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BREAST CANCER;
ROLE OF TAMOXIFEN AS SELECTIVE ESTROGEN RECEPTOR MODULATOR IN PREVENTING BONE LOSS, REDUCING SERUM CHOLESTEROL AND ACTIVITY OF LIVER ENZYMES IN PATIENTS WITH DIFFERENT HORMONAL STATES.

DR. MUNIZA QAYYUM MALIK, MBBS, M.Phil
Department of Pharmacology
Fatima Jinnah Medical College and
Sir Ganga Ram Hospital, Lahore

DR. SHAHEEN RASHEED, MBBS, MRD
Department of Oncology
Fatima Jinnah Medical College and
Sir Ganga Ram Hospital, Lahore

DR. RUKHSHAN KHURSHID, Ph.D
Department of Biochemistry
Fatima Jinnah Medical College and
Sir Ganga Ram Hospital, Lahore

Dr. Asima Malik, MBBS, M.Phil
Department of Biochemistry
Fatima Jinnah Medical College and
Sir Ganga Ram Hospital, Lahore

Dr. Hurriat Afzal, MBBS, FCPS
Department of Surgery
Fatima Jinnah Medical College and
Sir Ganga Ram Hospital, Lahore

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ABSTRACT... **Objective:** To assess the alterations of serum cholesterol, liver and bone enzyme with breast cancer patient taking tamoxifen with different hormaonal status. **Study Design:** Experimental study. Period: April to September, 2006 (24 weeks). **Setting:** The study was carried out on serum samples that were obtained from out department of Oncology, Sir Ganga Ram Hospital of Lahore. **Materials and Method:** The study included 68 (serum specimen) of breast cancer patients. These patients were different stages of menstruation (postmenarche, perimenopausal and post menopausal). Clinical history and provisional diagnosis were also noted. **Results:** These patients (68 women) with breast cancer were divided into three major groups; (1) Postmenarche patient, (2) perimenopausal (3) post menopausal status. It is observed that the level of serum cholesterol, ALT and serum alkaline phosphatase in post menarche women were within the normal limits. While women in perimenopausal and post menopausal age groups, had increased level of serum cholesterol ($P<0.01$) and alkaline phosphatase. Level of ALT however was observed on border line. **Conclusions:** It is therefore concluded that tamoxifen either prevents or shows no effect on the bone and liver function as well as on cholesterol in postmenarche patients. While in case of perimenopausal and postmenopausal breast cancer patients who received tamoxifen, it may induce increase in cholesterol level and bone resorption, which may be due to decreased level of estrogen. However, further research is needed to reach better conclusions.

Key words: Breast cancer, status of menstruation, biochemical parameters, tamoxifen

INTRODUCTION

Estrogenic hormones act via the estrogen receptors (ERs), ER-alpha and ER-beta. These receptors are present in more than half of breast tumors, and has been

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Correspondence Address:
Dr. Muniza Qayyum Malik, MBBS, M.Phil
Assistant Professor Dept. Of Pharmacology
Fatima Jinnah Medical College, Lahore
mqm5266@gmail.com

the most widely targeted protein in breast cancer therapy[1,2]. Estrogen receptors have been localized to the cell plasma membrane, where signal transduction mediates some estradiol (E2) actions. It is found that the translocation of ERalpha to the membrane in the absence of estrogen is dependent on the serine at position 522 of the ERalpha protein. Mutation of serine 522 to alanine results in a 62% decrease in membrane localization[3,4,5]. Selective ER modulators (SERMs), tamoxifen and relexofen are reported. Suppression of ER activity by SERMs has proven to be of great benefit in the treatment of breast cancers and also in the prevention of breast cancer in women at high risk for the disease[2]. However, it was found that this minor change of one methylene group of ER transforms a potent estrogenic agonist into an antagonist in vitro[5].

Tamoxifen, is the first antiestrogen, inhibiting the proliferative effects of estrogen that are mediated through the ER in postmenopausal bone due to its partial estrogen agonist activity. It also helps in prevention of osteoporosis and coronary heart disease however, its long-term use is potentially associated with negative side effects, such as increased risk of thromboembolic disease and endometrial cancer[6,7]. SERM including tamoxifen bind ER, alter receptor conformation, and facilitate binding of coregulatory proteins that activate or repress transcriptional activation of estrogen target genes[1].

Previous studies have revealed that exogenous estrogen has a beneficial effect on the lipid profile. It is significantly associated with a more favorable lipid profile, including lower total and LDL-cholesterol and triglycerides and higher HDL-cholesterol among controls in post menopausal women. These relations were independent of demographic and metabolic factors and health behaviors. Another study found that the patients who had received six cycles of CMF tomaxifen had shown low RBC, WBC and platelet count, elevated levels of SGPT, alkaline phosphatase and lactate dehydrogenase as compared to newly diagnosed breast cancer patients[9]. It is found that the assessment of bone metastases by bone markers of bone formation could be a promising alternative[10]. However some studies found no changes in S-calcium, S-phosphorus or S-alkaline phosphatase ALT, albumin, LDH, calcitonin, or estradiol in patients treated with tamoxifen[11,12,13].

