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ARAŞTIRMA / RESEARCH

Effect of neoadjuvant chemotherapy on estrogen receptor, progesterone receptor, Cerb-B_2, vascular endothelial growth factor and Ki-67 in patients with locally advanced breast cancer

Lokal ileri evre meme kanserli hastalarda, neoadjuvan kemoterapinin östrojen reseptörleri, progesterone reseptörleri, Cerb-B_2, vasküler endotelyal büyüme faktörü ve Ki-67 üzerine etkisi

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Abstract

Purpose: The aim of this study is aimed to demonstrate the changes in the tumor diameter and expressions of vascular endothelial growth factor (VEGF), estrogen receptor (ER), progesterone receptor (PR), Ki-67, and Cerb-B2 status after neoadjuvant chemotherapy in the patients with locally advanced breast cancer.

Materials and Methods: Sixty-nine patients who diagnosed with locally advanced breast cancer and treated with were prospectively evaluated. The tumor diameter and VEGF, Ki-67, ER, PR, and Cerb-B2 expressions tested by immunohistochemistry (IHC) were evaluated before and after neoadjuvant chemotherapy.

Results: There was a statistically significant reduction in the tumor diameter and in the expression of VEGF, Ki-67, ER, PR, and Cerb-B2 after neoadjuvant chemotherapy.

Conclusion: The significant reduction in VEGF expression suggests that the tumor angiogenesis and its metastatic ability may be reduced by neoadjuvant chemotherapy. The significant change in the Ki-67 proliferation index may suggest the reduced proliferative activity of malignant cells with neoadjuvant chemotherapy.

Keywords: Breast cancer; neoadjuvant chemotherapy; VEGF; Ki-67; ER; PR; Cerb-B2

Öz

Amaç: Bu çalışmada lokal ileri evre meme kanserli hastalarda neoadjuvan kemoterapi ile tümör çapı, tümörlü dokuda çalışılan vasküler endotelyal büyüme faktörü (VEGF), östrojen reseptörü (ER), progesteron reseptörü (PR), Ki-67 ve Cerb-B2 ekspresyonlarındaki değişimin gösterilmesi amaçlanmıştır.

Gereç ve Yöntem: Çukurova Üniversitesi Tıp Fakültesi Genel Cerrahi ve Tıbbi Onkoloji Bilim Dalı'nda 2008 ve 2013 yılları arasında lokal ileri meme kanseri nedeniyle tedavi gören 69 hastanın verileri prospektif olarak araştırılmıştır. Tümör çapı, tümörlü dokuda çalışılan VEGF, Ki-67, ER, PR ve Cerb-B2 ekspresyonları immunhistokimyasal (İHK) yöntem ile neoadjuvan kemoterapi öncesi ve sonrası dönemde karşılaştırmalı olarak değerlendirilmiştir.

Bulgular: Neoadjuvan kemoterapi sonrası tümör çapı, VEGF, Ki-67, ER, PR ve Cerb-B2 ekspresyonlarında istatistiksel olarak anlamlı düşüş saptandı.

Sonuç: Tümör dokusunda çalışılan VEGF düzeyindeki anlamlı düşme, tümörün anjiyogenezinin ve bu yolla metastaz yapabilme yeteneğinin neoadjuvan kemoterapi etkisiyle azalabileceği sonucunu telkin etmektedir. Tümör dokusunda çalışılan Ki-67 proliferasyon indeksinde anlamlı değişim; malign hücre proliferasyonunun neoadjuvan kemoterapi etkisiyle azaldığını gösterebilir.

Anahtar kelimeler: Meme kanseri, neoadjuvan kemoterapi, VEGF, Ki-67, ER, PR, Cerb-B2.

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INTRODUCTION

Breast cancer is a systemic disease, chemotherapy and radiotherapy are added to the treatment, in addition to surgical treatment. Despite the advances in diagnosis, the locally advanced breast cancer cases are common, especially in underdeveloped countries[1-4]. Neoadjuvant chemotherapy (NAC) administered in locally advanced breast cancer (LABC) improves the chance of breast-conserving surgery (BCS) and operability in the inoperable cancers[4-9].

Because the LABC patient group is a very heterogeneous disease group, the types of treatment vary widely. NAC regimens containing anthracycline and taxane are preferably administered sequentially and until the maximum tumor response is achieved. Treatment response should be evaluated clinically and radiologically prior to surgery and pathologically after surgery[1-9].

