Original Article

Efficacy, cardiotoxicity and factors affecting pathologic complete response of neoadjuvant chemotherapy with anthracycline-containing verses anthracycline-free regimens plus dual HER2 blockade for HER2-positive early-stage breast cancer: a retrospective study

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Background: The aim of this study was to compare the efficacy, cardiotoxicity and factors affecting pathologic complete response (pCR) of neoadjuvant chemotherapy (NACT) regimen TCbHP (docetaxel/nab-paclitaxel, carboplatin, trastuzumab and pertuzumab) and AC-THP (doxorubicin, cyclophosphamide followed by docetaxel/nab-paclitaxel, trastuzumab and pertuzumab) for human epidermal growth factor receptor 2-positive (HER2+) early-stage breast cancer at a retrospective cohort.

Methods: This retrospective study included the patients with HER2+ early-stage breast cancer who received NACT with the regimen TCbHP or AC-THP and then underwent surgery from 2019 to 2022. pCR rate and breast-conserving rate were calculated to evaluate the efficacy of the regimens. Left ventricular ejection fraction (LVEF) from echocardiograms and abnormal electrocardiographs (ECGs) were collected to evaluate the cardiotoxicity of the two regimens. Association between the characteristics of the breast cancer lesions by magnetic resonance imaging (MRI) and the pCR rate were also explored.

Results: A total of 159 patients were enrolled, including 48 patients in the AC-THP group and 111 patients in the TCbHP group. The pCR rate of the TCbHP group 64.0% (71/111) was significantly higher than that of for the the AC-THP group 37.5% (18/48) (P=0.002). Estrogen receptor (ER) status (P=0.011, OR: 0.437, 95% CI: 0.231–0.829), progesterone receptor (PR) status (P=0.001, OR: 0.309, 95% CI: 0.157–0.608) and IHC HER2 status (P=0.003, OR: 7.167, 95% CI: 1.970–26.076) were significantly correlated with the pCR rate. LVEF decreased at 6 and 12 months after treatment in the AC-THP group (P=0.024 and 0.040), which only decreased after 6 months of treatment in the TCbHP group (P=0.048). Post-NACT MRI characteristics including mass features (P<0.001) and enhancement type (P<0.001) were significantly associated with pCR rate.

Conclusions: Early-stage HER2+ breast cancer treated with the TCbHP regimen has a higher pCR rate

than the AC-THP group. The TCbHP regimen appears to have lower cardiotoxicity than the AC-THP regimen in terms of LVEF. Mass features and enhancement type at post-NACT MRI significantly associated with the pCR rate of breast cancer patients.

Keywords: Early-stage breast cancer; human epidermal growth factor receptor 2-positive; pathological complete response; cardiotoxicity; magnetic resonance imaging

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Introduction

The incidence of breast cancer ranks the first in female malignancy with an increasing trend (1-3). Human epidermal growth factor receptor 2 (HER2) overexpression occurs in 20–25% of breast cancer patients (4), and is associated with aggressive behavior and poor prognosis (5). Neoadjuvant chemotherapy (NACT) can significantly improve the prognosis of patients with HER2-positive breast cancer, contribute to tumor degradation and improve breast retention rate, which has become a standard of therapy for breast cancer (6). Some reliable prognostic indicators for NACT are widely used in the treatment of breast cancer, such as pathologic complete response (pCR) and Miller-Payne rating system (7,8). The prognosis of patients with pCR after neoadjuvant chemotherapy is significantly better than that of the non-pCR patients (9-11).

According to the National Comprehensive Cancer Network (NCCN) guidelines (Version 2. 2022), TCbHP (taxane, carboplatin, trastuzumab and pertuzumab) regimen is the preferred targeted therapy for patients with HER2-positive breast cancer, while AC-THP (anthracycline, cyclophosphamide, taxane, trastuzumab and pertuzumab) regimen is another option. The main difference between the two regimens is the type of cytotoxic drugs used. The data from the TRAIN-2 and TRYPHAENA clinical trial revealed no significant difference in pCR after dual HER2 blockade with or without anthracycline (12,13), but the cytotoxic drugs included in these trials were not exactly the same as those were recommended by the NCCN guidelines. In the two trials, the anthracycline-containing regimens lasted only six cycles, and was accompanied by the use of 5-fluorouraci, which is not currently recommended by NCCN. The neoCARH trial compared the pCR rate and safety of E (epirubicin) C-TH and TCbH regimen, but dual her2 blockade was not designed (14). Therefore, the objective of the present retrospective analysis was to compare the efficacy and cardiac safety of the two regimens, TCbHP and AC-THP, as neoadjuvant therapy in women with HER2-positive breast cancer in a non-clinical trial setting.

