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Leuprolide Acetate Treatment for Ovarian Cysts in Breast Cancer Patients Under Tamoxifen Therapy

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ABSTRACT

OBJECTIVE: The aim of this study is to evaluate the outcomes of gonadotropin-releasing hormone agonist treatment for ovarian cysts, which are developed during tamoxifen use due to breast cancer.

STUDY DESIGN: This was a retrospective cohort study including the patients who were under tamoxifen treatment due to stage I-III breast cancer and who were administered leuprolide acetate for ovarian cysts with low malignancy risk between 2012-2020.

RESULTS: Leuprolide acetate was administered to a total of 16 patients with ovarian cysts. The median age was 39.5 (33-52), the median size of the ovarian cyst was 42.5 (39-79) mm, and the median duration of tamoxifen use was 22 (7-36) months. Leuprolide acetate was administered at doses of 3.75 mg for 1 month at 10 (62.5%) patients, 7.5 mg in two months at 3 (18.75%) patients, and 11.25 mg in three months at 3 (18.75%) patients. Ovarian cysts were regressed after treatment at 13 patients, while 3 patients underwent surgery.

CONCLUSION: Leuprolide acetate can be used as an option in the treatment of ovarian cysts that develop in breast cancer patients under tamoxifen therapy.

Keywords: Breast neoplasms, Gonadotropin-releasing hormone, Ovary, Ovarian cyst, Tamoxifen

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Introduction

Breast cancer is the most frequently diagnosed cancer in women and the leading cause of death in women's cancers worldwide (1). Tamoxifen, which is a selective estrogen receptor modulator, is widely used in breast cancer patients with positive estrogen receptors to reduce the risk of recurrence (2). Adjuvant tamoxifen therapy applied for 5 years to premenopausal patients with breast cancer creates anti-estrogenic effects on the breast. However, it may cause weak estrogenic effects on the endometrium and ovaries (3).

While many studies are explaining the relationship of tamoxifen with endometrial pathologies, there are few studies on the relationship of tamoxifen with ovarian cysts and the management of patients with ovarian cysts under tamoxifen therapy (4,5).

Although the characteristics of low malignancy risk adnexal masses have been determined in the normal female population, the breast cancer population is different as the existence of breast cancer increases the likelihood of malignancy of the adnexal mass (6). While it is observed that ovarian cysts seen in women using tamoxifen are mostly benign and regress spontaneously during follow-up, the increased risk of malignancy due to patient characteristics causes intense anxiety for both the physician and the patient.

There are studies suggesting interruption of tamoxifen therapy when an ovarian cyst develops during tamoxifen use due to breast cancer (7,8). Particularly, for functional ovarian cysts, the use of treatments to accelerate the resolution of the cyst is considered. Among these treatments, suppressive therapies containing estrogen are not approved for breast cancer patients, instead, alternative treatments which do not include exogenous estrogen such as gonadotropin-releasing hormone (GnRH) agonists stand out as an option to be preferred. It has been reported that GnRH agonists can be used in clinical practice for

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the treatment of ovarian cysts in breast cancer patients using tamoxifen to suppress ovarian cysts in some small series (9-11).

In this study, we aimed to present our experiences of leuprolide acetate usage, without discontinuing tamoxifen treatment, in the management of ovarian cysts that develop in breast cancer patients under tamoxifen therapy.

Material and Method

This was a retrospective cohort study including the patients who were under tamoxifen treatment due to stage I-III breast cancer and who were administered leuprolide acetate for ovarian cysts with low malignancy risk between 2012-2020.

Upon clinical evaluation, women who were found to have adnexal masses with high malignancy potential were excluded as they underwent surgical treatment. Management of ovarian cysts in women who did not use tamoxifen was not included. Leuprolide acetate administration for ovarian cysts developing under tamoxifen therapy in patients with cancer other than breast etiology was excluded (1 patient was administered tamoxifen due to colon cancer). Patients who did not have ovarian cysts and who were administered leuprolide acetate due to abnormal uterine bleeding were also excluded (5 patients).

Age of the included patients with breast cancer, stage of the disease, and duration of tamoxifen therapy were recorded. Tamoxifen therapy was routinely used at a dose of 20 mg/day in all patients with positive hormone receptors. An annual gynecological examination and pelvic ultrasonography were performed before and after the initiation of tamoxifen treatment. Age at the time of detection of the ovarian cyst, obstetric history, menstrual pattern, complaints at presentation, comorbidities, and serum CA 125 levels of all patients was recorded. Size and ultrasonographic (US) characteristics of ovarian cysts were examined. In premenopausal patients, a hypoechogenic cystic structure greater than 30 mm in the ovary was defined as an ovarian cyst. Leuprolide treatment was suggested for patients who have ovarian cysts larger than 30 mm with low malignant potential.

