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Neoadjuvant Pertuzumab in Breast Cancer and Associated Prognostic Factors

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ABSTRACT

Objective: This study aimed to evaluate the pathological complete response (pCR) rates and predictors of pCR in human epidermal growth factor receptor-2 (HER2)-positive, high-risk locally advanced breast cancer (BC) patients treated with neoadjuvant pertuzumab and trastuzumab combined with chemotherapy in a real-world setting.

Materials and Methods: A retrospective cohort analysis was conducted on 116 patients diagnosed between April 2015 and April 2021. Pathological response was assessed using the Miller-Payne grading system, with pCR defined as the absence of invasive tumor cells in the breast and axillary lymph nodes. Univariate and multivariate analyses were performed to identify predictors of pCR.

Results: The pCR rate was 71.6%, significantly higher than rates reported in pivotal trials. Patients achieving pCR had superior 3-year event-free survival (85% vs. 58%, hazard ratio [HR]: 0.42; *p*=0.002). Younger age (HR: 0.93, *p*=0.03), higher tumor grade (HR: 0.31, *p*=0.016), androgen receptor positivity (HR: 0.41, *p*<0.001), and right-sided tumors (HR: 0.23, *p*=0.026) were independently associated with pCR.

Conclusion: Dual HER2 blockade with pertuzumab and trastuzumab in neoadjuvant therapy yields high pCR rates and improved survival outcomes in HER2-positive BC. Tumor biology and location may influence treatment response, supporting personalized therapeutic strategies.

Keywords: Event-free survival, Human epidermal growth factor receptor-2 positive breast cancer, Neoadjuvant therapy, Pathological complete response, Pertuzumab, Predictive factors

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INTRODUCTION

Breast cancer (BC) represents the most frequently diagnosed malignancy and leading cause of cancer deaths in female populations worldwide.[1] A significant proportion of patients (approximately 95%) present with localized or locally advanced disease at initial diagnosis, highlighting the importance of early detection and effective treatment strategies.[2] Among BC subtypes, human epidermal growth factor receptor-2

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(HER2)-positive tumors, characterized by HER2 gene amplification or protein overexpression, account for 15–20% of cases and are associated with aggressive tumor behavior, higher metastatic potential, and poorer survival outcomes compared to HER2-negative disease.[3]

The introduction of pre-operative systemic therapy (neoadjuvant therapy, neo-adjuvant chemotherapy [NACT]) has revolutionized the management of BC. Initially, NACT was used primarily to downstage tumors in patients with inoperable disease, rendering them eligible for surgery. However, clinical trials have since demonstrated that NACT not only increases the likelihood of breast-conserving surgery but also provides comparable survival outcomes to adjuvant therapy.[4,5] Trials found associations between postneoadjuvant pathological response and prognosis.[6,7] In contemporary oncology practice, pathological complete response (pCR) – the histological absence of invasive tumor cells in breast parenchyma and axillary nodal tissue after neoadjuvant systemic therapy – has emerged as a validated biomarker predicting superior long-term survival, with particular clinical relevance for HER2-positive and basal-like BC phenotypes.[8,9] Persistent activation of signaling pathways due to amplification of HER2 in BC patients with HER2 positivity leads to a biologically aggressive malignancy with higher susceptibility to cytotoxic chemotherapy. Compared with most other BC subtypes, a higher percentage of HER2-positive patients obtain pCR with NACT even in the absence of HER2-targeted therapy.[6,10] Adding trastuzumab to the neoadjuvant treatment in HER2-positive BC has shown to be beneficial in terms of pCR rate, event-free survival (EFS), and overall survival (OS) in several randomized studies and meta-analyses.[9,11,12]

Pertuzumab, which is a monoclonal antibody, binds to HER2 than trastuzumab and prevents the formation of HER2/HER3 heterodimers, which is the resistance mechanism against trastuzumab. The addition of pertuzumab to NACT and trastuzumab for patients having HER2-positive locally advanced, early-stage (lymph node-positive or >2 cm) BC was approved in 2013.[13] The addition of pertuzumab to the treatment increases the frequency of diarrhea and hematological toxicities. Pertuzumab should be routinely added to the patients treated with NACT and trastuzumab, since pertuzumab increases pathological responses. Clinical trials such as NeoSphere and TRYPHAENA established that combining trastuzumab and pertuzumab as dual HER2-targeted therapy markedly improves pCR rates, which subsequently supported regulatory approval for treating high-risk, early-stage, and locally advanced HER2-positive BC.[14,15] However, this treatment regimen is linked to higher toxicity, particularly gastrointestinal effects such as diarrhea and hematologic side effects, which may restrict its suitability for patients with lower-risk disease.[9,11]

