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Pathological complete response and survival of HER2-positive invasive breast cancer following docetaxel, carboplatin, and trastuzumab neoadjuvant therapy: a Vietnamese experience

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ABSTRACT

Introduction. Neoadjuvant chemotherapy for HER2-positive breast cancer consists of a chemotherapy regimen plus trastuzumab with or without pertuzumab. The use of trastuzumab has been shown to improve pathological complete response (pCR), disease-free survival (DFS), and overall survival (OS). Purposes: To evaluate the efficacy and safety of neoadjuvant docetaxel, carboplatin, and trastuzumab (TCH) in the treatment of HER2-positive breast cancer in Vietnamese patients.

Material and methods. This retrospective study reviewed stage II–III HER2-positive breast cancer patients who received neoadjuvant docetaxel, carboplatin, and trastuzumab (TCH) at the Vietnamese National Cancer Hospital. The primary endpoint was the pCR rate which was defined as the absence of invasive tumor in the breast and axillary nodes (ypT0/is, ypN0). The secondary endpoints were DFS, OS, and toxicities.

Results. The complete and partial clinical response of 51 patients were 33.3% and 58.8%, respectively. The pCR rate was 41.2%; there was a significantly higher response in cT1-2 patients compared to cT3-4 ones (61.1% *vs.* 39.3%, p = 0.033). Three-year estimated DFS and OS rates were 81.3% and 93.0%, respectively. Treatment was generally well tolerated. Grade 3/4 neutropenia and anemia were uncommon (21.6% and 7.8%). No symptomatic cardiac dysfunction occurred.

Conclusions. Neoadjuvant TCH, non-anthracycline chemotherapy with single anti-HER2 regimen achieved high efficacy, with a good pCR rate and favorable tolerability in stage II or III HER2-positive breast cancer patients.

Key words: breast cancer, HER2-positive, neoadjuvant chemotherapy, pCR, TCH

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Introduction

Breast cancer (BC) is one of the most common cancers and the leading cause of malignancy-related mortality in women worldwide [1, 2]. In Vietnam, breast cancer is the most common cancer and the fourth leading cause of cancer-related death in women. The International Agency for Research on Cancer reported an estimated 21 555 new cases and 9 345 deaths of breast cancer in Vietnam [2]. Treatment for breast cancer is complex due to its heterogeneity and various molecular subtypes. Among them, newly diagnosed patients in the HER2 overexpression subtype, which was previously considered as an aggressive phenotype with poor prognosis [3–5], accounted for 15–20% of patients.

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Neoadjuvant chemotherapy (NAC) is commonly used for breast cancer patients not only with locally advanced stage but also patients in an early stage, especially with poor prognosis with triple-negative and HER2--positive tumors [6, 7]. In addition to increasing the rate of breast-conserving surgery [8], NAC permits evaluation of the effectiveness of systemic treatments to guide adjuvant treatment [9]. Response to NAC also provides important prognostic information. Patients with pathological complete response (pCR) were reported to have better long-term outcomes [10–12]. NAC for HER2-positive breast cancer consists of chemotherapy and HER2-directed therapy, specifically trastuzumab, with or without pertuzumab. The use of trastuzumab has been shown to improve pCR, disease-free survival, and overall survival [13]. Nevertheless, the addition of trastuzumab to standard therapy may increase toxicity, particularly cardiovascular toxicity [13, 14]. This toxicity is increased when trastuzumab is used concurrently with an anthracycline-containing chemotherapy regimen. Due to concerns about cardiotoxicity, anthracycline-free chemotherapy plus trastuzumab have been explored. The addition of carboplatin and docetaxel to trastuzumab (TCH regimen) was shown to have a synergistic effect in some studies [15–17]. The pCR rates achieved by the TCH regimen in the neoadjuvant setting ranged from 39% to 76% [17–20]. This regimen has less incidence of acute toxicity, cardiotoxicity, and more favorable tolerability. However, most evidence about the efficacy of this regimen was from the adjuvant setting or phase II studies [20–22]. In the GETN(A)-1 trial, a multicenter neoadjuvant study, 70 patients with HER2-positive breast cancer with diagnosed stage II–III received trastuzumab 4 mg/kg (day 1), followed by 2 mg/kg weekly, plus docetaxel 75 mg/m^2 every 3 weeks, and carboplatin (AUC 6) for six cycles before surgery. The pCR rate (ypT0/is ypN0) was 39%, and the objective response rate (ORR) was 95%. Sixty-four percent of the patients had breast conservation and no symptomatic cardiac dysfunction occurred [23]. However, the efficacy and safety of TCH regimens for neoadjuvant therapy have not been evaluated in Vietnamese women with HER2-positive breast cancer. Thus, we conducted this study to evaluate the pCR rates, toxicity profile as well as preliminary results for DFS and OS of the TCH regimen in HER2-positive breast cancer patients with stage II–III in Vietnam.

