The Professional Medical Journal
www.theprofesional.com

ORIGINAL PROF-2771

LIVER ENZYMES;

ALTERATIONS IN THE PROFILE DURING BREAST CANCER TREATMENT OF DIABETIC AND CARDIAC PATIENTS.

Dr. Uzma Raza[1], Dr. Aziza Khannum[2], Dr. Shahnawaz Jamali[3]

1. Professor,
   Department of Biochemistry,
   Hamdard College of Medicine and Dentistry,
   Hamdard University, Karachi.
2. Professor,
   Department of Biochemistry,
   Al Tibri Medical College, Karachi.
3. Associate Professor,
   Department of pharmacology,
   Hamdard College of Medicine and Dentistry,
   Hamdard University, Karachi.

Correspondence Address:
Dr. Uzma Raza
Department of Biochemistry,
Hamdard College of Medicine and Dentistry,
Karachi, Pakistan.
raza.uzma@hotmail.com

Article received on:
14/01/2015
Accepted for publication:
16/03/2015
Received after proof reading:
02/06/2015

ABSTRACT… Objective: To study the effect of breast cancer treatment on liver enzymes in diabetic and cardiac breast cancer females. **Study Design:** Cross-sectional type of study. **Setting:** Liaquat National Hospital Karachi. **Period:** January 2008 to January 2010. **Patients and Methods:** Total 47 breast cancer patients. Out of these, 22 were diabetic and 25 were cardiac patients, visiting the oncology OPD of the hospital. Patients with metastasis to distant organs were excluded from the study. Treatment was carried under the supervision of an oncologist. Samples were collected twice during the study. First sample was collected at disease presentation before starting any type of treatment and second time, sample was collected 14 weeks after the last chemotherapy dose. **Statistical analysis:** Data was analyzed using statistical package (SPSS version 11.0). "Students t-test"and analysis of variance (ANOVA) was used to analyze the means and standard deviations of quantitative/continuous variables. In all statistical analysis $p<0.05$ was considered significant. **Results:** In all patient groups after treatment alkaline phosphatase was significantly high as compared to that before treatment ($p<0.05$) whereas alanine transaminase increased significantly without including Tamoxifen in the treatment. Variation pattern of liver enzyme was the same in both patient groups. **Conclusions:** Altered profile of liver enzyme was similar in both patient groups therefor the variations cannot be attributed to hyperglycemia in diabetic females and the alterations in liver enzymes were attributed to liver damage by chemotherapy and fatty infiltration of liver induced by Tamoxifen.

Key words: Liver enzymes, Breast cancer, Diabetic and Cardiac patients.

Article Citation: Raza U, Khannum A, Jamali S. Liver enzymes;alterations in the profile during breast cancer treatment of diabetic and cardiac patients.. Professional Med J 2015;22(6):745-751.

INTRODUCTION

The relationship between diabetes mellitus and cancer risk was investigated and it was found that between 1983 and 1992 cases of cancer presented were 9,991 and out of these, breast cancer cases were 3,4159.[1] It was also reported that 16% of breast cancer patients were diabetic.[2] There exist a relationship between diabetes and liver involvement and according to Past studies risk for liver cancer remain elevated even ten years after the diagnosis of diabetes.[1] Liver plays an important role in controlling the blood sugar level and response to its increased or decreased production, therefore it is hypothesized that any oxidative stress in liver may impact blood sugar regulation in breast carcinoma patients.[3] Patients groups included in the study were with and without lymph node metastasis. Axillary lymph node metastasis have been reported to effect the disease control and disease free life of the patients, more death cases were reported if cancer metastasized in the lymph nodes.[4,5] Cancer treatment not only damages cancer cells, but also originates various liver disease, the toxicity developed may not only be attributed to chemotherapy but it may also be due to antiemetic, analgesics and antibiotics used during the treatment.[6,7] Toxic liver injury was reported to produce necrosis,fibrosis,cholestasis and vascular injury.[8]

Present study covers the important aspects of cancer chemotherapy in diabetic and cardiac patients. Cancer treatment is accompanied by number of side effects depending on the type and duration of the treatment. Present study was designed to evaluate the effect of various treatment strategies on liver enzymes in diabetic and cardiac patients. Criteria for therapy selection

includes, increased treatment efficacy with decreased toxicity level. Treatment was based on the prognostic factors associated with breast cancer such as number of involved axillary lymph nodes, tumor size, histological grade and hormone receptor status.

