

Neoadjuvant therapy for early human epidermal growth factor receptor 2 positive breast cancer in China: A multicenter real-world study (CSBrS-015)

Yuanjia Cheng, Hongyu Xiang, Ling Xin, Xuening Duan, Yinhua Liu; Chinese Society of Breast Surgery (CSBrS), Chinese Society of Surgery of Chinese Medical Association

Breast Disease Center, Peking University First Hospital, Beijing 100034, China.

Abstract

Background: Pertuzumab has been approved for application in China by the National Medical Products Administration, and both national and international guidelines make recommendations for the use of neoadjuvant treatment with trastuzumab or trastuzumab + pertuzumab plus chemotherapy regimens for patients with indications. The goal of this study was to investigate the short-term clinical efficacy of the neoadjuvant therapies trastuzumab and trastuzumab+pertuzumab for patients with early human epidermal growth factor receptor 2 (HER2)-positive breast cancer in China.

Methods: A real-world study was conducted using the clinicopathological data of patients with early HER2-positive breast cancer who were admitted to the member hospitals of the Chinese Society of Breast Surgery, Chinese Surgical Society of Chinese Medical Association between March 2019 and December 2020. This study analyzed the efficacy and tolerance of trastuzumab + chemotherapy and trastuzumab+pertuzumab+chemotherapy in patients with early HER2-positive breast cancer. The Response Evaluation Criteria in Solid Tumors 1.1 was adopted to evaluate clinical efficacy. The pathological efficacy was evaluated using the MillerPayne grade. The Common Terminology Criteria for Adverse Events (version 5.0) was adopted to evaluate adverse events (AEs). The propensity scores were subjected to propensity score matching using the R language (1:1 matching with a maximum allowable difference of 0.05 between the two groups). Efficacy was compared using the chi-square test, and correlation analysis was performed using linear regression.

Results: A total of 1032 patients with early HER2-positive breast cancer met the enrollment criteria and were included in this study. Among these patients, 472 received neoadjuvant trastuzumab+chemotherapy (the trastuzumab group), and 560 received neoadjuvant trastuzumab+pertuzumab+chemotherapy (the trastuzumab+pertuzumab group). The overall pathologic complete response (pCR) rate was 47.2% (487/1032), while the pCR rates of the trastuzumab and trastuzumab+pertuzumab groups were 34.5% (163/472) and 57.9% (324/560), respectively, and the difference was significant ($P < 0.001$). The incidence of grade 4 AEs was 24/321 (7.5%) in the trastuzumab+pertuzumab group, and there were no cases in which the left ventricular ejection fraction decreased by more than 10%.

Conclusions: Patients in the trastuzumab+pertuzumab group had a higher pCR rate than those in the trastuzumab group, and the toxic side effects were tolerable.

Keywords: Breast neoplasms; Molecular targeted therapy; Multicenter study; Neoadjuvant therapy; Human epidermal growth factor receptor 2 (HER2); Trastuzumab; Pertuzumab

Introduction

A few clinical studies and meta-analyses have confirmed that a pathologic complete response (pCR) rate of 30% to 60% can be achieved in patients with early human epidermal growth factor receptor 2 (HER2)-positive breast cancer who have received neoadjuvant therapies, including trastuzumab + chemotherapy and trastuzumab

+ pertuzumab + chemotherapy.^[1-3] And such neoadjuvant therapies are also beneficial to overall survival (OS) and disease-free survival (DFS).^[3,4] In China's perspective, National Medical Products Administration (NMPA) approved the use of pertuzumab as neoadjuvant therapy for early HER2-positive breast cancer as early as March 2019. In 2021, the Breast Cancer Diagnosis and Treatment Guidelines of the Chinese Society of Clinical Oncology (CSCO) recommended, with a high level of

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.1097/CM9.0000000000002197

Correspondence to: Prof. Yinhua Liu, Breast Disease Center, Peking University First Hospital, Beijing 100034, China
E-Mail: liuyinhua7520@163.com

Copyright © 2022 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2022;135(19)

Received: 07-11-2022; Online: 20-10-2022 Edited by: Yuanyuan Ji

supporting evidence, that early HER2-positive breast cancer with indications should receive neoadjuvant therapies, including trastuzumab + chemotherapy and trastuzumab + pertuzumab + chemotherapy. However, to date, there have been few reports on the clinical efficacy of these neoadjuvant therapies in HER2-positive breast cancer in different regions of China. The Chinese Society of Breast Surgery (CSBrS), therefore, conducted a multicenter study (CSBrS-015) of the clinicopathological data of patients with early HER2-positive breast cancer who received neoadjuvant trastuzumab + chemotherapy or trastuzumab + pertuzumab + chemotherapy at 30 hospitals between March 2019 and December 2020 and analyzed the short-term efficacy and toxic side effects of these neoadjuvant therapies. The purpose of the study was to promote the standardization of the use of neoadjuvant therapy for early HER2-positive breast cancer in China.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the local ethics committee of Peking University First Hospital (No. 2021-152). This clinical study was a retrospective study, collected only the patients' clinical data, and did not interfere with the patients' treatment plans. Therefore, this study did not pose physical risks to the patients. In addition, patient information was protected from being leaked. The application for exemption of informed consent was submitted, and the exemption was approved.

