Original Article

Gynecologic Clinicopathological Evaluation of Women with Breast Cancer Using Tamoxifen

Tamoksifen Kullanan Meme Kanserli Kadınların Jinekolojik Açıdan Klinikopatolojik Değerlendirilmesi

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ABSTRACT

Introduction: Tamoxifen is a selective estrogen modulator agent used in breast cancer women. While it has an antiestrogenic effect in the breast, it has estrogenic and antiestrogenic effects in the genital system. It has side effects such as endometrial polyps, hyperplasia, cancer, and ovarian cysts in the uterus and ovaries. In our study, we examined the gynecological clinical and pathological features of patients using tamoxifen

Materials and Methods: In this retrospective study, 183 women's, using tamoxifen for breast cancer, demographic data, comorbidities, menopausal status, admission symptoms, ultrasound findings, endometrial sampling results, tamoxifen duration of use were obtained from patient files and evaluated.

Results: The mean age of 183 patients included in our study was 53.86±10.04. Ovarian cysts were detected in 22 (12%) patients, 15.6% of premenopausal and 8.6% of postmenopausal patients. 13.7% of all patients, 17.8% of premenopausal, and 9.7% of postmenopausal patients had abnormal uterine bleeding. Endometrial sampling was performed in 54.1% of the patients. Endometrial biopsy results were unsatisfactory in 18.6% of the patients, benign findings in 15.3%, atrophy in 6.6%, polyps in 9.3%, hyperplasia without atypia in 2.2%, hyperplasia with atypia in 1.1%, and cancer in 1.1%. Abnormal uterine bleeding rates were statistically higher in those who received treatment at 60 months or more than under 60 months.

Discussion and Conclusion: Tamoxifen is associated with pathologies such as polyps, hyperplasia, cancer, and ovarian cyst. Uterine pathologies usually present with abnormal uterine bleeding. As the duration of tamoxifen use increases, the rate of abnormal uterine bleeding also increases.

Keywords: Breast Cancer, Tamoxifen, Ovarian Cysts, Endometrium, Polyps, Endometrial Hyperplasia

ÖZET

Giriş: Tamoksifen, meme kanserli kadınlarda kullanılan bir selektif östrojen modülatör ajandır. Memede antiöstrojenik etkiye sahipken, genital sistemde östrojenik ve antiöstrojenik etkileri vardır. Uterus ve overlerde; endometrial polip, hiperplazi, kanser, over kistleri gibi yan etkileri vardır. Çalışmamızda tamoksifen kullanan hastaların jinekolojik açıdan klinik ve patolojik özelliklerini inceledik.

Gereç ve Yöntem: Bu retrospektif çalışmada, meme kanseri için tamoksifen kullanan 183 kadının demografik verileri, komorbiditeleri, menopoz durumu, başvuru semptomları, ultrason bulguları, endometriyal örnekleme sonuçları, tamoksifen kullanım süreleri hasta dosyalarından elde edilerek değerlendirildi.

Bulgular: Çalışmamıza dâhil edilen 183 hastanın yaş ortalaması 53,86±10,04 idi. Toplam 22 (%12) hastada over kisti saptandı. Premenopozal hastaların %15,6'sında ve postmenopozal hastaların %8,6'sında kist tespit edildi. Tüm hastaların %13,7'sinde, premenopozal hastaların %17,8'inde ve postmenopozal hastaların %9,7'sinde anormal uterin kanama görüldü. Hastaların %54,1'inde

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endometriyal örnekleme yapıldı. Hastaların %18,6'sında endometriyal biyopsi sonuçları yetersiz, %15,3'ünde benign bulgular, %6,6'sında atrofi, %9,3'ünde polip, %2,2'sinde atipisiz hiperplazi, %1,1'inde atipili hiperplazi ve %1,1'inde kanser saptandı. Anormal uterin kanama oranları, 60 ay veya üzerinde tedavi görenlerde, 60 ayın altında tedavi görenlere göre istatistiksel olarak daha yüksekti.
Tartışma ve Sonuç: Tamoksifen, polip, hiperplazi, kanser ve over kisti gibi patolojilerle ilişkilidir. Uterus patolojileri genellikle anormal uterin kanama ile kendini gösterir. Tamoksifen kullanım süresi arttıkça anormal uterin kanama oranı da artmaktadır.

