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— Case report—

Sixteen cases of HER2-positive Breast Cancer treated with Neoadjuvant Chemotherapy with Pertuzumab

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Abstract Pertuzumab is a molecular-targeted drug that binds to the extracellular domain of human epidermal growth factor receptor 2 (HER2) and inhibits dimer formation. The combined use of pertuzumab and trastuzumab for HER2-positive breast cancer has been reported to significantly increase the rate of pathological complete response (pCR) compared to that with trastuzumab monotherapy. We reported the outcomes of HER2-positive breast cancer treated with neoadjuvant chemotherapy with pertuzumab. Sixteen patients with stages II–III HER2-positive breast cancer were treated with 4 cycles of docetaxel (75 mg/m^2) with trastuzumab and pertuzumab, followed by 4 cycles of 5-fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (500 mg/m^2). The participants were in the age range of 45–76 years; T1, T2 and T3 stages were reported in 2, 11, and 3 cases, respectively, and N0 and N1 stages were reported in 6 and 10 cases, respectively. Luminal HER2 and HER2-enriched subtypes were noted in 8 cases each. In all cases, scheduled chemotherapy was completely implemented. Grade 3, 2b, 1a and 1b histology were observed in 11, 3, 1, and 1 cases, respectively. The rate of pCR (ypT0/is + ypN0) was 69%, whereas the objective response rate was 94%. In 12 cases, breast-conserving surgery was undertaken, whereas 4 patients underwent total mastectomy. Pertuzumab did not cause any complications, including cardiac dysfunction.

Keywords: HER2-positive breast cancer, Pertuzumab, Neoadjuvant chemotherapy, pCR

Introduction

Neoadjuvant chemotherapy is increasingly being administered to patients with locally advanced breast cancer as well as to patients with operable breast cancer, to facilitate downstaging for breast-conserving surgery. Survival outcomes of such a strategy were reported to be comparable to those of adjuvant chemotherapy[1]. The human epidermal growth factor receptor 2 (HER2) is overexpressed and/or its gene is amplified in 15–20% of breast cancers; overexpression and/or gene amplification is associated with a high risk of breast cancer recurrence and metastasis[2]. The standard-of-care neoadjuvant regimens for the treatment of HER2-positive breast cancer comprise conventional systemic chemotherapy plus trastuzumab-based therapy[3]. The rate of pathological complete response (pCR) with conventional systemic chemotherapy plus HER2 blockade range from 25% to 65%, with dual HER2-targeted regimens producing higher pCR rates than trastuzumab monotherapy[4-6]. pCR in the breast and nodes is associated with prolonged event-free survival and overall survival (OS) in patients with HER2-positive breast cancer[3, 7].

This report presents a case series of 16 patients with HER2-positive breast cancer treated with neoadjuvant chemotherapy with pertuzumab.

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Between October 2013 and April 2019, 16 patients with HER2-positive breast cancer, stages II–III (T1–3, N0–1, M0) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were enrolled (Table 1). The median age in this report population was 58 (range 45–76) years, and the median tumor size was 35 (range 18–65) mm. All patients underwent pretreatment core needle or vacuum-assisted biopsy and were diagnosed with invasive cancer. Clinical T1, T2, and T3 disease were noted in 2(12%), 11 (69%), and 3 (19%) patients, respectively. Eight (50%) patients each had hormone receptor (HR)-positive and HR-negative breast cancer. HER2-positive status was defined as 3+ overexpression detected on immunohistochemical testing or HER2 amplification on fluorescence in situ hybridization. Neoadjuvant chemotherapy consisted of 4 cycles (every 3 weeks) of docetaxel (75 mg/m^2) with trastuzumab (loading dose 8 mg/kg, followed by 6 mg/kg) and pertuzumab (loading dose 840mg, followed by 420 mg), followed by 4 cycles (every 3 weeks) of the FEC regimen (5-fluorouracil, 500 mg/m^2; epirubicin, 100 mg/m^2; and cyclophosphamide, 500 mg/m^2) . The protocol was approved by the Institutional Cancer Medical Promotion Committee. All patients provided written informed consent prior to treatment initiation.

Table 1. Baseline Patient Demographics (n = 16)

Parameter	
Woman, n (%)	16 (100)
Median age, years (range)	58 (45-76)
Menopsusal status, n (%)	
Premenopausal	5 (31)
Postmenopausal	11 (69)
ECOG performance status, n (%)	
0	15 (94)
1	1 (6)
Histology, n (%)	
Invasive ductal carcinoma	16 (100)
Invasive lobular carcinoma	0 (0)
Special types	0 (0)
Clinical Tumor stage, n (%)	
T1	2 (12)
T2	11 (69)
T3	3 (19)
Clinical nodal stage, n (%)	
N0	6 (37)
N1≦	10 (63)
Subtype, n (%)	
HER2-enriched	8 (50)
Luminal HER2	8 (50)

ER; estrogen receptor, PgR; progesterone receptor, HER2; human epidermal growth factor receptor type 2, FISH; fluorescent in situ hybridization, ECOG; Eastern Cooperative Oncology Group

All patients completed the chemotherapy on schedule, and received primary prophylaxis with granulocyte-colony stimulating factor (G-CSF). The incidence of treatment-related adverse events is summarized in Table 2. Hematological toxicity manifested as anemia and hepatic dysfunction in 1 (6%) and 3 (19%) patients, respectively. Non-hematological toxicities, such as peripheral neuropathy (100%; n = 16), nausea (31%; n = 5), and stomatitis, skin eruption and arthralgia (25%; n = 4) were observed. Peripheral neuropathy in 2 patients (13%) was reported as the only grade 3/4 toxicity. None of the patients developed clinically symptomatic heart failure or cardiac dysfunction.