Subjects

In March 2019, the NMPA approved the use of pertuzumab as neoadjuvant therapy for early HER2-positive breast cancer. Therefore, the subjects selected for this study were patients diagnosed with early HER2-positive invasive breast cancer who received neoadjuvant trastuzumab + chemotherapy or trastuzumab + pertuzumab + chemotherapy at member hospitals of the CSBrS between March 1, 2019 and December 31, 2020.

Participating units

The CSBrS includes 40 Grade A tertiary hospitals, all of which have independent breast surgery wards. A total of 30 member hospitals participated in this study and provided valid cases.

Inclusion criteria

The inclusion criteria were as follows: A diagnosis of HER2-positive female breast cancer by core needle biopsy; indications for neoadjuvant therapy^[5,6]; neoadjuvant therapy with trastuzumab + chemotherapy or trastuzumab + pertuzumab + chemotherapy according to the National Comprehensive Cancer Network (NCCN) Breast Cancer Clinical Practice Guidelines or the CSCO Breast Cancer Diagnosis and Treatment Guidelines; at least of four cycles of the neoadjuvant therapy and the scheduled surgical treatment; and complete clinicopathological data. Among

the patients included in this study, those who received neoadjuvant trastuzumab + chemotherapy comprised the trastuzumab group, while those who received neoadjuvant trastuzumab + pertuzumab + chemotherapy comprised the trastuzumab + pertuzumab group.

Exclusion criteria

The exclusion criteria were as follows: distant metastasis; incomplete clinicopathological data; fewer than four cycles of neoadjuvant therapy; or incomplete surgical treatment.

Determination of HER2 positivity

Immunohistochemistry (IHC) results were interpreted according to the 2018 American Society of Clinical Oncology/American Society of Pathology HER2 guidelines.^[7] The evaluation criteria for HER2 staining results were as follows: 0/1+ (negative): no stained cells, or the tumor cells displayed blurred/weak and incomplete cell membrane staining; 2+ (uncertain): >10% of the tumor cells displayed weak/moderate but intact cell membrane staining; 3+ (positive): >10% of the tumor cells showed strong and intact cell membrane staining. For patients with uncertain IHC results (2+), fluorescence *in situ* hybridization was further performed, and the evaluation criteria were as follows: HER2 positive: HER2/Chromosome 17 centromere (CEP17) ratio ≥ 2 and average HER2 copy number ≥ 4.0 signals/cell, or average HER2 copy number ≥ 6.0 signals/cell; HER2 negative: HER2/CEP17 ratio ≥ 2 and average HER2 copy number <4.0 signals/cell, or HER2/CEP17 ratio <2.0 and average HER2 copy number <6.0 signals/cell.

Neoadjuvant therapies

The NCCN Breast Cancer Clinical Practice Guidelines and the CSCO Breast Cancer Diagnosis and Treatment Guidelines^[5,6] recommend the following neoadjuvant therapies of trastuzumab and chemotherapy [Table 1]: The TCbH regimen (taxanes + carboplatin + trastuzumab), TH regimen (taxanes + trastuzumab), AC-TH regimen (anthracyclines + cyclophosphamide, sequential taxanes + trastuzumab), and TC + H regimen (taxanes + cyclophosphamide + trastuzumab). Neoadjuvant therapies combining trastuzumab + pertuzumab with chemotherapy include the TCbHP regimen (taxanes + carboplatin + trastuzumab + pertuzumab), THP regimen (taxanes + trastuzumab + pertuzumab), and AC-THP regimen (anthracyclines + cyclophosphamide, taxanes + trastuzumab + pertuzumab).

Before each cycle of the neoadjuvant therapy, the patients underwent routine peripheral blood tests and biochemical examinations to confirm that there were no contraindications to chemotherapy. After chemotherapy, the patients were given granulocyte colony-stimulating factor if needed. The left ventricular ejection fraction (LVEF) of the patients was evaluated by echocardiography before and every 3 months after the therapy. The patients received at least four cycles of therapy with the targeted drugs in addition to surgery.

Table 1: The regimens for the 1032 patients with early HER2-positive breast cancer.

Groups	Number of patients treated (%)	Evaluation of pathological efficacy	
		Number of patients who achieved pCR	pCR rate (%)
Trastuzumab group			
TH	22 (2.1)	6	27.3
TCbH	273 (26.5)	96	35.2
AC/EC-TH	161 (15.6)	58	36.0
TC (CTX) H	16 (1.6)	3	18.8
Trastuzumab + pertuzumab group			
THP	77 (7.5)	47	61.0
TCbHP	319 (30.9)	183	57.4
AC/EC-THP	164 (15.9)	94	57.3

HER2: Human epidermal growth factor receptor 2; pCR: Pathologic complete response. TH regimen: taxanes + trastuzumab; TCbH regimen: taxanes + carboplatin + trastuzumab; THP regimen: taxanes + trastuzumab + pertuzumab; TCbHP regimen: taxanes + carboplatin + trastuzumab + pertuzumab; AC/EC-TH: pirarubicin/epirubicin followed by taxanes + trastuzumab; TC(CTX)H: taxanes + cyclophosphamide + trastuzumab; AC/EC-THP: pirarubicin/epirubicin followed by taxanes + trastuzumab + pertuzumab.

