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ORIGINAL ARTICLE

Timing of paclitaxel treatment in pre-operative or post-operative does not affect survival in breast cancer patients

Jiayu Wang*, Shanshan Chen*, Binghe Xu, Peng Yuan, Fei Ma, Qing Li, Pin Zhang, Ruigang Cai, Ying Fan, Yang Luo & Qiao Li

Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China

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Correspondence
Binghe Xu, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, No. 17 Panjiayuan Nanli, Beijing 100021, China.
Tel: +86 10 8778 8826
Fax: +86 10 8771 5711
Email: xubinghebm@163.com

*Co-first authors.

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Abstract

Background: Two epirubicin and paclitaxel-based neoadjuvant chemotherapy regimens were compared in breast cancer patients.

Methods: We enrolled 309 breast cancer patients who received two types of regimens: cyclophosphamide + epirubicin dose-dense neoadjuvant chemotherapy followed by sequential postoperative paclitaxel single-drug medication, and paclitaxel + epirubicin standard neoadjuvant chemotherapy followed by two cycles of the same chemotherapy after surgery. The primary endpoint was a pathological complete response (pCR) and the secondary endpoints were disease-free and overall survival.

Results: The median follow-up time was 65 months. The overall pCRs for pathological efficacy and efficacy of primary lesions were 14.4% and 29.3%, respectively ($P < 0.001$). The pCR of the paclitaxel + epirubicin group was significantly higher than in the cyclophosphamide + epirubicin group (17.3% vs. 9.2%; $P = 0.0345$), but the five-year disease-free survival rates in both groups were not significantly different (82.9% vs. 75.3%; $P = 0.916$).

Conclusions: The results of our study indicated that the timing of paclitaxel therapy, either preoperative or postoperative, does not affect survival times in breast cancer patients.

Introduction

Breast cancer is a common malignancy in women, with a morbidity of 50–60 per 100 000.[1] The basic principle for breast cancer treatment is the adoption of comprehensive therapies based on surgery and individualized treatment regimens according to patient condition. According to Fisher's theory, breast cancer is a systemic disease; therefore, systemic chemotherapy should be used throughout the cycle of breast cancer treatment, with chemotherapy being the most fundamental part of systemic therapy.[2] Neoadjuvant chemotherapy (NCT) has gradually been applied to operable breast cancers since the 1980s. Many trials have confirmed the effectiveness of NCT in reducing the tumor stage, improving the resection rate of locally advanced breast cancer, and providing the opportunity to perform breast-conserving surgery.[3,4] The majority of studies to date suggest that an anthracycline-based regimen is the most effective therapy.[3] A meta-analysis revealed that adding paclitaxel to an anthracycline-based regimen could increase the opportunity for breast-conserving surgery.[4] To date, dose-dense (DD) chemotherapy has been confirmed to lead to survival benefits in adjuvant therapies, but less information is available as to the efficacy of a DD NCT.[5] In their study, Braud *et al.* observed epirubicin, cyclophosphamide, and vinorelbine as NCT in 30 T2–T3 progressive stage breast cancer patients. Their results showed that a clinical objective response was observed in 24 patients, a complete response in 14, and a partial response in 10, while 29 patients received surgical treatments after their NCT.[6] Although NCT has been widely used for early-stage breast cancer in recent years, there is no ideal recommended consensus. The main regimens studied in neoadjuvant settings include cyclophosphamide + doxorubicin (AC) followed by taxane and a DD regimen. Therefore, we conducted this prospectively study to compare the two epirubicin and paclitaxel-based NCT regimens in breast cancer patients.