Material and methods

Study design

In this single-center, retrospective study, 51 HER2--positive breast cancer patients with stage II–III who were treated with a neoadjuvant TCH regimen from January 2015 to December 2021 at the Vietnamese National Cancer Hospital were recruited. The eligible patients need to meet all the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, histopathological diagnosis of invasive breast cancer and immunohistochemical result of HER2-positive, staging II–III (cT1-4, cN0-3, M0), received neoadjuvant therapy with a TCH regimen, a baseline left ventricular ejection fraction (LVEF) of ≥ 50%, adequate hematologic, renal, and hepatic functions. Patients with the following criteria were excluded: bilateral breast cancer or metastatic breast disease; any previous treatment for breast cancer including surgery, radiation, chemotherapy, or endocrine therapy; pre-existing malignancy other than breast cancer; any prior treatment with cytotoxic drugs, in situ carcinoma, another breast malignancy (ex. malignant phyllode tumor). The diagnosis of BC was confirmed by histological evaluation of the biopsy specimens before treatment. An immunohistochemical (IHC) examination was performed before treatment. HER2-positive status was determined by IHC (3+) or IHC (2+) and positive fluorescence in situ hybridization (FISH) using the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) 2018 guidelines. This study was approved by the research committee of the National Cancer Hospital, Vietnam.

Treatment procedures

All patients had their clinical staging evaluated at diagnosis, using the 8th edition of the American Joint Committee on Cancer (AJCC). Physical examination, mammography, and ultrasound were usually performed at baseline and after every three chemotherapy cycles to evaluate clinical response. Treatment includes six cycles of docetaxel 75 mg/m^2, carboplatin AUC6, and trastuzumab 6 mg/kg every 3 weeks (8 mg/kg loading dose). For each cycle, prophylactic G-CSF support was administered on days 2 to 5. Echocardiography to evaluate cardiac function was performed before initiation of therapy, after the third and sixth cycles. Then, LVEF assessments were carried out every 3 months and 1 year after the last cycle of treatment or whenever clinically indicated. After the completion of neoadjuvant chemotherapy, surgery was performed to remove the tumor by conservative surgery or modified radical mastectomy, combined with axillary lymph node dissection within 4–6 weeks after the final dose of chemotherapy. Following surgery, adjuvant endocrine therapy and radiotherapy were administered if indicated. Adjuvant trastuzumab (loading dose 8 mg/kg, followed by 6 mg/kg every 21 days) was continued postoperatively for up to 18 cycles.

Tumor response and toxicity assessment

Clinical response was evaluated by palpation after each treatment cycle and by mammary ultrasound, mammography, or magnetic resonance imaging before surgery, using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Following surgery, tumors were evaluated in their maximum diameter. Tumor and nodal samples were examined with histopathological tests to assess the pathological response. The pCR was defined as the absence of invasive tumor in breast and axillary lymph nodes (ypT0/is ypN0). Disease-free survival (DFS) was defined as the period between the date of surgery and the date of disease relapse (including distant metastases, local and regional recurrence) or death, whichever occurred first. Overall survival (OS) was measured from the date of the diagnosis to death due to any cause. Toxicities after and during six courses of chemotherapy were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.

Variables of interest

Variables used for analyzing include age (< 50 and ≥ 50 years), performance status (PS) (PS = 0 and PS = 1), menopausal status (premenopausal and postmenopausal), histologic grade (ductal carcinoma and others), clinical tumor stage (T1–T2 and T3–T4), clinical lymph nodal stage (N0–N1 and N2–N3), clinical stage (stage II and stage III), ER/PgR status (positive and negative), and pathological response (pCR and non pCR). All 51 patients were contacted via phone or messages to collect real-time information.

