Treatment outcomes of neoadjuvant chemotherapy with dose-dense AC-T regimen for patients with stage II, III breast cancer

Nguyen Thi Minh Phuong, Pham Dinh Phuc, Nguyen Ngoc Minh Tien, Phan Minh Tam

108 Military Central Hospital

Summary

Objective: To evaluate the treatment outcomes of neoadjuvant chemotherapy with dose-dense AC-T (dd AC-T) regimen on stage II, III breast cancer (BC) patients, and to assess several clinical and subclinical factors associated with treatment response in these patients. *Subject and method:* This was a cross-sectional, prospective study with longitudinal follow-up, no control group. The study was conducted on 44 stage II, III BC patients receiving NAC with dd AC-T regimen at Department of General Oncology, Institute of Oncology, 108 Military Central Hospital from June 2018 to August 2022. *Result:* After receiving NAC, CEA, CA15-3 mean concentrations and tumor size decreased statistically ($p<0.05$). Regarding clinical response according to RECIST ver 1.1 criteria, the overall response rate (ORR) was 97.7%, in which the complete response (CR) rate accounted for 36.4%. All patients underwent surgery after receiving NAC. The rate of pathological complete response (pCR) was 31.8%. Several factors associated with treatment response include: Tumor size, skin involvement status, TNM stage, histopathology grade ($p<0.05$). Patients achieving clinical CR had a higher rate of pCR than the other group ($p<0.001$). *Conclusion:* NAC with ddAC-T regimen in treatment for stage II, III BC patients resulted in high clinical and pathological response. As a result, this is a good NAC option for these patients. Several factors associated with response include: Tumor size, skin involvement status, TNM stage, histology grade. Patients achieving clinical CR had a higher rate of pCR than the other group.

Keywords: Neoadjuvant chemotherapy, breast cancer, pathological response.

1. Background

Breast cancer (BC) is the most common cancer and also the leading cause of cancer death in women around the world [1]. Although the incidence of BC tends to increase every year, the mortality rate from the disease has gradually decreased because of advances in prevention, early detection, diagnosis and treatment. Neoadjuvant chemotherapy (NAC) was initially indicated for inoperable BC patients, but was later used more extensively. NAC for BC patients has many advantages including helping to make inoperable tumors operable, increasing the possibilities of breast conserving surgery, assessing the tumor's sensitivity to chemotherapy, providing the opportunity to have more time to complete specific tests as well as plan conservative or reconstructive surgery. Especially, pathological complete response (pCR) is a good prognostic indicator of recurrence-free survival (RFS) and overall survival (OS)… [2], [3].

The dose-dense chemotherapy regimen is the regimen with a shorter cycle than the classical 3-

***Received**: 11 October 2022, **Accepted**: 09 December 2022*

***Correspondence to**: Pham Dinh Phuc, Department of General Oncology, Institute of Oncology, 108 Military Central Hospital*

***Email:** phamdinhphuc.pbc@gmail.com*

week cycle. The 4AC-4T regimen (AC: Doxorubicine + Cyclophosphamide, T: Paclitaxel) consists of two highly effective chemical groups in the treatment for BC. Many studies have demonstrated the superior effectiveness of the dose-dense AC-T regimen in terms of survival and equivalent toxicity in comparison with the standard-dose regimen. As a result, dose-dense regimens are increasingly being used in NAC for BC [4].

There have been many large studies around the world showing that NAC for BC patients has an encouraging effect, helping to increase the rate of pCR after surgery, improve even free survival (EFS) and overall survival (OS) for patients [3], [5]. However, in Vietnam, there are not many studies on this issue. In particular, at 108 Military Central Hospital, there has been no research on NAC for BC patients. As a result, we conducted this study with the following objectives: *1) To evaluate the treatment outcomes of neoadjuvant chemotherapy with dose-dense AC-T regimen for stage II, III breast cancer patients. 2) To assess several clinical and subclinical factors associated with treatment response in these patients.*

2. Subjects and method

2.1. Subject

44 stage II, III BC patients indicated NAC with ddAC-T regimen, followed by surgery at 108 Military Central Hospital from June 2018 to August 2022.