Clinical response was evaluated using two-dimensional measurements on magnetic resonance imaging or ultrasonography according to the Response Evaluation Criteria in Solid Tumors (RECIST)[8]. Histological response after the completion of the chemotherapy regimen was evaluated according to the histopathological criteria for the assessment of therapeutic response in breast cancer[9], based on breast and axillary lymph node resection specimens. For the purposes of this report, pCR was defined as no evidence of a residual invasive component in both the breast and axilla (Grade 3, ypT0/is yoN0).

Eleven (69%) patients achieved pCR (ypT0/is ypN0). The rate of pCR for patients with HER2-enriched and luminal HER2 subtypes were 63% (5/8) and 75% (6/8), respectively (Fig. 1). Based on the RECIST criteria, we observed complete response (CR) and partial response (PR) in 12 (75%) and 3 (19%) patients, respectively, which corresponded to an objective response rate (ORR) of 94%.

Patients underwent definitive breast cancer surgery between 21 days and 6 weeks after the last dose of neoadjuvant therapy. Twelve (75%) patients underwent breast-conserving surgery, 3 patients (19%) underwent total mastectomy, and 1 patient underwent nipple conservative total mastectomy; the type of surgery was selected on a large amount of residual disease, patient preference, or a patient's desire for breast reconstruction (Table 3).

Table 2. Summary of Adverse Events

Event	All grades		Grade 3/4	
	n	(%)	n	(%)
Nonhematological toxicities				
stomatitis	4	25	0	0
anorexia	1	6	0	0
nausea	5	31	0	0
vomiting	1	6	0	0
diarrhea	3	19	0	0
skin eruption	4	25	0	0
arthralgia and/or myalgia	4	25	0	0
peripheral neuropathy	16	100	2	13
infusion reaction	2	13	0	0
cardiac disorders	0	0	0	0
Hematologic toxicities				
anemia	1	6	0	0
neutropenia	0	0	0	0
febrile neutropenia	0	0	0	0
thrombocytopenia	0	0	0	0
hepatic dysfunction	3	19	0	0

Within 8 weeks of surgery, patients resumed dual HER2-targeted therapy (trastuzumab and pertuzumab). Adjuvant radiotherapy and endocrine therapy were administered as clinically indicated the by the local practice.

All patients treated with this regimen have remained healthy without any recurrence.

Discussion

Breast cancer patients who achieve pCR are known to have better long-term survival than patients who achieve a lower-grade response. In particular, patients with HER2-positive breast cancer who received chemotherapy in combination with trastuzumab showed a higher pCR rate, which was directly related to improved survival outcomes[3,7,10].

Pertuzumab is a humanized monoclonal antibody that inhibits the dimerization of HER2 with other HER-receptors (HER1–4). The combination of pertuzumab and trastuzumab showed further benefits with significantly improved progression-free survival (PFS)/OS in patients with advanced breast cancer[11]. In the NeoSphere study, the combination of pertuzumab and trastuzumab plus docetaxel was highly efficacious in the neoadjuvant setting, with an increase of 17.8% in pCR (ypT0/is ypN0) rates, compared with the pCR rate of trastuzumab plus docetaxel[4]. Similar benefits were demonstrated in the TRYPHAENA[5] and BERENICE[6] studies. At present, the standard-of-care for HER2-positive

