Journal of Biosciences and Medicines, 2020, 8, 110-121
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Liver Function Tests in Patients of Acute Leukemia before and after Induction Chemotherapy

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How to cite this paper: Islam, T., Rahman, A.K.M.S., Hasan, M.K., Jahan, F., Mondal, M.C., Ferdoushi, S., Alam, S., Ahsan, M.K., Tasnim, J. and Tohura, S. (2020) Liver Function Tests in Patients of Acute Leukemia before and after Induction Chemotherapy. *Journal of Biosciences and Medicines*, **8**, 110-121.
https://doi.org/10.4236/jbm.2020.82009

Received: January 25, 2020
Accepted: February 17, 2020
Published: February 20, 2020

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 process itself. **Objective:** To evaluate the status of liver function in acute leukemia patients before and after induction chemotherapy. **Methodology:** This was a prospective cross-sectional study conducted in the Department of Biochemistry, Dhaka Medical College, Dhaka, Bangladesh from January 2017 to December 2017 on fifty (50) 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 0.89 ± 0.64 mg/dl. It was significantly ($p < 0.001$) raised to 1.55 ± 1.05 mg/dl at day 14 of chemotherapy, and again significantly ($p < 0.002$) reduced to 0.72 ± 0.35 mg/dl at day 30 of chemotherapy as compared to day 1. Similarly the mean serum ALT at day 1 was 47.46 ± 15.00 U/L which significantly

($p < 0.001$) raised to 87.08 ± 57.45 U/L at day 14 of chemotherapy and significantly ($p < 0.001$) reduced at day 30 of chemotherapy to 37.79 ± 11.69 U/L as compared to day 1. The mean serum aspartate transaminase (AST) before chemotherapy at day 1 was 38.00 ± 7.34 U/L that significantly ($p < 0.001$) increased to 44.96 ± 8.29 U/L at day 14 of chemotherapy and significantly ($p < 0.001$) decreased to 32.29 ± 4.78 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

1. 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 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 (AML/ALL) 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. Steato-hepatitis 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 anthracyclines, vincristine, 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. Asperginase 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 [9] [11] [12] [13] [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.

2. Materials and Methods

This prospective cross sectional study was conducted in the Department of Biochemistry, Dhaka Medical College, Dhaka, Bangladesh from January 2017 to December 2017. This study was approved by the Ethical Review Committee of

Dhaka Medical College Dhaka, Bangladesh. A total of fifty (50) 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 10 - 65 years of both sexes were selected purposively. Patients of chronic myeloid leukemia (CML), patients having any previous or pre-existing liver disease, pregnant/lactating women or women taking oral contraceptives, 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 a pre-tested data collection sheet.

2.1. Collection, Preservation and Analysis of Blood Samples

With all aseptic precautions 6 ml of venous blood was collected from median cubital vein of each study participant by disposable syringe before starting chemotherapy (Day 1). The needle was detached from the nozzle and blood from the syringe was transferred into a dry, clean and plain test tube with a gentle push to avoid hemolysis. Test tubes containing blood sample were labeled and coded for identification and kept in slanting position till formation of clot, then centrifuged at 3000 rpm for 5 minutes at 25˚C temperature and the separated serum was kept in labeled eppendorf after proper labeling. From each eppendorf; about 1000 µL of serum was used for serum total bilirubin, 100 µL for ALT and 100 µL for AST. Serum total bilirubin was measured by DMSO method, serum AST and ALT were measured by kinetic method [15] [16]. All the biochemical tests were carried out as early as possible. Whenever there was a delay, the sample was stored at −20˚C, to avoid loss of bioactivity and contamination. The 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. All the biochemical tests were performed at the Department of Biochemistry, Dhaka Medical College, Dhaka, Bangladesh. The outcome variables-serum total bilirubin, serum AST, serum ALT were analyzed and compared by statistical tests.

2.2. Liver Function Tests (LFTs)

Normal level of biochemical parameters that were used in this study [16]:

- Bilirubin (Total): 0.3 - 1 mg/dl;
- ALT (Alanine Transaminase): <45 U/L (Male), <34 (Female);
- AST (Aspartate Transaminase): <35 U/L (Male), <31 (Female).

2.3. Statistical Analysis of Data

All data were recorded in a pre-tested data collection sheet. Data cleaning, vali-

dation and analysis were performed using the Statistical Package for Social Science (SPSS) software for Windows version-22. Categorical data were presented as frequency/percentage and continuous variable was expressed as mean ± SD (standard deviation) and were compared by paired "t" test. Level of significance was defined as p value < 0.05 at 95% confidence interval.

