Original article:

Effect of chemotherapy on liver parameters in acute myeloid leukemia (AML)

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ABSTRACT

Introduction: Acute myeloid leukemia is a hematologic malignancy of the myeloid line of white blood cells in the bone marrow. It is the most common type of acute leukemia in adults with an incidence of approximate 3.7 cases/100,000 patients causing up to 180,000 deaths each year world-wide.

Aim and Objectives: To study the effect of chemotherapy on liver parameters in acute myeloid leukemia.

Material and Methods: This study was conducted in the Department of Biochemistry, in collaboration with the Department of Medicine (Clinical Hematology unit); Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak. Twenty newly diagnosed patients of AML and twenty age and sex matched healthy controls were taken up for study. The diagnosis was made by history, clinical examination, total and differential leukocyte count, bone marrow examination and cytogenetic studies. AML patients were given induction chemotherapy with cytarabine and anthracycline. Liver parameters (ALP, AST, ALT, serum protein, serum bilirubin) were estimated in AML patients before chemotherapy and in twenty age and sex matched healthy controls using reagent kits, spectrophotometric method (Randox Suzuka autoanalyzer)**.** Follow up was taken at first complete remission or at 5 weeks (whichever is earlier).

Results: ALT and AST levels were raised in AML patients after chemotherapy compared to before chemotherapy. ALP and total bilirubin levels were raised more than the normal reference value in AML patients before chemotherapy as well as after chemotherapy.

Conclusion: Chemotherapeutic agents may cause hypersensitivity reactions or direct hepatic toxicity, however, liver injury during cancer chemotherapy may not always reflect hepatotoxic anticancer drugs; the clinician must also consider reactions to antibiotics, analgesics, antiemetics, or other medications.

Keywords: Acute myeloid leukemia, Chemotherapy

INTRODUCTION

Acute myeloid leukemia consists of a heterogeneous group of diseases. This disease results from abnormal self-renewal and suppressed differentiation of hematopoietic progenitor cells, which leads to replacement of normal marrow elements.[1] Acute myeloid leukemia annual incidence in India varied from 0.9 to 1.5 per 100,000 children.[2] In AML malignant transformation of a myeloid precursor cell usually occurs at a very early stage of myeloid development. The symptoms of AML are caused by

replacement of normal bone marrow with leukemic cells, which causes a drop in red blood cells, platelets and normal white blood cells. These symptoms include fatigue, shortness of breath, increased risk of infection, easy bruising and bleeding and organ infiltration resulting in death within one year of diagnosis in the absence of treatment.

AML is characterized by a high degree of heterogeneity with respect to chromosome abnormalities, gene mutations, and changes in expression of multiple genes and microRNAs. Cytogenetic abnormalities can be detected in approximately 50% to 60% of newly diagnosed AML patients.[3] Treatment of AML include chemotherapy (induction and consolidation), radiation therapy, targeted therapy and bone marrow transplant.[4]

Induction chemotherapy is given to all the patients. In present study AML patients received combination chemotherapy consisting of cytosine arabinoside (cytarabine/ ara-C) and daunorubicine intravenously (the standard 3 plus 7 regimen). In this regime in induction phase daunorubicin (60 mg/m^2 body surface area/day) is given by intravenous infusion in 30 minutes for 3 days and cytarabine (100-200 mg/m^2 body surface area/day) is given for 7 days. Remission occurs when blast makeup is no more than 5% of the bone marrow. After remission is achieved patient receive consolidation chemotherapy in the form of high dose of cytarabine as a dose of $3mg/m^2$ body surface area twice daily on days 1, 3, 5 minimum of two cycles (average 1-4).[5,6]

Cytosine arabinoside (ara-C) belongs to the antimetabolite class of anticancer drugs which also include 5-fluorouracil (5-FU), 6-mercaptopurine, azathioprine, 6-thioguanine, methotrexate, and gemcitabine. Ara-C is currently the mainstay of treatment of acute myelogenous leukemia and its variants. It differs from the naturally occurring pyrimidine, cytidine, in that arabinoside replaces ribose as the sugar moiety attached to the pyrimidine base. Intracellularly, ara-C is metabolized in three successive phosphorylation reactions to the triphosphate derivative ara-CTP, which inhibits DNA synthesis both by inhibition of DNA polymerase and misincorporation into the DNA molecule. Its effects are thus limited to cells actively synthesizing DNA.