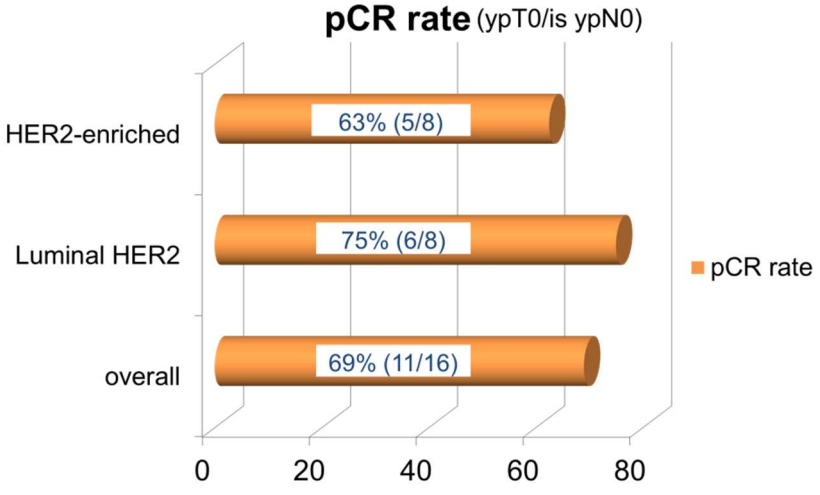

Fig. 1. The pCR rates according to Subtype

Table 3. Therapeutic Results

Parameter	n (%)
Histological response	
Grade 3 (ypT0 ypN0)	9 (56)
Grade 3 (ypTis ypN0)	2 (12)
Grdae 2	3 (19)
Grade 1	2 (12)
Grade 0	0 (0)
Overall response rate prior to surgery	
CR	12 (75)
PR	3 (19)
SD	1 (6)
PD	
Definitive surgery	
Mastectomy	4 (25)
Breast-conserving surgery	12 (75)

pCR; pathological complete response, CR; complete response, PR; partial response, SD; stable disease, PD; progressive disease

breast cancer stage M0 at primary diagnosis is neoadjuvant treatment with a combination of taxane-containing chemotherapy and a dual blockade with pertuzumab and trastuzumab[12]. In this report, the administration of pertuzumab and trastuzumab plus docetaxel, followed by FEC regimen, resulted in a higher pCR rate (69%), and ORR (94%).

In the present report, the rates of pCR for patients with HR-positive and HR-negative breast cancer were 75% and 63%, respectively. A previous meta-analysis demonstrated a trend for higher pCR rates in non-luminal HER2 tumors than in luminal HER2 tumors[13]. Indeed, the pCR rates were 26% and 63% for HR-positive and HR-negative breast cancer, respectively, in the NeoSphere study[4], and 46–50% and 65–84%, respectively, in the TRYPHAENA study[5]. This discrepancy might be explained by the findings of a recent translational study, which showed that phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) mutations are associated with reduced rates of pCR with anti-HER2 therapy for HER2-positive tumors, regardless of HR status[14].

Clinicians are increasingly faced with challenges regarding how to efficiently use and sequence the multitude of therapies available for cancer. For example, if a patient achieves pCR following neoadjuvant pertuzumab-based therapy, pertuzumab therapy for 1 year along with trastuzumab in the adjuvant setting could be continued, or one could consider scaling back therapy and omitting further pertuzumab administration, given the prognostic significance of pCR. Furthermore, given the prognostic significance of pCR in HER2-positive disease, novel trial designs featuring a reduction in therapy after achieving pCR, or conversely, escalation of therapy when pCR is not achieved, are warranted. In recent years, the KATHERINE study[15] reported that the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant trastuzumab emtansine (T-DM1) than with trastuzumab alone among patients with HER2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant therapy. The apparent loss of HER2-positive status in patients with residual disease after neoadjuvant therapy has been reported[16], although no studies were designed to specifically address the activity of pertuzumab and/or T-DM1 in this subgroup.

The predictive accuracy of the therapeutic response could be improved in future clinical studies, though the stratification of intrinsic subtypes of HER2-positive breast cancer by molecular biomarkers, such as *PIK3CA* mutations. In addition, further analyses should be concluded to define the rate of HER2 loss in postsurgical specimens. The lack of a control arm and the small sample size are key limitations of this report.

In conclusion, neoadjuvant chemotherapy consisted of 4 cycles of docetaxel with trastuzumab and pertuzumab followed by 4 cycles of the FEC regimen showed a higher rate of pCR and safety in patients with HER2-positive breast cancer.

Consent for publication

Informed consent for publication of this case report was obtained using the opt-out system.

Completing interests

The authors declare that they have no competing interests.

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HER2 陽性乳癌に対して Pertuzumab を用いた術前化学療法を施行した 16 例

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和文抄録： Pertuzumab は HER2 の細胞外ドメインに結合し、ダイマー形成を阻害するである。種々の試験において、trastuzumab 単独よりも Pertuzumab を併用した方が病理学的完全奏効率(pCR)を有意に上昇すると報告されている。今回、我々は HER2 陽性乳癌に対して Pertuzumab を用いた術前化学療法を行った。16 名の StageII～III の HER2 陽性乳患者に、Pertuzumab、Trastuzumab、Docetaxel（75 mg/m^2）4 コース、その後に FEC100 療法 4 コースを施行した。年齢は 45～76 歳で、T1、T2、T3 はそれぞれ 2 例、11 例、3 例、N0、N1 はそれぞれ 6 例、10 例であった。Luminal HER2 type、HER2 enrich type ともに 8 例であった。すべての症例で予定された化学療法が完全施行できた。組織学的効果は Grade3、2b、1a、1b がそれぞれ 11 例、3 例、1 例、1 例であった。pCR（ypT0/is + ypN0）率は 69%で、奏功率は 94%であった。Pertuzumab による心機能障害等の副作用は認められなかった。

キーワード： HER2 陽性乳癌、Pertuzumab、術前化学療法、pCR