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Research Article

Predictors of Pathological Complete Response in Hormone Receptor-Negative HER2-Positive Breast Cancer Receiving Neoadjuvant Therapy

Aykut Özmen, Gökmen Umut Erdem

Department of Medical Oncology, Başakşehir Çam and Sakura City Hospital, Istanbul, Türkiye

Abstract

Objectives: Neoadjuvant anti-HER2-based therapy has significantly improved pathological complete response (pCR) rates in HER2-positive breast cancer. Hormone receptor-negative/HER2-positive (HR-/HER2+) tumors are known to demonstrate higher sensitivity to chemotherapy and HER2-targeted agents; however, predictive factors associated with pCR within this biologically distinct subgroup remain insufficiently defined. This study aimed to evaluate clinicopathological and laboratory factors associated with pCR in HR-/HER2+ breast cancer patients treated with neoadjuvant therapy.

Methods: This study retrospectively evaluated 57 patients with HR-negative/HER2-positive breast cancer who underwent neoadjuvant HER2-targeted treatment followed by curative-intent surgery at XXX between January 2020 and January 2024. Data regarding patient characteristics, tumor features, laboratory measurements, treatment patterns, and surgical management were extracted from electronic health records and analyzed retrospectively. Pathological complete response was defined as ypT0/isN0. Univariate and multivariate logistic regression analyses were performed to identify predictors associated with pCR.

Results: Among 57 patients, 40 (70.2%) achieved pCR. The pCR cohort predominantly consisted of patients with histological grade III tumors (85.0% vs. 15.0% for grade I–II, p=0.002) and normal baseline CA 15-3 levels (87.5% vs. 12.5% for elevated, p=0.01). Other variables, including age, body mass index, menopausal status, tumor size, nodal status, Ki-67 index, CEA levels, and inflammatory markers, showed no significant association with pCR. Multivariate analysis confirmed grade III disease (OR: 9.0; 95% CI: 2.14–37.9; p=0.003) and normal CA 15-3 levels (OR: 7.1; 95% CI: 1.54–32.8; p=0.01) as independent predictors of pCR.

Conclusion: In HR-/HER2+ breast cancer, high histological grade and normal baseline CA 15-3 levels independently predict pCR following neoadjuvant anti-HER2 therapy. These findings can optimize risk stratification and personalize treatment in this aggressive subtype.

Keywords: CA 15-3, HER2-positive breast cancer, histological grade, hormone receptor-negative, neoadjuvant therapy, pathological complete response

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Address for correspondence: Aykut Özmen, MD, Department of Medical Oncology, Başakşehir Çam and Sakura City Hospital, Istanbul, Türkiye
Phone: +90 505 316 16 00 **E-mail:** draykutozmen@hotmail.com

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Breast cancer comprises several molecularly defined subtypes, each associated with unique biological features and differing responses to systemic therapies.[1] Approximately one-fifth of breast cancers exhibit HER2 overexpression or amplification, a subtype traditionally linked to rapid tumor growth and unfavorable prognosis.[2] The widespread adoption of HER2-targeted therapies, including trastuzumab and pertuzumab, has significantly altered the natural history of HER2-positive breast cancer, resulting in improved survival across disease stages.[3]

For patients presenting with stage II–III HER2-positive disease, systemic treatment before surgery is currently regarded as the preferred therapeutic strategy.[4] Pathological response following neoadjuvant treatment provides important prognostic information and is associated with long-term clinical outcomes.[5] Numerous studies have shown that eradication of invasive disease at surgery is associated with superior long-term oncologic outcomes, especially in aggressive subtypes such as HER2-positive and triple-negative breast cancer.[6]

The incorporation of combined trastuzumab and pertuzumab therapy into chemotherapy regimens has substantially improved pCR rates in HER2-positive disease.[7] Landmark studies including NeoSphere, TRYPHAENA, and TRAIN-2 demonstrated pCR rates approaching 60–70% with contemporary anti-HER2-based neoadjuvant regimens.[7–9] Importantly, hormone receptor-negative/HER2-positive (HR-/HER2+) tumors have been reported to exhibit higher pCR rates than hormone receptor-positive tumors in several studies.[10] This observation may reflect the distinct biology of HR-negative/HER2-positive tumors, which have been associated with greater HER2 pathway activation and increased treatment sensitivity.[11]