MTHODOLOGY & STUDY DESIGN

The study design was cross-sectional and was conducted on 47 female breast cancer patients with infiltrating ductal carcinoma. Patients were selected from the oncology clinic of a teaching hospital at Karachi, Pakistan with uncovered medical insurance. The project was ethically approved under the guidance of oncologist. Breast carcinoma of all the patients was proved by biopsy. Questionnaire included questions on their health status and medical history.

INCLUSION CRITERIA

- Patients selected had primary breast carcinoma in one breast only
- Patients were non-metastatic, to distant sites at the time of diagnosis.

PAST DISEASE HISTORY

On the basis of past disease history patients were grouped as follows:

1. Breast cancer patients with diabetes, without any cardiac problem.
2. Breast cancer patients with cardiac problems without diabetes

BLOOD SAMPLES COLLECTION FOR BIOCHEMICAL EVALUATIONS

1. At the time of disease diagnosed.
2. Fourteen (14) weeks after last chemotherapy dose. During these fourteen weeks treatment with radiotherapy was completed and eight weeks tamoxifen treatment was included. Tamoxifen was further continued for five years.

TREATMENT PLAN

Treatment plans were suggested according to the economical status and personal will of the patient. Surgery was the first treatment procedure, two to three weeks after surgery, chemotherapy was started and each cycle was given with the interval of three weeks. In some cases chemotherapy was the first treatment procedure followed by surgery and the remaining cycles of chemotherapy were given after surgery. One week after completion of chemotherapy radiotherapy was started and was carried for six weeks with five days per week. Patients with hormone receptor positive tumour were treated with hormonal therapy, which was later continued for five years.

TREATMENT COMBINATION AND SEQUENCE

Treatment plans suggested by the oncologist was based on tumour histopathology. This included surgery, chemotherapy, radiotherapy and hormonal therapy. For hormone receptor negative patients, hormonal therapy was excluded from the treatment pattern.

- Surgery + chemotherapy + radiotherapy + hormonal therapy
- Chemotherapy + Surgery + chemotherapy + radiotherapy + hormonal therapy
- Chemotherapy + surgery + chemotherapy + radiotherapy
- Surgery + chemotherapy + radiotherapy
- Surgery + radiotherapy + hormonal therapy
- Chemotherapy + Surgery + chemotherapy

Required dose to be injected = recommended dose x BSA

Body surface area (BSA) = √height x weight / 3600

Chemotherapy types and recommended doses:

5-fluorouracil (F)	**500mg/m²**
Adriamycin (A)	**50 mg/m²**
Cyclophosphamide (C)	**500 mg/m²**
Paclitaxel (T)	**90 mg/m²**
Methotrexate (M)	**40 mg/m²**

- **5-fluorouracil, Adriamycin, cyclophosphamide (FAC)**

Six cycles of this chemotherapy were given at the interval of three weeks in two patterns:

a. Post-surgery
b. Pre and Post surgery (depending upon the size of tumour and lymph nodes involvement)

- **Adriamycin, cyclophosphamide (AC)**
  Four cycles of this chemotherapy were given at the interval of three weeks, post-surgery.
- **Adriamycin, cyclophosphamide (AC) followed by Paclitaxel (T)**
  Four cycles of post-surgery AC was given at the interval of three weeks and this chemotherapy was then followed by twelve weekly doses of Taxol post-surgery.
- **Cyclophosphamide,Methotrexate, 5-fluoro-uracil (CMF)**
  Six cycles of CMF were given at the interval of three weeks, post-surgery.

Dose of Radiotherapy
Total dose 60 grey for six weeks with five days a week. Radiation was 2grey/ day with photon and 2grey/day with electron.

HORMONAL THERAPY
Antiestrogen Nolvodex (Tamoxifen) available in 30 tablets pack at the dose of 10 mg/tablet. Recommended dose was 20mg/day. Duration of treatment was 5 years.

For hormone receptor positive patients Nolvodex was started after radiotherapy and it was continued for five years.

