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Research Article

ADVERSE EFFECT OF LETROZOLE ON LIPID PROFILE IN POSTMENOPAUSAL BREAST CANCER PATIENTS

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A B S T R A C T

Back ground: Letrozole, a third generation aromatase inhibitor, is considered superior to tamoxifine in the treatment of all stages of breast cancer. The decrease in estrogen levels due to letrozole treatment is found to have an adverse effect on lipid profile. Data regarding the effect of duration of letrozole treatment on lipid profile is limited. The present study was indented to study the effect of letrozole treatment on total cholesterol, LDL cholesterol, HDL cholesterol and triacylglycerol in postmenopausal breast cancer patients at baseline and after 3 months.

Material and methods: Ninety five Postmenopausal estrogen receptor positive breast cancer patients receiving letrozole were recruited. Patients with hypothyroidism, diabetes mellitus, liver or renal disease, proteinuria, alcoholism, patients taking drugs known to influence lipid metabolism were excluded. 5 ml of venous sample was collected at baseline and after 3 months of letrozole treatment for lipid profile analyses. Paired t-test was used to compare baseline line and 3 months data.

Results: The mean age of the study subjects was 55.80 ± 8.63 years. There was a statistically significant increase in the level of total cholesterol (p= 0.02), LDL-C (p=0.00) and decrease in the level of HDL-C (p=0.00), atherogenic risk ratios: Log (total cholesterol/HDL-C) (P<0.005) and LDL -C/HDL - C (P<0.005) after 3 months of letrozole treatment. There was no difference in the levels of TAG and VLDL-C.

Conclusion: We conclude that letrozole at a dose of 2.5mg per day for three months has an adverse effect on the serum lipid profile in postmenopausal women with breast cancer

INTRODUCTION

Breast cancer is the most common cancer in female worldwide. It has also ranked first among cancers in Indian females with age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women.

Hormonal therapy plays a pivotal role among the numerous treatment modalities available for treatment of breast cancer. About two-third of breast cancer patients have estrogen and progesterone receptor positive, who may benefit from anti-estrogen therapy (Goss 2003). Tamoxifen which is considered as gold standard acts by competitively inhibiting estrogen. Tamoxifen has a beneficial effect on bone and lipid metabolism by having partial estrogen-agonist action(Zidan *et al*. 2004). Third generation aromatase inhibitors like letrozole, anastrozole has been demonstrated to be superior to tamoxifen in all stages of breasts cancer(Smith and Dowsett 2003).

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The major source of estrogen production in postmenopausal women is from non-glandular tissues like subcutaneous tissue. It is found that serum Estrogen levels are higher in Breast cancer patients than healthy individuals. Breast cancer patients were found to have more estrogen when compared to healthy individuals. Aromatase inhibitors (AI) act by inhibiting the peripheral aromatisation of androgens to estrogen leading to reduction of estrogen production(Campos 2004).

Letrozole which is a non-steroidal AI is better tolerated than other AI. At a dose of 2.5mg once daily, it was found to supress the levels of estrogen throughout the treatment. This decrease in estrogen levels due to letrozole treatment is found to have adverse effect on lipid profile. Few studies have demonstrated that letrozole increase the levels of total cholesterol (TC), low density lipoprotein (LDL-C), and decreases the level of high density lipoprotein(Elisaf *et al*. 2001). Hence the study was indented to study the effect of letrozole treatment on total cholesterol, LDL cholesterol, HDL cholesterol, triacylgycerol and very low density cholesterol in postmenopausal breast cancer patients treated with letrozole for 3 months.

MATERIAL AND METHODS

The study was conducted in Department of Biochemistry in collaboration with the Department of Surgery and Medical Biometrics & Informatics, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India. The study was approved by JIPMER research committee and Institute Ethics Committee (Human studies). A written informed consent was obtained from all the patients.

Ninety five consecutive postmenopausal breast cancer estrogen receptor positive were recruited in the study at the time of initiation of letrozole and were followed up for a period of 3 months. Patients with hypothyroidism (Thyroid stimulating hormone > 10 mIu/L) diabetes mellitus, liver or renal disease, proteinuria, alcoholism, patients taking drugs known to influence lipid metabolism were excluded from the study. Patient's age, anthropometric measurements like height and weight were recorded. Body mass index was calculated using the formula BMI=Weight in kg/height in meters^2.

After an overnight fast, 5 ml of venous sample was collected from all the study subjects at the time of recruitment and after 3 months of letrozole treatment. The blood samples were centrifuged for 15 min (3000rpm), serum was separated and processed for lipid profile parameters. Serum triacylglycerol-TAG (Glycerol phosphate oxidase -Peroxidase method using reagent kit from Genuine Biosystem, Chennai, India), Total cholesterol (cholesterol oxidase method using reagent kit from Genuine Biosystem, Chennai, India), Serum high density lipoprotein cholesterol (direct enzymatic colorimetric method using reagent kits from ACCUCARE, India), Very low density lipoprotein was calculated from TAG by the formula TAG/5, Low density lipoprotein cholesterol is calculated by the Friedwald's formula LDL-C = Total cholesterol- (HDL-C) - (VLDL-C). The formula was used if TAG is < 400 mg/dL(Friedewald, Levy, and Fredrickson 1972). Atherogenic ratios LDL-C/HDL-C and TC/HDL-C were calculated

Statistical analysis

The study parameters were normally distributed and were expressed as mean ±SD. The difference in the parameters before and after letrozole treatment was compared using paired t test. All statistical analysis was carried out at 5% level of significance for two-tailed significance using JASP software

RESULTS

The mean age of the study population was 56 yrs and the mean age of menopause of the study subjects were 47 yrs (Table 1). Invasive ductal carcinoma was the common primary invasive tumor (84%) and the invasive lobular carcinoma was present in 16% of the study subjects. The common site of metastasis was to the bones.