Methods

Patients

We collected clinical data from patients admitted to our hospital and treated with NCT who met the following inclusion criteria: (i) histologically-proven ductal invasive carcinoma; (ii) no surgery, radiotherapy, chemotherapy or other anti-tumor therapies administered before NCT; (iii) aged between 18 and 70 years and an Eastern Cooperative Oncology Group (ECOG) performance score (PS) ≤2; (iv) at least one measurable lesion which met Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 standard before NCT; and (v) no dysfunction of the major organs before NCT and normal blood, liver, kidney, and heart function. Exclusion criteria were: (i) a history of HIV infection; (ii) pregnant or breastfeeding; (iii) distant metastasis; (iv) a history of organ transplantation before NCT; and (v) existence of serious disease affecting the function of vital organs or obvious neurological/mental disorders, as well as uncontrolled acute infections or contraindications to use adrenal corticosteroids. The last follow-up took place in May 2016, after a median follow-up of 70 months. Because of the limited follow up period, there was a low mortality rate in the two groups, and statistical comparison of the median overall survival (OS) rates was not possible. All enrolled patients signed written informed consent and the study was approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College.

Treatments

Enrolled patients were divided randomly into two groups: cyclophosphamide + epirubicin (CE) and paclitaxel + epirubicin (TE). Patients in the CE group were treated with 600 mg/m^2 cyclophosphamide and 80 mg/m^2 epirubicin intravenously (IV) on day 1 every 14 days for four cycles, followed by postoperative 175 mg/m^2 paclitaxel IV on day 1 every 14 days for four cycles. Patients in the TE group were treated with 75 mg/m^2 epirubicin IV on day 1, and 175 mg/m^2 paclitaxel IV on day 2 every 21 days for four cycles, followed by two further postoperative cycles of the same regimen. The total dosage of epirubicin was 450 mg/m^2 in the TE group and 320 mg/m^2 in the CE group, whereas the total dosage of paclitaxel was 1050 mg/m^2 in the TE and 700 mg/m^2 in the CE group.

Efficacy assessments

Tumor assessment was performed at baseline and every two cycles according to RECIST version 1.0. Outcome parameters included: clinical efficacy (tumor assessment by clinical examination and imaging data), pathological efficacy (tumor assessment by pathologic report after surgery), and efficacy of primary lesions (not including the axillary lymph nodes), which were subclassified into complete response (CR), partial response (PR), and objective response rate (ORR) and compared between the two groups.

Statistical analysis

A chi-square test was used to evaluate the correlation between efficacy and patient gender, age, tumor size, presence of inflammatory breast cancer, lymph node status, general condition of the patient (ECOG PS), and NCT regimen. Cox proportional hazards regression models were used to determine the association of the prognostic factors with survival outcomes (disease-free survival [DFS]). Statistical analysis was conducted using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients

A total of 309 patients were enrolled between January 2003 and December 2008. One hundred and ninety-eight (64.1%) were premenopausal, 233 (75.4%) were aged over 40 years, 252 (81.6%) had an ECOG PS of 0, 39 (12.6%) had inflammatory breast cancer, and 213 (68.9%) had positive axillary lymph nodes detected by physical examination (Table 1). The final follow-up was conducted in May 2016, after a median follow-up duration of 70 months.

Treatment

The CE group included 119 cases, while the TE group comprised 190 cases. Baseline characteristics including menstrual status, ECOG PS, and the proportion of inflammatory breast cancer were similar between the two groups (Table 1).

The median NCT treatment in all patients was four cycles (range 2–4). Two hundred and eighty-five (92.2%) patients underwent modified radical mastectomy after NCT, 21 (6.8%) underwent breast-conserving surgery, and three (1.0%) did not undergo surgery for various reasons. A total of 186 (60.2%) patients received adjuvant radiotherapy and 250 (80.9%) received adjuvant chemotherapy after surgery. Fifty-nine patients (19.1%), including nine pCR patients, declined postoperative adjuvant chemotherapy. In the 250 patients who received adjuvant chemotherapy, 206 followed the designed regimen while 44 regimens were altered because of poor pathological efficacy. In the 206 patients who completed the chemotherapy course,

