

Comparison of the effectiveness and toxicity of neoadjuvant chemotherapy regimens, capecitabine/epirubicin/cyclophosphamide vs 5-fluorouracil/epirubicin/cyclophosphamide, followed by adjuvant, capecitabine/docetaxel vs docetaxel, in patients with operable breast cancer

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Abstract: The aim of this study was to compare the effectiveness and toxicity of neoadjuvant chemotherapy regimens, xeloda/epirubicin/cyclophosphamide (XEC) vs 5-fluorouracil/epirubicin/cyclophosphamide (FEC), followed by adjuvant chemotherapy regimens, capecitabine/taxotere (XT) vs taxotere (T), in axillary lymph node (LN)-positive early-stage breast cancer. In this randomized, Phase III trial, 137 patients with operable primary breast cancer (T2-0, N0-1) who were tested axillary LN positive through aspiration biopsy of axillary LNs were randomized (1:1) to four 3-weekly cycles of XEC or FEC. Patients underwent surgery within 4–6 weeks after the fourth cycle, followed by four adjuvant cycles of 3-weekly XT or T. The primary end point was tumor pathological complete response. Toxicity profiles were secondary objectives. In total, 131 patients had clinical and radiological evaluation of response and underwent surgery. Treatment with XEC led to an increased rate of pathological complete response in primary tumor (18% vs 6%, respectively, $P=0.027$) and objective remission rate (87% vs 73%, $P=0.048$) compared to FEC. Clinical complete response occurred in 20% and 7% for XEC and FEC, respectively. Compared to FEC, XEC was associated with more hand-foot syndrome (57% vs 11%, $P<0.001$) and 3/4 grade nausea/vomiting/diarrhea (30% vs 14%, $P=0.034$) but less phlebitis (3% vs 14%, $P=0.035$). XT and T adjuvant chemotherapy regimens were well tolerated: treatment-related 3/4 grade adverse events occurred in 28% and 17% of patients receiving XT and T, respectively.

Keywords: breast cancer, capecitabine, docetaxel, neoadjuvant chemotherapy, curative effect, toxic side effects

Introduction

Breast cancer is a type of most commonly highly metastatic malignant tumor among females.¹ Neoadjuvant chemotherapy was first used as induced chemotherapy or primary chemotherapy to treat locally advanced and inoperable breast cancer. Patients with breast cancer with pathological complete response (pCR) after neoadjuvant chemotherapy were able to achieve better overall survival rate.^{2,3} Therefore, pursuing the pCR becomes the primary goal in neoadjuvant chemotherapy.

Neoadjuvant chemotherapy can be used to evaluate the therapeutic effect of tumors, and the evaluation of neoadjuvant chemotherapy has advantages in providing prognosis

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and adjusting treatment strategy compared to other treatments. Therefore, with the development of research in neoadjuvant chemotherapy, its application has expanded from locally advanced to early and medium stage in breast cancer.⁴ Neoadjuvant chemotherapy is the best *in vivo* chemosensitivity test because an effective follow-up plan can be made according to the reaction of tumor during chemotherapy treatment, and it is an important method of achieving individualized treatment in operable breast cancer.^{5,6} The advantage of neoadjuvant chemotherapy in operable breast cancer before operation can not only decrease the size of large tumors and clinical staging but also narrow the area of operative surgical resection and kill small metastasized micrometastases prior to surgery. An objective evaluation of resistance to chemotherapy in cancer and prognosis by clinical and pathological response is another advantage.⁷ The pCR rate can be mainly used to predict the long-term outcomes of neoadjuvant chemotherapy and also as a surrogate end point in clinical trials.⁸