In our clinic, Leuprolide acetate (Lucrin depotÒ 3.75 mg, Abbott) was administered as 3.75 mg subcutaneous/intramuscular injections per month in the management of patients who were under tamoxifen treatment due to breast cancer and who were detected to have low malignancy risk adnexal cysts. The patients were evaluated monthly, and in case the cyst persisted, 3 doses once a month were completed under monthly US controls. Clinical characteristics such as dose and duration of leuprolide application, the response of patients after treatment, treatment-related side effects, and need for surgery in patients who were administered leuprolide acetate for ovarian cysts were recorded. All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the Ethics Committee of Baskent University (Ethics approval reference number: KA22/230, Ethic approval date: 25/05/2022). All procedures were performed according to the Declaration of Helsinki.

Statistics

SPSS 21.0 program was used for the statistical analysis of the data. Categorical measurements were defined as numbers and percentages and continuous measurements were summarized as median and range. Definitive statistics were performed.

Results

Leuprolide acetate was administered to 16 patients in whom an ovarian cyst was developed during tamoxifen use due to breast cancer. The clinical findings of the patients are shown in Table I. There were 14 (87.5%) patients who were amenorrheic for less than one year in total. The median time

Table I: *Clinical characteristics of the study group*

Median age, years (range)	39.5 (33-52)
Median gravidity, parity (range)	2 (0-3), 2 (0-3)
Symptomatology, n (%)	
- asymptomatic	10 (62.5%)
- vaginal bleeding	5 (31.25%)
- pelvic pain	1 (6.25%)
Median size of ovarian cyst, mm (range)	42.5 (39-79)
Presence of the septation of the cyst, n (%)	6 (37.5%)
Bilaterality, n (%)	5 (31.25%)
Median serum CA 125 level, IU/L (range)	10.8 (4.2-47.8)
Median age at the diagnosis of breast cancer, years (range)	38 (30-50)
Tumor stage, n (%)	
Stage I	14 (87.5%)
Stage II	1 (6.25%)
Stage III	1 (6.25%)
Median duration of tamoxifen treatment, mo (range)	22 (7-36)

for amenorrhea was 7 (1-36) months. Five of the patients were found to have comorbidities accompanying breast cancer (Hodgkin lymphoma, a history of immature teratoma, hypothyroidism, rheumatoid arthritis, diabetes mellitus).

Leuprolide was administered at a dose of 3.75 mg for 1 month at 10 (62.5%) patients, 7.5 mg in two months at 3 (18.75%) patients, and 11.25 mg in 3 months at 3 (18.75%) patients. Except for transient pain and redness at the injection site due to leuprolide use, no major side effects were observed in any of the patients.

It was observed that ovarian cysts were completely regressed at the end of the treatment in 13 (81.25%) patients who were administered leuprolide acetate. Leuprolide treatment was applied for 1 month in 8 (61.5%), 2 months in 3 (23.1%), and 3 months in 2 (15.4%) of the 13 patients whose ovarian cysts were completely regressed. The clinical outcomes of the three patients who necessitated surgery are summarized in Table II. It was observed that in all cases CA125 levels were within the normal range established for premenopausal and postmenopausal women and pathological results were found to be benign.

Discussion

According to the results of our study, after 1-3 months of leuprolide acetate application, 81.25% of the ovarian cysts resolved without the need for surgical intervention. Furthermore, a single dose was sufficient in 61.5% of the cases. Our clinical experience, which is a very important finding for patients with breast cancer, also constitutes the largest series on the use of GnRH agonists in ovarian cysts.

Ovarian hyperstimulation, ovarian cyst, and supraphysiological estradiol levels due to the use of tamoxifen for breast cancer have been reported in 11-17% of the cases (12, 13). In a study, the prevalence of ovarian cysts in patients using tamoxifen has been reported as 19.4% in premenopausal and 6.3% in postmenopausal women (14). Tamoxifen, with the anti-estrogenic effect, causes continuous gonadotropin production in the pituitary gland and leads to ovarian stimulation. Besides, tamoxifen causes abnormal follicle development by directly stimulating massive steroidogenesis in ovaries independent of gonadotropin stimulation (15-17). However, the effect of tamoxifen on the ovary is still not fully understood and different patterns of ovarian response can be seen (18).

In a study, in which 19.3% of ovarian cysts were detected during tamoxifen use, the risk of developing ovarian cysts was higher (58.3%) in patients with the ongoing menstrual cycle (those with amenorrhea with less than 1 year) (19). In another study, in which ovarian cysts were detected in 24 of 142 cases using tamoxifen, regression analysis revealed that the risk of ovarian cysts was found to be associated with young age, being amenorrheic for less than 1 year, high serum estradiol levels, and not having received high dose chemotherapy (20). Consistently, in our study, it was observed that 87.5% of the cases were amenorrheic for less than one year.