Anahtar kelimeler: Meme Kanseri, Tamoksifen, Over Kistleri, Endometriyum, Polipler, Endometriyal Hiperplazi

Introduction

Tamoxifen is an aromatase inhibitor that has been used for over 40 years in the prevention and treatment of breast cancer. Tamoxifen reduces epithelial cell proliferation by antiestrogenic activity in breast tissue [1].

Tamoxifen is a non-steroidal selective estrogen receptor modulator (SERM). It can act as an estrogen agonist or antagonist in the female genital tract at different periods and different tissues. The spectrum of side effects of tamoxifen on the genital tract is variable and broad. It increases the risk of endometrial polyp, endometrial hyperplasia, endometrial carcinoma, uterine sarcoma and carcinoma, ovarian cyst [2,3].

In this study, we aimed to evaluate pathological findings such as endometrial sampling results and clinical findings such as age, ultrasound findings, presence of vaginal bleeding symptoms, duration of drug use, co-morbidities, and determine the relationship between them in women with breast cancer using tamoxifen.

Material and Method

This study was approved by the ethics committee for clinical studies (approval number: 2021/01) of Zonguldak Bülent Ecevit University, Turkey. and was conducted in accordance with the Declaration of Helsinki. The study was planned retrospectively. Patients who used 20 mg tamoxifen daily for breast cancer and applied to the Gynecology and Obstetrics Clinic of Zonguldak Bülent Ecevit University Faculty of Medicine between April 2012 and December 2020 were included in the study. Demographic data, co-morbidities (Hypertension, diabetes mellitus and others such as hypothyroidism, hyperthyroidism, coronary artery disease, heart failure, asthma), menopausal status, admission symptoms, ultrasound findings, endometrial sampling results, tamoxifen duration of use were obtained from patient files. We excluded patients who had a history of endometrial pathology before tamoxifen use, underwent a hysterectomy, with a history of cancer other than breast cancer, and missing data for clinical characteristics or ultrasonography.

Endometrial biopsy was performed on the patients with the clinician's decision. Pipelle aspiration, dilatation and curettage or hysteroscopy methods were preferred. Pathology results of the endometrial biopsy were classified as ınsufficient, atrophy, benign findings, polyp, hyperplasia without atypia, hyperplasia with atypia, and cancer.

SPSS 22 program (Version 22.0. Armonk, NY: IBM Corp) was used in the analysis of the Kolmogorov Smirnov test was used as the normal distribution test. Data are presented as mean (standard deviation), median (min-max/IQR), number and percentage. Mann-Whitney U test, t-test, and Chi-square test were used in the analysis. A value of $p<0.05$ was considered statistically significant.

Table-1: The clinical features of the patients

	n (%)
Co-morbidities	
None	107 (58.5)
HT	21 (11.5)
DM	2 (1.1)
HT+DM	13 (7.1)
Other	40 (21.9)
Menopausal Status	
Premenopause	90 (49.2)
Postmenopause	93 (50.8)
Abnormal Uterine Bleeding	
(-)	158 (86.3)
(+)	25 (13.7)
Ovarian Cyst	
(-)	161 (88)
(+)	22 (12)
Endometrial Sampling	
(-)	84 (45.9)
(+)	99 (54.1)
Total	183 (100)

HT: Hypertension, DM: Diabetes Mellitus

Table-2: Pathology results of endometrial biopsy

	n (%)
Insufficient	34 (18.6)
Atrophy	12 (6.6)
Benign Findings	28 (15.3)
Polyp	17 (9.3)
Hyperplasia without atypia	4 (2.2)
Hyperplasia with atypia	2 (1.1)
Cancer	2 (1.1)

Results

The mean age of 183 patients included in our study was 53.86±10.04 (min=34-max=86). Ninty (49.2%) of the patients were in the premenopausal period, and 93 (50.8%) were in the postmenopausal period. The clinical features of the patients are shown in Table-1. The pathology results of the endometrial biopsy are given in Table-2. The distribution of the presence of abnormal uterine bleeding, ovarian cyst, and endometrial biopsy results according to menopausal status are shown in Table-3.

