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ORIGINAL ARTICLE

Evaluation of factors predicting pathologic complete response in locally advanced HER2 positive breast cancer treated with neoadjuvant pertuzumab, trastuzumab and chemotherapy; Real life data

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Summary

Purpose: *Recently, neoadjuvant treatment approach has gained importance in locally advanced HER-2 positive breast cancer. Adding pertuzumab increases pathological complete response (pCR). In this study, we aimed to examine the clinicopathologic features that predict the pCR in patients receiving neoadjuvant pertuzumab, trastuzumab, and chemotherapy in locally advanced HER2 positive breast cancer.*

Methods: *Locally advanced HER2 positive breast cancer patients who were followed up in 4 different oncology centers and received 4 cycles of pertuzumab, trastuzumab and taxane were retrospectively evaluated. A total of 58 (92%) patients received anthracycline chemotherapy before combination of dual her-2 blockade and taxanes. Fisher's and chi-square tests were used for nominal variables and numeric data analyses.*

Results: *A total of 63 female patients were included in the study. Their median age was 46 years (21-75) and 40 (63.5%) patients were premenopausal. Median tumor size was 25 mm (2-70) and there were 22 (34.9%) patients with Stage 3a. pCR was 66% and 75% in the whole group and in the hormone negative group, respectively. Statistically significant increase was found in pCR in patients with grade 3 tumors and cerbB2 with 3+ immunohistochemical staining. No relationship was found between pCR and age at diagnosis, menopausal status, tumor infiltrating lymphocyte, dose-dense anthracycline, Ki67≥40, body mass index (BMI) ≥30 kg/m^2 and accompanying DCIS.*

Conclusion: *Four cycles of pertuzumab, trastuzumab and taxane after neoadjuvant anthracycline for locally advanced HER2 breast cancer are associated with increased pCR in patients with grade 3 tumors and high cerbB2 expression.*

Key words: *neoadjuvant therapy, breast cancer, pertuzumab*

Introduction

The incidence of locally advanced breast cancer is 10-15% and varies by population (6-73%). The proportion of patients with stage 3a and stage 3b in an epidemiological study in Turkey were 14% and 6% respectively [1]. Inflammatory breast cancer rate is less than 2%, and its incidence is higher in developing countries. The frequency of HER2 positive breast cancer is 20-25% [2]. T and N stages can regress with neoadjuvant chemotherapy and patients can gain the chance of operability and breast conserving surgery (BCS)[3]. In addition, early treatment of subclinical distant metastasis

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can be achieved with neoadjuvant therapy[4]. It was shown that sequential use of anthracycline and taxane and use of dose-dense anthracycline increased the pathological complete response (pCR) and increased the rate of BCS[5]. With neoadjuvant chemotherapy, the pCR rate can be 20-65%. Adding trastuzumab to chemotherapy doubles the pCR rate (43 vs 20%) [6] and is associated with increased disease-free survival (DFS) and overall survival (OS) in those with pCR[7]. In the TECHNO study, a pCR of 39% was obtained by adding trastuzumab to taxane after combined cyclophosphamide-epirubicine (CE) chemotherapy[6]. In addition, DFS (HR 2.5, 95% CI 1.2-5.1) and OS (HR 4.9, 95% CI 1.4-17.4) were found better in those with pCR than in those without [6]. The pCR rates were further increased by adding pertuzumab alongside trastuzumab as a neoadjuvant therapy. In the phase 2 neoSphere study, the pCR rate was increased by adding neoadjuvant docetaxel and trastuzumab alongside pertuzumab (29 versus 46%) [8]. In addition, in another phase 2 study, tryphane, by adding pertuzumab to trastuzumab-docetaxel, the pCR was 51% in the anthracycline-free arm (carboplatin arm), while the pCR was 45 and 50% in the anthracycline arms [9].

In this study, we aimed to examine the clinicopathologic features that predict the pCR in patients receiving neoadjuvant pertuzumab, trastuzumab, and chemotherapy in locally advanced her-2 positive breast cancer.

