

# Efficacy and safety of TE/TEC/intensive paclitaxel neoadjuvant chemotherapy for the treatment of breast cancer

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**Abstract.** Efficacy and safety of paclitaxel/docetaxel + epirubicin (TE), paclitaxel/docetaxel + epirubicin + cytoxan (TEC) and intensive paclitaxel (IP) neoadjuvant chemotherapy (NCT) were compared for the treatment of breast cancer. The clinical data of 326 patients with stage II-III unilateral primary breast cancer treated in Shengjing Hospital of China Medical University from January 2012 to April 2016 were retrospectively analyzed. All patients received NCT for 4 cycles, including 115 cases of TE group, 109 cases of TEC group, and 102 cases of paclitaxel weekly group. The clinical efficacy was evaluated and complete response (CR) + partial response (PR) indicated clinically effective. The pathological effect was evaluated and the grade III+IV+V indicated pathologically effective. The rates of clinical efficacy and pathological CR (pCR) were compared, and the incidence of adverse reactions was also observed. The effects of different molecular typing on clinical efficacy and pCR were compared. Our results showed that the clinical effective rates in TE, TEC and IP groups were 80.9, 89.0 and 77.5%, respectively, and there were no statistically significant differences ( $P=0.074$ ). The pCR rates in the three groups were 9.57, 8.26 and 5.88%, respectively, and the differences were not statistically significant ( $P=0.602$ ). The incidence rate of neutropenia was statistically different among the three groups of patients ( $P<0.001$ ), which was the highest in TEC group and the lowest in IP group. There were no statistically significant differences in the incidence rates of adverse reactions ( $P>0.05$ ). Estrogen receptor (ER)-negative, progesterone receptor (PR)-negative and human epidermal growth factor receptor-2 (HER-2)-positive states were significantly correlated with the high clinical effective rate and high pCR rate ( $P<0.05$ ). In conclusion, IP has the lowest incidence rate of neutropenia. Additionally, ER-negative, PR-negative

and HER-2-positive states are significantly correlated with the high clinical effective rate and high pCR rate.

## Introduction

Neoadjuvant chemotherapy (NCT) refers to the preoperative chemotherapy for operable patients, which is one of the important treatment means for primary breast cancer in the progressive stage. Preoperative chemotherapy can reduce the tumor staging, locally control the lesion and improve the resectable rate, which can also provide the *in vivo* drug susceptibility information to guide the subsequent medication, so it has been widely used in clinic (1,2). However, there have been no unified standards yet for selecting the NCT regimen and frequency for breast cancer. How to choose the most appropriate NCT regimen for patients has always been a hot issue in the breast cancer treatment research. According to clinical practice, the pathological complete response (pCR) of neoadjuvant systemic chemotherapy (NST) regimen combining anthracycline with paclitaxel is superior to the simple anthracycline-based chemotherapy regimen in the treatment of breast cancer. The advantages of anthracycline and paclitaxel in NST of breast cancer become increasingly prominent, and improving the efficacy and safety of chemotherapy is the emphasis in research on NST of breast cancer (3,4).

In this study, the efficacy and adverse reactions were compared among paclitaxel/docetaxel + epirubicin (TE) regimen, paclitaxel/docetaxel + epirubicin + cytoxan (TEC) regimen and IP in NCT for breast cancer, and the efficacy of different chemotherapy regimens in NCT and their correlation with molecular typing were investigated, hoping to provide a theoretical basis and references for the selection of NCT regimen and individualized treatment of breast cancer.

## Patients and methods

**Objects of study.** A total of 326 patients diagnosed with breast cancer for the first time in Shengjing Hospital of China Medical University (Shenyang, China) from January 2012 to April 2016 were collected in this study. Breast cancer in all patients was confirmed pathologically via biopsy using hollow needle, and patients received no radiotherapy, chemotherapy or endocrine therapy before treatment. All patients had the evaluable unilateral primary tumor lesions, and received blood routine, liver

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**Key words:** breast cancer, neoadjuvant chemotherapy, efficacy, adverse reactions, paclitaxel, molecular typing

Table I. Demographics and general clinical data of all breast cancer patients.

