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De-escalation of neoadjuvant taxane and carboplatin therapy in HER2-positive breast cancer with dual HER2 blockade: a multicenter real-world experience in China

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Abstract

Background TCbHP (taxane + carboplatin + trastuzumab + pertuzumab) is the preferred neoadjuvant therapy regimen for human epidermal growth factor receptor 2 (HER2)-positive breast cancer. However, no consensus exists regarding whether specific populations may be exempt from carboplatin, allowing for de-escalation to the THP (taxane + trastuzumab + pertuzumab) regimen. Additionally, the optimal number of cycles for neoadjuvant THP remains unclear. We compared the efficacy and safety of neoadjuvant TCbHP and THP regimens, providing clinicians with a nuanced perspective to guide their treatment regimen selection.

Methods This multicenter real-world study included patients with HER2-positive breast cancer undergoing neoadjuvant TCbHP or THP between March 2019 and February 2023. Efficacy was assessed through the pathological complete response (pCR) rate, while safety was evaluated through monitoring adverse events.

Results Among 220 patients, 103 received 6 cycles of TCbHP (TCbHP×6), 83 received 6 cycles of THP (THP×6), and 34 received 4 cycles of THP (THP×4). The TCbHP×6 cohort exhibited a 66% pCR rate compared with 53% in the THP×6 cohort ($P = 0.072$). Subgroup analysis revealed that in patients aged ≤ 50 years, those with hormone receptor (HR)-negative status, and those with clinical stage T2, the pCR rate of the TCbHP×6 regimen was significantly higher than the THP×6 regimen ($P < 0.05$). The TCbHP×6 cohort reported higher frequencies of any-grade adverse events (99% versus 86.7%) and grade 3–4 events (49.5% versus 12%) than the THP×6 cohort. Propensity score matching identified 27 patient pairs between the THP×6 and THP×4 cohorts, indicating a significantly higher pCR rate for the THP×6 regimen than the THP×4 regimen (63% versus 29.6%, $P = 0.029$).

Conclusions The TCbHP×6 regimen is favored for individuals aged ≤ 50 years and those aged > 50, ≤60 years with HR-negative status or clinical stage T2-4. For patients in compromised general condition or lacking the specified

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indications, the THP×6 regimen emerges as a lower-toxicity alternative with satisfactory efficacy. To ensure treatment efficacy, a minimum of 6 cycles of neoadjuvant THP is required.

Keywords Breast cancer, Human epidermal growth factor receptor 2, Neoadjuvant therapy, Carboplatin, Pathological complete response

Introduction

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer, constituting 15–20% of all invasive cases, is characterized by heightened tumor cell proliferation and invasiveness compared with HER2-negative breast cancer [1–3]. Neoadjuvant chemotherapy combined with HER2-targeted therapy has become the gold standard for treating locally advanced and some early-stage HER2-positive breast cancer [4]. The pursuit of a pathological complete response (pCR) after neoadjuvant therapy, known to significantly enhance patient prognosis [5, 6], has prompted research focused on optimizing regimens for HER2-positive breast cancer [7]. The NeoSphere and PEONY trials established dual HER2 blockade with trastuzumab and pertuzumab combined with chemotherapy as the standard neoadjuvant therapy for HER2-positive breast cancer [8, 9]. The subsequent KRISTINE and TRAIN-2 trials further confirmed the efficacy and safety of carboplatin-containing chemotherapy in combination with dual HER2-targeted therapy [10, 11]. Based on these clinical findings, both taxane+carboplatin+trastuzumab+pertuzumab (TCbHP) and taxane+trastuzumab+pertuzumab (THP) are endorsed as standard neoadjuvant therapy regimens for HER2-positive breast cancer by the National Comprehensive Cancer Network and Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guidelines [12, 13].

Despite the widespread adoption of the neoadjuvant TCbHP regimen due to its relatively higher pCR rates [14, 15], its incorporation of carboplatin results in a higher incidence of adverse events than the THP regimen. Some patients may face challenges tolerating these adverse events, leading to carboplatin dose reduction, discontinuation, or a switch to the THP regimen [7, 16]. Severe cases may experience treatment delays. Thus, not all patients are suitable for the TCbHP regimen. Choosing an appropriate neoadjuvant regimen tailored to individual patients can minimize adverse events while ensuring treatment efficacy, ultimately enhancing patients' quality of life [17].

We herein thus compare the efficacy and safety of neoadjuvant TCbHP and THP regimens in patients with HER2-positive breast cancer. Additionally, we investigate populations that may be exempt from carboplatin, allowing for a suitable de-escalation to taxane alone when coupled with neoadjuvant dual-targeted HER2 therapy. This study also evaluates the efficacy of 6 versus 4 cycles of neoadjuvant THP, aiming to determine the optimal number of cycles for THP therapy. The overarching goal of the present study is to optimize neoadjuvant therapy strategies for patients with HER2-positive breast cancer and provide a valuable reference for treatment regimen selection.

