Neoadjuvant pertuzumab in non-metastatic HER2-positive breast tumors: Multicentric study in Peru (NeoHer)

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Abstract. Several clinical trials have demonstrated the benefit of adding pertuzumab to trastuzumab plus neoadjuvant chemotherapy in the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer. The comparison of outcomes between nonrandomized groups of patients who received similar treatments in routine practice remains difficult. The present study aimed to evaluate the pathological complete response (pCR) rates achieved with pertuzumab among patients in routine clinical care in Peru using real-world data. The definition of pCR used was the absence of residual invasive cancer from the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy. A total of 44 patients with non-metastatic HER2-positive breast cancer (stages II and III) treated with pertuzumab in the neoadjuvant setting and who underwent surgery at three private clinics in Lima (Peru) were retrospectively evaluated. The pCR was the efficacy endpoint and it was determined and compared with the results from other clinical trials. Furthermore, safety data were described. The median age was 44 years (interquartile range, 39.5-50.5 years) and 65.9% of patients were premenopausal. Regarding the clinical stage, 56.8% were IIA/IIB and 36.4% were IIIA/IIIB/IIIC. All treatment schemes included concurrent trastuzumab. The patients' treatment comprised neoadjuvant therapy of docetaxel/trastuzumab/pertuzumab (THP) with a median of 4 cycles in 30 patients (68.2%) or docetaxel/trastuzumab/pertuzumab/carboplatin (THPCarb) with a median of 6 cycles in 14 patients (31.8%). In total, 70.5% of patients experienced pCR; among hormone receptor-negative cases, 75.0% achieved pCR and in tumors expressing hormone receptors, the rate of pCR was 66.7%. Of those patients subjected to neoadjuvant treatment with THP, 66.7% (20/30) achieved pCR, whereas 78.6% (11/14) of patients who received THPCarb had a pCR. The incidence of drug-related adverse events was 59.1% and in none of the patients, administration was discontinued due to toxicity. The present results of Peruvian patients with HER2 breast cancer treated according to clinical routine demonstrated that dual blockade of HER2 with trastuzumab and pertuzumab in the neoadjuvant setting achieved high rates of pCR even in hormone receptor-positive patients. These results are consistent with those of randomized controlled trials, with a good safety profile.

Introduction

Human epidermal growth factor receptor 2 (HER2) overexpression (or HER2-positive) is present in ~30% of breast tumors and is known to be associated with poor prognosis (1). In Peru, two independent studies based in hospital registries in two different referral cancer centers reported a frequency of HER2-positive breast tumors of 19.8 and 29.4%, respectively (2,3), which are similar to frequencies reported elsewhere. The use of anti-HER2 monoclonal antibody in addition to chemotherapy produced an improvement in survival compared with chemotherapy alone, changing the clinical outcomes of this type of breast tumor (4). The first one of these anti-HER2 monoclonal antibodies, trastuzumab, has higher pathological complete response (pCR) rates when used concurrently with anthracyclines compared to its non-concurrent use, as indicated in a meta-analysis of 5 studies [odds ratio (OR): 2.36; 95% CI: 1.69-3.30] (5).

Pertuzumab was Food and Drug Administration (FDA)-approved for use as a neoadjuvant treatment after the results of the NEOSPHERE and TRYPHAENA trials (6). Although trastuzumab and pertuzumab share the same target, these antibodies lack pharmacokinetic drug-drug interactions and they have complementary mechanisms to increase the anti-proliferative activity and as a consequence

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improve the clinical prognosis (7). One systematic review on stage I-III HER2-positive breast cancer indicated a higher rate of pCR among patients with pertuzumab and trastuzumab compared with those on trastuzumab alone (OR=1.33; 95% CI, 1.08-1.63) (8). Regarding its safety, treatment with trastuzumab and pertuzumab had a manageable toxicity profile with rare events of significant toxicity even in combination with anthracyclines (9). In addition, this combination represents an attractive cost-effective therapy for patients with HER2-positive early breast cancer (10).