Methods

Our study was designed as a multi-center study with the participation of 4 different oncology centers in Ankara. Patients with locally advanced HER-2 positive breast cancer who received pertuzumab-trastuzumab combined with taxane were retrospectively evaluated. Female patients aged 18 years and above were included the study. HER2 status was determined by immunohistochemical (IHC) staining. Tumors having a score of 3 (+) were considered as HER2-positive. Tumors scoring 2 (+) for HER2 expression were subsequently analyzed by fluorescence *in situ* hybridization (FISH) and were considered as HER2-positive if HER2 amplification was present in FISH [10] . HER2 FISH positive result was defined as HER2/CEP17 ratio ≥2.0 or average HER2 copy number ≥6.0 signals per cell. The kit used was Ventana's anti-her-2/neu (4B5) rabbit monoclonal primary antibody. Patients with second primary cancer, metastatic disease, or male breast cancer were not included in the study. Estrogen (ER) and progesterone receptor (PR) nuclear staining ≥ 1% was accepted as ER and/or PR-positive by IHC evaluation according to the ASCO/CAP guidelines [11]. The study was approved by the ethics committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision number 2020-09/804). In addition, the study was approved by the Ministry of Health of Turkey pharmaceutical and medical device organizations (25.02.2021, E-24931227-506.01-354158). Locally advanced breast cancer was defined as T3-4 and/or clinical lymph node positivity. Patients with locally advanced breast cancer were also described as operable (T1-3 and N0, N1) and inoperable (T4 and/or N2, N3).

A total of 63 patients were included in the study between 2018-2020. Patients received 4 cycles of pertuzumab-trastuzumab and taxane combination. Docetaxel and paclitaxel were characterized as taxanes. The pertuzumab loading dose was 840 mg, followed by 420 mg every 3 weeks. Trastuzumab was given every 3 weeks at 8 mg/kg (cycle 1), followed by 6 mg/kg in the following cycles. Docetaxel was given at 75 mg/m^2, escalating, if tolerated, to 100 mg/m^2 every 3 weeks. Paclitaxel was given at 175 mg/m^2 every 3 weeks or 80 mg/m^2 on days 1, 8, and 15. A total of 58 (92%) patients received a combination of dual HER2 blockade and taxane after neoadjuvant anthracycline chemotherapy. Anthracycline protocol was administered to patients as adriamycin, cyclophosphamide (AC) or fluorouracil, epirubicin, cyclophosphamide (FEC). It contained 60 mg/m^2 adriamycin + 600 mg/m^2 cyclophosphamide every 3 weeks in the AC protocol. The FEC protocol contained fluorouracil 600 mg/m^2, epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 intravenously every 3 weeks. The patients then underwent surgery and afterwards received adjuvant trastuzumab or trastuzumab emtansine (TDM)-1 for 1 year.

Cardiac function was assessed by transthoracic echocardiography (ECHO) prior to treatment and was repeated every 3 months during treatment. Primary cardiac endpoints were defined as follows: Class III/IV heart failure (New York Heart Association/NYHA/Functional Classification/NYH [12]) 10-15% decrease in LVEF, or LVEF<50%. Tumor infiltrating lymphocytes (TILs) were evaluated from pathology blocks stained with hematoxylin and eosin. Body mass index (BMI) (kg/m^2) was calculated as weight (kg) divided by square of height (m^2). Body surface area was calculated according to the Mosteller formula. The Mosteller formula takes the square root of the height (cm) multiplied by the weight (kg) divided by 3600. Physical examination and breast ultrasonography/mammography or breast MRI, abdominal ultrasonography and chest radiography were used for post-treatment evaluation. Tumor response evaluation was made according to RECIST 1.1[13]. Partial response (PR) was defined as 30% tumor shrinkage. Progression was defined as 20% tumor increase or new lesion. Those that did not shrink as much as the partial response and did not grow as much as the progressive disease were defined as stable disease=SD (< 30% less shrinkage, <20% less growth). pCR was defined as the absence of invasive tumor cells in the primary tumor site and regional lymph nodes.