In all patients, endometrial thickness, presence of an ovarian cyst, cyst size, and endometrial sampling results were compared according to the duration of tamoxifen use (under 60 months and above), and no significant difference was found between the groups (respectively p= 0.817, p=0.144, p=0.217, p=0.077). In both premenopausal and postmenopausal patient groups, again, there was no significant difference between the groups (for the premenopausal patient group respectively p=0.782, p=0.171, p=0.429, p=0.199 and for the postmenopausal patient group respectively, p=0.757, p=0.710, p=0.286, p=0.294). In all patients and both premenopausal and postmenopausal patient groups, the relationship between tamoxifen duration and vaginal bleeding was examined, and there was a statistically significant difference. It was found that bleeding rates were higher in the group that received treatment for 60 months or more (p=0.001, p=0.009 and p=0.008, respectively) (Table-4).

Discussion

Tamoxifen is an anti-cancer drug with low toxicity, high efficacy, easily accessible and applicable, used in the treatment of breast cancer. In 1977, the Food and Drug Administration (FDA) approved the use of tamoxifen in the adjuvant treatment of breast cancer [4]. In 1998, it was used in prophylactic treatment in patients with a high risk of breast cancer [5]. In 2013, it was shown that increasing the treatment period from 5 years to 10 years provides a life advantage [6].

Tamoxifen is a selective estrogen modulator agent used in women with estrogen receptor-positive breast cancer. It exerts different effects in different tissues. Tamoxifen inhibits estrogen by binding to the estrogen receptor in breast tissue, thus preventing tumor proliferation. It can act as an agonist or antagonist in different sites of the female genital tract [7,8]. Therefore it has various side effects in different systems. It is associated with sexual dysfunction, vaginal discharge, hot flashes, blood clots, and menstrual irregularities.

Table-3: Distribution of presence of abnormal uterine bleeding, ovarian cyst, and endometrial biopsy results according to menopausal status

	Menopausal Status	
	Premenopause	Postmenopause
Abnormal Uterine Bleeding		
(-)	74 (82.2)	84 (90.3)
(+)	16 (17.8)	9 (9.7)
Ovarian Cyst		
(-)	76 (84.4)	85 (91.4)
(+)	14 (15.6)	8 (8.6)
Endometrial Sampling		
(-)	41 (45.6)	43 (46.2)
(+)	49 (54.4)	50 (53.8)
Endometrial Biopsy Results		
Insufficient	12 (13.3)	22 (23.7)
Atrophy	4 (4.4)	8 (8.6)
Benign Findings	15 (16.7)	13 (14)
Polyp	13 (14.4)	4 (4.3)
Hyperplasia without atypia	3 (3.3)	1 (1.1)
Hyperplasia with atypia	1 (1.1)	1 (1.1)
Cancer	1 (1.1)	1 (1.1)
Total	90 (100)	93 (100)

Table-4: Tamoxifen duration and vaginal bleeding

		Tamoxifen duration		
		0-59 months	60 months<	P
All patients				
Vaginal bleeding				
	(-)	115 (92)	37 (71.2)	0.001*
	(+)	10 (8)	15 (28.8)	
Premenopause Vaginal bleeding				
	(-)	58 (87.9)	12 (60)	0.009*
	(+)	8 (12.1)	8 (40)	
Postmenopause Vaginal bleeding				
	(-)	57 (96.6)	25 (78.1)	0.008*
	(+)	2 (3.4)	7 (21.9)	

p<0.005 was regarded as statistically significant

Uterine pathology usually presents with abnormal uterine bleeding in patients using tamoxifen. Abnormal uterine bleeding requires further investigation. Ultrasonography and/or endometrial sampling is performed. Surveillance with ultrasonography and/or endometrial biopsy to detect endometrial cancer is not recommended for asymptomatic patients using tamoxifen, as it increases unnecessary intervention and is not cost-effective. The American College of Obstetricians and Gynecologists (ACOG) stated that "Premenopausal women treated with tamoxifen have no known increased risk of uterine cancer and as such require no additional monitoring beyond routine gynecologic care" but ACOG also advised that patients on tamoxifen should report any abnormal vaginal symptoms, including staining, leukorrhea, spotting, bloody discharge [9].

Abnormal uterine bleeding is seen in 50% of premenopausal patients and 25% of postmenopausal patients using tamoxifen [10-12]. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-2 study, it was reported that 24.4% of 4693 postmenopausal patients receiving tamoxifen treatment

experienced some degree of vaginal bleeding [12]. A total of 75,170 pre- or postmenopausal breast cancer cases who received adjuvant endocrine therapy in a study evaluated; in premenopausal – using tamoxifen frequency of gynecological symptoms is 20%, while the probability of gynecological intervention is 34%, for postmenopausal patients the rates were 12% and 11%, respectively [13]. In our study, 13.7% of all patients, 17.8% of pre-menopausal and 9.7% of postmenopausal patients using tamoxifen had abnormal uterine bleeding.