Daunorubicine belongs to the antitumor antibiotics class of anticancer drugs which also include doxorubicin, mitoxantrone, bleomycin, mitomycin, mithramycin (plicamycin), and dactinomycin. Daunorubicine, an anthracycline antibiotic, acts through DNA intercalation, alteration of membrane function, and free radical formation.[7] It is extensively metabolized in the liver, and liver antioxidant capacity, including that provided by glutathione production, may protect against free radical injury.[8]

Pre-existing medical problems, tumor, immunosuppression, hepatitis viruses and other infections, and nutritional deficiencies or total parenteral nutrition all may affect a host's susceptibility to liver injury. Attributing liver injury to a toxic reaction is therefore difficult.[9,10] Although many pharmaceuticals can cause liver injury, most hepatotoxic drug reactions are idiosyncratic, due to immunologic mechanisms or variations in host metabolic response.[11]

MATERIAL AND METHODS

The present study was conducted in the Department of Biochemistry, in collaboration with the Department of Medicine (Clinical Hematology unit); Pt. B.D. Sharma PGIMS, Rohtak. Twenty patients after confirmed diagnoses of acute myeloid leukemia were enrolled in the study. Diagnosis was based on blast cells 20% or more in peripheral blood smear/bone marrow by immunophenotyping

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(IPT)/flowcytometry. AML patients were given induction chemotherapy with cytarabine and anthracycline. Twenty healthy age and sex matched volunteers served as controls.

The patients were divided as under:

Group I (n=20) – AML patients before chemotherapy

Group II (n=20) – AML patients after chemotherapy

Group III (n=20) – healthy age and sex matched controls

All biochemical investigations were done on autoanalyzer (Randox Suzuka, United Kingdom, model no.6L7WD5J) using kits provided by Randox laboratories with the following principles:

S No.	INVESTIGATION	PRINCIPLE
1.	Total bilirubin	Total bilirubin is determined in the presence of caffeine, which releases albumin bound bilirubin. The bilirubin then reacts with diazotized sulphanillic acid to form azobilirubin which is purple/ reddish purple in colour. Intensity of colour is directly proportional to the amount of bilirubin in the serum.[12]
2.	Aspartate aminotransferase	α-oxoglutarate reacts with L-aspartate in presence of AST to form L-glutamate and oxaloacetate. The indicator reaction utilizes oxaloacetate for kinetic determination of NADH consumption using malate dehydrogenase enzyme at 340 nm.[13]
3.	Alanine aminotransferase	α-Oxoglutarate reacts with L-alanine in presence of ALT to form L-glutamate and pyruvate. The indicator reaction utilizes pyruvate for kinetic determination of NADH consumption using lactate dehydrogenase enzyme at 340 nm.[13]
4.	Alkaline phosphatase	The substrate p-nitrophenyl phosphate is hydrolyzed by ALP in presence of Mg^{++} ions to form yellow coloured p-nitrophenol compound, OD of which is measured at 405 nm.[14]
5.	Total serum protein	A coloured complex is formed between protein and cupric ions in an alkaline medium.[15]

STATISTICAL ANALYSIS

IBM SPSS ver. 20 was used for various statistical analysis. Student t-test was applied to the data confirming to normal distribution. Statistical analysis was expressed by mean $\pm$ standard deviation. For all tests a probability <0.05 was considered significant. Charts and graphs were prepared using IBM SPSS ver. 20 and Microsoft Excel programs.

