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The Role of Gnrh Analogues in 36-Month Disease-Free Survival in Non-Menopausal Patients with Hormone Receptor-Positive Breast Cancer

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ABSTRACT

BACKGROUND AND OBJECTIVE: The effectiveness of ovarian function suppression therapies in patients with non-menopausal breast cancer has not yet been established. This study was performed to evaluate the role of gonadotropin-releasing hormone agonist (GnRH agonist) receptor in reducing local recurrence or metastasis in non-menopausal women with localized breast cancer.

METHODS: This clinical trial was performed on 104 non-menopausal women with localized and advanced localized breast cancer (in stages 2 and 3) with positive hormone receptor (HR^+) in the two groups of control and intervention with GnRH analog. The control group received standard treatment at the time of the study, which included tamoxifen. The GnRHa group received 3.75 mg triptorelin subcutaneously per month in addition to the standard treatment. Patients were evaluated for local recurrence and metastasis within 36 months.

FINDINGS: The mean age of patients was 39.78±3.99 years. 9 patients in the control group (mean metastasis time of 17±6.65 months) and 6 patients in the GnRHa group (mean metastasis time of 14.33±8.12 months) had metastasis (p=0.498). The 36-month disease-free survival was 83.3% in the control group and 88% in the GnRHa group (p=0.518). 36-month disease-free survival in patients with HER2, 1+ or higher levels was greater in the GnRHa group compared to controls (p=0.049). In patients who received GnRH analogues, patients with HER2/neu 1+ and above had 20.7% less metastasis than patients with HER2 0 (p=0.029). However, this significant difference was not seen in the control group and other variables.

CONCLUSION: According to the results of this study, GnRH analogues do not have a significant effect on reducing the rate of metastasis in patients who received it compared to other patients in a short-term period.

KEY WORDS: *Breast Neoplasm, Triptorelin, Gonadotropin-Releasing Hormone (Gnrh), Erbb-2 Receptor.*

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Introduction

The role of the expression of three factors of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2/neu) antigen is well known in the function and growth of breast cells and breast cancer in humans. Targeted treatment of patients whose malignant cells express these receptors has long been an important part of breast cancer treatment regimens (1, 2).

The estrogen and progesterone hormones are mainly controlled by the reproductive axis (hypothalamic-pituitary- ovarian axis). Gonadotropin-releasing hormone (GnRH) is produced and secreted by the hypothalamus as the main regulator of this axis. Irregular secretion of this hormone is the main controller of the secretion of two other hormones called Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) by the anterior pituitary gland. FSH and LH also affect the secretion and reproductive and non-reproductive function of many other organs by affecting the gonads (3).

This hormonal system is a good treatment target for breast cancer. Selective Estrogen Receptor Modulators (SERMs) - the best known of these drugs is tamoxifen - compete with estrogen over the receptor and inhibit its effect. Studies on tamoxifen have shown that 5-year intake of this drug in women with breast cancer under 45 years of age increases the overall 15-year survival by 10.6%. For this reason, this treatment has long been used as part of the standard treatment for many breast cancer patients (4).

In addition, luteinizing hormone-releasing hormone agonist (GnRH) analogs reversibly inhibit the production of endogenous GnRH in the hypothalamus, thereby significantly reducing ovarian activity, which is called Ovarian Function Suppression (OFS) (3). In addition, these drugs appear to be effective on a type of GnRH receptor that is located directly in cancer cells (5, 6). Buserelin, Goserelin, Leuprolin and Triptorelin (Decapeptyl or Diphereline) are the most important drugs in this category. There have been very different and sometimes contradictory results in studies on the effectiveness of ovarian function suppression therapies, including GnRH agonists. Some older studies, most of which used Goserelin to induce suppression of ovarian function, failed to find significant benefit in treatment with GnRH analogues compared to tamoxifen (7). Other studies have reported some level of clinical benefit in some breast cancer patients (8). However, attention to Triptorelin has increased in the expression of newer studies. However, the results obtained from these studies are still not enough to reach a definitive solution (9). According to the above issues, the present study was performed to investigate the role of Triptorelin -as a GnRH analogue- in reducing metastasis and increasing disease-free survival in 36 months in non-menopausal patients with hormone receptor-positive breast cancer.