Table 1 Patient characteristics

	CE group 119 cases (%)	TE group 190 cases (%)
Age (years)		
≤40	21 (17.6)	55 (28.9)
>40	98 (82.4)	135 (71.1)
Menstrual status		
Menstruating	77 (64.7)	121 (63.7)
Menopause	42 (35.3)	69 (36.3)
ECOG PS		
0	93 (78.2)	159 (83.7)
1–2	26 (21.8)	31 (16.3)
Clinical tumor size		
≤5 cm	66 (55.5)	79 (41.6)
>5 cm	53 (44.5)	111 (58.4)
Inflammatory cancer		
No	108 (90.8)	162 (85.3)
Yes	11 (9.2)	28 (14.7)
Axillary lymph nodes		
N0	51 (42.9)	45 (23.7)
N1–2	68 (57.1)	145 (76.3)

CE, cyclophosphamide + epirubicin; ECOG, Eastern Cooperative Oncology Group; PS, performance score; TE, paclitaxel + epirubicin.

130 patients in the TE group (130/190, 68.4%) received the remaining two cycles of the TE regimen, whereas 76 cases in the CE group (76/119, 63.9%) received four cycles of paclitaxel after surgery (Fig 1).

Efficacy

A pathological efficacy comparison of the two NCT regimens showed that the TE regimen was superior to the CE regimen in terms of a short-term curative effect, with a pCR of 17.3% versus 9.2%, ($P = 0.034$) and an ORR of 81.1% versus 68.9%, ($P = 0.011$) (Table 2). In general, the pCR of all lesions compared with primary lesions alone was significantly lower (14.2% vs. 29.2%; $P < 0.001$).

The initial superiority of the TE regimen did not translate into a survival advantage. The DFS was similar in the TE and CE (DD) groups, with five-year DFS rates of 82.9% and 75.3%, respectively ($P = 0.916$), even though the total dosage of epirubicin and paclitaxel was higher in the TE than in the CE group (Fig 2).

In subgroup analysis, the TE and CE (DD) groups had similar DFS rates after adjuvant chemotherapy with a paclitaxel-based regimen, including estrogen receptor positive, human epidermal growth factor receptor 2 positive or viscera metastasis.

Discussion

The role of paclitaxel in adjuvant treatment for operable breast cancer has been proven in several phase III trials, such as CALGB 9344, NSABP B28, BCIRG 001, and PACS 01.[7–12] Based on the results from a meta-analysis by Bria *et al.*, paclitaxel-containing regimens reduce the recurrence rate of early breast cancer by 14% and the mortality risk by 13%, with absolute benefits of 3.3% DFS and 2% OS.

Many studies have confirmed the efficacy of anthracycline/taxane-based regimens in neoadjuvant treatment, such as NSABP B-18, EORTC 10902, and NSABP B-27.

Our results demonstrated that during the NCT period, the pathological efficacy of the CE regimen was inferior to the TE regimen, with an ORR of 68.9% versus 81.1%, ($P = 0.011$) and CR rates of 9.2% in the CE versus 17.3% in the TE group, ($P = 0.034$). However, the better initial therapeutic outcome of the TE regimen did not translate into a survival advantage after surgery, with five-year DFS rates of 82.9% in the CE and 75.3% in the TE group ($P = 0.916$). Postoperative administration of paclitaxel may have improved the DFS rate in patients who achieved PR after the preoperative EC regimen. This may indicate that paclitaxel use in NCT or adjuvant chemotherapy will not affect the survival benefit produced by paclitaxel.

The overall pCRs for pathological efficacy and efficacy of primary lesions were 14.4% and 29.3% ($P < 0.001$), indicating that primary lesions are generally more sensitive to chemotherapy.