After the therapeutic success of phase II trials on neoadjuvant therapy, the FDA approved pertuzumab, and since then, numerous phase III studies have been performed; in addition, an increasing number of studies on pertuzumab with real-world data were performed with the aim to evaluate whether the results obtained in trials are similar to those from routine clinical practice (11-14). However, evidence from low- and middle-income countries (LMICs) is currently lacking, and hence, the present study was implemented to estimate the rates of pCR in patients with HER2-positive non-metastatic breast cancer treated according to clinical routine in Peru with pertuzumab with neoadjuvant chemotherapy.

Materials and methods

Study design. NeoHer is a multicenter observational study, which aims to evaluate the use of pertuzumab in addition to neoadjuvant chemotherapy and concomitant trastuzumab in patients with HER2-positive non-metastatic breast cancer treated in the clinical routine. The independent Institutional Review Board (IRB) of Via Libre (Lima, Peru) approved the protocol of the present study. This IRB is properly accredited and registered by the National Institute of Health of Peru.

Patients. The clinical records of patients with breast cancer from three private clinics in Lima (Peru), namely Oncosalud-AUNA, Clinica Internacional and Aliada, between January 2014 and December 2016, were retrospectively reviewed. The inclusion criteria were as follows: Female patients aged ≥18 years with a pathological diagnosis of non-metastatic HER2+ breast cancer (regardless of hormone receptor status), treatment with any regimen that included pertuzumab in addition to neoadjuvant chemotherapy and trastuzumab, and patients who were subjected to breast surgery after neoadjuvant treatment. Patients with concomitant cancer treatment or a history of another malignancy were excluded.

The assessment of the estrogen receptor (ER), progesterone receptor (PR) and HER2 status was only performed in core biopsies and it was not centralized. All procedures were conducted according to local protocols following the American Society of Clinical Oncology/College of American Pathologists guidelines (15).

Study variables. The primary variable was the pCR status (classified as yes or no). pCR is defined as the absence of residual invasive cancer on H&E evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy [i.e., ypT0/Tis ypN0 in the current American Joint Committee on Cancer (AJCC) staging system], or as the absence of residual invasive and *in situ*

Table I. Clinicopathological characteristics of the patients and patterns of treatment in Peruvian patients with non-metastatic human epidermal growth factor receptor 2-positive breast cancer receiving pertuzumab in the neoadjuvant setting (n=44).

Characteristic	Value
Median age, years (IQR)	44.0 (39.5-50.5)
Median BMI, kg/m^2 (IQR)	24.0 (21.9-28.8)
Menopausal status	
Premenopausal	29 (65.9)
Postmenopausal	15 (34.1)
Smoking status	
Non-smokers	42 (94.4)
Smokers	2 (4.6)
Family history	
No	30 (68.2)
Yes	14 (31.8)
Comorbidity	
No	36 (81.8)
Yes	8 (18.2)
Median tumor size, mm (IQR)	45.5 (38.8-60.0)
T stage	
T1	1 (2.3)
T2	20 (45.4)
T3	16 (36.4)
T4	7 (15.9)
N stage	
N0	14 (31.8)
N1	24 (54.6)
N2	6 (13.6)
Clinical stage	
IIA/IIB	25 (56.8)
IIIA/IIIB/IIIC	16 (36.4)
Inflammatory	3 (6.8)
Histology	
Ductal	39 (88.6)
Others (non-lobular)	5 (11.4)
Histological grade	
GII	20 (45.4)
GIII	23 (52.3)
Unknown	1 (2.3)
Hormone-receptor status	
ER-positive and/or PR-positive	24 (54.5)
ER-negative and PR-negative	20 (45.5)
Neoadjuvant scheme	
THP-based	30 (68,2)
THPCarb-based	14 (31,8)
THP median number of cycles (min-max)	4 (2-6)
THPCarb median number of cycles (min-max)	6 (4-15)
Type of surgery	
Mastectomy	31 (70.5)
Breast-conserving	13 (29.5)

Values are expressed as n (%) unless otherwise specified. BMI, body mass index; IQR, interquartile range; min-max, minimum-maximum values; ER, estrogen receptor; PR, progesterone receptor; THP, docetaxel/trastuzumab/pertuzumab; THPCarb, docetaxel/trastuzumab/pertuzumab/carboplatin.