Statistics

All statistical analyses were performed using the SPSS software, version 20.0 for Windows (SPSS, Inc., Chicago, ILL, USA). Fisher's and chi-square tests were used for nominal variables and numeric data analyses. A p value ≤0.05 was accepted as statistically significant in all analyses.

Results

A total of 63 female patients were included in the study. The clinicopathologic characteristics of the patients are shown in Table 1. Median patient age was 46 years (21-75) and 40 (63.5%) patients were premenopausal. Pathologically, 49 patients (77.8%) had invasive ductal cancer (IDC). A total of 43 patients (68%) had grade 3 disease. Inflammatory breast cancer was present in 6 (9.5%) patients. Approximately 44 (80%) of the patients had unifocal disease, 13 patients (20.6%) had multifocal, and 6 patients (9.5%) had multicentric disease. TILs were evaluated in 12 (19%) patients and the median TIL value was 20 (1-90). Median tumor size was 25 mm (2-70) and there were 39 (61.9%) patients with cT2. There were 20 (31.7%) and 22 (35%) patients with stage 2b and 3a, respectively. In addition, hormone positivity was found in 42 (66.3%) patients. Immunohistochemically, there were 55 (87%) patients with cerbB2 positivity (3+). Inoperable patients were 31 (49.2%). The median body surface area and BMI of the patients were 1.66 m^2 (1.4-2.2) and 26.3 kg/m^2 (18.6-44.4), respectively. The median follow-up period of the patients was 18 (11-39) months. Basal median ejection fraction (EF) value of the patients was 60% (55-68). No toxicity, which was a primary cardiac endpoint, developed in patients. Only 7 patients had a 5-10% reduction in EF. In total, 61 (95%) of patients received neoadjuvant anthracycline (one patient did not receive the anthracycline protocol, one patient received

Table 1. Patient clinicopathologic characteristics

Parameters	*n (%)*	*Parameters*	*n (%)*
Women	63 (100)	cN0	1 (1.6)
Menopause		cN1	28 (44.4)
Premenopausal	40 (63.5)	cN2	24 (38.1)
Perimenopausal	6 (9.5)	cN3	7 (11.1)
Postmenopausal	17 (27)	cN positive	62 (98.4)
Right breast cancer	37 (58.7)	cN negative	1 (1.6)
Left breast cancer	24 (38.1)	Stage	
Pathology		2a	7 (11.1
IDC	49 (77.8)	2b	20 (31.7)
NOS	12 (19)	3a	22 (34.9)
Mucinous	1 (1.6)	3b	5 (7.9)
Inflammatory breast cancer	6 (9.5)	3c	9 (14.3)
Accompanying DCIS		ER	
Yes	20 (31.7)	Positive	38 (60.3)
No	43 (68.3)	Negative	25 (39.7)
Grade		PR	
Grade2	19 (30.2)	Negative	28 (44.4)
Grade3	43 (68.3	Positive	35 (55.6)
cerbB2		Hormone receptor	
IHC 3+	55 (87.3)	Positive	42 (66.3)
FISH	8 (12.7)	Negative	21 (33.3)
LVI		HER2 IHC	
Yes	10 (15.9)	2+	7 (11.1)
No	17 (27)	3+	55 (87.3)
PNI		Unifocal	44 (79.8)
Yes	3 (4.8)	Multifocal	13 (20.6)
No	20 (31.7)	Multicentric	6 (9.5)
cT			
T1	10 (15.9)		
T2	39 (61.9)		
T3	8 (12.7)		
T4	6 (9.5)		