Methods

After approval by the ethics committee of Babol University of Medical Sciences with the code MUBABOL.REC.1390.6 and registration in the clinical trial system with the code IRCT20090311001760N47, this nonblinded randomized clinical trial was conducted on 104 non-menopausal women (under 50 years old or more than 18 years old) with breast cancer (paraclinical tests and FSH tests used to confirm menopause) (according to the NCCN guidelines, menopausal women are the women under 60 years of age who do not have more than 12 months of menstrual cycle, above or equal to 60 years, under 60 years of age receiving hormone therapy with serum estradiol levels), hormone-receptor-positive histopathology (+HR) including estrogen receptor positive (+ER) or progesterone receptor positive (+PR) or both, and stage II and III of breast cancer.

Patients at stage I (very good survival) and stage IV (distant metastasis), patients with other severe medical conditions such as heart failure, severe uncontrolled lung disease, severe liver cirrhosis and any other systemic disease that may change the patient's prognosis, discontinuation of intervention due to drug side effects were not included in the study. In this study, non-menopausal patients with breast cancer who had referred to Rajaee Hospital in Babolsar for treatment from 2011 to 2016 and were eligible to participate in the study based on the inclusion and exclusion criteria mentioned above were asked to join the study. Patients were free to participate or leave the study at any time, and all of them filled out a written informed consent form. The diagnosis of breast cancer was confirmed based on histological findings, and patients underwent appropriate surgical treatment at the time of study. Each patient was randomly assigned to Triptorelin or control group. Patients in Triptorelin group and control group received the necessary treatments, chemotherapy, radiotherapy and hormone therapy with tamoxifen according to the clinical guidelines of the day. In

addition to the standard treatment mentioned above, patients in the Triptorelin group received subcutaneous injection of Triptorelin (3.75 mg) monthly for at least two years and were followed for local recurrence and distant metastasis over a 36-month period. Follow-up for local recurrence and distant metastasis was performed by clinical examination, history, abdominal ultrasound and periodic mammography and other paraclinical studies in a targeted manner based on the history and examination obtained. The endpoints of follow-up in this study included the end of the 36-month period, local recurrence or distant metastasis, voluntary withdrawal from the study, or due to Triptorelin side effects or death due to causes other than breast cancer recurrence. Individuals who were excluded from the study before the end of the follow-up period (withdrawal, drug side effects, or death due to causes other than breast cancer recurrence) were excluded from the final statistical analysis.

After collecting data from all patients, the factors of age, body mass index (BMI), primary tumor size (T), lymph node status of the patient (N) and stage of breast cancer, initial chemotherapy regimen, expression level of HER2 in immunohistochemistry as well as expression status of HER2 were evaluated as increased or non-increased in both control and GnRHa groups. To evaluate the age of patients, they were divided into two groups of under 40 years and over 40 years. Furthermore, in terms of body mass index, patients were divided into three categories: less than 25 (without overweight), 25 to 30 (with overweight) and more than 30 (obese).

Tumor size, lymph node status, and disease stage indices were determined based on the American Joint Committee on Cancer (AJCC) Staging Manual before and at the time of diagnosis and were confirmed at the beginning of the trial. Furthermore, before the start of treatment, each patient based on HER2 level in immunohistochemistry was assigned into two groups of increased expression (level +3 in immunohistochemistry or borderline values of +2 in immunohistochemistry that had increased HER2 expression in FISH test) and without increased expression (negative values or +1 in immunohistochemistry or borderline values of +2 that did not have increased HER2 expression in FISH test). In addition to the above classification, HER2 expression level factor in immunohistochemistry tests was also considered separately in the statistical analysis. Patients were also divided into three groups of AC-T (Doxorubicin, Cyclophosphamide and Paclitaxel), CMF (Cyclophosphamide, Methotrexate and Fluorouracil) and CAF (Cyclophosphamide, Doxorubicin and Fluorouracil) according to the chemotherapy regimen they received. Data were analyzed using SPSS software version 23 and Independent t-Test, Cox Regression and Kaplan-Meyer statistical tests along with Log Rank test and $p<0.05$ was considered significant.