Evaluation of efficacy

The Response Evaluation Criteria in Solid Tumors 1.1 was adopted to evaluate clinical efficacy.^[8] The breast lesions were evaluated before the neoadjuvant therapy and after every two cycles of the therapy using dynamic contrast-enhanced magnetic resonance imaging or breast ultrasound. The pathological efficacy was evaluated using the Miller-Payne grade,^[9] and core needle biopsy specimens collected before the neoadjuvant therapy were compared with histopathological specimens collected after the surgery. pCR was defined as the absence of invasive cancer in the breast and axillary lymph nodes (ypTis/0ypN0).

Surgery

Surgery was performed within 4 weeks after the last chemotherapy session. cN0 patients who had a negative sentinel lymph node biopsy before the neoadjuvant therapy did not undergo axillary lymph node dissection. After receiving neoadjuvant therapy, pN1 patients underwent level II axillary lymph node dissection. The typical surgical methods include breast-conserving surgery, simple mastectomy, and modified radical mastectomy (Auchincloss). Breast reconstruction surgery will be performed on patients who are willing to preserve the shape of the breast but do not have the conditions for breast conserving.

Safety evaluation

The Common Terminology Criteria for Adverse Events (version 5.0) were adopted to evaluate adverse events (AEs). Evaluation of the respiratory, circulatory, digestive, blood, skin, and urinary system was performed. The following classification of AEs was used: Grade 1 AEs are minor AEs that are asymptomatic or mild, have only clinical or diagnostic findings, and require no treatment. Grade 2 AEs are moderate AEs that limit the performance of age-appropriate instrumental activities of daily living and require minor, local, or non-invasive treatment. Grade 3 AEs are severe or medically significant but not immediately life-threatening, could lead to hospitalization or prolongation of hospitalization, are disabling, and could

limit self-care activities of daily living. Grade 4 AEs are life-threatening and require urgent treatment. Grade 5 AEs are AE-related deaths. The clinicians collected the relevant AEs after each cycle of therapy through telephone calls, social media software, and questionnaires. The types and severity of the patients' AEs were evaluated and recorded.

Statistical analysis

Data analysis was performed using SPSS 26.0 statistical software (IBM, Armonk, NY, USA) and the R language (RStudio, Boston, MA, USA). Measurement data are described as the minimum, maximum, median, and quartiles, while count and grade data are described as case numbers and percentages. The propensity scores were subjected to propensity score matching (PSM) using the R language (1:1 matching with a maximum allowable difference of 0.05 between the two groups). Efficacy was compared using the Chi-square test, and correlation analysis was performed using linear regression. A *P* value <0.05 indicated that the difference was statistically significant.

Results

General information

From 1 March 2019 to 31 December 2020, 30 member hospitals of the CSBrS participated in this study, of which a total of 27,455 patients were diagnosed with early invasive breast cancer. Among those patients, 6135 had HER2-positive breast cancer, accounting for 22.3% of the patients with invasive breast cancer during the same period. A total of 1838 patients received trastuzumab + chemotherapy or trastuzumab + pertuzumab + chemotherapy neoadjuvant therapies, accounting for 30.0% of the patients with early HER2-positive breast cancer. And each hospital has a different ratio, which varies from a range of 1.9% to 67.6% [Figure 1]. Excluding unqualified cases, a total of 1032 patients who met the inclusion criteria were included in this study [Table 2, Figure 2]. The median age of the patients was 50 years (range: 21–77 years; interquartile range: 43–56 years).