IDC: invasive ductal cancer, NOS: not otherwise specified, LVI: lymphosvascular invasion, PNI: perineural invasion

the anthracycline protocol as an adjuvant). As an anthracycline protocol, AC mostly was used in 53 (84%) patients, and also FEC protocol was used in 7 (11%) patients. The patients received a total median 400 mg of anthracycline (336-540 mg). Dose-dense anthracycline was administered in 11 (17.5%) patients. Neoadjuvant platinum was not applied to the patients. Docetaxel was administered in 60 (95%) patients along with pertuzumab and trastuzumab as neoadjuvant, while paclitaxel was administered in 3 (5%) patients (Table 2). Sixty-one (97%) patients were operated after neoadjuvant therapy (one of the remaining patients denied the operation, the other patient developed cranial metastasis during treatment). While modified radical mastectomy (MRM) was performed in 82.5% of the patients, 7 (11.5%) patients underwent BCS. pCR and PR were obtained in 42 (66.7%) and 19 (30%) patients, respectively. In the hormone receptor negative group, the pCR rate was 75%. The data evaluating the parameters predicting pCR are shown in Table 3. We found statistically significantly higher pCR in patients with grade 3 pathology and 3+ cerbB2 positivity in IHC. No relationship was found between pCR and age at diagnosis >45, menopausal status, TILs, dose-dense anthracycline, Ki67 ≥40, and BMI ≥30 kg/m^2. A total of 54 (85%) patients received trastuzumab and 4 (6%) patients received TDM-1 as adjuvant therapy. In addition, 49 (78%) patients received adjuvant radiotherapy (RT) and 35 (58.2%) patients received adjuvant hormone therapy. A total of 92.1% of the patients completed the planned neoadjuvant chemotherapy combined with anti-HER2 therapy and postoperative adjuvant anti-HER-2 therapy. Recurrence developed in four patients and one did not want to be operated on.

Table 2. Treatment protocols and effectiveness

Protocols	*n (%)*
AC-PTD-Surgery-T/TDM-1	55 (87)
FEC-PTD-Surgery-T/TDM-1	3 (5)
PTD-FEC-Surgery-T/TDM-1	3 (5)
PTD-Surgery-FEC-T/TDM-1	1 (2)
PTD-Surgery-T/TDM-1	1 (2)
Taking anthracycline first	
Yes	58 (92)
No	5 (8)
Anthracycline protocol	
AC	53 (84)
FEC	7 (11)
Pertuzumab protocol	
Pertuzumab-Trastuzumab-Docetaxel	60 (95)
Pertuzumab-Trastuzumab-Paclitaxel	3 (5)
Dose-dense anthracycline	
Yes	11 (17.5)
No	50 (79)
Operation type	
MRM-SNLD	11 (17.5)
MRM-AD	43 (68)
BCS-SNLD	4 (6.5)
BCS-AD	3 (5)
Response	
CR	42 (66.7)
PR	19 (30.2)
Adjuvant chemotherapy	
Trastuzumab	54 (85.7)
TDM-1	4 (6.3)
No	2 (3)
Hormone therapy type	
Tamoxifen	22 (35.5)
Anastrozole	2 (3.2)
Letrozole	10 (17.5)
Exemestane	1 (2)
Radiotherapy	
Yes	49 (78)
No	7 (11)
Recurrence	
Yes	4 (6.3)
No	57 (90.5)

PTD: pertuzumab-trastuzumab-docetaxel. AC: adriamycin cyclophosphamide. FEC: fluorouracil epirubicin cyclophosphamide. AD: axillary dissection. SNLD: sentinel lymph node dissection. CR: complete response, PR: partial response.

Treatment toxicities are shown in Table 4. The most common toxicity was neutropenia and it was seen in 38 (60%) patients. Grade 3-4 neutropenia was seen in 16 (26%) patients. Febrile neutropenia (FEN) also developed in 5 (8%) patients. Grade 3-4 anemia or thrombocytopenia was not observed. Grade 2 anemia and thrombocytopenia were seen in 17 (27%) and 1 (2%) patients, respectively. Chemotherapy dose reduction was done in 5 (8%) patients. GCSF prophylaxis was applied to 40 (65%) patients. Other toxicities noted concerned the gastrointestinal system.