LIVER FUNCTION TEST
For all estimations, kit was provided by Roche Diagnostics GmbH, D-68298 Mannheim, Germany and Chemistry analyzer Hitachi 912 was used for analysis and was provided by Roche diagnostic Basil Germany. **Total bilirubin** was estimated by the method developed by Wahlefeld et al 1972.[9] **Direct Bilirubin** was estimated by the Roche Diagnostics direct bilirubin method is based on the Jendrassik-Grof procedure.[10] **Alanine Transaminase** was estimated by the international Federation of Clinical Chemistry (IFCC) recommended standardized methods for the determination of Alanine transaminase (ALT).[11] **The Estimation of Alkaline Phosphatase** was carried out by the the assay method is standardized against (IFCC) International Federation of Clinical Chemistry.[12]

STATISTICAL ANALYSIS
Statistical package for social science (SPSS version 11.0) was used for data feeding and analysis. Means and standard deviations of quantitative/continuous variables in breast cancer cases and control was analyzed by Student's "t-test" and analysis of variance (ANOVA). In all statistical analysis, only p-values < 0.05 are considered significant.

RESULTS
Total 47 breast cancer patients were included in the study, out of which 22 patients were diabetic without any reported cardiac problems and 25 patients were cardiac patients not suffering from diabetes. Patients were also grouped on the basis of lymph node metastasis. The treatment plan was decided by the oncologist after considering the histopathological features of the tumor and economical affording of the patient. Treatment included surgery (Sur), chemotherapy (Chemo), radiotherapy (RT) and endocrine therapy (HT) in adjuvant and neo-adjuvant settings. The chemotherapy selected were the combinations of Cyclophosphamide (C), Adriamycin (A), 5-Fluorouracil (F), Paclitaxel (T) and Methotrexate (M) as FAC, CMF, AC and AC–T.Variations in the liver function enzymes were expressed as mean ± SEM and the number of cases are given in parenthesis. . In all cases $p<0.05$ was taken as significant.

Table-I presents the variations in the liver function test of diabetic breast cancer patients with lymph node metastasis before and after the treatment and **Table-II** documents the variations in the liver function test of diabetic breast cancer patients without lymph node metastasis before and after the treatment. In both groups of patients significant increase in the Alanine transaminase level was observed on treatment including surgery, chemotherapy and radiotherapy as compared to that before treatment whereas no significant change in the Alanine transaminase level was found on the treatment including Tamoxifen therapy. Alkaline phosphatase level of the patients was significantly high after every treatment combination as compared to that before treatment.

Liver function test	Treatment Pattern of Diabetic breast cancer Patients									
	Surgery + chemotherapy+ hormonal therapy with and without radiotherapy (06)		Surgery + chemotherapy+ radiotherapy (04)		Surgery + hormonal therapy + radiotherapy (03)		Chemotherapy + surgery+ Chemotherapy + Hormonal therapy + Radiotherapy (02)		Chemotherapy + surgery + chemotherapy with and without radiotherapy (03)	
	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Bilirubin (Total) mg/dL	0.53±0.05	0.66±0.04	0.50±0.16	0.65±0.11	0.45±0.03	0.64±0.02	0.45±0.07	0.61±0.16	0.54±0.04	0.68±0.10
Bilirubin (Direct) mg/dL	0.08±0.03	0.17±0.06	0.06±0.05	0.10±0.05	0.11±0.02	0.19±0.01	0.03±0.01	0.13±0.10	0.07±0.04	0.20±0.10
Bilirubin (Indirect) mg/dL	0.45±0.03	0.48±0.06	0.32±0.09	0.55±0.14	0.34±0.01	0.45±0.03	0.43±0.06	0.57±0.19	0.47±0.02	0.48±0.05
Alanine Transaminase U/L	33.33±0.61	35.33±2.51	29.75±1.92	ε41.50±1.10	35.67±2.47	42.33±2.15	36.50±0.71	37.00±1.41	33.00±0.70	ε40.60±0.81
Alkaline Phosphatase U/L	93.50±2.59	ε119.00±2.52	84.25±3.54	ε120.50±3.71	90.00±3.52	ε112.00±1.77	107.50±3.53	ε131.00±1.41	80.67±2.15	ε118.00±6.46

Table-I. Liver function test of diabetic breast cancer patients with lymph node metastasis before and after treatment.
ε p < 0.05 as compared to the patients before starting any treatment

