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Investigation of the Effect of Low-positive HER-2 on Neoadjuvant Chemotherapy Response in Hormone-positive Breast Cancer Patients

Düşük-pozitif HER-2'nin Hormon-pozitif Meme Kanseri Hastalarında Neoadjuvant Kemotepi Yanıtına Etkisinin İncelenmesi

Kubilay Karaboyun[1], Meltem Öznur[2], Ahmet Yolcu[3], Yakup İriağaç[1], Selçuk Seber[1]

[1]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Medical Oncology, Tekirdağ, Turkey
[2]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Pathology, Tekirdağ, Turkey
[3]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Radiation Oncology, Tekirdağ, Turkey

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ABSTRACT

Objective: Recently, it has been suggested that low-positive human epidermal growth factor receptor-2 (HER-2) is a separate group of breast cancer. We examined the effect of low-positive HER-2 on neoadjuvant chemotherapy (NACT).

Methods: This retrospective study included female patients aged >18 years who were diagnosed with histologically proven breast cancer between January 1, 2016, and January 1, 2020, and had breast surgery after NACT. Patients with triple-negative, estrogen receptor (<10%) weak positive, HER-2 immunohistochemical (IHC) scores 3+ or 2+/FISH-positive patients, and metastatic patients were excluded. Pathological complete response (pCR) was defined as the no invasive and *in situ* residue in the breast and lymph nodes in surgery after NACT.

Results: One hundred twenty seven patients were included in this study. HER-2 IHC-score "0" patients were 55 (43.3%), "1+" patients were 52 (40.9%), and "2+" patients were 20 (15.7%). Nine (7.1%) patients showed a complete response to NACT. In the univariate analysis with clinicopathological variables of the patients to predict the complete response to NACT; estrogen receptor [odds ratio (OR): 0.97, 95% confidence interval (CI): 0.96-0.99, p=0.012], Ki-67 (OR: 1.12, 95% CI: 1.06-1.18, p<0.001), tumor grade (OR: 0.036, 95% CI: 1.13-30.36, p=0.036), and lymphovascular invasion (OR: 0.11, 95% CI: 0.01-0.93, p=0.043) showed the predictive features. In the multivariate analysis, Ki-67 (OR: 1.10, 95% CI: 0.04-1.17, p=0.001) was found to be an independent predictor of pCR.

Conclusion: We determined that the low-positive-HER2 group has no effect on the treatment response in patients treated with NACT. We found that Ki-67 was an independent predictive for pCR.

Keywords: Breast cancer, neoadjuvant chemotherapy, low-positive HER-2

ÖZ

Amaç: Son zamanlarda düşük-pozitif insan epidermal büyüme faktör reseptörü-2'nin (HER-2) ayrı bir meme kanseri grubu olduğu ileri sürülmüştür. Düşük-pozitif HER-2'nin neoadjuvan kemoterapi (NACT) üzerindeki etkisini incelemeyi amaçladık.

Yöntemler: Bu retrospektif çalışma, 1 Ocak 2016 ile 1 Ocak 2020 tarihleri arasında histolojik olarak kanıtlanmış meme kanseri tanısı almış ve NACT sonrası meme ameliyatı olmuş 18 yaş üstü kadın hastaları içermektedir. Triple negatif, östrojen reseptörü (<%10) zayıf pozitif, HER-2 immünohistokimyasal (IHC) 3+ veya HER-2 IHC 2+/FISH pozitif hastalar ve metastatik hastalar çalışma dışı bırakıldı. Hastaların klinikopatolojik özellikleri hastane tıbbi elektronik kayıt sisteminden elde edildi. Patolojik tam yanıt (pCR), NACT sonrası cerrahide meme ve lenf düğümlerinde invaziv ve *in situ* kalıntı olmaması olarak tanımlandı.

Bulgular: Bu çalışmaya 127 hasta dahil edildi. HER-2 IHC skoru "0" hasta sayısı 55 (%43,3), "1+" olan 52 (%40,9) ve "2+" hasta sayısı 20 (%15,7) idi. Dokuz (%7,1) hasta NACT'ye tam yanıt verdi. NACT'ye tam yanıtı tahmin etmek için hastaların klinikopatolojik değişkenleri ile tek değişkenli analizde;

ORCID IDs of the authors: K.K. 0000-0002-1783-8075; M.Ö. 0000-0002-6396-3168; A.Y. 0000-0002-4525-2020; Y.İ. 0000-0001-7411-1705; S.S. 0000-0001-9081-2405.