Statistics

All collected data were analyzed and measured by SPSS 20.0 software. Fisher's exact test and Pearson Chi-square test were used to evaluate impact of various factors on the pCR. Disease-free survival and overall survival were estimated by the Kaplan-Meier method. A 2-sided p value of <0.05 was considered statistically significant.

Results

Patient characteristics and treatment

Between February 2015 to December 2021 in the National Cancer Hospital, Vietnam, 51 patients with stage II–III HER2-positive breast cancer were enrolled in the study. All patients received six courses of NAC chemotherapy. Table 1 shows the baseline clinicopathological features of patients. The median age was 46 years old and over half of the women were premenopausal. Considering the cTNM, BCs were staged in

Table 1. Baseline characteristics of 51 patients with HER2+ invasive breast cancer carcinoma

Parameter	n	[%]
Age [years]		
Median (range)	46.0 (26–70 years)	
< 50 years	30	58.5
≥ 50 years	21	41.2
Performance status		
0	42	82.4
1	9	17.6
Menopausal status		
Premenopausal	32	62.7
Postmenopausal	19	37.3
Histology		
Invasive ductal carcinoma, NOS	39	76.5
Invasive lobular carcinoma	9	17.6
Invasive mucinous carcinoma	2	3.9
Invasive carcinoma, unclassified	1	2.0
Histological grade		
1	1	2.0
2	34	66.7
3	16	31.4
Clinical tumor stage		
T1	1	2.0
T2	17	33.3
T3	21	41.2
T4	12	23.5
Clinical nodal stage		
N0	8	15.7
N1	12	23.5
N2	27	52.9
N3	4	7.8
Clinical stage		
II	13	25.5
IIIA	22	43.1
IIIB	12	23.5
IIIC	4	7.8
ER/PgR status		
Negative	13	25.5
Positive	38	74.5
Operation type		
Mastectomy	44	86.3
Breast-conserving surgery	7	13.7
Clinical response		
CR	17	33.3
PR	30	58.8
SD	4	7.8
PD	0	0.0
Pathologic response		
pCR	21	41.2
Non-pCR	30	58.8

CR — complete response; ER — estrogen receptor; NOS — not otherwise specified; pCR — pathologic complete response; PD — progressive disease; PgR — progesterone receptor; PR — partial response; SD — stable response

Table 2. Factors associated with a pathologic complete response (pCR)

Factors	pCR		Analysis		p
	No.	%	OR	95% CI	
Age [years]					
< 50 years	12	40.0	1 (reference)		
≥ 50 years	9	42.9	0.889	0.287–2.756	0.838
Histologic type					
Ductal carcinoma, NOS	17	42.5	1 (reference)		
Other	4	36.4	1.293	0.326–5.137	0.714
Histologic grade					
1 or 2	17	48.6	1 (reference)		
3	4	25.0	2.833	0.763–10.516	0.112
Clinical tumor stage					
T1–T2	11	61.1	1 (reference)		
T3–T4	10	30.3	3.614	1.084–12.046	0.033
Clinical lymph node status					
N0–N1	8	40.0	1 (reference)		
N2–N3	13	41.9	0.923	0.294–2.898	0.891
Clinical stage					
II	6	46.2	1 (reference)		
III	15	39.5	1.314	0.369–4.679	0.673
ER/PgR status					
Negative	8	61.5	1 (reference)		
Positive	13	34.2	3.077	0.836–11.323	0.084

CI — confidence interval; ER — estrogen receptor; NOS — not otherwise specified; OR — overall survival; PgR — progesterone receptor

T3 and N2 which were the most common (43.1 and 52.9%, respectively). Therefore, BCs with stage IIIA (39.2%) and stage IIIB (35.3%) were more common than the other stages. Concerning pathological features, invasive ductal carcinoma, not otherwise specified (NOS) was the most common. Histological grade II was the most common (66.7%). Most patients (74.5%) were positive for hormone receptors (estrogen and/or progesterone receptor; HR) while 25.5% were HR-negative.