Table II. Analysis of variables influencing the pCR in patients with human epidermal growth factor receptor 2-positive breast cancer treated with neoadjuvant pertuzumab.

	Residual disease			pCR		
Characteristic	THP (n=10)	THPCarb (n=3)	Total (n=13)	THP (n=20)	THPCarb (n=11)	Total (n=31)
Median tumor size, mm (IQR)	50.0 (30.0-100.0)	46.0 (40.0-150.0)	46.0 (40.0-60.0)	47.5 (40.0-60.0)	36.1 (30.0-55.0)	45 (35.0-60.0)
Median BMI, kg/m^2	24.0 (21.6-45.0)	25.4 (21.9-27.2)	24.7 (21.9-28.5)	23.3 (22.0-27.3)	24.5 (23.0-30.7)	23.9 (22.2-28.8)
T stage						
T1/T2	4 (19.0)	1 (4.8)	5 (23.8)	8 (38.1)	8 (38.1)	16 (76.2)
T3/T4	6 (26.1)	2 (8.7)	8 (34.8)	12 (52.2)	3 (13.0)	15 (65.2)
N stage						
N0	4 (28.6)	0 (0.0)	4 (28.6)	6 (42.9)	4 (28.6)	10 (71.4)
N1/N2	6 (20.0)	3 (10.0)	9 (30.0)	14 (46.7)	7 (23.3)	21 (70.0)
Clinical stage						
IIA/IIB	7 (28.0)	1 (4.0)	8 (32.0)	9 (36.0)	8 (32.0)	17 (68.0)
IIIA/IIIB/IIIC	2 (12.5)	2 (12.5)	4 (25.0)	9 (56.3)	3 (18.8)	12 (75.0)
Histology						
Ductal	10 (25.6)	2 (5.2)	12 (30.8)	19 (48.7)	8 (20.5)	27 (69.2)
Others (non-lobular)	0 (0.0)	1 (20.0)	1 (20.0)	1 (20.0)	3 (60.0)	4 (80.0)
Histological grade						
GII	5 (25.0)	1 (5.0)	6 (30.0)	10 (50.0)	4 (20.0)	14 (70.0)
GIII	5 (21.7)	2 (8.7)	7 (30.4)	9 (39.1)	7 (30.4)	16 (69.6)
Hormone-receptor status						
ER-positive and/or PR-positive	7 (29.1)	1 (4.2)	8 (33.3)	8 (33.3)	8 (33.3)	16 (66.7)
ER-negative and PR-negative	3 (15.0)	2 (10.0)	5 (25.0)	12 (60.0)	3 (15.0)	15 (75.0)

Values are expressed as n (%) unless otherwise specified. BMI, body mass index; IQR, interquartile range; ER, estrogen receptor; PR, progesterone receptor; THP, docetaxel/trastuzumab/pertuzumab; THPCarb, docetaxel/trastuzumab/pertuzumab/carboplatin; pCR, pathological complete response.

cancer on H&E evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0 ypN0 in the current AJCC staging system) (16). The type of breast surgery was dependent on the mastologist's decision based on local practice and the decision regarding axillary dissection was made according to the status of sentinel lymph node assessment.

Secondary variables included age at diagnosis, body mass index (BMI), smoking status, family history of breast cancer, comorbidities, regimen of neoadjuvant chemotherapy, type of surgery, treatment discontinuation, dose interruption, hormone receptor status, menopausal status, tumor size, tumor node metastasis (TNM by the AJCC staging system) and clinical stage, status of lymph nodes, histological type, histological grade and adverse events (AE) according to the Common Terminology Criteria for AE, v. 5.0 (17).

Statistical analysis. A descriptive analysis of the data was performed. A convenience sample was analyzed comprising cases treated with neoadjuvant pertuzumab during the study treatment. Analyses were performed with Stata 16.0 (StataCorp LP).

