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ORIGINAL ARTICLE

Phase II study of docetaxel, capecitabine, and cisplatin as neoadjuvant chemotherapy for locally advanced breast cancer

Yen-Shen Lu · Dar-Ren Chen · Ling-Min Tseng · Dah-Cherng Yeh · Shou-Tung Chen · Chia-Ming Hsieh · Hwei-Chung Wang · Hsien-Tang Yeh · Sung-Hsin Kuo · Chiun-Sheng Huang

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Abstract
Purpose Docetaxel, capecitabine, and cisplatin are effective chemotherapeutic agents for breast cancer with significant synergistic cytotoxicity demonstrated by in vitro studies. The purpose of this study was to assess the efficacy of a combination of docetaxel, capecitabine, and cisplatin (TXP) in patients diagnosed with locally advanced breast cancer (LABC).
Methods Patients ($n = 42$) with chemotherapy-naïve LABC (stage IIIa or IIIb) were enrolled. The chemotherapeutic regimen consisted of 4–6 cycles of intravenous docetaxel (60 mg/m^2) and cisplatin (50 mg/m^2) on day 1, plus oral capecitabine (1,800 mg/m^2/day) on day 1–14, repeated every 3 weeks. Upon completion of therapy, the primary tumor was resected when not contraindicated.
Results Median patient age was 48.5 years (range 31–66 years). Median tumor size was 6.8 cm (range 2.7–15 cm), 29 patients were node-positive, and 12 patients were hormone receptor positive. A total of 216 cycles (median 5; range 3–6 cycles) were administered without prophylactic G-CSF. The predominant toxicities were grade 3/4 neutropenia (30%/28%) and no grade 3/4 thrombocytopenia, febrile neutropenia, or grade 4 non-hematological toxicities were observed. Grade 3 non-hematological toxicities included hand-foot syndrome (5.6%) and vomiting (0.5%). The overall clinical response rate was 97.6% (41/42). Six of the 42 patients (14.3%) achieved a complete pathological response. Of 22 patients who completed 6 cycles of combination treatment, the complete pathological response was 27.3% (6/22).
Conclusions A combination of TXP can be administered safely without prophylactic G-CSF, and appears to be an effective neoadjuvant regimen in patients with LABC.

The authors D.-R. Chen, L.-M. Tseng and D.-C. Yeh contributed equally to this work.

Y.-S. Lu · S.-H. Kuo
Department of Oncology,
National Taiwan University Hospital, Taipei, Taiwan, ROC
e-mail: yslu@ntu.edu.tw

D.-R. Chen · S.-T. Chen
Department of Surgery,
Changhua Christian Hospital, Changhua, Taiwan, ROC

L.-M. Tseng
Department of Surgery,
Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan, ROC

D.-C. Yeh
Department of Surgery, Taichung Veterans General Hospital,
Taichung, Taiwan, ROC

C.-M. Hsieh
Department of Surgery,
Taiwan Adventist Hospital, Taipei, Taiwan, ROC

H.-C. Wang
Department of Surgery,
China Medical University Hospital, Taichung, Taiwan, ROC

H.-T. Yeh
Department of Surgery, Lotung Poh-Ai Hospital,
Yilan County, Taiwan, ROC

C.-S. Huang (✉)
Department of Surgery, National Taiwan University Hospital,
No. 7, Chung-Shan South Road, Taipei 100, Taiwan, ROC
e-mail: huangcs@ntu.edu.tw

Keywords Locally advanced breast cancer · Neoadjuvant chemotherapy · Docetaxel · Cisplatin · Capecitabine

Introduction

Breast cancer is a predominant malignancy for women all over the world including those living in Taiwan [1]. Breast cancer is currently ranked the second most common female cancer accounting for approximately 15% of all cancers diagnosed annually in Taiwan [2]. Despite advances in breast cancer management, many patients eventually develop metastatic diseases. This is particularly true for patients with locally advanced breast cancer (LABC) making LABC cases clinically challenging. Within mammography-screened populations, stage III breast cancer seldom comprises more than 5% of the diagnoses. In contrast, LABC constitutes up to 20% of breast cancers in medically underserved populations in the United States and up to 75% of breast cancers in developing countries [3].