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RESULTS

Table 1: Distribution of baseline parameters in AML patients and control

	Males			Females		
Parameters	AML (n=12)	Control (n=12)	p value	AML (n=8)	Control (n=8)	p value
Mean age (years)	35.33±14.88	35.66±12.87	0.952	39.37±17.52	39.25±17.65	0.988
Mean Hb (g/dL)	6.84±1.42	14.11±1.43	<0.001	5.5±1.66	13.59±1.15	<0.001
Mean TLC (cells/µL)	25000 ± 11862.85	7083.33 ± 1505.04	<0.001	22687.50± 9307.97	7550 ± 2061.20	<0.001

Age distribution was similar in male AML patients and controls (p=0.952) and female AML patients and controls (p=0.988). The mean age for patients was 36.95±15.28 (range 14 to 61 years). The Hb (g/dL) levels were significantly decreased in both male (6.84±1.42) and female AML patients before chemotherapy (5.5±1.66) as compared to male controls (14.11±1.43) and female controls (13.59±1.15) (p <0.001). The TLC (cells/µL) levels were increased in male AML patients before chemotherapy (25000±11862.85) as compared to male controls (7083.33±1505.04) and found to be statistically highly significant (p<0.001). TLC levels were also increased in female AML patients before chemotherapy (22687.50±9307.97) as compared to female controls (7550±2061.20) and found to be statistically highly significant (p <0.001). The mean blast count (%) levels were decreased in male AML patients (60.66±11.47) as compared to female AML patients before chemotherapy (61.62±11.98) and found to be statistically insignificant (p=0.861).

Table 3: Comparison of hematological investigations among all three groups

	Group I (Before chemotherapy)	Group II (After chemotherapy)	Group III (Control)	Gr. I vs. II	Gr. I vs. III	Gr. II vs. III	Analysis of Variance (ANOVA)
Mean Hb (g/dL)	7.50±1.70	8.27±1.31	13.8±1.26	0.120	<0.01	<0.01	<0.001
Mean TLC (cells/µL)	24075 ± 10711.86	14950 ± 7214.56	7270 ± 1712.21	<0.01	<0.01	<0.01	<0.001
Platelet count (cells/ µL)	52500 ± 24095.20	102000 ± 24408.79	248750 ± 64110.82	<0.01	<0.01	<0.01	<0.001

Mean Hb (g/dL) comparison of all the three groups showed that group III had higher mean Hb level as compared to group I and II i.e. 13.8±1.26, 7.50±1.70 and 8.27±1.31, respectively. On statistical

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analysis the difference among Gr. I vs. III and Gr. II vs. III found to be significant ($p < 0.01$ & $p < 0.01$ respectively) and Gr. I vs. II found to be insignificant ($p = 0.120$). On applying Analysis of Variance for multigroup comparison, this difference found to be statistically significant ($p < 0.001$). Mean TLC (cells/ µL) comparison of all the three groups illustrates that group I had higher mean TLC level as compared to group II and III i.e. 24075±10711.86, 14950±7214.56 and 7270±1712.21, respectively. On statistical analysis the difference among all the three groups Gr. I vs. II, Gr. I vs. III and Gr. II vs. III found to be significant ($p < 0.01$, $p < 0.01$ & $p < 0.01$ respectively). On applying Analysis of Variance for multigroup comparison, this difference found to be statistically highly significant ($p < 0.001$). Mean platelet count (cells/ µL) comparison of all the three groups demonstrates that group III had higher mean platelet count as compared to group I and II i.e. 248750±64110.82, 52500±24095.20, 102000±24408.79, respectively. On statistical analysis the difference among all the three groups Gr. I vs. II, Gr. I vs. III and Gr. II vs. III found to be significant ($p < 0.01$, $p < 0.01$ & $p < 0.01$ respectively). On applying Analysis of Variance for multigroup comparison, this difference found to be statistically significant ($p < 0.001$).

Table 4: Comparison of liver function tests in all three groups

Parameters	Group I (Before chemotherapy)	Group II (After chemotherapy)	Group III (Control)	Gr. I vs. II	Gr. I vs. III	Gr. II vs. III	Analysis of Variance (ANOVA)
Aspartate aminotransferase (IU/L)	31.9±22.88	38.45±19.38	16.5±4.91	0.334	<0.01	<0.01	<0.001
Alanine aminotransferase (IU/L)	28.35±14.88	33.1±18.20	15.5±3.95	0.372	<0.01	<0.01	<0.001
Alkaline phosphatase (IU/L)	102.05±25.53	100.9±30.18	64±20.77	0.897	<0.01	<0.01	<0.001
Total Serum Protein (g/dL)	6.90±1.02	6.81±1.07	7.34±0.86	0.78	0.106	0.09	0.201
Total bilirubin (mg/dL)	1.65±0.72	1.27±0.58	0.38±0.176	0.07	<0.01	<0.01	<0.001