Parameters	TE group n=115	TEC group n=109	IP group n=102	$\chi^2$ value	P-value
Age (years)				0.507	0.776
<50	54 (47.0%)	52 (47.7%)	44 (43.1%)		
≥50	61 (53.0%)	57 (52.3%)	58 (56.9%)		
Menopausal status				0.029	0.986
Premenopausal	52 (45.2%)	49 (45.0%)	47 (46.1%)		
Postmenopausal	63 (54.8%)	60 (55.0%)	55 (53.9%)		
Clinical tumor size				1.802	0.772
T <sub>1</sub>	3 (2.6%)	2 (1.8%)	2 (2.0%)		
T <sub>2</sub> -T <sub>3</sub>	87 (75.7%)	79 (72.5%)	70 (68.6%)		
T <sub>4</sub>	25 (21.7%)	28 (25.7%)	30 (29.4%)		
Lymph node metastasis				3.466	0.483
N <sub>0</sub>	5 (4.3%)	3 (2.8%)	1 (9.8%)		
N <sub>1</sub> -N <sub>2</sub>	73 (63.5%)	67 (61.5%)	71 (69.7%)		
N <sub>3</sub>	37 (32.2%)	39 (35.7%)	30 (29.5%)		
TNM stage				0.508	0.776
II	81 (70.4%)	72 (66.1%)	69 (67.6%)		
III	34 (29.6%)	37 (33.9%)	33 (32.4%)		
HER-2 status				0.295	0.863
+	56 (48.7%)	52 (47.7%)	46 (45.1%)		
-	59 (51.3%)	57 (52.3%)	56 (54.9%)		
ER status				0.476	0.788
+	51 (44.3%)	51 (46.8%)	50 (49.0%)		
-	64 (55.7%)	58 (53.2%)	52 (51.0%)		
PR status				0.435	0.805
+	47 (40.9%)	48 (44.0%)	46 (45.1%)		
-	68 (59.1%)	61 (56.0%)	56 (54.9%)		

TE, docetaxel and epirubicin; TEC, docetaxel, epirubicin and cyclophosphamide; IP, intensive paclitaxel; TNM, tumor-node-metastasis; HER-2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor.

and kidney function, chest X-ray, abdominal ultrasound, bone scan, electrocardiography, echocardiography and pulmonary function examinations before treatment, and the patients with distant metastasis and severe cardiopulmonary dysfunction were excluded. Patients signed an informed consent, and this study was approved by the Medical Ethics Committee of Shengjing Hospital of China Medical University.

Patients were aged 46.4±7.9 years, including 150 patients aged <50 years and 176 patients aged ≥50 years. There were 148 premenopausal patients and 178 postmenopausal patients. According to the tumor-node-metastasis (TNM) staging of tumor developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), there were 7 patients in T<sub>1</sub>, 236 patients in T<sub>2</sub>-3 and 83 patients in T<sub>4</sub>. According to preoperative axillary lymph node ultrasound and puncture pathology, no axillary lymph node metastasis was defined as N<sub>0</sub>, axillary lymph node metastasis as N<sub>1</sub>, mixed type as N<sub>2</sub>, and axillary lymph node metastasis complicated with internal mammary lymph node metastasis or supraclavicular lymph node metastasis

as N<sub>3</sub>, so there were 9 patients in N<sub>0</sub>, 211 patients in N<sub>1</sub>-2 and 106 patients in N<sub>3</sub>. Estrogen receptor (ER) was positive in 152 cases and negative in 174 cases. Progesterone receptor (PR) was positive in 142 cases and negative in 184 cases. Human epidermal growth factor receptor-2 (HER-2) was positive in 154 cases and negative in 172 cases. There were no statistically significant differences in age (P=0.776), menstrual status (P=0.986), tumor size (P=0.772), lymph node metastasis (P=0.483), clinical TNM staging (P=0.776) and molecular typing (P>0.05), among the patients enrolled, and data were comparable (Table I).