Among novel chemotherapeutic drugs introduced in the 1990s, taxanes emerged as the most powerful compounds for treating breast cancer [4–6]. Docetaxel is, in general, more cytotoxic to cancer cells than paclitaxel and is one of the most effective cytotoxic agents against breast cancer [7–9]. Docetaxel monotherapy typically involves one of two regimens: either docetaxel 60–100 mg/m^2 every 3 weeks or docetaxel 35–40 mg/m^2 weekly for 6 weeks followed by a 2-week treatment break [10–12]. A phase III study conducted at the MD Anderson Cancer Center by Rivera et al. reported that patients treated with docetaxel every 3 weeks had a higher response rate than patients treated with weekly docetaxel; however, the groups had similar progression-free survival (PFS) and overall survival (OS) [13].

Efficacy of capecitabine in combination with either paclitaxel or docetaxel has been studied previously. Preclinical data indicated that both taxanes induced upregulation of thymidine phosphorylase in tumor tissues resulting in a synergistic effect between a taxane and capecitabine [14]. A phase III multicenter study compared capecitabine (2,500 mg/m^2/day, days 1–14) in combination with docetaxel (75 mg/m^2, day 1 of a 21-day cycle) to docetaxel alone (100 mg/m^2, day 1 of a 21-day cycle) in anthracycline-pretreated patients with advanced breast cancer. Included patients were those with systemic metastatic disease who have had received an anthracylcine containing regimen either in adjuvant or metastatic setting. Of the 511 enrolled patients, median survival in the capecitabine/docetaxel group was 14.5 months vs. 11.5 months for docetaxel alone ($P = 0.0126$) [15]. Time to progression was 6.1 months vs. 4.2 months ($P = 0.001$) and tumor response rates were 42% vs. 30% ($P = 0.006$) in the capecitabine/docetaxel and docetaxel groups, respectively. There were more non-hematological adverse events with the combination regimen including more diarrhea, stomatitis, hand-foot syndrome, nausea, and vomiting (Grade 3/4, 78%). Response rates and disease-free survival were similar in the subset of patients treated with a lower dosing regimen (docetaxel 60 mg/m^2 plus capecitabine 2,000 mg/m^2/day) and the toxicity was lower. Several groups have studied the activity of capecitabine/docetaxel-based neoadjuvant therapy for breast cancer and achieved clinical response rates ranging from 79 to 90% and pathologically complete response (pCR) rates of 10–21% [16–18].

Platinums are active agents against breast carcinoma. Despite lacking prospective randomized studies, cisplatin monotherapy reportedly had higher response rates than carboplatin in the front-line treatment of metastatic breast carcinoma [19]. For patients with chemotherapy naïve breast cancer, single-agent cisplatin had response rates of 42–54% [20–22]. Emerging literature published by Crown et al. suggested that taxane-platinum combinations might have substantial activities against breast cancer [23]. In addition, several studies confirmed that docetaxel/platinum salt combinations could produce significant responses with response rates in the range of 55–70% in anthracycline-pretreated advanced breast cancer [24–26]. Cisplatin is known to be renal toxic, however, it is widely speculated in clinical practice that prolonging cisplatin infusion time will alleviate the toxicity while preserving its efficacy. Jacobs and colleagues demonstrated that a 24-h infusion of cisplatin (average dose, 80 mg/m^2 every 3 weeks) in patients with advanced head and neck cancer yielded a response equivalent to that of bolus injection while greatly reducing the toxicity profile [27]. Our study group also found that 24-h cisplatin infusion in advanced breast cancer was void of renal toxicity [28].

The purpose of this study was to assess the efficacy of a combination of three chemotherapeutic agents as a neoadjuvant regimen for LABC: docetaxel (T, 60 mg/m^2, 1-h infusion) followed by cisplatin (P, 50 mg/m^2, 24-h infusion) on day 1, plus oral capecitabine (X, 1,800 mg/m^2) on day 1–14. The treatment cycle was repeated every 3 weeks. Considering that each drug by itself has activity against breast cancer, there is little overlap in the toxicity profiles of each drug, and the previously documented synergism of the drugs, it is hypothesized that this combination will result in good result rates with relatively few adverse events.