3. 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 fifty (50) acute leukemia patients were selected as study subjects. Of them thirty (30) were male and twenty (20) were female, among females most of them were housewives and male to female ratio was 1.5:1.0. Mean age of the patients were 42.45 ± 9.99 years. Almost one third (32.0%) of the patients were in 4th decade. Majority (63.0%) patients came from lower-middle income family. In all age groups majority (90%) of the study subjects had no knowledge about leukemia.

Grouping of subjects:

Group A (50): Day 1 (Before chemotherapy);

Group B (50): At 14th day of chemotherapy;

Group C (50): At 30th day of chemotherapy.

Among total 50 study populations, 31 (62%) were acute myeloid leukemia (AML) and 19 (38%) were acute lymphoblastic leukemia (ALL) (Table 1).

Mean (± SD) serum total bilirubin of the study population before chemotherapy (Day 1), at 14th day of chemotherapy and 30th day of chemotherapy were 0.89 ± 0.64 mg/dl, 1.55 ± 1.05 mg/dl and 0.72 ± 0.35 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).

Mean (± SD) serum alanine transaminase (ALT) of the study population before chemotherapy (Day 1), at 14th day of chemotherapy and 30th day of chemotherapy were 47.46 ± 15.00 U/L, 87.08 ± 57.45 U/L and 37.79 ± 11.69 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).

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

Table 1. Distribution of the study subjects according to the type of leukemia (n = 50).

	Frequency (n)	Percentage (%)
AML	31	62.0
ALL	19	38.0

n = Number of study subjects.

Table 2. Comparison of serum total bilirubin before chemotherapy (Day 1), 14th day of chemotherapy and 30th day of chemotherapy (n = 50).

Group	Day of treatment	Mean ± SD (Range)	Comparison	p value
A	Day 1 (Before chemotherapy)	0.89 ± 0.64 mg/dl (0.20 - 2.50)	A vs B	<0.001
B	14th day of chemotherapy	1.55 ± 1.05 mg/dl (0.30 - 3.70)	B vs C	<0.001
C	30th day of chemotherapy	0.72 ± 0.35 mg/dl (0.25 - 1.60)	A vs C	0.002

Values are expressed in Mean ± 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.

Table 3. Comparison of serum alanine transaminase (ALT) before chemotherapy (Day 1), 14th day of chemotherapy and 30th day of chemotherapy (n = 50).

Group	Day of treatment	Mean ± SD (Range)	Comparison	p value
A	Day 1 (Before chemotherapy)	47.46 ± 15.00 U/L (27.00 - 80.00)	A vs B	<0.001
B	14th day of chemotherapy	87.08 ± 57.45 U/L (32.00 - 251.00)	B vs C	<0.001
C	30th day of chemotherapy	37.79 ± 11.69 U/L (21.00 - 88.60)	A vs C	<0.001

Values are expressed in Mean ± 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.

were 38.00 ± 7.34 U/L, 44.96 ± 8.29 U/L and 32.29 ± 4.78 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).

The mean serum total bilirubin during diagnosis/before chemotherapy at day 1 was 0.89 mg/dl. It was raised to 1.55 mg/dl at day 14 of chemotherapy and then reduced to 0.72 mg/dl at day 30 of chemotherapy as showing in Figure 1.

The mean serum alanine transaminase (ALT) before chemotherapy at day 1 was 47.46 U/L, which was raised to 87.08 U/L at day 14 of chemotherapy and then reduced to 37.79 U/L at day 30 of chemotherapy as showing in Figure 2.

The mean serum aspartate transaminase (AST) before chemotherapy at day 1 was 38.00 U/L that was raised to 44.96 U/L at day 14 of chemotherapy and then reduced to 32.29 U/L at day 30 of chemotherapy as showing in Figure 3.

4. Discussion

The present study was undertaken to observe the liver function status in newly diagnosed patients of acute leukemia before chemotherapy, at 14th and 30th day of induction chemotherapy. For this purpose a total of fifty (50) subjects were selected.

Table 4. Comparison of serum aspartate transaminase (AST) before chemotherapy (Day 1), 14th day of chemotherapy & 30th day of chemotherapy (n = 50).

Group	Day of treatment	Mean ± SD (Range)	Comparison	p value
A	Day 1 (Before chemotherapy)	38.00 ± 7.34 U/L (25.00 - 49.00)	A vs B	<0.001
B	14th day of chemotherapy	44.96 ± 8.29 U/L (29.00 - 59.00)	B vs C	<0.001
C	30th day of chemotherapy	32.29 ± 4.78 U/L (24.00 - 40.00)	A vs C	<0.001

Values are expressed in Mean ± 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.