Results

Clinicopathological features. In total, 44 patients with HER2-positive breast cancer were identified during the study period and included in the present retrospective review. The median age was 44.0 years [interquartile range (IQR), 39.5-50.5 years] and the median BMI was 24.0 kg/m^2 (IQR, 21.9-28.8 kg/m^2). In total, 15 patients (34.1%) were postmenopausal. The clinicopathological characteristics of the patients are provided in Table I.

The median tumor size was 45.5 mm (IQR, 38.8-60.0 mm). Regarding tumor stage, the most frequent was T2 (45.4%; n=20) and in terms of regional lymph node stage, N1 was the most frequent (54.6%; n=24) (Table I). Patients with clinical stages IIA/IIB were more frequent (56.8%; n=25) and three cases presented with inflammatory disease (6.8%). Furthermore, 88.6% (n=39) of tumors had ductal histology, and regarding grading, 45.4% (n=20) of cases had grade II tumors and 52.3% (n=23) grade III tumors. A total of 54.5% (n=24) of tumors had expression of hormonal receptors (Table I).

Treatments. All cases received pertuzumab concurrently with trastuzumab in different schemes as described in Table I. The most frequent scheme was neoadjuvant docetaxel/trastuzumab/pertuzumab (THP; 68.2%, n=30). Of these patients, 3 were initiated with doxorubicin-based chemotherapy while awaiting approval of dual-HER2 treatment by the insurance company; however, after completion of this chemotherapy, they received the dual blockade. A total of 14 participants (31.8%) were treated with docetaxel/trastuzumab/pertuzumab/carboplatin (THPCarb) (Table I). Mastectomy was performed in 70.5% (n=31) of patients and 29.5% had breast-conserving surgery (n=13). A total of 31 patients (70.5%) achieved pCR; among the hormone receptor-negative cases, 75% achieved pCR and in tumors expressing hormone receptors, the pCR rate was 66.7% (Table II). Of those patients who received neoadjuvant treatment with THP, 66.7% achieved pCR, whereas in patients who received THPCarb, the pCR rate was 78.6%.

Safety of pertuzumab. Any AEs were experienced in 26 patients (59.1%). Among them, 88.5% (n=23) presented with grade 1 AEs, 61.5% (n=16) with grade 2 AEs and 26.9% (n=7) with grade 3 AEs. Diarrhea was the most frequent adverse event (36.4%; n=16), and of the affected patients, 93.8% (n=15) presented with diarrhea grade 1, 43.8% (n=7) with grade 2 and 31.3% (n=5) with grade 3. Nausea and vomiting were present in 31.8% (n=14) (Table III).

Table III. Adverse events related to treatment with pertuzumab.

Adverse event	Value
Any	26 (59.1)
Diarrhea	16
Nausea/vomiting	14
Neutropenia	5
Rash	5
Erythema	3
Mucositis	3
Dyspnea	3
Neuropathies	2
Dehydration	1
Febrile neutropenia	1
Bone pain	1
Lower-limb pain	1
Gastritis	1
Dry cough	1
Hypoalbuminemia	1
Decreased muscular strength	1
Multiple lesions in thorax and both legs	1
Itchy skin lesions	1
Hand-foot syndrome	1

Values are expressed as n (%) or n.

Discussion

The generation of real-world evidence in oncology provides a valuable tool to determine the performance of approved interventions in a setting different from clinical trials (18). The present study reported on the use of pertuzumab in patients treated in clinical routine in three private centers in Peru, where all patients received dual blockade of HER2 with combined treatment of pertuzumab and trastuzumab with concomitant chemotherapy. Higher rates of pCR (70.5%) in comparison with other studies performed in similar settings (even in clinical trials) were obtained. For instance, the NEOPSHERE study achieved a pCR rate of 45.8% with THP, compared with 29.0% of patients treated with a combination of trastuzumab plus docetaxel (19). Another study (TRYPHAENA) reported pCR rates of 63.6% in patients treated with THPCarb (Arm C) (20) (Table IV). A systematic review indicated that the combination of pertuzumab and trastuzumab in stage I-III HER2 positive had a higher pCR rate compared with the regiment without pertuzumab (OR=1.3; 95% CI: 1.1-1.6; n=1,448, 4 studies) (8).