Results

In this study, 115 non-menopausal women with breast cancer between the ages of 18 and 47 years after receiving initial treatment including surgery and chemotherapy and radiotherapy were included in the study. Eleven people were excluded from the study according to the exclusion criteria or withdrawal. Finally, a total of 104 samples were examined (54 in the control group, 50 in the Triptorelin group). The mean age of all participants in the study was 39.78±3.99 years, which was 40.48±3.52 years for the control group and 39.02±4.35 years for the study group. In order to facilitate statistical analysis, individuals were divided into age groups under 40 years and over 40 years. The mean total BMI of patients was 29.04 kg/m2, the mean in the control group was 29.56 kg/m2 and in the Triptorelin group was 28.49 kg/m2. At baseline, 73 patients were in stage 2 of breast cancer, 37 of whom were in the control group and 36 in the Triptorelin group. Thirty-one patients were in stage 3, 17 of whom were in the control group and 14 in the Triptorelin group.

All patients were estrogen receptor positive (+ER). Four patients had progesterone receptor negative (-PR) (5.2%), 3 of whom were in the control group and 1 in the Triptorelin group. Due to the low number of -PR patients, this variable was not included in the final analysis. In immunohistochemistry (IHC) reports to measure HER2 / neu levels in tumor cells, 57 patients had zero levels and 47 patients had +1 levels and above. According to the results obtained from IHC and additional tests for borderline levels of HER2, tumor cells had increased HER2 expression in 28 patients (26.9%). All of these patients in our study were candidates for anti-HER2 therapy with Trastuzumab. After collecting data for 36 months from participants in the control and Triptorelin groups, a total of 15 patients (14.4%) had distant metastasis and no patient had local recurrence. 9 of these patients were in the control group (16.7% of the participants in the control group) and 6 patients were in the Triptorelin group (12% of the

participants in the Triptorelin group). The mean time of metastasis in the control group was 17±6.65 months and in the Triptorelin group was 14.33±8.12 months. The mean time of metastasis in all samples was 15.93±7.2 months. Independent t-test to compare the mean recurrence time in the two groups did not show a significant difference (p=0.498). The Kaplan-Meier statistical model was implemented for the outcomes of the control and Triptorelin groups, which can be seen in Figure 1. The 36-month disease-free survival was 83.3% in the control group and 88% in the Triptorelin group. The use of Log Rank test indicates that there is no significant difference in the final outcome (recurrence and metastasis) between the two groups of Triptorelin and control (p=0.518).

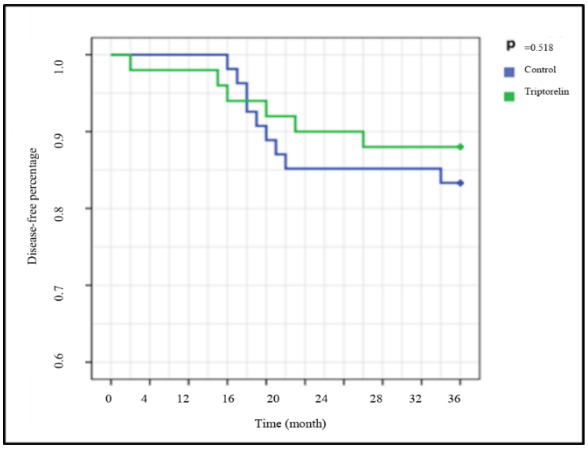

Figure 1. Survival fraction in Kaplan-Meyer statistical model to compare disease – free survival in control and Triptorelin groups in 104 non-menopausal women with hormone receptor-positive breast cancer

Cox Regression test showed that the only variable that had an effect on 36-month survival was the stage of cancer (p=0.023). Patients who received Triptorelin in addition to standard treatment had slightly lower metastasis (RH=0.502) compared to patients who received standard breast cancer treatment alone, but this difference was not statistically significant in Cox regression (similar to Kaplan-Meier model) (p=0.252). In the Triptorelin group, patients with a HER2 level of +1 or higher were compared with patients with a zero level of HER2 in terms of 36-month disease-free survival. 29 people were in HER2 group with zero level and 21 people were in HER2 group with +1 level and higher. In the HER2 group with +1 level and higher, 6 patients had metastasis, but in patients whose HER2 level was zero, no metastasis was observed (79.3% survival versus 100%), and in the Log Rank test in Kaplan-Meier statistical model, this difference was statistically significant (p=0.029).

In patients receiving Triptorelin (intervention group), 28 patients had HER2 negative and 26 patients had HER2 1+ or higher. In the HER2 negative group 5 patients and in the HER2 positive group 4 patients had metastasis (82.1% vs. 84.6% survival). In Log Rank test, this difference was not statistically different (p = 0.792). The above comparison was also performed for patients who had increased HER2 expression and received specific Trastuzumab treatment compared with patients who did not have increased expression and did not receive such treatment, and no significant difference was observed (Table 2). Except for the IHC level in the Triptorelin group, none of these cases had a significant effect on the rate of metastasis (p<0.05).