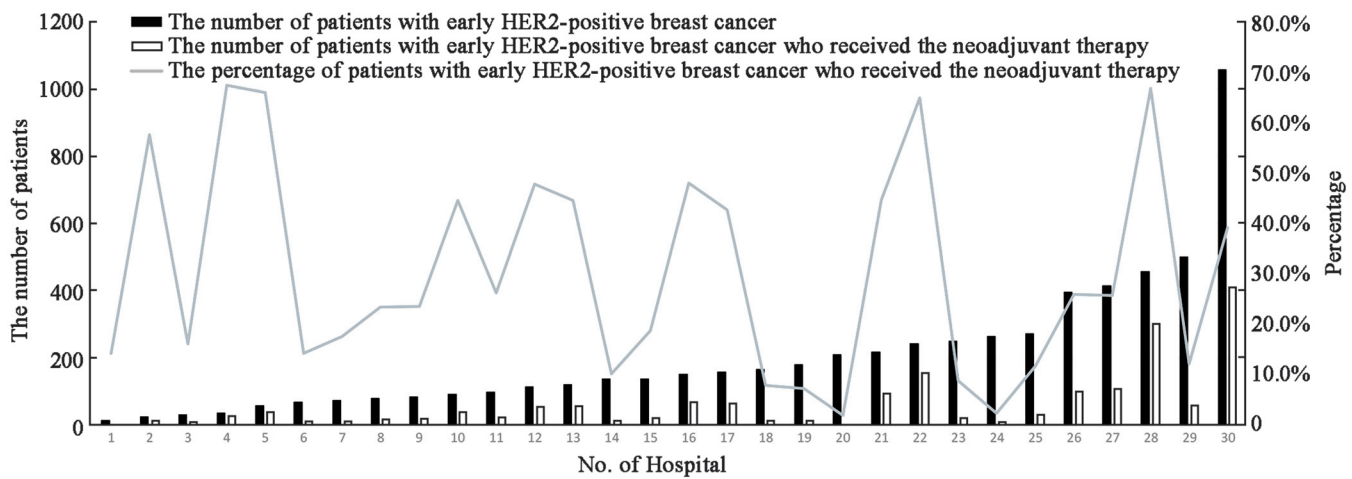


Figure 1: The percentages of patients with early HER2-positive breast cancer who received the neoadjuvant therapy at 30 hospitals in China. HER2: Human epidermal growth factor receptor 2.

Table 2: Clinicopathological data of patients with early HER2-positive breast cancer before and after PSM.

Items	Before matching (N = 1032)		P values	After matching (N = 798)		P values
	Trastuzumab group (n = 472)	Trastuzumab + pertuzumab group (n = 560)		Trastuzumab group (n = 399)	Trastuzumab + pertuzumab group (n = 399)	
Age			<0.001			1.000
<35 years	31 (3.0%)	78 (7.6%)		30 (3.8%)	31 (3.9%)	
≥35 years	441 (42.7%)	482 (46.7%)		369 (46.2%)	368 (46.1%)	
T stage			<0.050			0.436
T1	61 (5.9%)	49 (4.7%)		47 (5.9%)	37 (4.6%)	
T2	330 (32.0%)	393 (38.1%)		297 (37.2%)	298 (37.3%)	
T3	64 (6.2%)	79 (7.7%)		42 (6.2%)	44 (5.5%)	
T4	17 (1.6%)	39 (3.8%)		13 (1.6%)	20 (2.5%)	
N stage			<0.001			0.671
N0	189 (18.3%)	132 (12.8%)		128 (16.0%)	128 (16.0%)	
N1 + N1mi	222 (21.5%)	269 (26.1%)		210 (26.3%)	220 (27.6%)	
N2	43 (4.2%)	85 (8.2%)		43 (5.4%)	33 (4.1%)	
N3	18 (1.7%)	74 (7.2%)		18 (2.3%)	18 (2.3%)	
Clinical stage			<0.001			1.000
Stage I	16 (1.6%)	5 (0.5%)		5 (0.6%)	5 (0.6%)	
Stage II	357 (34.6%)	340 (32.9%)		304 (38.1%)	304 (38.1%)	
Stage III	99 (9.6%)	215 (20.8%)		90 (11.3%)	90 (11.3%)	
Hormone receptor status			0.204			1.000
HR+	284 (27.5%)	315 (30.5%)		227 (28.4%)	228 (28.6%)	
HR-	188 (18.2%)	245 (23.7%)		172 (21.6%)	171 (21.4%)	

Data were presented as n (%). HER2: Human epidermal growth factor receptor 2; PSM: Propensity score matching; HR: Hormone receptor.

Comparison of clinical data

A total of 1032 patients who met the inclusion criteria were included in this study. Among these patients, 472 (45.7%) were included in the trastuzumab group, and 560 (54.3%) were included in the trastuzumab + pertuzumab group [Table 1]. In the initial data, there were statistical differences between the two groups in age, T stage, N stage, and clinical stage; however, there was no statistical difference in hormone receptor status. The 30 participating hospitals are distributed across 18 provinces, municipalities, and autonomous regions in China; there was no statistical correlation between the percentage of

patients who underwent trastuzumab + pertuzumab + chemotherapy neoadjuvant therapy and the regional economic development level (per capita gross domestic product [GDP]) ($P = 0.8$, $B = 3.9E-7$, $t = 0.3$).

Pathological efficacy of the neoadjuvant therapies

Evaluation of pathological efficacy and analysis of correlation factors were performed. The overall pCR rate was 47.2% (487/1032), and the pCR rates of the trastuzumab group and the trastuzumab + pertuzumab group were 34.5% (163/472) and 57.9% (324/560),

