Section A-Research Paper
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Efficacy of Neoadjuvant chemotherapy for early stage of breast cancer in Viet Nam

Running head: Neoadjuvant chemotherapy for breast cancer

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Statements and Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by LTA, NTT, NTMH. The first draft of the manuscript was written by LTA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Consent to participate

Informed consent was obtained from all patients for being included in the study.

Abstract

Background: Neoadjuvant chemotherapy (NAC) is increasingly used in breast cancer (BC), especially for downstaging the primary tumor in the breast and the metastatic axillary lymph nodes. Accurate evaluations of the response to neoadjuvant chemotherapy provide important information on the impact of systemic therapies on breast cancer biology, prognosis, and guidance for further therapy. This study was

to assess short-term and oncological outcomes of NAC for early stage of breast cancer in Vietnamese population.

Methods: A retrospective study was conducted from January 2020 to December 2022 with 200 patients who completed NAC for early stage of BC. The patients then underwent a radical surgery or not depending on clinical response. Short-term outcomes included clinical response based on the Response Evaluation Criteria in Solid Tumor version 1.1, adverse events assessed by the National Cancer Institute-Common Toxicity Criteria for Adverse Event, and rate of pCR (pathological complete responses) which is associated with recurrence and death.

Results: Mean age was 52 years and 99.5% of patients were female. All patients were classified clinically as stage II (47%) and stage III (53%). Clinical responses were achieved in all patients, but only 6/200 patients (3.0%) got complete clinical responses. Most patients (99.5%) underwent surgery after NAC but pCR was only 17.1%. Two-year progression free survival (PFS) was 86.6%. Patients with pCR had significantly higher survival rate than those without complete response.

Conclusions: NAC for early stage of breast cancer is safe and increasing radical surgery. Even when pCR is not achieved, NAC nevertheless allows us to triage patients who did not achieve pCR so that they can be treated using additional therapy. Therefore, accurate evaluation of the response to NAC is the key factor that influences therapeutic decision-making.

Key words: Breast cancer; Neoadjuvant chemotherapy; pathological complete responses; Tumor response; disease free survival

Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide. Neoadjuvant chemotherapy (NAC) has been demonstrated to be of great clinical value in locally advanced and inoperable breast cancer. [1] Firstly introduced in the early 1980s in patients with locally advanced disease, main benefit of neoadjuvant chemotherapy was its potential to increase breast conservation, which were associated with less morbidity and improved body image compared with complete breast removal. [2] However, there was concern about local control after downstaging of the tumours and the delay to surgery in patients with tumours resistant to chemotherapy.

NAC was a useful tool that provided information on the impact of systemic therapies on breast cancer biology. [3] Previous research has indicated that patients who attain pathological complete response (pCR) to NAC have significantly longer overall survival (OS) and disease-free survival (DFS), particularly for triple negative and HER2+ breast cancer. [4-6] It was therefore important to identify those patients who are most likely to benefit from NAC treatment and to understand the advantages of NAC with respect to long-term outcomes.

In Vietnam, breast cancer is also the most common disease in women with the annual number of new cases of 21,555 cases. [1] Treatment of breast cancer is typical of a combination of existing treatments in cancer in which surgery still plays a major role, especially in patients with stage I-III. Chemotherapy in addition to adjuvant effects also has the role of adjuvant treatment, palliative treatment, radiotherapy to reduce the rate of local and regional recurrence. The outcome of treatment depends on many factors, and some factors are considered to be of known prognostic significance: age, tumor size, lymph node metastasis status, histopathology, histologic grade, invasion of lymphatic and vascular infiltration, endocrine receptor status, Her-2, Ki-67,... [7].