Table 1. Results of Cox regression model on different variables in 104 non-menopausal women with hormone receptor positive breast cancer

Variable	Beta coefficient β	Standard error SE	Wald	Degrees of freedom df	P-value	HR (CI 95%)
Age Group	- 0.786	0.629	1.560	1	0.212	0.456 (0.133-1.564)
BMI			0.034	2	0.983	
BMI (1)	0.162	0.892	0.033	1	0.856	1.175 (0.205-6.754)
BMI (2)	0.109	0.944	0.013	1	0.908	1.116 (0.175-7.098)
Stage	2.208	0.975	5.132	1	0.023	9.097 (1.347-61.455)
T	- 1.162	0.759	2.343	1	0.126	0.313 (0.701-1.385)
N	- 0.712	0.911	0.611	1	0.434	0.490 (0.802-2.926)
Increased HER2 expression	0.282	0.736	0.147	1	0.702	1.326 (0.313-5.615)
IHC and Trastuzumab levels	- 2.166	1.222	3.143	1	0.076	0.115 (0.010-1.257)
Chemotherapy			0.485	2	0.875	
Chemotherapy (1)	- 0.328	0.836	0.154	1	0.695	0.720 (0.140-3.706)
Chemotherapy (2)	- 0.532	0.809	0.432	1	0.511	0.587 (0.120-2.869)
Triptorelin	- 0.688	0.601	1.311	1	0.252	0.502 (0.155-1.632)

Table 2. Comparison of the effect of each variable and the rate of metastasis over a period of 36 months in control and Triptorelin patients in different subgroups in 104 non-menopausal women with hormone receptor positive breast cancer

Subgroup	Control group (number of metastases) and 36-month DFS	P-value in log rank test	Triptorelin group (number of metastases) and 36-month DFS	P-value in log rank test
Age				
40 ≥	24 (4) 83.3 %	0.940	28 (5) 82.1 %	0.154
40 <	30 (5) 83.3 %		22 (1) 95.5 (%)	
Stage				
II	37 (4) 89.2 %	0.091	36 (3) 91.7 %	0.162
III	17 (5) 70.6 %		14 (3) 78.6 %	
HER2/neu level at IHC				
Negative	28 (5) 82.1 %	0.792	29 (6) 79.3 %	0.029
+1 and more	26 (4) 84.6 %		21 (0) 100 %	
Trastuzumab intake (increased HER2 expression)				
No	38 (8) 78.9 %	0.186	32 (6) 84.2 %	0.154
Yes	16 (1) 93.8 %		12 (0) 100 %	
N				
N0	16 (1) 93.8 %	0.199	14 (1) 92.9 %	0.512
N + (N1 and more)	38 (8) 78.9 %		36 (5) 86.1 %	
T				
T2 and less	41 (8) 80.5 %	0.333 0.940	41 (4) 90.2 %	0.273 0.154
T3 and more	24 (4) 83.3 %		28 (5) 82.1 %	

