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ORIGINAL ARTICLE

Efficacy of neoadjuvant chemotherapy and Annexin A3 expression in breast cancer

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Summary

Purpose: *To observe the efficacy of neoadjuvant chemotherapy (NAC) in patients with breast cancer (BC) and to investigate the effect of Annexin A3 (ANXA3) expression.*

Methods: *158 patients with BC treated in Yantai Yuhuangding Hospital from September 2015 to December 2017 were retrospectively analyzed. Among them, 83 cases were treated with epirubicin + cyclophosphamide + 5-fluorouracil (CEF group), 75 cases with epirubicin + cyclophosphamide + docetaxel (TEC group), with 3 cycles of chemotherapy. The efficacy and adverse reactions of the two NAC regimens were compared and analyzed. Tissue specimens were collected before and 10 days after the administration of chemotherapy in order to detect the expression of ANXA3 by qRT-PCR in each group.*

Results: *There were significant differences in the rates of complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) between the two groups (z=10.716, p=0.013). The clinical effectiveness rate in the TEC group was significantly higher than that in the CEF group (p<0.05). There was no difference in the pathology grade between the two groups (p>0.05); however, the pathological effective rate in the TEC group was significantly higher than that in the CEF group (p<0.05). There was no difference in the rate of bone marrow suppression between the two groups (p>0.05). While there was no difference in the relative expression of ANXA3 between the two groups before chemotherapy, the relative expression of ANXA3 in the TEC group was lower than that in the CEF group after NAC (p<0.05). The relative expression in both groups after chemotherapy was lower than that before NAC (p<0.05).*

Conclusion: *Compared with CEF regimen, NAC with TEC regimen can improve the clinical and pathological effectiveness rate, inhibit the expression of ANXA3, and improve the prognosis of patients, thus having a certain application prospect in NAC.*

Key words: *breast cancer, neoadjuvant chemotherapy, annexin a3, epirubicin + cyclophosphamide + 5-fluorouracil, epirubicin + cyclophosphamide + docetaxel*

Introduction

Breast cancer (BC) is the most common malignant tumor in middle-aged women, with the highest incidence of cancer in females [1]. At present, its etiology has not been fully elucidated, which may be related to the expression of some genes, environmental factors and living habits, with a certain regional feature [2,3]. Nowadays, there are two main treatments for the disease: surgical resection and chemotherapy. Radical mastectomy is the most fundamental solution; however, because of the cosmetic problems due to the special location of BC, chemotherapy can precede surgery and save the appearance and function of breast better than surgery and has thus become the first choice for patients and clinicians [4]. A relative new chemotherapeutic model (neoadjuvant chemotherapy/NAC, also known as local treatment-consolidation chemotherapy), has been proposed for BC [5]. Some

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studies have shown that NAC has a very important effect on the efficacy of the new chemotherapy model, which can significantly reduce metastasis after chemotherapy and improve the prognosis of BC patients [6].

NAC refers to chemotherapy for locally advanced malignant tumor before local treatment, which can monitor the effect of chemotherapy in vivo, compared with the traditional postoperative chemotherapy. Because NAC is performed before radical surgery in BC, it can reduce the tumor size, reduce the area of resection during radical mastectomy, increase the breast conserving rate of radical mastectomy, decrease the clinical stage, and obviously improve the survival time of patients [7-9]. At present, the commonly used chemotherapeutic drugs are anthracyclines and taxanes, with the most commonly used chemotherapeutic regimens being CEF (cyclophosphamide, epirubicin combined with 5-Fluorouracil) and TEC (epirubicin, cyclophosphamide combined with docetaxel) [10]. There are a lot of chemotherapeutic drugs and combinations available for NAC. However, there are some risks in the application of NAC, such as a possible delay in the curative treatment of patients due to ineffective NAC or an increase in the risk of subsequent treatment in patients with previous obvious side effects, such as various immune responses after NAC. Therefore, it is very important to select a NAC regimen with significant efficacy and low side effects [11].

Annexin A3 (ANXA3), a calcium-dependent phospholipid binding protein, is mainly involved in signal transduction of cell proliferation, apoptosis and differentiation, inflammation, occurrence and tumor development [12]. Studies have shown that ANXA3 is significantly higher in BC patients compared with healthy people and is negatively correlated with prognosis and overall survival [13]. Therefore, ANXA3 can be used as a prognostic indicator. By comparing the efficacy of CEF and TEC, two commonly used NAC regimens, and expression changes of ANXA3, we can select a NAC regimen which is safe, effective, and beneficial for the prognosis.