Corresponding Author/Sorumlu Yazar: Kubilay Karaboyun, E-mail: kubilaykaraboyun@gmail.com

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östrojen reseptörü [odds ratio (OR): 0,97, %95 confidence interval (CI): 0,96-0,99, p=0,012], Ki-67 (OR: 1,12, %95 CI: 1,06-1,18, p<0,001), tümör derecesi (OR: 0,036, %95 CI: 1,13-30,36, p=0,036) ve lenfovasküler invazyon (OR: 0,11, %95 CI: 0,01-0,93, p=0,043) prediktif özellik gösterdi. Çok değişkenli analizde Ki-67 (OR: 1,10, %95 CI: 0,04-1,17, p=0,001) pCR'nin bağımsız bir göstergesi olarak bulundu.

Sonuç: NACT ile tedavi edilen hastalarda düşük-pozitif HER-2 grubunun tedavi yanıtı üzerinde etkisinin olmadığını belirledik. Ki-67'nin pCR için bağımsız prediktif olduğunu bulduk.

Anahtar kelimeler: Meme kanseri, neoadjuvan kemoterapi, düşük-pozitif HER-2

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer worldwide, excluding skin cancer, and is the leading cause of cancer related mortality in women (1). In developed countries, the majority of newly diagnosed breast cancer patients are diagnosed at an early or locally advanced stage. Early-stage breast cancer patients are usually treated with primary surgery (lumpectomy or mastectomy), whereas some early-stage patients with human epidermal growth factor receptor-2 (HER-2) positive or triple-negative molecular features and locally advanced breast cancer patients are managed with multimodal therapy combining systemic and locoregional therapies (2). Achieving pathological complete response (pCR) with neoadjuvant chemotherapy (NACT) is a strong predictor of treatment response and can be considered a surrogate marker of treatment efficacy. Early identification of features that can predict the pCR may allow a better selection of patients who will benefit from treatment and may protect the patient from potentially ineffective treatments. In many meta-analyses, prognostic improvement in pCR to neoadjuvant therapy has been reported, especially in tumors with aggressive behavior such as HER-2-positive or triple-negative (3-5).

Neoadjuvant therapy for hormone receptor (HR)-positive and HER-2-negative breast cancer is considered for women with larger tumors and/or locally advanced breast cancer. Well-differentiated tumors with low proliferation rate and HR expression are less likely to obtain a pCR after NACT (6). However, in these well-differentiated slowly proliferating tumors, a relatively poor response to treatment was not associated with a poor prognostic response (7). In clinical practice, HER-2 immunohistochemical (IHC) scores 0, 1+, or IHC 2+/ FISH-negative patients are classified as HER-2-negative by IHC staining methods. However, recently Schettini et al. (8) reported that patients with low-positive HER-2 breast cancer (HER-2 1+ by IHC or HER-2 2+/ FISH negative) may be a distinct group. In the Destiny-Breast04 study, trastuzumab deruxtecan, an antibody-chemotherapy conjugate, was shown to provide a progression-free survival and the overall survival advantage in hormone-positive and negative subgroups compared with chemotherapy (physician choice) in low-positive HER-2-positive disease who had previously received chemotherapy (9). Future improvements in the prognosis of the HR-positive/HER-2-negative patient group with new treatments, and the identification of predictors that will affect the pCR that can be achieved with currently existing clinicopathological features have gained importance again.

In this study, in hormone-positive patients, we investigated the effect of HER-2 IHC scores 0, 1+, and 2+/FISH-negative breast cancer for pathologic complete response to NACT and we aimed to determine the other clinicopathological features that may predict pCR.

