PRELIMINARY RESULTS OF THE 4AC-4THP NEOADJUVANT TREATMENT FOR HER2 POSITIVE BREAST CANCER

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The aim is to assess the preliminary efficacy of the 4AC-4THP neoadjuvant treatment regimen in patients diagnosed with HER2-positive breast cancer. This retrospective descriptive study included 38 eligible patients with confirmed HER2-positive breast cancer treated with the 4AC-4THP neoadjuvant regimen from January 2016 to February 2025 at Hanoi Medical University Hospital, Vietnam National Cancer Hospital, and Hanoi Oncology Hospital. The results show that among the 38 patients enrolled in the study, the median age was 43.29 years old (range 28 - 62). The cohort included 21 patients (55.3%) in stage II and 17 patients (44.7%) in stage III. The average tumor size measured 42.05mm, with a hormone receptor positivity rate of 34.2%. The total pathological complete response (tpCR) was achieved in 78.9% (30 out of 38 patients). No statistically significant correlation-was observed between tpCR rates and factors such as age, clinical stage, tumor size, histological grade, Ki-67 index, hormone receptor status, or treatment regimen. There was no evidence of disease progression during the neoadjuvant treatment. The most frequent grade 3 and 4 adverse events were neutropenia and nausea/vomiting, reported at rates of 13.1% and 10.5%, respectively. No patient experienced treatment discontinuation due to cardiovascular events or other serious adverse effects. The 4AC-4THP neoadjuvant regimen demonstrates high efficacy and an acceptable safety profile in the treatment of HER2-positive breast cancer in this cohort.

Keywords: HER2-positive breast cancer, neoadjuvant treatment, 4AC-4THP regimen, tpCR.

I. INTRODUCTION

Breast cancer (BC) is the most prevalent malignancy among women globally and the leading cause of cancer-related mortality in females.[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 therapy-also referred to as preoperative systemic therapy-involves administering systemic treatment prior to surgical intervention and has been shown to yield comparable outcomes in terms of overall survival when compared to adjuvant therapy. Moreover, neoadjuvant therapy offers distinct advantages over adjuvant therapy, such as the possibility of converting unresectable disease to resectable status, increasing the rate of breast-conserving surgery, and facilitating the assessment of tumor response during treatment.[3]

Neoadjuvant treatment of HER2-positive breast cancer using a chemotherapy regimen combined with dual HER2-targeted therapy (trastuzumab and pertuzumab) has

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demonstrated higher response rates compared to chemotherapy combined with trastuzumab alone.[4,5] One of the preferred regimens for neoadjuvant treatment in HER2-positive breast cancer is the 4AC-4THP regimen. However, there is a lack of studies evaluating the efficacy of this regimen in Vietnam. Therefore, we conducted this study to access he preliminary efficacy of the 4AC-4THP neoadjuvant treatment regimen in patients diagnosed with HER2-positive breast cancer.

II. MATERIALS AND METHODS

1. Subjects

Thirty-eight patients diagnosed with HER2-positive breast cancer received neoadjuvant treatment using the 4AC-4THP regimen at Vietnam National Cancer Hospital, Hanoi Oncology Hospital, and Hanoi Medical University Hospital from January 2016 to February 2025.

Inclusion Criteria

- Histopathologically confirmed diagnosis of invasive ductal carcinoma of the breast.
- HER2 positivity confirmed by immunohistochemistry or FISH/Dual-ISH assays.
- Aged 18 years and older.
- 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.
- LEVF ≥ 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.
- Non-compliance with the prescribed treatment regimen.

2. Methods

Study Design: This study is a retrospective descriptive analysis.

Sample Size: A convenience sampling method was employed, resulting in the inclusion of 38 patients who met the established inclusion and exclusion criteria.

Methodology:

- Medical records were collected according to the designated study case record template.
- Selection of patients who fulfilled the eligibility criteria for participation in the study.
- Documentation of clinical symptoms and paraclinical findings recorded prior to and during the treatment phase.
- Assessment of treatment outcomes related to the neoadjuvant regimen.
- Data analysis was performed utilizing appropriate statistical methods.

