

## Comparison of Docetaxel, Doxorubicin and Cyclophosphamide (TAC) with 5-Fluorouracil, Doxorubicin and Cyclophosphamide (FAC) Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer: A Phase III Clinical Trial

Shapour Omidvari\*, Sare Hosseini\*, Yaghoob Ashouri\*, Sedigeh Tahmasebi\*\*, Abdolrasoul Talei\*\*, Hamid Nasrolahi\*, Niloofar Ahmadloo\*, Mansour Ansari\*, Ahmad Mosalaei\*, Mohammad Mohammadianpanah\*

\*Department of Radiation Oncology, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

\*\*Department of Surgery, Shahid Faghihi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

### Abstract

**Background:** The present study aimed to compare the rates of complete clinical and pathologic response to docetaxel, doxorubicin and cyclophosphamide (TAC) vs. 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) as neoadjuvant chemotherapy in women with locally advanced breast cancer.

**Methods:** One hundred women with pathologically confirmed newly diagnosed locally advanced (T3-T4 or N2-N3) breast cancer were randomly assigned to receive a median of four cycles of either 5-fluorouracil (600 mg/m<sup>2</sup>), doxorubicin (60 mg/m<sup>2</sup>) and cyclophosphamide (600 mg/m<sup>2</sup>) every three weeks or docetaxel (75 mg/m<sup>2</sup>), doxorubicin (50 mg/m<sup>2</sup>) and cyclophosphamide (500 mg/m<sup>2</sup>) every three weeks followed by modified radical mastectomy. Complete clinical and pathologic response rates and toxicity were the primary and secondary outcome measures of the study.

**Results:** Median age for all patients was 43.4 years (range 25-63 years). Patients in the TAC arm achieved a higher clinical (16%) response rate than those in the FAC arm (4%,  $P=0.046$ ). The pathologic response rate was also higher in the TAC arm compared to the FAC arm [TAC (20%) vs. FAC (6%),  $P=0.037$ ]. Estrogen receptor-negative status correlated with a higher clinical [TAC (19%) vs. FAC (4%),  $P=0.032$ ] and pathologic [TAC (23%) vs. FAC (4%),  $P=0.011$ ] response rate in both arms. All patients generally tolerated treatment well, and treatment-related toxicities were manageable.

**Conclusion:** Combined treatment with TAC led to higher rates of complete clinical and pathologic response with acceptable toxicity compared to FAC in patients with locally advanced breast cancer. However, further follow-up is needed to translate this response into improvements in survival.

**Keywords:** Locally advanced breast cancer, Neoadjuvant chemotherapy, Docetaxel, Doxorubicin, Complete pathologic response, Phase III clinical trial

♦Corresponding Author:  
Mohammad Mohammadianpanah,  
MD, Cancer Research Center,  
Department of Radiation  
Oncology, Namazi Hospital,  
Shiraz, Iran  
Tel/Fax: +98-711-647 4320  
Email: mohpanah@sums.ac.ir;  
mohpanah@gmail.com

## Introduction

Breast cancer is the most common cancer in women, and its incidence is increasing.<sup>1</sup> Although screening mammography detects a high proportion of early breast cancers, locally advanced breast cancer remains a major health problem in women, particularly in developing countries. Despite progress in the treatment of these patients, treatment outcome and prognosis is poor.

Currently, all patients with locally advanced breast cancer are candidates for neoadjuvant treatment.<sup>2, 3</sup> Neoadjuvant chemotherapy was initially used for patients with inoperable breast cancer. Although it has not been shown to increase survival, neoadjuvant chemotherapy offers the physician and patient the possibility to evaluate in vivo tumor response. This treatment approach may also make breast-conserving surgery a possibility.<sup>4</sup> It has been shown that complete pathologic response is a predictor of the efficacy of neoadjuvant therapy. In addition, some studies have suggested that a combined taxane and anthracyclin-based chemotherapy regimen is better than either alone in younger patients.<sup>4</sup>

The present study was designed to compare the rates of complete clinical and pathologic response of docetaxel, doxorubicin and cyclophosphamide (TAC) vs. 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) as neoadjuvant chemotherapy in women with locally advanced breast cancer.