Although breast cancer is a disease with a fairly good prognosis, the 5-year overall survival rate is high, but this rate is still highly variable among patient groups when classified according to a number of epidemiological and epidemiological factors. According to SEER, the 5-year overall survival rate of all breast cancer patients in the period 2007-2013 was 89.7%. [8] In Vietnam, some previous studies on the results of cancer treatment showed that the 5-year overall survival time with stage II-III patients varied between 75%-84% depending on the study. [9]

Our hospital is a tertiary oncological center of Southern Vietnam with an estimated population of nearly 47 million people. Since 2019, we have had MDT for all new breast cancer patients. The safety and effectiveness of these NAC need to be evaluated and reported, particularly this is one of the first studies on NAC for BC stage IB-IIIC in Vietnamese population. We therefore performed this study to evaluate short-term and oncological outcomes of NAC and to explore factors associated with the clinical outcomes in BC stage IB-IIIC patients.

Methods

We retrospectively reviewed all patients with stage IB-IIIC of BC who had received NAC from Jan 2020 to December 2022 in our hospital. The institutional ethics committee had approved to conduct the study. We included patients ≥18 years of age who were histologically confirmed of stage IB-IIIC of BC. Stage IB-IIIC of BC was defined by a tumor invading regional lymph nodes (i.e., N stage 1-3) or local structures (i.e., T stage 3-4), and early stage of BC (i.e., especially HER2 positive) in accordance with the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system (8^{th} edition).[10]

Neoadjuvant chemotherapy

All patients were received 6-8 cycles of NAC regimens and then were assessed for clinical response. There were some modifications of the doses to manage toxicities. In case of grade-4 hematological toxicities, we reduced the doses of NAC regimens by 20%. In case of grade-3 or 4 non-hematological toxicities, we reduced the doses of NAC regimens by 20%. In case of cardiovascular events, we reduced the dose of anti Her2 by 15% and stop using of anti-Her2 if cardiovascular events happenned twice. In case of doxorubicin in NAC regiment, granulocyte colony-stimulating factor (G-CSF) was used.

Patient evaluation

A multidisciplinary consultation was routinely performed for staging and treatment planning for all patients. We evaluated the clinical stage at baseline and every three or four cycles when the patients were receiving NAC using ultrasound of abdomen, breast, thyroid gland, cervical lymph nodes and chest X-rays. After completing the NAC, if a patient was evaluated as clinical response (SD,PR,CR), he/she was introduced for surgery. Otherwise, the patient was introduced to continue chemotherapy. After the multi-modality treatment, patients were followed in a 3-month interval in 5 years for hormonal therapies, and a 6-month interval afterwards. At each visit, evaluations included physical examination, routine complete blood count and blood chemistry, electrocardiogram, and the Eastern Cooperative Oncology Group (ECOG) performance status and CT scan were performed every six months to assess the progression of the disease; 18-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT fusion images were used in some patients when necessary. Clinical staging was done using the AJCC TNM staging system (8^{th} edition).

Outcomes assessment

We used the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 [11] to evaluate clinical response after completing the NAC with four categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR was defined by the disappearance of all lesions and pathologic lymph nodes detected before treatment. PR was defined by a ≥30% decrease in sum of the diameters of the lesions compared to before treatment without new lesions. PD was defined by a ≥20% increase in sum of the diameters of the lesions or having any new lesion. SD was any case that did not qualify for PR or PD. Tumor down-staging was evaluated and defined by either T or N down-staging (i.e., a reduction in the T or N descriptor compared to before treatment). In all patients who underwent surgery, pathologic complete response (pCR) was also assessed and was defined by the absence of residual cancer cells in the specimens of the tumor and all dissected lymph nodes. [12]

Oncological outcomes included overall survival (OS) and disease-free survival (DFS). OS was defined as the time from the first dose of the NAC to death from any cause, and DFS was the time from the day of operation to the detection of any disease progression, or death from any cause. Disease progression included recurrences and/or metastases, which was categorized into two subgroups: (1) 'visceral metastasis' type included any metastasis to the to the lung, liver or other distant organ; (2) 'non-visceral metastasis' type included any recurrence in regional or distant lymph node or any metastasis to the brain, bone at the time disease progression was diagnosed.