MRI is more accurate than X-ray and ultrasound in assessing the extent of the primary tumor and the response to NACT (15,16). Several previous studies have reported that MRI features after or during NACT were highly correlated with pCR (17-19). However, these articles often did not have a good classification and arrangement of different chemotherapy regimens for patients with different pathological types, so they might have ignored the possible influence of different chemotherapy drugs (such HER2 blockade drugs) on the diagnostic value of MRI. In the clinical practice, primary tumor needs to be surgically resected together with other surgical performance such as axillary lymph nodes evaluation. And pathological evaluation was performed for the resected primary tumor

Highlight box

Key findings

- Early-stage HER2+ breast cancer treated with neoadjuvant chemotherapy (NACT) with the TCbHP regimen has a higher pCR rate than the AC-THP regimen. The TCbHP regimen has lower cardiotoxicity than the AC-THP regimen in terms of LVEF. Mass features and enhancement type at post-NACT MRI significantly associated with the pCR rate of HER2+ breast cancer.

What is known and what is new?

- Known: The TCbHP regimen was more effective in NACT for early-stage HER2+ breast cancer than the AC-THP regimen in terms of the pCR rate.
- New: The TCbHP regimen has lower cardiotoxicity than the AC-THP regimen in terms of LVEF. Some post-NACT MRI variables significantly associated with the pCR rate of breast cancer.

What is the implication, and what should change now?

- The number of the patients enrolled in the study was small. Studies with larger sample size help to prove these conclusions further.

and the axillary lymph nodes to decide whether pCR was reached, which is essential for deciding the postoperative treatment strategy. However, it normally takes about two weeks or longer for the pathological evaluation before the postoperative treatment regimen can be decided. Therefore, if a reliable pCR prediction model can be established to know whether patients can achieve pCR before we get the pathological results, patients can be given appropriate treatment in time. Therefore, we attempted to conduct a preliminary exploration by exploring the relationship between some imaging features on MRI images and pCR. Therefore, we summarized and sorted out the MRI image information of breast cancer patients to study the correlation between post-NACT MRI image features and pCR under the condition that the differences in chemotherapy regimens were minimized. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2547/rc).

Methods

Patients

In this retrospective study, we collected the information of breast cancer patients from Renmin Hospital of Wuhan University and Hubei Cancer Hospital from March 2019 to September 2022. Inclusion criteria were: (I) HER2-positive status was confirmed by immunohistochemistry (IHC3+) or fluorescence in situ hybridization (FISH, IHC 2+); (II) The patient completed one of the preoperative neoadjuvant therapy regimens, i.e., TCbHP or AC-THP; (III) After completion of the neoadjuvant chemotherapy, the patient received breast conserving surgery or modified radical mastectomy, and the postoperative pathological tissue was evaluated for the efficacy of NACT, including MP staging and whether the residual tumor load reached pCR; (IV) 159 patients met the inclusion criteria and were included in our analysis. The study was approved by the Ethics Committee of Renmin Hospital of Wuhan University (No. WDRY2021-KS009) and conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients provided their written informed consent.

Treatments

Patients in the AC-THP group were given four cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) intravenously, followed by four cycles of docetaxel (100 mg/m^2) or nab-paclitaxel (260 mg/m^2), and trastuzumab plus pertuzumab every 3 weeks. Patients in the TCbHP group were treated with docetaxel (75 mg/m^2) or nab-paclitaxel (260 mg/m^2), carboplatin (area under the concentration-time curve =6 mg/mL/min) given every 3 weeks for six cycles concurrently with trastuzumab and pertuzumab. In the two groups, trastuzumab (initially given at a loading dose of 8 mg/kg, followed by 6 mg/kg) and pertuzumab (initially given at a loading dose of 840 mg, followed by 420 mg) were used every 3 weeks. After completion of the NACT, surgery was performed. Then, trastuzumab and pertuzumab were continued to be used to complete a full year of therapy (not all the patients competed the follow-up treatment).

Date collection

At baseline for the 159 patients, biopsies of the primary tumor were taken for histological diagnosis, including local assessment of estrogen receptor (ER), progesterone receptor (PR) and Ki67. The positive expression of estrogen receptor and progesterone receptor was based on positive staining of nucleus ≥1%, while positive staining of nucleus <1% was considered negative. The expression cut-off of Ki67 was 30% (high expression >30%; Low expression ≤30%). pCR was defined as the absence of invasive carcinoma in breast tissue and axillary lymph nodes (ypT0/isypN0).

Patients who completed postoperative targeted therapy were electronically reviewed to collect information regarding ECG and echocardiograms. The echocardiograms were used to acquire patients' left ventricular ejection fraction (LVEF) for one year from the patients starting the NACT treatment. LVEF declined 10% from baseline to <50% was regarded as severe cardiac dysfunction. We recorded the ECG abnormalities after patients received NACT. The ECG abnormalities before NACT was defined as pre-treatment ECG events. And the ECG abnormalities occurred after NACT was defined as new ECG events. The ECG abnormalities were manually evaluated by a professional cardiologist.

We also collected MRI imaging results of patients after their last preoperative chemotherapy cycle and extracted some imaging information, including the presence or absence of a mass, the nature of the enhancement. MRI imaging features were evaluated by two experienced breast radiologists. The description of MRI features referred to the study of Kim *et al.* (20).