Abnormal uterine bleeding in patients using tamoxifen is more associated with endometrial pathologies such as endometrial polyps, hyperplasia, and cancer [11]. Endometrial polyps are the most common endometrial pathology. Polyps occur in 11% of postmenopausal cases using tamoxifen for more than four years. Polyp rate is 7% in patients using premenopausal tamoxifen, not different from the general population. The risk of endometrial hyperplasia and cancer increases for postmenopausal patients [14]. Tamoxifen results in a two- to threefold increased risk of endometrial cancer in postmenopausal patients at five years. In our study, endometrial sampling was performed in 54.1% of the patients. Endometrial biopsy results were unsatisfactory in 18.6% of the patients, benign findings in 15.3%, atrophy in 6.6%, polyps in 9.3%, hyperplasia without atypia in 2.2%, hyperplasia with atypia in 1.1%, and cancer in 1.1%. In the study in which the endometrial biopsy results of 821 patients who used tamoxifen for breast cancer were examined, 77.2% normal histological findings, 21% endometrial polyps, 7% endometrial hyperplasia, 7% endometrial cancer were found [15]. In their study of AlZaabi et al., 10.3% of 204 patients with breast cancer using tamoxifen underwent endometrial biopsy. Two (0.98%) endometrial cancer, one (0.50%) serous carcinoma, three (1.47%) atrophic endometrium, one (0.50%) chronic endometritis and three (1.47%) inactive endometrium was detected in the pathological examination of endometrial biopsies [16]. In our study, polyps were observed in 4.3% of postmenopausal patients and 14.4% of premenopausal patients using tamoxifen. Although the incidence of polyps in postmenopausal patients seems to be low, there are also studies that found a low rate of 4.1%, similar to our study [17].

Screening of an asymptomatic patient using tamoxifen with routine gynecological ultrasonography is not recommended. Ultra-sonography in asymptomatic postmeno-pausal patients has high false positives and results in many unnecessary additional interventions [14]. In our study, 13.7% of all patients, 17.8% of premenopausal and 9.7% of postmenopausal patients using tamoxifen had abnormal uterine bleeding, but endometrial sampling was performed in 54.1% of the patients. Although the rate of abnormal uterine bleeding is similar or less than the literature, the rate of endometrial sampling is high. However, pathological findings rates detected in endometrial sampling are similar to the literature. As self-criticism, we can say that we have made unnecessary gynecological interventions.

Until 2013, the recommended duration for tamoxifen use was five years. However, after it was observed that increasing the treatment to 10 years decreased the deaths due to breast cancer, the treatment period was extended in eligible patients. Of course, this led to an increase in side effects. The risk of endometrial cancer is associated with the duration of tamoxifen use. In the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial (n = 12,894), the risk of endometrial cancer was significantly higher at ten years compared with five years (RR 1.74, 95% CI 1.30- 2.34) [18,19].

In our study, endometrial sampling results were compared according to the duration of

tamoxifen use (under 60 months and above), and no significant difference was found between the groups, but it was found that abnormal uterine bleeding rates were statistically higher in the group who received treatment at 60 months or more than under 60 months. While we observed an increase in abnormal uterine bleeding rates according to the duration of tamoxifen use in our study, we could not detect a difference between the endometrial sample results. This may be due to the low number of patients.

Tamoxifen can affect the ovary. Tamoxifen exposure can be related to the development of ovarian cysts or an increased risk of ovarian cancer [20,21]. Metindir et al. stated that ovarian cysts were seen in 19.3% of the patients using tamoxifen. Cyst was observed in 49.1% of premenopausal women and 1.1% of postmenopausal women [22]. In the study of Kim et al., the prevalence of ovarian cyst in women using tamoxifen was 19.4% for pre and 6.3% for postmenopausal patients [23]. These ratios were 16.3% and 4.6%, respectively, in the study of Lee et al. [17]. Similar to other studies, in our study, ovarian cyst was detected in 22 (12%) patients, 15.6% of premenopausal patients, and 8.6% of postmenopausal patients.