The best preoperative treatment should achieve a high pCR rate by neoadjuvant chemotherapy. The effect of the chemotherapy regimen, capecitabine/epirubicin/cyclophosphamide (XEC), as a neoadjuvant chemotherapy regimen has been reported to be better than that of 5-fluorouracil (5-FU)/epirubicin/cyclophosphamide (FEC), with a good tolerance; thus, it is advisable to use XEC instead of FEC during neoadjuvant or adjuvant chemotherapy treatment.⁹ Lee et al¹⁰ claimed that the efficacy of capecitabine (Xeloda®, F. Hoffmann La-Roche, Basel, Switzerland)/ docetaxel (Taxotere®, Sanofi-Aventis, Paris, France) (XT) neoadjuvant chemotherapy was better than doxorubicin/ cyclophosphamide (AC), because the pCR rate of the former was significantly improved and treatment-related G3/4 adverse events were relatively lower. Other data^{11,22} proved that capecitabine which treated patients with metastatic breast cancer was a valid single reagent and well tolerated. A meta-analysis also reported that capecitabine should be used in neoadjuvant chemotherapy, and treatment with XT was the first-line chemotherapy regimen with an effective rate of 42%.¹³ Another meta-analysis also reported that treatment with XT can effectively improve the efficacy of adjuvant chemotherapy and is highly likely to become a new adjuvant chemotherapy regimen.¹⁴

The primary objective of this study was to compare the tumor pCR rate achieved with four 3-weekly cycles of XEC vs FEC when used as neoadjuvant chemotherapy for patients with axillary lymph node (LN)-positive stage II/III and operable breast cancer.

Patients and methods

Study design

This was a randomized, open-label, single-center clinical trial comparing XEC with FEC as a neoadjuvant chemotherapy

for patients with axillary LN-positive stage II/III and operable breast cancer. All the patients provided written informed consent before enrollment. Furthermore, all the procedures performed in this study involving human participants followed the ethical standards of the Medical ethics committee of the Affiliated Cancer Hospital of Guangxi Medical University who approved the study and followed the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The trial profile is shown in Figure 1. Patients were randomized to one of two treatment arms: capecitabine (Xeloda®; Shanghai Roche Pharmaceuticals Ltd., Shanghai, People's Republic of China) 1,000 mg/m² orally twice daily on days 1–14, plus epirubicin (Pfizer, Inc., New York, NY, USA) 100 mg/m² infusion on day 1, plus cyclophosphamide (Endoxan®, Baxter Oncology GmbH, Halle, Germany) 500 mg/m² infusion on day 1 every 3 weeks for four cycles, or 5-FU (Shanghai Xudong Haipu Pharmaceutical Co. Ltd., Shanghai, People's Republic of China) 500 mg/m² infusion on day 1, plus epirubicin 100 mg/m² infusion on day 1, plus cyclophosphamide 500 mg/m² infusion on day 1 every 3 weeks for four cycles before surgery. The first assessment of curative effect was performed within 24–48 hours before the third cycle of chemotherapy when the second cycle was over, and the second assessment was performed within 24–48 hours after the fourth cycle. If the evaluation was considered invalid, then the patients were categorized as invalid group and the others underwent surgery after the fourth cycle of neoadjuvant chemotherapy and then crossed over to receive the other treatment regimens as adjuvant therapy. In the XEC arm, four-cycle adjuvant chemotherapy of XT was given: capecitabine 1,000 mg/m² orally twice daily on days 1–14, plus docetaxel (Jiangsu Hengrui Medicine Co. Ltd., Lianyungang, People's Republic of China) 75 mg/m² infusion on day 1 every 3 weeks. In the FEC arm, four-cycle adjuvant chemotherapy of T was given: docetaxel 75 mg/m² infusion on day 1 every 3 weeks. All patients positive for human epidermal growth factor receptor 2 (HER2) were not using trastuzumab while receiving adjuvant chemotherapy because it might increase the cardiac toxicity of chemotherapy drugs. Upon completion of the adjuvant chemotherapy, all patients received radiotherapy and were concurrently treated with tamoxifen or letrozole when hormone receptor (HR) was positive.