Despite the high efficacy of contemporary neoadjuvant treatments, a subset of patients still fails to achieve pCR. Identifying predictive factors associated with treatment response remains clinically important for optimizing individualized therapeutic strategies and improving patient outcomes.[2] Previous studies have explored the association of various clinicopathological and laboratory characteristics, such as tumor grade, HER2 expression level, Ki-67 proliferation index, inflammatory markers, and serum tumor markers, with pCR; however, the available evidence remains inconclusive.[12–14]

Although many previous studies evaluated heterogeneous HER2-positive populations including both hormone receptor-positive and hormone receptor-negative subtypes, data specifically focusing on the HR-negative/HER2-positive subgroup remain limited. Given the distinct biological characteristics and treatment responsiveness of this subgroup, identifying predictors of pCR in HR-/HER2+ disease may provide clinically relevant insights. Therefore, the present study aimed to investigate clinicopathological and laboratory factors associated with pathological complete response in patients with HR-/HER2+ breast cancer receiving neoadjuvant anti-HER2 therapy at a single tertiary oncology center.

Methods

Study Design and Patient Population

This retrospective single-center study included consecutive patients diagnosed with HR-/HER2+ breast cancer who received neoadjuvant chemotherapy followed by curative surgery between January 2020 and January 2024 at XXX.

Inclusion criteria were:

- Age ≥ 18 years,
- Histologically confirmed invasive breast carcinoma,
- Hormone receptor-negative disease defined as estrogen receptor (ER) and progesterone receptor (PR) expression < 1%,
- HER2-positive status defined as HER2 immunohistochemistry (IHC) 3+ or HER2 IHC 2+ with fluorescence in situ hybridization (FISH) amplification,
- Stage II–III disease,
- Completion of neoadjuvant treatment and surgery.

Patients with metastatic disease, bilateral breast cancer, another active malignancy, incomplete pathological data, or progression precluding surgery were excluded.

Ethical approval was obtained from the Başakşehir Çam and Sakura City Hospital Ethics Committee (12/06/2024/2024-03). The study was conducted in accordance with the Declaration of Helsinki.

Data Collection

Demographic, clinicopathological, laboratory, treatment-related, and surgical data were retrospectively collected from institutional electronic medical records. Evaluated variables included patient characteristics (age, BMI, menopausal status, smoking history, hypertension, diabetes mellitus), tumor features (clinical stage, tumor size, nodal status, histological grade, Ki-67 index, HER2 status), treatment details (neoadjuvant regimen, breast and axillary surgical procedures), and pretreatment laboratory markers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), CEA, and CA 15-3.

Neoadjuvant Treatment

Patients received either the EC/AC-THP regimen (epirubicin

or doxorubicin plus cyclophosphamide, followed by a taxane, trastuzumab, and pertuzumab) or the DCbHP regimen (docetaxel, carboplatin, trastuzumab, and pertuzumab).

Pathological Response Assessment

Pathological complete response was defined as the absence of residual invasive carcinoma in both the breast tissue and axillary lymph nodes (ypT0/is N0). Based on postoperative pathological evaluation, patients were subsequently categorized into pCR and non-pCR groups.

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Continuous data are presented as medians with minimum and maximum values, whereas categorical variables are summarized as counts and percentages. Group comparisons were performed using appropriate parametric or nonparametric tests according to variable type. Variables showing significance in univariate testing were subsequently entered into multivariable logistic regression models. Statistical significance was defined as a two-sided p-value < 0.05.

Results

Baseline Characteristics

The study cohort consisted of 57 patients diagnosed with HR-negative/HER2-positive breast cancer. The median age was 49.8 years (range: 31–74 years). Twenty-nine patients (50.9%) were premenopausal or perimenopausal, while 28 patients (49.1%) were postmenopausal.

Clinical T1–2 disease was present in 45 patients (78.9%), whereas 12 patients (21.1%) had T3–4 tumors. Lymph node positivity was detected in 40 patients (70.2%). The median tumor size was 30 mm (range: 8–100 mm), and the median Ki-67 index was 35% (range: 10–90%). HER2 IHC 3+ expression was observed in 54 patients (94.7%), while three patients (5.3%) had HER2 IHC 2+/FISH-positive disease (Table 1).