**Patients and methods.** TE regimen: 75 mg/m<sup>2</sup> docetaxel + 75 mg/m<sup>2</sup> epirubicin, intravenous drip at 1st day, and 21 days as 1 cycle. TEC regimen: 75 mg/m<sup>2</sup> docetaxel + 75 mg/m<sup>2</sup> epirubicin + 600 mg/m<sup>2</sup> cytoxan, intravenous drip at 1st day, and 21 days as 1 cycle. IP: weekly administration of 75 mg/m<sup>2</sup> paclitaxel. The 3 kinds of chemotherapy regimens were all performed for 4 cycles. At 0.5 h before administration of chemotherapeutic drugs, 10 mg dexamethasone was

Table II. Clinical effective rates in three neoadjuvant chemotherapy groups.

Parameters	TE group n=115	TEC group n=109	IP group n=102	$\chi^2$ value	P-value
CCR+CPR	93	97	79	5.197	0.074
SD+PD	22	12	23		
Clinical effective rate	80.9%	89.0%	77.5%		

TE, docetaxel and epirubicin; TEC, docetaxel, epirubicin and cyclophosphamide; IP, intensive paclitaxel; CCR, clinical complete response; CPR, clinical partial response; SD, stable disease; PD, progressive disease.

routinely given to prevent allergy, proton pump inhibitor (omeprazole or lansoprazole) to suppress acid, and 5-hydroxytryptamine inhibitor (tropisetron hydrochloride or ramosetron) to stop vomiting. When the absolute value of neutrophils was  $<2 \times 10^9/l$ , the recombinant human granulocyte colony-stimulating factor (300  $\mu\text{g}$  Ruibai or 150  $\mu\text{g}$  filgrastim) was injected subcutaneously to increase leukocytes. During chemotherapy, the liver function was monitored, and liver protecting treatment was performed if the level of alanine aminotransferase (ALT) or aspartate transaminase (AST) was 1.5 times higher than the normal high value. Patients received echocardiography again if the heart rate was significantly accelerated compared with that before chemotherapy or arrhythmia occurred in electrocardiogram. When the accumulated dose of anthracycline was 300  $\text{mg}/\text{m}^2$ , dexrazoxane was given to protect the heart. After each cycle of chemotherapy, B-ultrasound and clinical physical examinations were performed to evaluate clinical efficacy and adverse reactions. If the disease was progressive according to the evaluation, the chemotherapy regimen would be changed or operative treatment would be considered.

**Pathological evaluation.** After pathological diagnosis, immunohistochemical analysis was performed. ER, PR, HER-2 status and proliferation index (percentage of Ki-67-stained cells) in the paraffin-embedded tumor samples were detected via immunohistochemical method. The intensity and percentage of each antibody of the stained cells were detected. According to the regulations of the American Society of Clinical Oncology and College of American Pathologists (ASCO-CAP) in 2010, ER and PR were considered as negative ( $<1\%$ ) or positive ( $\geq 1\%$ ), indicating the percentage of nuclear immune remission. At least 30% cells in HER-2-positive patients were strongly stained in the membrane, and more than 14% positive staining in the cell nucleus indicated slightly higher level of Ki-67. Primary rabbit monoclonal ER antibody (dilution, 1:100; cat. no. ab79413); rabbit monoclonal PR antibody (dilution, 1:100; cat. no. ab16661); mouse monoclonal HER-2 (also called ErbB2) antibody (dilution, 1:100; cat. no. ab16901) and rabbit monoclonal Ki-67 antibody (dilution, 1:100; cat. no. ab16667) were all purchased from Abcam (Cambridge, MA, USA).

**Therapeutic evaluation criteria.** The clinical and pathological response effects of NCT were evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST, Version 1.1). At the end of treatment, the response rate was

evaluated in 326 patients with breast cancer. Clinical complete response (CCR): no residual breast and axillary lymph nodes, clinical partial response (CPR): decrease of tumor diameter by 30% or above, progressive disease (PD): increase of the maximum tumor diameter by 20% or occurrence of new diseases, and stable disease (SD): tumors not meeting the criteria of objective PR or PD. In this study, CR or PR (PR+CR) indicated clinically effective, while SD and PD (SD+PD) indicated clinically ineffective. pCR referred to no cancerous component or only *in situ* cancerous component found in the primary lesions and draining lymph nodes in surgical specimens, and no distant metastases in liver, lung, bone and brain.