Eligibility criteria

To be included in the study, patients should have biopsy-proven, newly diagnosed stage II/III, and operable breast

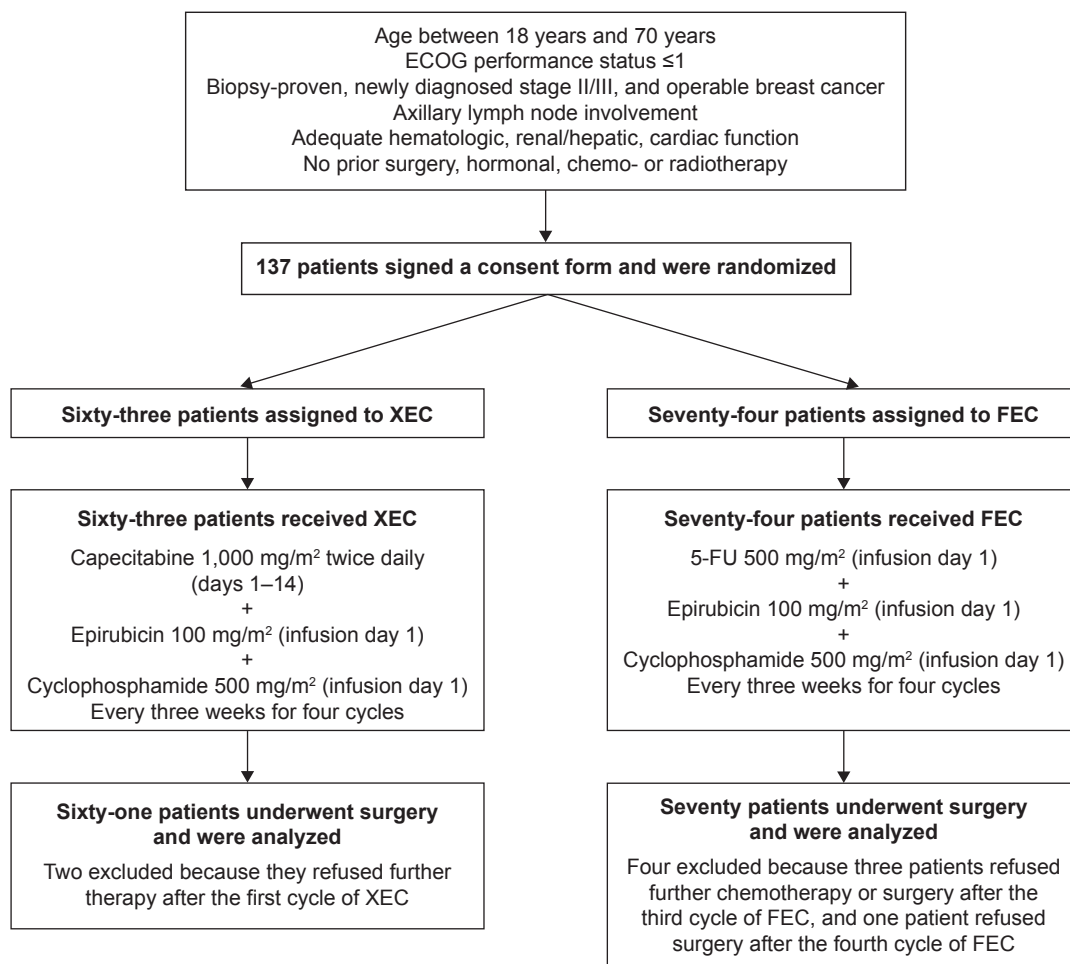


Figure 1 Trial profile.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FEC, 5-FU/epirubicin/cyclophosphamide; 5-FU, 5-fluorouracil; XEC, capecitabine/epirubicin/cyclophosphamide.