Materials and methods

Patients

This was a multicenter, retrospective, real-world analysis conducted in China (Research number: CSCO BC RWS 2401). Patients with HER2-positive breast cancer diagnosed at four medical institutions between March 2019 and February 2023 were reviewed based on the following inclusion criteria: patients (1) were female and over 18 years of age, (2) were pathologically confirmed as HER2-positive invasive breast cancer, (3) with indications of neoadjuvant therapy and received neoadjuvant THP or TCbHP therapy, (4) with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, and (5) with a baseline left ventricular ejection fraction of ≥ 50%. The indications for neoadjuvant therapy in HER2-positive breast cancer were as follows: (1) primary breast tumors ≥ 2 cm, (2) with axillary lymph node metastasis, (3) desire for breast-conserving surgery, this is countered by the tumor-to-breast ratio, or (4) locally advanced breast cancer [13].

Patients were excluded in case of any one of the following: (1) surgery was not performed after neoadjuvant therapy, (2) with severe co-morbidity and other active malignancies, (3) clinicopathological information was incomplete, and (4) distant metastasis occurred at the time of diagnosis. Patients were staged according to the Eighth Edition of the American Joint Committee on Cancer Staging Manual [18].

This study was approved by the institutional review board of The Fifth Medical Center of Chinese PLA General Hospital (approval number: KY-2024-7-99-1). Consent forms were waived due to the retrospective character of the study.

Pathological and immunohistochemical examination

The primary diagnosis of primary breast tumors relied on ultrasound-guided core needle biopsy, supplemented by the assessment of suspicious regional lymph nodes. Immunohistochemistry determined the status of estrogen receptor, progesterone receptor, Ki-67, and HER2. Hormone receptor (HR) positivity was defined as ≥ 1% of cells exhibiting positive immunohistochemistry staining

for estrogen receptor and/or progesterone receptor. HER2 status was considered positive for cases with immunohistochemistry results of 3+or 2+along with HER2 gene amplification (Fluorescence in situ hybridization-positive).

Treatment allocation and compliance monitoring

All patients adhered to a standard neoadjuvant therapy regimen as per the CSCO Breast Cancer Guideline: (1) 6 cycles of taxane+carboplatin+trastuzumab+pertuzumab (TCbHP×6), (2) 6 cycles of taxane+trastuzumab+pertuzumab (THP×6), and (3) 4 cycles of taxane+trastuzumab+pertuzumab (THP×4) [13]. Since the real-world nature of this study, the treatment allocation was not randomized. The physicians introduced the advantage of each regimen to the patient: the TCbHP regimen demonstrated relatively better efficacy, while the THP regimen displayed lower toxicity, and more numbers of treatment cycles may increase the pCR rate. The treatment regimen was determined considering both the patient's preference and condition. Each patient was provided with a self-monitoring form (Supplementary Material Table S1) to track the drug, dosage, and timing of medication.

Schedules of neoadjuvant therapy

Taxanes included docetaxel and albumin-bound paclitaxel. In both TCbHP and THP regimens, albumin-bound paclitaxel was administered at the recommended dose of 125 mg/m^2 on days 1 and 8, or 250 mg/m^2 on day 1. Docetaxel was administered at 75 mg/m^2 on day 1 in the TCbHP regimen and 80–100 mg/m^2 on day 1 in the THP regimen, respectively. Carboplatin was administered to achieve an area under the concentration-time curve of 6 mg/mL/min on day 1 or 3 mg/mL/min on days 1 and 8. Trastuzumab and pertuzumab loading doses were 8 mg/kg and 840 mg, respectively, followed by maintenance doses of 6 mg/kg and 420 mg. All drugs were intravenously administered every 21 days, and initial doses could be adjusted based on the patient's condition. Dose reductions were implemented for patients unable to tolerate adverse reactions. Taxane and carboplatin were allowed to be reduced once, with the minimum dosage not lower than 85% of the initial dosage. If the patients remained intolerant, carboplatin was discontinued. Surgery was performed 3–4 weeks after the final neoadjuvant therapy dose.

Efficacy and safety assessment

The primary endpoint was the percentage of pCR, defined as the absence of invasive tumor cells in the breast and axilla, with allowed in-situ lesions (ypT0/is ypN0). Pathologists evaluated tissues after lumpectomies or mastectomies. Clinical efficacy was assessed by ultrasonography and magnetic resonance imaging every two treatment cycles using Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) [19]. Radiologic tumor responses were classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease.

Adverse events occurring during hospitalization were monitored through medical consultations, imaging examinations, and laboratory tests. The self-monitoring form (Supplementary Material Table S1) was employed to monitor adverse events post-discharge. The patients were asked to undertake routine blood tests every 3–4 days and biochemical tests every 7 days after their discharge. The test results and the occurrence of any adverse events were recorded daily. The self-monitoring form was retrieved at the patient's subsequent hospitalization, and the occurrence of adverse events was recorded in the medical record system. The left ventricular ejection fraction was monitored every 2–3 treatment cycles by echocardiography. All adverse events were graded according to Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

Continuous variables were summarized by median and interquartile range (IQR), whereas categorical variables were summarized by frequencies and percentages. The χ^2 test was used to compare the pCR rate differences between treatment regimens and across subgroup levels, incorporating age, menopausal status, HR status, clinical T stages, clinical N stages, and histological grades in the subgroup analysis. The 95% confidence intervals (CIs) for between-group pCR rate differences were calculated using a normal approximation.

