degraded in the intestine by bacteria into urobilinogen, which is partly excreted in the urine. Increased production, reduced uptake and low glucuronidation capacity of liver can increase plasma unconjugated bilirubin levels. In cases of inherited or acquired deficiencies of bilirubin storage or excretion, both conjugated and unconjugated bilirubin accumulates in the plasma. Conjugated bilirubin is less tightly bound to albumin and is excreted in the urine [5]. Aminotransferase levels are sensitive indicators of liver-cell injury and are helpful in recognizing hepatocellular diseases such as hepatitis. Both aminotransferases, i.e. alanine transaminase (ALT) and aspartate transaminase (AST) are normally present in serum at low levels, usually less than 30 to 40 U per liter (U/L). ALT catalyzes the transfer of amino groups to form the hepatic metabolite oxaloacetate. It is found abundantly in the cytosol of the hepatocyte, about 3000 times that of serum. Hepatocellular injury causes release of ALT in serum with its impaired catabolism. It results in its plasma half-life of 47 ± 10 hours and therefore high serum ALT level. Although it is generally thought to specific for the liver also found in the kidney and in much smaller quantities in heart and skeletal muscle cells. AST is found in cells throughout the body but mostly in the heart and liver. It is present to a lesser extent in other tissues e.g., in decreasing order of concentration, in skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes. Therefore AST also usually rise immediately after hepatocellular injury and reaches a higher level than ALT initially. Then if the damage is ongoing, ALT will become higher than AST within 24 to 48 hours, because of its longer plasma half-life. ALT is also more commonly elevated than AST in chronic hepatocellular injury; however, as fibrosis progresses, ALT activities typically decline and the ratio of AST to ALT gradually increases, as it is true for cirrhosis. Both enzymes are released into the blood in increasing amounts when the liver cell membrane is damaged. The liver transaminases are considered the most sensitive indicator for hepatocellular necrosis (hepatitis). These enzymes play a role in gluconeogenesis by supplying amino acid for TCA cycle. ALT is more specific marker than AST for liver injury, since it is mostly found in liver tissue, localized to hepatocytes cytosol [6]. Abnormal liver biochemistries are regularly observed in Pediatric all patients, most often in their treatment course and usually reflect hepatic injury secondary to therapeutic interventions related to drugs, infection, veno-occlusive disease or ischemia. Higher leucocyte count, serum uric acid and lactate dehydrogenase (LDH) are more commonly seen in ALL patients. Patients with acute leukemia (ALL/AML) commonly present with elevated aminotransferases along with hyperbilirubinemia. This is likely due to hepatic injury from leukemic infiltrates [7]. The univariate analysis found that patients with T-cell ALL are more likely to present with hepatitis than patients with B-lineage ALL [7]. The liver is the largest and the central parenchymatous organ of the body for intermediary metabolism in a balanced regulation. The administration of chemotherapy is a challenge for the tight regulations and balance of the metabolic processes. As most of the drugs tend to be lipophilic, they are readily taken up by the liver. Up to 85% of patients develop liver steatosis with chemotherapy. Steatohepatitis is the more serious event, especially if accompanied by increase in

serum bilirubin level [8]. The major mechanisms underlying chemotherapy related hepatotoxicity are based on the production of reactive metabolites generated by oxidation reactions, immunological injury or alterations in mitochondrial function. Underlying liver disease and hepatic involvement by tumor are important modifiers of liver injury and its reversibility is not universal after drug cessation. Chemotherapy can also exacerbate underlying liver disease particularly hepatitis B leading to worsening hepatic function [9]. Induction chemotherapy in standard treatment protocols for all includes vincristine, anthracyclines, asparaginase, intrathecal methotrexate and steroids. AML is relatively chemotherapy resistant disease especially in older patients who are rarely cured. The current standard of care includes intensive chemotherapy followed by consolidation therapy or allogenic stem cell transplantation [10]. Since asparaginase, vincristine and anthracyclines require hepatic metabolic detoxification, hepatic dysfunction may influence the risk of toxicity. Asparaginase is an integral component of multi-agent chemotherapy regimen for the treatment of childhood acute lymphoblastic leukemia and is associated with hepatic toxicity [11]. Its toxicities include hypersensitivity, pancreatitis, thrombosis, encephalopathy and liver dysfunction [12]. A widely used combination for induction of acute myeloid leukaemia (AML) is the cell cycle-specific agent cytarabine by continuous infusion for 7 days and the non-cell-cycle-specific anthracycline antibiotic daunorubicin intravenously for 3 days [2]. Doxorubicin and daunorubicin are extensively metabolized in the liver. Idiosyncratic liver injury has been reported with both drugs [9]. Mitoxantrone, another anthracycline antibiotic, may have a lower incidence of serious toxicities than other anthracycline anticancer drugs. When used in leukemic patients, the drug produces transient elevation in liver transaminases [13]. Chemotherapy and bone marrow transplantation are the treatment of acute leukemia. Their toxicities are common cause of morbidity and mortality of leukemia patients. Recent studies reported that altered liver function specially ALT, AST and total bilirubin in acute leukemia patients during diagnosis and after induction chemotherapy may delay the treatment schedule and even the patient may expire due to hepatotoxicity [14]. The next important factor after diagnosis of acute leukemia is to select a specific chemotherapy regime. Careful assessment of liver function is mandatory to select or modify the treatment regimen. Abnormalities of liver function tests after starting chemotherapy may be due to therapy rather than progressive disease, and this distinction is of critical importance [13]. Chemotherapeutic agents may cause hypersensitivity reactions or direct hepatic toxicity, and altered liver function may alter drug metabolism and cause an increased risk of non-hepatic toxicity [13]. Therefore, the aim of current study was to measure and compare the liver function tests in patients of acute leukemia before and after starting chemotherapy to develop awareness regarding liver function.