cancer with axillary LN involved. Operable breast cancer was defined as a tumor with a diameter of >1 cm diagnosed by ultrasonography or magnetic resonance imaging (MRI). The axillary LN positivity was determined by fine-needle aspiration cytology of axillary LN. Further, the eligibility criteria included patients aged 18–70 years, with an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 and adequate hematologic (absolute neutrophil count ≥1,500/mm³, platelet count ≥10,000/mm³, hemoglobin ≥10 g/dL), renal (serum creatinine ≤1.5 mg/dL), cardiac (confirmed by normal or nonspecific ECG or multigated acquisition scan taken within 1 month of enrollment), and hepatic (total bilirubin ≤1.5 mg/dL, aspartate aminotransferase, alanine transaminase, alkaline phosphatase ≤2.5× upper normal limit) functions. Patients were excluded if they had undergone prior surgery, hormonal treatment, chemotherapy, or radiotherapy, or had a history of cancer except for in situ uterine cervical cancer or non-melanotic skin

cancer, any distant metastasis, or any serious concomitant systemic disorder.

Patient evaluations

The three-dimensional size of the primary breast tumor was measured by physical examination, ultrasound, and molybdenum target or MRI. These measuring methods started within 1–2 days before the first cycle of neoadjuvant chemotherapy, before the third cycle, and after the fourth cycle.

Clinical response was assessed using the response evaluation criteria in solid tumors¹⁵ and was categorized into invalid, partial response, clinical complete response (cCR), and pCR. In this study, pCR was defined such that invasive carcinoma was not found in both primary site and axillary node; however, pCR was considered if the ductal carcinoma remained in situ in the primary site.¹⁶

Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0.

Statistical methods

The primary objective of this study was to compare pCR rates between the XEC and FEC groups. Chi-square test was used in the comparison of clinical and pathological response rates and toxicities in the two treatment groups, while Fisher's exact test was used when the cell expectation was less than six. Breslow–Day test for homogeneity was performed to determine whether significant treatment by subgroup interactions existed with respect to pCR. All statistical analyses were performed using SPSS Version 20.0 (IBM Corporation, Armonk, NY, USA) with significance determined at $P < 0.05$.

Results

Patient characteristics

A total of 137 patients were enrolled in this study between January 2011 and December 2013. Of these, 131 patients had clinical and radiological evaluation of response and completed surgery and were randomly assigned to the XEC ($n=61$) and FEC ($n=70$) groups. The reasons why the six subjects were withdrawn from the study were as follows: three patients refused further chemotherapy or surgery after the third cycle of FEC, one patient refused surgery after the fourth cycle of FEC, and two patients refused any further therapy after the first cycle of XEC.

Patients' baseline characteristics were balanced between the two treatment arms (Table 1). Patients in each treatment arm were well matched for age, ECOG performance status, clinical T-stage, pathological pattern, clinical N-stage, estrogen receptor, progesterone receptor, and HER2 status. Invasive ductal carcinoma ($n=47$, 77%) was the most common pathological pattern. All patients had an ECOG performance status of 0 or 1. HR and HER2 were positive in 64% (XEC vs FEC: 64% vs 64%) and 29% (XEC vs FEC: 28% vs 30%) of patients, respectively.

Efficacy

Of the 131 patients evaluable for response, one patient in the XEC arm and two patients in the FEC arm did not complete treatment due to tumor progression or stable disease and received alternative chemotherapy prior to surgery. Treatment with XEC led to an increased rate of pCR (18% vs 6%, $P=0.027$), cCR (20% vs 7%, $P=0.033$), and objective remission rate (ORR; 87% vs 73%, $P=0.048$) compared with FEC (Table 2). No patient progressed in the XEC arm, whereas eight patients progressed in the FEC arm (13%, $P=0.004$).

