Effects of Letrozole Versus Tamoxifen on Serum Lipids, Coagulation Parameters and Bone Mineral Density in Asymptomatic Postmenopausal Women with Breast Cancer

Asemptomatik Postmenopozal Meme Kanserli Hastalarda Letrozol ile Tamoksifenin Serum Lipit, Koagulasyon Parametreleri ve Kemik Mineral Yoğunluğu Üzerine Etkileri

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ABSTRACT Objective: Letrozole and tamoxifen are frequently used in treatment of postmenopausal women with breast cancer. The goal of this study was to evaluate the effects of letrozole and tamoxifen on serum lipids, coagulation parameters and bone mineral density (BMD) in asymptomatic postmenopausal patients in our department. **Material and Methods:** Included in this study were twenty-nine postmenopausal breast cancer women taking 20 mg daily of tamoxifen (14 patients) (group 1) and 2.5 mg daily of letrozole (15 patients) (group 2). Lipid parameters and coagulation measures such as activated partial thromboplastin time (APTT), prothrombin time (PT) and international normalized ratio (INR) were examined. T and Z scores of BMD of femur neck and lumbar spine were examined between two groups. **Results:** Demographic, clinical variables and hormonal situation did not differ between the groups. APTT levels in letrozole group were significantly longer than the tamoxifen group (24.90 ± 5.48 and19.64 ± 1.07, p= .03). But for the other parameters comprising PT and INR and lipid profiles, there was no significant difference between two groups. Although lumbar vertebral and femoral BMD of group 1 was higher than group 2, there was no statistically significant difference. **Conclusion:** The results of this study suggest that APTT shows an increased level in postmenopausal breast cancer patients receiving letrozole for hormonal therapy when we compared to tamoxifen taking patients. In addition, by comparing letrozole versus tamoxifen trials on the lipid profile and BMD of the postmenopausal breast cancer patients, there was no difference for the lipid parameters in this report.

Key Words: Breast neoplasms; tamoxifen; letrozole; blood coagulation; lipids; bone density

ÖZET Amaç: Postmenopozal meme kanserli kadınların tedavisinde letrozol ve tamoksifen sıklıkla kullanılmaktadır. Bu çalışmanın amacı, bölümümüzdeki asemptomatik postmenopozal hastalarda letrozol ve tamoksifenin serum lipid, koagülasyon değerlerine ve kemik mineral yoğunluğu (KMY)'na etkisini hesaplamaktır. **Gereç ve Yöntemler:** Bu çalışmaya günlük 20 mg tamoksifen alan (14 hasta) (grup 1) ve günlük 2.5 mg letrozol alan (15 hasta) (grup 2) 25 postmenopozal meme kanserli hasta dâhil edildi. Lipid parametreleri ve aktif pars,yel tromboplastin zamanı (APTT), protrombin zamanı (PT) ve uluslararası normalleştirilmiş oran (INR) içeren koagulasyon ölçümleri çalışıldı. Femur boynu ve lumbar vertebranın KMY'nin T ve Z skoruna her iki grupta bakıldı. **Bulgular:** Demografik, klinik değişkenler ve hormonal durum açısından gruplar arasında fark yoktur. Letrozol grubunda APTT seviyeleri tamoksifen grubuna göre anlamlı olarak uzundu (24.90 ± 5.48 ve 19.64 ± 1.07, p= .03). Fakat PT ve INR'yi içeren diğer parametreler ve lipid profilleri açısından gruplar arasında anlamlı fark yoktu. Lumbar vertebra ve femoral KMY grup 1'de grup 2'ye göre yüksek olmasına karşın anlamlı fark yoktu. **Sonuç:** Bu çalışmanın sonuçları hormonal terapi için letrozol kullanan postmenopozal meme kanserli hastalarda tamoksifene göre artmış APTT seviyelerinin olabileceğini öne sürdü. Fakat PT ve INR gibi diğer koagülasyon parametrelerinde her iki grup için herhangi bir fark saptanmadı. Ayrıca bu çalışmada, postmenopozal meme kanserli hastaların lipit profili ve KMY'leri letrozol ve tomaksifen grupları arasında karşılaştırıldığında anlamlı fark yoktur.