Statistical analysis

Patient characteristics and all outcomes were described by the number of patients and percentage for qualitative variables, and mean and standard deviation (SD) for quantitative variables. The survival outcomes (OS and PFS) were analyzed using the Kaplan-Meier method to estimate 1-year and 2-year PFS with 95% confidence intervals (CIs). The results were plotted by Kaplan-Meier curves for all patients and by subgroups with and without pCR. Factors associated with pCR and survival outcomes were assessed by univariable logistic regression and Cox proportional hazard models respectively. Results from the models were reported by odds ratio (OR) for logistic regression models and hazard ratio (HR) for Cox models with the corresponding 95% CIs. All statistical analyses were done using the statistical software SPSS version 20.0.

Results

From Jan 2020 to December 2022, 200 patients with stage IB-IIIC of BC completed NAC and were eligible to be included in this study. Mean age was 52 years and female were predominant (only one patient was male). Almost half of the patients (43.5%) aged 41-55, 27% of patients aged 56-65, 16.5% of patients are younger the age of 40 and 13% of patients are older than 65. Breast tumor in the right and left side were equal, both were 96 patients (48%), only 3 patients (1.5%) had tumors at bilateral breasts. Most patients were categorized as stage II (47%), stage III (53%) (Table 1).

The NAC regimen was intended to use in all patients, of which 40.5% of patients used 4 Adriamycin Cyclophosphamide – 4 Docetaxel regimen, chemotherapy combined anti-HER2 was used in 31.5% of HER2 positive BC but 10.5% of HER2 positive BC actually received doublet regimen of anti-HER2. Adjuvant radiotherapy was performed in 178 patients (89%); most patients received 42.56Gy/16Fx of radiation, only 2 patients with BCS received the dose of 60Gy/30Fx. Regarding tumor responses, CR was achieved in 6 patients (3.0%); 131 (65.5%) had PR and 62 (31%) had SD and 1 (0.5%) had PD. Tumor down-staging was observed in 137 patients (68.5%). However, due to the patients' preference, 199/200 patients (99.5%) underwent surgery. Among those, 34 patients (17.1%) achieved a pCR (Table 2).

Mean length of follow-up was 13.8 months. There were 14 patients (7.0%) with disease progression but no death. The most common type of disease progression was hematogenous type (35.7%), followed by mixed (28.6%), loco-regional (28.6%), and peritoneal (7.1%) types. Two-year DFS were 86.6% respectively (Table 3, Figure 1).

We found the NAC significantly associated with pCR: patients received chemotherapy combined with anti-HER2 had higher rate of pCR than patients with other regimens ($p<0.05$). As expected, patients without CR (PR or SD or PD) had significantly lower survival rate compared to patients with CR ($p=0.028$ for DFS respectively) (Figure 2).

Discussion

Our study summarized the benefit of NAC in Vietnamese patients with stage IB-IIIC of BC. The regimens were generally used is 4AC-4Docetaxel with 40.5% of the patients, followed by TAC (24%), TCH (18.5%). The NAC was effective with 68.5% of the patients achieved clinical responses (PR, CR). However, patients with pCR were 7%; two-year DFS in our study were 86.6% respectively. We found that patients with CR had better survival outcome than those without CR.

The rate of pCR varies dramatically among breast cancer subtypes. Triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2 (HER2)-positive tumors breast cancers can achieve pCR rates greater than 60% [13-16]. It is commonly acknowledged that pCR is associated with better long-term survival [17, 18]. Based on the results of 12 international trials and 11955 patients, Cortazar et al. confirmed the strongest association between pCR and long-term outcomes in TNBC patients (event-free survival, EFS: hazard ratio = 0.24, 95% CI: 0.18-0.33; OS: hazard ratio = 0.16, 95% CI: 0.11-0.25) and in those with HER2- positive and hormone-receptor (HR)-negative tumors who received trastuzumab (EFS: hazard ratio = 0.15, 95% CI: 0.09-0.27; OS: 0.08, 95% CI: 0.03, 0.22) [17]. Similar results were obtained by von Minckwitz et al. [19]. These studies provide the information for selecting patients who are NAC-sensitive or even surgery-omissible after NAC. These increased pCR rates have also led to the studies on omitting surgery for a selected subgroup. When compared with our study, surgical benefit after neoadjuvant chemotherapy was demonstrated, but our rate of achieved pCR was low and because of the median follow-up time was short, the sample size was small, so we need more follow-up time and larger sample sizes to see if there is a similarity with other studies.

