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Pathological Complete Response with the 4AC-4THP Regimen in Neoadjuvant Treatment of HER2-Positive Breast Cancer: A Multicenter Retrospective Analysis in Vietnam

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ABSTRACT

Background: Evidence on the effectiveness of the 4AC–4THP neoadjuvant regimen in Vietnamese patients with HER2-positive breast cancer is limited. This study evaluated pathological response rates and associated clinical factors in patients treated with this regimen.

Methods: A retrospective review was conducted using medical records of 50 consecutive HER2-positive breast cancer patients who received neoadjuvant 4AC–4THP therapy at three institutions in northern Vietnam between January 2016 and October 2024. Pathological response was assessed using Chevallier's criteria, with complete pathological response defined as ypT0/Tis ypN0.

Results: Fifty eligible patients treated at Hanoi Medical University Hospital, Vietnam National Cancer Hospital, and Hanoi Oncology Hospital were included. The median age was 41 years (range: 26–67). Most patients were premenopausal (82%), while 18% were postmenopausal; 42% had hormone receptor-positive disease. The overall clinical complete response (cCR) rate for both tumors and lymph nodes was 46% (23/50). The pathological complete response (pCR) rate was 78% (39/50). Breast pCR (bpCR) was achieved in 80% (40/50) of patients, and nodal pCR (npCR) was observed in 94.1% (32/34) of patients with lymph node involvement. No significant associations were found between pCR and age, tumor grade, lymph node stage, disease stage, or hormone receptor status ($p > 0.05$; all ORs and 95% CIs crossed unity).

Conclusion: Neoadjuvant 4AC–4THP demonstrated high therapeutic efficacy in HER2-positive breast cancer, achieving a pCR rate of 78.0%.

INTRODUCTION

Breast cancer (BC) is the most prevalent malignancy among women globally and the leading cause of cancer-related mortality among females. In Vietnam, breast cancer is the most common cancer in females with 24,563 (28.9%) new cases in 2022, ranked as the fourth leading cause of death (10,003 deaths) in both genders.[1] The HER2-positive breast cancer subtype is often associated with a poor prognosis, aggressive progression, and an increased likelihood of early recurrence.[2]

Neoadjuvant systemic therapy has become the standard of care for patients with HER2-positive breast cancer presenting with locally advanced disease (≥T2) or regional lymph node involvement. Pathological complete response (pCR) is characterized by the complete absence of invasive

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carcinoma in the resected breast tissue and all evaluated regional lymph nodes following neoadjuvant treatment (ypT0/Tis ypN0).[3,4] Achievement of pCR at the time of surgery has been shown to correlate with improved clinical outcomes, particularly in patients with HER2-positive, hormone receptor (HR)-negative breast cancer, as evidenced by the pooled analysis from the CTNeoBC study. Across all the subgroups analyzed, pCR was significantly associated with enhanced event-free survival (EFS) (HR 0.48; 95% CI 0.43–0.54) and overall survival (OS) (HR 0.36; 95% CI 0.31–0.42).[5]

The integration of trastuzumab into neoadjuvant chemotherapy regimens has been demonstrated to significantly enhance both pathological complete response (pCR) rates and event-free survival (EFS) compared to chemotherapy alone, as illustrated by findings from the NOAH trial.[6] Consistent improvements in pCR outcomes have also been reported in the TECHNO and GeparQuattro studies, where trastuzumab was incorporated into standard chemotherapy protocols.[7,8]

Pertuzumab exerts its anti-tumor effect by binding to the extracellular domain II of HER2, thereby inhibiting ligand-dependent HER2–HER3 dimerization.[9] This mechanism of action complements that of trastuzumab. The NeoSphere trial reported a pCR rate of approximately 45% in patients treated with pertuzumab plus trastuzumab and docetaxel, compared to 29% in those receiving trastuzumab and docetaxel alone.[10] The combination of pertuzumab with trastuzumab and docetaxel was further investigated in the CLEOPATRA trial, which demonstrated a significant overall survival benefit (56.5 months vs 40.8 months).[11] Based on these findings, dual HER2-blockade with trastuzumab and pertuzumab in combination with standard neoadjuvant chemotherapy has become the established standard of care.[12]