Dose-dense 4AC-4T consists of two-week cycles including 4 cycles of AC (Doxorubicine 60mg/m^2, cyclophosphamide 600mg/m^2, day 1) and 4 cycles of T (Paclitaxel 175mg/m^2, day 1) for a total of 8 cycles.

Inclusion criteria: Patients who were definitively diagnosed with stage II, III invasive BC, indicated to NAC with ddAC-T regimen, and had normal liver and kidney function, and normal range of complete blood count.

Exclusion criteria: Patients refused to participate in the study or had contraindication to chemotherapy, or a history of other cancer. Pregnancy and breastfeeding women were excluded from the study.

Study design: This was a cross-sectional, prospective study with longitudinal follow-up, no control group.

2.2. Method

Data were collected and analyzed by statistical algorithms of SPSS 25.0 software. The statistical methods used include:

Descriptive statistics: Mean, standard deviation, percentage.

Comparative ratio analysis: Chi square test ($p<0.05$), Fisher's Exact test.

Comparing 2 means.

2.3. Applied criteria in the research

The TNM classification of BC according to the 8th AJCC (2017).

Response Evaluation Criteria In Solid Tumor (RECIST) version 1.1.

The St. Gallen surrogate molecular subtypes criteria (2017) in primary BC.

Pathological response was evaluated according to the Chevallier's classification.

3. Result

3.1. Clinical and subclinical characteristics

The mean age of the study patients was 51.89 ± 1.64 years, of which the highest was 73 years old, and the lowest was 29 years old.

The mean concentration of marker CEA, CA15-3 were 7.23 ± 7.87 (ng/ml), and 33.97 ± 16.46 (U/ml), respectively.

The mean size of the largest diameter of lesions (LDL) before treatment was 4.35 ± 1.62cm. Most of the lesions had the largest diameter from 2-5cm with the rate of 61.4%.

Histopathological features: The most common types were ductal invasive carcinoma (DIC) and not otherwise specified (NOS) with the rate of 40.9% and 54.5%, respectively. Tumors with grade 2 and 3 accounted for mainly 54.5% and 45.5%, respectively.

The rate of patients with positive hormonal receptors was 52.3%; 38.6% of patients had gene HER-2 overexpression.

According to the St Gallen's molecular subtype classification, the most common ones were triple negative and non-luminal, HER-2 positive with a regular rate of 25%.

The majority of the patients were in stage III, accounting for 77.2%.

3.2. Treatment outcomes

Table 1. LDL mean tumor size and markers concentrations changes after treatment

Features	Evaluation time	$\bar{X} \pm SD$	p
Tumor size	Before NAC	4.35 ± 1.62	<0.001
	After NAC	1.08 ± 1.27	
	Difference value	3.26 ± 1.38	
CEA (ng/ml)	Before NAC	7.23 ± 7.87	0.007
	After NAC	4.38 ± 2.32	
	Difference value	2.85 ± 6.66	
CA15-3 (U/ml)	Before NAC	33.97 ± 16.47	<0.001
	After NAC	19.90 ± 7.53	
	Difference value	14.07 ± 13.67	

The mean tumor size and markers concentrations decreased significantly after treatment ($p<0.05$).

Table 2. Evaluation of clinical treatment response according to RECIST 1.1 criteria

Response	Sample size (n = 44)	Percentage (%)
Complete response (CR)	16	36.4
Partial response (PR)	27	61.4
Stable disease (SD)	1	2.2
Progression disease (PD)	0	0

The percentage overall response was 97.7%, of which the rate of CR was 36.4%.