Of the 57 patients, 4 received neoadjuvant therapy without pertuzumab (EC/AC-TH regimen). Among the remaining 53 patients who received pertuzumab-based dual anti-HER2 blockade, 31 (58.5%) were treated with the EC/AC-THP regimen, and 22 (41.5%) received the DCbHP regimen.

Pathological Complete Response Rates

Among the 57 enrolled patients with HR-/HER2+ breast cancer, 40 (70.2%) achieved a pathological complete response (pCR) following neoadjuvant therapy. When stratified by treatment regimen, pCR rates were 64.5% (20/31) in the EC-THP group, 77.3% (17/22) in the TCHP group, and 75.0% (3/4) in the EC-TH group. Conversely, the proportions of patients who did not achieve pCR were 35.5% (11/31), 22.7% (5/22), and 25.0% (1/4), respectively.

Factors Associated with pCR

In univariate analysis, histological grade and baseline CA 15-3 levels were significantly associated with pCR. Specifically, the pCR cohort predominantly consisted of patients with grade III tumors (85.0% vs. 15.0% for grade I–II; p=0.002) and normal baseline CA 15-3 levels (87.5% vs. 12.5% for elevated levels; p=0.01). Other demographic and clinicopathological variables—including age, BMI, menopausal status, comorbidities (smoking history, hypertension, diabetes mellitus), tumor size, nodal status, HER2 expression, Ki-67 index, chemotherapy regimen, CEA levels, and inflammatory markers (NLR, PLR, MLR)—showed no statistically significant association with pCR ($p > 0.05$ for all) (Table 2). In multivariate logistic regression analysis, grade III histology (OR: 9.0; 95% CI: 2.14–37.9; p=0.003) and normal baseline CA 15-3 levels (OR: 7.1; 95% CI: 1.54–32.8; p=0.01) were confirmed as independent predictors of pCR (Table 3).

Follow-up Outcomes

At a median follow-up of 26 months, disease recurrence developed in 6 of the 57 patients (10.5%). The recurrence rate was markedly lower in the pCR group compared to the non-pCR group (2.5%.[1/40] vs. 29.4%.[5/17]). Overall mortality in the study cohort was limited to a single patient (1.8%). Notably, this death occurred in the non-pCR group (1/17, 5.9%), whereas no mortality was observed among patients who achieved pCR (0/40, 0%).

Discussion

Our analysis demonstrated excellent treatment efficacy among patients with HR-negative/HER2-positive breast cancer receiving neoadjuvant HER2-directed therapy, resulting in a pathological complete response rate exceeding 70%. Notably, histological grade III disease and normal baseline CA 15-3 levels emerged as independent predictors of achieving pCR. In contrast, conventional systemic inflammatory markers—including NLR, PLR, and MLR—failed to show any significant association with treatment response.

The pCR rate of 70.2% observed in our cohort is notably high and consistent with previously reported outcomes for HR-/HER2+ disease treated with contemporary dual HER2 blockade. While clinical trials have demonstrated varying overall pCR rates with these regimens—ranging from approximately 46% in the NeoSphere trial to 66–68% in the TRYPHAENA and TRAIN-2 trials—responses are consis-