Methods

Subjects

The clinical data of 158 BC patients, aged 45.57±24.38 years, treated in the mammary gland department of the Yantai Yuhuangding Hospital from September 2015 to December 2017, were retrospectively analyzed. Among them treated with NAC, 83 cases were treated with CEF regimen (CEF group) and 75 cases with TEC regimen (TEC group). Inclusion criteria were as follows: women over 18 years old; patients histologically diagnosed with BC; patients newly diagnosed as BC with no previous treatment; patients undergoing surgical treatment after NAC; patients with no distant organ metastasis; patients who have signed informed consent. The following parameters were defined as the exclusion criteria: patients with incomplete clinical data; pregnant and lactating patients; patients with poor compliance or failing to complete the trial in accordance with the treatment plan for other reasons.

This study was approved by the hospital ethics committee.

Materials and reagents

Epirubicin hydrochloride (Zhejiang Hisun Pharmaceutical Co., Ltd. SFDA Approval No. H20041211); Cyclophosphamide (Qilu Pharmaceutical Co., Ltd. SFDA Approval No. H20057626); Docetaxel (Qilu Pharmaceutical Co., Ltd. SFDA Approval No. H20041129); 5-fluorouracil (Shanghai Xudong HaiPu Pharmaceutical Co., Ltd. SFDA Approval No. H31020593); TransScript Green Two-Step qRT-PCR SuperMix Kit (Beijing Transgen Biotechnology Co., Ltd. AQ201-01); Primer sequence (Wuhan Sangon Biotechnology Co., Ltd.)

Treatment regimens and grouping

TEC regimen in TEC group: 60mg/m^2 epirubicin hydrochloride, 600mg/m^2 cyclophosphamide, 75mg/m^2 docetaxel; CEF regimen in CEF group: 60mg/m^2 epirubicin hydrochloride, 600mg/m^2 cyclophosphamide, 500mg/m^2 5-fluorouracil. All drugs were injected intravenously and chemotherapy was administered once every 3 weeks as a course of treatment, for a total of 3 cycles. Granulocyte colony-stimulating factor (G-CSF) was used when the grade of leukopenia was more than III. Other adverse reactions such as nausea and vomiting were treated symptomatically. Surgical operation was selected according to the efficacy results of chemotherapy (10 days after NAC). Breast-conserving surgery was performed when the tumor diameter was reduced to 3 cm or less and radical mastectomy was performed if chemotherapy was ineffective.

Evaluation of clinical efficacy

The efficacy of primary tumor after chemotherapy was evaluated according to the efficacy evaluation criteria for solid tumor of UICC [14]. Clinical effective rate = CR + PR.

Table 1. Grading of bone marrow suppression

Bone marrow suppression	*Leukocytes (×10^{9}l)*	*Granulocytes (×10^{9}l)*
0	≥4.0	≥2.0
I	3.0-3.99	1.5-1.99
II	2.0-2.99	1.0-1.4
III	1.0-1.99	0.5-0.9
IV	<1.0	<0.5

Evaluation of pathologic efficacy

Pathological specimens were evaluated and graded according to Miller Payne criteria [15]. Pathological effectiveness rate = (grade III + grade IV + grade V) / Total number. The specific conditions of each pathological effect grading are: grade I: the infiltrating cancer cells are reduced without change or individual changes, but the total number is basically unchanged; grade II: invasive cancer cells reduced by≤30%; grade III: infiltrating cancer cells decreased by 30-90%; grade IV: invasive cancer cells reduced by≥90%, residual single or small clusters of cancer cells; V grade: primary tumor lesions without invasive cancer cells, residual carcinoma *in situ*, also known as pathological complete remission (pCR).

Evaluation of adverse reactions after chemotherapy

The possible adverse reactions such as bone marrow suppression (BMS), nausea and vomiting, cardiotoxicity etc. were monitored and recorded and the degree of BMS was graded according to the WHO evaluation criteria for adverse reactions of chemotherapy [16]. When the degree of suppression was grade III or higher, G-CSF was used for supportive therapy (Table 1).