METHODS

In this retrospective study, high-risk female patients (with axillary nodal involvement) over the age of 18 who were diagnosed with histologically proven breast cancer between January 1, 2016, and January 1, 2020, and had breast surgery after NACT were included. Patients with triple-negative, estrogen receptor (<10%) weak positive, HER-2 IHC 3+ or HER-2 IHC 2+/FISH-positive patients, and metastatic patients were excluded. Patients received standard 4 cycles of cyclophosphamide (600 mg/m^2) and epirubicin (90 mg/m^2) every 3 weeks, followed by weekly paclitaxel (80 mg/m^2) for 12 weeks or 4 cycles of docetaxel (75 mg/m^2) every 3 weeks as NACT. Estrogen receptor and progesterone receptor expression and HER-2 status of tumors were obtained from the results of immunohistochemistry or fluorescent *in situ* hybridization in breast cancer tissue obtained by core needle biopsy before NACT. pCR was defined as the no invasive and *in situ* residue in the breast and lymph nodes in surgery after NACT. Patients' clinicopathologic features such as age, HR expression, HER-2 status, histological type, lymphovascular invasion (LVI), grade, and pre-operative tumor diameter were obtained from the hospital medical electronic record system. The study was approved by the Tekirdağ Namık Kemal University Non-Invasive Clinical Research Ethics Committee in accordance with the Declaration of Helsinki (protocol no: 2020.238.10.06, date: 27.10.2020).

Statistical Analysis

SPSS version 26.0 (SPSS Inc., Chicago, III) was used for all statistical analyses. Continuous variables are represented with the median and range. Categorical variables were summarized using frequency and percentage. Univariate and multivariate analysis with a logistic regression model were applied to predict pCR. P<0.05 was considered statistically significant.

RESULTS

Clinical Features of the Patients

One hundred twenty seven patients were included in this study. The median age of the patients was 50 (28-73). While 104 patients (81.9%) had invasive ductal histology, 5 patients (3.9%) had

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invasive lobular histology. The median Ki-67 percentage, estrogen receptor expression rate, and progesterone receptor expression rate were 25%, 95%, and 40%, respectively. HER-2 IHC scores: the number of "0" patients were 55 (43.3%), "1+" patients were 52 (40.9%), and "2+" patients were 20 (15.7%). While 64 patients (50.4) had grade 2 tumors, 33 patients (26%) had grade 3 tumors. The number of LVI-positive patients was 62 (48.8%). Nine (7.1%) patients showed a complete response to NACT (Table 1).

Univariate and Multivariate Analysis

In the univariate analysis with clinicopathological variables of the patients to predict the complete response to NACT; estrogen receptor expression [odds ratio (OR): 0.97, 95% confidence interval (CI): 0.96-0.99, p=0.012], Ki-67 (OR: 1.12, 95% CI: 1.06-1.18, p<0.001), tumor grade (OR: 0.036, 95% CI: 1.13-30.36, p=0.036), and LVI (OR: 0.11, 95% CI: 0.01-0.93, p=0.043) showed the predictive feature (Table 2).

Table 1. Clinical-pathological characteristics

	n	%
Age		
>50	56	44.4
≤50	71	55.6
Histological type		
Invasive ductal	104	81.9%
Invasive lobular	5	3.9%
Others	18	14.2%
Estrogen receptor	95*	10-100**
Progesterone receptor	40*	1-100**
Ki-67	25*	1-80
HER-2		
0	55	43.3
1+	52	40.9
2+	20	15.7
Grade		
Grade 1	8	7.6
Grade 2	64	50.4
Grade 3	33	26
LVI	16.0%	21
Positive	62	48.8
Negative	63	48.9
Clinical tumor diameter		
T1	26	20.5
T2	91	71.7
T3	8	6.3
T4	2	1.5
Pathological complete response	9	7.1

HER-2: human epidermal growth factor-2, LVI: lymphovascular invasion, *median, **range

In the multivariate analysis with variables found to be significant in the univariate analysis, Ki-67 (OR: 1.10, 95% CI: 0.04-1.17, p=0.001) was found to be an independent predictor of pCR (Table 3).

DISCUSSION

In this study, we investigated the effect of low-positive HER-2 in predicting a complete response to NACT in patients with hormone-positive breast cancer. We found that patients with HER-2 scores "0", "1+" and "2+" had no effect on complete response to NACT. In univariate analysis with other clinicopathological factors: estrogen receptor, Ki-67, tumor grade and LVI were found to be predictive for pCR. In the multivariate analysis, Ki-67 was determined as an independent predictor of pCR.