Tumor ORRs were not significantly different among the various molecular types of breast cancer between the two arms ($P > 0.05$) as shown in Table 3. The ORR was greater

Table 1 Patient characteristics

Characteristics	XEC (n=61)	FEC (n=70)	P-value*
Number of patients			
Enrolled	63	74	0.689
Dropouts	2	4	
Age (years)			
Median (range)	43 (19–68)	42 (21–69)	0.215
ECOG performance status			
0	39	44	0.898
I	22	26	
Clinical T-stage			
≥5 cm	35	39	0.848
<5 cm	26	31	
Pathological pattern			
Invasive ductal carcinoma	47	53	0.570
Mucinous carcinoma	2	1	
Cribiform carcinoma	1	0	
Clinical N-stage			
N1	28	35	0.842
N2	23	23	
N3	10	12	
HR			
Positive	39	45	0.967
Negative	22	25	
HER2			
Positive	17	21	0.814
Negative	41	44	
Unknown	3	5	
Molecular type			
Triple negative	12	11	0.553
Non-triple negative	49	59	

Notes: *P-value by chi-square test or Fisher's exact test when the cell expectation was less than six; for comparison of age distribution 2 sample, t-test was used. Her-2(+) meant it was positive in FISH or CISH test or (+++) in ICH test according to NCCN in 2011. In 2010, guidance for investigations of ER and PR in breast cancer was developed by ASCO and CAP where professors recommended that the positive criteria of ER and PR were ≥1% of positive nuclear staining.

Abbreviations: ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; CISH, chromogenic in situ hybridization; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; FEC, 5-FU/epirubicin/cyclophosphamide; 5-FU, 5-fluorouracil; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICH, immunohistochemistry; NCCN, National Comprehensive Cancer Network; PR, progesterone receptor; XEC, capecitabine/epirubicin/cyclophosphamide.

Table 2 Pathological and clinical tumor response

Variables	XEC (n=61) (%)	FEC (n=70) (%)	P-value*
pCR in tumor	11 (18)	4 (6)	0.027
ORR	53 (87)	51 (73)	0.048
cCR	12 (20)	5 (7)	0.033
Partial response	41 (67)	46 (66)	0.865
Stable disease	8 (13)	10 (14)	0.846
Progressive disease	0 (0)	9 (13)	0.004

Note: *P-value by chi-square test or Fisher's exact test when the cell expectation was <6.

Abbreviations: cCR, clinical complete response; FEC, 5-FU/epirubicin/cyclophosphamide; 5-FU, 5-fluorouracil; ORR, objective remission rate; pCR, pathological complete response; XEC, capecitabine/epirubicin/cyclophosphamide.

Table 3 Tumor ORRs between the two arms

Variables	XEC (n=61) (%)	FEC (n=70) (%)	P-value*
Luminal-A	8 (89)	10 (77)	0.616
Luminal-B			
HER2 negative	20 (87)	18 (72)	0.292
HER2 positive	6 (86)	5 (71)	1.000
HER2 overexpression	8 (80)	10 (71)	0.659
Triple negative	11 (92)	8 (73)	0.571

Note: *P-value by chi-square test or Fisher's exact test when the cell expectation was less than six.

Abbreviations: FEC, 5-FU/epirubicin/cyclophosphamide; 5-FU, 5-fluorouracil; HER2, human epidermal growth factor receptor 2; ORR, objective remission rate; XEC, capecitabine/epirubicin/cyclophosphamide.

in XEC than in FEC in triple-negative breast cancer (TNBC) without statistical significance (92% vs 73%, $P=0.571$).

An exploratory analysis of pCR rate according to major subgroups (age, T-stage, N-stage, HR status, HER2 status, molecular type, and clinical response) was performed (Table 4). Although the subset analysis might not have enough power to detect the differences, XEC appeared more effective than FEC, particularly in patients with TNBC (83% vs 22%; $P=0.009$; interaction $P=0.028$).