Besides, the US Food and Drug Administration established the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) group, which analyzed 12 pooled neoadjuvant randomized controlled trials on pCR association with long-term outcome. [20] The group concluded that the association between pCR and long- term outcome was greatest in aggressive breast cancer subtypes. Pathologic complete response, defined as no pathological remnant tumor in the primary breast or lymph nodes except for insitu disease (ypT0/is ypN0), was achieved the highest (50.3%) after trastuzumab, an anti-HER2 receptor monoclonal antibody in HER2-positive/hormone receptor (HR)-negative breast cancer. The pCR rates after NAC were also high in TNBC (33.6%), HER2-positive/HR-negative breast cancer treated without trastuzumab (30.2%), and grade 3 HR-positive/HER2-negative breast cancer (16.2%). In our recent retrospective clinical study, the pCR rates were significantly higher in HER2-positive/ HR-negative breast cancer (52.9%) and TNBC (34.2%), compared to HR-positive breast cancer (14.7%). [21] In contrast, the association between pCR and long-term outcome was weakest for HR-positive subtypes, in which pCR

(ypT0/is ypN0) rates were the lowest (7.5%). Lower pCR rates were also observed in luminal-A type tumors (6.4%), and higher rates in luminal B type tumors (11%–22%). [22-26] However, we had results of pCR and short-term outcome were less than upper trials, such as pCR rates after NAC were 30.2% in group of Her2 positive, 6.8% in luminal A,B subtypes, 4% in TNBC subtype.

We found several limitations in this study. Firstly, the study was retrospectively designed in a single center, thus, the generalizability of the results would be limited. Secondly, we did not have a comparison group to better prove the benefit of the NAC treatment. Third, the sample size was relatively small and the follow-up period was limited.

In conclusion, neoadjuvant chemotherapy was effective for early stages of BC. The benefit of NAC was downstaging of the disease, increasing surgical rates thereby improving the patient's survival, specifically the two-year DFS of 86.6%. We need more follow-up time, larger sample size and standardized treatment procedure especially pCR determination procedure to get better results.

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Table 1. Baseline characteristics

	All patients (N=200)
Age (years)	52 (25-87)
Sex	
Male	1 (0.5)
Female	199 (99.5)
Tumor location	
Left side	101 (50.5)
Right side	96 (48)
Bilateral side	3 (1.5)
Amout of tumor	
One tumor	190 (95)
Multiple tumor	10 (5)
Clinical stage	
2A	28 (14)
2B	66 (33)
3A	26 (13)
3B	66 (33)
3C	14 (7)

Summary statistics are mean ± standard deviation or n (%).

Table 2. Treatments and response assessment

	N	All patients (N=200)
Neoadjuvant regiment	200	
AC-T		81 (40.5)

	N	All patients (N=200)
TAC		48 (24)
TC		8 (4)
TCH		37 (18.5)
TCHP		20 (10)
AC-TH		5 (2.5)
AC-THP		1 (0.5)
Radiation	200	178 (89)
Number of radiation doses	178	
42.56Gy/16Fx		175 (98.3)
60Gy/30Fx		3 (1.7)
Scheduled surgery for tumor resection	200	199(99.5)
Clinical response after neoadjuvant therapy	200	
CR		6 (3)
PR		131(65.5)
SD		62 (31)
PD		1 (0.5)
Downstaging	200	137 (68.5)
Pathologic response	199	
pCR		34 (17.1)
Not pCR		165 (82.9)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; pCR, pathologic

Table 3. Long-term outcomes

	N	All patients (N=200)