## Materials and Methods

We conducted this prospective, randomized phase III clinical trial at the Radiation Oncology Department of Namazi Hospital, Shiraz University of Medical Sciences (Shiraz, Iran) between March 2009 and April 2010. The University Ethics Committee approved this protocol, which was designed in accordance with the Declaration of Helsinki.

## Patients

One hundred women with pathologically proved, newly-diagnosed, locally-advanced breast cancer (clinical stage T3-T4 or N2-N3 according

to AJCC 2007)<sup>5</sup> were enrolled in the study. All women were native Iranians referred for neoadjuvant chemotherapy, and all had palpable breast masses diagnosed by fine needle aspiration biopsy or Tru-cut biopsies. The patients were assigned according to a random number table taken from [www.random.org](http://www.random.org) to receive either FAC or TAC neoadjuvant chemotherapy. All were informed about the purpose of the study, the potential benefits of neoadjuvant treatment, and the risks and benefits of participation in the study. Chemotherapy-induced adverse effects such as hematologic suppression, nausea, vomiting, hair loss and nail change were disclosed to all patients. Each woman provided a signed informed consent form before she was enrolled in the study.

To be included, the patient had to be in good health (Karnofsky performance status  $\geq 70$ ), with normal or acceptable bone marrow, hepatic, cardiovascular and renal function tests, i.e., hemoglobin  $>100$  g/L, neutrophil count  $>1.5 \times 10^9/L$ , platelet count  $>100 \times 10^9/L$ , creatinine  $<2$  mg/dL, bilirubin  $<2$  mg/dL, alanine aminotransferase and aspartate aminotransferase  $<1.5 \times$  the upper normal limit, and alkaline phosphatase  $<1.5 \times$  the upper normal limit. Metastatic work-up consisted of chest X-ray, abdominal and pelvic ultrasonography and whole-body bone scintigraphy. The exclusion criteria were patient refusal, previous excisional biopsy, and comorbid medical conditions (heart disease, uncontrolled diabetes mellitus, psychiatric disease, and liver or kidney failure or insufficiency). In addition, we excluded patients who had previously received radiotherapy, hormone therapy or chemotherapy with any agent and those with evidence of metastases.

## Chemotherapy

Chemotherapy consisted of a median of four cycles (range 3-5) of either FAC (5-fluorouracil 600 mg/m<sup>2</sup>, doxorubicin 60 mg/m<sup>2</sup> and cyclophosphamide 600 mg/m<sup>2</sup>) or TAC (docetaxel 75 mg/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup>) administered every three weeks. In the TAC arm, filgrastim [recombinant

**Table 1.** Patient characteristics in the TAC and FAC arms.

Characteristics	Total (%)	TAC arm (%)	FAC arm (%)	<i>P</i> value
<b>Number of patients</b>	100	50	50	1.0
<b>Mean age (years)</b>	43.4	42.3	44.5	0.6
<b>Clinical stage</b>				
IIB (T3N0M0)	20	9	11	
IIIA (T3N1-N2)	26	15	11	
IIIB (T4N0-N2)	54	26	28	0.641
<b>ER<sup>a</sup> status</b>				
Positive	49	23	26	
Negative	26	16	10	
Unknown	25	11	14	0.307
<b>PR status</b>				
Positive	36	15	21	
Negative	39	24	15	
Unknown	25	11	14	0.085
<b>HER-2 status<sup>b</sup></b>				
Positive (3+)	36	23	13	
Negative or 1+	28	14	14	
Unknown or 2+	36	13	23	0.62

<sup>a</sup> Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor

<sup>b</sup> HER-2 was measured by immunohistochemistry with or without fluorescence in situ hybridization.

human granulocyte colony stimulating factor (G-CSF); 5 µg/kg] was prescribed for hematologic support during the fifth to ninth days after each cycle. All patients subsequently underwent modified radical mastectomy after the last (median fourth) cycle of neoadjuvant chemotherapy. None received trastuzumab during neoadjuvant chemotherapy. Eligible patients, however, received this agent after surgery and completion of neoadjuvant chemotherapy. Treatment-related side effects such as myelosuppression, nausea and vomiting were managed according to the National Comprehensive Cancer Network (NCCN) protocols.<sup>6</sup> No patients had treatment modifications (e.g., delay, dose reduction or both).

