Endometrial Histologic Changes in Breast Cancer Patients Receiving Endocrine Therapy

Endokrin Terapisi Alan Meme Kanserli Hastalarda Endometriyal Histolojik Değişiklikler

Gökalp ÖNER, MD,[a]
Bülent ÖZÇELİK, MD,[a]
Tuncay ÖZGÜN, MD,[a]
Çağdaş TÜRKYILMAZ, MD,[a]
Semih ULUDAĞ, MD,[a]
Serdar SERİN, MD[a]

[a]Department of Obstetrics and Gynecology,
Faculty of Medicine, Erciyes University, Kayseri

Geliş Tarihi/*Received:* 29.08.2008
Kabul Tarihi/*Accepted:* 06.11.2008

This study was presented as a poster at Congress of 11th National Gynecologic Oncology (30 April-04 May, 2008).

Yazışma Adresi/*Correspondence:*
Gökalp ÖNER, MD
Erciyes University, Faculty of Medicine, Department of Obstetrics and Gynecology, Kayseri
TÜRKİYE/TURKEY
gokalpw85@mynet.com

ABSTRACT Objective: To investigate the effects of adjuvant hormonal therapies on endometrium in the hormone receptor-positive breast cancer patients. **Material and Methods:** A cross-sectional study was performed in 60 asymptomatic premenopausal or postmenopausal breast cancer patients receiving hormonal therapy at least one year. Of the patients receiving tamoxifen, 14 were postmenopausal (group 1) and 23 patients were premenopausal (group 2), letrozole using patients (group 3) were postmenopausal and all of the patients using tamoxifen combined with goserelin (group 4) were premenopausal. All patients underwent a gynecological examination combined with transvaginal ultrasound and patients with an endometrial thickness of > 4 mm were offered endometrial biopsy. **Results:** Demographic, clinical variables and hormonal situation did not differ between the groups. There was a statistically significance for endometrial thickness between group 1 and group 3 ($p< 0.001$) but in groups 2 and 4 there was no significant difference. The most frequently observed abnormal lesions in groups were endometrial polyps (35.7%) in group 1, proliferative endometrium (26.1%) in group 2, atrophic endometrium (26.7%) in group 3, and atrophic (12.5%) or proliferative (12.5%) endometrium in group 4. **Conclusion:** As compared with tamoxifen, letrozole treatment was significantly associated with a reduced endometrial thickness but there was no difference for the endometrial thickness and pathologies between the tamoxifen and goserelin using groups. So, this implies that aromatase inhibitor therapy would be more beneficial than other therapies in postmenopausal breast cancer patients for preventing the endometrial follow-up and unnecessary interventions. However, in premenopausal group, alternative treatment modalities may need to improve.

Key Words: Breast neoplasms; aromatase inhibitors; tamoxifen; goserelin; endometrium

ÖZET Amaç: Hormon reseptör pozitif meme kanserli hastalarda adjuvan hormonal terapinin endometriyuma etkisini inceledik. **Gereç ve Yöntemler:** En az bir yıl hormonal terapi almış asemptomatik premenopozal veya postmenopozal 60 meme kanserli hastada kesitsel bir çalışma gerçekleştirilmiştir. Tamoksifen alan hastaların 14 (grup 1)'ü postmenopozal, 23 (grup 2)'ü premenopozal, letrozol kullanan hastalar (grup 3) postmenopozal ve goserelin ile kombine edilmiş tamoksifen kullanan tüm hastalar (grup 4) premenopozaldı. Tüm hastalara transvajinal ultrasound ile kombine edilmiş jinekolojik muayene yapıldı ve endometriyal kalınlık > 4 mm olan hastalara endometriyal biyopsi tercih edildi. **Bulgular:** Demografik, klinik değişkenler ve hormonal durum açısından gruplar arasında farklılık saptanmamıştır. Grup 1 ve grup 3 arasında endometriyal kalınlık için anlamlı bir fark bulunmaktadır ($p< 0.001$) fakat grup 2 ve 4'te anlamlı bir fark tespit edilmemiştir. Gruplarda sıklıkla görülen anormal lezyonlar; grup 1'de endometriyal polip (%35.7), grup 2'de proliferatif endometriyum (%26.1), grup 3'te atrofik endometriyum (%26.7) ve grup 4'te atrofik (%12.5) veya proliferatif endometriyumdur (%12.5). **Sonuç:** Tamoksifenle kıyaslandığında letrozol tedavisi, incelmiş endometriyumla anlamlı ilişkilidir fakat tamoksifen ve goserelin kullanan gruplar arasında endometriyal kalınlık ve patolojiler arasında fark yoktur. Bundan dolayı postmenopozal meme kanserli hastalarda endometriyal takip ve gereksiz girişimleri önlemek için aromataz inhibitör terapisi diğer tedavilere göre daha faydalı olabilecek gibi görünmektedir. Fakat premenopozal grupta alternatif tedavi modalitelerinin geliştirilmesi gerekebilmektedir.