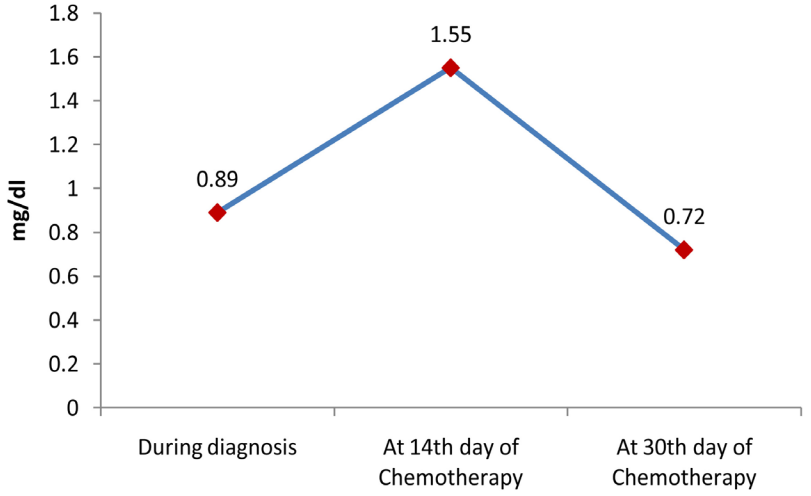

Figure 1. Line diagram showing serum total bilirubin (mg/dl) during diagnosis/before chemotherapy (Day 1), at 14th day of chemotherapy and 30th day of chemotherapy.

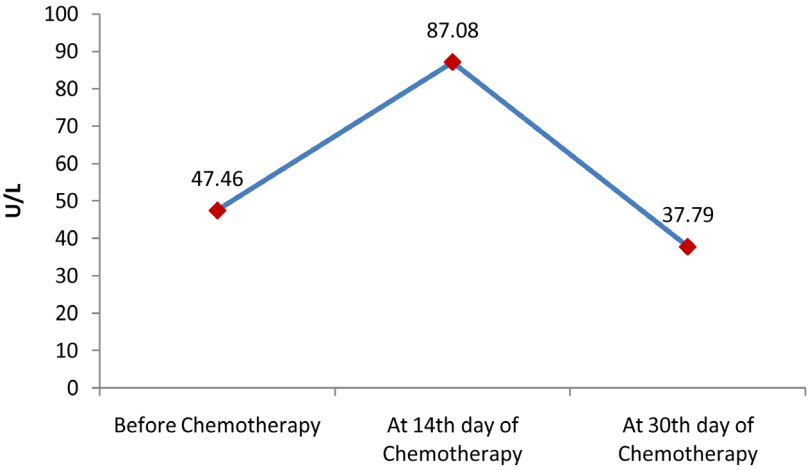

Figure 2. Line diagram showing serum ALT (U/L) before chemotherapy (Day 1), at 14th day of chemotherapy and 30th day of chemotherapy.

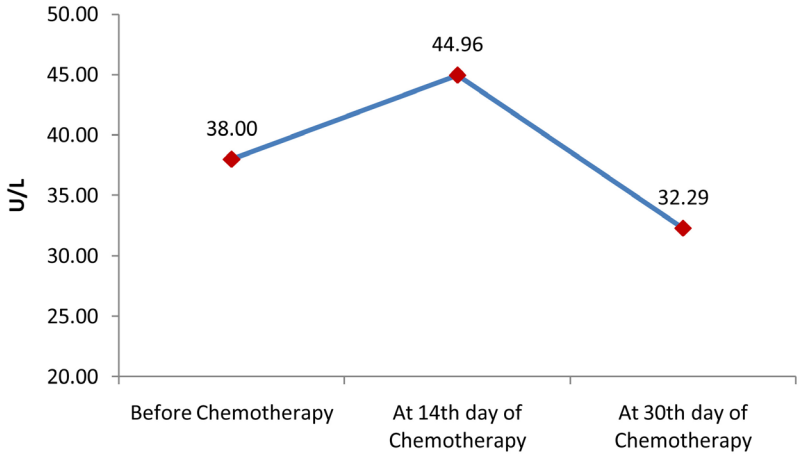

Figure 3. Line diagram showing serum AST (U/L) before chemotherapy (Day 1), at 14th day of chemotherapy and 30th day of chemotherapy.

In the present study, among total fifty (50) acute leukemia patients, acute myeloid leukemia (AML) patients were 31 (62%) and acute lymphoblastic leukemia patients were 19 (38%).