Despite these advances, access to dual HER2-targeted therapy (trastuzumab-pertuzumab) remains limited for many HER2-positive breast cancer patients in Vietnam due to various socioeconomic and healthcare-related barriers. A 2024 survey in Vietnam revealed that only 37.5% of patients with HER2 overexpression received trastuzumab for at least one cycle (partially covered by insurance at 60%), and a mere 2.1% were treated with pertuzumab (not covered by insurance).[13] Due to this limitation, there is a paucity of data regarding the efficacy of dual HER2-targeted therapy in the neoadjuvant treatment of breast cancer in Vietnam. In Vietnam, anthracycline-containing regimens such as 4AC (anthracycline/cyclophosphamide)-4THP (taxane/trastuzumab/pertuzumab) remain widely used due to their proven efficacy, long-term data, flexible implementation in available healthcare settings, and acceptable tolerability. Meta-analyses and long-term follow-up support the use of anthracyclines as a cornerstone for high-risk breast cancer when used in appropriate patients with safe cumulative doses and careful cardiac monitoring. Cardiac safety data from TRYPHAENA and BERENICE trials showed low rates of grade 3–4 heart failure (<2%), with most left ventricular dysfunction reversible after treatment interruption. These findings indicate that anthracyclines can be safely incorporated into neoadjuvant regimens for HER2-positive breast cancer with proper cardiac surveillance. Therefore, this research was conducted to evaluate the response rate of the 4AC-4THP regimen in Vietnamese women with HER2-positive breast cancer.

METHODS

Study design

This study is a retrospective analysis of 50 women diagnosed with HER2-positive breast cancer at stages II or III, who underwent neoadjuvant treatment with AC-THP regimen at three oncology treatment centers in Northern Vietnam from January 2016 to October 2024. Histopathological response evaluation was based on Chevallier's criteria, in which complete pathological response was defined as ypT0/Tis ypN0. The study was approved by the Ethics Committee of Hanoi Medical University.

Eligible participants and materials

We selected patients who met the following inclusion criteria:

- Age: 18 and older
- Histopathologically confirmed diagnosis of invasive breast carcinoma by core needle biopsy.
- Immunohistochemical (IHC) assessment was performed on pre-treatment core needle biopsy specimens according to the St. Gallen 2013 classification; HER2 positivity was established with a result of 3+ on IHC or 2+ on IHC combined with positive ISH results. HER2 status was determined according to the ASCO/CAP 2018 guidelines.[14]
- TNM staging was done according to AJCC 8th edition, through clinical examination combined with information from breast ultrasound, mammography, magnetic resonance imaging and other paraclinical evaluations for metastatic assessment. Baseline nodal status was determined based on clinical examination and imaging assessment. In cases with suspicious lymph nodes, fine-needle aspiration (FNA) or core

needle biopsy was performed to confirm nodal metastasis.
- Administration of the 4AC-4THP neoadjuvant treatment regimen.
- Absence of contraindications to anthracycline medications, including significant cardiovascular conditions such as congestive heart failure, myocarditis, and myocardial infarction.
- Hematological and biochemical indices permitting chemotherapy.
- LVEF (Left Ventricular Ejection Fraction) ≥ 50%.
- Availability of comprehensive medical records.

Exclusion Criteria:
- Presence of bilateral breast cancer or a second primary malignancy.
- Stage IV breast cancer according to the AJCC 8th edition classification.
- Existence of other significant comorbidities with an imminent risk of mortality.
- Patients who did not follow the prescribed treatment regimen as intended.

All the patients meeting the inclusion criteria were included, without selective exclusion or record-based filtering. Non-compliance and significant comorbidities were identified retrospectively from medical records, including physician notes and relevant laboratory or imaging findings.