### Assessment of tumor response and toxicity

Complete physical examination focused on evaluation of the breast and axillary lymph nodes including bidimensional tumor measurement (by caliper), detection of differences in breast sizes, skin thickness and warmth. Patients underwent assessments before intervention and prior to each cycle of chemotherapy. Tumor diameter was assessed by sonography before the first and after the fourth chemotherapy cycle.

The outcomes were compared between treatment arms according to the longest tumor diameter measured after each cycle of chemotherapy. The last measurement was done after the fourth cycle of chemotherapy. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST)<sup>7</sup> as follows: complete response was the complete disappearance of all assessable breast lesions by physical exam. Partial response was a reduction of more than 30% in the sum of the longest diameters of all measurable breast tumors compared to baseline; stable disease was a reduction of less than 30% or an increase of less than 20% in the sum of the longest diameters of all measurable tumors. Progressive disease was defined as an increase of more than 20% in the longest diameters of the original measurable tumors or the appearance of a new lesion. Toxicity was assessed according to the EORTC/RTOG criteria<sup>8</sup> after each cycle of chemotherapy. The primary endpoints of the study were the rates of complete clinical and pathologic response, and a secondary endpoint was toxicity.

**Table 2.** Percentage frequencies of pathologic and clinical tumor response rates in the TAC and FAC arms.

Response	TAC arm (n=50)	FAC arm (n=50)	P value
Complete pathologic response	20	6	0.037
Complete clinical response	16	4	0.046
Partial clinical response	78	68	0.260
Overall clinical response	94	72	0.003

## Statistics

Clinical and histological variables were analyzed with the SPSS version 17.0 software (SPSS, Chicago, IL). Measurements and results were compared by *t*-tests, chi-squared, Fisher's exact and Mann Whitney tests. A *P* value less than 0.05 was considered significant.

## Results

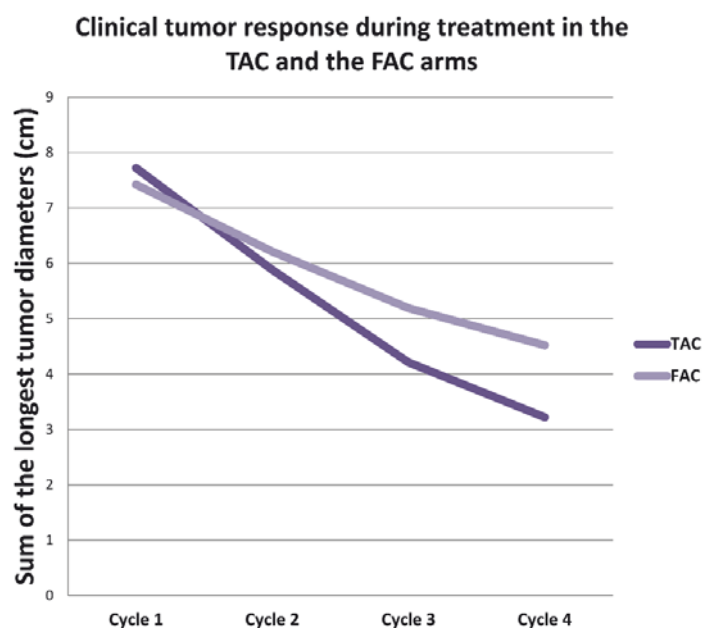
### *Patients' characteristics and treatment*

One hundred women entered the study and all completed the study successfully. Patients were 25-63 years old (mean age 43.4 years). The mean age in the TAC arm was 42.3 years, and mean age in the FAC arm was 44.5 years (Table 1). All patients received a median of four cycles of neoadjuvant chemotherapy with no treatment modifications (delay, dose reduction or treatment discontinuation). The mean largest clinical tumor

size at the time of intervention was 7.85 cm (range 3–15 cm) in the TAC arm and 7.42 cm (range 4–13 cm) in the FAC arm (not statistically significant,  $P=0.45$ ). Similarly, the mean largest radiologic tumor size at the time of intervention was slightly larger in the TAC arm (7.35 cm) vs. the FAC arm (7.10 cm,  $P=0.34$ ). Table 1 shows the patient characteristics in both arms at the time of intervention.