Surgery should be performed including the primary tumor bed in patients who will undergo breast conserving surgery after the NAC. Modified radical mastectomy after NAC is the main surgical method in inoperable cases and inflammatory breast cancer. Post NAC sentinel lymph node biopsy has been applied in recent years. All patients who complete NAC therapy should be given radiotherapy in the postoperative period regardless of NAC response[2-10]. 5 years of disease-free and overall survival with additional treatment modalities for multimodal NAC in LABC, is 84% in stage III A and ranges between 35-50% in stage III B[2-10]. The aim of this study is to evaluate the changes in tumor diameter and the expression of vascular endothelial growth factor (VEGF), Ki-67, estrogen receptor (ER), progesterone receptor (PR), and Cerb-B_2 in patients under NAC due to LABC.

MATERIALS AND METHODS

The present study included 69 patients diagnosed with LABC, who admitted to the Çukurova University Faculty of Medicine Department of General Surgery and Medical Oncology. Inclusion criteria was LABC (Stage-IIB and Stage-III) based on the TNM classification defined by the "American Joint Committee on Cancer" (AJCC). Patients with a different stage than IIB-IIIA and III B, who were considered to be inoperable and who underwent palliative NAC were not included in the study. The study was approved by the Cukurova University Ethics Committee (Date: 19.01.2012, Decision Number: 2/7). The patients were informed and provided consent. The patient registration forms were completed, which included the age, demographics, contact details, menopausal status, pre- and post-NAC tumor diameter, histological type, clinical and radiological status of the lymph node, the type of the surgery performed, the duration of follow-up, the status of recurrence and survival, and the pre- and post-treatment VEGF, Ki-67, ER, PR and Cerb-B_2 expressions.

The imaging studies of the cases were evaluated in the Radiology Clinic of Çukurova University. In the pre-neoadjuvant chemotherapy evaluation, breast ultrasound and dynamic breast MRI were used for all the patients. We also used mammography for patients aged 35 and over. After NAC, breast MRI only was used to assess the response. Following neoadjuvant chemotherapy, dynamic breast magnetic resonance imaging (MRI) was conducted for radiological follow-up. In the radiological imaging after neoadjuvant chemotherapy, reduction in tumor size and axillary lymph node negativity was evaluated.

Surgical technique, oncological treatment and pathological evaluation

Out of 69 patients, modified radical mastectomy was performed in 62 patients (89.9%), breast-conserving surgery was performed in 6 cases (8.7%) and radical mastectomy underwent for one patient. According to these findings, metalic clips were placed for patients who underwent breast-conserving surgery. The patients were treated by anthracycline + cyclophosphamide or taxan containing regimens. The survival and recurrence follow-up was determined based on the clinical and radiological follow-ups.

Tumor tissues diagnosed prior to neoadjuvant chemotherapy and specimens extracted from patients operated after neoadjuvant chemotherapy were evaluated at the Pathology Clinic of Çukurova University. The pathological specimens were prepared from the paraffin blocks of the patients and they were processed with the BASIC AEC Detection kit (Ventana 5266041 -760 – 020) in the Ventana Benchmark XT automated immunohistochemical staining device. Monoclonal

Mouse Anti –Human, DAKO M 7273, 1/30 dilution was used for VEGF, Polyclonal Rabbit Anti – Human, DAKO A0485, 1/300 dilution was used for Cerb-B_2, Monoclonal Mouse Anti – Human, DAKO M 7240, 1/100 dilution was used for Ki- 67 Antigen, Mouse Monoclonal Antibody, NCL – L-ER – 6F11, 1/60 dilution was used for ER, Polyclonal Rabbit Anti-Human, DAKO A0098, 1/50 dilution was used for PR detection.

Statistical analysis

The statistical analysis of the data was made using SPSS 17.0 package. The categorical measurements were summarized in number and percentage, and the continuous measurements were summarized with mean and standard deviation. The categorical variables were compared using chi-square test or Fisher's test. The chi-square test was used for the values with distributions for which the data could be expressed in n and %. The continuous measurements were compared between the groups by checking the distributions; The Kruskal-Wallis Test was used on the parameters were not normally distributed; the paired comparisons of the groups were made using Mann-Whitney U-test and the pre- and post-chemotherapy comparisons were made using Wilcoxon test. The statistical significance level was considered 0.05 for all tests.

RESULTS

The study included a total of 69 patients who were treated by NAC due to LABC. The average length of follow-up for the patients was 20 months (min: 8 - max: 48 months), and the mean duration of NAC was 3.9 ±1.2 months. All of the patients were female; 30 (43.5%) patients were in premenopausal and 39 (56.5%) patients were in postmenopausal stage. The mean age was 53 (range: 28-76) years. Sixty-two (89.8%) patients had invasive ductal carcinoma, six (9.6%) patients had invasive lobular carcinoma and one (0.6%) patient had medullary carcinoma. The mean tumor diameter for the patients was 4.4 ± 2.0 cm before NAC and 1.3 ± 1.3 cm after NAC (p=0.0001). Before NAC; 23 patients (%33.3) was on stage IIB, 46 patients (%66.6) was on stage IIIa.