Detection of ANXA3 expression by qRT-PCR in each group

Tissue specimens obtained from pathological biopsy or breast puncture were collected before and 10 days after chemotherapy in order to detect the expression of ANXA3 by qRT-PCR. The obtained breast tissue was split and extracted by Trizol reagent. The concentration and purity of RNA were identified by UV spectrophotometer; when optical density (OD) 260/OD280 was between 1.8 and 2.0, the specimen was qualified. Twenty μL reverse transcription system: 1 μg total RNAs, 4 μL 5 ×TransScript®All-in-One SuperMix for qPCR, 1 μL gDNA Remover; the rest was filled with RNase-free water. Reverse transcription procedures: 42°C for 15min, 85°C for 5 s. Amplification using 20 μL reaction system: 0.4μl 2×TransStart® Tin Green aPCR SuperMix, 0.4 μL upstream and 0.4 μL downstream primer, 2 μL 10×cDNA, the rest was filled with RNase-free water. Amplification procedure: 40 cycles of predenaturation at 94°C for 30 s, followed by 94°C for 5 s, 60°C for 30 s. With GAPDH as the internal parameter, the upstream and downstream sequences were 5'-GGTGGTGCTAAGCGTGTTA-3' and 5'-CCCTCCACAATGCCAA-3', respectively. The upstream and downstream sequences of the target gene ANXA3 were 5'-GCGGGAACAAACGAAGATGC-3' and 5'-AGTCACCAGATGTTTCGGAACTA-3', respectively. QRT-PCR results were statistically evaluated by $2^{-\Delta\Delta Ct}$ method.

Statistics

SPSS 19.0 Software System (IBM, SPSS, Chicago, IL, USA) was used for data processing; the quantitative data were expressed in the form of mean ± standard deviation. T-test was used for comparison between the two groups; Paired t-test was used for comparison between the same group before and after treatment; qualitative data were expressed in percentages and evaluated by x^2 test. Rank sum test was used for ranked data; Significance level α=0.05.

Table 2. General data of patients in two groups

	TEC group (n=75) n (%)	*CEF group (n=83) n (%)*	*$t/x^2/z$*	*p value*
Age, years, mean±SD	47.82±25.43	41.43±22.54	1.664	0.098
Clinical stage			0.301	0.584
I/II	51(68.00)	53(63.86)		
III/IV	24(32.00)	30(36.14)		
Cervical lymph node metastasis			0.521	0.471
Yes	64(85.33)	74(89.16)		
No	11(14.67)	9(10.84)		
Menopausal status			1.811	0.178
Pre-menopause	52(69.33)	49(59.04)		
Post-menopause	23(30.67)	34(40.96)		
ER			0.417	0.519
+	35(46.67)	43(51.81)		
-	40(53.33)	40(48.19)		
PR			1.113	0.292
+	29(38.67)	39(46.99)		
-	46(61.33)	44(53.01)		
HER-2			5.675	0.059
-/+	46(61.33)	61(73.49)		
++	10(13.33)	13(15.66)		
+++	19(25.33)	9(10.84)		

Results

Comparison of general clinical data between the two groups

There was no significant difference in age, clinical stage, cervical lymph node metastasis, menopausal status, and the rate of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2) expression between CEF and TEC group (p>0.05, Table 2).

Comparison of clinical efficacy after chemotherapy

In TEC group, there were 50 cases of CR (66.67%), 13 cases of PR (17.33%), 9 cases of SD (12.00%), 3 cases of PD (4.00%), with a clinical effectiveness rate of 84.00% compared to 34 cases of CR (40.96%), 22 cases of PR (26.51%), 21 cases of SD (25.30%), 6 cases of PD (7.23%), with a clinical effectiveness rate of 67.47% in CEF group. There were significant differences in CR, SD, and PD between the two groups (z=10.716, p=0.013) and the clinical effectiveness rate in TEC group was significantly higher than that in CEF group (x^2=5.791, p<0.016, Table 3 and Figure 1).