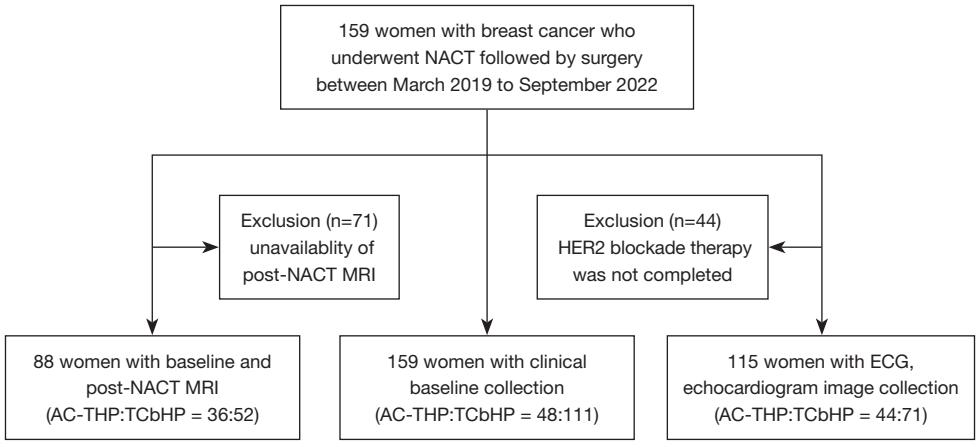

Figure 1 Study flowchart. NACT, neoadjuvant chemotherapy; MRI, magnetic resonance imaging; ECG, electrocardiograph.

Statistical analysis

We used the chi-square test or Fischer's exact test to test for differences in categorical variables between the groups. The univariate and multivariate Logistic regression analyses were performed to analyze the effects of covariates that might be associated with pCR. We used SPSS for Windows version 23.0 (SPSS Inc., Chicago, USA) to finish statistical analysis, and statistical significance was defined as a P value <0.05.

Results

One hundred fifty-nine patients were enrolled in the present study for baseline investigation, including 48 patients in the AC-THP group and 111 patients in the TCbHP group. 44 patients who did not completed targeted therapy were excluded, and the remaining patients were enrolled in cardiotoxicity analysis, including 44 patients in the AC-THP group and 71 patients in the TCbHP group. Also, 71 patients without MRI images were excluded and 88 patients were included in the MRI analysis (*Figure 1*). *Table 1* presents the baseline information of patients. Age was divided from 50 years old. In this cohort, 67.3% (107/159) of the patients was ≥50 years old, and 32.7% (52/159) of the patients was <50 years old. The overall positive rate of ER and PR were 47.2% (75/159) and 35.2% (56/159). The percentage of HER2 status by IHC 3+ was 89.3% (142/159), and that of 2+ was 10.7% (17/159). 71 (44.7%) of 159 patients had a Ki67 value ≤30%, and 88 (55.3%) of 159 patients had a Ki67 value >30%. The details of the T and N stage of the patients were also shown in *Table 1*. As for the American Joint Committee on Cancer (AJCC) clinical classification, the stage I accounted for 1.9% (3/159), the stage II accounted for 54.1% (86/159), and the stage III accounted for 44.0% (70/159). The characteristics mentioned above had no significant difference between the two groups, except for the ER and PR status (P=0.046 and 0.009; *Table 1*).

Within the 159 patients included in this study, 48 patients completed 8 cycles of neoadjuvant therapy with the AC-THP regimen and 111 patients completed 6 cycles of neoadjuvant therapy with the TCbHP regimen. In the AC-THP group, 18 of 48 patients (37.5%) achieved a pCR, compared with 71 of 111 patients (64.0%) in the TCbHP group (P=0.002). In the AC-THP group, 4 of 48 patients (8.3%) received the breast conserving surgeries, compared with 18 of 111 patients (16.2%) in the TCbHP group (P=0.141). The MP classification was also significantly different in the two groups (P<0.001; *Table 2*). The two regimens had no significant difference in breast conserving rate (P=0.141). Besides, the pCR rates and the regimen of each group of the clinical trials TRYPHAENA, GeparSepto, TRAIN-2 and BERENICE were summarized in *Table 3* (12,13,21,22).

We also investigated the differences in pCR rates in subgroups and found that the ER (P=0.008), PR status (P<0.001) and IHC HER2 (P=0.001) status had statistical difference (*Table 4*). The univariate analysis of the relationship between these characteristics and pCR rate showed that ER status (P=0.011, OR: 0.437, 95% CI: 0.231–0.829), PR status (P=0.001, OR: 0.309, 95% CI: 0.157–0.608), IHC HER2 status (P=0.001, OR: 7.167, 95% CI: 1.970–26.076) and regimen (P=0.002, OR:

Table 1 Baseline characteristics

Characteristics	NACT regimens		Total (n=159), n (%)	P value
	AC-THP (n=48), n (%)	TCbHP (n=111), n (%)		
Median age (years) [range]	51 [27, 73]	53 [28, 69]		
Age (years)				0.082
<50	20 (41.7)	32 (28.8)	52 (32.7)	
≥50	28 (58.3)	79 (71.2)	107 (67.3)	
ER status				0.046
Negative	20 (41.7)	64 (57.7)	84 (52.8)	
Positive	28 (58.3)	47 (42.3)	75 (47.2)	
PR status				0.009
Negative	24 (50.0)	79 (71.2)	103 (64.8)	
Positive	24 (50.0)	32 (28.8)	56 (35.2)	
HER2 status by IHC				0.095
2+	8 (16.7)	9 (8.1)	17 (10.7)	
3+	40 (83.3)	102 (91.9)	142 (89.3)	
Ki67 value (%)				0.490
≤30	22 (45.8)	49 (44.1)	71 (44.7)	
>30	26 (54.2)	62 (55.9)	88 (55.3)	
T classification				0. 499
1	5 (10.4)	5 (4.5)	10 (6.3)	
2	33 (68.8)	84 (75.7)	117 (73.6)	
3	9 (18.8)	20 (18.0)	29 (18.2)	
4	1 (2.1)	2 (1.8)	3 (1.9)	
N classification				0.628
0	11 (22.9)	36 (32.4)	47 (29.6)	
1	20 (41.7)	37 (33.3)	57 (35.8)	
2	13 (27.1)	28 (25.2)	41 (25.8)	
3	4 (8.3)	10 (9.0)	14 (8.8)	
AJCC clinical classification				0.550
Stage I	1 (2.1)	2 (1.8)	3 (1.9)	
Stage II	23 (47.9)	63 (56.8)	86 (54.1)	
Stage III	24 (50.0)	46 (41.4)	70 (44.0)	

NACT, neoadjuvant chemotherapy; AC-THP, doxorubicin, cyclophosphamide followed by docetaxel/nab-paclitaxel, trastuzumab and pertuzumab; TCbHP, docetaxel/nab-paclitaxel, carboplatin, trastuzumab and pertuzumab; ER, estrogen receptor; PR, progestogen receptor; IHC, immunohistochemistry; HER2, human epidermal growth factor receptor 2; AJCC, American Joint Committee on Cancer.

0.338, 95% CI: 0.168–0.681) were significantly correlated with pCR rate. In the multivariate analysis, PR status (P=0.032, OR: 0.297, 95% CI: 0.110–0.799), IHC HER2 status (P=0.013, OR: 6.130, 95% CI: 1.516–24.793), T classification (P=0.027, OR: 0.316, 95% CI: 0.114–0.877) and regimen (P=0.037, OR: 2.293, 95% CI: 1.053–4.994) were independent predictors of pCR rate. Age, Ki67 value, N classification, AJCC clinical classification had no significant correlation with pCR rate in both univariate and multivariate analyses (*Table 5*).

Table 2 Surgical method and postoperative pathological response

Index	NACT regimens		P value
	AC-THP (n=48), n (%)	TCbHP (n=111), n (%)	
Surgical method			0.141
Mastectomy	44 (91.7)	93 (83.8)	
BCS	4 (8.3)	18 (16.2)	
MP classification			<0.001
1	1 (2.1)	0 (0)	
2	5 (10.4)	5 (4.5)	
3	14 (29.2)	8 (7.2)	
4	9 (18.8)	25 (22.5)	
5	19 (39.6)	73 (65.8)	
Pathological evaluation			0.002
Non-pCR	30 (62.5)	40 (36.0)	
pCR	18 (37.5)	71 (64.0)	

NACT, neoadjuvant chemotherapy; AC-THP, doxorubicin, cyclophosphamide followed by docetaxel/nab-paclitaxel, trastuzumab and pertuzumab; TCbHP, docetaxel/nab-paclitaxel, carboplatin, trastuzumab and pertuzumab; BCS, breast conserving surgery; MP, Miller-Payne.

The cardiotoxicity of these two regimens were also observed and analyzed in terms of LVEF in echocardiograms and ECG. The mean LVEF of patients at baseline, 6 months and 12months were 63.4%, 61.2%, 61.0% in the AC-THP group and 62.9%, 60.6%, 61.2% in the TCbHP group. Generally, the mean LVEF of patients decreased within the extension of treatment time. LVEF decreased after 6 and 12 months of NACT treatment in the AC-THP group, respectively (P=0.024 and 0.040; *Figure 2A*). In the TCbHP group, the decrease of LVEF was only significant after 6 months of NACT treatment (P=0.048), but not statistically significant after 12 months (P=0.078; *Figure 2B*). No patient had an LVEF decrease to less than 50% during the treatment in both groups. In addition, we collected patients' ECG and analyzed the abnormal ECG changes (*Table 6*). 26 patients (59.1%) had new ECG abnormities in the AC-THP group, while the TCbHP group was 53 patients (74.6%). There was no statistical difference in the overall incidence of abnormal ECG events between the two groups (P=0.062). Sinus tachycardia (33.0%), T-wave inversion (38.3%) and ST deviation with T-wave change (20.0%) were the most common ECG abnormalities observed in the two groups, and among the three types of abnormal ECG events,