Anahtar Kelimeler: Meme kanserleri; aromataz inhibitörleri; tamoksifen; goserelin; endometriyum

Turkiye Klinikleri J Gynecol Obst 2009;19(1):25-9

Antagonizing the growth stimulatory effects of estrogen is an established clinical approach to patients with hormone dependent breast cancer.[1] Therefore tamoxifen, letrozole and goserelin are prescribed for depleting estrogen concentrations by binding receptor or inhibiting synthesis or depressing ovarian steroidogenesis.

Tamoxifen is a non-steroidal triphenylethylene derivative, which is widely used as a hormonal therapy increasing survival and disease free interval of breast cancer patients.[2] As its estrogenic action on female genital tract, it may cause benign disease like atrophy, polyps, hyperplasia and malignant disease like adenocarcinoma and carcinosarcoma.[3] The risk of postmenopausal endometrial cancer due to exposure of tamoxifen increases two to four times.[4] Transvaginal ultrasound examination (TVUS) is an advised method to minimize endometrial cancer morbidity and mortality in tamoxifen treated asymptomatic patients although there is no consensus about how to follow-up these patients.[5,6]

Letrozole is one of the third generation aromatase inhibitors (AI), which have been shown to produce clinical remissions of disease in patients with breast cancer.[7] Data from the studies comparing AIs with tamoxifen have suggested that AIs may have low endometrial pathologies such as endometrium cancer and reduce requirement for investigational procedures.[8] Additionally, AIs may reverse tamoxifen-associated endometrial thickening and reduced unnecessary second-line endometrial investigations.[9] So based on a different biochemical pathway, aromatase inhibitors therapy should result in a safer pharmacologic profile on endometrium.

Goserelin, a gonadotropin-releasing hormone (GnRH) analogue, reduces plasma/serum estrogen levels in pre- or perimenopausal women, and is indicated in hormone receptor-positive breast cancer patients. Goserelin is used either alone or in combination with tamoxifen as an adjuvant systemic therapy.[10]

TVUS is a screening method for measuring endometrial thickness and it may be helpful to use diagnostic tools such as biopsy suction device (Pipelle), hysteroscopy and curettages for the histological examinations of endometrial pathologies.[9,11] However, there is discordance between sonographic and histologic endometrial finding in 45-90% of these patients; below the cut off value for the thickness of the endometrial double layer of 4-5 mm is negligible.[12]

The purpose of our report was to evaluate the effects of adjuvant hormonal therapies on endometrium in the hormone receptor-positive breast cancer patients. Also, in this study we compared the relationship between TVUS and histological endometrial findings.

MATERIAL AND METHODS

A cross-sectional study was performed in 60 asymptomatic hormone receptor-positive premenopausal or postmenopausal breast cancer patients receiving hormonal therapy at least one year. All patients underwent a gynecological examination combined with TVUS and patients with an endometrial thickness of > 4 mm were offered endometrial biopsy using biopsy-suction device (Pipelle) during the hormonal treatment period. Women were premenopausal and postmenopausal that was either physiological or chemo-induced and it was established when at least 12 months elapsed from the last menstrual period. No patient recorded abnormal vaginal bleeding. Endometrial pathologies were considered as normal endometrium, atrophic endometrium, proliferative endometrium, polyps, simple hyperplasia and endometrial cancer. All polyps were hysteroscopically removed. Four groups of patients were evaluated; of the patients receiving tamoxifen (20 mg/day), 14 were postmenopausal (group 1) and 23 patients were premenopausal (group 2), letrozole (2.5 mg/day) using patients (group 3) were postmenopausal and all of the patients using tamoxifen combined with goserelin (3.6 mg/month) (group 4) were premenopausal. 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

Demographic, clinical characteristics (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) of patients are reported in Table 1 and the variables evaluated were not significantly different between the groups except LH levels of group 2 and 4. In Table 1, we report the data related to endometrial thickness and there was a statistically significance for endometrial thickness between group 1 and group 3 ($p< 0.001$) but no statistically significant differences were found in groups 2 and 4. The second-line endometrial investigations were preferred by endometrial biopsy with Pipelle and 51 patients (85%) who had an endometrial thickness of > 4 mm, underwent biopsy.