Table 3. Evaluation of pathological response according to Chevallier's classification

Pathological response according to Chevallier's classification	Sample size (n = 44)	Percentage (%)
Group 1: Disappearance of all tumors both on macroscopic and microscopic assessment.	12	27.3
Group 2: In situ carcinoma present but no residual invasive tumor and no metastatic lymph nodes.	2	4.5
Group 3: Invasive carcinoma present with stromal changes (sclerosis, fibrosis).	29	65.9
Group 4: Few modifications of the appearance of the tumor.	1	2.3

The rate of patients achieving pCR after treatment was 31.8%, the proportion of residual disease (RD) after surgery was 68.2%.

3.3. Several factors associated with treatment response

Table 4. Association between clinical features and response to treatment

Clinical features		Clinical response			Pathological response		
		CR n (%)	non-CR n (%)	p (χ^2)	pCR n (%)	RD n (%)	p (χ^2)
Age group	≤ 50	9 (45.0)	11 (55.0)	0.539	4 (20.0)	16 (80.0)	0.195
	> 50	8 (33.3)	16 (66.7)		10 (41.7)	14 (58.3)	
Tumor size	≤ 5cm	13 (48.1)	14 (51.9)	0.040	12 (44.4)	15 (55.6)	0.024
	> 5cm	3 (17.6)	14 (82.4)		2 (11.8)	15 (88.2)	
Skin involvement status	No	14 (50.0)	14 (50.0)	0.013	13 (46.4)	15 (53.6)	0.006
	Yes	2 (12.5)	14 (87.5)		1 (6.3)	15 (93.7)	
TNM stage	II	7 (70.0)	3 (30.0)	0.017	7 (70.0)	3 (30.0)	0.006
	III	10 (29.4)	24 (70.6)		7 (20.6)	27 (79.4)	
Histopathological features							
Histological type	IDC	9 (50.0)	9 (50.0)	0.202	7 (38.9)	11 (61.1)	0.515
	Other	7 (26.9)	19 (73.1)		7 (26.9)	19 (73.1)	
Histological grade	Grade 1, 2	5 (20.8)	19 (79.2)	0.021	4 (16.7)	20 (83.3)	0.025
	Grade 3	11 (55.0)	9 (45.0)		10 (50.0)	10 (50.0)	
Immunohistochemistry features							
Hormonal Receptor	Positive	6 (26.1)	17 (73.9)	0.211	5 (21.7)	18 (78.3)	0.197
	Negative	10 (47.6)	11 (52.4)		9 (42.9)	12 (57.1)	
Gene HER-2 overexpression	Yes	6 (31.6)	13 (68.4)	0.753	6 (31.6)	13 (68.4)	0.618
	No	10 (40.0)	15 (60.0)		8 (32.0)	17 (68.0)	
St.Gallen molecular subtypes	Triple negative	6 (54.5)	5 (45.5)	0.278	4 (40.0)	6 (60.0)	0.456
	Non-triple negative	10 (30.3)	23 (69.7)		6 (17.7)	28 (82.3)	

The factors related to the response to treatment include: histological grade, tumor size, skin involvement status, TNM stage of the disease (p<0.05).

Table 5. Association between clinical response and pathological response

Clinical \ Pathological	pCR	RD	Total
CR	12	4	16
Non-CR	2	26	28
Total	14	30	44
p<0.001			

The rate of pCR in the clinical CR group was statistically significantly higher than in the other group (p<0.001).

4. Discussion

4.1. Evaluations of treatment response

In the past, clinicians were concerned whether neoadjuvant therapy would delay the application of localized therapies such as surgery and radiotherapy for early removal of cancer lesions because the tumor may respond poorly to chemotherapy, progress and even distant metastasize distantly. However, through many studies during the past decades, neoadjuvant chemotherapy has brought many benefits [3].