Propensity score matching (PSM) was performed to adjust for baseline characteristic differences between the THP×6 and THP×4 cohorts. The matching algorithm was constructed through 1:1 nearest-neighbor matching within caliper=0.2 and without replacement. The propensity score for each patient was calculated with a logistic regression model, which included the following variables: age, menopausal status, histological grade, HR status, clinical T stage, and clinical N stage. Standardized mean difference (MD) was applied to examine the balance between continuous variables, while raw MD was employed for categorical variables [20, 21]. All statistical analyses were executed using R software version 4.3.2 [22]. Two-sided $P<0.05$ was considered to indicate statistical significance.

Results

Patient characteristics

Among 576 patients diagnosed with locally advanced or early-stage HER2-positive breast cancer between March

2019 and February 2023, 220 eligible patients were included, as illustrated in Fig. 1. The TCbHP×6 cohort comprised 103 patients, the THP×6 cohort included 83 patients, and the THP×4 cohort encompassed 34 patients. The median ages were 48 (IQR 40–55), 51 (IQR 42.5–56), and 55 (IQR 52–57.8) years, respectively (Table 1).

In the THP×6 and THP×4 cohorts, all patients had invasive ductal carcinoma. Thus, the pathological type was not included in the matching model. The MD of each variable is shown in Fig. 2, where an MD greater than 0.1 can be considered a sign of imbalance [21]. PSM identified 27 patient pairs between the THP×6 and THP×4 cohorts (Table 1). After PSM, the MDs for all variables were less than 0.1, indicating no significant variable imbalance. A love plot was drawn to visualize the variable balances before and after PSM (Fig. 2), and the balance of each variable was visualized in Supplementary Material Figure S1.

Efficacy evaluation

As shown in Table 2, within the THP×6 cohort, 26.5% (22/83) of patients achieved CR, 65.1% (54/83) achieved PR, and 8.4% (7/83) were classified as SD. In the TCbHP×6 cohort, 26.2% (27/103), 68.9% (71/103), and 4.9% (5/103) achieved CR, PR, and SD, respectively. No patient experienced progressive disease in either cohort, and no significant difference in clinical efficacy was observed between the two cohorts ($P=0.601$).

Furthermore, pCR was attained by 53% (44/83) in the THP×6 cohort and 66% (68/103) in the TCbHP×6 cohort, with an absolute difference of -13% (95% CI: -27.1–1.1%, Fig. 3). In the total population, no significant difference in pCR rates was noted between the THP×6 and TCbHP×6 cohorts ($P=0.072$). Subgroup analysis revealed a numerically higher pCR rate for the TCbHP×6 regimen in all subgroups except for the cT1 and cT3-4 subgroups. Significantly higher pCR rates were observed for the TCbHP×6 regimen in subgroups aged ≤ 50 years, HR negative, and cT2 ($P<0.05$, Fig. 3).

Within the THP×4 cohort, 17.6% (6/34) achieved CR, 70.6% (24/34) achieved PR, and 11.8% (4/34) had SD,