In Table 2 represents the endometrial pathologies; the most frequently observed abnormal endometrial lesions in groups were endometrial polyps (35.7%) in group 1, atrophic endometrium (26.7%) in group 3, proliferative endometrium (26.1%) in group 2 and atrophic (12.5%) or proliferative (12.5%) endometrium in group 4. In group 2, we found 2 patients showing simple hyperplasia without atypia and endometrial cancer were not observed in none of patients. Since the start of endocrine therapy, we detected an overall rate of emerging pathologies such as polyp, and endometrial hyperplasia in 35.7% of group 1, 21.7% of gro-

TABLE 1: Demographic, clinical variables and hormonal situations of the patients and comparison of endometrial thickness in the groups.

	Group 1 postmenopausal (Tamoxifen)	Group 3 postmenopausal (Letrozole)	p	Group 2 premenopausal (Tamoxifen)	Group 4 premenopausal (Tamoxifen and goserelin)	p
Number of patients	14	15		23	8	
Age	57.73 ± 11.59	58.14 ± 5.88	NS	43.52 ± 5.41	42.75 ± 6.18	NS
Parity	4.27 ± 2.55	3.57 ± 2.68	NS	3.26 ± 1.21	4.00 ± 2.39	NS
Menarche	13.67 ± 1.05	13.57 ± 0.76	NS	13.21 ± 0.85	13.00 ± 0.54	NS
Menopause	46.73 ± 4.85	48.71 ± 2.81	NS	41.82 ± 4.85	41.25 ± 5.92	NS
Body mass index	30.28 ± 5.39	28.63 ± 4.11	NS	29.12 ± 4.54	30.23 ± 4.37	NS
Chemotherapy	100%	100%	NS	100%	100%	NS
Radiotherapy	73.3%	64.3%	NS	78%	62.5%	NS
Time therapy (months)	16.47 ± 8.30	26.43 ± 19.99	NS	21.52 ± 11.55	16.12 ± 5.86	NS
FSH	48.48 ± 28.13	57.44 ± 29.79	NS	44.07 ± 45.27	12.73 ± 14.67	NS
LH	26.11 ± 12.02	23.71 ± 9.74	NS	20.97 ± 14.83	6.68 ± 7.68	SS (p= 0.02)
E2	23.04 ± 16.75	18.14 ± 13.69	NS	125.13 ± 236.9	23.91 ± 14.05	NS
Endometrial thickness	10.14 ± 5.59	4.06 ± 1.07	SS (p< 0.001)	9.24 ± 4.69	7.58 ± 4.11	NS

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone.

TABLE 2: Endometrial pathologies.

	Group 1 (Tamoxifen)		Group 2 (Tamoxifen)		Group 3 (Letrozole)		Group 4 (Tamoxifen and Goserelin)	
	n	%	n	%	n	%	n	%
Normal endometrium	6	42.9	10	43.4	6	40	4	50
Atrophic endometrium	2	14.3	0	0.0	4	26.7	1	12.5
Proliferative endometrium	1	7	6	26.1	0	0.0	1	12.5
Polyps	5	35.7	3	13	2	13.3	0	0.0
Simple hyperplasia	0	0.0	2	8.7	0	0.0	0	0.0
Endometrial cancer	0	0.0	0	0.0	0	0.0	0	0.0

up 2, 13.3% of group 3 and 0.0% of group 4. The emerging rate of the endometrial pathologies did not differ significantly between the postmenopausal patients with tamoxifen (35.7%) and letrozole (13.3%) (p= 0.215).

We also assessed the relation between the thickness of endometrium and endometrial pathologies. However, there was a statistically significant difference between group 1 and group 3 for the endometrial polyp and atrophic endometrium (p< 0.001), the endometrial thickness for patients with histologically unremarkable and abnormal endometrium was not statistically different between the other groups.