The adverse and toxic side effects were evaluated according to the CETAE grading criteria (grade I-V) of the National Cancer Institute (NCI). Grades III-IV toxic and side effects were the major causes affecting chemotherapy, and grade V indicated death.

**Statistical analysis.** Statistical Product and Service Solutions (SPSS) 13.0 software (SPSS, Chicago, IL, USA) was used for statistical processing. Test indexes in this study were normally distributed according to the W-test. Continuous variables were presented as mean  $\pm$  standard deviation, and the variance was homogeneous according to the Levene test. Chi-square test was used for categorical data. Comparison between multiple groups was performed by using one-way ANOVA test followed by post hoc test (Least Significant Difference).  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**Clinical effective rates in TE, TEC and IP groups.** The clinical effective rates in TE, TEC and IP groups were 80.9% (93/115), 89.0% (97/109) and 77.5% (79/102), respectively, displaying no statistically significant differences among the three groups ( $P=0.074$ ) (Table II).

**pCR rates in TE, TEC and IP groups.** The pCR rates in TE, TEC and IP groups were 9.57% (11/115), 8.26% (9/100) and 5.88% (6/96), respectively, showing no statistically significant differences among the three groups ( $P=0.602$ ) (Table III).

**Adverse reactions.** After chemotherapy, adverse reactions in different degrees, such as neutropenia, thrombocytopenia, decreased hemoglobin, gastrointestinal reactions, hepatic dysfunction, cardiotoxicity and alopecia, occurred in the

Table III. pCR rates in three neoadjuvant chemotherapy groups.

Parameters	TE group n=115	TEC group n=109	IP group n=102	$\chi^2$ value	P-value
pCR (cases)	11	9	6	1.017	0.602
Not pCR (cases)	104	100	96		
pCR rate (%)	9.57	8.26	5.88		

pCR, pathological complete response; TE, docetaxel and epirubicin; TEC, docetaxel, epirubicin and cyclophosphamide; IP, intensive paclitaxel.

Table IV. Comparison of adverse reaction in three neoadjuvant chemotherapy groups.

Parameters	TE group n=115	TEC group n=109	IP group n=102	$\chi^2$ value	P-value
Neutropenia	26 (22.6%)	41 (37.6%)	7 (6.9%)	28.40	0.001
Anemia	14 (12.2%)	20 (18.3%)	8 (7.8%)	5.261	0.072
Thrombocytopenia	22 (19.1%)	25 (22.9%)	12 (11.8%)	4.564	0.102
Gastrointestinal AR	75 (65.2%)	77 (70.6%)	60 (58.8%)	3.239	0.198
Liver function damage	29 (25.2%)	31 (28.4%)	17 (16.7%)	4.300	0.117
Cardiotoxicity	50 (43.5%)	53 (48.6%)	40 (39.2%)	1.905	0.386
Alopecia	78 (67.8%)	79 (72.5%)	62 (60.8%)	3.301	0.192

TE, docetaxel and epirubicin; TEC, docetaxel, epirubicin and cyclophosphamide; IP, intensive paclitaxel; AR, adverse reaction.