Regarding clinical response, we evaluated based on RECIST 1.1 criteria, after receiving 8 cycles of 4AC-4T regimen NAC, the ORR was 97.7%, of which the rate of CR accounted for 36.4%. Only one patient reduced tumor size on imaging but did not PR according to RECIST 1.1 criteria. The mean tumor size decreased significantly after the treatment course (p<0.001), this result was also consistent with the ORR of 97.7%. Our results are higher than some domestic studies such as Le Thanh Duc (2013) with ORR and CR of 92% and 31.4%, respectively; Nguyen Thi Thuy's (2016) were 96.6% and 25.4%, Hong's (2013) were 80.9% and 21.3% [6], [7], [8]. It is possible that our study used a 3-agent and dose-dense regimen, so the effectiveness is higher than that of Le Thanh Duc (2013). In addition, our study had 22.8% of patients in stage II, the prognosis would be better than patients in the above mentioned studies in stage III.

However, this result was lower than some studies such as D.T.K.Anh with the rate of CR was 50.8%, or Nguyen Viet Cuong (2020) with an ORR and CR of 100% and 46.7%, respectively [9], [10]. This difference might be caused by the higher proportion of stage II BC patients in these studies. In D.T.K.Anh's study, the mean tumor size before treatment was 3cm, while in our study it was 4.35cm.

In the study, we monitored and evaluated the change in the concentration of cancer markers CEA, CA15-3. The results showed that the concentration of these markers decreased statistically after NAC (CEA with p=0.007, CA15-3 with p<0.001). The studies of Nguyen Thu Thuy, Le Thanh Duc also gave similar results [7], [6]. Cancer markers, especially CA15-3, play an important role in monitoring response to BC treatment. Hayes et al evaluated the change in concentration of marker CA15-3 during chemotherapy in BC patients, and found that the concentration of this marker increases in patients with PD, is mostly stable in SD patients, and decreases in the majority of ones with treatment response [11].

Other than clinical response, the pathological response is very important in the evaluation of NAC for BC patients. There are several different histological response classification systems in the world, of which the Chevallier system is widely used. Many recent studies have consistently established histopathological complete response (pCR) criteria including patients in groups 1 and 2 according to the Chevallier classification. Our study applied this option. All of 44 patients in our study underwent surgery after receiving NAC. The results showed that 31.8% of patients achieved pCR and 68.2% of patients had RD. The rate pCR in our study was higher than that of Le Thanh Duc's (2013) at 16.8%, Nguyen Thi Thuy (2016) was 18.6%, D.T.K.Anh's (2008) was 23.7%, Ha Thanh Kien's (2018) was 27.8%, Hong's (2013) was 18.9% [6], [7], [9], [5], [8]. The reason for this difference may be that our study included stage II BC patients with better prognoses, easier to achieve pCR than stage III patients in other studies.

Compared with the study of D.T.K.Anh, although the stage of patients in our study was later, D.T.K.Anh took the pCR standard only including group 1 according to Chevallier's classification, so the pCR rate decreased [9]. Our study showed a lower pCR rate than that of Nguyen Viet Cuong (2020) with a pCR rate of 63.3%. It might be caused by the smaller mean size of the tumor, the earlier stage than in our study and only studied in the group of patients with gene HER2 overexpression, using the AC-T regimen in combination with trastuzumab. However, this is still an impressive pCR result [10].

4.2. Several factors associated with treatment response

Factors affecting clinical and pathological response include: Tumor size, skin involvement status, TNM stage and histopathology grade. In particular, the study also recorded a higher rate of pCR in the clinical CR group compared with the other group ($p<0.001$). Tumor size is one of the factors related to tumor response to treatment. The larger tumor size, the harder for the chemical agents to penetrate the cancer cells. Moreover, tumor size is also related to axillary lymph node metastasis, the larger the tumor, the higher the rate of axillary lymph node metastasis, thereby the less likely to achieve a complete response (complete loss of both lymph nodes and tumor) [12]. Skin involving tumor is a manifestation of the disease at later stages because the tumor must grow to a certain size to be able to reach the skin and and become fixed into the chest wall. Stage III disease with larger tumor size and more invasion, more lymph nodes, and more fusion will be more difficult to achieve a CR than stage II tumors. The histopathological features are closely related to the proliferation rate, the higher the histopathological grade, the higher the proliferation rate, the more cancer cells are in the S phase of the mitotic cycle, thereby being more sensitive to chemical agents. This result was similar to Le Thanh Duc (2013), Nguyen Thi Thuy (2016), Ha Thanh Kien (2018), Gajdos et al (2002)…[7], [6], [9], [5], [12].