PURPOSE OF STUDY

This prospective study was designed to evaluate the effect of adjuvant tamoxifen in estrogen receptor positive breast cancer women (including premenopausal, perimenopausal and post menopausal women) on the level of serum cholesterol, liver/bone enzyme in concomitantly in women with 2nd and 3rd stage breast cancer.

MATERIAL AND METHODS

Serum samples of 68 consecutive patients of breast cancer, lymph node positive, ER positive stage II & III being treated at department of Oncology F.J.M.C were taken over a period of 6 months from April to December 2006. The patients were comprised as 12 women with postmenarche (Group A), 23 women with perimenopausal (Group B) and 33 postmenopausal (Group C). All of these patients were given FAC (5-Fluoruracil, Doxorubicin and Cyclophosphamite) 6 cycles followed by 20mg Tamoxifen. Level of serum cholesterol, ALT and alkaline phosphatase were estimated by standard kit method[14].

P-values were calculated by student t-test using SPSS version 11.

Group	Hormonal status	No.
A	Post menarche	12
B	Perimenopausal	23
C	Postmenopausal	33

Table. Variations in biochemical parameters in different status of women with breast cancer taking tamoxifen.				
Values expressed as mean ±SD			No of patients in parenthesis.	
Status of women	Age (yrs)	S.chol (mg/dl)	ALT (u/l)	AIK. Phos (KAU)
Post menarche (12)	33.14 ± 4.26	177.1 ± 57.0	9.17 ± 5.60	7.49 ± 2.18
Perimenopausal (23)	40.9 ± 1.56	203.0 ± 45.53	12.30 ± 8.16	7.84 ± 1.88
Post menopausal (33)	52.9 ± 8.54	210.6 ± 45.77*	12.36 ± 6.58	8.99 ± 3.43
*P= <0.01= Significant difference.				

RESULTS

Women with breast cancer were divided into 3 groups i.e. group A comprised post menarche, group B were perimenopausal and group C were post menopausal women. Among these, group A having a mean age of 33.14 yrs, group B with mean age 40.9 years and group C with mean age 52.9 years. Level of serum cholesterol, alanine transferase and alkaline phosphatase were estimated in all groups. It is observed that women with post menarche status have low level of serum cholesterol, ALT and alkaline phosphatase as compared to the levels of these parameters with perimenopausal and post menopausal women, however a significant difference (P<0.01) was observed only in the level of serum cholesterol when compared this level with the level of post menopausal women.

DISCUSSION

Signal transduction pathways of the ER alpha (alpha)- and beta (beta)-SERM complexes may help in the new drug discoveries and a menu of preventive medicine in clinical practice[8].

Present study found a normal level of serum cholesterol, alanine transferase and alkaline phosphatase in patients with postmenarche status when compared these levels with normal subjects (data not shown). Present study in accord with a study found that if tamoxifen was given together with adjuvant chemotherapy in postmenarche patients, no changes in liver enzyme were detected[15]. Some studies reported that adjuvant therapy with selective estrogen receptor modifiers spares bone loss in postmenopausal women but not in postmenarche women[16,17].

Present study found an increased level of serum cholesterol, alanine transferase and alkaline phosphatase in patients with perimenopausal/post menopausal status when compared these levels with normal subjects (data not shown). However, only cholesterol level was significantly increased in postmenopausal group only. Present study in against with a study found that if tamoxifen was given together with adjuvant chemotherapy in post menopausal patients, a significant change in liver enzyme was detected[18]. Our study is also in contrast to the study who reported that adjuvant therapy with selective estrogen receptor modifiers spares bone loss in postmenopausal women[19]. However study is in accord with a study who reported that tamoxifen using for 5 years may induce a change in the function of liver and bone function[20,21]. The findings of a group of workers showed that bone metabolic markers including alkaline phosphatase would be useful to detect, to monitor, and to predict prognosis of bone metastases. Increased level of alkaline phosphatase was also noted with the passage of level of menstruation. A study, suggest that fibroblast growth factor expressed by a great proportion of malignant breast and it may be one of the factor, involved in the formation of osteosclerotic bone metastases. However a study found that tomaxifen found to maintain bone density[22].

CONCLUSIONS

It is therefore concluded that tamoxifen either prevents or shows no effect on the bone and liver function as well as on cholesterol in postmenarche patients. While in case of perimenopausal and postmenopausal breast cancer patients who received tamoxifen, it may induces a change in cholesterol level and bone resorption, which

may be due to decreased level of estrogen. However, further research is needed to reach a better conclusion.

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