Comparison of pathological effects after chemotherapy

In TEC group, there were 10 cases of grade V (13.33%) effect, 19 cases of grade IV (25.33%) effect, 30 cases of grade III (40.00%) effect, 12 cases of grade II (16.00%) effect, 4 cases of grade I (5.33%) effect, with a pathological effective rate of 78.67% compared to 9 cases of grade V (10.84%), 14 cases of grade IV (16.87%), 28 cases of grade III (33.73%), 27 cases of grade II (32.53%), 5 cases of grade I (6.02%), with a pathological effective rate of 61.45% in CEF group. There was no difference in pathological effectiveness grading between the two groups (z=6.330, p=0.176); however, the pathological effective rate in TEC group was significantly higher than that in CEF group (x^2=4.648, p=0.031; Table 4 and Figure 2).

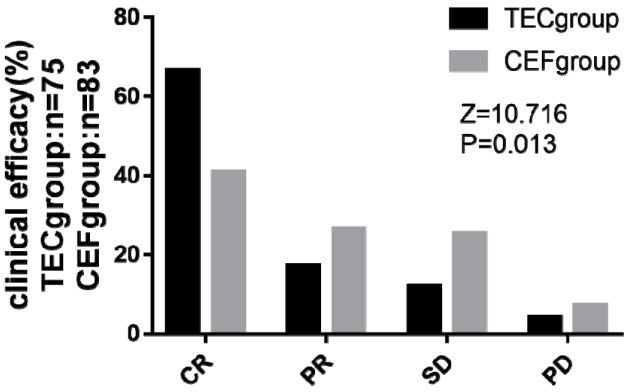

Figure 1. Comparison of clinical efficacy between the two groups showing significant difference in CR, SD and PD between the two groups (p=0.013).

Table 3. Clinical effect in the two groups after chemotherapy

Clinical effect	*TEC group (n=75) n (%)*	*CEF group (n=83) n (%)*	*z/x^2*	*p value*
			10.716	0.013
CR	50 (66.67)	34 (40.96)		
PR	13 (17.33)	22 (26.51)		
SD	9 (12.00)	21 (25.30)		
PD	3 (4.00)	6 (7.23)		
Clinical effective rate	63 (84)	56 (67.47)	5.791	0.016

Table 4. Pathological effect in the two groups after chemotherapy

Pathological effect	*TEC group (n=75) n (%)*	*CEF group (n=83) n (%)*	*z/x^2*	*p value*
			6.330	0.176
Grade I	4 (5.33)	5 (6.02)		
Grade II	12 (16.00)	27 (32.53)		
Grade III	30 (40.00)	28 (33.73)		
Grade IV	19 (25.33)	14 (16.87)		
Grade V	10 (13.33)	9 (10.84)		
Pathological effective rate	59 (78.67)	51 (61.45)	4.648	0.031

Comparison of adverse reactions between the two groups

Comparison of BMS: in TEC group, there were 28 cases of grade 0 BMS (37.33%), 14 cases of grade I (18.67%) BMS, 14 cases of grade II (18.67%) BMS, 6 cases of grade III (8.00%) BMS, 13 cases of grade IV (17.33%) BMS compared to 31 cases of grade 0 (37.35%), 21 cases of grade I (25.30%), 16 cases of grade II (19.28%), 8 cases of grade III (9.64%), and 7 cases of grade IV (8.43%) in CEF group . There was no difference in the rate of BMS between the two groups (z=2.663, p=0.616, Figure 3).

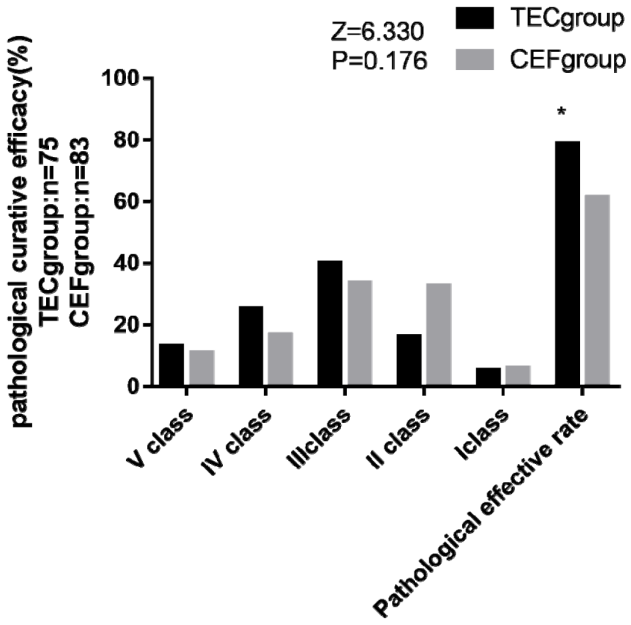

Figure 2. Comparison of pathological effects between the two groups showing no difference in pathological grade between the two groups (p>0.05). *compared with CEF group, p>0.05.