Safety

Safety was assessed in all 131 patients. The tolerance in XEC and FEC regimens was good (Table 5). In terms of 3/4 grade

Table 4 Tumor pCR rates in patient subgroups

Subset	XEC (%)	FEC (%)	P-value*	Interaction P
Age (years)				
<50	4 (10)	1 (2)	0.184	0.873
≥50	7 (37)	3 (13)	0.143	
T-stage				
<5 cm	7 (27)	3 (10)	0.160	0.795
≥5 cm	4 (11)	1 (3)	0.183	
N-stage				
N1	6 (21)	3 (9)	0.170	0.583
N2/N3	5 (15)	1 (3)	0.101	
HR				
Positive	4 (10)	2 (4)	0.409	0.529
Negative	7 (32)	2 (8)	0.063	
HER2				
Positive	3 (18)	1 (5)	0.307	0.870
Negative/unknown	8 (18)	3 (6)	0.072	
Molecular type				
Triple negative	10 (83)	2 (22)	0.009	0.028
Non-triple negative	1 (2)	2 (3)	1.000	
Clinical response				
CR	5 (42)	1 (20)	0.600	0.995
PR/SD/PD	6 (12)	3 (5)	0.307	

Note: *P-value by chi-square test or Fisher's exact test when the cell expectation was less than six.

Abbreviations: CR, complete response; FEC, 5-FU/epirubicin/cyclophosphamide; 5-FU, 5-fluorouracil; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; pCR, pathological complete response; PD, progressive disease; PR, partial response; SD, stable disease; XEC, capecitabine/epirubicin/cyclophosphamide.

Table 5 Treatment-related clinical adverse events in XEC and FEC arms

Adverse Event	XEC (n=61) (%)	FEC (n=70) (%)	P-value*
3/4 grade adverse events	34 (56)	28 (40)	0.072
3/4 grade leukopenia	11 (18)	11 (16)	0.723
3/4 grade nausea, vomiting, and diarrhea	18 (30)	10 (14)	0.034
3/4 grade mucositis	5 (8)	7 (10)	0.721
HFS	35 (57)	8 (11)	0.000
Phlebitis	2 (3)	10 (14)	0.035
Arthralgia and myalgia	3 (5)	6 (8)	0.502
Alopecia	52 (85)	62 (89)	0.572

Note: *P-value by chi-square test or Fisher's exact test when the cell expectation was less than six.

Abbreviations: FEC, 5-FU/epirubicin/cyclophosphamide; 5-FU, 5-fluorouracil; HFS, hand-foot syndrome; XEC, capecitabine/epirubicin/cyclophosphamide.

treatment-related clinical adverse events, there were more cases of hand-foot syndrome (HFS; 57% vs 11%, $P<0.001$) and 3/4 grade nausea/vomiting/diarrhea (30% vs 14%, $P=0.034$) but less cases of phlebitis (3% vs 14%, $P=0.035$) in XEC compared with FEC. The incidence of 3/4 grade leukopenia (18% vs 16%, $P=0.723$), arthralgia/myalgia (5% vs 8%, $P=0.502$), alopecia (85% vs 89%, $P=0.572$), and 3/4 grade mucositis (8% vs 10%, $P=0.721$) was lower in XEC than in FEC, but the difference between the two groups was not statistically significant.

XT and T adjuvant chemotherapy regimens were well tolerated (Table 6). In terms of 3/4 grade treatment-related clinical adverse events, there were more cases of HFS (16% vs 0%, $P<0.001$) in XT compared to T, and the treatment-related 3/4 grade adverse events occurred in 28% and 17% of patients receiving XT and T, respectively. XT and T were associated with a similar rate of 3/4 grade leukopenia (20% vs 14%, $P=0.411$), 3/4 grade nausea/vomiting/diarrhea (7% vs 1%, $P=0.126$), 3/4 grade mucositis (3% vs 1%, $P=0.922$), and alopecia (100% vs 99%, $P=1.000$).