Table 3 Clinical trials and their regimens on the use of dual HER2 blockade

Trial	Regimens	pCR rate (%) (ypT0/isypN0)
TRYPHAEN (13)	A1: 3FEC (q3w) + 3HP (q3w) → 3Doc (q3w) + 3HP (q3w)	61.6
	B1: 3FEC (q3w) → 3Doc (q3w) + 3HP (q3w)	57.3
	C1: 6DocCb (q3w) + 6HP (q3w)	66.2
GeparSepto (21)	A2: 4Pac (q3w) + 4HP (q3w) → 4EC (q3w) + 4HP (q3w)	62.9
	B2: 4nabPac (q3w) + 4HP (q3w) → 4EC (q3w) + 4HP (q3w)	69.3
TRAIN-2 (12)	A3: 3FEC (q3w) + 3HP (q3w) → 6PacCb (q3w) + 6HP (q3w)	67.0
	B3: 9PacCb (q3w) + 9HP (q3w)	68.0
BERENICE (22)	A2:4AC(q2w) →12Pac(qw) + 4HP(q3w)	61.8
	B2:4FEC(q3w) →4Doc(q3w) + 4HP(q3w)	60.7

The number before the drugs represents the number of cycles. F, 5-fluorouraci; E, epirubicin; A, doxorubicin; C, cyclophosphamide; Doc, docetaxel; Pac, paclitaxel; nabPac, nab-paclitaxel; Cb, carboplatin; H, trastuzumab; P, pertuzumab; qw, every week; q2w, every 2 weeks; q3w, every 3 weeks.

Table 4 Differences in pCR rates in subgroup analysis

Characteristics	Pathological evaluation		P value
	Non-pCR (n=36), n (%)	pCR (n=43), n (%)	
Age (years)			0.110
<50	27 (51.9)	25 (48.1)	
≥50	43 (40.2)	64 (59.8)	
ER status			0.008
Negative	29 (34.5)	55 (65.5)	
Positive	41 (54.7)	34 (45.3)	
PR status			<0.001
Negative	35 (34.0)	68 (66.0)	
Positive	35 (62.5)	21 (37.5)	
IHC HER2 status			0.001
2+	14 (82.4)	3 (17.6)	
3+	56 (39.4)	86 (60.6)	
Ki67 value			0.469
≤30	32 (45.1)	39 (54.9)	
>30	38 (43.2)	50 (56.8)	
T classification			0.207
1	5 (50.0)	5 (50.0)	
2	46 (39.3)	71 (60.7)	
3	17 (58.6)	12 (41.4)	
4	2 (66.7)	1 (33.3)	
N classification			0.925
0	19 (40.4)	28 (59.6)	
1	27 (47.4)	30 (52.6)	
2	18 (43.9)	23 (56.1)	
3	6 (42.9)	8 (57.1)	
AJCC clinical classification			0.142
Stage I	2 (66.7)	1 (33.3)	
Stage II	32 (37.2)	54 (62.8)	
Stage III	36 (51.4)	34 (48.6)	

pCR, pathologic complete response; ER, estrogen receptor; PR, progestogen receptor; IHC, immunohistochemistry; HER2, human epidermal growth factor receptor 2; AJCC, American Joint Committee on Cancer.

there were no significant differences in the two regimens (P=0.338, 0.449, 0.269).

A total of 88 patients with post-NACT MRI image data after the last circle of chemotherapy and before surgery were collected, including 36 patients of AC-THP group and 52 patients of TCbHP group. The relationship between pathological results and clinical characteristics, post-NACT MRI images characteristics was explored in *Table* 7. The results showed that, in addition to ER status, PR status, IHC HER2 status and NACT regimens, mass features and enhancement type at post-NACT MRI were also independent predictors of pCR.

Discussion

Although several phase III randomized controlled trials (RCTs) have compared the efficacy and safety of dual HER2 blockade NACT with or without anthracycline-containing chemotherapy regimens in early stage HER2-positive breast cancer, such as TRYPHAENA and TRAIN-2, the cytotoxic drugs included in these trials were not exactly the same as the NACT regimens recommended by the newest version NCCN guideline (12,13). Therefore, the clinicians have no direct reference data when choosing the treatment strategy for such kind of patients. The purpose of this real-world retrospective study was to compare the efficacy and safety of neoadjuvant chemotherapy regimens TCbHP *vs.* AC-THP for HER2-positive early breast cancer. Our results showed that the two regimens had significant difference in the pCR rates (37.5% *vs.* 64.0%, P=0.002), the TCbHP regimen had a higher pCR rate on the numerical than the AC-THP regimen. In the TRYPHAENA trial, although the carboplatin-containing regimen (docetaxel, carboplatin, trastuzumab and pertuzumab) had a higher pCR rate (66.2%) than the anthracycline-containing regimens (61.6% for the fluorouracil, epirubicin, cyclophosphamide, trastuzumab, pertuzumab followed by docetaxel, trastuzumab, pertuzumab regimen and 57.3% for the fluorouracil, epirubicin, cyclophosphamide followed by docetaxel, trastuzumab, pertuzumab regimen) on the numerical, which was similar to our results. While another retrospective Chinese study had a 76.1% pCR rate for the TCbHP regimen (23). In the neoCARH trial, the carboplatin-containing regimen in combination with single HER2 blockade (trastuzumab) had a higher pCR rate than the anthracycline-containing regimen in combination with trastuzumab (56% *vs.* 37%, P=0.032), which was similar to our results (14). A recent meta-analysis shown that there