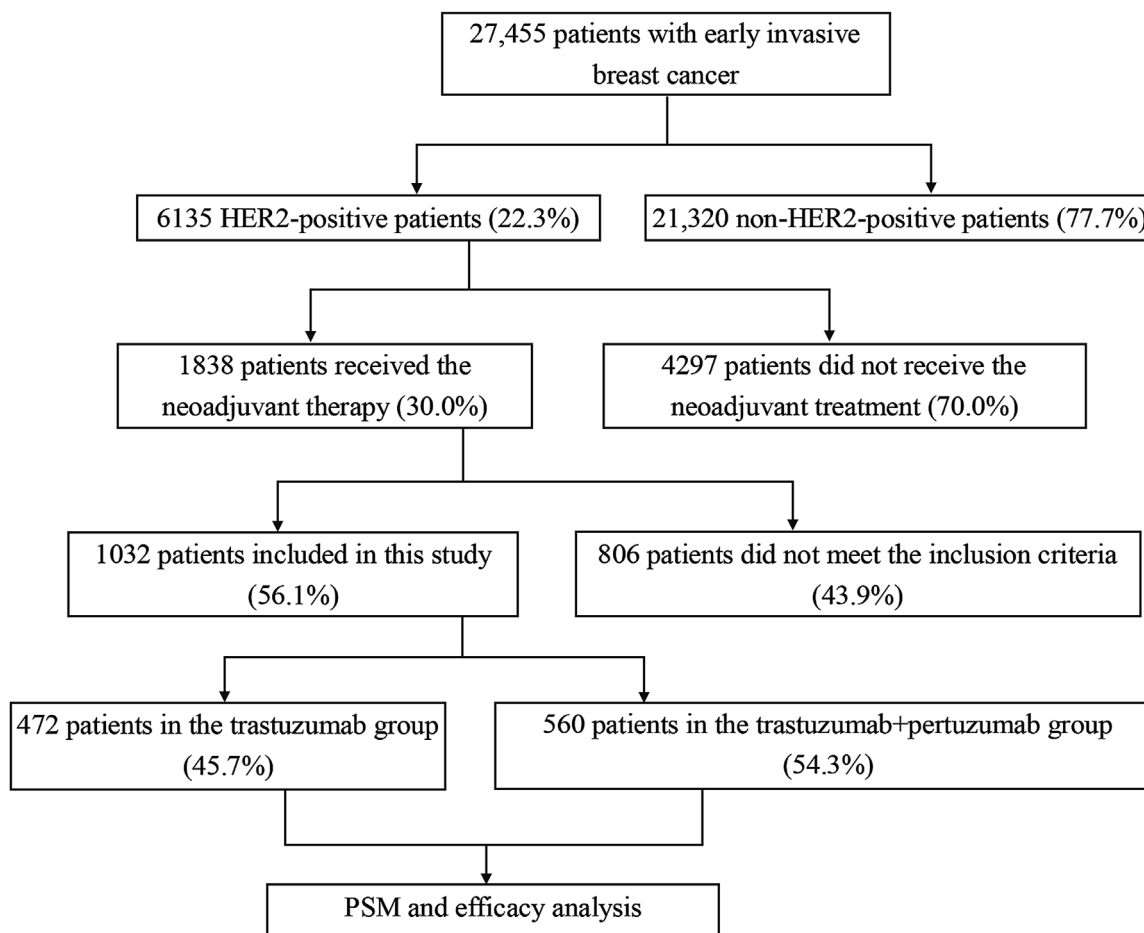


Figure 2: Flow chart of inclusion of the study subjects. PSM: Propensity score matching. HER2: Human epidermal growth factor receptor 2.

Table 3: Comparison of pathological efficacy between the two groups after PSM (n).

Categories	pCR	non-pCR	Total	Pearson Chi-square	P value
Trastuzumab group	140	259	399	20.6	<0.001
Trastuzumab + pertuzumab group	227	172	399		
Total	367	431	798		

pCR: Pathologic complete response; PSM: Propensity score matching.

respectively. After confounding factors (age, T stage, N stage, clinical stage, and hormone receptor status) were eliminated and PSM was conducted, a total of 798 patients were included in the statistical analysis, and each group included 399 patients. There was a statistical difference in the pCR rate between the two groups ($P < 0.001$, $\chi^2 = 20.6$) [Table 3].

Safety evaluation of of trastuzumab + pertuzumab + chemotherapy

Among the 560 patients who completed the neoadjuvant therapy of trastuzumab + pertuzumab + chemotherapy, 321 had complete records of AEs. Specifically, 24 patients (7.5%) had Grade 4 AEs, and the others had AEs of Grade 3 or lower that did not delay the therapy. The top three AEs were reduced granulocyte count (31.2%), hair loss

(25.9%), and nausea and vomiting (22.1%) [Table 4]. No large decrease in LVEF (ie, >10%) or other serious cardiovascular AEs were observed in any of the patients at the enrollment or during follow-up.

Discussion

The incidence of breast cancer in China is increasing year by year,^[10] while 15% to 20% out of total breast cancer cases are HER2 positive.^[11] At present, trastuzumab and pertuzumab are both approved by the NMPA for marketing in China and are covered by social medical insurance, providing diversified treatment options for patients with HER2-positive breast cancer. In recent years, the recommendations from the NCCN Breast Cancer Clinical Practice Guidelines on neoadjuvant therapy for early HER2-positive breast cancer have been continuously updated. The medical practice in China is

Table 4: The main AEs of patients with early HER2-positive breast cancer before and after PSM (N= 321).