Materials and Methods

This prospective cross sectional study was conducted in the Department of Pediatric Hematology & Oncology Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh from January 2022 to December 2023. This study was approved by the Ethical Review Committee of Bangladesh Shishu Hospital & Institute. A total of sixty (60) newly

diagnosed acute leukemia (AML and ALL) patients were selected according to the statistical calculation following selection criteria. Patients of acute leukemia on chemotherapy, age between 1-18 years of both sexes were selected purposively. Patients of chronic myeloid leukemia (CML), patients having any previous or pre-existing liver disease, acute leukemia who were taking anti-tubercular drugs, acute leukemia having acute/chronic renal failure or other known malignancy were excluded from the study.

After selection of the subjects the objectives, nature, purpose and potential risk of all procedures used for the study were explained in details and informed written consent were taken from each participant. Participant's particulars, detailed history and findings of clinical examination were recorded in data collection sheet.

With all aseptic precautions 3 ml of venous blood was collected before starting chemotherapy (Day 1), second and third blood samples were collected by following the same procedure from same study participants at 14th day and at 30th day of chemotherapy. Investigations such as serum total bilirubin, ALT and AST was done and result was recorded. All the biochemical tests were performed at our Biochemistry department. The outcome variables-serum total bilirubin, serum AST, serum ALT were analyzed and compared by statistical tests. In our study S. Bilirubin (Total): 0.3 - 1 mg/dl, ALT (Alanine Transaminase): <45 U/L (Male), <34 (Female) and AST (Aspartate Transaminase): <35 U/L (Male), <31 (Female) taken as normal [15].

Statistical Analysis of Data

All data were recorded in a pre-tested data collection sheet. Data cleaning, validation and analysis were performed using

the Statistical Package for Social Science (SPSS) software for Windows version-23. Categorical data were presented as frequency/percentage and continuous variable was expressed as mean \pm SD (standard deviation) and were compared by paired "t" test. Level of significance was defined as p value < 0.05 at 95% confidence interval.

Results

This prospective study was carried out to evaluate the assessment of liver function in acute leukemia patients before starting chemotherapy (Day 1), at 14th day and at 30th day of induction chemotherapy. A total of sixty (60) acute leukemia patients were selected as study subjects. Of them thirty two (32) were male and twenty eight (28) were female, male to female ratio was 1.14:1.0. Mean age of the patients were 4.45 \pm 2.99 years.

Grouping of subjects

- **Group A (60):** Day 1 (Before chemotherapy).
- **Group B (60):** At 14th day of chemotherapy.
- **Group C (60):** At 30th day of chemotherapy.

Table 1: Distribution of the study subjects according to the type of leukemia (n = 60). n = Number of study subjects.

	Frequency (n)	Percentage (%)
ALL	40	66.67
AML	20	33.33

Among total 60 study populations, 40 (66.67%) were acute lymphoblastic leukemia (ALL) and 20 (33.33%) were acute myeloid leukemia (AML) (Table 1).

Table 2: Comparison of serum total bilirubin before chemotherapy (Day 1), 14th day of chemotherapy and 30th day of chemotherapy (n = 60).