Anahtar Kelimeler: Meme tümörleri; tamoksifen; letrozole; kan pıhtılaşması; lipidler; kemik yoğunluğu

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Antagonizing the growth-stimulatory effects of estrogen is an established clinical approach to patients with hormone-dependent breast cancer. The major source of estrogen in postmenopausal women arises from the aromatization of peripheral androgens catalysed by the enzyme aromatase. The ovaries, adrenal gland and adipose tissue are the main sources of the peripheral androgens in postmenopausal women. Tamoxifen is the first line endocrine therapy for breast cancer and it competes with estrogen for binding to the estrogen receptor.[1,2] Although it acts against breast cancer primarily as an anti-estrogen, it has also found partial estrogenic activity, which may explain its beneficial effect on lipid metabolism and favorable changes in the lipid profiles, such as lower total cholesterol and low-density lipoprotein (LDL).[3]

The aromatase inhibitors (AI) act by inhibiting estrogen synthesis and deplete estrogen concentrations in the circulation, tumor, and peritumoral tissue and are thus a useful alternative antiestrogenic strategy to tamoxifen. Letrozole is one of the third generation aromatase inhibitors and may show adverse changes in lipid metabolism associated with low estrogen levels, reported as an increase in serum total cholesterol and LDL.[4]

Estrogen is known to reduce total cholesterol, LDL and to increase high-density lipoprotein (HDL) levels. Additionally, the effect on triglycerides (TG) is not as clear.[5] The otherwise postmenopausal women are already at risk for cardiovascular disease and thus concern has been raised about the possible effects of chronic estrogen suppression on lipid metabolism. Because cardiovascular disease is the most common cause death in postmenopausal women, effects on this outcome could play an important role in the risk-benefit analysis of hormonal therapy, including tamoxifen and letrozole.[6] However, estrogen replacement does not reduce the risk of cardiovascular disease as evidence by the Women's Health Initiative (WHI) study.

Estrogen therapy, tamoxifen are associated with an increased risk of venous thrombosis; however, the mechanisms by which each drug increases venous thrombosis propensity are not fully understood. Cosman et al reported an increase in factor VII and D-dimer and a decrease in protein S following ET.[7] The authors also noticed an increase in factor VIII, factor IX and von Willebrand factor and a decrease in protein C and antitrombin. In the other study, tamoxifen and hormone replacement therapy had no adverse changes in coagulation factors. Thromboembolic disease is a well-documented side effect o tamoxifen therapy that can cause considerable morbidity and mortality. Fewer thromboembolic adverse events were reported in patients taking an AI than in those taking tamoxifen.[8]

Bone loss may be a potential side effect of aromatase inhibitors due to depletes estrogen levels and when compared with tamoxifen, letrozole included a higher risk factor for the osteoporosis.[1]

The goal of this work was to study the effects of letrozole and tamoxifen on serum lipids, coagulation parameters and bone mineral density (BMD) in asymptomatic postmenopausal women.

MATERIAL AND METHODS

A cross-sectional study was performed in asymptomatic postmenopausal breast cancer patients receiving hormonal therapy at least one year. Included in this study were twenty-nine postmenopausal breast cancer women taking 20 mg daily of tamoxifen (14 patients) (group1) or 2.5 mg daily of letrozole (15 patients) (group2). Both of the groups took drugs as a first-line therapy. All of the patients receiving letrozole had taken calcium 1500 mg and vitamin D 400 IU daily. Lipid parameters including cholesterol, HDL cholesterol, LDL cholesterol and TG and coagulation measures such as activated partial thromboplastin time (APTT), prothrombin time (PT) and international normalized ratio (INR) were examined. These measurements were performed at least twelve hour fasting status. Age, parity, age at menarche and at menopause, body mass index (BMI), smoking history, history of drugs use, duration of therapy were recorded for each woman. All patients underwent breast surgery for breast cancer that was positive for estrogen receptors, progesterone receptors, or both and were observed after accomplishment of

chemotherapy and/or radiotherapy. Menopausal status was defined when at least 12 months elapsed since the last menstrual period; it was either physiological or chemo-induced and, in this latter case, a stable rise in FSH levels was required for patient's inclusion. No patient had received drugs that influenced the coagulation measurements and had any history of thromboembolic events.

Serum estradiol (E2), follicle-stimulating hormone (FSH) and luteinizing hormone were measured by specific radioimmunoassay. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Bone mineral density (BMD) T and Z scores of femur neck and lumbar spine were examined between two groups using dual energy X-ray absorptiometry (DXA; Hologic QDR 1000 densitometer).