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Liver function tests of all the three groups showed:

Aspartate aminotransferase (IU/L) found to be higher in group II as compared to group I and III i.e. 38.45±19.38, 31.9±22.88 and 16.5±4.91, respectively. On statistical analysis the difference among Gr. I vs. III and Gr. II vs. III found to be significant ($p < 0.01$ & $p < 0.01$ respectively) and Gr. I vs. II found to be insignificant ($p = 0.334$). Alanine aminotransferase (IU/L) found to be higher in group II as compared to group I and III i.e. 33.1±18.20, 28.35±14.88 and 15.5±3.95 respectively. On statistical analysis the difference among Gr. I vs. III and Gr. II vs. III found to be significant ($p < 0.01$& $p < 0.01$ respectively) and Gr. I vs. II found to be insignificant ($p = 0.372$). Alkaline phosphatase (IU/L) found to be higher in group I as compared to group II and III i.e. 102.05±25.33, 100.9±30.18 and 64±20.77, respectively. On statistical analysis the difference among Gr. I vs. III and Gr. II vs. III found to be significant ($p < 0.01$& $p < 0.01$ respectively) and Gr. I vs. II found to be insignificant ($p = 0.897$).

All these investigations on applying Analysis of Variance for multigroup comparison, also found to be statistically highly significant ($p < 0.001$).

Total serum protein (g/dL) found to be lower in group II as compared to group I and group III i.e. 6.81±1.07, 6.90±1.02 and 7.34±0.86, respectively. On statistical analysis the difference among three groups found to be

insignificant and Analysis of Variance also showed insignificant results.Total bilirubin (mg/dL) found to be higher in group I as compared to group II and III i.e. 1.65±0.72, 1.27±0.58 and 0.38±0.176, respectively. On statistical analysis the difference among Gr. I vs. III and Gr. II vs. III found to be significant ($p < 0.01$& $p < 0.01$ respectively) and Gr. I vs. II found to be insignificant ($p = 0.07$). On applying Analysis of Variance for multigroup comparison, this difference also found to be statistically highly significant ($p < 0.001$).

DISCUSSION

Acute Myeloid Leukemia (AML) is a stem cell disorder in which the cells of myeloid lineage undergo massive clonal expansion. In AML rapid increase of immature blood cells occur resulting in failure of bone marrow to produce normal cellular elements of blood. There is accumulation of abnormal white cells (neoplastic/leukemic) in the bone marrow leading to bone marrow failure, raised circulating white cell count and infiltration of organs (e.g. liver, spleen, lymph nodes, brain). It is one of the leading causes of cancer deaths.

Chemotherapy, radiation therapy and allogeneic bone marrow transplantation are the most effective treatment options currently available but these therapies frequently fail to maintain long term eradication of the disease and 75% of AML patients experience a relapse within 2 years of remission.[16] n the present study out of 20 AML cases; 12 were males (60%) and 8 were females (40%). The distribution of females and males were similar in cases and controls. In our study at the time of diagnosis the male patients (n=12) had a median age 31 years and female (n=8) patients had a median age 36 years. The Hb levels were significantly decreased in both male and female AML patients before chemotherapy as compared to controls ($p < 0.001$). Anemia is a constant feature in all acute leukemias. Anemia, in the present study correlates well with the studies done by Preethi and Mathur et al.[17,18]

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Anemia in majority of cases is due to bone marrow infiltration leading to decreased production of red blood cells. Rarely anemia may occur due to decreased red cell life span and autoimmune destruction. Disturbed hematopoiesis leads to the most common presenting manifestations of AML such as anemia, infection and bleeding tendency.