Table 1. Univariate analysis of prognostic factors associated with pCR

Parameters	All Patients n=57 (%100)	Non-pCR n=17 (%29.8)	pCR n=40 (%70.2)	Univariate Analysis OR (%95 CI)	p
Age					
Median	49.8	50.0	49.5		0.70
Range	31-74	32.5-72	31-74	1.00 (0.96-1.05)	
BMI					
Median	29.0	29.2	28.8		0.73
Range	19.6-45.4	23.4-38.5	19.6-45.4	1.02 (0.90-1.14)	
Menopausal status					
Postmenopausal	28 (49.1)	10 (58.8)	18 (45.0)		0.34
Pre/perimenopausal	29 (50.9)	7 (41.2)	22(55.0)	0.57 (0.18-1.80)	
Hypertension					
Absent	39 (68.4)	10 (58.8)	29 (72.5)		0.31
Presen	18 (31.6)	7 (41.2)	11 (27.5)	1.84 (0.56-6.06)	
Diabetes Mellitus					
Absent	48 (84.2)	14 (82.4)	34 (85.0)		0.80
Present	9 (15.8)	3 (17.6)	6 (15.0)	1.21 (0.26-5.54)	
History of smoking					
Absent	37 (64.9)	10 (58.8)	27 (67.5)		0.44
Present	16 (28.1)	6 (35.3)	10 (25.0)	1.62 (0.46-5.62)	
Tumor T stage					
cT1-2	45 (78.9)	11 (64.7)	34 (85.0)		0.09
cT3-4	12 (21.1)	6 (35.3)	6 (15.0)	3.09 (0.82-11.5)	
Tumor Size (mm)					
Median	30	30	30		0.18
Range	8-100	8-100	15-70	1.02 (0.99-1.05)	
Lymph node status					
Negative	17 (29.8)	3 (17.6)	14 (35.0)		0.19
Positive	40 (70.2)	14 (82.4)	26 (65.0)	2.51 (0.61-10.25)	
HER2 status					
2+	3 (5.3)	2 (11.8)	1 (2.5)		0.19
3+	54 (94.7)	15 (88.2)	39 (97.5)	0.19 (0.01-2.28)	
Histological Grade					
I-II	12 (21.1)	10 (58.8)	6 (15.0)		**0.002**
III	39 (68.4)	7 (41.2)	34 (85.0)	0.12 (0.03-0.45)	
Ki-67 index					
Median	35	40	35		0.32
Range	10-90	10-90	10-65	1.02 (0.98-1.06)	
HP regimen					
EC/AC-THP	31 (58.5)	11 (68.8)	20 (54.1)		0.32
DCbHP	22 (41.5)	5 (31.3)	17 (45.9)	0.53 (0.15-1.84)	
Tumor localization					0.13
Left breast	29 (50.9)	6 (35.3)	23 (57.5)		
Right breast	28 (49.1)	11 (64.7)	17 (42.5)	2.48 (0.76-8.03)	
Type of Surgery					
Breast-conserving surgery	34 (59.6)	8 (47.1)	26 (65.0)	2.08 (0.66-6.61)	0.21
Mastectomy	23 (40.4)	9 (52.9)	14 (35.0)		
Axillary Surgery					0.19
SLNB/TAD	31 (54.4)	7 (41.2)	24 (60.0)		
ALND	26 (45.6)	10 (58.8)	16 (40.0)	2.14 (0.67-6.79)	

BMI: Body Mass Index; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; Ki-67: Ki-67 proliferation index; cT1-2 / cT3-4: Clinical tumor stage 1-2 / 3-4; SLNB: Sentinel lymph node biopsy; TAD: Targeted axillary dissection; ALND: Axillary lymph node dissection; pCR: Pathological complete response; DCbHP: Docetaxel, carboplatin, trastuzumab, pertuzumab; EC/AC-THP: Epirubicin/cyclophosphamide or adriamycin/cyclophosphamide followed by Taxane, Trastuzumab, Pertuzumab.

Table 2. Distribution of pre-NAC laboratory values according to pathological complete response (pCR) status

Parameters	Category	Non-pCR n=17 (%)	pCR n=40 (%)	p
NLR (Median)	<1.93	10 (58.8)	18 (45.0)	
	≥1.93	7 (41.2)	22 (55.0)	0.34
PLR (Median)	<121.359	7(41.2)	20 (50)	
	≥121.359	10 (58.8)	20 (50)	0.54
MLR (Median)	<0.22	7 (41.2)	18 (45.0)	
	≥0.22	10 (58.8)	22 (55.0)	0.79
CA 15-3	Normal	9 (52.9)	35 (87.5)	
	High	8 (47.1)	5 (12.5)	**0.01**
CEA	Normal	12 (70.6)	32 (80.0)	
	High	4 (23.5)	5 (12.5)	
	Unknown	1(5.9)	3 (7.5)	0.57

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; CA 15-3: Cancer antigen 15-3; CEA: Carcinoembryonic antigen; pCR: Pathologic complete response.