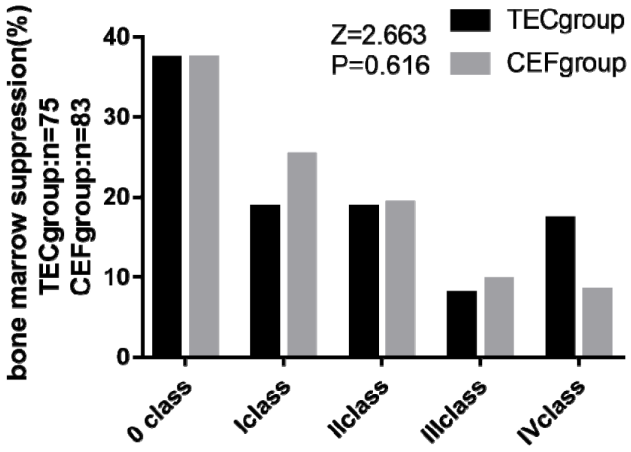

Figure 3. Comparison of bone marrow suppression between the two groups showing no difference in the rate of bone marrow suppression between the two groups (p=0.616).

Comparison of other adverse reactions: In TEC group, there were 66 cases of nausea and vomiting (88.00%), 8 cases of diarrhea (10.67%), 33 cases of cardiotoxicity (44.00%), and 16 cases of neurotoxicity (21.33%) versus 75 cases of nausea and vomiting (90.36%), 12 cases of diarrhea (14.46%), 41 cases of cardiotoxicity (49.40%), and 18 cases of neurotoxicity (21.69%) in CEF group. There was no significant difference in other adverse reactions between the two groups (p>0.05).

Comparison of relative expression of ANXA3 in different groups

The relative expression of ANXA3 before and after chemotherapy in TEC group was 1.021±0.450 and 0.234±0.320, respectively; the relative expression of ANXA3 before and after chemotherapy in CEF group was 1.123 ±0.43 and 0.621 ±0.330, respectively. There was no difference in the relative expression of ANXA3 between the two groups before chemotherapy, while the relative expression of ANXA3 in the TEC group was lower than that in the CEF group after NAC (p<0.05). The relative expression in both groups after chemotherapy was significantly lower than that before NAC (p<0.05; Figure 4).

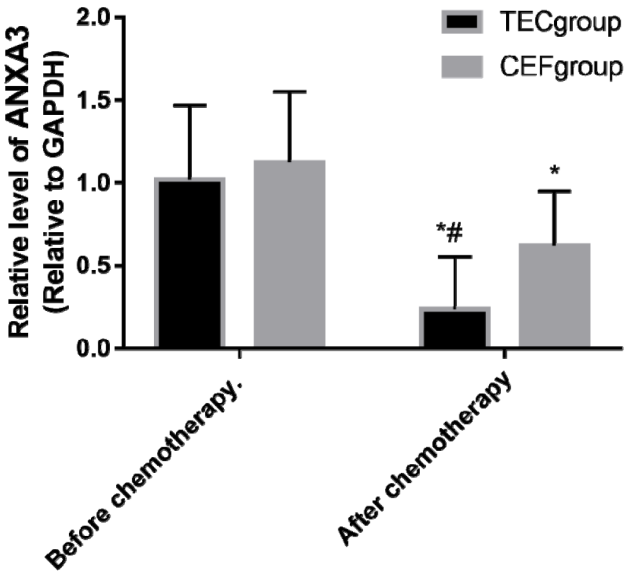

Figure 4. Comparison of relative expression of ANXA3 in different groups. There was no difference in the relative expression of ANXA3 between the two groups before chemotherapy, while the relative expression of ANXA3 in the TEC group was significantly lower than that in the CEF group after chemotherapy (p<0.05), and the relative expression in both groups after chemotherapy was significantly lower than that before chemotherapy (p<0.05). *compared with the same group before treatment, p<0.05; #compared with CEF group, p<0.05.