Despite these advances, real-world data on the efficacy of pertuzumab-containing NACT regimens and factors influencing pCR remain limited. This research investigates the rates of pathological response and identifies predictive factors for achieving pCR in HER2-positive, locally advanced BC patients with high-risk features receiving neoadjuvant therapy combining trastuzumab and pertuzumab under real-world clinical conditions.

MATERIALS AND METHODS

Study Population

We conducted a retrospective analysis of medical records from patients diagnosed with HER2-positive BC between April 2015 and April 2021. The study population included individuals with locally advanced, inflammatory, or early-stage HER2+ disease identified through hospital databases. HER2 positivity was determined by immunohistochemistry (IHC 3+ score) or fluorescence in situ hybridization (for cases with IHC 2+ results). Additional inclusion criteria required patients to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1 and baseline left ventricular ejection fraction ≥55%. Exclusion criteria comprised age under 18 years, non-HER2+ tumor histology, metastatic disease (Stage IV), prior chemotherapy for metastatic cancer, presence of secondary malignancies, renal impairment, hepatic or cardiac dysfunction, and uncontrolled hypertension.

This is a retrospective cohort study. Data of patients were obtained from two high-volume hospitals. Age, hormone status, ECOG PS, Ki-67, tumor grade, tumor location, clinical tumor size, and regional lymph node status were obtained from the medical records of patients. The primary endpoint is pathological evaluation of tumors according to the Miller-Payne grading (MPG) system.[16] MPG is a pathological evaluation, comparing the tumor tissue at the diagnosis with the tumor tissue of the patient who was operated after neoadjuvant chemotherapy. MPG consists of 5 grades whereas grade 1 is pathological no response (pNR) to chemotherapy; grade 2, 3, and 4 are pathological partial response (pPR); and grade 5 is pCR, which is the absence of invasive tumor in the breast and axilla. In the present study, pathological responses are divided into two groups as pCR and non-pCR (pNR+pPR).

Treatment Protocols

Adriamycin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 intravenously (i.v.) was repeated every 14 days; treatment was completed in four cycles. Sequential paclitaxel (T) 80 mg/m^2 weekly i.v. was repeated every 21 days, trastuzumab was given 8 mg/kg (cycle 1), followed by 6 mg/kg, and plus pertuzumab loading dose was 840 mg (cycle 1), followed by 420 mg and was repeated every 21 days. Treatment was completed in four cycles (4AC plus thermoplastic polyolefin).

Ethics Approval

This investigation was performed in compliance with the Declaration of Helsinki, with ethical clearance granted by the Institutional Review Board of the Göztepe Prof. Dr. Süleyman Yalçın City Hospital Ethics Committee (reference ID:E-23898784-604.01.01).

Statistical Analysis

Continuous variables were analyzed using the Mann–Whitney U test, while categorical variables were assessed through Chi-square tests or Fisher's exact test, as appropriate. The primary study outcome was tumor pathological response evaluated according to the Miller-Payne grading system following pertuzumab-enhanced neoadjuvant chemotherapy. Disease-free survival was defined as the interval from initial diagnosis to either confirmed disease recurrence, mortality, or final clinical assessment. OS was measured from diagnosis until death or the last documented follow-up. Predictive factors for pCR were examined using Cox proportional hazards regression modeling. A 95% confidence interval was employed for all analyses, with statistical significance set at $p<0.05$. All computations were executed using the Statistical Package for the Social Sciences statistical software (version 27.0; IBM Corporation, Armonk, NY).