Clinical and pathological response

Based on the RECIST criteria, the clinical response and degree were investigated, complete response (CR), partial response (PR), and ORR were 33.3%, 58.8%, and 92.2%, respectively. Seven patients (13.7%) underwent breast-conserving surgery. Pathological complete response was achieved in 41.2% (Tab. 1). Table 2 presents the relationship between clinical and paraclinical features and pCR for HER2-positive BC. Pathological complete response rate was higher in hormone receptor-negative patients compared to hormone receptor-positive patients (61.5% *vs.* 34.2%, p = 0.084). Pretreatment tumor stage was significantly related to response to NAC. Lower cT-stage (cT1-2 *vs.* cT3-4) was a significant predictor of higher pCR rate (p = 0.033), i.e. pCR rates were 61.1% and 30.3% for cT1-T2 stage and cT3-T4 stage, respectively. In addition, the pCR rate was not significantly different irrespective of age groups, clinical lymph node status, histologic grade, and histologic type (p > 0.05).

Long-term outcomes

The median follow-up was 33.0 months. Eight of 51 patients (15.7%) had experienced at least one event. Five patients (9.8%) experienced local relapse (including local lymph node relapses), and 6 patients (11.8%) had metastatic relapses. Estimated 3-year DFS was 81.3% (Fig. 1). Patients who achieved pCR after NAC had better DFS than the ones with residual disease although the difference was not statistically significant (89.7% *vs.* 72.3%, p = 0.220) (Fig. 2). Additionally, DFS was not significantly different with age group, histologic type, histologic grade, clinical tumor stage, clinical lymph node stage, clinical stage and HR status (Tab. 3). Two patients (3.9%) died at 31 months and 34 months. One patient (1.9%) died of lung metastases and the other

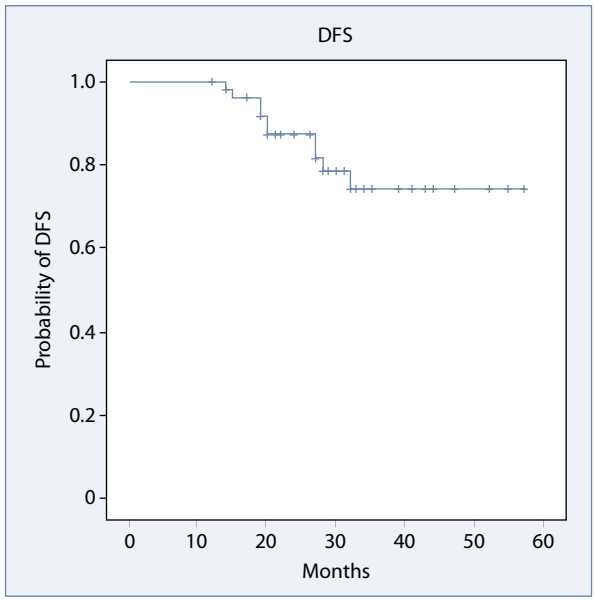

Figure 1. Disease-free survival of HER2+ invasive breast cancers. Kaplan-Meier curve displayed the estimated 3-year disease-free survival (DFS) was 81.3%

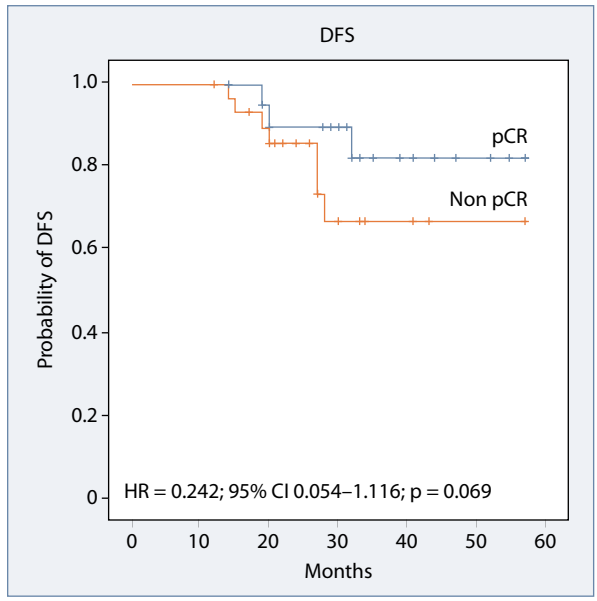

Figure 2. Disease-free survival (DFS) of pathologic response status in HER2+ invasive breast cancers. The Log-rank test displayed that there was not a significant difference between these DFS curves of combination of pCR and non-pCR for infiltrating HER2+ breast cancers; CI — confidence interval; HR — hazard ratio; pCR — pathologic complete response