Liver function test	Treatment pattern of cardiac breast cancer patients									
	Surgery + chemotherapy+ hormonal therapy with and without radiotherapy (05)		Surgery + chemotherapy+ radiotherapy (02)		Surgery + hormonal therapy + radiotherapy (01)		Chemotherapy + surgery+ Chemotherapy + Hormonal therapy + Radiotherapy (02)		Chemotherapy + surgery + chemotherapy with and without radiotherapy (04)	
	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Bilirubin (Total) mg/dL	0.44±0.03	0.63±0.07	0.54±0.01	0.66±0.03	0.44	0.49	0.53±0.06	0.73±0.11	0.55±0.09	0.65±0.05
Bilirubin (Direct) mg/dL	0.08±0.03	0.08±0.02	0.06±0.04	0.09±0.01	0.09	0.11	0.10±0.06	0.25±0.07	0.10±0.05	0.10±0.02
Bilirubin (Indirect) mg/dL	0.36±0.03	0.55±0.06	0.48±0.04	0.58±0.04	0.35	0.38	0.42±0.10	0.78±0.25	0.43±0.10	0.68±0.11
Alanine transaminase U/L	33.40±1.031	34.80±1.70	30.50±2.12	ε41.50±2.12	31.00	41.00	35.00±1.41	37.50±3.53	29.25±0.86	ε41.75±1.72
Alkaline Phosphatase U/L	77.20±5.90	ε118.00±4.90	82.00±2.82	ε131.50±2.12	95.00	108.00	77.50±2.12	ε119.00±2.82	89.00±3.67	ε116.75±4.26

Table-II. Liver function test of cardiac breast cancer patients with lymph node metastasis before and after treatment
ε p < 0.05 as compared to the patients before starting any treatment

Table-III presents the variations in the liver function test of diabetic breast cancer patients with lymph node metastasis. Results present significantly high level of alkaline phosphatase on treatment including hormonal therapy in the treatment pattern as compared to that before treatment. Table-IV presents the variations in the liver function test of cardiac breast cancer patients without lymph node metastasis and without diabetes. Results present significantly high Alanine transaminase level after treatment with post-surgery, chemotherapy and radiotherapy as compared to that before treatment. Whereas significantly high alkaline phosphatase level was observed after every treatment pattern as compared to that before treatment.

Liver function test	Treatment pattern of diabetic Breast cancer patients	
	Surgery + chemotherapy + hormonal therapy with and without radiotherapy (04)	
	Before Treatment	After Treatment
Bilirubin (Total) mg/dl	0.26±0.02	0.35±0.02
Bilirubin (Direct) mg/dl	0.06±0.03	0.09±0.03
Bilirubin (Indirect) mg/dl	0.20±0.01	0.26±0.03
Alanine Transaminase U/l	32.00±1.41	39.00±3.08
Alkaline Phosphatase U/l	87.75±3.49	ε118.75±1.72

Table-III. Liver function test of diabetic breast cancer patients without lymph node metastasis before and after treatment

ε p < 0.05 as compared to the patients before starting the treatment.

Liver function test	Treatment pattern of cardiac Breast cancer patients					
	Surgery + chemotherapy + hormonal therapy with and without radiotherapy (05)		Surgery + chemotherapy + radiotherapy (02)		Surgery + hormonal therapy + radiotherapy (04)	
	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Bilirubin (Total) mg/dl	0.25±0.03	0.31±0.01	0.35±0.02	0.31±0.01	0.30±0.01	0.34±0.003
Bilirubin (Direct) mg/dl	0.05±0.02	0.08±0.02	0.08±0.02	0.08±0.04	0.05±0.03	0.07±0.02
Bilirubin (Indirect) mg/dl	0.21±0.03	0.23±0.03	0.22±0.03	0.23±0.04	0.25±0.03	0.26±0.02
Alanine Transaminase U/l	36.60±1.34	41.40±2.26	29.50±2.12	ε49.00±1.41	30.50±1.00	39.25±2.50
Alkaline Phosphatase U/l	87.40±4.39	ε118.00±2.83	91.00±1.41	ε121.50±2.12	85.00±5.23	ε118.25±3.59

Table-IV. Liver function test of cardiac breast cancer patients without lymph node metastasis before and after treatment.

ε $p < 0.05$ as compared to the patients before starting the treatment.