Group	Day of treatment	Mean \pm SD (Range)	Comparison	p value
A	Day 1 (Before chemotherapy)	0.78 \pm 0.72 mg/dl (0.30 - 2.20)	A vs B	0.001
B	14 th day of chemotherapy	1.32 \pm 0.95 mg/dl (0.32 - 3.10)	B vs C	0.001
C	30 th day of chemotherapy	0.71 \pm 0.45 mg/dl (0.27 - 1.54)	A vs C	0.002

Mean (\pm SD) serum total bilirubin of the study population before chemotherapy (Day 1), at 14th day of chemotherapy and 30th day of chemotherapy were 0.78 \pm 0.72 mg/dl, 1.32 \pm 0.95 mg/dl and 0.71 \pm 0.45 mg/dl respectively. It was observed that serum total bilirubin was significantly

increased (p < 0.001) from baseline (Day 1) at 14th day of chemotherapy which was significantly decreased (p<0.002) from baseline (Day 1) at 30th day of chemotherapy (Table 2).

Table 3: Comparison of serum alanine transaminase (ALT) before chemotherapy (Day 1), 14th day of chemotherapy and 30th day of chemotherapy (n = 60).

Group	Day of treatment	Mean \pm SD (Range)	Comparison	p value
A	Day 1 (Before chemotherapy)	43.55 \pm 12.23 U/L (25.00 - 78.00)	A vs. B	0.001
B	14 th day of chemotherapy	89.04 \pm 58.22 U/L (31.00 - 244.00)	B vs. C	0.001
C	30 th day of chemotherapy	35.44 \pm 9.23 U/L (20.00 - 84.55)	A vs. C	0.001

Mean (\pm SD) serum alanine transaminase (ALT) of the study population before chemotherapy (Day 1), at 14th day of chemotherapy and 30th day of chemotherapy were 43.55 \pm 12.23 U/L, 89.04 \pm 58.22 U/L and 35.44 \pm 9.23 U/L respectively. It was observed that serum ALT was

significantly increased (p<0.001) from baseline (Day 1) at 14th day of chemotherapy which was significantly decreased (p<0.001) from baseline (Day 1) at 30th day of chemotherapy (Table 3).

Table 4: Comparison of serum aspartate transaminase (AST) before chemotherapy (Day 1), 14th day of chemotherapy & 30th day of chemotherapy (n = 60).

Group	Day of treatment	Mean \pm SD (Range)	Comparison	p value
A	Day 1 (Before chemotherapy)	37.12 \pm 6.22 U/L (24.00 - 47.00)	A vs B	0.001
B	14 th day of chemotherapy	45.43 \pm 6.21 U/L (27.00 - 57.00)	B vs C	0.001
C	30 th day of chemotherapy	34.21 \pm 4.33 U/L (22.00 - 42.00)	A vs C	0.001

Mean (\pm SD) serum aspartate transaminase (AST) of the study population before chemotherapy (Day 1), at 14th day of chemotherapy and 30th day of chemotherapy.

Values are expressed in Mean \pm SD; Values within parenthesis indicate range; Paired “t” test was done to measure the level of significance; n = Number of subjects; $p < 0.05$ statistically significant; Group A: Day 1 (Before chemotherapy); Group B: 14th day of chemotherapy; Group C: 30th day of chemotherapy.

Mean (\pm SD) serum aspartate transaminase (AST) of the study population before chemotherapy (Day 1), at 14th day of chemotherapy and 30th day of chemotherapy were 37.12 \pm 6.22 U/L, 45.43 \pm 6.21 U/L and 34.21 \pm 4.33 U/L respectively. It was observed that serum AST was significantly increased ($p < 0.001$) from baseline (Day 1) at 14th day of chemotherapy which was significantly decreased ($p < 0.001$) from baseline (Day 1) at 30th day of chemotherapy (Table 4).