AE	Grade 1	Grade 2	Grade 3	Grade 4	Total	Percentage (%)
Reduced granulocyte count	31	30	23	16	100	31.2
Hair loss	4	6	73	0	83	25.9
Nausea and vomiting	28	31	10	2	71	22.1
Diarrhea	26	28	8	3	65	20.2
Numbness in hands and feet	24	14	0	0	38	11.8
Fatigue	28	3	0	0	31	9.7
Muscle pain/bone pain	18	9	1	0	28	8.7
Mucosal/skin changes	16	6	5	1	28	8.7
Liver damage	7	9	3	0	19	5.9
Constipation	9	1	3	0	13	4.0
Anemia	5	5	0	1	11	3.4
Reduced platelet count	0	7	1	1	9	2.8

Values were shown as *n* or percentage. AE: Adverse events.

consistently aligned, as CSCO Breast Cancer Diagnosis and Treatment Guidelines from 2021 recommended, with a high level of supporting evidence, that patients with early HER2-positive breast cancer should receive neoadjuvant trastuzumab + chemotherapy or trastuzumab + pertuzumab + chemotherapy.^[5,6] On this basis, the conducted multicenter study (CSBrS-015) in China by CSBrS demonstrates both real-world treatment practice status and result, which is meant to eventually widely confirm the regional treatment effect and accelerate the standardization of the use of neoadjuvant therapies for early HER2-positive breast cancer in China.

The CSBrS-015 study included a total of 27,455 patients with new-onset early invasive breast cancer at 30 member hospitals of the CSBrS between March 2019 and December 2020. Among these patients, 6135 had HER2-positive breast cancer, accounting for 22.3% of the breast cancer patients admitted during the same period; this number is consistent with the percentage of HER2-positive breast cancer cases reported in the literature.^[11]

In recent years, international and Chinese clinical practice guidelines have explicitly stated that early HER2-positive breast cancer ($\geq T2$ or $\geq N1$) is an indication for neoadjuvant therapy.^[5,6] A survey conducted in the United Kingdom showed that approximately 40% of patients with early HER2-positive breast cancer received neoadjuvant therapy,^[12] compared with the 26.9% reported in a study conducted in the United States.^[13] In the present study, 1838 (30.0%) out of 6135 patients with early HER2-positive breast cancer received various neoadjuvant therapy regimens. However, the proportion of patients receiving neoadjuvant therapy varied from 1.9% to 67.6% among different hospitals, showing a distributional difference. This phenomenon indicates that the clinical implementation of neoadjuvant therapy for early HER2-positive breast cancer needs to be further standardized in China.

The NeoSphere study published in 2012 established the role of the dual-targeted therapy of trastuzumab + pertuzumab in neoadjuvant therapy.^[11] The PEONY study, a phase III clinical trial based on an Asian population, preliminarily

demonstrated that dual-targeted therapy, as a form of neoadjuvant therapy, can significantly increase the pCR rate.^[14] A large-scale meta-analysis also proposed that dual-targeted therapy combined with neoadjuvant chemotherapy significantly increased the pCR rate.^[15] This study showed that age, N stage, and clinical stage (tumor-node-metastasis [TNM]) had an impact on clinicians' choice of trastuzumab + chemotherapy *vs.* trastuzumab + pertuzumab + chemotherapy as neoadjuvant therapy. Clinicians were more inclined to choose neoadjuvant therapy with trastuzumab + pertuzumab for patients who were younger than 35 years old and had N stage or clinically advanced cancers.

Selecting an effective neoadjuvant therapy specifically for early HER2-positive breast cancer can achieve a high pCR rate, and patients who achieve pCR can have a longer DFS and OS than patients who have not achieved pCR.^[3,4] Studies have shown that early HER2-positive breast cancer patients who receive trastuzumab + pertuzumab + chemotherapy have a pCR rate of 55% to 66.2%.^[2,15] In this study, neoadjuvant therapy with trastuzumab + chemotherapy yielded a pCR rate of 34.5%, compared to the pCR rate of 57.9% of neoadjuvant therapy of trastuzumab + pertuzumab + chemotherapy. The pCR rate of the dual-targeted therapy was significantly higher than that of the single-targeted therapy. After PSM, there was a statistical difference in the pCR rate between the two groups ($P < 0.001$, $\chi^2 = 20.6$), which is consistent with the literature reports.^[14,15] In our study, a total of 1032 patients received different neoadjuvant therapies. Specifically, 560 patients, 54.3% of the total 1032 received neoadjuvant therapy with trastuzumab + pertuzumab + chemotherapy, which yielded a high pCR rate. However, 45.7% of the patients received neoadjuvant therapy with trastuzumab + chemotherapy, which yielded an unsatisfactory pCR rate. We believe that the outcome confirms that in the Chinese population, the pCR rate of the standard dual-target treatment regimen is better than that of the single-target regimen, which is consistent with the general practice and cognition of the international clinical community. Scientifically and objectively determining the indications for neoadjuvant therapy and standardizing the implementation of neoadjuvant therapy provide an

important basis for improving the clinical diagnosis and treatment of early HER2-positive breast cancer. A few clinical trials have confirmed the clinical value of dual-targeted therapy (trastuzumab + pertuzumab) combined with chemotherapy. This study also demonstrated that, at the current stage, neoadjuvant therapy with trastuzumab + pertuzumab + chemotherapy can significantly improve the pCR rate. In addition, although the patients who received the dual-targeted neoadjuvant therapy were at more advanced clinical stages, a higher pCR rate was achieved nevertheless. These results also indicate the clinical value of dual-targeted neoadjuvant therapy. As a real-world study, this study found no correlation between the proportion of patients who received dual-targeted neoadjuvant therapy and the regional per capita GDP. Pertuzumab only recently became available on the market in China. In some regions of China, pertuzumab has not been added to the medical insurance formulary and is not available at hospital pharmacies; therefore, some patients still choose trastuzumab and chemotherapy as neoadjuvant therapy due to cost. In the meanwhile, clinicians need to pay constant attention to updating the treatment concept as well.