The TLC levels were significantly increased in AML patients before chemotherapy as compared to controls ($p<0.001$). In the present study, TLC ranged between 10000 – 45000 cells/µL with a mean of 24075±10711.8 cells/µL. Mean platelet count in AML patients before chemotherapy was lower as compared to controls and this difference found to be statistically highly significant ($p <0.001$). Similar results were reported by Preethi and Mathur et al in AML patients before chemotherapy.[17,18]Aspartate aminotransferase (IU/L) found to be higher in group II as compared to group I and III and this difference found to be statistically highly significant ($p <0.001$). Alanine aminotransferase (IU/L) found to be higher in group II as compared to group I and III and this difference also found to be statistically significant ($p <0.001$). These aminotransferases are normally present in the serum in low concentration; these enzymes are released into the blood in greater amounts when there is damage to the liver cell membrane resulting in increased permeability. ALT and AST levels are higher in before chemotherapy group compared to control group may be due to infiltration of liver by leukemic cells. Alamin et al and Stefen et al showed elevation of ALT and AST levels in after chemotherapy group compared to before chemotherapy group similar to our study.[19,20] In contrast to our results, Byrd et al showed decreased levels of ALT and AST in after chemotherapy group as compared to before chemotherapy group.[21]

Alkaline phosphatase (IU/L) levels were higher in group I compared to group II and group III and this difference found to be statistically significant ($p <0.001$)**.** In agreement to our results, study done by Wandroo et al showed similar findings where ALP levels were raised more than the normal reference value in AML patients before chemotherapy as well as after chemotherapy.[22] Similar findings were present in AML cases in a study conducted by Alamin et al.[19] Toxic liver injury can reproduce virtually any known pattern of injury, including necrosis, steatosis, fibrosis, cholestasis, and vascular injury.[23] Liver injury during cancer chemotherapy may not always reflect hepatotoxic anticancer drugs; the clinician must also consider reactions to antibiotics, analgesics, antiemetics, or other medications. Although many pharmaceuticals can cause liver injury, most hepatotoxic drug reactions are idiosyncratic, due to immunologic mechanisms or variations in host metabolic response.[11] These reactions are not typically dose-dependent. Dose-dependent, predictable toxic effects of a medication or its metabolites are less common.

In a study conducted by Ellison R et al abnormal liver function tests were reported in 37 of 85 leukemic patients treated with ara -C, but many had liver function abnormalities prior to treatment. [24] No definite evidence of hepatotoxicity could be found because of the presence of confounding factors such as sepsis or hemolysis, or resolution of biochemical abnormalities despite continuation of therapy. Ever since, establishing the drug as a hepatotoxin has been especially difficult, since leukemic patients have frequently received transfusions, are subject to infections, are on multiple medications, and are

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not candidates for liver biopsy because of their usual thrombocytopenia. In patients in whom biopsies have been possible, drug-induced cholestasis has been demonstrated.[25,26] In a study conducted by Donehower et al 24 of 27 leukemic patients given high-dose ara-C by continuous infusion over 72 hours developed abnormal liver function tests, although the effects were reversible and not dose-limiting.[27]

Aapro et al described eight patients with impaired liver function who developed severe pancytopenia and mucositis while receiving doxorubicin.[28] This experience led to recommendations for dose reductions for altered hepatic function, but hepatotoxicity from doxorubicin is rare. In a study conducted by Aviles et al, six patients with acute lymphoblastic leukemia were treated with induction therapy using vincristine, prednisone, and doxorubicin.[29] Shortly after administration, increases in AST, ALT, and bilirubin were seen, with focal infiltration by inflammatory cells and steatosis on liver biopsies. This was considered an idiosyncratic reaction.

CONCLUSION

Chemotherapeutic agents, alone or in combination, may cause hypersensitivity reactions or direct hepatic toxicity, and altered liver function may alter drug metabolism and cause an increased risk of nonhepatic toxicity. However, liver injury during cancer chemotherapy may not always reflect hepatotoxic anticancer drugs; the clinician must also consider reactions to antibiotics, analgesics, antiemetics, or other medications.

Pre-existing medical problems, tumor, immunosuppression, hepatitis viruses and other infections, and nutritional deficiencies or total parenteral nutrition all may affect a host's susceptibility to liver injury. Attributing liver injury to a toxic reaction is therefore difficult.

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