Table 3. Factors affecting disease-free survival

Factors	No.	HR	95% CI	p
Age [years]				
< 50 years	30	1 (reference)		
≥ 50 years	21	0.331	0.067–1.645	0.177
Histologic type				
Ductal carcinoma, NOS	40	1 (reference)		
Other	11	1.276	0.260–6.262	0.764
Histologic grade				
1 or 2	35	1 (reference)		
3	16	0.287	0.041–2.023	0.210
Clinical tumor stage				
T1–T2	18	1 (reference)		
T3–T4	33	0.716	0.151–3.407	0.675
Clinical lymph node status				
N0–N1	20	1 (reference)		
N2–N3	31	0.913	0.519–153.186	0.132
Clinical stage				
II	13	1 (reference)		
III	38	1.030	0.044–23.930	0.985
ER/PgR status				
Negative	13	1 (reference)		
Positive	38	3.477	0.356–33.962	0.284
Pathologic response				
Non pCR	30	1 (reference)		
pCR	21	0.246	0.054–1.116	0.069

CI — confidence interval; ER — estrogen receptor; HR — hazard ratio; NOS — not otherwise specified; pCR — pathologic complete response; PgR — progesterone receptor

(1.9%) died of bone and brain metastases. Both patients (3.9%) did not achieve pCR after surgery. Estimated 3-year OS was 93.0% (Fig. 3).

Safety and tolerability

Toxicities in our patients are presented in Table 4. Anemia and neutropenia were the most common serious (grade 3/4) adverse events. All patients completed 6 cycles of planned chemotherapy, with 12 patients requiring dose adjustments due to toxicity. None of the patients had LVEF decline or clinical symptoms of heart failure. There were no deaths related to treatment.

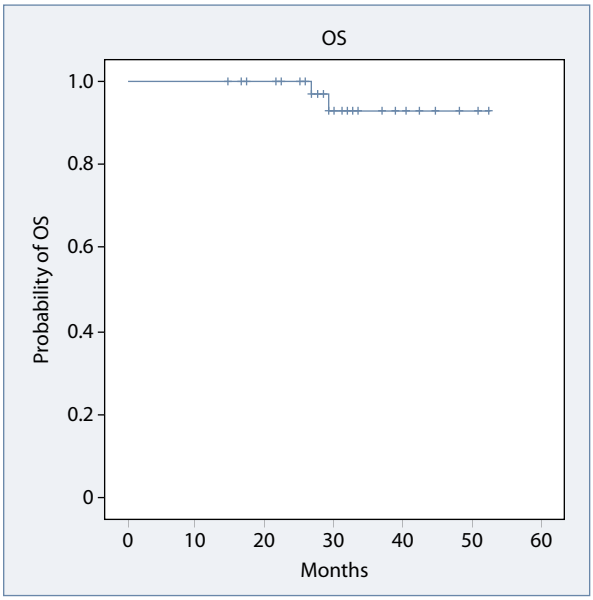

Figure. 3. Overall survival (OS) of HER2+ invasive breast cancers. Kaplan-Meier curve displayed the estimated 3-year OS was observed in 93.0%