Denkert et al. (10), in the pooled data analysis of 4 different prospective studies, suggested that low-positive HER-2-positive breast cancer is a separate subgroup from the HER-2 IHC score "0" tumors with clinicopathological features such as hormone positivity and complete response rates to treatment. Shao et al. (11), in their study that included triple-negative and hormone-positive HER-2 IHC score "0" and low-positive HER-2 patients showed that HER-2 score "0" and "low" was an independent predictor for pCR in both the hormone-positive and triple-negative group. Our study showed that HER-2 IHC scores "0" and "low" positivity had no predictive effect on pCR in patients that including only hormone-positive tumors.

The Ki-67 labeling index appears to be a useful marker to identify high-risk patients in hormone-positive/HER-2-negative breast cancer. Measurement of Ki-67 as a marker of cell proliferation has been reported to be associated with the response to therapy in previous studies (12-14). Kim et al. (15), in their study on patients receiving anthracycline-based NACT, determined the 25% cut-off value for Ki-67 as a predictor of pCR. In another study, Jain et al. (16) showed that Ki-67 and high-grade tumors are markers that predict pCR. However, the relationship between pCR and prognosis in hormone-positive tumors is unclear, and markers that will replace the prognosis are being investigated. In line with the literature, in our study, the Ki-67 proliferation index was found to be an independent predictor of pCR.

Estrogen receptor expression, as Ki-67, is also seen as a predictor for pCR in studies. In a study, it was reported that estrogen level predicts a complete response in the nomogram model established for pCR (17). In another study, it was shown that estrogen positivity has an impact on pCR (18). In our study, estrogen receptor level was associated with pCR.

Study Limitations

Our study had some limitations. First, the study was designed retrospectively. Morover, the number of patients is relatively low according to the other studies investigating pCR, especially the number of patients with an HER-2 IHC score 2+. The strength of our study is that patients with aggressive tumors such as triple-negative and HER-2-positive with known strong associations with pCR were excluded, and patients with only hormone-positive were included.

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Table 2. Univariate analysis of factors predicting pathological response

		Univariate analysis	
Variable	**Category**	**OR (95% CI)**	**p-value***
Age	≤50/>50	1.02 (0.26-3.97)	0.982
Histological type	Ductal/lobuler/other	0.78 (0.26-2.38)	0.061
Estrogen receptor	Continuous	0.97 (0.96-0.99)	**0.012**
Progesteron receptor	Continuous	0.99 (0.97-1.01)	0.399
Ki-67	Continuous	1.12 (1.06-1.18)	**<0.001**
HER-2	0/1+/2+	2.16 (0.85-5.46)	0.104
Grade	1/2/3	5.84 (1.13-30.36)	**0.036**
Tumor diameter	T1/T2/T3/T4	0.93 (0.85-1.02)	0.135
LVI	Positive/negative	0.11 (0.01-0.93)	**0.043**

HER-2: human epidermal growth factor-2, LVI: lymphovascular invasion, OR: odds ratio, CI: confidence interval, *significant values are indicated bold

Table 3. Multivariate analysis of factors predicting pathological response

Variable	Category	OR (95% CI)	p-value[f]
Estrogen receptor	Continuous	-	-
Ki-67	Continuous	1.10 (1.04-1.17)	0.001
Grade	1/2/3	-	-
LVI	Positive/negative	-	-

[f]forward:LR method, LVI: lymphovascular invasion, OR: odds ratio, CI: confidence interval

CONCLUSION

As a result, in hormone-positive breast cancer, we determined that the low-positive HER-2 group has no effect on the treatment response in patients treated with NACT. On the other hand, we found that Ki-67, estrogen receptor, LVI, and tumor grade were predictive for pCR.

Ethics Committee Approval: The study was approved by the Tekirdağ Namık Kemal University Non-Invasive Clinical Research Ethics Committee in accordance with the Declaration of Helsinki (protocol no: 2020.238.10.06, date: 27.10.2020).

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