DISCUSSIONS

Diabetes and cancer were identified as severe and chronic diseases. Epidemiological studies have indicated the risk of several types of cancer including liver, in diabetic patients. It is difficult to accurately assess cancer risk in diabetic patients due to confounding factors such as diabetes duration, drugs used for treatment and disease complications.[13] Previous studies have reported that the pathogenesis of drug induced hepatocellular injury can be assessed by the predominant rise in the transaminases which results from the demise of hepatocytes due to necrosis. Increased levels of alkaline phosphatase was also reported which results from the injury to the bile ductular cells either directly by the drug or indirectly by an adaptive immune response.[14] Present study reported that in diabetic and cardiac breast cancer patients with lymph node metastasis, alanine transaminase level was significantly high after treatment as compared to that before treatment with post-surgery, chemotherapy and radiotherapy without including Tamoxifen. According to the present study, no significant change in the level of alanine transaminase upon Tamoxifen included treatment was observed (Table-I and II). This result supports the previous study reporting that protective action of Tamoxifen in reducing the liver enzymes increased by chemotherapy.[15] Present study in table-I and II also shows significantly high level of alkaline phosphatase after treatment as compared to that before treatment. Hepatotoxicity in past studies was presented by the increased level of serum alkaline phosphatase and this pattern reflects histologically cholestasis with variable parenchymal necrosis (6). It was also reported that concurrent administration of adjuvant chemotherapy and radiotherapy leads to unacceptable high level of acute toxicity.[16]

Present study also evaluated the variations in liver function of diabetic and cardiac breast cancer patients without lymph node metastasis. In diabetic breast cancer patients alkaline phosphatase was significantly high after the treatment (Table-III). Abnormal liver functions have been reported in patients on treatment with 5-FU, Doxorubicin and Cyclophosphamide. The abnormalities were observed in the first three months after the treatment and returned to normal within the year.[17] According to the present study in cardiac patients, alanine transaminase level was significantly high without including Tamoxifen in the treatment whereas alkaline phosphatase level was significantly increased after various adjuvant treatments as compared to that before treatment (Table-IV). Transaminases and alkaline phosphatase are the indicators of hepatocellular damage and increased serum

activities of alkaline phosphatase was reported in cholestasis. Hepatic enzyme pattern has been differentiated from the cholestatic pattern by the raised level of transaminases.[18]

Previous studies predict that liver toxicity after breast cancer treatment may result due to the drug or its metabolites. The genetical factors may also influence the liver toxicity produced by the drug. It was reported that patients receiving Tamoxifen with and without chemotherapy developed fatty liver and the transaminase levels were increased and the elevations were more significant in the patients receiving Tamoxifen along with chemotherapy (19 and 20). The toxicity development was related to how the chemotherapeutic agent (cyclophosphamide) was metabolized. Increased exposure to cyclophosphamide and its metabolite 4-hydrocy-cylophosphamide produced liver toxicity. The toxin damaged the sinusoidal endothelial cells of the liver, the damage was more when patient was treated by chemotherapy along with radiotherapy. It was proposed that chemotherapy treatment reduces the hepatic cell glutathione and therefor liver cells were more damaged.[21] Past studies correlated raised alkaline phosphatase level with reduced drug clearance.[22]

CONCLUSIONS

Present study evaluated the variations in liver function test of diabetic and cardiac breast cancer patients at disease presentation and after the treatment. Present study predicts the development of hepatobillary disease due to the breast cancer treatment which can be assessed by the raised level of alkaline phosphatase. In patients treated without Tamoxifen, alanine transaminase levels were also raised along with alkaline phosphatase and this suggests the hepatocellular damage along with hepatobillary disease. Chemotherapy metabolites, responsible for the liver cell damage and renal dis-functioning may play an important role in drug induced toxicity since renal impairment interferes with the drug clearance. Elevations in the liver enzymes were attributed to the liver damage on chemotherapy treatment and to the fatty infiltration of liver induced by Tamoxifen. The protective effect of Tamoxifen on alanine transaminase level was also reported by the study.Post treatment alterations in liver enzyme patterns was similar in both diabetic and cardiac patients therefor present study concludes that diabetes was not responsible for the variation in enzyme pattern in breast carcinoma female patients.

REFERENCES

1. La Vecchia C, Negri E, Franceschi S, D'Avanzo B, Boyle P. **A case-control study of diabetes mellitus and cancer risk.** Br J Cancer. Nov 1994; 70(5): 950-953.

2. Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B. **Diabetes Mellitus and breast cancer.** The Lancet Oncology. Feb 2005; 6(2):103-111.

3. Lim JS, et al. **Is serum gamma-glutamyltransferase inversely associated with serum antioxidants as a marker of oxidative stress?** Free Radic Biol Med, 2004; 37(7): 1018-23.