### Efficacy

During treatment, clinical tumor size tended to decrease in both arms (Figure 1). The mean largest clinical tumor size after the fourth cycle of neoadjuvant chemotherapy was 3.22 cm (range 0–7 cm) in the TAC arm and 4.52 cm (range 0–10 cm) in the FAC arm ( $P=0.001$ ). Figure 1 illustrates clinical tumor response in the TAC and FAC arms during the course of neoadjuvant chemotherapy.



**Figure 1.** Clinical tumor response during treatment in the TAC and FAC arms in 100 women with pathologically proved, newly-diagnosed, locally-advanced breast cancer.

**Table 3.** Percentage frequencies of treatment-related grade 1-2 acute toxicity in 100 patients with locally advanced breast carcinoma treated with TAC or FAC.

Toxicity	TAC regimen (n=50)	FAC regimen (n=50)
Myelosuppression	100%	88%
Stomatitis	62%	48%
Nausea and vomiting	92%	94%
Alopecia	100%	100%

After the fourth cycle, the mean largest radiologic tumor size in the TAC arm was significantly smaller (1.83 cm vs. 2.23 cm,  $P=0.001$ ) compared to the FAC arm. Complete clinical response rate was higher in the TAC arm (16%) vs. the FAC arm (4%,  $P=0.046$ ). In addition, the rate of pathological response was higher in the TAC arm (20%) than in the FAC arm (6%,  $P=0.037$  (Table 2). Estrogen receptor negative status correlated with a high clinical [19% (TAC) vs. 4% (FAC),  $P=0.032$ ] and pathologic [23% (TAC) vs. 4% (FAC),  $P=0.011$ ] response rate in both arms.

### Tolerability and safety

All patients generally tolerated treatment well with manageable treatment-related toxicities. The most common toxicities in both arms were grades I-II nausea, vomiting, stomatitis, fatigue and neutropenia. Almost all patients developed profound alopecia. Only one patient in the TAC arm developed grade 3 neutropenia; however, no grades 3-4 nausea or vomiting occurred (Table 3).

### Discussion

Breast cancer is the most common cancer and a major cause of cancer mortality in women worldwide. Locally advanced breast carcinomas (T3, T4 or N2-N3) have a poor prognosis. Neoadjuvant systemic treatments offer earlier control and eradication of potential subclinical metastatic foci, shrinkage of the primary tumor (associated with increased rates of resectability and breast conserving surgery), and direct assessment of tumor response to therapy.<sup>9</sup> There is increasing interest in the use of neoadjuvant chemotherapy in premenopausal breast cancer with large (>5 cm) breast tumors to increase the rate of breast-conserving surgery.<sup>10</sup> Therefore, neoadjuvant

chemotherapy is considered the standard of care in premenopausal patients with locally advanced breast cancer, particularly in unresectable disease.<sup>9</sup>

Anthracycline-based chemotherapy has been considered one of the most efficacious chemotherapy regimens for neoadjuvant treatment in patients with breast cancer. Complete pathologic response to neoadjuvant treatment is a good prognostic factor in women with breast cancer. Doxorubicin is the most active agent used for metastatic breast cancer in clinical practice. This chemotherapeutic agent replaced methotrexate, and its combinations with other drugs became standard treatment.<sup>11-13</sup> Widely studied novel antineoplastic drugs such as docetaxel also play an important role. Docetaxel is a highly active agent in breast cancer and has no cross-resistance with doxorubicin.<sup>13</sup> Some studies have evaluated the effect of adding taxanes to doxorubicin-based chemotherapy.<sup>14, 15</sup> For adjuvant therapy, strong evidence supports the addition of four cycles of a taxane to four cycles of doxorubicin/cyclophosphamide to improve disease-free and overall survival rates in both node-positive and node-negative breast cancer patients.<sup>14-17</sup> In addition, some reports have concluded that TAC improves disease-free and overall survival compared to FAC.<sup>13,18</sup>