Discussion

In the present study, among total sixty (60) acute leukemia patients, acute lymphoblastic leukemia (AML) patients were 40 (66.67%) and acute myeloid leukemia patients were 20 (33.33%). This study showed that before starting chemotherapy, mean serum total bilirubin level in acute leukemia patients was 0.78 \pm 0.72 mg/dl. Similar findings were observed in the previous studies as reported that conjugated hyperbilirubinemia of acute leukemia at presentation is common which may require treatment modification and dose reduction [16, 17]. At 14th day of chemotherapy, mean serum total bilirubin level in acute leukemia patients was 1.32 \pm 0.95 mg/dl which was significantly ($p < 0.001$) higher than the value measured before starting chemotherapy (0.78 \pm 0.72 mg/dl). This finding was consistent with previous studies as observed that induction chemotherapy appears to result hyperbilirubinemia [16, 17]. This may be due to pre-hepatic hyperbilirubinemia because of hemolytic anemia as a result of action chemotherapy [18]. At 30th day of chemotherapy, mean serum total bilirubin in acute leukemia patients was 0.71 \pm 0.45 mg/dl which was significantly ($p < 0.002$) lower than the value measured before starting chemotherapy (0.78 \pm 0.72 mg/dl). Similar findings were observed in previous studies [15, 16, 17] as showed that decrease of serum total bilirubin on 7th day & 18th day of chemotherapy [16]. At 14th day of chemotherapy mean serum total bilirubin in acute leukemia patients was 1.32 \pm 0.95 mg/dl & there was significant change ($p < 0.001$) of serum total bilirubin between 14th day of chemotherapy and 30th day of chemotherapy (0.71 \pm 0.45 mg/dl). This finding was similar to the previous study as reported that serum total bilirubin and indirect bilirubin significantly increase during chemotherapy compared to their levels before chemotherapy [15]. In this current study before starting chemotherapy, mean serum alanine transaminases (ALT) level in acute leukemia patients was 47.46 \pm 15.00 U/L. Similar finding was observed in previous studies as showed that elevated alanine transaminases (ALT) are common at initial presentation of acute leukemia and are likely due to hepatic injury from leukemic infiltrates [19, 20]. At 14th day of chemotherapy mean level of serum ALT was 89.04 \pm 58.22 U/L which was significantly ($p < 0.001$) higher than the value measured

before starting chemotherapy (43.55 \pm 12.23 U/L). This finding was consistent with previous reports as stated that chemotherapy-induced hepatotoxicity is a common cause of abnormal liver function test in patients with acute leukemia [17]. It mainly occurs in an idiosyncratic manner and is generally reversible and nonfatal [21]. In this study it was observed that at 30th day of chemotherapy mean level of serum ALT in acute leukemia patients was 35.44 \pm 9.23 U/L which was significantly ($p < 0.001$) lower from the value measured before starting chemotherapy (43.55 \pm 12.23 U/L). This observation was consistent with other studies as showed that chemotherapy-induced hepatotoxicity is transient and generally reversible [17, 21]. It was observed that at 14th day of chemotherapy the mean serum ALT in acute leukemia patients was 89.04 \pm 58.22 U/L and there was significant change ($p < 0.001$) of serum ALT between 14th day of chemotherapy and 30th day of chemotherapy (35.44 \pm 9.23 U/L). Similar findings were observed in the previous studies as showed that chemotherapy-induced hepatotoxicity is reversible [21]. In current study it was found that the mean serum aspartate transaminase (AST) level before starting chemotherapy in acute leukemia patients was 37.12 \pm 6.22 U/L. This observation was consistent with previous studies as reported that elevated serum aspartate transaminase (AST) is common at initial presentation of acute leukemia due to hepatic injury from leukemic infiltrates [19, 20]. In this study it was showed that at 14th day of chemotherapy mean level of serum AST in acute leukemia patients was 45.43 \pm 6.21 U/L, which was significantly higher ($p < 0.001$) than the value measured before starting chemotherapy (37.12 \pm 6.22 U/L). This finding was accorded with previous studies as showed that chemotherapy-induced hepatotoxicity is common in patients with acute leukemia [20]. In this study it was observed that at 30th day of chemotherapy mean level of serum AST in acute leukemia patients was 34.21 \pm 4.33 U/L, which was significantly ($p < 0.001$) lower from the value measured before starting chemotherapy (37.12 \pm 6.22 U/L). This result was consistent with previous study as showed that chemotherapy-induced hepatotoxicity is nonfatal and reversible [21]. At 14th day of chemotherapy the mean serum level of serum AST in acute leukemia patients was 45.43 \pm 6.21 U/L & there was significant change of serum AST ($p < 0.001$) between 14th day of chemotherapy and 30th day of chemotherapy (34.21 \pm 4.33 U/L). Similar findings were observed in previous studies as showed that chemotherapy-induced hepatotoxicity is reversible [19, 20]. Hepatotoxicity from chemotherapy occurs frequently in an unpredictable or idiosyncratic fashion and preexisting liver injury increases this risk. This study revealed that elevations in liver function tests due to leukemia itself or chemotherapy. Therefore patients who received chemotherapy require careful assessment of liver function during treatment to determine which drugs may not be appropriate and which drug dose should be modified.

Conclusion

This study concluded that serum total bilirubin, ALT and AST increase in response to chemotherapeutic drugs during treatment of acute leukemia. Liver function test should be regularly evaluated during the treatment of patients with acute leukemia.

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