Table 5 Univariate and multivariate analysis of characteristics associated with pCR

Characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years) (<50 versus ≥50)	1.607 (0.825–3.133)	0.163	1.664 (0.772–3.587) 4	0.194
ER status (negative versus positive)	0.437(0.231–0.829)	0.011	0.984 (0.388–2.499)	0.951
PR status (negative versus positive)	0.309 (0.157–0.608)	0.001	0.297 (0.110–0.799)	0.032
IHC HER2 status (2+ versus 3+)	7.167 (1.970–26.076)	0.003	6.130 (1.516–24.793)	0.013
Ki67 value (≤30 versus >30)	1.080 (0.575–2.026)	0.812	0.735 (0.357–1.513)	0.440
T classification (T1-2 versus T3-4)	0.459 (0.208–1.011)	0.503	0.316 (0.114–0.877)	0.027
N classification (N0 versus N1-3)	0.812 (0.407–1.620)	0.554	1.025 (0.413–2.544)	0.836
AJCC clinical classification (Stage I-II versus stage III)	0.584 (0.310–1.101)	0.096	0.773 (0.300–1.996)	0.676
Regimen (AC-THP versus TCbHP)	0.338 (0.168–0.681)	0.002	2.293 (1.053–4.994)	0.037

pCR, pathologic complete response; OR, odds ratio; CI, confidence interval; ER, estrogen receptor; PR, progestogen receptor; IHC, immunohistochemistry; HER2, human epidermal growth factor receptor 2; AJCC, American Joint Committee on Cancer; AC-THP, doxorubicin, cyclophosphamide followed by docetaxel/nab-paclitaxel, trastuzumab and pertuzumab; TCbHP, docetaxel/nab-paclitaxel, carboplatin, trastuzumab and pertuzumab.

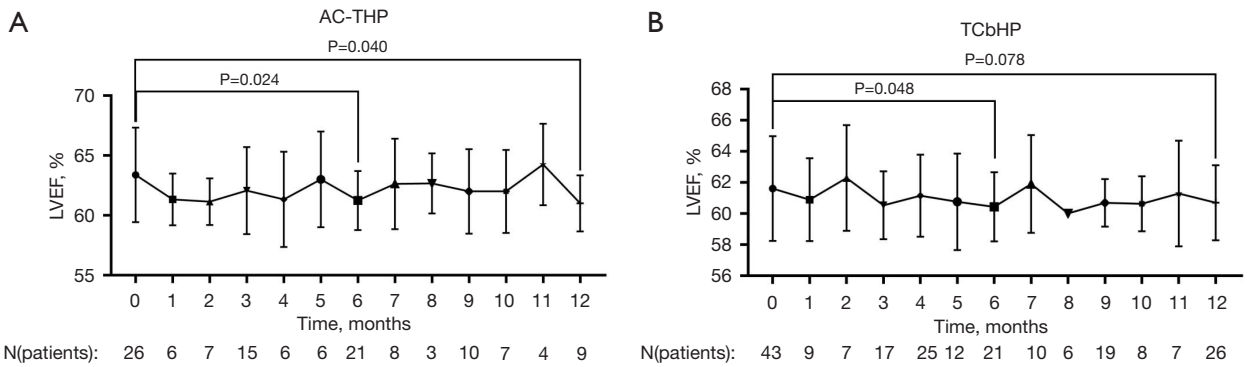

Figure 2 Mean left ventricular ejection fraction per month for one year over time from initiation of HER2 blockade drugs. AC-THP group (A), TCbHP group (B). The LVEF at baseline was compared with LVEF at 6- and 12-month using Welch's t test. AC-THP, doxorubicin, cyclophosphamide followed by docetaxel/nab-paclitaxel, trastuzumab and pertuzumab; TCbHP, docetaxel/nab-paclitaxel, carboplatin, trastuzumab and pertuzumab; LVEF, left ventricular ejection fraction.

was no statistically significant difference in treatment outcomes in terms of pCR rate between anthracycline-containing and non-anthracycline-containing regimens (24). In general, the pCR rate of the HER2-positive early-stage breast cancer treated with anthracycline-containing regimen in combination with dual HER2 blockade in our study was lower than others.

On the other hand, the TRAIN-2 study showed that for the HER2-positive early-stage breast cancer when the NACT cycles increased to 9 cycles, the pCR rates of the anthracycline-containing regimen and carboplatin-containing regimen were 67.0% and 68.0%, respectively, which were not significantly higher than the pCR rate reported by the other clinical trials (12). Therefore, the benefits did not appear to be cost-effective when elongating the treatment cycle.