Regarding the treatment regimen, patients received neoadjuvant therapy based on the 4AC-4THP regimen. The 4AC regimen consisted of Doxorubicin at a dose of 60 mg/m² and Cyclophosphamide at 600 mg/m², administered every 2 weeks (dose-dense) or every 3 weeks with granulocyte colony-stimulating factor support. The 4THP regimen included Trastuzumab at 8 mg/kg for the first cycle and 6 mg/kg from the second cycle, combined with Pertuzumab at 840 mg for the first cycle and 420 mg from the second cycle, along with a taxane (Docetaxel at 75-100 mg/m² every 3 weeks or Paclitaxel at 80 mg/m² on days 1, 8, and 15 of every 3-week cycle, or Paclitaxel at 175 mg/m² every 2 weeks). G-CSF was administered according to institutional guidelines for patients at risk of neutropenia. All the patients underwent radical surgery following neoadjuvant treatment, with subsequent adjuvant therapy including HER2-targeted therapy, radiotherapy, and endocrine treatment depending on treatment response, disease stage, and immunohistochemical characteristics.

Information was extracted from medical records, including demographic characteristics of the patients (age, menopausal status, comorbidities, obstetric history) and tumor characteristics (location, size, histological classification, tumor grade, immunohistochemical features, disease stage), in addition to clinical response and histopathological response in the breast and lymph nodes. Pathological response was evaluated using Chevallier's criteria.[15] According to the Chevallier system we have the following:

pCR (pathological complete response): defined as the disappearance of all the tumor or DCIS in breast with no invasive carcinoma and negative lymph nodes.

pPR (pathological partial response): defined as presence of invasive carcinoma with stromal alterations.

pNR (pathological no response): defined as little modification in the original tumor appearance.

Data were verified for completeness, and standardized procedures were applied across centers to ensure consistency in data collection and recording. All cases were re-reviewed once prior to data analysis by experienced pathologists who are faculty members at Hanoi Medical University.

Statistical analysis

The primary outcome was pathological complete response (pCR), defined as a binary variable (yes/no). The analysis proceeded in two steps:

Univariable logistic regression was first performed for each candidate variable, including age, tumor stage, lymph node stage, overall clinical stage, hormone receptor status, Ki-67 index, tumor grade, and treatment compliance.

Variables with a p-value < 0.2 in the univariable analysis were considered eligible for inclusion in the multivariable model. From these, two predictors were selected for the multivariable logistic regression based on both statistical criteria and clinical relevance, ensuring adherence to the EPV constraint.

Odds ratios (ORs) with 95% confidence intervals (95% CI) and p-values were reported for both univariable and multivariable models. All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA), and a two-sided p-value < 0.05 was considered statistically significant. No imputation was performed due to the very low rate of missing values.

RESULTS

Patients and treatment

A total of 50 patients were diagnosed with HER2-positive breast cancer at stages IIA–IIIC who received treatment from January 2016 to October 2024 at Hanoi Medical University Hospital, Vietnam National Cancer Hospital, and Hanoi Oncology Hospital. These patients met the established inclusion

criteria and were included in the analysis. The median age of the cohort was 41 years (range, 26–67 years), and the median tumor size was 37.5 mm. Of these 50 patients, 41 (82%) were premenopausal, while 9 (18%) were postmenopausal. Furthermore, 21 patients (42%) exhibited hormone receptor-positive status, and 1 patient's HER2 status was confirmed via in-situ hybridization (ISH) testing. The characteristics of the study population are summarized in Table 1.

All of the patients underwent radical surgery; of these, 47 patients (94.0%) received modified radical mastectomy, while 3 patients (6.0%) underwent breast-conserving surgery.