Table 3. Multivariate analysis of prognostic factors associated with pCR

		OR	95% CI	p
Histological grade	I-II & ≥ III	9.0	2.14-37.9	**0.003**
CA 15-3	High & Normal	7.1	1.54-32.8	**0.01**

pCR: Pathologic complete response; OR: Odds ratio; CA 15-3: Cancer antigen 15-3.

tently higher among hormone receptor-negative patients, reaching between 63% and 89% in this specific subgroup.[7–9] This robust response likely stems from the fact that HR-/HER2+ tumors represent a highly "HER2-addicted" biological subtype. Their profound dependence on the HER2 pathway renders them exceptionally sensitive to the combined effects of HER2-targeted blockade and cytotoxic chemotherapy.[10,11]

Tumor differentiation emerged as an important determinant of treatment response, with grade III lesions demonstrating significantly greater pCR rates than lower-grade tumors. This finding is biologically plausible, as high-grade tumors typically demonstrate increased proliferative activity and higher chemosensitivity. Pivotal trials such as NeoSphere and TRAIN-2 primarily emphasized hormone receptor negativity as the main driver of higher pCR rates. Although this hormone-negative phenotype is inherently linked to highly proliferative and aggressive tumor characteristics [7,8], direct evidence specifically highlighting histological grade comes from real-world data. Previous real-world studies evaluating predictors of pCR in HER2-positive breast cancer have identified high histological grade as a favorable predictive factor for treatment response.[15] Together, these findings support the concept that more aggressive tumor biology in HER2-positive disease may paradoxically confer greater sensitivity to systemic treatment.

In contrast to histological grade, the Ki-67 index was not associated with pCR. Because HR-negative/HER2-positive tumors are inherently highly proliferative, the discriminative utility of Ki-67 is likely diminished in this homogeneous subgroup. Moreover, its predictive role remains highly controversial in the literature due to arbitrary cutoffs and significant inter-observer variability.[16]

Beyond histological grade, pretreatment CA 15-3 levels provided additional prognostic information regarding treatment sensitivity. Patients with normal baseline values experienced significantly greater pCR rates than those with elevated concentrations. Elevated CA 15-3 may reflect increased tumor burden or biologically aggressive disease with lower treatment sensitivity. Although CA 15-3 is commonly used in monitoring metastatic breast cancer, its role as a predictive biomarker in the neoadjuvant setting remains insufficiently investigated. Major neoadjuvant HER2-positive breast cancer trials, including NeoSphere, TRAIN-2, TRYPHAENA, and DESTINY-Breast11, primarily focused on treatment efficacy and survival outcomes and did not specifically evaluate baseline CA 15-3 as a predictor of pathological complete response.[7–9,17] Previous studies evaluating serum tumor markers in breast cancer have generally demonstrated associations between elevated CA 15-3 levels, increased tumor burden, advanced disease stage, and poorer oncologic outcomes.[18,19] In a retrospective study by Shao et al.[19], elevated pretreatment CA 15-3 levels were associated with unfavorable treatment outcomes across different breast cancer subtypes. At the molecular level, this reduced treatment sensitivity is explained by the fact that CA 15-3 is the soluble form of the MUC1 glycoprotein, whose cleaved form (MUC1*) has been preclinically shown to drive resistance to both trastuzumab and standard chemotherapy.[20] Consequently, tumors with normal CA 15-3 levels may lack this specific evasion mechanism, potentially explaining the superior treatment responses observed in our cohort.

In addition to serum tumor markers, inflammatory biomarkers have also been investigated as potential predictors of neoadjuvant treatment response. Although some studies suggest a correlation between lower inflammatory indices and improved pCR rates[13,21], we found no significant association between baseline NLR, PLR, or MLR and pCR. This lack of significance is consistent with several other reports and meta-analyses in the literature.[22–24]

Several limitations should be considered when interpreting these findings. First, the retrospective nature of the analysis

and the inclusion of patients from a single institution may have introduced unavoidable selection bias. Second, the relatively small sample size limits statistical power. Third, survival analyses could not be robustly evaluated due to the absence of recurrence events during the available follow-up period. Nevertheless, the homogeneous HR-negative/HER2-positive patient population and real-world treatment data represent important strengths of the study.

Conclusion

Contemporary HER2-targeted neoadjuvant regimens yielded favorable pathological response rates in patients with HR-negative/HER2-positive breast cancer. Histological grade III disease and normal baseline CA 15-3 levels were identified as independent predictors of pCR, whereas inflammatory biomarkers including NLR, PLR, and MLR were not associated with treatment response. These observations may aid in refining patient selection and tailoring treatment strategies for individuals with HER2-positive disease.

Disclosure

Ethics Committee Approval: Ethical approval was obtained from the Başakşehir Çam and Sakura City Hospital Ethics Committee (12/06/2024 Number: 2024-03).

Informed Consent: The requirement for informed consent was waived by the Ethics Committee due to the retrospective nature of the study.

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