Discussion

BC is the most common malignant tumor in women, accounting for 1/4 of new malignancies in females [17]. Its morbidity and mortality are increasing year after year and the age of onset of disease tends to be lower. NAC, one of the most important methods in the comprehensive treatment of breast cancer, can reduce the clinical stage, create the opportunity of operation for patients who are not operable at first view and improve the breast-conserving rate of patients destined to undergo radical mastectomy [18,19]. ANXA3 is almost not expressed in healthy populations, but it is expressed in BC patients and is negatively correlated with prognosis, which can be used to predict prognosis [20]. By comparing the efficacy of CEF vs. TEC and expression changes of ANXA3, one can select a NAC regimen which is safe, effective, and beneficial for the prognosis.

You-Fu et al. [21] studied the efficacy and toxicity of TEC and CEF regimens in preoperative chemotherapy for BC and found that the clinical efficacy in TEC group was better compared with CEF group, which was consistent with the results of this paper. However, they found that the degree of BMS in TEC group was lower than in CEF group, which did not coincide with our conclusion. The reason for this inconsistent finding might be due to the fact that although the number of patients with BMS in the two groups was quite large, the sample size was a little smaller after subgroup analysis of BMS according the its degree, which was less than 20 patients in each grade, making the results not universal. Therefore, the sample size should be expanded to ensure that there are enough samples in subgroups after dividing all the samples according to the grade for subsequent analysis. Wei et al. [3] also studied the efficacy and toxicity of TEC and CEF regimens in preoperative chemotherapy for BC and found that there was no significant difference in adverse reactions between the two groups, which was also consistent with this paper. The results of this study showed that there was no difference in pathological grade between the two groups, but the pathological effective rate in TEC group was significantly higher than that in CEF group, which proved that the chemotherapy effect of TEC was better than that of CEF, considering from the pathological point of view. The clinical evaluation can be carried out in the course of chemotherapy and can guide the formulation of the next treatment plan, but it can be influenced by many factors such as doctor's experience, examination technique etc. Nevertheless, its accuracy is not as good as the pathological evaluation. As a gold standard for evaluating chemotherapy efficacy, pathological evaluation and clinical evaluation are complementary to each other in evaluating the efficacy of NAC chemotherapy [22].

There was no difference in the relative expression of ANXA3 between the two groups before chemotherapy, while the relative expression in both groups after NAC was lower than that before chemotherapy and the relative expression of ANXA3 in the TEC group was lower than that in the CEF group after NAC. These results showed that the relative expression of ANXA3 decreased after chemotherapy and the effect of TEC chemotherapy on decreasing the relative expression of ANXA3 was more obvious, which suggested improvement of the prognosis. The study of Kim et al. [23] on the expression and function of ANXA3 in BC cells found that the expression level of ANXA3 in MDAMB 231, HCC-70, and HCC-1954 BC cells was higher than that in normal breast cells. The silencing of ANXA3 inhibited the proliferation, invasion, healing, and creating colony formation of BC cells by decreasing the expression of cyclin-dependent kinase proteins and increasing the expression of E2F1 and p27 proteins. The drugs in TEC and CEF groups might regulate the biological functions of BC cells, such as proliferation, invasion etc., thus inhibiting the growth of tumor tissue and reducing the diameter of the primary lesion to facilitate the subsequent radical surgery by regulating the expression of ANXA3. Zeng et al. [24] studied the clinical significance of Annexin A3 in BC and found that the expression of Annexin A3 in BC tissues was higher than that in normal breast tissues, and was closely related to tumor size and axillary lymph node metastasis, while ANXA3 was involved in the regulation of apoptosis by affecting the balance of Bcl-2/Bax. In this paper, the significant decrease of ANXA3 and the more obvious effect of NAC with TEC indicated that the tumor volume reduced after chemotherapy and the efficacy of TEC was more apparent, which was consistent with the results of clinical and pathological effects. In future experiments, associated chemotherapeutic drugs for the treatment of BC cells can be used to detect the expression of ANXA3 and other related proteins in BC cells and further analyze and verify the related signal pathways, which can provide a new target for the targeted therapy of BC.

In conclusion, compared with CEF regimen, NAC with TEC regimen can improve the clinical and pathological effective rate, inhibit the expression of ANXA3 and improve the prognosis of patients, thus having a certain application prospect in NAC.

Conflict of interests

The authors declare no conflict of interests.

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