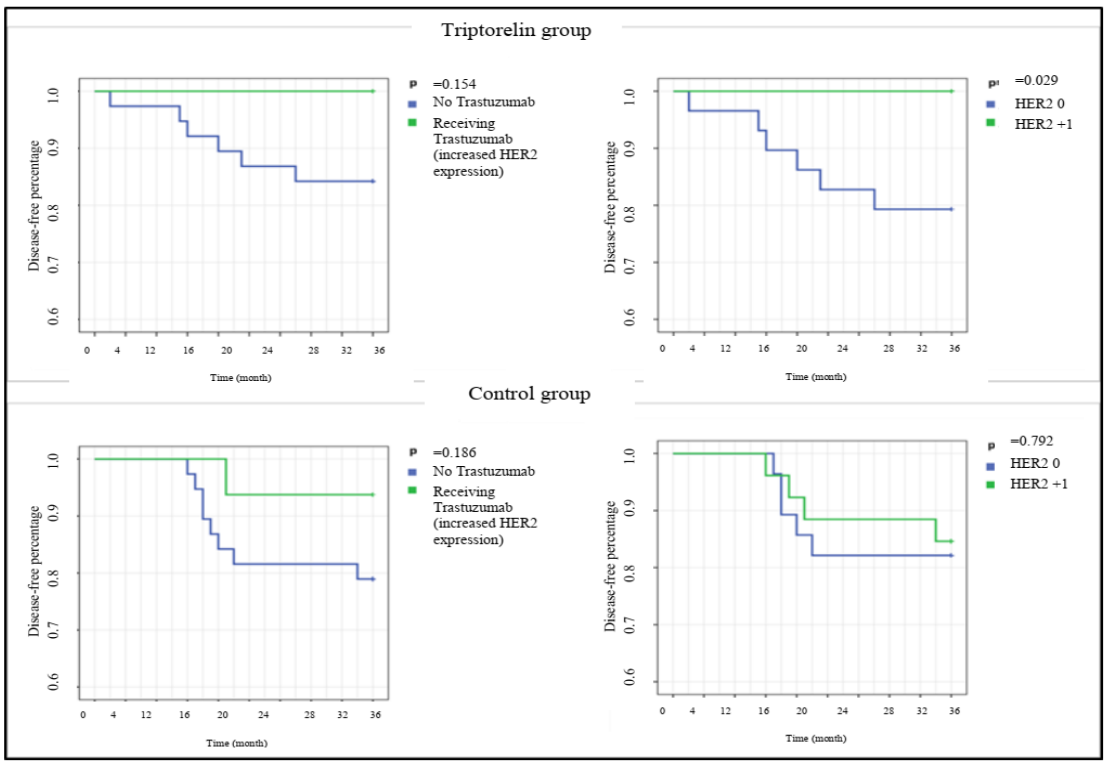

Figure 2. Kaplan-Meyer survival models to compare the effect of HER2 and Trastuzumab levels on 36-month metastasis in control and Triptorelin patients in 104 non-menopausal women with hormone receptor positive breast cancer

Discussion

Breast cancer is the most common cancer in women. In Western countries, approximately 20% of these women are under the age of 50, while in African and Middle Eastern countries, the average age of breast cancer is barely over 50 (8). The role of chemotherapy and radiotherapy in these patients is almost completely understood. The use of hormone therapy is also known in patients with estrogen or progesterone-positive receptors. In perimenopausal women (with ovarian function) with low risk for the disease, tamoxifen is appropriate for five years, and in people at high risk for the disease, one can continue taking tamoxifen for another five years (ten years in total) and use aromatase inhibitors instead of tamoxifen if one becomes menopause. However, one of the most important challenges for breast cancer in people with positive hormone receptors and perimenopause is the role of ovarian function suppression and its use and effectiveness in breast cancer patients who are in stages I and III of the disease, which is not well defined (4).

Ovarian function suppression can be accomplished by bilateral ovarian resection (oophorectomy), the use of GnRH analogues such as Triptorelin or goserelin, or pelvic radiotherapy. In two of the biggest trials (TEXT and SOFT) which are in fact the most important trials on the role of ovarian suppression in non-menopausal women with breast cancer, ovarian function suppression trial (SOFT) and Tamoxifen and Exemestane trial (TEXT) separately investigated the therapeutic role and quality of life of patients with ovarian suppression in a subgroup of patients (240 patients) under 35 years of age.

In general, the recurrence rate in this group is higher than older people and the five-year disease-free period in patients who received chemotherapy and then took tamoxifen alone was 67.1%. By adding ovarian suppression to tamoxifen and exemestane, this rate increased to 77.3% and 81.6%, respectively. Adding ovarian suppression in addition to tamoxifen at this age will bring significant clinical benefits, and adding an aromatase inhibitor will increase the benefits in these women. However, all age groups will experience some degree of complication, and in this age group, endocrine complications are more, and in general, the symptoms will improve after six months, except for joint and bone pain in the tamoxifen group, and vaginal dryness, and loss of sexual desire in the group receiving aromatase (9). In the evaluation of all patients in TEXT and SOFT trials which was performed on 3047 patients, all perimenopausal patients after surgery who had positive hormone estrogen and progesterone receptors (above 10%) were included in the study and underwent selective chemotherapy (only 53% of patients received chemotherapy). Patients were divided into three groups, one group received only tamoxifen, one group received ovarian suppression with tamoxifen and the third group received ovarian suppression with exemestane. In the initial report, with a follow-up of 5.6 years, no significant difference in DFS levels was observed in individuals receiving ovarian suppression in addition to tamoxifen (9, 10) (as in our study), but after 8 years of follow-up, DFS and OS in the ovarian suppression group with tamoxifen were significantly better than tamoxifen alone. Tamoxifen combined with ovarian suppression reduced the relative risk of recurrence, other invasive cancer, or death by 24% compared to tamoxifen alone, meaning an absolute difference of 4.2% in DFS levels over 8 years. Exemestane, along with ovarian suppression, produced even higher DFS rates by 7% compared with tamoxifen alone.