For neoadjuvant therapy, some evidence suggests the superiority of TAC to FAC, and that the combination of docetaxel and cyclophosphamide is an acceptable alternative to treatment with doxorubicin and cyclophosphamide.<sup>19-21</sup> Kaya et al., in a retrospective single-arm study, evaluated the efficacy of epirubicin and docetaxel for neoadjuvant therapy, and found a complete pathologic response rate of 10% in patients with locally advanced invasive breast cancer.<sup>22</sup> In



another retrospective study, Andrade et al. compared TAC with 5-fluorouracil, epirubicin and cyclophosphamide. Their study endpoints were complete clinical and pathologic response, and their data favored TAC.<sup>23</sup> Yang et al., in a prospective study of 48 women with breast cancer, compared epirubicin and paclitaxel with 5-Fu, epirubicin and cyclophosphamide. Although the response rate was higher in the epirubicin and paclitaxel arm, no complete pathologic responses were observed.<sup>24</sup>

Complete pathologic response, which means no evidence of residual invasive disease in the primary site, correlates with improved survival.<sup>10</sup> In the present study, complete clinical and pathologic response rates were significantly higher in the TAC arm. We detected the greatest decrease in tumor size in both arms after the first chemotherapy cycle. In addition, the difference of tumor size between the two arms increased with time (Figure 1).

After chemotherapy, hematologic complications can be life-threatening.<sup>25</sup> Without prophylactic G-CSF, the TAC regimen has been shown to result in grade 3-4 neutropenia and a 25% rate of neutropenic fever.<sup>18, 25</sup> Our patients who received TAC were supported by prophylactic G-CSF. Only 2% developed grade 3 and 4 neutropenia; however, no neutropenic fever was detected. All patients in the present study were treated on an outpatient basis and complete blood counts were checked just before each chemotherapy cycle, but not weekly. Therefore, the nadir neutrophil count during the first and second weeks of each cycle might have been missed and the frequency of grade 3 and 4 myelosuppression underestimated. However, all patients had to report post-chemotherapy complications such as fever, stomatitis, diarrhea and vomiting by phone.

Two of the most prevalent side effects of chemotherapy are nausea and vomiting. In our study the incidence of nausea and vomiting in the TAC arm was less than in the FAC arm. Our patients tolerated TAC, although their main complaints was musculoskeletal pain. This

problem did not occur in the FAC arm. In another study, patients had skeletal complaints only in the docetaxel arm.<sup>16</sup>

Batra et al. compared TAC to FAC and found that oral mucositis, neutropenic fever, diarrhea and infection were more frequent in the TAC arm. The frequency of anemia, thrombocytopenia, nausea, vomiting and abdominal pain was equal in both arms. The difference between our study and the trial reported by Batra et al. may be due to prophylactic G-CSF administration in our study.<sup>26</sup>

The limited data of the present study and data from large published trials support a combined doxorubicin and docetaxel regimen for neoadjuvant treatment.<sup>1, 21, 27</sup> Despite the superiority of taxane-based regimens in locally advanced breast cancer, anthracycline-based combinations remain the cornerstone of adjuvant therapy in early breast cancer.<sup>28, 29</sup> Longer follow-up is needed to determine whether the difference in clinical tumor response in our patients would result in a survival advantage. Patients who entered the study are currently under routine follow-up to determine disease-free and overall survival.

## Conclusion

In patients with locally advanced breast cancer, TAC provides a higher clinical and pathologic response rate with manageable toxicity compared to FAC. However, further follow-up is needed to translate this response into improvements in survival.

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