DISCUSSION

It is estimate that women with breast cancer have 1.72 times the risk of developing endometrium cancer.[13] However, tamoxifen is still the worldwide most common and first choice endocrine drug to treat breast cancer; it may be responsible for the endometrial morbidity in women chronically exposed to the drug.[14] Therefore, varied opinions are existed due to the endometrial effects of the tamoxifen-treated patients. Accordingly, alternative endocrine treatments such as aromatase inhibitors have been compared to tamoxifen not only in terms of efficacy but also focusing on their toxicity profiles. In a big randomized study, comparing adjuvant letrozole wit tamoxifen, a lower prevalence of endometrial pathologies was found in letrozole group.[15] However, we did not find any atypical lesions in patients; the emerging rates of the endometrial pathologies during tamoxifen (35.7%) therapy and letrozole therapy (13.3%) were consistent with the results published in previous reports.[9,16] In three prospective studies with systematic baseline endometrial study during tamoxifen treatment, emerging abnormalities were found in 14% (0.0% atypical), 30.4% (2.7% atypical) and 43.0% (5.2% atypical) of cases though 25 months, 48 months, and 60 months of follow-up, respectively.[16-18] In most of study, a lower prevalence of emerging pathology was observed with aromatase inhibitors therapy and aromatase inhibitors may reverse uterine changes associated with tamoxifen[9,15,19] Although, in our study we studied with a limited number of patients who received goserelin, we found lower rates of endometrial pathologies in this group. A lower rate of hysteroscopical investigations may be need by the hormonal treatment with letrozole or goserelin.

The authors concluded that tamoxifen significantly increases endometrial thickness already detectable by transvaginal ultrasound, however; aromatase inhibitors may prevent endometrial growth and lower tamoxifen-induced endometrial thickening.[4,15,19] Also, there was a positive correlation between endometrial thickness and the duration of tamoxifen usage in asymptomatic postmenopausal breast cancer patients.[20] In this study, a significant decline in the endometrial thickness is observed in patients receiving letrozole, compared with patients continuing tamoxifen therapy. Despite aromatase inhibitors therapy resulted in a significant reduction in the proportion of patients with endometrial thickness > 4 mm in this study, similar to other studies, there is no effect on endometrial thickening, leading to a substantial reduction of unnecessary second-line endometrial investigations. Additionally, goserelin act by down-regulating of pituitary GnRH receptors and reduce only the source of estradiol production in the ovaries. For this reason, it may be thought that there is no effect on endometrial outcomes of tamoxifen. Likewise, in our report, there is not statistically significant difference between tamoxifen and the goserelin combined therapy for endometrial thickness. Further studies are needed to clarify whether the relation between hormonal therapy and endometrium.

Similar to our results, other studies with a longer follow-up period have confirmed the lack of a stimulatory effect of aromatase inhibitors on the endometrium and when compared the other protocols, the endometrial thickness in patients receiving aromatase inhibitors was ≤ 5 mm and aromatase inhibitors had a lower incidence of endometrial pathologies.[19,21] Accordingly, the rate of unnecessary endometrial sampling may be decreased and investigation periods were elongated dependent on the base of endometrial thickness and

pathologies. So, this implies that aromatase inhibitor therapy would be more beneficial than other therapies in postmenopausal breast cancer patients. But, in premenopausal group, it seems that alternative treatment modalities may require for endometrial follow-up and excessive interferences.

In conclusion, as compared with tamoxifen, letrozole treatment was significantly associated with a reduced endometrial thickness but there was no difference for the endometrial pathologies in postmenopausal patients with breast cancer. So this shows that the absence of a stimulatory effect on endometrium may be one of the benefits gained with aromatase inhibitor therapy and may decrease the need for gynecological interventions. Also in the premenopausal breast cancer patients receiving neither only tamoxifen nor combined with goserelin for hormonal treatment, there was no difference for the endometrial thickness and pathologies.