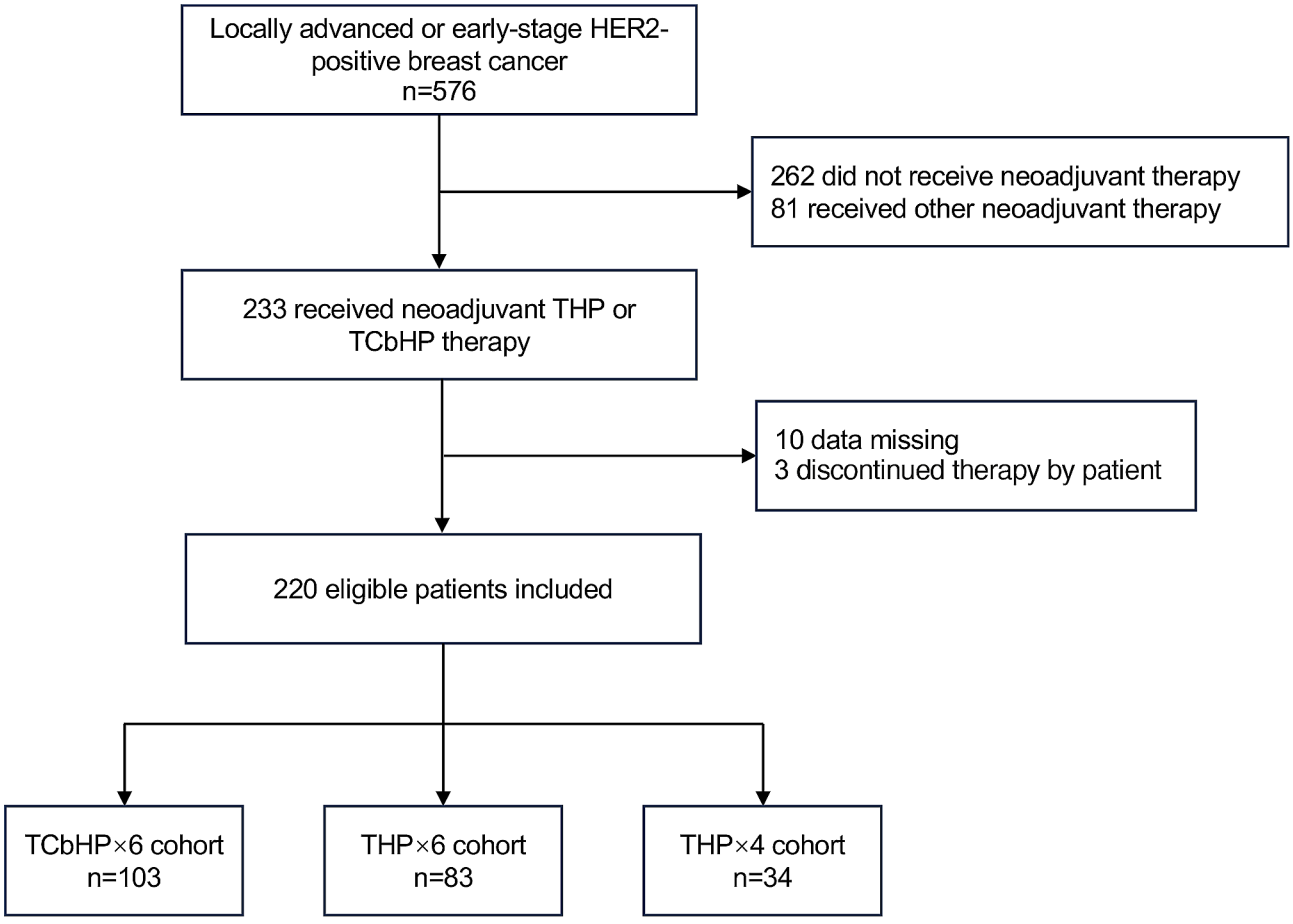

Fig. 1 Flow chart of patient selection. HER2: human epidermal growth factor receptor 2; THP: taxane + trastuzumab + pertuzumab; TCbHP: taxane + carboplatin + trastuzumab + pertuzumab

Table 1 Clinicopathological characteristics of patients with HER2-positive breast cancer receiving neoadjuvant TCbHP or THP therapy in this study

Characteristics, *n* (%)	TCbHP×6 cohort	THP×6 cohort	THP×4 cohort	THP×6 matched cohort	THP×4 matched cohort
	(*n* = 103)	(*n* = 83)	(*n* = 34)	(*n* = 27)	(*n* = 27)
Age (year)					
Median (IQR)	48 (40, 55)	51 (42.5, 56)	55 (52, 57.8)	55 (45, 62.5)	55 (52, 57.5)
≤ 50	58 (56.3)	40 (48.2)	8 (23.5)	10 (37)	7 (25.9)
> 50	45 (43.7)	43 (51.8)	26 (76.5)	17 (63)	20 (74.1)
Menopausal status					
Premenopausal	68 (66)	44 (53)	11 (32.4)	10 (37)	10 (37)
Postmenopausal	35 (34)	39 (47)	23 (67.6)	17 (63)	17 (63)
Histological grade					
Unknown	23 (22.3)	12 (14.5)	3 (8.8)	3 (11.1)	3 (11.1)
II	48 (46.6)	54 (65.1)	22 (64.7)	19 (70.4)	17 (63)
III	32 (31.1)	17 (20.5)	9 (26.5)	5 (18.5)	7 (25.9)
HR status					
Negative	45 (43.7)	39 (47)	24 (70.6)	17 (63)	17 (63)
Positive	58 (56.3)	44 (53)	10 (29.4)	10 (37)	10 (37)
Clinical T stage					
T1	14 (13.6)	7 (8.4)	4 (11.8)	3 (11.1)	3 (11.1)
T2	72 (69.9)	60 (72.3)	16 (47.1)	13 (48.1)	13 (48.1)
T3-4	17 (16.5)	16 (19.3)	14 (41.2)	11 (40.7)	11 (40.7)
Clinical N stage					
N0	30 (29.1)	35 (42.2)	11 (32.4)	8 (29.6)	9 (33.3)
N1	57 (55.3)	35 (42.2)	15 (44.1)	15 (55.6)	14 (51.9)
N2-3	16 (15.5)	13 (15.7)	8 (23.5)	4 (14.8)	4 (14.8)
Pathological type					
IDC	99 (96.1)	83 (100)	34 (100)	27 (100)	27 (100)
Others	4 (3.9)	0	0	0	0

Abbreviations: HER2, human epidermal growth factor receptor 2; TCbHP×6, six cycles of taxane + carboplatin + trastuzumab + pertuzumab; THP×6/4, six/four cycles of taxane + trastuzumab + pertuzumab; IQR, interquartile range; HR, hormone receptor; IDC, invasive ductal carcinoma

with no significant difference compared with the THP×6 cohort (P=0.53, Table 2). The pCR rate in the THP×4 cohort was 35.3% (12/34), showing no significant difference compared with the THP×6 cohort (P=0.124, Table 2). In the THP×4 matched cohort, the CR, PR, and SD rates were 18.5% (5/27), 70.4% (19/27), and 11.1% (3/27), respectively, with no significant difference compared with the THP×6 matched cohort (33.3%, 55.6%, and 11.1%, respectively, P=0.471). The pCR rate in the THP×6 matched cohort was 63% (17/27), which was significantly higher than the 29.6% (8/27) achieved in the THP×4 matched cohort (P=0.029, Table 2).