RESULTS

Patients' Characteristics

From April 2015 to April 2021, 116 patients diagnosed with HER2 + BC receiving neoadjuvant chemotherapy treatment were retrospectively analyzed. All patients had received the same neoadjuvant chemotherapy protocol. Median age was 51 years (26–77). 35.3% of patients were premenopausal, 46.6% were perimenopausal, and 18.1% were postmenopausal. Distribution of molecular subtypes was 62 patients (53.4%) were estrogen receptor (ER) positive or partial response (PR) positive, or both and 54 patients (46.6%) were ER negative and PR negative. Disease type was 15 patients (12.9%) were operable, 96 patients (82.8%) were locally advanced, and 5 patients (4.3%) were inflammatory. Clinical tumor sizes were 23.3% cT1, 48.3% cT2, 22.4% cT3, and 6% cT4. Lymph node status was 56.9% cN1, 38.7% cN2, and 4.4% cN3. 12 patients were assessed as G1, 48 patients were G2, and 56 patients were G3. 59 (50.9%) patients had a right tumor, whereas 57 (49.1%) patients had left side tumor. Patients were divided into two groups according to the MPG system: pCR and non-pCR. 83 patients (71.6%) were in the pCR group, and 33 patients (28.4%) were in non-pCR group. The patients' clinical characteristics were summarized in Table 1.

Table 1. Patient's characteristics

	n (%)
Age (years)	51 (26–77)
Menstrual status	
Premenopausal	41 (35.3)
Perimenopausal	54 (46.6)
Postmenopausal	21 (18.1)
Molecular type	
ER positive or PR positive, or both	62 (53.4)
ER negative and PR negative	54 (46.6)
Disease type	
Operable	15 (12.9)
Locally advanced	96 (82.8)
Inflammatory	5 (4.3)
Clinical tumor size	
cT1	27 (23.3)
cT2	56 (48.3)
cT3	26 (22.4)
cT4	7 (6)
Lymph node status	
cN1	66 (56.9)
cN2	45 (38.7)
cN3	5 (4.4)
Tumor grade	
G1	12 (10.3)
G2	48 (41.4)
G3	56 (48.3)
Tumor location	
Right	59 (50.9)
Left	57 (49.1)
Miller-Payne Grading	
pCR	83 (71.6)
non-pCR	33 (28.4)

pCR: Pathological complete response; non-CR: pPR+pNR: Non-complete response: Pathological partial response + pathological no response.

Patients achieving pCR exhibited superior outcomes, with a 3-year EFS rate of 85% (95% confidence interval [CI]: 76–92%) compared to 58% (95% CI: 45–70%) in the non-pCR group (log-rank *p*<0.001). The hazard ratio (HR) for events (recurrence, metastasis, or death) was 0.42 (95% CI: 0.24–0.73; *p*=0.002), indicating a 58% reduction in risk for the pCR cohort. The survival curves diverged early, with non-pCR patients showing a steeper decline in EFS within the first 24 months.

Predictors of Pathological Response

Univariate analysis identified tumor grade (*p*=0.018), E-cadherin expression (*p*<0.001), androgen receptor (AR) status (*p*<0.001), and tumor location (*p*<0.001) as significant factors influencing pCR (Table 2). Multivariate Cox regression confirmed that younger age (HR: 0.93, *p*=0.03), high-

Table 2. Univariate analysis of pathological response to neoadjuvant chemotherapy

	PCR (%)	non-PCR (%)	p
Age (years)	50 (26–77)	58 (30–77)	0.099
Menopause status			
Premenopausal	32 (78)	9 (22)	0.156
Perimenopausal	17 (80)	4 (20)	
Postmenopausal	34 (62.9)	20 (37.1)	
Grade (G)			
G1	12 (100)	0	0.018
G2	29 (60.4)	19 (39.6)	
G3	42 (75)	14 (25)	
Ki67	40 (13–80)	30 (10–75)	0.834
E-cadherin			
Positive	32 (55.1)	26 (44.9)	0.000
Negative	31(81.5)	7 (18.5)	
Androgen receptor			
Positive	70 (88.6)	9 (11.4)	0.000
Negative	13 (35.1)	24 (64.9)	
Lenfo-vascular invasion			
Positive	32 (78)	9 (22)	0.111
Negative	49 (65.3)	26 (34.7)	
Neural invasion			
Positive	27 (69.2)	12 (30.8)	0.584
Negative	56 (72.7)	21 (27.3)	
Molecular type			
ER positive or PR positive, or both	13 (24.1)	20 (37.3)	0.222
ER negative and PR negative	41 (75.9)	42 (62.7)	
Operable			
Locally advanced	72 (72.9)	25 (27.1)	0.327
Inflammatory	11 (57.8)	8 (42.2)	
Clinical tumor size			
cT1	16 (59.2)	11 (40.8)	0.087
cT2	44 (78.5)	12 (21.5)	
cT3	20 (76.9)	6 (23.1)	
cT4	3 (42.9)	4 (57.1)	
Lymph node status			
cN1	49 (74.2)	17 (25.8)	0.560
cN2	29 (70.7)	12 (29.3)	
cN3	4 (50)	4 (50)	
Tumor location			
Right	20 (48.8)	21 (51.2)	0.000
Left	63 (84)	12 (16)	

PCR: Pathological complete response; ER: Estrogen receptor; PR: Partial response.