4. Kim KJ, Huh SJ, Yang JH, Park W, Nam SJ, Kim JH, Lee JH, Kang SS, Lee JE, Kang MK, Park YJ, Nam HR. **Treatment results and prognostic factors of early breast cancer treated with breast conserving operation and radiotherapy.** Jpn. J. Clin. Oncol.2005; 35: 126-33.

5. Michaelson JS, Chen LL, Silverstein MJ, Mihm MC Jr., Sober AJ, Tanabe KK, Smith BL, Younger J. **How cancer at the primary site and in lymph nodes contributes to the risk of cancer death.** Cancer. 2009; 115: 5095-5107.

6. Paul MF, King D, Michael C, Perry. **Hepatotoxicity of chemotherapy.** The Oncologist. 2001; 6: 162-176.

7. Grieco A, Forgione A, Meile A, Vero V, Greco AV, Gasbarrini A, Gasbarrini G. **Fatty Liver and Drugs.** Eur. Rev. Med. Pharmacol. Sci. 2005;9: 261-3.

8. Maria VAJ, Victorino RMM. **Development and validation of a clinical scale for diagnosis of drug-induced hepatitis.** Hepatology. 1997; 26: 664-669.

9. WahlefeldAW, Herz G, Brent E. **Modification of Malloy-Evelyn method for a simple, reliable determination of total bilirubin in serum.** Scand J. Clin. Lab. Invest. 1972; 29: 11-12.

10. Jendrassik L, Grof P. **Vereinfachte photo metrische Methoden Zur Bestimug des Bilirubins.** Biochem Z. 1938; 297: 81-89.

11. Bergmeyer HU, Herder M, Rej R. **Approved recommendation on IFCC method for the measurement of catalytic concentration of enzymes.** Part 3, IFCC methods for Alanine aminotransferase. J. Clin Chem Biochem. 1985; 24: 481-489.

12. Tietz NW etal. **Use of Anticoagulants in Diagnostic Laboratory investigation.** J Clin Chem Clin Biochem. 1983; 21: 731-748.

13. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. **Diabates and Cancer.** Endocr Relat Cancer. Dec 2009; 16(4):1103-23.

14. Abboud G, Kaplowitz N. **Drug induced liver injury.** Drug. Saf. 2007; 30:277-94.

15. Hervikoski PP, Kumpulaineu EJ, Johansson RT. **Hepatotoxicity caused by adjuvant CMF/CNF in breast cancer patients and reversal by Tamoxifen.** Breast Cancer Treat. 1997; 44: 269-74.

16. Feits WE, van Helvoirt RP, Nortier JW, van der Tweel I, Struikmans H. **Acutetoxicity of concurrent adjuvant radiotherapy and chemotherapy (CMF or AC) in breast cancer patients. A prospective, comparative, non-randomized study.** Eur J. Cancer. 2003; 39: 1081-8.

17. Larroquette CA, Hortobagyi GN, Buzdar AU et al. **Subclinical hepatic toxicity during chemotherapy for breast cancer.** JAMA. 1986; 256: 2988-2990.

18. Renner EL, Dallenbeach A. **[Increased Liver enzymes: what should be done?]** Ther. Umsch. 1992; 49:281-6.

19. Kaplowitz N. **Drug induced liver injury.** Clin. Infect. Dis. 2004; 38: S44-8.

20. Liu CL, Huang JK, Cheng SP, Cheng YC, Lee JJ, Liu TP. **Fatty liver and transaminase changes with adjuvant Tamoxifen therapy.** Anticancer drugs. 2006; 17: 709-13.

21. George B. Mc Donald, John T. Slattery, Michelle E. Bouvier, Song Ren. Ami L Batchelder, Thomas F. Kalhorn, H. Gray Schoch, Claudio Anasetti and Ted Gooley. **Cyclophosphamide metabolism, liver toxicity and mortality following hematopoietic stem cell transplantation.** Blood. 2003; 101: 2043-2048.

22. Twelves CJ, Dobbs NA, Michael Y, Summers LA, Gregory W, Harper PG, Rubens RD, Richards MA. **Clinical pharmacokinetics of epirubicin: importance of liver biochemistry tests.** Br. J. Cancer 1992; 66: 765-9.

"The future belongs to those who prepare for it today."

Malcolm X

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr. Uzma Raza	Research Conduction	
2	Dr. Aziza Khannum	ResearchSupervisor	
3	Dr. Shahnawaz Jamali	Coordinated in collection & compilation of data.	