Table 1. Patient Characteristics and Treatment

	Characteristics	Number (n=50)	Percentage (%)
Age	<40	20	40.0
	≥40	30	60.0
Menopausal status	Menopausal	9	18.0
	Pre-Menopausal	41	82.0
Tumor stage	cT1	2	4.0
	cT2	34	68.0
	cT3	10	20.0
	cT4	4	8.0
Lymh node stage	cN0	16	32.0
	cN1	17	34.0
	cN2	12	24.0
	cN3	5	10.0
Primary Stage	IIA	16	32.0
	IIB	12	24.0
	IIIA	14	28.0
	IIIB	3	6.0
	IIIC	5	10.0
Histopathology	Invasive breast carcinoma – NST	39	78.0
	Other invasive breast carcinomas	11	22.0
Tumor grade	2	33	66.0
	3	17	34.0
Hormon Receptor Status	Positive (ER and/or PR positive)	21	42.0
	Negative	29	58.0
HER2 status	IHC (+++)	49	98.0
	IHC (++) – Dual-ISH (+)	1	2.0
Ki-67	< 20%	2	4.0
	≥ 20%	48	96.0
AC regimen	AC dose-dense (2-week)	46	92.0
	AC 3-week	4	8.0
THP regimen	Docetaxel – HP	25	50.0
	Paclitaxel weekly – HP	7	14.0
	Paclitaxel 2-week – HP	18	36.0
Type of Surgery	MRM	47	94.0
	Conservative	3	6.0

ER, estrogen receptor; PR, progesterone receptor; AC, anthracycline, cyclophosphamide; THP, taxane, trastuzumab, pertuzumab; MRM, modified radical mastectomy.

Clinical and Pathological response

The overall clinical complete response (cCR) rate for both tumors and lymph nodes was 46% (23 out of 50) according to the RECIST 1.1 criteria, with the cCR rate for breast tumors at 58% (29 out of 50) and for lymph nodes at 91.2% (31 out of 34). The total pathological complete response (tpCR) rate for both the primary tumor and axillary lymph nodes was 78% (39 out of 50). bpCR was achieved in 40 out of 50 patients (80%) for breast tumors and npCR was achieved in 32 out of 34 patients (94.1%) for lymph nodes. There was 1 patient with stable disease following neoadjuvant treatment, and no patients experienced disease progression.

Figure 1 presents detailed information on response rates in both breast tumors and lymph nodes.