The statistical analysis was based on Mann Whitney U test, t test and two proportion z test. All statistical significance was set at $p< 0.05$ SPSS software Version 11.0 was used for all statistical analysis.

RESULTS

In group 1, the average period of tamoxifen intake was 16.47 ± 8.30 months and the average period of letrozole usage was 26.43 ± 19.99 months (Table 1). As shown in Table 1, demographic, clinical variables (age, parity, age at menarche and menopause, body mass index, previous chemotherapy and radiotherapy) and hormonal situation (follicle-stimulating hormone, luteinizing hormone and estradiol levels) did not differ in the letrozole and tamoxifen groups (Table 1). In Table 2, we reported the data related to coagulation measurements and lipid parameters in group1 and group 2. There was a significant difference between tamoxifen and letrozole in APTT levels (p= 0.03) and in letrozole group APTT levels were significantly longer than the tamoxifen group. But for the other parameters comprising PT and INR and lipid profiles, there was no significant difference between two groups (Table 2).

The number of patients exceeding the threshold defined by the lipid parameters at any one time during the study is summarized in Table 3. The percentage of TG and HDL levels beyond the threshold in group 1 (42.86% and 35.71%) were more than group 2 (33.33% and 20%) and total cholesterol and LDL in group 1 (35.71% and 14%) were lower than group 2 (53.33% and 20%) (Table 3). Although the two treatment groups demonstrated differences in the percentage changes, no statistically significant differences were found between the two treatment groups in terms of the number of patients reaching the threshold (Table 3).

Although lumbar vertebral and femoral BMD of tamoxifen was higher than letrozole, there was no statistically significant difference. BMD below the threshold for osteoporosis (≥2.5 below the mean) was found in 4 patients (30.8%) of letrozole group and 3 patients (21.4%) in tamoxifen group (Table 4).

TABLE 1: Demographic, clinical variables and hormonal situations of the patients (mean ± SD).

	Group 1 (TMX)	Group 2 (AI)	P values
Age	57.73 ± 11.59	58.14 ± 5.88	0.8
Parity	4.27 ± 2.55	3.57 ± 2.68	0.3
Menarche	13.67 ± 1.05	13.57 ± 0.76	0.8
Menopause	46.73 ± 4.85	48.71 ± 2.81	0.3
Body mass index	30.28 ± 5.39	28.63 ± 4.11	0.4
Chemotherapy	100%	100%	0.8
Radiotherapy	73.3%	64.3%	0.1
Time therapy (months)	16.47 ± 8.30	26.43 ± 19.99	0.06
FSH	48.48 ± 28.13	57.44 ± 29.79	0.1
LH	26.11 ± 12.02	23.71 ± 9.74	0.6
E2	23.04 ± 16.75	18.14 ± 13.69	0.5

TABLE 2: Effects of tamoxifen and letrozole on serum lipid parameters and coagulation measurements (mean ± SD).

	Group 1 (TMX)	Group 2 (Aİ)	P values
Total cholesterol	202 ± 36.54	212 ± 45.37	0.6
Total TG	168 ± 86.12	133.67 ± 118.87	0.4
LDL	130.26 ± 33.16	143.25 ± 31.23	0.3
HDL	37.72 ± 14.37	41.97 ± 8.84	0.4
APTT	19.64 ± 1.07	24.90 ± 5.48	0.03
PT	11.13 ± 0.84	11.54 ± 0.89	0.4
INR	0.91 ± 0.04	0.96 ± 0.09	0.1

DISCUSSION

AIs have become the first choice endocrine therapy for postmenopausal breast cancer patients.[9]

TABLE 3: Number of patients exceeding threshold defined by the lipid parameters.

	Group 1 (TMX)	Group 2 (Aİ)	P values
Total cholesterol	35.71% (>200 mg/dl)	53.33% (>200 mg/dl)	0.3
Total TG	42.86% (>160 mg/dl)	33.33% (>160 mg/dl)	0.6
LDL	14% (>170 mg/dl)	20% (>170 mg/dl)	0.7
HDL	35.71% (<35 mg/dl)	20% (<35 mg/dl)	0.3

When compared with tamoxifen both in the adjuvant and metastatic states, AIs are associated with superior activity and well tolerability. Third generation AIs are biochemically more selective and potent and also show superior clinical activity compared with the other AIs.[9] Additionally, many other trials have reported that AIs had superior activity and better general tolerability when compared with tamoxifen.[10] Although the effects of third generation AIs has not been directly compared with tamoxifen for coagulation and lipid parameters in double blind, randomized controlled trials. In our study, we compared two endocrine treatment modalities using postmenopausal breast cancer patients for these parameters.