Studies have shown that the common AEs of neoadjuvant trastuzumab + pertuzumab + chemotherapy include hair loss, reduced granulocyte count, diarrhea, nausea and vomiting, anemia, and elevated transaminase level.^[1,14] In this study, the top three AEs were reduced granulocyte count (31.2%), hair loss (25.9%), and nausea and vomiting (22.1%). More than 30% of the patients developed granulocyte deficiency, and 5.4% developed Grade 4 myelosuppression. Granulocyte deficiency with fever can increase the mortality of patients and prolong the length of hospital stay; in addition, it is the main reason for the reduction or delay of chemotherapy.^[16] In this study, a total of 321 patients who received neoadjuvant trastuzumab + pertuzumab + chemotherapy had complete safety data during treatment. Of these patients, 24 (7.5%) had Grade 4 AEs, including 18 with Grade 4 myelosuppression. These findings are similar to other reports. All other AEs were Grade 3 and below, and none of them caused serious harm to the patients or delayed the therapy. The establishment of good clinical pharmacist supervision and follow-up system for high-risk patients, the strengthening of primary prevention, and the rational use of drugs such as recombinant human granulocyte colony-stimulating factor and pegylated recombinant human granulocyte colony-stimulating factor are the keys to effectively reducing the incidence of common hematological toxic events (such as granulocyte deficiency) and improving patient compliance and treatment continuity.

The overall safety of the dual-targeted neoadjuvant therapy considered in this study was consistent with that reported in the literature,^[1,14] and the toxic side effects of the neoadjuvant therapy were controllable. One study proposed that the high incidence of diarrhea associated with dual-targeted neoadjuvant therapy might be related to pertuzumab.^[15] In this study, the patients who received the dual-targeted neoadjuvant therapy had a high incidence of nausea, vomiting, and diarrhea. However, >80% of the AEs were Grade 1–2 and did not delay

treatment. The cardiac safety of targeted drug therapies has received ongoing attention, and regular cardiac ultrasound monitoring is necessary during treatment. No serious cardiovascular AEs, such as a decrease of >10% in the LVEF, were observed in this study. The neoadjuvant therapy displayed good cardiac safety, which is consistent with reports.^[1,14]

This study was a multicenter real-world study. Although the pCR rate reached 57.9% in the patients who received neoadjuvant therapy with trastuzumab + pertuzumab + chemotherapy, 42.1% of the patients did not obtain pCR. We believe that the follow-up treatment of non-pCR patients should be individualized, with full consideration of the residual tumor load after neoadjuvant therapy. At the same time, due to the short time to market of the new targeted drug and the lack of relevant long-term prognostic results, we need to supplement relevant follow-up information in new multi-center studies.

In conclusion, patients who received neoadjuvant therapy with trastuzumab + pertuzumab + chemotherapy had a pCR rate superior to that of patients who received neoadjuvant therapy with trastuzumab + chemotherapy, and the toxic side effects were tolerable. This multi-center real-world study of the Chinese population confirmed that in the Chinese population, the pCR rate of the standard dual-target treatment regimen is better than that of the single-target regimen to further promote the popularization of standardization throughout the country.

Acknowledgments

We thank all the members of the Chinese Society of Breast Surgery for providing valid cases. Ailin Song, Lanzhou University Second Hospital; Dahua Mao, Affiliated Wudang Hospital of Guizhou Medical University; Dedian Chen, Yunnan Cancer Hospital; Feng Jin, the First Affiliated Hospital of China Medical University; Hongchuan Jiang, Beijing Chao-Yang Hospital, Capital Medical University; Hua Kang, Xuanwu Hospital, Capital Medical University; Jian Huang, the Second Affiliated Hospital of Zhejiang University School of Medicine; Jiandong Wang, Chinese PLA General Hospital; Jianghua Ou, Cancer Hospital Affiliated to Xinjiang Medical University; Jianguo Zhang, the Second Affiliated Hospital of Harbin Medical University; Jinghua Zhang, Tangshan maternal and child health care hospital; Jinping Liu, Sichuan Provincial People's Hospital; Jun Jiang, The First Hospital Affiliated to Army Medical University/Southwest Hospital; Ke Liu, Jilin Cancer Hospital; Kejin Wu, Obstetrics and Gynecology Hospital of Fudan University; Peifen Fu, the First Affiliated Hospital of Zhejiang University School of Medicine; Rui Ling, Xijing Hospital of Air Force Medical University; Shu Wang, Peking University People's Hospital; Wei Zhu, Zhongshan Hospital of Fudan University; Xiang Qu, Beijing Friendship Hospital, Capital Medical University; Xingsong Tian, Shandong Provincial Hospital; Yi Zhao, Shengjing Hospital of China Medical University; Yonghui Liu, the Second Affiliated Hospital of Nanchang University; Yunjiang Liu, The Fourth Hospital of Hebei Medical University; Zhenzhen Liu, Henan Cancer Hospital;

Zhigang Yu, the Second Hospital of Shandong University; Zhimin Fan, the First Bethune Hospital of Jilin University; Zhongwei Cao, Inner Mongolia People's Hospital; Zuowei Zhao, the Second Hospital of Dalian Medical University.