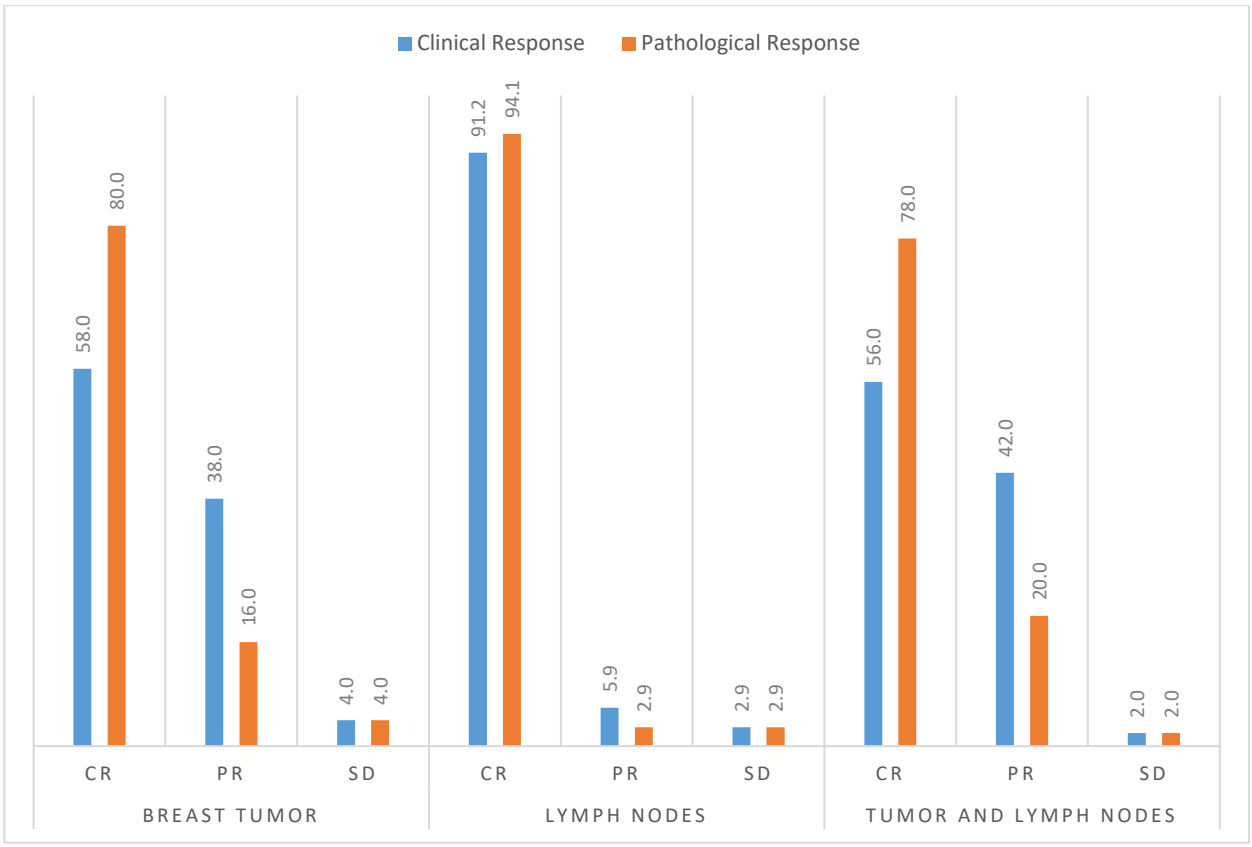

Figure 1. Clinical and Pathological Response**.** CR, complete response; PR, partial response; SD, stable disease.

Table 2. Pathological Response by related factors

Related factors		Univariate logistic regression		Multivariate logistic regression	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Age	<40	1.00 (Reference)	-	1.00 (Reference)	-
	≥40	0.259 (0.049–1.359)	0.110	0.334 (0.059–1.881)	0.214
Lymph Node Stage	cN0	1.00 (Reference)	-	-	-
	cN1	1.083 (0.087-13.538)	0.950	-	-
	cN2	0.600 (0.053-6.795)	0.680	-	-
	cN3	1.250 (0.087-17.975)	0.870	-	-
Primary Stage	IIA	1.00 (Reference)	-	-	-
	IIB	3.750 (0.190-74.065)	0.385	-	-
	IIIA	0.250 (0.021-2.945)	0.271	-	-
	IIIB	0.917 (0.073-11.577)	0.946	-	-
	IIIC	NE (Not Estimable)	-	-	-
Hormon Receptor Status	Positive (ER and/or PR positive)	1.00 (Reference)	-	-	-
	Negative	0.521 (0.135-2.011)	0.344	-	-
Tumor grade	2	1.00 (Reference)	-	1.00 (Reference)	-
	3	3.055 (0.771-12.100)	0.112	0.441 (0.104-1.875)	0.268

CI = confidence interval; OR = Odds Ratio.

No statistically significant associations with pCR were observed in the multivariate logistic regression model, which included only age and tumor grade — the two variables that met the inclusion threshold ($p < 0.2$) in the univariate analyses while still complying with the events-per-variable constraint ($p > 0.05$ for both).

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Echocardiography was performed at baseline, after 4AC, after 4THP, and before surgery. No clinical cardiac events were reported. Declines in LVEF were asymptomatic and reversible in most cases. Most non-cardiac toxicities were mild to moderate and manageable with supportive care. No treatment-related deaths or permanent discontinuation of therapy due to toxicity were reported.