Discussion

In our study, 66.7% of the whole group and 75% of the hormone receptor (HR) negative group achieved pCR with dual HER2 blockade combined with neoadjuvant chemotherapy (pertuzumab, trastuzumab). Among the parameters evaluated for pCR, the presence of grade 3 tumors and having patients -2 +3 in IHC were significantly associated with higher pCR.

HER2 is a transmembrane glycoprotein from the EGF receptor family and has tyrosine kinase ac-

tivity. HER2 protein is overexpressed as a result of the amplification of the Erbb2 gene. Trastuzumab and pertuzumab are monoclonal antibodies that block intracellular signal transmission by binding to different subdomains of extracellular cerb2 receptors. pCR was statistically significantly higher in those 3+ stained in IHC. Higher HER2 receptor expression is associated with stronger efficacy of monoclonal antibodies.

Statistically significantly higher rates of pCR were obtained in patients with grade 3 tumors. Poorly differentiated tumors have a high mitotic index, which is associated with better chemotherapy response.

While the rate of pCR with neoadjuvant pertuzumab was 46% in the Neosphere study, it was 66% in the current study. This may be particularly related to the administration of neoadjuvant anthracycline. While anthracycline (3 cycles FEC) was administered as an adjuvant in the Neosphere

Table 3. Evaluation of parameters predicting pCR

Parameter	*pCR (+) n=42*	*pCR (-) n=19*	*p*
Hormone receptor, n (%)			0.46
Negative	15 (36)	5 (26)	
Positive	27 (74)	14 (74)	
ER, n (%)			0.29
Positive	24 (57)	13 (68)	
negative	18 (43)	6 (32)	
Grade, n (%)			0.017
3	32 (78)	9 (47)	
2	9 (22)	10 (53)	
Dose-dense anthracycline, n (%)			0.53
Yes	8 (19)	3 (16)	
No	34 (81)	16 (84)	
Accompanying DCIS, n (%)			0.09
Yes	11 (26)	9 (47)	
No	31 (74)	10 (53)	
Menopause, n (%)			0.095
Premenopausal	33 (79)	11 (58)	
Postmenopausal	9 (21)	8 (42)	
Unifocal, n (%)			0.29
Yes	31 (74)	12 (63)	
No	11 (36)	7 (27)	
Ki67, n (%)			0.73
≥ 40	25 (63)	11 (58)	
<40	15 (37)	8 (42)	
TIL, n (%)			0.15
≥ 20	7 (70)	0	
<20	3 (30)	2 (100)	
Diagnose age, n (%)			0.16
<45	19 (45)	5 (26)	
≥ 45	23 (55)	14 (74)	
HER2 IHC, n (%)			0.028
Yes	39 (95)	14 (74)	
No	2 (5)	5 (26)	
BMI, n (%)			0.85
<30	29 (71)	13 (68)	
≥ 30	12 (29)	6 (32)	
Neutropenia, n (%)			0.44
Yes	11 (27)	4 (21)	
No	30 (73)	15 (79)	

pCR: pathological complete response. ER: estrogen receptor . DCIS: ductal carcinoma *in situ*. TIL: tumor-infiltrating lymphocytes, IHC: immunohistochemical. BMI: body mass index

Table 4. Evaluation of toxicity

Patients	*n (%)*
Neutropenia	
Grade1	15 (24)
Grade2	7 (11)
Grade3	10 (16)
Grade4	6 (10)
Anemia	
Grade1	30 (48)
Grade2	17 (27)
Febrile neutropenia	5 (8)
Thrombocytopenia	
Grade 1	8 (13)
Grade 2	1 (2)
ALT-AST elevation	
Grade 1	16 (26)
Grade 2	1 (2)
Nausea	
Grade1	23 (37)
Grade2	2 (3)
Vomiting	
Grade 1	15 (24)
Grade 2	1 (2)
Mucositis	
Grade 1	4 (7)
Grade 2	1 (2)
Diarrhea	
Grade 1	5 (8)
Grade 2	2 (3)
Grade 3	1 (2)
GCSF prophylaxis	
Yes	41 (65)
No	21(33)

ALT: alanine aminostransferase, AST: aspartate aminotransferase

study, 95% of the patients in the present study received anthracycline as neoadjuvant (84%, 4 cycles AC).