Safety evaluation

Table 3 presents the incidence of adverse events in the TCbHP×6 and THP×6 cohorts. The TCbHP×6 cohort exhibited higher frequencies of any-grade adverse events (99% vs. 86.7%) and grade 3–4 events (49.5% vs. 12%) than the THP×6 cohort. Except for peripheral sensory neuropathy and palmar-plantar erythrodysesthesia syndrome, the incidences of all other adverse events were higher in the TCbHP×6 cohort than in the THP×6 cohort. The most common grade 3–4 hematological adverse events in the TCbHP×6 cohort were decreased white blood cell and decreased neutrophil count (both 23.3%), while those in the THP×6 cohort were anemia and decreased neutrophil count (both 3.6%). The most common non-hematological adverse event in the TCbHP×6 cohort was nausea (50.5%), while that in the THP×6 cohort was fatigue and peripheral sensory neuropathy (both 31.3%). No patient experienced a decreased ejection fraction throughout the neoadjuvant therapy period.

In the TCbHP×6 cohort, dose reduction or regimen adjustment due to adverse events occurred in 32 (31.1%) patients. Among them, 5 cases had taxane reductions, 5 had carboplatin reductions, 3 had both taxane and carboplatin reductions, and 19 had carboplatin discontinuations. The adverse events leading to carboplatin discontinuation are detailed in Supplementary Material Table S2. In the THP×6 cohort, no patient underwent dose reduction or regimen adjustment.

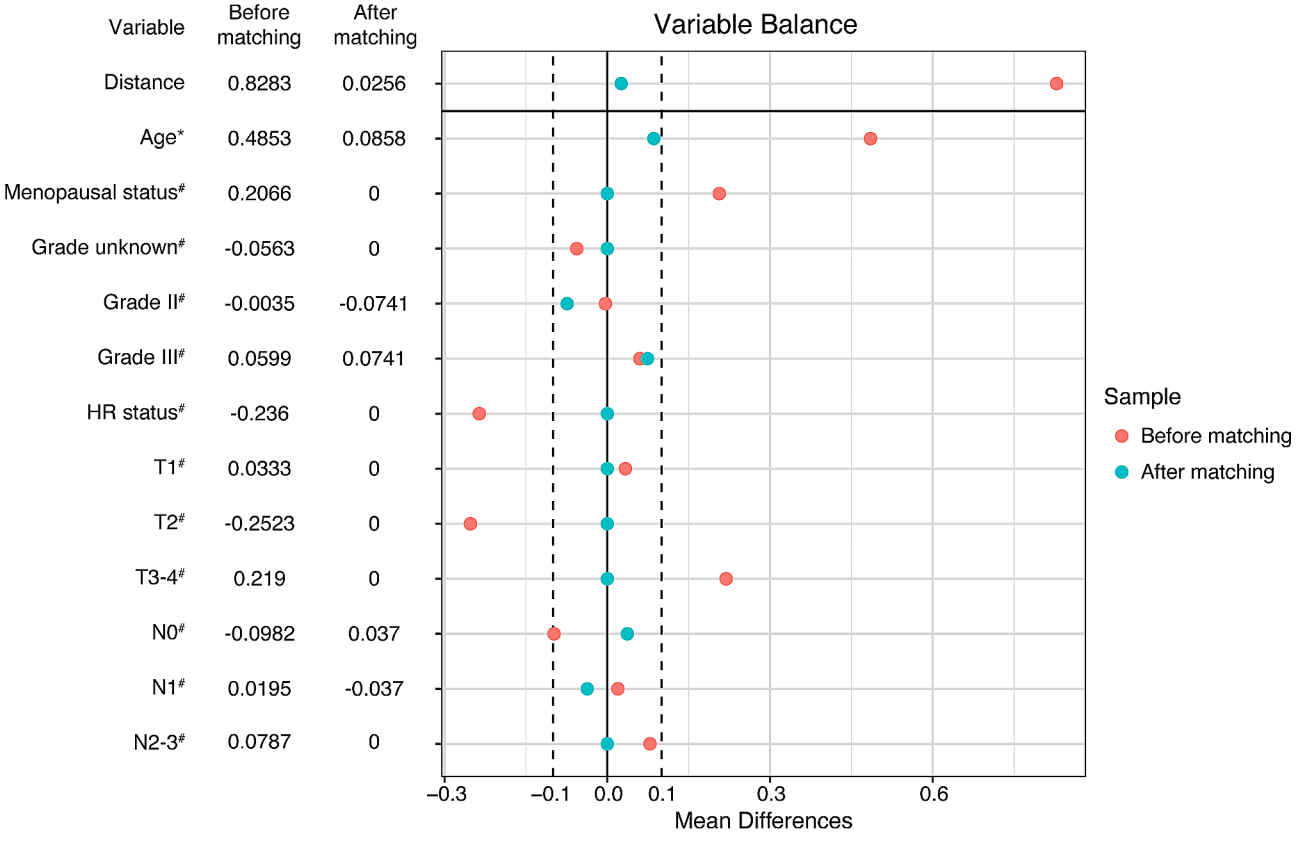

Fig. 2 Mean differences of variables before and after matching between the THP×6 and THP×4 cohorts. The dashed lines represent the suggested threshold mean difference of less than 0.1. THP×6/4: six/four cycles of taxane + trastuzumab + pertuzumab. *Standardized mean difference. #Raw mean difference