Before NAC, the VEGF expression could not be identified in 23 patients; the VEGF expression was identified as (+) in 32 (46.4%) patients and (++) in 14 (20.3%) patients. After NAC, the VEGF expression could not be identified in 60 (87%) patients, the VEGF expression was identified as (+) in nine (13%) patients. The mean VEGF expression in the tumor tissues was 0.9 ± 0.7 before NAC compared to 0.1 ± 0.3 after NAC. When compared the pre- and post-chemotherapy VEGF expressions, there was a statistically significant difference (p=0.0001). The mean percentage of Ki-67 in the tumor tissues was 33.7% ±25.0 before NAC compared to 9.8% ± 18.7 after NAC (p=0.0001).

The mean ER and PR expressions in the tumor tissues were 56.0% ± 38.4 and 34.3% ± 34.5, respectively before NAC. These values decreased after NAC to 27.1% ± 35.1 and 13.3% ± 26.1, respectively and differences were statistically significant (p=0.0001).

Before NAC, Cerb-B_2 was not identified in nine patients, it was (+) in 11 (16%) patients, (++) in 29 (42%) patients, and (+++) in 20 (29%) patients. After NAC, Cerb-B_2 was not identified in 36 (52.2%) patients; it was (+) in 13 (18.8%) patients, (++) in ten (14.5%) patients and (+++) in ten (14.5%) patients. The mean level of Cerb-B_2 was 1.9 ± 0.9 before NAC compared to 0.9 ± 1.2 after NAC. There was a statistically significant difference in the Cerb-B_2 levels in the tumor tissues before and after NAC (p=0.0001). The pre- and post-NCT tumor diameters, the levels of VEGF, Ki-67, ER, PR, and Cerb-B_2 of the patients are summarized in Table 1.

Table 1. Changes of the variables before and after NAC (n: 69)

Variables	Before NAC Med (Min-Max)	After NAC Med (Min-Max)	p
Tumor diameter (cm)	4 (0.8-10)	1 (0-5)	0.0001
VEGF (+))	1 (0-2)	0 (0-1)	0.0001
Ki-67 (+ %)		0 (0-90)	0.0001
ER (+ %)	60 (0-100)	10 (0-100)	0.0001
PR (+ %)	20 (0-100)	0 (0-95)	0.0001
Cerb-B2 (+)	2 (0-3)	0 (0-3)	0.0001

VEGF:Vascular endothelial growth factor. ER: Estrogen receptor . PR: Progesterone receptor

DISCUSSION

LABC includes patients of the Stage-IIB and Stage-III group which is inoperable at diagnosis; these patients account for 20-25% of all breast cancer cases [2-11]. Since 1980 when breast cancer was

considered as a systemic disease, the systemic chemotherapy courses were initiated and a clinical and radiological response were achieved in 70-80% of cases and a pathological complete response in 10% of LABC cases [3-11] . NAC was shown to create changes in some parameters such as the tumor diameter, VEGF, ER, PR, Ki-67, and Cerb-B_2[12-27]. The present study aimed to evaluate the change in the tumor diameter and angiogenic and oncogenic expressions and also hormone receptor changes after NAC. Patients were treated with well-known and accepted drug regimens including anthracycline + cyclophosphamide or taxane one time in two weeks, for 12 to 24 weeks as the NAC. Granulocyte Colony Stimulating Factor has not been added to treatment. Trastuzumab was given to only Cerb-B_2 ++ and Cerb-B_2 +++ patients, Cerb-B_2 ++ patients were confirmed with FISH. After NAC; value of Ki-67 was significantly high in the patients who died during study. Other parameters were not related to survey.

Measurement of the pre-NAC tumor diameter via the dynamic breast MR is the most commonly used method. The post-NAC tumor diameter was measured by pathological examination of the surgical specimen. Partridge et al. conducted a study to investigate 62 patients diagnosed with LABC and showed that the average tumor diameter was 5.2 cm before NAC and 2.8 cm after NAC [28]. A similar study showed that the average tumor diameter decreased [29]. In the present study, the tumor size was measured by MRI and in the surgical specimen; and decrease in tumor size was statistically significant as reported in literature.