Table 6 Treatment-related clinical adverse events in XT and T arms

Adverse Event	XT (n=61) (%)	T (n=70) (%)	P-value*
3/4 grade adverse events	17 (28)	12 (17)	0.140
3/4 grade leukopenia	12 (20)	10 (14)	0.411
3/4 grade nausea, vomiting, and diarrhea	4 (7)	1 (1)	0.126
3/4 grade mucositis	1 (3)	1 (1)	0.922
HFS	10 (16)	0 (0)	0.000
Alopecia	61 (100)	69 (99)	1.000

Note: *P-value by chi-square test or Fisher's exact test when the cell expectation was less than six.

Abbreviations: HFS, hand-foot syndrome; XT, capecitabine/docetaxel; T, docetaxel.

Discussion

The incidence of breast cancer has a rising tendency in developed cities in the People's Republic of China and becomes the first morbidity of malignant tumor among females.¹⁷ The treatment is conventional surgery assisted with chemotherapy and radiotherapy, while distant metastasis and local relapse are the main reasons for mortality in breast carcinoma.

Neoadjuvant chemotherapy before surgery is one of the main treatments for locally advanced breast cancer. It not only narrows the primary lesion and regional LNs, degrades clinical staging, increases the chances in patients who could not be operated before, and improves the resection rate and the breast conserving rate but also controls subclinical lesions effectively, reduces tumor loading, and improves the prognosis. Furthermore, it could reduce the chances of distant metastasis by destroying distantly potential micrometastasis and provide evidence for sequential treatment through judging the sensitivity of tumors to chemotherapy.^{18,19} Currently, neoadjuvant chemotherapy has become a standard treatment for invasive breast cancer in stage II/III, but there is no unified standard in the specific treatment including cyclophosphamide/methotrexate/5-FU, 5-FU/adriamycin/cyclophosphamide, FEC, and docetaxel/doxorubicin/cyclophosphamide.^{20,21}

Neoadjuvant chemotherapy has provided an opportunity for studying the biological effects of systemic treatment in breast cancer and can be used to choose effective index for predicting the prognosis in clinical settings. Early systemic chemotherapy can induce apoptosis of tumor cells and reduce the metastasis rate in surgery.²² The pathological response in the primary tumor after neoadjuvant chemotherapy is closely related to prognosis. Patients with pCR have an 86% 5-year survival rate and achieve an obvious survival benefit. Therefore, we can evaluate the effect of chemotherapy through pathological response condition of the primary tumor and predict the prognosis.^{18,20,23,24} Patients who responded well to neoadjuvant chemotherapy especially those with pCR, have a significantly improved disease-free survival rate.²⁵

Capecitabine, as an antimetabolite, is a new-generation oral derivative of FU. After ingestion, it is rapidly nearly completely absorbed as an active compound in the gastrointestinal tract and is converted into 5-FU via a three-step enzymatic pathway.^{26,27} After two intermediate steps involving carboxylesterase in the liver and cytidine deaminase in the liver and/or tumor tissue, the final metabolite is converted into 5-FU by thymidine phosphorylase. Thymidine phosphorylase as the last enzyme in the activation of capecitabine

has a higher concentration in malignant cells compared to healthy tissue, especially in breast cancer and gastric carcinoma causing DNA dyssynthesis in cancer tissue to achieve an antitumor effect, thus having selective and targeted antitumor effect.²⁸ Therefore, cancer tissue can convert more capecitabine into 5-FU, with less concentration in healthy tissue, so that 5-FU does not injure the healthy tissue and has less toxic and side effects. In conclusion, capecitabine is an oral chemotherapy drug with less toxicity and has a unique advantage in the treatment of breast cancer.