Conclusion

Tamoxifen has some effects on the female genital tract. Uterine pathologies usually present with abnormal uterine bleeding. While it is generally associated with pathologies such as polyps, hyperplasia, and cancer in the uterus, it also increases the incidence of cysts in the ovary. Intervention should not be performed on patients without symptoms to prevent unnecessary intervention in patients using tamoxifen.

REFERENCES

1. Riggs BL, Hartmann LC. Selective estrogen-receptor modulators mechanisms of action and application to clinical practice. N Engl J Med 2003; 348: 618-29.
2. Jankowitz RC, Davidson NE. Adjuvan endocrine therapy for breast cancer: How long is enough? Oncology 2013; 27: 1-4.
3. Davies C, Godwin J, Gray R, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patientlevel meta-analysis of randomised trials. Lancet. 2011; 378: 771-784.
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015; 386: 1341-1352.
5. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998; 90: 1371-1388.
6. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomized trial. Lancet. 2013; 381: 805-816.
7. Osborne C, Elledge RM, Fuqua SA. Estrogen Receptors in Breast Cancer Therapy. Sci Med 1996; 3: 32-41.
8. Jordan VC, Morrow M. Tamoxifen, raloxifene, and the prevention of breast cancer. Endocr Rev 1999; 20: 253-7.
9. Committee Opinion No. 601: Tamoxifen and uterine cancer. Obstet Gynecol 2014; 123: 1394. Reaffirmed 2021.
10. Buijs C, Willemse PH, de Vries EG, et al. Effect of tamoxifen on the endometrium and the menstrual cycle of premenopausal breast cancer patients. Int J Gynecol Cancer 2009; 19: 677-81.
11. Cheng WF, Lin HH, Torng PL, Huang SC. Comparison of endometrial changes among

symptomatic tamoxifen-treated and nontreated premenopausal and postmenopausal breast cancer patients. Gynecol Oncol 1997; 66: 233-7.
12. Runowicz CD, Costantino JP, Wickerham DL, et al. Gynecologic conditions in participants in the NSABP breast cancer prevention study of tamoxifen and raloxifene (STAR). Am J Obstet Gynecol 2011; 205: 535.e1.
13. Chalas E, Costantino JP, Wickerham DL, et al. Benign gynecologic conditions among participants in the Breast Cancer Prevention Trial. Am J Obstet Gynecol. 2005; 192: 1230-7.
14. Güleç, ÜK, Paydaş S, Güzel AB. Tamoksifen kullanan hastaların jinekolojik yönden değerlendirilmesi. Arşiv Kaynak Tarama Dergisi. 2021; 30: 45-51.
15. Jeon J, Kim SE, Lee DY, Choi D. Factors associated with endometrial pathology during tamoxifen therapy in women with breast cancer: a retrospective analysis of 821 biopsies. Breast Cancer Res Treat. 2020; 179: 125-130.
16. AlZaabi A, AlAmri H, ALAjmi G, et al. Endometrial Surveillance in Tamoxifen and Letrozole Treated Breast Cancer Patients. Cureus. 2021; 13: e20030.
17. Lee S, Kim YH, Kim SC, et al. The effect of tamoxifen therapy on the endometrium and ovarian cyst formation in patients with breast cancer. Obstet Gynecol Sci. 2018; 61: 615-620.
18. Gray RG, Rea D, Handley K, et al. aTTom: Long-term effects of continuing adjuvan tamoxifen to 10 years versus stopping at 5 years in 6.953 women with early breast cancer. Lancet. 2013; 381: 805-816.
19. Runowicz CD, Costantino JP, Wickerham DL, et al. Gynecologic conditions in participants in the NSABP breast cancer prevention study of tamoxifen and raloxifene (STAR). Am J Obstet Gynecol. 2011; 205: 535.e1.
20. Cohen I, Beyth Y, Tepper R, et al. Ovarian tumors in postmenopausal breast cancer patients treated with tamoxifen. Gynecol Oncol 1996; 60: 54-58.
21. Seoud MA, Johnson J, Weed JC Jr. Gynecologic tumors in tamoxifen-treated women with breast cancer. Obstet Gynecol 1993; 82: 165-169.
22. Metindir J, Aslan S, Bilir G. Ovarian cyst formation in patients using tamoxifen for breast cancer. Jpn J Clin Oncol 2005; 35: 607-611.
23. Kim HS, Jeon YT, Kim YB. The effect of adjuvant hormonal therapy on the endometrium and ovary of breast cancer patients. J Gynecol Oncol 2008; 19: 256-260.

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