	N	All patients (N=200)
Length of follow-up (months)	200	13.8 ± 9.7
Disease progression	200	14 (7)
Type of disease progression	14	
Visceral metastasis		
Liver		1
Bone-Lung		2
Liver-lung		1
Ovarian		1
Non visceral metastasis		
Chest wall recurrence		3
Axilary lymph node recurrence		1
Bone		2
Brain		2
Bone-abdominal lymph node		1
Survival probability (95% CI) (%)		
1-year DFS		95
2-year DFS		86.6

CI, confidence interval; DFS, disease-free survival

Figure 1: Kapplan-Meier curves of DFS

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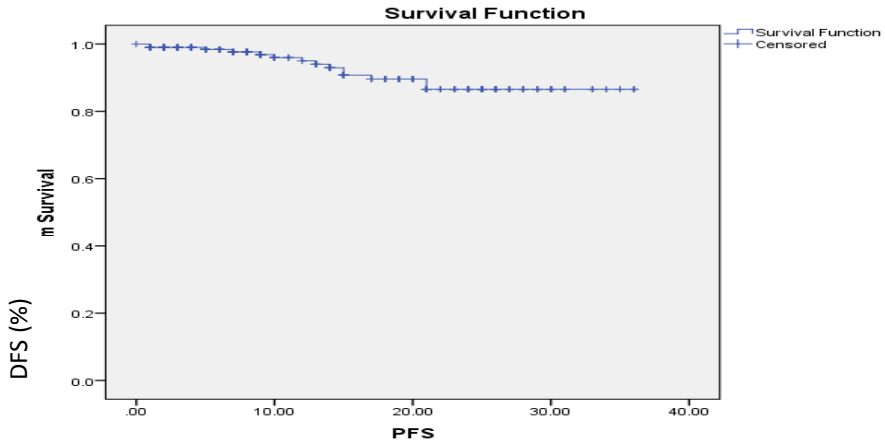