In the subgroup analysis, the results of the univariate analysis shown that the HR status and the IHC HER2 status had an impact on the overall pCR rate of the early stage HER2-positive breast cancer patients receiving dual HER2

Table 6 Comparison of abnormal ECG changes

Abnormal ECG changes	AC-THP (n=44), n (%)	TCbHP (n=71), n (%)	Total (n=115), n (%)	P value
Number of patients with pre-treatment ECG events	11 (25.0)	24 (33.8)	35 (30.4)	0.216
Number of patients with new ECG events	26 (59.1)	53 (74.6)	79 (68.7)	0.062
Sinus tachycardia	13 (29.5)	25 (35.2)	38 (33.0)	0.338
Ventricular premature complex(es)	3 (6.8)	5 (7.0)	8 (7.0)	0.256
Atrial premature complex(es)	2 (5.6)	2 (4.7)	4 (5.0)	0.638
Junctional premature complex(es)	0 (0)	1 (1.4)	1 (0.9)	
T-wave inversion	16 (36.4)	28 (39.4)	44 (38.3)	0.449
Aggravated T wave inversion	0 (0)	5 (7.0)	5 (4.3)	
ST deviation with T-wave change	5 (15.9)	16 (22.5)	23 (20.0)	0.269
Aggravated ST deviation with T-wave change	1 (2.3)	3 (4.2)	4 (3.5)	
ST deviation	2 (4.5)	6 (8.5)	8 (7.0)	0.346
First-degree atrioventricular block	0 (0.0)	2 (4.7)	2 (2.5)	
Prolonged QTc	1 (2.3)	2 (2.8)	3 (2.6)	
Left ventricular high voltage	3 (6.8)	1 (1.4)	4 (3.5)	
Low voltage	2 (4.5)	1 (1.4)	3 (2.6)	
Inferior wall embryo R wave	0 (0)	1 (1.4)	1 (0.9)	

ECG, electrocardiograph; AC-THP, doxorubicin, cyclophosphamide followed by docetaxel/nab-paclitaxel, trastuzumab and pertuzumab; TCbHP, docetaxel/nab-paclitaxel, carboplatin, trastuzumab and pertuzumab; ST, ST-segment; QT, QT-segment; QTc, corrected QT interval.

blockade containing NACT. The HR-negative breast cancer had a higher pCR rate in both the chemotherapy regimens with and without anthracyclines in the presence of dual HER2 blockade, and the patients with higher scores in IHC HER2 status were more likely to achieve a pCR. The subgroup analysis of the TRYPHAENA and TRAIN-2 trials had the same conclusions (12,13). The baseline of HR status in the AC-THP group and TCbHP group was not balanced, therefore, the difference of the pCR rate in AC-THP regimen and TCbHP regimen in our study might be biased by the difference of HR status between the two groups. But in the studies of TRYPHAENA and neoCARH trial, the pCR rate of TCbHP regimen was higher than that of AC-THP regimen, which was the same as our conclusion (13,14). On the other hand, the anthracycline regimen and the non-anthracycline regimen had the similar breast-conserving rate (8.3% and 16.2%, P=0.141). In the TRAIN-2 study, the breast-conserving rates of the anthracycline regimen and the non-anthracycline regimen also had no significant difference (56% and 60%, P=0.33) (12), but our proportions of patients undergoing breast-conserving surgery were relatively low.

Echocardiograms and ECG were performed on patients to evaluate the cardiotoxicity. In general, the AC-THP regimen had a longer duration of cardiotoxicity than the TCbHP regimen. This might attribute to the cardiotoxicity of the anthracycline in the AC-THP regimen. Besides, the GeparSepto trial observed the cardiotoxicity when the anthracycline and HER2 blockade were used concurrently (21). And in the anthracycline-contain regimens for the HER2+ patients (paclitaxel/nab-paclitaxel, trastuzumab, pertuzumab followed by epirubicin, cyclophosphamide, trastuzumab, pertuzumab), 7.3% of the patients showed the LVEF decreases to <50% or a ≥10% LVEF decrease from baseline. No patient had a severe cardiac dysfunction (LVEF decrease to less than 50%) during the treatment, both regimens had generally good tolerability in cardiotoxicity. In conclusion, according to our data, non-anthracycline regimen might have lower cardiotoxicity than the anthracycline regimen in terms of LVEF for the NACT of HER2+ breast cancer, but studies with larger sample sizes are needed to confirm our

Table 7 Demographic and clinicopathological characteristics and baseline MRI imaging features according to pathological reaction