Discussion

Breast cancer patients with HER2 overexpression typically demonstrate a poor prognosis due to high malignancy. In the adjuvant setting, this poor prognosis has been significantly improved by anti-HER2 therapy with trastuzumab [24]. In the neoadjuvant setting, the addition of a HER2-targeted therapy to chemotherapy has resulted in an increased rate of pCR and improved DFS and OS [25]. In recent years, the TCH regimen has been increasingly used in some countries but in Vietnam, this regimen has not been widely applied. Our study aimed to evaluate the safety and efficacy of the TCH regimen in a neoadjuvant setting for HER2--positive breast cancer in daily clinical practice. The ORR and pCR were obtained in 92.2% and 41.2% patients, respectively. This result was slightly lower than the results described in previous publications (Tab. 5 [15, 17, 23, 26, 27]). Sugitani et al. [17] reported on 50 HER2-positive patients with stage I–III invasive breast cancer, a pCR of 52% with the TCH regimen. Meanwhile, a retrospective analysis of Echavarria et al. [15] on 84 HER2-positive patients with stage I–III receiving the same regimen demonstrated that clinical characteristics were 2.4%, 65.5%, and 32.1% for

Table 4. Selected adverse events on six-course chemotherapy

Event	All grade		Grade 3/4	
	n1	[%]	n2	[%]
Hematologic toxicities				
Anemia	37	72.5	4	7.8
Neutropenia	23	45.1	11	21.6
Thrombocytopenia	10	19.6	2	3.9
Nonhematologic toxicities				
Infection with neutropenia	0	0	0	0
Infusion reaction	6	11.8	0	0
Mouth ulcer	20	39.2	0	0
Anorexia	39	76.5	1	1.9
Vomiting	10	19.6	0	0
Diarrhea	17	33.3	0	0
Peripheral neuropathy	26	51.0	0	0
Renal toxicity	0	0	0	0
Cardiac toxicity	0	0	0	0
Hepatic dysfunction	18	35.3	0	0

Table 5. Clinical trials and observational analysis on the use of docetaxel–carboplatin–trastuzumab regimen

	n	cCR [%]	PR [%]	ORR [%]	ypT0/isN0 [%]	Design
Sugitani et al. [17]	50	10	56	66	52	Phase II trial
Echavarria et al. [15]	84	34.5	63.1	97.6	47.6	Retrospective analysis
Coudert et al. [23]	70	85	10	95	39	Phase II trial
Kolberg et al. [26]	78				43.6	Retrospective analysis
Bayraktar et al. [27]	65	58.9	19.6	78.5	43.3	Retrospective analysis

cCR — clinical complete response; ORR — objective response rate; PR — partial response; ypT/isN0 — lack of invasive tumor in the breast and axillary lymph nodes

stages I, II, and III, respectively, and the pCR rate was 47.6%. In another study of 39 BC patients who were treated with AC-TH or TCH regimens, Phung et al. [28] showed that clinical complete response (cCR) and pCR rate was obtained in 33.3% and 64.1%, respectively. This observed difference may be due to slightly different patient characteristics. Notably, our cohort had a lower proportion of patients with HR-negative disease (25.5%) as compared to Echavarria et al.'s [15] (45.5%) and Sugitani et al.'s [17] (50.0%) research, which is a subset known to be more sensitive to NAC. Additionally, in our study, another reason is that stage III patients were accounted for a higher percentage than in other studies.

Previous meta-analyses demonstrated lower pCR rates in luminal/HER2 than in non-luminal/HER2 tumors. The KRISTINE trial showed that HR-negative breast cancer patients had up to 19% higher pCR rates than HR-positive patients [29]. This discrepancy might be explained that PIK3CA mutations are associated with reduced rates of pCR to anti-HER2 therapy in HER2--positive/HR-positive tumors [30, 31]. In our study, patients with hormone receptor-negative tumors also had a better response to chemotherapy than the ones with HR-positive tumors (61.5% *vs.* 34.2%). However, we did not observe a statistically significant difference in the pCR rate between two groups, which could be due to our relatively small sample size. Our results show that higher cT-stages have significantly lower pCR rates than lower cT-stages (cT3-4 *vs.* cT1-2; $p < 0.033$). The cT-stage is one of the most important predictors of pCR in breast cancer patients. A study by Caudle et al. [32] on 1 762 patients showed that the tumor stage was a predictive factor of disease progression. Jin et al. [33] also concluded that tumor size was an independent predictor of pathological complete response. The patients with larger tumor sizes were less likely to achieve pCR than those with smaller tumor sizes. The pCR rates for cT1, cT2, cT3, and cT4 were 23.6%, 13.6%, 11.9%, and 10.3%, respectively [33]. Goorts et al. [34] ($n = 2\,366$) showed that for cT1, cT2, cT3, and cT4, pCR rates were 31%, 22%, 18%, and 17%, respectively. Lower cT-stage was a significant predictor of higher pCR rate ($p < 0.001$) [34]. So, clinicians should take cT-stage into account when estimating the likelihood of achieving pCR in an individual patient.