Funding

The study was supported by the Beijing Medical Award Foundation "Research on the clinical efficacy of liquid biopsy in the detection of breast cancer" (No. 2016–2019); Beijing Science and Technology Innovation Medical Development Foundation (No. KC2021-JX-0044-22); Youth Cultivation Fund of the Beijing Medical Award Foundation (No. 20180502); and Interdisciplinary Clinical Research Project of Peking University First Hospital (2019CR38).

Conflicts of interest

None.

References

- Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, *et al.* Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012;13:25–32. doi: 10.1016/s1470-2045(11)70336-9.
- Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, *et al.* Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol* 2013;24:2278–2284. doi: 10.1093/annonc/mdt182.
- Broglio KR, Quintana M, Foster M, Olinger M, McGlothlin A, Berry SM, *et al.* Association of pathologic complete response to neoadjuvant therapy in HER2-positive breast cancer with long-term outcomes: a meta-analysis. *JAMA Oncol* 2016;2:751–760. doi: 10.1001/jamaoncol.2015.6113.
- Spring LM, Fell G, Arfe A, Sharma C, Greenup R, Reynolds KL, *et al.* Pathologic complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: A comprehensive meta-analysis. *Clin Cancer Res* 2020;26:2838–2848. doi: 10.1158/1078-0432.ccr-19-3492.
- NCCN. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (Version 1.2021) [EB/OL]. Plymouth Meeting: NCCN 2021[2021-01-15]. Available at: <http://www.nccn.org>. [Accessed 15 Jan, 2021].
- Chinese Society of Clinical Oncology CSCO. Breast Cancer Diagnosis and Treatment Guidelines 2021 (in Chinese). Beijing: People's Medical Publishing House, 2021.
- Wolff AC, Hammond MEH, Allison KH, Harvey BE, McShane LM, Dowsett M. HER2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update Summary. *J Oncol Pract* 2018;14:437–441. doi: 10.1200/jop.18.00206.
- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–247. doi: 10.1016/j.ejca.2008.10.026.
- Ogston KN, Miller ID, Payne S, Hutcheon AW, Sarkar TK, Smith I, *et al.* A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival. *Breast* 2003;12:320–327. doi: 10.1016/s0960-9776(03)00106-1.
- Luo C, Li N, Lu B, Cai J, Lu M, Zhang Y, *et al.* Global and regional trends in incidence and mortality of female breast cancer and associated factors at national level in 2000 to 2019. *Chin Med J* 2021;135:42–51. doi: 10.1097/cm9.0000000000001814.
- Escrivá-de-Romaní S, Arumí M, Bellet M, Saura C. HER2-positive breast cancer: current and new therapeutic strategies. *Breast* 2018;39:80–88. doi: 10.1016/j.breast.2018.03.006.
- Whitehead I, Irwin GW, Bannon F, Coles CE, Copson E, Cutress RI, *et al.* The NeST (neoadjuvant systemic therapy in breast cancer) study: National Practice Questionnaire of United Kingdom multidisciplinary decision making. *BMC Cancer* 2021;21:1–9. doi: 10.1186/s12885-020-07757-6.
- Mougalian SS, Soulos PR, Killelea BK, Lannin DR, Abu-Khalaf MM, DiGiovanna MP, *et al.* Use of neoadjuvant chemotherapy for patients with stage I to III breast cancer in the United States. *Cancer* 2015;121:2544–2552. doi: 10.1002/cncr.29348.
- Shao Z, Pang D, Yang H, Li W, Wang S, Cui S, *et al.* Efficacy, safety, and tolerability of pertuzumab, trastuzumab, and docetaxel for patients with early or locally advanced ERBB2-positive breast cancer in Asia. *JAMA Oncol* 2020;6:e193692. doi: 10.1001/jamaoncol.2019.3692.
- Chen S, Liang Y, Feng Z, Wang M. Efficacy and safety of HER2 inhibitors in combination with or without pertuzumab for HER2-positive breast cancer: a systematic review and meta-analysis. *BMC Cancer* 2019;19:1–15. doi: 10.1186/s12885-019-6132-0.
- Klastersky J, de Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M, *et al.* Management of febrile neutropaenia: ESMO clinical practice guidelines. *Ann Oncol* 2016;27 (Suppl 5):v111–v118. doi: 10.1093/annonc/mdw325.

How to cite this article: Cheng Y, Xiang H, Xin L, Duan X, Liu Y; Chinese Society of Breast Surgery (CSBrS), Chinese Society of Surgery of Chinese Medical Association. Neoadjuvant therapy for early human epidermal growth factor receptor 2 positive breast cancer in China: A multicenter real-world study (CSBrS-015). *Chin Med J* 2022;135:2311–2318. doi: 10.1097/CM9.0000000000002197