Table 3. Toxicities in patients receiving the 4AC-4THP neoadjuvant regimen

Cardiac Parameters	Number of Patients (n=50)	Percentage (%)
Cardiotoxicity		
Symptomatic heart failure	0	0.0%
Any decrease in LVEF	40	80%
LVEF < 50% or a decline of ≥10 percentage points	0	0.0%
Mean reduction in LVEF (overall)	-	8.05% (mean)
Mean reduction after AC phase	-	6.10% (mean)
Mean reduction after THP phase	-	1.95% (mean)
Discontinuation of anti-HER2 therapy due to cardiotoxicity	0	0.0%
Non-Cardiac Toxicityies (Grade 3-4)		
Neutropenia	9	18.0% Mostly occurred during AC dose-dense (8/9 cases)
Anemia	0 (0%)	
Thrombocytopenia	0 (0%)	
Fatigue, anorexia	0 (0%)	
Oral Mucositis	2	4.0% Primarily during AC phase
Diarrhea	0 (0%)	
Peripheral neuropathy	0 (0%)	Almost related to paclitaxel use in THP regimen; all Grade 1–2
Infusion-related reaction (taxane)	0 (0%)	

DISCUSSION

The rate of pathological complete response (pCR) is often a primary endpoint in neoadjuvant breast cancer treatment studies. Studies have indicated that achieving pCR is associated with decreased rates of recurrence and mortality.[16] The combination of chemotherapy with trastuzumab and pertuzumab significantly improves pCR rates in neoadjuvant treatment settings.[12]

In the present study, the total pCR rate was achieved at 78.0%, with pCR rates for breast tumors and lymph nodes found to be 80.0% and 94.1%, respectively. These results are significantly higher than those from the NEOSPHERE study. In the NEOSPHERE study, the population was stratified into four treatment groups, which included trastuzumab combined with docetaxel, pertuzumab combined with trastuzumab and docetaxel, trastuzumab combined with pertuzumab, and docetaxel combined with pertuzumab. The primary objective of the NEOSPHERE study was to evaluate the overall histopathological response at the time of surgical intervention. The results indicated that the group treated with the neoadjuvant regimen of docetaxel combined with trastuzumab and pertuzumab achieved a complete histopathological response in breast tumors (bpCR) of 45.8% and an overall total pathological complete response (pCR) for both breast and lymph nodes of 39.3%, which was statistically significant compared to the other groups; however, these rates were lower than those found in the current study. It is hypothesized that the lower pCR rates observed in the NEOSPHERE study may be partially attributed to the specific chemotherapy regimen utilized, as their protocol employed docetaxel as a single-agent therapy.[10] In practice, combination therapies involving HER2-targeted agents such as ACTH(P) or TCH(P) are generally associated with higher response rates. Consequently, to achieve higher response rates, the AC-THP regimen was selected, which is also incorporated into several guidelines for neoadjuvant treatment of HER2-positive breast cancer.

In the TRYPHAENA study pCR rates were reported to range from 54.7% to 63.6% across treatment groups, with the highest response rate observed in the TCHP group. While the primary objective of the TRYPHAENA study was not to evaluate pCR, its secondary outcomes yielded pCR results in the TCHP group that were closely aligned with the findings of the current study, despite differences in the chemotherapy regimens utilized.[17] Thus, the AC-THP regimen demonstrates efficacy comparable to that of larger international studies. Our results are higher than those reported by Phùng Thị Huyền (2020), who found a pCR rate of 64.1% (n=39 patients) for the ACTH or TCH regimen.[18] Furthermore, Phùng Thị Huyền (2021) published findings indicating a pCR rate of 80% with the ACTHP and TCHP regimens among 20 patients, which closely aligns with the results of our study.[19] These findings, along with data from other studies, suggest that the addition of pertuzumab to

chemotherapy regimens combined with trastuzumab enhances the likelihood of achieving pCR in HER2-positive breast cancer.