According to an Inal et al. study, including 24 premenopausal and 27 postmenopausal breast cancer patients using tamoxifen, ovarian cysts were developed in 9 patients. Tamoxifen was discontinued and the patients were observed for three months. While the ovarian cysts regressed spontaneously within three months in 7 patients, surgery was needed in 2 patients. The authors stated that interrupting tamoxifen treatment in patients with ovarian cysts is an acceptable approach, while surgical intervention is appropriate for ovarian cysts larger than 5 cm in diameter (7). Most of the tamoxifen-related premenopausal ovarian cysts resolve spontaneously when tamoxifen treatment is discontinued (5). However, ovarian cysts can be resolved by adding GnRH agonists to the treatment as an alternative, without the need to discontinue the current tamoxifen application, and the literature supports this treatment approach (10). Furthermore, successful results were obtained in our patients with the application of GnRH agonists regardless of the ovarian cyst size, including cases where the diameter of the ovarian cyst was over 5 cm.

In patients with breast cancer, cystic formations of the ovary cause serious conflict. While ovarian cysts may be functional in premenopausal patients, metastasis of breast cancer or primary ovarian malignancy may also be encountered (breast cancer patients have a slightly higher risk of ovarian carcinogenesis) (21). Therefore, patients using tamoxifen

Table II: *Clinical data of the patients who underwent surgery after leuprolide acetate administration*

	Age, years	Ovarian cyst size, mm	Bilaterality /presence of septation	Median duration of tamoxifen treatment, mo (range)	Administration of leuprolide acetate (n, dosage)	Operation	Patologic findings
1st case	36	65	- /+	13	3, 11.25 mg	TLH+BSO*	Persistent luteinised cyst
2nd case	39	40, 20	+/-	13	1, 3.75 mg	TLH+BSO	Adenomyosis, endometriosis
3rd case	45	40	-/+	26	1, 3.75 mg	TLH+BSO	Persistent ovarian cyst, endometrial hyperplasia without atypia

**TLH+BSO= Total laparoscopic hysterectomy + bilateral salpingo-oophorectomy*

should be under close gynecological follow-up. While medical treatment providing ovarian suppression should be kept in mind in selected patients to prevent unnecessary surgery, in cases with persistent ovarian cysts surgical exploration should be planned to rule out malignancy.

GnRH agonists downregulate the GnRH receptors in the anterior pituitary, thus they provide alternative ovarian ablation by desensitizing gonadotropic cells. They provide this effect by preventing the bioactive luteinizing hormone and follicular stimulating hormone secretion completely and reversibly and causing inhibition of the ovarian function (22,23). Based on this effect of GnRH agonists, it has been shown that the administration of triptorelin in 14 patients using tamoxifen reduced serum 17b estradiol levels and regressed ovarian cysts (15). It has also been reported that ovarian cysts regress within 3-6 months of injection of triptorelin (10, 24). In literature, goserelin, which is used as another GnRH analog, has also been reported to be beneficial in ovarian cysts. In addition, it has been stated that the use of GnRH analogs such as goserelin and leuprolide may also be appropriate in ≤5 cm benign ovarian cysts developed in postmenopausal patients using tamoxifen (9). In our study, the effect of leuprolide, which is a different GnRH agonist, was demonstrated. Similarly, it was found that ovarian cysts disappeared in 13 of 16 patients, however, serum estradiol levels were not assessed in patients treated with leuprolide, instead, ovarian cysts were followed by monthly US evaluation.

The main limitations of our study are the retrospective structure, limited number of included patients, and absence of a control group, which would provide the opportunity to compare whether the cysts would regress with observational treatment. Surgery was performed in three cases, which can be described as leuprolide treatment failure. In two of these patients, optimal three doses were not completed; hysterectomy plus bilateral salpingo-oophorectomy were performed due to endometriosis, persistent pain in one patient, and accompanying endometrial hyperplasia in the other patient. In all three cases, bilateral salpingo-oophorectomy plus hysterectomy was performed upon the persistent request of the patients, after necessary information. On the other hand, it has been observed that additional factors accompanying ovarian cysts can change the treatment approach in these patients. Although our patient series is limited, leuprolide acetate treatment was found to be successful in 81.25% of simple ovarian cysts.

Utilization of GnRH agonists in addition to postoperative tamoxifen treatment in patients with premenopausal breast cancer for two years increases the disease-free survival (25, 26). Owing to their positive effect on survival, GnRH agonists are frequently used in adjuvant therapy. Therefore, in cases where GnRH agonists are not administered in adjuvant therapy, utilization of leuprolide acetate without interrupting protective tamoxifen treatment will be beneficial and safe in the management of low malignancy risk ovarian cysts, which develop during tamoxifen use.

Conclusion

We present the largest series on leuprolide use for the management of ovarian cysts that develop during tamoxifen therapy for breast cancer. However, regarding the efficacy and safety of leuprolide use, prospective studies including a larger number of patients are needed.

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