Table I Clinical characteristics of the study population (n=95)

Age (Mean ± SD)	55.80 ± 8.63 yrs
BMI (Mean ± SD)	26.52 ± 4.7 kg/m^2
Prior adjuvant chemotherapy (n)	42
Prior adjuvant hormonal therapy (n)	55
Prior hormonal treatment for metastatic disease (n)	15
Metastatic sites (n)	
Lymph nodes	7
Pleura	5
Skin	4
Bone	13

There was statistically significant increase in the levels of total cholesterol, LDL-C and decrease in the levels of HDL-C after three months when compared to baseline (Table 2). There was no significant difference in the levels of triacylglycerol and VLDL-C before and after letrozole treatment. The atherogenic risk ratio was more at baseline and there was also significant increase in the ratio after 3 months of treatment.

Table II Effect of letrozole on serum lipid profile parameters (n=95)

SI.NO	Parameter in mg/dL	Baseline	After 3 months	P value
1	Total cholesterol (TC)	199.3 ± 36.18	204 .57 ± 34.81	0.02
2	High Density Lipoprotein-C (HDL-C)	32.5 ± 6.07	30.84 ± 4.93	< 0.001
3	Triacylglycerol	126.57 ± 39.01	127.98 ± 38.59	0.14
4	Very Low Density Lipoprotein	25.29 ± 7.79	25.62 ± 7.64	0.099
5	Low Density Lipoprotein-C (LDL-C)	141.66 ± 31.5	148.10 ± 31.47	< 0.001
6	LDL-C/HDL-C	4.53 ±1.28	4.94 ± 1.38	< 0.001
7	TC/HDL-C	6.34 ± 1.45	6.79 ± 1.51	< 0.001

DISCUSSION

Third generation aromatase inhibitors viz letrozole are widely used in the treatment of early and advanced postmenopausal breast cancer. Letrozole acts by inhibiting peripheral estrogen production from androgens. Estrogen has got favourable effect on lipid profile. It is known to decrease total cholesterol, LDL cholesterol and to a little extent increase the levels of HDL cholesterol. Previous studies have shown that estrogen inhibits lipid oxidation which is highly atherogenic(Reddy Kilim and Chandala 2013). However the effect of letrozole on lipid profile is still controversial. Hence the present study was undertaken to study the effect of letrozole on lipid profile and atherogenic risk ratio in breast cancer patients.

In our study we found that letrozole at a dose of 2.5mg per day for 3 months had significantly altered the lipid profile. There was significant increase in Total cholesterol and LDL-C and decrease in HDL-C over a study period of 3 months. This report is in agreement to the study done by Elisaf *et al* in 20 breast cancer patients treated with letrozole. In addition they have also reported that letrozole had increased Lp(a) and decreased ApoA1/ApoB ratio(Elisaf *et al*. 2001). In another study letrozole had been reported to cause increase in cholesterol in 3.8% of letrozole treated patients in Letrozole International Trial Group.

However our results contradict the report of a previous study done by Wasan *et al* which showed that letrozole did not significantly alter lipid profile for 36 months in non-hyperlipidemic postmenopausal breast cancer patients treated with letrozole following adjuvant tamoxifen therapy of at least 5 yrs(Wasan 2005). Wynne studied the effect of letrozole on lipid profile on 32 breast cancer patients and reported that letrozole had no effect on lipid profile after 3 months(Harper-Wynne *et al*. 2002).

Unlike Tamoxifine which has got favourable effect on lipid profile, letrozole has unfavourable effect on lipid profile in breast cancer patients. In BIG 1-98 trail mild to moderate hypercholesterolaemia was seen in 43.6 % of letrozole treated patients when compared to 18.2 % of tamoxifen treated patients. Thromboembolic events were more in tamoxifen treated patients (grades 3-5, 2 vs 0.8%), whereas incidence of cardiovascular events were more in letrozole treated patients (grades 3-5, 3.6 vs 2.5%). But this difference was not

statistically (Breast International Group (BIG) 1-98 Collaborative Group *et al*. 2005).

These adverse effects on lipid profile parameters may be related to estrogen lowering effect of letrozole. Aromatase inhibitors may affect the enzymatic pathways in liver or may interfere with bile acid secretion leading to hypercholesterolemia. The favourable effect of tamoxifen on lipid profile is due to the inhibition of conversion of delta-8 cholesterol to lathosterol. This leads to down regulation of cholesterol synthesis (Gylling *et al*. 1995). The unfavourable effect of letrozole on lipid profile may increase cardiovascular mortality and morbidity. Limitations of our study is that the patients were not followed for a long time. However, future studies in this context must be ushered to reveal the long-term effects of letrozole on lipid profile. Based on the study results, we suggest that monitoring lipid profile every 3 months during letrozole treatment would minimise the cardiovascular risk to a certain extent.

In conclusion, this prospective study is one of the few studies to assess the effects of letrozole on lipid profile. Three months of letrozole treatment can significantly increase the total and LDL cholesterol, simultaneously decreasing the HDL cholesterol with no change in triglyceride levels. Also the atherogenic risk ratio is increased by letrozole.

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