Figure 2: Kapplan-Meier curves of DFS of IHC subtypes

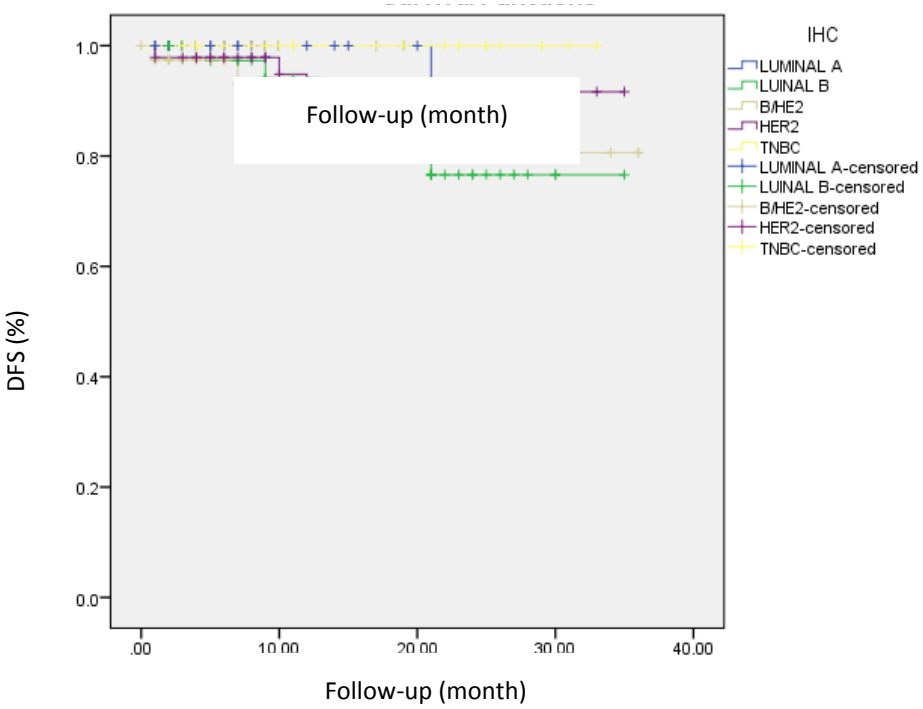

Figure 3: Kapplan-Meier curves of DFS of pCR group

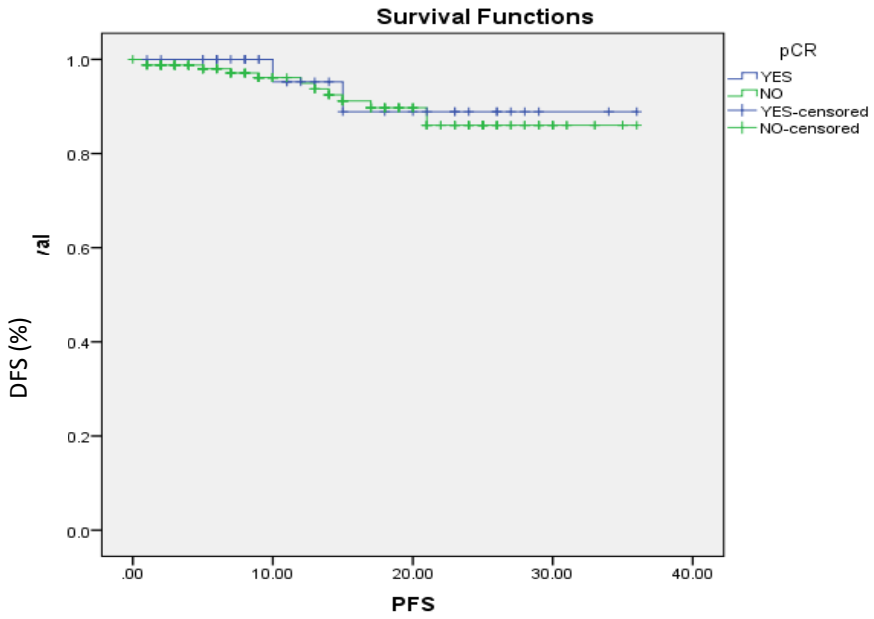

Figure 4: Kapplan-M Follow-up (month) response group

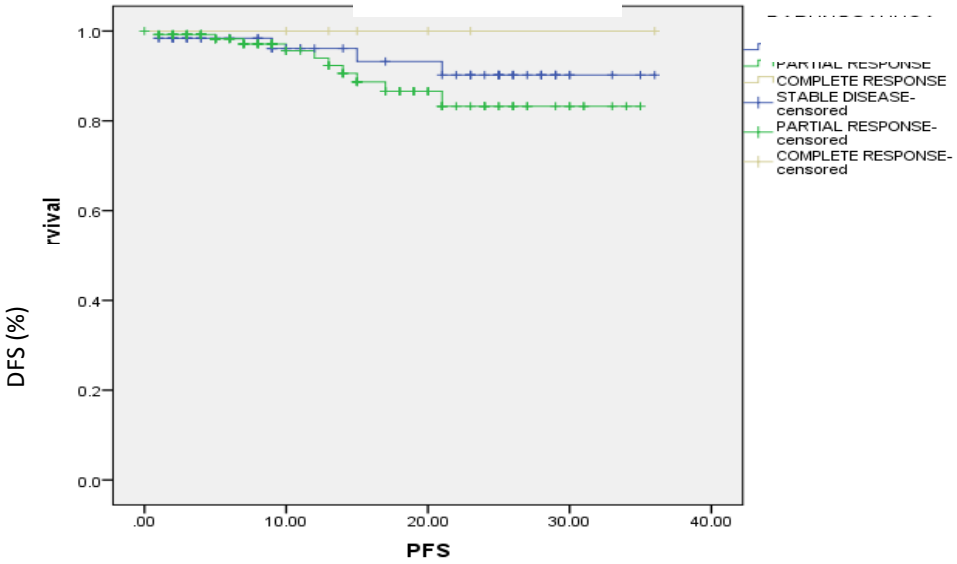

Figure 5: Chart of downstaging after NAC