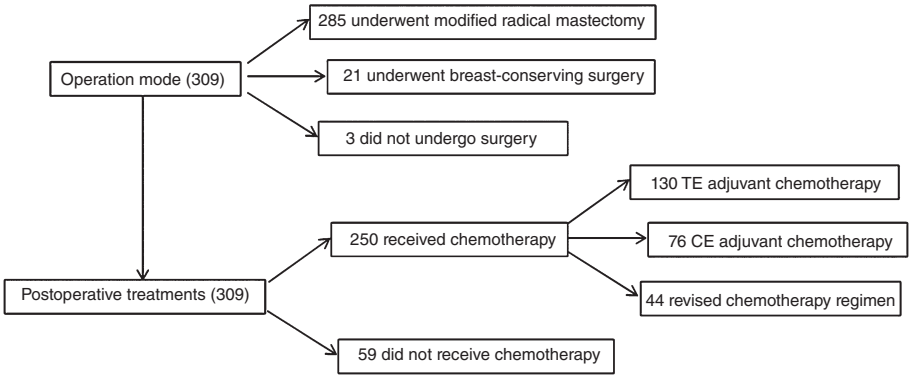

Figure 1 Further neoadjuvant chemotherapy treatment in breast cancer patients. CE, cyclophosphamide + epirubicin; TE, paclitaxel + epirubicin.

Table 2 Comparison of efficacy between neoadjuvant chemotherapy regimens

	CE 119 cases (%)			TE 190 cases (%)			
	CR	PR	ORR	CR	PR	ORR	Total CR
Clinic efficacy	9 (7.6)	71 (59.7)	80 (67.2)	14 (7.4)	136 (71.6)	150 (78.9)	
Pathological efficacy	11 (9.2)†	71 (59.7)	82 (68.9)‡	33 (17.3)†	121 (63.7)	154 (81.1)‡	44 (14.2)§
Efficacy of primary lesions	23 (19.3)	65 (54.6)	88 (73.9)	67 (35.3)	87 (45.8)	154 (81.1)	90 (29.2)§

†The paclitaxel + epirubicin (TE) regimen was superior to the cyclophosphamide + epirubicin (CE) regimen with a pathological complete response (pCR) of 17.3% versus 9.2% ($P = 0.034$). ‡The TE regimen was superior to the CE regimen with an overall response rate (ORR) of 81.1% versus 68.9% ($P = 0.011$). §The pCR rate of all lesions compared with primary lesions alone was significantly lower (14.2% vs. 29.2%; $P < 0.001$). PR, partial response.

In recent years, pCR has been considered an important prognostic marker and is used as a surrogate outcome of survival in breast cancer patients; however, pCR rates vary widely according to the molecular subtype. Tumors exhibiting high proliferation, such as human epidermal growth factor receptor 2 positive or triple-negative breast cancer not only have higher pCR rates but the pCR rates in these subtypes appear to be closely associated with DFS and OS. The United States Food and Drug Administration-led meta analysis of neoadjuvant studies (CTNeoBC) confirmed that the strongest association between pCR and long-term survival only occurred in patients with aggressive breast cancer subtypes.[13] In our subgroup analysis, the TE and CE (DD) groups had similar DFS rates for each molecular subtype after adjuvant chemotherapy with a paclitaxel-based regimen. This result demonstrated that pCR was not a perfect prognostic marker for neoadjuvant therapy. Because only a few patients died in the two groups, a statistical median OS comparison could not reliably be carried out.

In conclusion, the results of our study show that the timing of paclitaxel use, either preoperative or postoperative, does not affect survival in breast cancer patients.

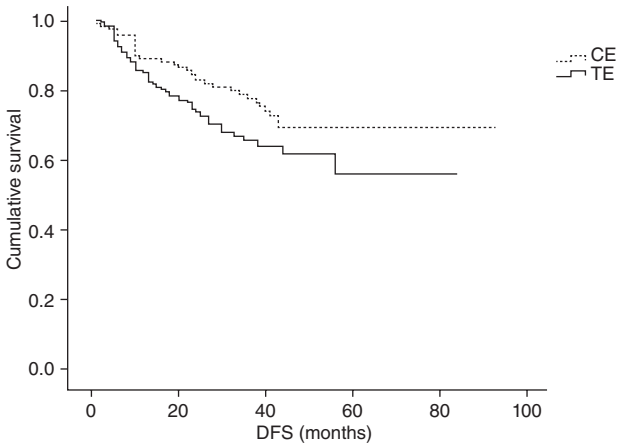

Figure 2 Comparison of disease-free survival (DFS) between patients with cyclophosphamide + epirubicin (CE) and paclitaxel + epirubicin (TE) regimens ($P = 0.916$).

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Disclosure

No authors report any conflict of interest.

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