three groups of patients. Such gastrointestinal reactions as nausea and vomiting occurred in 75 cases (65.2%, 75/115) in TE group, 77 cases (70.6%, 77/109) in TEC group and 60 cases (58.8%, 66/102) in IP group, and there were no statistically significant differences ( $\chi^2=3.239$ ,  $P=0.198$ ). No severe nausea and vomiting (grade III and IV) occurred in the three groups of patients. Neutropenia occurred in 26 cases (22.6%, 26/115) in TE group, 41 cases (37.6%, 41/109) in TEC group and 7 cases (6.9%, 7/102) in IP group, and differences were statistically significant ( $\chi^2=28.4$ ,  $P<0.001$ ). The pairwise comparisons revealed that the incidence rate of neutropenia in TEC group was significantly higher than that in TE group ( $P=0.0192$ ), and it was also significantly higher in TE group than that in IP group ( $P=0.0012$ ). There were 50 cases (43.5%, 50/115), 53 cases (48.6%, 53/109) and 40 cases (39.2%, 40/102) of cardiotoxicity in the three groups, respectively, and there were no statistically significant differences ( $\chi^2=1.905$ ,  $P=0.386$ ). No cardiotoxicity above grade II occurred in the three groups. No statistically significant differences were found in the incidence of such adverse reactions as thrombocytopenia, decreased hemoglobin, hepatic dysfunction and alopecia among the three groups ( $P>0.05$ ). All patients were treated with dexamethasone before chemotherapy, and there were no allergic reactions, such as bronchial asthma and hypotension, and pleural effusion. The adverse and toxic side effects were alleviated after treatment, and there was no case whose chemotherapy was terminated due to intolerance to adverse and toxic side effects of chemotherapy. Adverse and toxic side effects were compared among the three groups of patients (Table IV).

*Impact of molecular typing on efficacy.* The clinical effective rate under ER-negative state was 90.8%, which was significantly higher than that under ER-positive state (73.0%,  $P<0.001$ ). The clinical effective rate under PR-negative state was 92.9%, which was obviously higher than that under PR-positive state (69.0%,  $P<0.001$ ). The clinical effective rate under HER-2-positive state (87.7%) was also remarkably higher than that under HER-2-negative state (77.9%,  $P=0.028$ ). The ER-negative, PR-negative and HER-2-positive states were significantly correlated with the high pCR rate ( $P<0.05$ ) (Table V).

## Discussion

Compared with postoperative adjuvant chemotherapy, the significance of NCT lies in lowering the tumor staging, transforming inoperable patients into operable patients, making it possible to perform breast-conserving surgery for all patients, providing *in vivo* drug susceptibility information to guide subsequent medications, reducing tumor cell viability to reduce intraoperative metastasis, eliminating small metastases in the body via early systemic therapy, and improving prognosis and providing prognostic indexes for patients with pCR (5). Currently, it is recognized internationally that NCT can be performed for patients who should receive postoperative chemotherapy. According to the recommendation of the National Comprehensive Cancer Network (NCCN) guideline, NCT can also be performed first for patients who can undergo local surgery of breast cancer in stage IIA, IIB and IIIA. Breast cancer patients with indications can benefit from NCT (6).

Table V. Effect of molecular subtype on clinical effective rate and pCR in all breast cancer patients.

Parameter status	CCR+CPR (cases)	SD+PD (cases)	CER (%)	P-value	pCR	P-value
ER (+)	111	51	73.0	0.001	10 (6.7%)	0.042
ER (-)	158	16	90.8		16 (9.2%)	
PR (+)	98	44	69.0	0.001	8 (5.6%)	0.021
PR (-)	171	13	92.9		18 (9.8%)	
HER-2 (+)	135	19	87.7	0.028	17 (11.0%)	0.015
HER-2 (-)	134	38	77.9		9 (5.2%)	

TE, docetaxel and epirubicin; TEC, docetaxel, epirubicin and cyclophosphamide; IP, intensive paclitaxel; CCR, clinical complete response; CPR, clinical partial response; SD, stable disease; PD, progressive disease; pCR, pathological complete response; CER, clinical effective rate; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

Although current studies have shown that preoperative chemotherapy is not sufficient to improve the long-term survival rate of the overall population with breast cancer, results of a National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 large-scale randomized clinical study in 2001 manifested that the efficacy of preoperative chemotherapy is at least consistent with that of postoperative adjuvant chemotherapy, and many advanced patients who lose operation opportunity receive the operative treatment after preoperative chemotherapy, having significantly improved survival time (7). According to statistics, the overall clinical efficacy of NCT can be up to 60-90% currently, and 3%-30% patients can achieve pCR. At the same time, studies have revealed that patients who achieve pCR through NCT can obtain the ultimate survival advantage (8). pCR is currently one of the indexes of evaluating the efficacy of NCT or predicting the prognosis of patients.