Table 2 Comparison of efficacy among different cohorts

Tumor responses, *n* (%)	TCbHP×6 cohort (*n* = 103)	THP×6 cohort (*n* = 83)	*P*-value	THP×6 cohort (*n* = 83)	THP×4 cohort (*n* = 34)	*P*-value	THP×6 matched cohort (*n* = 27)	THP×4 matched cohort (*n* = 27)	*P*-value
Clinical response			0.601			0.53			0.471
CR	27 (26.2)	22 (26.5)		22 (26.5)	6 (17.6)		9 (33.3)	5 (18.5)	
PR	71 (68.9)	54 (65.1)		54 (65.1)	24 (70.6)		15 (55.6)	19 (70.4)	
SD	5 (4.9)	7 (8.4)		7 (8.4)	4 (11.8)		3 (11.1)	3 (11.1)	
PD	0	0		0	0		0	0	
Pathological response			0.072			0.124			0.029
pCR	68 (66)	44 (53)		44 (53)	12 (35.3)		17 (63)	8 (29.6)	
Non-pCR	35 (34)	39 (47)		39 (47)	22 (64.7)		10 (37)	19 (70.4)	

Abbreviations: TCbHP×6: six cycles of taxane + carboplatin + trastuzumab + pertuzumab; THP×6/4: six/four cycles of taxane + trastuzumab + pertuzumab; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; pCR, pathological complete response

Discussion

For the neoadjuvant therapy of HER2-positive breast cancer, the 2022 CSCO Breast Cancer Guideline recommends prioritizing the TCbHP×6 regimen while considering the THP×6 regimen for patients aged > 60 years due to their generally poorer condition [13]. However, the clinical data available to facilitate informed decision-making for treatment regimens is limited. Thus, we aimed to identify the suitable population for receiving neoadjuvant TCbHP. Our findings revealed that, in patients aged ≤ 50 years, those with HR-negative status, and those with clinical stage T2, the incorporation of carboplatin significantly increased the pCR rate. Furthermore, this study's results revealed that 6 cycles of THP yielded a significantly higher pCR rate than 4 cycles. We believe that these findings would help guide physicians to determine an appropriate treatment regimen.