Numerous studies have sought to identify predictive factors for pCR among the studied populations. The TECHNO study found no significant differences in pCR rates when comparing variables such as age (<40; ≥40), histological type, tumor grade, tumor stage, lymph node status, and hormone receptor status.[7] Conversely, the Gepar Quattro study reported a higher pCR rate in the hormone receptor-negative group (43.5%), while the hormone receptor-positive group achieved only 23.4% ($p < 0.001$).[8] The NOAH study noted significant differences in pCR rates between stage II (75%) and stage III (40%) with $p = 0.03$.[6] After conducting univariate logistic regression analyses for all candidate variables, age and tumor grade met the selection threshold ($p < 0.2$) and were included in the multivariable model, in accordance with the events-per-variable constraint. In multivariable analysis, neither age nor tumor grade was significantly associated with pCR. Specifically, patients aged ≥40 years had a lower, though not statistically significant, likelihood of achieving pCR compared with those <40 years ($p = 0.214$; OR 0.334, 95% CI: 0.059–1.881). Likewise, higher tumor grade was not significantly associated with pCR ($p = 0.268$; OR 0.441, 95% CI: 0.104–1.875). The results of our study are consistent with the TECHNO study, as there were no significant correlations between the investigated factors and pCR rates.[7]

Several factors may explain why no variables were identified as significant predictors of pCR. The overall pCR rate was very high (78%), leaving few non-pCR cases and limiting statistical discrimination between the subgroups. The small sample size ($n = 50$) further reduced analytical power and restricted the number of variables eligible for multivariable modeling. Moreover, all the patients received the same neoadjuvant regimen (4AC–4THP), resulting in substantial clinical and biological homogeneity. Some subgroups contained very few patients, producing unstable OR estimates. Collectively, these factors likely contributed to the absence of statistically significant predictors of pCR.

Our study demonstrated that the 4AC-4THP neoadjuvant regimen was generally well-tolerated, with no cases of symptomatic heart failure or treatment discontinuation due to cardiotoxicity. Although 80% of the patients experienced some degree of LVEF reduction, the mean decline was modest (8.05%) and no patient met the threshold for clinically significant cardiotoxicity (LVEF < 50% or ≥10-point drop). These findings are consistent with contemporary reports showing that dual HER2 blockade combined with anthracycline-based therapy can cause measurable but mostly reversible decreases in LVEF, particularly when cardiac monitoring is performed rigorously. Regarding non-cardiac adverse events, grade 3–4 neutropenia occurred in 18% of patients—predominantly during the dose-dense AC phase—which aligns with the known myelosuppressive risk of anthracyclines. Other severe toxicities were uncommon, and no grade 3–4 anemia, thrombocytopenia, diarrhea, neuropathy, or infusion reactions were observed. Mucositis was infrequent and confined to the AC component. Overall, the toxicity profile observed in our cohort suggests that the 4AC-4THP regimen is manageable with appropriate supportive care and may be safer than previously reported for sequential anthracycline and dual HER2 blockade.

Limitations

This study has several limitations. Its retrospective design introduces risks of selection and information bias. The small sample size and uneven subgroup distributions limited statistical power and led to unstable or non-estimable ORs. Variability in diagnostic and pathological assessment across the three institutions may have introduced heterogeneity. Advanced molecular markers were not consistently available and could not be analyzed. Finally, the absence of a comparison arm prevents causal inference or direct comparison of 4AC–4THP with other neoadjuvant regimens.

CONCLUSION

The 4AC-4THP regimen in neoadjuvant treatment for HER2-positive breast cancer has shown high therapeutic efficacy, achieving a pathological complete response (pCR) rate of 78.0%. Based on these findings, it is imperative to undertake additional research to investigate the survival benefit associated with this treatment protocol in HER2-positive breast cancer patients.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest or financial ties to disclose with the contents of this article.

ETHICAL CONSIDERATIONS

The study complied with the 1964 Helsinki Declaration and was approved by the Ethics Committee of Hanoi Medical University (IRB-VN 01001), along with the ethical approval certificate number 934/GCN-HĐĐĐNCYSH-ĐHYHN. All participants were informed about the aims of the study and provided written informed consent prior to participation. Personal identifiers were removed

during data abstraction, and all data were stored securely in password-protected databases accessible only to study investigators.

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DATA AVAILABILITY

The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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AI DISCLOSURE

This manuscript was not created using any generative AI methods for design, analysis, or writing.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Dinh Anh Tran. The first draft of the manuscript was written by Dinh Anh Tran, and all authors provided comments on previous versions. All authors read and approved the final manuscript.

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