Characteristics	Pathological evaluation		P value
	Non-pCR, (n=36), n (%)	pCR, (n=52), n (%)	
Age (years)			0.185
<50	16 (44.4)	17 (32.7)	
≥50	20 (55.6)	35 (67.3)	
ER status			0.024
Negative	15 (41.7)	34 (65.4)	
Positive	21 (58.3)	18 (34.6)	
PR status			0.010
Negative	19 (52.8)	41 (78.8)	
Positive	17 (47.2)	11 (21.2)	
IHC HER2 status			0.007
2+	7 (19.4)	1 (1.9)	
3+	29 (80.6)	51 (98.1)	
Ki67 value			0.274
≤30	17 (47.2)	20 (38.5)	
>30	38 (43.2)	32 (61.5)	
T classification			0. 215
T1-2	28 (77.8)	45 (86.5)	
T3-4	8 (22.2)	7 (13.5)	
N classification			0.237
N0	11 (30.6)	21 (40.4)	
N1-3	25 (69.4)	31 (59.6)	
AJCC clinical classification			0.326
Stage I-II	21 (58.3)	34 (65.4)	
Stage III	15 (41.7)	18 (34.6)	
NACT regimens			<0.001
pCR	7 (19.4)	39 (75.0)	
Non-pCR	29 (80.6)	13 (25.0)	
Mass at post-NACT MRI			<0.001
Nonexistence	30 (96.8)	3 (6.8)	
Existence	1 (3.2)	41 (93.2)	
Enhancement type at post-NACT MRI			<0.001
Foci or no enhancement	6 (16.7)	25 (48.1)	
Mass with or without NME	29 (80.6)	15 (28.8)	
NME	1 (2.8)	12 (23.1)	

MRI, magnetic resonance imaging; pCR, pathologic complete response; OR, odds ratio; CI, confidence interval; ER, estrogen receptor; PR, progestogen receptor; IHC, immunohistochemistry; HER2, human epidermal growth factor receptor 2; AJCC, American Joint Committee on Cancer; NACT, neoadjuvant chemotherapy; NME, non-mass enhancement.

conclusions in the future.

As for the ECG data, T-wave Inversion and ST Deviation with T-Wave change are the most common ECG abnormalities observed in the present study, which were the early manifestation of myocardial ischemia. In our study, 36.4% *vs.* 39.4% of the patients showed the T-wave Inversion in the AC-THP group and the TCbHP group, respectively, and the two groups had no statistically difference (P=0.449). Similarly, the occurrence rate of the ST Deviation with T-Wave change in the two groups was not significantly different (15.9% *vs.* 22.5%, P=0.269). In a prospective study of patients with breast cancer who underwent ACT (anthracycline, cyclophosphamide, taxane), significant QTc (corrected QT interval) prolongation were observed (25). At the same time, Tanriverdi reported that long-term receipt of trastuzumab significantly prolonged the QTc interval and increased QTd (QT dispersion) in patients with early-stage breast cancer (26). Therefore, we also observed the QTc prolongation in the present study to evaluate the cardiotoxicity of the two regimens. 2.8% *vs.* 4.7% of the patients showed the QTc prolongation in the AC-THP group and the TCbHP group, respectively. The TCbHP group had a higher proportion of new ECG events occurrence than the AC-THP group (81.4% *vs.* 69.4%), although there was no statistical difference (P=0.198). This may due to the higher initial ECG events occurrence rate in the TCbHP group (37.2%) than in the AC-THP group (22.2%).

In addition, according to the MRI image information we collected from the patient after chemotherapy, the presence of tumor and the type of enhancement also help to infer whether the patient achieved pCR. This is consistent with the conclusion of MRI image model related studies (20,27). Therefore, MRI images are important for the diagnosis of pathological reaction after NACT for breast cancer patients. Due to the small number of patients in our study, we did not compare the differences in MRI features between different chemotherapy regimens. In the future, we hope to use a larger sample size of patients with different chemotherapy regimens to carry out this discussion.

This study has several limitations. Firstly, the number of the patients enrolled in the study was small, and the small sample size may result in limited statistical power. Secondly, patients who received AC-THP regimen harbored more HR-positive breast cancer than those with TCbHP regimen in our study, and the difference of the pCR rate would be biased by the difference of HR status between the two regimens. However, as mentioned above, several results in previous studies support our conclusion. We need to add more cases in the future before we draw the final conclusion. In addition, as the nature of a retrospective study, the choice of chemotherapy regimen might be biased, the RCT needs to be conducted in the future to exclude this issue. Moreover, adverse reactions except for the cardiotoxicity in patients were not recorded, which may lead to the under-reported adverse toxicities. Finally, the relatively short follow-up period limited our ability to evaluate long-term survival and safety outcomes. Larger sample size and more rigorous clinical paired studies are needed to address these issues in the future.

Conclusions

Early-stage HER2+ breast cancer treated with the TCbHP regimen has a higher pCR rate and MP classification than the AC-THP group. The TCbHP regimen appears to have lower cardiotoxicity than the AC-THP regimen in terms of LVEF. Mass features and enhancement type at post-NACT MRI significantly associated with the pCR rate of breast cancer patients.

The TCbHP regimen was more effective for early-stage HER2+ breast cancer than the AC-THP regimen in terms of the pCR rate and MP classification. Both regimens had generally good tolerability in cardiotoxicity, although the TCbHP regimen appeared to have lower cardiotoxicity than the AC-THP regimen in terms of LVEF. Severe cardiac dysfunction was not observed in the two regimens. Mass features and enhancement type at post-NACT MRI significantly associated with the pCR rate of breast cancer patients.

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Footnote

Reporting Checklist: The authors have completed the

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2547/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of Renmin Hospital of Wuhan University (No. WDRY2021-KS009) and conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients provided their written informed consent.

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