Treatment Regimen in the Study: The AC-THP regimen consists of Doxorubicin administered at a dose of 60 mg/m² and Cyclophosphamide at 600 mg/m², delivered every 2 weeks (dose-dense) or every 3 weeks. This is followed by Trastuzumab at 8 mg/kg in cycle 1 and 6 mg/kg starting from cycle 2, in combination with Pertuzumab at 840mg in cycle 1 and 420mg from cycle 2. Additionally, Taxane (Docetaxel at 75 - 100 mg/m² every 3 weeks, or Paclitaxel at 80 mg/m² on days 1, 8, and 15 every 3 weeks, or Paclitaxel at 175 mg/m² every 2 weeks) is incorporated.

Study Variables and Metrics*:*

Patient Demographics: Age, performance status, menopausal status, tumor characteristics (tumor size, immunohistochemistry profile, Dual-ISH results, histological type, tumor grade), axillary lymph node status prior to treatment, disease stage, and treatment regimen.

Treatment Outcomes: Evaluation of response and adverse effects associated with the regimen.

Clinical tumor and lymph node response were assessed using the RECIST 1.1 criteria, categorized into four response levels: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) after every four cycles.

Histopathological response for the tumor and lymph nodes, as well as both combined, was classified according to Chevallier's criteria. Based on this classification, responses were divided into two categories: pathological complete response (pCR) and non-pathological complete response (No pCR). A complete histopathological response in both the tumor and lymph nodes is termed total pathological complete response (tpCR), while cases that do not meet this criterion are classified as No tpCR.

Adverse events were classified according to the CTCAE version 5.0: clinical toxicities were evaluated through direct examination, whereas hematologic toxicities were assessed via clinical examination and hematologic tests following each treatment cycle.

Data Analysis

The study employed SPSS statistical software version 20.0 for data analysis. This encompassed descriptive statistics, Chi-square tests for comparing categorical variables, and T-test for comparing means between groups.

3. Research ethics

The study complied with the Declaration of Helsinki on ethical principles for medical research involving human subjects and was approved by the Ethics Committee of Hanoi Medical University (IRB-VN01001), along with the ethical approval certificate number 934/GCN-HDDDNCYSH-DHYHN, September 25, 2023.

III. RESULT

Table 1. Clinical and Pathological Response

Treatment response		No. Patients (n = 38)	Rate(%)
Clinical Response			
Breast tumor	CR	7	18,4
	PR	30	78,9
	SD	1	2,6
	Total	38	100
Lymph Nodes	CR	13	54,2
	PR	11	45,8
	SD	0	0
	Total	24	100

Treatment response		No. Patients (n = 38)	Rate(%)
Clinical Response			
Tumor and Lymph Node	CR	6	15,8
	PR	31	81,6
	SD	1	2,6
	Total	38	100
Pathological Response			
bpCR	pCR	31	81,6
	No pCR	7	18,4
	Total	38	100
npCR	pCR	22	91,7
	No pCR	2	8,3
	Total	24	100
tpCR	tpCR	30	78,9
	No tpCR	8	21,1
	Total	38	100

bpCR-breast pathological complete response, npCR-nodes pathological complete response

Clinical response was assessed according to RECIST 1.1 criteria, with an overall response rate (including complete response and partial response) for both tumor and lymph nodes reaching 81.6%. One patient had stable disease, and no patients reported disease progression during the treatment. The total pathological complete response (tpCR) rate was 78.9%.

Table 2. Respone rate with related factors

Related factors	No tpCR	tpCR	p
Age			
< 40	2	13	0,518
40 - 60	6	16	
> 60	0	1	
Tumor Stage			
cT1	0	2	0,490
cT2	5	21	
cT3	3	5	
cT4	0	2	

Related factors	No tpCR	tpCR	p
Lymph Node Stage			
cN0	3	11	0,997
cN1	2	8	
cN2	2	8	
cN3	1	3	
Primary Stage			
IIA	1	11	0,590
IIB	3	6	
IIIA	3	8	
IIIB	0	2	
IIIC	1	3	
Histopathology			
Invasive breast carcinoma – NST	6	23	0,842
Invasive tubular carcinoma	2	6	
Other invasive breast carcinomas	0	1	
Tumor Grade			
2	4	20	0,385
3	4	10	
Hormon Receptor Status			
Positive (ER and/or PR positive)	4	9	0,289
Negative	4	21	
Ki-67			
< 20%	0	2	0,453
≥ 20%	8	28	
AC regimen			
AC dose-dense (2-week)	7	27	0,838
AC 3-week	1	3	
THP regimen			
Docetaxel – HP	4	18	0,537
Paclitaxel weekly – HP	2	9	
Paclitaxel 2-week – HP	2	3	

NST-no special type, ER-estrogen receptor, PR-progesterone receptor

No statistically significant difference was observed in the rates of total pathological complete response (tpCR) when analyzing the association with factors such as age, tumor stage, lymph node stage, disease stage, tumor histopathology, tumor grade, Ki-67 index, hormone receptor status, and treatment regimen ($p > 0.05$).