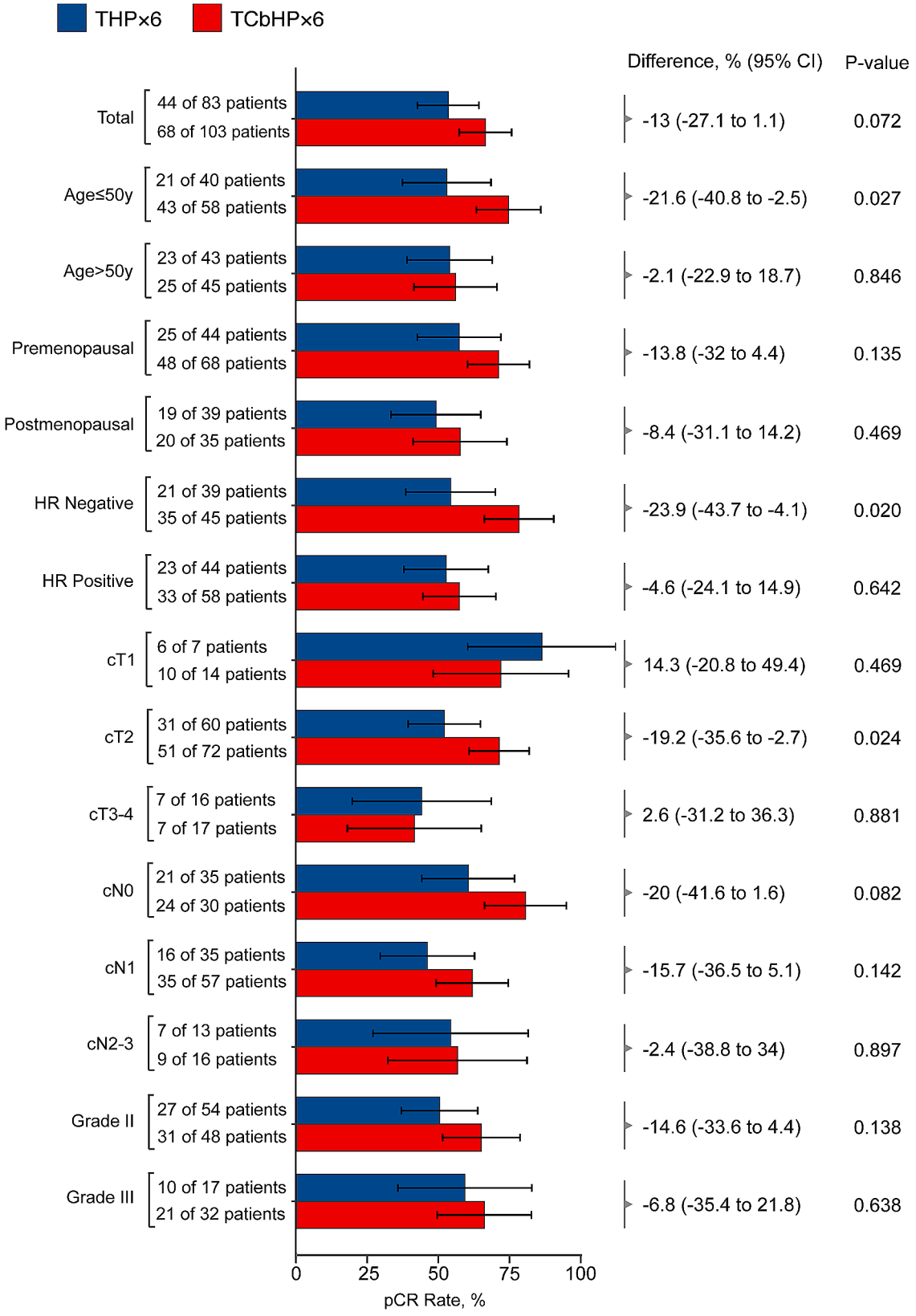

Fig. 3 Differences in the pCR rates between the THP×6 and the TCbHP×6 regimens in the total population and subgroups. pCR: pathological complete response; THP×6: six cycles of taxane + trastuzumab + pertuzumab; TCbHP×6: six cycles of taxane + carboplatin + trastuzumab + pertuzumab; HR: hormone receptor

Table 3 Treatment-related adverse events in the THP×6 and TCbHP×6 cohorts

Adverse events, *n* (%)	TCbHP×6 cohort (*n* = 103)		THP×6 cohort (*n* = 83)	
	Any grade	Grade3–4	Any grade	Grade3–4
Any	102 (99)	51 (49.5)	72 (86.7)	10 (12)
Anemia	81 (78.6)	7 (6.8)	53 (63.9)	3 (3.6)
White blood cell decreased	69 (67)	24 (23.3)	12 (14.5)	2 (2.4)
Neutrophil count decreased	58 (56.3)	24 (23.3)	13 (15.7)	3 (3.6)
Nausea	52 (50.5)	0	14 (16.9)	0
Platelet count decreased	42 (40.8)	2 (1.9)	3 (3.6)	0
Vomiting	39 (37.9)	0	10 (12.1)	0
Fatigue	38 (36.9)	1 (0.97)	26 (31.3)	0
Diarrhea	32 (31.1)	2 (1.9)	19 (22.9)	0
Peripheral sensory neuropathy	23 (22.3)	0	26 (31.3)	0
Febrile neutropenia	20 (19.4)	20 (19.4)	2 (2.4)	2 (2.4)
Allergic reaction	17 (16.5)	0	10 (12)	0
Alanine aminotransferase increased	15 (14.5)	2 (1.9)	5 (6)	1 (1.2)
Palmar-plantar erythrodysesthesia syndrome	11 (10.7)	0	11 (13.3)	1 (1.2)
Mucositis oral	10 (9.7)	0	2 (2.4)	0
Sinus tachycardia	9 (8.7)	0	2 (2.4)	0
Aspartate aminotransferase increased	9 (8.7)	2 (1.9)	3 (3.6)	1 (1.2)
Abdominal pain	7 (6.8)	0	3 (3.6)	0
Headache	3 (2.9)	0	1 (1.2)	0
Ejection fraction decreased	0	0	0	0

Abbreviations: THP×6, six cycles of taxane + trastuzumab + pertuzumab; TCbHP×6, six cycles of taxane + carboplatin + trastuzumab + pertuzumab

Subgroup analysis showed that in the TCbHP×6 cohort, the pCR rate for the age ≤ 50 years subgroup reached 74.1%, whereas it was 55.6% for the age > 50 years subgroup. Notably, these results were consistent with the TRAIN-2 trial, where after 9 cycles of neoadjuvant paclitaxel + carboplatin + trastuzumab + pertuzumab, the age < 50 years subgroup achieved a 70.9% pCR rate, while the age ≥ 50 years subgroup recorded 64.6% [11]. This concordance underscores that younger patients derive more substantial benefits from a carboplatin-containing regimen, enhancing the achievement of a pCR. Moreover, several antecedent studies have consistently indicated that patients with HR-negative, HER2-positive breast cancer are predisposed to a higher likelihood of achieving a pCR with neoadjuvant chemotherapy plus HER2-targeted therapy when juxtaposed with HR-positive cases [10, 11, 23]. In line with these observations, the KRISTINE trial demonstrated a stark contrast in the pCR rates between the HR-negative and HR-positive subgroups, reporting 71.1% and 46.4%, respectively, for patients receiving 6 cycles of neoadjuvant docetaxel + carboplatin + trastuzumab + pertuzumab [10]. Correspondingly, our study exhibited pCR rates of 77.8% and 56.9% for these respective subgroups. Acknowledging that de-escalation therapy may lead to a significant reduction in the pCR rate, the recommendation leans toward adopting a more aggressive treatment approach for cases aged ≤ 50 years and those with HR-negative status. Consequently, the TCbHP×6 regimen emerges as the preferred choice for optimizing outcomes in these specific patient cohorts.

A noteworthy disparity in pCR rates was observed in the cT2 subgroup, whereas no significant differences were noted in the cT1 or cT3-4 subgroups. Potential explanations for these outcomes could be attributed to patients with cT1 presenting a limited tumor burden (≤ 2 cm), where the THP×6 regimen suffices to achieve a relatively high pCR rate. Consequently, the incorporation of carboplatin in this scenario may not lead to a significant enhancement in the pCR rate. On the contrary, for patients with cT3-4, defined by tumors exceeding 5 cm or demonstrating direct extension to the chest wall and/or skin, neither the THP×6 nor TCbHP×6 regimen demonstrated enhanced efficacy. As a result, the difference in pCR rates between the two regimens did not reach statistical significance within these two subgroups. The THP×6 regimen demonstrated higher pCR rates in the cT1 and cT3-4 subgroups than the TCbHP×6 regimen, possibly influenced by the smaller sample sizes. Given the poorer prognosis of patients with cT3-4, the TCbHP×6 regimen is preferentially recommended for both cT2 and cT3-4 patients, emphasizing the need for tailored treatment strategies based on specific clinical characteristics.