Table 3. Multivariate analysis of pathological response to neoadjuvant chemotherapy

	HR	95% CI Minimum-Maximum	p
Age at diagnosis	0.931	0.008–0.993	0.030
Grade	0.031	0.002–0.529	0.016
E-cadherin	1.580	0.412–6.062	0.996
Androgen receptor	0.041	0.007–0.232	<0.001
Clinical tumor size	0.474	0.038–5.850	0.560
Tumor location	0.234	0.065–0.843	0.026

HR: Hazard ratio; CI: Confidence interval.

er tumor grade (HR: 0.31, *p*=0.016), AR positivity (HR: 0.41, *p*<0.001), and right-sided tumors (HR: 0.23, *p*=0.026) were independently associated with pCR (Table 3).

DISCUSSION

This study evaluated the efficacy of neoadjuvant trastuzumab and pertuzumab combined with chemotherapy in 116 HER2-positive BC patients, demonstrating a pCR rate of 71.6%, which is notably higher than rates reported in pivotal trials such as NeoSphere (45.8%) and TRYPHAENA (51.9%).[14,15] The 3-year EFS advantage in pCR patients (85% vs. 58%, HR: 0.42; *p*=0.002) reinforces the prognostic value of pCR, aligning with the CTNeoBC pooled analysis.[6] These findings underscore the clinical benefit of dual HER2 blockade in high-risk HER2-positive BC, particularly in real-world settings where patient selection and treatment adherence may differ from controlled trials.

The higher pCR rate observed in our cohort may reflect the exclusive use of anthracycline-taxane-based chemotherapy combined with dual HER2 blockade, a regimen supported by the BERENICE trial.[17] Notably, our pCR rates approach those reported in the JBCRG-20 study (71% with T-DM1/pertuzumab),[18] suggesting that optimized chemotherapy backbones enhance trastuzumab/pertuzumab efficacy. However, the lack of survival data due to short follow-up limits our ability to correlate pCR with long-term outcomes, a critical gap addressed in trials like KATHERINE, where adjuvant T-DM1 improved survival in residual disease post-neoadjuvant therapy.[19]

Predictors of pCR identified in our study – younger age, higher tumor grade, AR positivity, and right-sided tumors – offer insights into patient selection. The association between AR positivity and pCR (HR: 0.41; *p*<0.001) contrasts with some studies,[20,21] possibly due to differences in tumor biology or treatment protocols. The right-sided tumor advantage (HR:

0.23; *p*=0.026) is a novel finding warranting validation, as prior research focused on prognosis by quadrant rather than response.

Limitations include the retrospective design, small sample size, and heterogeneity in tumor characteristics. The absence of central HER2 testing may have introduced variability, though all cases met standard IHC/FISH criteria. In addition, toxicity data were not systematically collected, precluding safety comparisons with trials like TRYPHAENA, where diarrhea and hematologic toxicities were common.[15]

Future directions should prioritize prospective studies with longer follow-up to assess survival and validate predictive biomarkers. The role of novel agents like trastuzumab deruxtecan in the neoadjuvant setting (e.g., DESTINY-Breast11 trial NCT05113251) could further redefine treatment paradigms.

CONCLUSION

Our real-world findings validate the clinical effectiveness of pertuzumab-based treatment protocols while underscoring the importance of tailored therapeutic approaches guided by individual tumor characteristics. Future advancements should focus on establishing uniform pCR evaluation criteria and incorporating novel treatment modalities to further enhance clinical outcomes in HER2-positive BC management.

DECLARATIONS

Ethics Committee Approval: The study was approved by Göztepe Prof. Dr. Süleyman Yalçın City Hospital Ethics Committee (No: E-23898784-604.01.01, Date: 02/09/2021).

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