REFERENCES

1. Goss PE, Qi S, Cheung AM, Hu H, Mendes M, Pritzker KP. Effects of steroidal aromatase inhibitor exemestane and the nonsteroidal aromatase inhibitor letrozole on bone and lipid metabolism in ovariectomized rats. Clin Cancer Research 2004;10(17):5717-23.
2. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998;351(9114):1451-67.
3. Deligdisch L, Kalir T, Cohen CJ, de Latour M, Le Bouedec G, Penault-Llorca F. Endometrial histopathology in 700 patients treated with tamoxifen for breast cancer. Gynecol Oncol 2000;78(2):181-6.
4. Gerber B, Krause A, Reimer T, Mylonas I, Makovitzky J, Kundt G, et al. Anastrozole versus tamoxifen treatment in postmenopausal women with endocrine-responsive breast cancer and tamoxifen induced endometrial pathology. Clin Cancer Res 2006;12(4):1245-50.
5. Suh-Burgmann EJ, Goodmann A. Surveillance for endometrial cancer in women receiving tamoxifen. An Intern Med 1999;131(2): 127-35.
6. Fung MF, Reid A, Faught W, Le T, Chenier C, Verma S, et al. Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen. Gynecol Oncol 2003;91(1):154-9.
7. Wasan KM, Goss PE, Pritchard PH, Shepherd L, Palmer MJ, Liu S, et al. The influence of letrozole on serum lipid concentrations in postmenopausal women with primary breast cancer who have completed 5 years of adjuvant tamoxifen (NCIC CTG MA. 17 L) Ann Onc 2005;16(5):707-15.
8. Perez EA. Safety of aromatase inhibitors in the adjuvant setting. Breast Cancer Res Treat 2007;105(Suppl 1):75-89.
9. Garuti G, Cellani F, Centinaio G, Montanari G, Nalli G, Luerti M. Prospective endometrial assessment of breast cancer patients treated with third generation aromatase inhibitors. Gynecol Oncol 2006;103(2):599-603.
10. Robertson JF, Blamey RW. The use of gonadotrophin-releasing hormone (GnRH) agonists in early and advanced breast cancer in pre- and perimenopausal women. Eur J Cancer 2003;39(7):861-9.
11. Seoud M, Shamseddine A, Khalil A, Salem Z, Saghir N, Bikhazi K, et al. Tamoxifen and endometrial pathologies: a prospective study. Gynecol Oncol 1999;75(1):15-9.
12. Granberg S, Wikland M, Karlsson B, Norström A, Friberg LG. Endometrial thickness as measured by endovaginal ultrasonography for identifying endometrial abnormality. Am J Obstet Gynecol 1991;164(1 Pt 1):47-52.
13. Adami HO, Krusemo UB, Bergkvist L, Persson I, Pettersson B. On the age-dependent association between cancer of the breast and endometrium. A nationwide cohort study. Br J Cancer 1987;55(1):77-80.
14. Neven P, Vernaeve H. Guidelines for monitoring patients taking tamoxifen treatment. Drug Saf 2000;22(1):1-11.
15. Breast International Group (BIG) 1-98 Collaborative Group, Thürlimann B, Keshaviah A, Coates AS, Mouridsen H, Mauriac L, Forbes JF, Paridaens R, Castiglione-Gertsch M, Gelber RD, Rabaglio M, Smith I, Wardley A, Price KN, Goldhirsch A. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005;353 (26):2747-57.
16. Garuti G, Grossi F, Centinaio G, Sita G, Nalli G, Luerti M. Pretreatment and prospective assessment of endometrium in menopausal women taking tamoxifen for breast cancer. Eur J Obstet Gynecol Reprod Biol 2007;132 (1):101-6.
17. Vosse M, Renard F, Coibion M, Neven P, Nogaret JM, Hertens D. Endometrial disorders in 406 breast cancer patients on tamoxifen: the case for less intensive monitoring. Eur J Obstet Gynecol Reprod Biol 2002;101 (1):58-63.
18. Neven P, De Muylder X, Van Belle Y, Van Hoff I, Vanderick G. Longitudinal hysteroscopic follow-up during tamoxifen treatment. Lancet 1998;351(9095):36.
19. Duffy S, Jackson TL, Landsdown M, Philips K, Wells M, Pollard S, et al. The ATAC (arimidex, tamoxifen, alone or in combination) adjuvant breast cancer trial: baseline endometrial sub-protocol data on the effectiveness of transvaginal ultrasonography and diagnostic hysteroscopy. Hum Reprod 2005;20(1):294-301.
20. Akhan SE, İyibozkurt AC, Öztekin M, Delier H, Topuz S, Turfanda A. Comparison of ultrasonography, hysteroscopy and histology of endometrium in asymptomatic postmenopausal breast cancer patients treated with tamoxifen. Turkiye Klinikleri J Gynecol Obst 2007;17(5): 342-9.
21. Coombes RC, Kilburn LS, Snowdon CF, Paridaens R, Coleman RE, Jones SE, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet 2007;369 (9561):559-70.