Estrogen is important to reduce cholesterol levels and also has positive effects on bone mineralization. Tamoxifen that has also particularly estrogenic properties has affected both lipid levels and bone mineralization in a favorable way.[11,12] Although long term toxicities of AIs did not well known, effects of inhibiting estrogen synthesis to inhibit aromatisation were important for cardiovascular and disease and osteoporosis as women age.

AIs both anastrozole and letrozole were associated with a significant increase in low-grade hypercholesterolemia when compared with tamoxifen.[13] Goss et al. revealed that exemestane significantly prevented the increase in serum cholesterol and low-density lipoprotein levels in ovariectomised rats, while letrozole did not. In a study that compared the effect of exemestane versus tamoxifen on lipid profile exhibited that LDL levels were higher, triglyceride levels were lower in exemestane arm.[14] In our study, although there was not any statistically significant difference, total cholesterol, LDL were higher in letrozole group and total TG and HDL were higher in tamoxifen group.

TABLE 4: Analysis of BMD (mean ± SD).

	Group 1	Group 2	P values
Total lumbar T scores	-0.76 ± 2.33	-1,82 ± 1.52	0.19
Total lumbar Z scores	+0.22 ± 2.27	-0.88 ± 1.46	0.25
Femur neck T scores	-1.73 ± 1.55	-1.76 ± 1.25	0.87
Femur neck Z scores	-0.35 ± 1.40	-0.47 ± 1.33	0.82
Total femur T scores	-1.46 ± 1.10	-1.35 ± 1.37	0.51
Total femur Z scores	-0.44 ± 0.86	-0.31 ± 1.29	0.78

In postmenopausal women, the risk of osteoporosis is increased due to estrogen deprivation. Aromatisation is the main source of estrogen in menopause and thus it is expected that all AIs decrease BMD when compared to placebo. Also, tamoxifen lowers the osteoporotic risk due to its estrogenic property on the bone when compared with tamoxifen.[12] Significant bone loss is reported in all studies during AIs use when compared with tamoxifen or placebo, but it appears lower with steroidal versus non-steroidal AIs. Although AIs especially exemestane were associated with high fracture rates than tamoxifen, there was no difference in the clinical fracture between letrozole and tamoxifen.[15-17] Although with a limited number of patients, our results display that there was no difference for BMD between letrozole and tamoxifen groups in postmenopausal breast cancer patients. There was not any patient with osteoporosis in our study.

In our study, we also evaluate the coagulation parameters such as APTT, PT and INR. To our knowledge, this is the first study investigating and comparing the effects of tamoxifen and letrozole for coagulation parameters. Tamoxifen is reported to slightly increase the risk of thrombosis in women with breast cancer.[18] Additionally the studies were showed that hypercoaguable state may be multifactorial in women with breast cancer. In a study tamoxifen significantly reduced plasma fibrinogen and antithrombin III levels.[19] Although decreased plasma fibrinogen levels might prevent arterial thrombosis, decreased antithrombin III levels resulted in increased thromboembolic ten-

dency. In this small serious of patients, letrozole had increased levels of APTT hen compared with tamoxifen.

When letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive breast cancer, their effects were comparable with different side effects.[13] Tamoxifen had more thromboembolic events, endometrial pathology, hot flashes, night sweats, and vaginal bleeding. On the other hand, letrozole had more bone fractures, arthralgia, low-grade cholesterol elevation, and cardiovascular events other than ischemic heart disease and cardiac failure. In our study, serum lipids, coagulation parameters and bone mineral density were examined in asymptomatic postmenopausal women with breast cancer.

In conclusion, the results of this study suggest that APTT shows an increased level in postmenopausal breast cancer patients receiving letrozole for hormonal therapy when we compared to tamoxifen taking patients but the other coagulation parameters such as PT and INR were not affected between each group. In addition, by comparing letrozole versus tamoxifen trials on the lipid profile of the postmenopausal breast cancer patients, there was no difference for the lipid parameters in this report. There was no difference for the effects of letrozole and tamoxifen on BMD in postmenopausal patients with breast cancer in our study.

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