The tumor cell needs angiogenic ability for proliferation, invasion, and metastasis. Angiogenesis is controlled by several endogenous factors. VEGF is the primary endogenous factor ensuring that the angiogenesis - anti-angiogenesis balance results in favor of angiogenesis[12,30] . There may be a change in the VEGF level after NAC. A study by Kim et al. found a reduction by 7-89% in the level of VEGF studied in the tumor tissue after NAC ($p < 0.05$)[12]. VEGF decrease was detected especially in postmenopausal cases. In the present study, VEGF decrease was observed both in premenopausal and postmenopausal patients.

The Ki-67 proliferation index detected by IHC is one of the most significant prognostic parameters in breast cancer. The prognosis is poor in cases with a higher Ki-67 proliferation index. When the literature was reviewed, it was noted that the Ki-67 score was found generally to be changed after NAC[13-16]. In the study by Burcombe et al. Before treatment median Ki-67 index was 24.9% and after treatment it was 18.1% (P=0.02); the median reduction in Ki-67 index after treatment was 21.2%. After chemotherapy, tumors that displayed over 75% reduction in Ki-67, were more likely to achieve a pathological response (77.8 *vs* 26.7%, P=0.004)[13]. However, a study by Arens et al. with a small sample size (25 cases) suggests an insignificant change of Ki-67 expression status after NAC treatment [14].

Koda et al. states that in primary breast tumors, Ki-67 indexes significantly decreased after neoadjuvant chemotherapy when compared to pre-treatment values, even though no change was observed in metastatic lymph nodes[15].In the present study, the mean Ki-67 level studied in the tumor tissues was 33.7% ± 25.0 before NCT compared to 9.8% ± 18.7 after NCT. The ER and PR levels are significant parameters to determine the response to NAC. Some previous studies showed that the clinical and pathological response was higher with NAC in the hormone receptor negative patients compared to the hormone receptor positive patients. But results are highly variable[17-25]. Colleoni et al. showed in a series of 399 patients that different changes in ER levels can occur with neoadjuvant chemotherapy in premenopausal and postmenopausal patients[17]. Faneyte et al. conducted a prospective study, where from a total of 49 patients, 35 showed no change in their ER status, 7 went from positive to negative and 7 went from negative to positive[18]. The studies by Avcı and Sun found no changes in the ER levels [19,31].

When the studies involving the PR levels were reviewed, Penault et al. conducted a retrospective analysis who were treated with anthracycline and found no changes in the PR expression [22]. A similar result was found by Schneider et al. in 37 patients [23]. The study by Kaya et al. found no significant changes in the PR expression [25]. There were no studies identifying association between the post-NAC change in the receptor level and the prognosis. The present study found reduced ER/PR expressions in half of the tumor tissues before NAC. We do not know the significance of this result yet, but we believe that the longer follow-up of the patients will provide information about this matter. Makris et al. demonstrated the negative effect of

Cerb-B_2 positivity on the response to NAC in their study, response was achieved in 57% of the Cerb-B2 positive patients compared to 93% of the Cerb-B2 negative patients [26]. Neubauer et al. reported that the after NAC Cerb-B2 expression change was observed from positive to negative in 11 patients (13%) [27]. Arens et al. found no change in the Cerb-B_2 expression [14]. Adams et al. in their study and administered anthracycline and taxane containing NAC, and found an increased Cerb-B_2 in the tumor tissues after NAC in the patients [21]. In the present study, Cerb-B_2 level positivity showed decreased in 39,1% of patients when compared before and after NAC the mean value of the Cerb-B_2 level positivity studied in the tumor tissues of the patients was 1.9±0.9 before NAC compared to 0.9±1.2 after NAC. There was a statistically significant difference for Cerb-B_2 before and after the NAC.

The contradictory results in studies researching change in Ki-67, ER, PR and Cerb-B_2 levels before and after NAC can be related to tumor subtypes, the variety of hormone receptor levels and the chemotherapeutic agents used.m The inadequacy of the data system used in data collection in our study, and the lack of studies on this research topic in the literature, are the main limitations of our study.

In conclusion, the treatment management and outcomes for the LABC patients highly variable; however, positive outcomes are achieved in the treatment. Response to CT is related to level of hormone receptor, proliferation index and Her-2 neu. Several studies have shown that prognostic parameters change with NAC. In our study tumor diameter significantly reduced decrease in patients receiving NAC. There was also a significant decrease in VEGF and Ki-67 proliferation index. The significant decrease in VEGF suggests that NAC reduces the tumor angiogenesis and metastatic ability significant decrease in Ki-67 proliferation index suggests that the proliferation of malignant cells will be reduced by NAC. We believe that randomized clinical studies evaluating the long-term outcomes of patients treated by NAC are required to determine the significance of the changes in ER, PR, and Cerb-B_2.

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