Table 3. Treatment Adverse Effects

Grade 3,4 - Adverse Effects	**n = 38**	**Rate**
Neutropenia	5	13,1
Febrile Neutropenia	1	2,6
Thrombocytopenia	0	0
Nausea/Vomiting	4	10,5
Renal Toxicity	0	0
Hepatic Toxicity	1	2,6
Heart Failure/LEVF decline leading to Treatment Delay/Discontinuation	0	0

The most frequently observed grade 3 and 4 toxicities were neutropenia and nausea/vomiting. No grade 3 or 4 toxicities were reported regarding thrombocytopenia, hepatic toxicity, or renal toxicity. Additionally, the study did not document any cases of heart failure or a significant reduction in left ventricular ejection fraction (LVEF) that resulted in treatment delays or discontinuation. There were 5 instances of treatment delays attributed to grade 3 and 4 toxicities related to neutropenia and febrile neutropenia, representing 1.6% of a total of 304 treatment cycles.

IV. DISCUSSION

The rate of pathological complete response (pCR) is often a primary endpoint in neoadjuvant breast cancer treatment studies.[6] Trials have indicated that achieving pCR is associated with decreased rates of recurrence and mortality. The combination of chemotherapy with trastuzumab and pertuzumab significantly improves pCR rates in neoadjuvant treatment settings.

In the present study, the pCR rate was reached at 78.9%, with pCR rates for breast tumors and lymph nodes reported at 81.6% and 91.7%, respectively. These results are significantly higher than those from the NEOSPHERE study.[5] In the NEOSPHERE trial, the study 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. 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 (tpCR) 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.[5] 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.

Another study, the TRYPHAENA trial, reported pCR rates ranging from 54.7% to 63.6% across treatment groups, with the highest response rate observed in the TCHP group.[4] 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. Thus, the AC-THP regimen demonstrates efficacy comparable to that of larger international studies. Our results are higher than those reported by Phung Thi Huyen (2020), who found a pCR rate of 64.1% (n=39 patients) for the ACTH or TCH regimen.[7] Furthermore, Phung Thi Huyen (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.[8] 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 including the TECHNO study, the Gepar Quattro, The NOAH study… The TECHNO study found no significant difference in pCR rates when comparing variables such as age (< 40; ≥ 40), histological type, tumor grade, tumor stage, lymph node status, and hormone receptor status.[9] 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% ($p < 0.001$).[10] The NOAH study noted significant differences in pCR rates between stage II (75%) and stage III (40%) with $p = 0.03$.[11] After analyzing the pCR rates concerning factors including age, tumor stage (T), lymph node stage (N), overall clinical stage, histological type, tumor grade, hormone receptor status, Ki-67 index, and treatment regimen through Table 2, the results of the present study are consistent with the TECHNO study, as there were no significant correlation between the investigated factors and pCR rates.[9]

The research indicates that the AC-THP regimen is well-tolerated. The most frequently reported grade 3 and 4 adverse effects were neutropenia and nausea/vomiting, with rates of 13.1% and 10.5%, respectively. These findings are consistent with those reported by Phung Thi Huyen (2021), which indicated a 15% rate of grade 3 and 4 neutropenia and a 10% incidence of grade 3 and 4 nausea/vomiting.[8] Cardiovascular adverse events remain a significant concern when using HER2-targeted therapies; however, the current study did not report any instance of severe cardiovascular events or treatment interruptions due to cardiac toxicity.

V. CONCLUSION

The AC-THP regimen in neoadjuvant treatment for HER2-positive breast cancer

has shown promising therapeutic efficacy in this cohort, achieving a pathological complete response (pCR) rate of 78.9% and exhibiting a favorable tolerance profile.

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Declarations

Authors' contributions: All authors contributed to the study conception and design. All authors read and approved the final manuscript.

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