Studies using routine clinical information from different settings described similar pCR rates to those reported in clinical trials: One study in Cleveland reported a 53% pCR in patients retrospectively identified in a cancer data registry (21); another at the Massachusetts General Hospital Cancer Center reviewed clinical information from 121 patients and reported a pCR of 63% with THPCarb (22). A recent multicentric study performed in patients from Germany indicated a pCR rate of 52.8% among those who used pertuzumab and trastuzumab, which was 22.6% higher compared with that in patients treated with trastuzumab only (23). Other important phase III studies are TRAIN-2 and KRISTINE: The first trial investigated whether the addition of anthracyclines is able to improve pCR compared to a carboplatin-taxane regimen (24). Patients were randomized to receive paclitaxel and carboplatin with trastuzumab and pertuzumab for nine cycles or an anthracycline-based regimen for three cycles, followed by THPCarb for six cycles. The proportion of patients with pCR (ypT0/is + ypN0) was 68% for the group without anthracycline and 67% for the group with anthracycline (P=0.95). The KRISTINE trial compared the efficacy of trastuzumab emtansine (T-DM1) plus pertuzumab, which did not comprise any systemic chemotherapy regimen, with docetaxel, carboplatin and trastuzumab plus pertuzumab (25). In this study, the proportion of patients with pCR (ypT0/is + ypN0) was lower with T-DM1 plus pertuzumab as compared with docetaxel, carboplatin and trastuzumab plus pertuzumab (44 vs. 56%, respectively; P=0.016).

The high rates of pCR obtained in the present study in contrast to those from other studies may be due to the heterogeneity in of HER2 patient populations and also differences in the definition of pCR, as indicated in Table III. Furthermore, the clinicopathological characteristics were different among

Table IV. Comparison of pCR in neoadjuvant trials including pertuzumab/trastuzumab with docetaxel + carboplatin.

Characteristic	NeoHer (n=44)	NeoSphere[a] (n=107)	TRYPHAE NA[b] (n=77)	KRISTINE (n=221)	TRAIN-2 (n=219)	JBCRG-20 (n=51)
Phase	IV	II	II	III	III	II
Median age, years (range)	44.0 (25-67)	50 (28.0-77.0)	50.0 (30.0-81.0)	49 (41-57)	48 (43-56)	53.0 (28-70)
Median tumor size, mm (IQR)	45.5 (38.8-60.0)	55 (20-150)	50 (15-200)	-	-	27.0 (11-58)
Regimen	THP or THPCarb	THP x 4	THPCarb x 6	THPCarb x 6	THPCarb x 9	THPCarb x 6
Definition of pCR	ypT0/is+ypN0	ypT0/is	ypT0/is+ypN0	ypT0/is+ypN0	ypT0/is+ypN0	ypT0/is+ypN0
pCR	31 (70.5)	49 (45.8)	49 (63.6)	123 (56)	140 (68.0)[c]	29 (56.9)
N stage						
N0	14 (31.8)	31 (29)[d]	-	-	76 (35.0)	34 (66.7)
N1	24 (54.6)	53 (50)[d]	-	-	-	17 (33.3)
N2	6 (13.6)	22 (21)[d]	-	-	-	-
N3	0 (0)	0 (0)	-	-	-	-
Disease type[e]						
Operable	32 (72.7)	65 (61)	49 (63.6)	-	-	-
Locally advanced	8 (18.2)	32 (30)	24 (31.2)	-	-	-
Inflammatory	3 (6.8)	10 (9)	4 (5.2)	-	-	-
Hormone receptor status						
ER-positive and/or PR-positive	24 (54.5)	50 (47)	40 (51.9)	138 (62.4)	126 (58.0)	30 (58.8)
ER-negative and PR-negative	20 (45.5)	57 (53)	37 (48.1)	83 (37.6)	93 (42.0)	21 (41.2)