Due to the complications of ovarian suppression and the results of trials, this treatment should not be used for all perimenopausal women with early-stage breast cancer. Ovarian suppression should be evaluated regarding the increase in acute and late complications. People who underwent bilateral oophorectomy without estrogen replacement showed an increased risk of depression, hyperlipidemia, cardiovascular disease, diabetes, osteoporosis, and even death.

The effects of ovarian suppression with tamoxifen or exemestane are similar to those of postmenopausal women. Patients taking tamoxifen with ovarian suppression had more hot flashes and sweating that improved with time, while those taking exemestane with ovarian suppression had vaginal dryness and decreased sexual desire that did not change much with time. The percentages of women who were assigned to receive ovarian suppression with tamoxifen or exemestane and could not continue the drug were 19.3% and 23.7%, respectively. Two trials of TEXT and SOFT were scheduled for further follow-up, as survival information and late complications are still preliminary. Overall, the addition of ovarian suppression in addition to tamoxifen significantly increased DFS levels in non-menopausal women compared to tamoxifen alone, and further improvement was seen in exemestane along with ovarian suppression. In women at high risk for receiving chemotherapy and those whose estradiol remained in

the perimenopausal state after chemotherapy, ovarian suppression resulted in a significant improvement in DFS. Such patients who received ovarian suppression with tamoxifen or exemestane had higher survival rates within 8 years compared to tamoxifen alone (9).

Overall, in our study, no significant difference was found between 36-month disease-free survival in the control and Triptorelin groups (as in the TEXT and SOFT trials in the 5.6-year study). However in the Triptorelin group, 36-month disease-free survival was significantly better in patients with HER2 +1 or higher compared to patients with HER2 0. Unfortunately, in TEXT and SOFT trial, it was a bit difficult to comment on HER2 receptors because trastuzumab therapy was administered from the middle of the study and only 60% of patients were able to receive the drug, but overall, hormone receptor-positive people benefited more from tamoxifen with ovarian suppression compared to tamoxifen alone. Therefore, patients whose tumor cells do not express elevated levels of HER2 can benefit from GnRH analog therapy. This reduction in metastasis was not present in patients who had increased expression and received trastuzumab. Therefore, the usefulness of GnRH analogues depended on whether or not they received trastuzumab (11).

However, in SOFT study, not all patients with elevated HER2 expression received specific treatment, and many researchers speculate that the clinical benefit observed was due to the presence of this group of HER2 + patients who did not receive specific treatment (9). In our study however, all patients who were considered to have increased HER2 were treated with trastuzumab. This may explain the lack of difference in the 36-month disease-free survival of patients with elevated HER2 in our study. The conclusion that patients with +1 levels or borderline levels that do not fall into the HER2 expression category may benefit from treatment with GnRH analogues has not been found in any other study. In fact, past studies suggest that these levels of HER2 are also expressed in normal cells. Therefore, according to clinical guidelines for the treatment of breast cancer, those patients who are considered to have elevated HER2 levels are eligible for trastuzumab treatment (12). This finding in our study may be due to its limited number of samples. However, it can be concluded that GnRH analogues, even in the presence of low levels of HER2 that are not elevated and do not receive specific treatment, can reduce the rate of metastasis (at least within 36 months of treatment). Of course, our study cannot prove this conclusively due to the small power it has because of the limited sample size. Therefore, answering the question of whether receiving GnRH analogues such as Triptorelin reduces metastasis in this group of patients requires further studies with larger sample size and longer follow-up.

Although our study did not find the effect of GnRH analogues to be beneficial in any factor other than the level of HER2 immunohistochemistry, it is important to note that the National Comprehensive Cancer Network (NCCN) clinical guideline (based on TEXT and SOFT trials for breast cancer) suggests that treatment for ovarian function suppression be considered in patients at high risk for recurrence (young age, lymph node involvement, and high-grade tumor) (12).

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