5. Conclusion

Neoadjuvant chemotherapy with dose-dense AC-T regimen in treatment for stage II, III BC patients resulted in clinical and pathological response. As a result, this is a good option in neoadjuvant chemotherapy for stage II, III breast cancer patients. Several factors associated with response include: tumor size, involving skin situation, TNM stage, histopathology grade. Patients achieving clinical CR had a higher rate of pCR than the other group.

References

1. Sung H, Ferlay J et al (2021) *Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries*. CA Cancer J Clin 71(3): 209-249.
2. Killelea BK, Yang VQ et al (2015) *Neoadjuvant chemotherapy for breast cancer increases the rate of breast conservation: Results from the National Cancer Database*. J Am Coll Surg 220(6): 1063-1069.
3. Cortazar P, Zhang L et al (2019) *Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis*. Lancet Onco J 393(10175): 986.
4. Hà Thành Kiên (2018) *Đánh giá kết quả hoá trị bổ trợ trước phẫu thuật phác đồ 4AC-4T liều dày trên bệnh nhân ung thư vú tại Bệnh viện K*. Luận văn Thạc sĩ y học, Trường Đại học Y Hà Nội.
5. Lena M, Zucali R et al (1978) *Combined chemotherapy-radiotherapy approach in locally advanced (T3b-T4) breast cancer*. Cancer Chemother Pharmacol 1(1): 53-59.
6. Lê Thanh Đức (2013) *Nghiên cứu hiệu quả hoá trị bổ trợ trước phẫu thuật phác đồ AP trong ung thư vú giai đoạn III*. Luận án bảo vệ Tiến sĩ, Trường Đại học Y Hà Nội.
7. Nguyễn Thị Thuỷ (2016) *Đánh giá kết quả hoá trị bổ trợ trước phác đồ 4AC-4T trên bệnh nhân ung thư vú giai đoạn III*. Luận văn tốt nghiệp bác sĩ nội trú, Trường Đại học Y Hà Nội.
8. Hong WS, Jeon JY et al (2013) *Comparison of neoadjuvant adriamycin and docetaxel versus adriamycin, cyclophosphamide followed by paclitaxel in patients with operable breast cancer*. J Korean Surg Soc 85(1): 7-14.
9. Đỗ Thị Kim Anh (2016) *Đánh giá hiệu quả hoá trị bổ trợ trước kết hợp phẫu thuật bảo tồn trên bệnh nhân ung thư vú giai đoạn II*. Luận văn bác sĩ chuyên khoa cấp II, Trường Đại học Y Hà Nội.
10. Nguyễn Việt Cường, Phùng Thị Huyền (2020) *Đánh giá đáp ứng hoá trị bổ trợ trước kết hợp trastuzumab trên bệnh nhân ung thư vú giai đoạn II, III*. Tạp chí Y học thực hành, 1141(5), tr. 36-39.
11. Hayes DF, Kufe DW et al (1986) *Comparison of circulating CA15-3 and carcinoembryonic antigen levels in patients with breast cancer*. J Clin Oncol 4(10): 1542-1550.
12. Gajdos C, Tartter PI, Estabrook A, Gistrak MA, Jaffer S, Bleiweiss IJ (2002) *Relationship of clinical and pathologic response to neoadjuvant chemotherapy and outcome of locally advanced breast cancer*. J Surg Oncol 80(1): 4-11.