It is recommended by the NCCN guideline and the St. Gallen expert consensus that the chemotherapy regimen containing paclitaxel and anthracycline is the first choice for NCT of breast cancer (9). At present, there is much application of double-combination or triple-combination regimens based on anthracycline and (or) paclitaxel in China, and the additional application of cytoxan can also obtain excellent efficacy in NCT (10). In the 1980s, Norton and Simon established a dose-dense model (11), based on which researchers further understood the tumor growth mode (12) and came up with a hypothesis that shortening the interval time of chemotherapy can kill the tumor cells more effectively. Therefore, paclitaxel-intensive regimen was introduced into the clinical trials for the treatment of breast cancer. There are studies that pCR in paclitaxel-intensive chemotherapy group is higher, and both 5-year disease-free survival (DFS) and overall survival (OS) are also significantly higher than those in traditional 3-week chemotherapy group (13,14). However, there are few studies on the efficacy of IP and the comparison with other chemotherapy regimens.

In this study, the clinical effective rate and pCR rate were compared among TE, TEC and IP groups. Results showed that there were no statistically significant differences in clinical effective rate and pCR rate among the three chemotherapy regimens, and no regimen with a better efficacy than other regimens was found. The difference in the incidence

of neutropenia was statistically significant among the three groups. According to further analyses, the incidence rate of neutropenia was the highest in TEC group and the lowest in IP group. The severe bone marrow suppression is the most important cause of chemotherapy delay or dose reduction for breast cancer, which, if not detected or controlled in time, can lead to febrile neutropenia and secondary refractory infection, prolong the hospitalization time, increase treatment expense and even cause death. In this study, there was no difference in the clinical efficacy of TE, TEC and IP neoadjuvant chemotherapy, but the incidence rate of neutropenia in IP group was remarkably lower than those in TEC and TE groups. Therefore, IP can be considered in NCT for breast cancer patients at an advanced age or with poorer general conditions.

The efficacy of NCT is affected by a variety of factors, among which molecular typing can better reflect the biological behaviors of the tumor and the gene type in disease. Moreover, molecular typing is considered to be closely related to the pathological features, outcome, and prognosis and treatment response of tumors (15). Studies have demonstrated that the pCR rate is higher in triple-negative and HER-2-positive patients, but DFS and OS are lower with relatively poor prognosis (16-18). At present, there are few reports on the molecular typing of breast cancer and the efficacy of NCT. In this study, ER-negative, PR-negative and HER-2-positive states in the three groups were significantly correlated with the high clinical efficacy and high pCR rate, which were consistent with research results world-wide. The possible reason why the efficacy is affected by ER and PR is that the negative expression of ER and PR inhibits cell proliferation/growth and the expression of proto-oncogenes, and promote the expression of tumor suppressor genes, thereby regulating tumor progression in patients with breast cancer. In the clinical practice of NCT, appropriate population can be selected based on molecular typing. For example, NCT can be applied for HER-2-positive breast cancer patients or hormone receptor-positive patients with high expression of Ki-67.

There are many shortcomings in this study. The sample size was too small, so more clinical research objects should be enrolled for the large-sample data analysis to study the efficacy of different NCT regimens. In this study, only clinical efficacy, pCR rate and short-term efficacy were analyzed,

patients were not followed up for a long time, and long-term survival and other relevant data were not collected, so whether there are differences in the long-term efficacy among the three regimens remains to be further explored and studied. It is hoped that multi-center clinical research on breast cancer NCT in the future can provide more accurate references for clinical decision and greater benefit for breast cancer patients.

In NCT for patients with stage II-III breast cancer, TE, TEC and IP neoadjuvant chemotherapy have similar efficacy. There are few adverse reactions and higher safety in IP group. ER-negative, PR-negative and HER-2-positive states are significantly correlated with the high clinical effective rate and high pCR rate.

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### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Authors' contributions

YL and FH designed the study and performed the experiments. ZX, ZZ and GW collected the data. YL and JS analyzed the data. YL and FH prepared the manuscript. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shengjing Hospital of China Medical University (Shenyang, China). Signed informed consents were obtained from the patients or guardians.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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