In our study, the median follow-up was 33.0 months. Two patients died at 31 months and 34 months and both of these patients did not achieve pCR after NAC. Estimated 3-year OS and DFS were 93.0% and 81.3%, respectively. In addition, 3-year DFS was better in the pCR group than in the non-pCR group (89.7% *vs.* 72.3%) although there was no significant difference, which may be due to the small study population and inadequate follow-up time. In addition, we found that patients who achieved pCR after NAC had better long-term outcomes despite not achieving statistical significance due to low event data [35].

The TCH regimen was generally well tolerated. Most adverse events were manageable. All the patients were able to complete the planned number of chemotherapy cycles. Anemia (7.8%), grade 3/4 neutropenia (21.6%), and thrombocytopenia (3.9%) were the most common adverse events. No patient experienced febrile neutropenia. In the TRYPHAENA trial, grade 3/4 neutropenia and febrile neutropenia were 46% and 17%, respectively. A study by Sugitani et al. [17] on breast cancer patients treated with a TCH regimen showed grade 3/4 neutropenia (36%), anemia (12%), thrombocytopenia (2%), and febrile neutropenia (6%). Echavarria et al. [15] reported febrile neutropenia and grade 3–4 neutropenia accounting for 6.0% and 16.7% of patients. Patients in our study had a considerably lower rate of adverse events presumably due to prophylactic administration of filgrastim to all patients.

None of the patients developed clinical congestive heart failure during the follow-up period. The safety of this regimen and reduced cardiac complication has also been demonstrated in previous studies in adjuvant and neoadjuvant settings [17, 18]. The BCIRG-006 study found that the anthracycline-free 1-year TCH regimen was associated with a lower risk of asymptomatic LVEF decline (9.4%) and congestive cardiac failure (CCF) (0.4%) compared to doxorubicin, cyclophosphamide, docetaxel, and trastuzumab (18.6% LVEF decline, 2% CCF) or doxorubicin, cyclophosphamide, and docetaxel

(11.2% LVEF decline, 0.7% CCF) [24]. When compared to other regimens that do not contain anthracyclines, the TCH regimen generally has a more favorable safety profile with regard to neutropenia and febrile neutropenia. On the other hand, patients treated with TCH regimens were associated with a significant reduction of cardiotoxicity [17, 24]. A study in Poland on 34 breast cancer patients treated with Neoadjuvant Pertuzumab Plus Trastuzumab in Combination with Docetaxel and Carboplatin regimen confirmed that the regimen is safe and relatively effective. No patients with myocardial dysfunction or a significant decrease in LVEF were observed [36].

Our study has a few limitations. Besides the retrospective nature, the relatively small sample size and short follow-up period may have precluded more significant results regarding predictive factors of pCR, DFS, or OS. Further studies with larger sample sizes may need to be conducted to fulfill these limitations.

Conclusions

In conclusion, neoadjuvant chemotherapy with a TCH regimen showed promising efficacy in HER2--positive breast cancer with high clinical and pathological CR rates while being safe and well-tolerated. This regimen should be used more in the neoadjuvant setting, especially in cases of concern with anthracycline toxicity.

Article Information and Declarations

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics statement

This study was approved by the research committee of Vietnam's National Cancer Hospital under number: 2147/QD-BVK.

Written informed consent was obtained for all patients before enrolling them in the study.

Author contributions

D.T.L.: should be considered the major author. He participated directly in diagnosis, treatment, and follow-up of the patients, performed the literature review, and assisted in drafting parts of the study and formatting the presented material.

K.H.D. and T.A.D.: took part in the diagnostic and treatment consultant and, assisted in the literature review.

L.T.B.: performed patient follow-up, review of patients' records, literature review, and assisted in drafting parts of the study.

C.V.N.: performed diagnostic consultation on the HE stains and immunohistochemical staining, and assisted in the literature review, drafting parts of the study, and formatting the presented material.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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