This study showed that before starting chemotherapy, mean serum total bilirubin level in acute leukemia patients was 0.89 ± 0.64 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 [7] [11] [12] [14] [15] [16] [17] [18].

At 14th day of chemotherapy, mean serum total blirubin level in acute leukemia patients was 1.55 ± 1.05 mg/dl which was significantly ($p < 0.001$) higher than the value measured before starting chemotherapy (0.89 ± 0.64 mg/dl). This finding was consistent with previous studies as observed that induction chemotherapy appears to result hyperbilirubinemia [7] [11] [12] [14] [15] [16] [17] [18]. This may be due to pre-hepatic hyperbilirubinemia because of hemolytic anemia as a result of action chemotherapy [19].

At 30th day of chemotherapy, mean serum total bilirubin in acute leukemia patients was 0.72 ± 0.35 mg/dl which was significantly ($p < 0.002$) lower than the value measured before starting chemotherapy (0.89 ± 0.64 mg/dl). Similar findings were observed in previous studies [7] [16] [17] [18] as showed that decrease of serum total bilirubin on 7th day & 18th day of chemotherapy [17].

At 14th day of chemotherapy mean serum total bilirubin in acute leukemia patients was 1.55 ± 1.05 mg/dl & there was significant change ($p < 0.001$) of serum total bilirubin between 14th day of chemotherapy and 30th day of chemotherapy (0.72 ± 0.35 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 [16].

In this current study before starting chemotherapy, mean serum alanine transaminases (ALT) level in acute leukemia patients was 47.46 ± 15.00 U/L. Similar finding was observed in previous studies as showed that elevated alanine trans-

aminases (ALT) are common at initial presentation of acute leukemia and are likely due to hepatic injury from leukemic infiltrates [7] [8] [9] [11] [18] [20] [21].

At 14th day of chemotherapy mean level of serum ALT was 87.08 ± 57.45 U/L which was significantly ($p < 0.001$) higher than the value measured before starting chemotherapy (47.46 ± 15.00 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 [11] [15] [18]. It mainly occurs in an idiosyncratic manner and is generally reversible and nonfatal [22].

In this study it was observed that at 30th day of chemotherapy mean level of serum ALT in acute leukemia patients was 37.79 ± 11.69 U/L which was significantly ($p < 0.001$) lower from the value measured before starting chemotherapy (47.46 ± 15.00 U/L). This observation was consistent with other studies as showed that chemotherapy-induced hepatotoxicity is transient and generally reversible [15] [18] [22].

It was observed that at 14th day of chemotherapy the mean serum ALT in acute leukemia patients was 87.08 ± 57.45 U/L and there was significant change ($p < 0.001$) of serum ALT between 14th day of chemotherapy and 30th day of chemotherapy (37.79 ± 11.69 U/L). Similar findings were observed in the previous studies as showed that chemotherapy-induced hepatotoxicity is reversible [15] [18] [22].

In current study it was found that the mean serum aspartate transaminase (AST) level before starting chemotherapy in acute leukemia patients was 38.00 ± 7.34 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 [7] [8] [9] [11] [20] [21].

In this study it was showed that at 14th day of chemotherapy mean level of serum AST in acute leukemia patients was 44.96 ± 8.29 U/L, which was significantly higher ($p < 0.001$) than the value measured before starting chemotherapy (38.00 ± 7.34 U/L). This finding was accorded with previous studies as showed that chemotherapy-induced hepatotoxicity is common in patients with acute leukemia [11] [12] [13] [14] [21].

In this study it was observed that at 30th day of chemotherapy mean level of serum AST in acute leukemia patients was 32.29 ± 4.78 U/L, which was significantly ($p < 0.001$) lower from the value measured before starting chemotherapy (38.00 ± 7.34 U/L). This result was consistent with previous study as showed that chemotherapy-induced hepatotoxicity is nonfatal and reversible [22].

At 14th day of chemotherapy the mean serum level of serum AST in acute leukemia patients was 44.96 ± 8.29 U/L & there was significant change of serum AST ($p < 0.001$) between 14th day of chemotherapy and 30th day of chemotherapy (32.29 ± 4.78 U/L). Similar findings were observed in previous studies as showed that chemotherapy-induced hepatotoxicity is reversible [20] [21].

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.

5. 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 leukemia.

Limitations

It was a single centre study with a relatively small sample size. Moreover other parameters of liver function tests (prothrombin time, serum albumin, gamma glutamyl transferase) were not done.

Recommendations

A multi-center prospective study with large sample size should be done to confirm the association of liver function with chemotherapeutic drugs.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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