Patients with stage II/III breast cancer were treated prior to surgery by neoadjuvant chemotherapy, including treatment regimens XEC and FEC where both were compared for efficacy and adverse events in this study. It was concluded from the results that compared to the FEC arm, XEC significantly increased both the tumor pCR rate (18% vs 6%, $P=0.027$) and the clinical response rate (87% vs 73%, $P=0.048$). A large-scale, multiple-center clinical research reported that patients with primary or metastatic breast cancer who could not be treated with anthracycline- and/or taxol-containing regimens can be treated with capecitabine. The effective rate of single-drug first-line treatment was found to be 15%–37%, and the median progression-free survival was from 3 to 5 months.²⁹ In the study by Kamal et al,³⁰ 257 patients with metastatic breast cancer were treated with capecitabine or taxol. The results showed that the overall survival rate and tumor specificity in patients treated with capecitabine or taxol were similar, and there was no significant difference in the survival benefit. In addition, the results from a multiple-center, randomized Phase III clinical trial showed that the effect of capecitabine was as good as the combination of vinorelbine plus gemcitabine, when compared between these drugs in patients who were treated ineffectively with anthracycline- and/or taxol-containing regimens.³¹ Therefore, capecitabine played an important role in both single drug and combination therapy. Capecitabine monotherapy or capecitabine-containing regimens can be used not only as first-line treatment in advanced breast cancer but also as second- or third-line treatment in locally advanced breast cancer due to its good tolerance to side effects.^{32–35} After success with combination therapy, sequential treatment until single-drug maintenance could prolong the survival time in advanced breast cancer patients.

One research³⁶ showed that TNBC was more sensitive to capecitabine and could achieve better pCR and cCR as neoadjuvant chemotherapy compared to non-TNBC. Other studies^{37,38} suggested that HR-positive tumors show resistance

to chemotherapeutic drugs and were difficult to achieve pCR. In this study, the fact that 92% of TNBC achieved ORR in XEC while only 73% in FEC implied that treatment with XEC would have better curative effect to TNBC than FEC. Since there was no statistically significant difference, the result may change if the number of subjects was increased. In addition, XEC achieved more tumor pCR (ten patients, 83%) compared with FEC (two patients, 22%) in TNBC ($P=0.009$; interaction $P=0.028$). At the same time, XEC had a trend toward increased pCR in patients with HR negative and HER2 negative/unknown. Similarly, due to small sample, the result may change after increasing the number of subjects, although there was no statistically significant difference.

In addition to superior efficacy, the tolerability of XEC was also compared to that of FEC. From the comparison of adverse events, the incidence rate of HFS in the XEC arm was higher (57% vs 11%, $P<0.001$) compared to the FEC arm. Several studies showed that the incidence rate of HFS in capecitabine-containing chemotherapy regimens was higher because of the characteristics of the drug, which was consistent with the results in this study.^{39,40} Severe HFS may lead to reduction in drug dosage; therefore, it is important to prevent and reduce the incidence rate and degree of this syndrome, and it is known that vitamin B6 can relieve the symptom of HFS caused by 5-FU. In this study, it is reported that oral capecitabine with a large dose of vitamin B6 (300 mg/d) can reduce the incidence rate and symptom of HFS. In addition, a retrospective study suggested that cyclooxygenase-specific inhibitor might have the same effect as the combination of capecitabine and vitamin B6, as well.⁴¹ There were more patients with 3/4 grade nausea/vomiting/diarrhea in the XEC arm than in the FEC arm (30% vs 14%; $P=0.034$), because capecitabine was absorbed in the gastrointestinal tract and needs to be taken orally for 2 weeks.

The side effects such as phlebitis, arthralgia/myalgia, alopecia, leukopenia, and 3/4 grade mucositis were lower in XEC than in FEC. Among them, there was a statistically significant difference in phlebitis. XT and T adjuvant chemotherapy regimens were well tolerated: treatment-related 3/4 grade adverse events occurred in 28% and 17% of patients receiving XT and T, without statistical significance, respectively. This indicated that the XEC followed by XT regimen can be safely implemented because of less side effects and toxicity.

Conclusion

This study showed that the XEC regimen was effective and had similar curative effect compared to the FEC regimen.

Due to its good tolerability and low incidence and severity of preventable adverse events, XEC regimen should be promoted and implemented in clinical practice.

Disclosure

The authors report no conflicts of interest in this work.

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