Safety analysis showed that the TCbHP×6 cohort displayed higher incidence rates for nearly all adverse events, particularly gastrointestinal and hematological toxicity, than the THP×6 cohort. This disparity in adverse event rates is primarily attributed to carboplatin. Numerous pooled analyses have consistently highlighted myelosuppression and gastrointestinal toxicity as the primary adverse events associated with carboplatin, often leading to dose reduction and treatment interruption [24–26]. Notably, both cohorts in this study exhibited no instances of decreased ejection fraction, underscoring one of the advantages of the THP and TCbHP regimens over anthracycline-containing regimens [27, 28]. The incidence of grade 3–4 adverse events in the THP×6 cohort was merely 12%, indicating an overall acceptable toxicity profile. Consequently, in specific populations where the benefits of incorporating carboplatin are limited, the THP×6 regimen emerges as a lower-toxicity alternative therapy while maintaining treatment efficacy.

Considering the efficacy and safety of the TCbHP×6 and THP×6 regimens, when combined with the

Guideline recommendations, we suggest making treatment decisions based on patient characteristics. The TCbHP×6 regimen is favored for individuals aged ≤ 50 years and those aged > 50, ≤60 years with HR-negative status or clinical stage T2-4. For patients in compromised general condition or lacking the abovementioned indications, de-escalating to the THP×6 regimen can be considered. Importantly, our study revealed that in patients aged > 50 years and HR-positive subgroups, the pCR rate of the THP×6 regimen was only 2.1% and 4.6% lower, respectively, than that of the TCbHP×6 regimen. In addition, for patients with stage T1, the efficacy of both regimens was comparable. Thus, we believe that such de-escalation has little impact on the prognosis of patients.

Numerous studies have delved into the efficacy of neoadjuvant docetaxel + trastuzumab + pertuzumab, offering varied perspectives. The NeoSphere and PEONY trials, employing 4 cycles of neoadjuvant therapy, yielded pCR rates of 45.8% and 39.3%, respectively [8, 9]. In the PREDIX HER2 trial, utilizing a 6-cycle approach, the reported pCR rate was 45.5% [29]. It is crucial to note that differences in study populations and baseline patient characteristics might contribute to variations in pCR rates among studies. To mitigate potential biases, this study utilized PSM to rectify baseline characteristic imbalances. After PSM, the THP×6 matched cohort demonstrated a significantly higher pCR rate than the THP×4 matched cohort (63% vs. 29.6%, $P=0.029$). Given this, de-escalating 6 cycles of neoadjuvant THP to 4 cycles is undesirable; a minimum of 6 cycles of THP therapy is required.

To the best of our knowledge, this study is the first to investigate individuals eligible for taxane alone, exempting carboplatin in the context of neoadjuvant dual-targeted HER2 therapy. Additionally, it pioneers a comparison of efficacy between 6 and 4 cycles of THP. However, inherent limitations exist. Firstly, inevitable selection bias might have affected the conclusions due to the real-world nature of the study. Secondly, since the comparable sample sizes of the TCbHP×6 and THP×6 cohorts, PSM was not performed between these two cohorts. Further validation through large randomized controlled trials is warranted. Thirdly, event-free survival data were not included, urging its incorporation in subsequent studies. Additionally, the underestimation of adverse events due to inadequate reporting underscores the need for more comprehensive reporting in future investigations.

Conclusions

In the realm of neoadjuvant therapy for patients with HER2-positive breast cancer, the THP×6 regimen emerges as a superior choice over the THP×4 regimen in terms of efficacy. Tailoring recommendations based on age, HR status, and clinical T stages, the TCbHP×6 regimen is advised for individuals aged ≤ 50 years and those aged > 50, ≤60 years with HR-negative status or cT2-4. For patients in compromised general condition or lacking the specified indications, de-escalating to the THP×6 regimen can be considered.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

HER2	Human epidermal growth factor receptor 2
pCR	Pathological complete response
TCbHP	Taxane + carboplatin + trastuzumab + pertuzumab
THP	Taxane + trastuzumab + pertuzumab
CSCO	Chinese Society of Clinical Oncology
HR	Hormone receptor
RECIST	Response Evaluation Criteria in Solid Tumors
CR	Complete response
PR	Partial response
SD	Stable disease
IQR	interquartile range
CI	Confidence interval
PSM	Propensity score matching
MD	Mean difference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-024-03468-5.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

S.W. wrote the manuscript and analyzed the data. L.B. assisted in analyzing data and interpreting the data. H.B.W., Z.G.Y., K.W., S.H.Z., T.W., J.B.L., and F.L. contributed to data collection. Z.F.J. and K.W. designed the study, conducted the study and revised the manuscript. All authors read and approved the final manuscript.

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Data availability

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Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of The Fifth Medical Center of Chinese PLA General Hospital (approval number: KY-2024-7-99-1). Consent forms were waived due to the retrospective character of the study.

Competing interests
The authors declare no competing interests.

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