In trypahane, another study in which pertuzumab and trastuzumab were evaluated with 3 cycles of FEC or after 3 cycles of FEC, the anthracycline-free (taxotere, carboplatin, herceptin, and pertuzumab) arm was also evaluated and the total pCR rates were 50%, 45%, and 51.9% respectively. In the present study, higher pCR (66%) was obtained with higher rate of locally advanced patients (57 versus 23%) and hormone responsive rate (66 versus 46%). This may be related to the administration of the combination with pertuzumab as 4 consecutive cycles after anthracycline.

Neoadjuvant dose-dense anthracycline with chemotherapy administration was shown to be associated with increased pCR in triple negative breast cancer. In the Berenica study, pCR was 61.8% in the group that received 4 cycles of pertuzumab-trastuzumab-docetaxel (PTD) after 4 cycles of AC [14]. The pCR was 60.7% in those started with 4 cycles of FEC. With the phase 3 Panther study, it has been shown that adjuvant dose-dense treatment with anthracycline improved DFS in HER2 positive breast cancer [15]. Similar results were observed in our study, where approximately 17% of patients received dose-dense anthracycline, and pCR was seen in 66% in this group.

When evaluated in terms of toxicity, grade 3 neutropenia was observed with a rate of 45% and febrile neutropenia at a rate of 8% in the Neoshper study. In our study, grade 3-4 neutropenia was 26%, and FEN 5%. In addition, in the Neosphere study, nausea and mucositis were seen in 38% and 26%, respectively, while in our study, nausea and mucositis were 26% and 9%, respectively. In addition, in this study, grade 2 and 3 diarrhea was seen in 3% and 2%, respectively. Similar to the literature, no serious cardiac toxicity associated with neoadjuvant PTD was observed in this study either [16].

It is known that the survival of obese breast cancer patients is poor. In addition, it is known that pCR responses are lower in neoadjuvant therapy. The pCR response relationship of obesity in patients with HER2 positive breast cancer has been evaluated in a limited number of studies, and it has been shown that this rate is also low in the obese group. This relationship could not be demonstrated in the present study and could be attributed to the relatively small number of patients.

It has been shown that high quantity of pretreatment TILs is associated with improved pCR in neoadjuvant therapy of HER2 positive breast cancer. The value of on-treatment TILs is unknown. While the cut off value for TILs was accepted as 60% in the CherLOB [17], GeparQuattro [18], GeparQuinto[19] and GeparSixto studies, it was accepted as 30% in the NeoALTTO study. The NeoALTTO trial randomized 455 women with HER2+ BC to 12 weeks neoadjuvant therapy with trastuzumab, lapatinib or combination with paclitaxel, followed by FEC after surgery [20]. Higher quantity of pretreatment TILs over 30% was shown to be associated with pCR. In the present study, pretreatment TILs could be evaluated in a limited number of patients (19%). A trend for pCR was assessed in the group with pretreatment TILs greater than 20%.

Limitations of our study include the retrospective design and low patient number. The short follow-up period of our study and our failure to provide disease-free survival is our other limita-

tion. On the other hand, we think that our study is valuable since it provides real-life data and evaluates several parameters for pCR in the combination of neoadjuvant pertuzumab and chemotherapy.

Consequently, we have found that 4 cycles of pertuzumab, trastuzumab, and taxane after neoadjuvant anthracycline therapy for locally advanced HER2 breast cancer are associated with increased pCR in patients with grade 3 tumors and high cerbB2 expression.

Conflict of interests

The authors declare no conflict of interests.

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