[a]NeoSphere Arm Group B (Pertuzumab plus trastuzumab and docetaxel). [b]TRYPHAENA Arm C (TCH + P X 6). [c]Based on 206 patients who were evaluable for the primary endpoint. If all non-evaluable patients were classified as no response, the percentage is 64%. [d]Data missing for one patient (information from NeoSphere study). [e]Operable (T2-3, N0-1, M0), locally advanced (T2-3, N2-3, M0 or T4a-c, any N, M0), inflammatory (T4d, any N, M0). Values are expressed as n (%) unless otherwise specified. IQR, interquartile range; ER, estrogen receptor; PR, progesterone receptor; THP, docetaxel/trastuzumab/pertuzumab; THPCarb, docetaxel/trastuzumab/pertuzumab/carboplatin; pCR, pathological complete response.

studies. For instance, compared with those in other previously published studies, the patients of the present study were younger and tumors were smaller (21,23-25).

Regarding safety, the present study suggested that the combination of pertuzumab plus trastuzumab in neoadjuvant regimes has a manageable toxicity profile without any cardiac events registered. The safety of this combination has been extensively evaluated even in older patients without any important differences with regard to younger patients (26,27). Certain studies have reported significantly lower rates of events of toxicity with the combination of pertuzumab and trastuzumab given with taxanes instead of with anthracyclines (22).

The search for biomarkers for pertuzumab is ongoing, and at present, the best predictor of response is molecular subtype HER2-enriched status (as established by PAM50), where for these types of tumor, a pCR of 83.3% was achieved, in contrast to 46.3% for non-HER2-enriched tumors (OR=5.8, 95% CI: 1.7-19.4). Rates of pCR varied according to intrinsic subtype determined at baseline (28). The Blueprint platform was also able to identify patients who were HER2-positive on immunohistochemistry that are more likely to respond to the combination of trastuzumab/pertuzumab (29) and other studies, such as the BERENICE trial, evaluating pertuzumab, trastuzumab and chemotherapy in patients with normal cardiac function, described similar results (30).

The frequency of residual disease was higher among patients with hormone receptor-positive status (33.3%) in comparison with hormone receptor-negative patients (25%). As in other clinical trials, the rates of pCR were low in the presence of hormone receptors and this is related to the type of neoadjuvant scheme.

Despite the cost-effectiveness described in the US or in Canada for the combination of pertuzumab and trastuzumab, certain studies performed in Latin America point at the lack of cost-effectiveness from a public health perspective (10,31,32).

The present study has certain limitations, including a small sample size that increased the risk of chance in the present results, a retrospective design that increased the risk of information bias and unmeasured confounders, and heterogeneous regimens of coadjutant chemotherapy treatment that make comparisons difficult in terms of adverse events and efficacy. However, the present study was the first, to the best of our knowledge, to evaluate and describe the use of pertuzumab in routine clinical use among Peruvian patients, with a high pCR

rate and an interesting safety profile; therefore, this real-world experience may help to refine and improve the potential use of pertuzumab in combination with trastuzumab in Peru and in similar settings at LMICs.

In conclusion, the neoadjuvant treatment of patients with HER2-positive non-metastatic breast cancer treated in the clinical routine in Peru with schemes based on the combination of trastuzumab and pertuzumab achieved a high rate of pCR even in tumors expressing hormone receptors, with a manageable profile of AEs. Further studies with larger samples and different populations are required to confirm these results.

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Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors contributed to the conception and design of the study. Material preparation and data collection were performed by SF, LR, CF, DV and HLG. The authenticity of raw data was verified by CF, DV and JAP. Data analysis was performed by DV and JAP. The first draft of the manuscript was written by JAP. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The IRB of Via Libre (Lima, Peru) approved the protocol of the present study. This study did not require any informed consent, as it was based on the review of medical charts only.

Patient consent for publication

Not applicable.

Competing interests

CF was an employee of Roche-Peru until mid-2019. Note that the funder of the study (Roche) participated in the design of the study. Data collection was performed by researchers working at the study sites. The data analysis was performed by an independent specialist paid by the funder. Finally, the corresponding author (HLG) prepared the initial draft of the report with support from a medical writer paid by the funder.

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