Materials and methods

Patients

Women with histologically-diagnosed (either open or core biopsy) LABC were eligible for inclusion into the study if

they had not previously received cytotoxic chemotherapy. Diagnosis of LABC was made according to the American Joint Committee on Cancer (AJCC) definition of T4 primary tumor, which included one or more of the following: a tumor measuring ≥5 cm; tumor involvement with the chest wall (ribs or intercostal or serratus anterior muscles) or skin (ipsilateral cutaneous edema, ulceration, or satellite nodules); clinically-evident inflammatory cancer; and, ipsilateral, fixed, axillary lymphadenopathy. All patients had unidimensionally measurable disease as shown by imaging as well as adequate bone marrow, liver, and kidney functions defined as white blood cell counts (WBCs) ≥4,000/μL, absolute neutrophil count ≥1,500/μL, platelets ≥100,000/μL, total bilirubin ≤2.0 mg/dL, transaminases <3 times the upper normal limit, serum creatinine ≤1.5 mg/dL, and creatinine clearance ≥60 mL/minute. This study was approved by the Joint Institutional Review Board and the Ethics Committee of the participating institutions. All patients provided written informed consent prior to the study enrollment.

Study design

This was an open label, multi-center prospective phase II clinical trial. The primary endpoint was the objective response rate after four cycles of protocol regimen treatment. Secondary endpoints included pathological response rate and treatment-related toxicities.

Chemotherapy

Chemotherapy regimen consisted of docetaxel (Taxotere®; Sanofi-Aventis), 60 mg/m^2 by 1-h intravenous infusion, immediately followed by cisplatin, 50 mg/m^2 by 24-h intravenous infusion on day 1 of a 3-week cycle, plus oral capecitabine (Xeloda®; Roche) 1,800 mg/m^2/day twice daily for 2 weeks followed by 1-week rest period. To minimize docetaxel-related hypersensitivity reactions and edema, all patients received prophylactic pre-medication with oral dexamethasone, 8 mg per day for 3 days, starting the evening prior to each docetaxel administration and with one additional 8 mg dose 1 h before the start of the docetaxel infusion. Antiemetic therapy was prescribed according to the guidelines of the American Society of Clinical Oncology [29]. The protocol was designed to have a minimum of 4 cycles of chemotherapy; additional cycles could be planned at the physician's discretion. Chemotherapy was administered on an outpatient basis. For safety and convenience reason, an indwelling intravenous catheter (Port-A-Cath) was placed before the start of the first chemotherapy course. Patients received the docetaxel infusion in the chemotherapy room and the cisplatin 24 h infusion by IV pump at home. Chemotherapy was administered on the scheduled treatment day if WBCs were ≥3,000/μL and the platelet count was ≥100,000/μL. In cases delayed for >1 week, the dose of docetaxel was then reduced by 20% in the next cycle. The cisplatin dose was reduced by 50% if creatinine clearance was ≤50 mL/minute or if serum creatinine level was ≥2.0 mg/dL. Further dose reductions of either docetaxel or cisplatin were not allowed and the protocol treatment was discontinued if treatment-induced toxicity failed to resolve. For capecitabine, treatment was interrupted in patients with grade 2 diarrhea or hand-foot syndrome until grade 1 or 0. If a patient had grade 3 or 4 toxicity (except fatigue/asthenia and transient arthralgia/myalgia), capecitabine was interrupted until resolved to grade 1 or 0. The dose was then decreased to 1,500 mg/m^2/day. Capeciatine dose was further reduced to 1,000 mg/m^2/day if a second appearance of grade 3/4 toxicities occurred. Prophylactic granulocyte colony-stimulating factor (G-CSF) and/or antibiotics were not permitted in this protocol.

Evaluation of tumor response

During treatment, patients were evaluated week by obtaining a routine history, performing a physical examination, and performing a hemogram weekly. Serum biochemistry and electrolyte panel were performed prior to the start of each chemotherapy cycle or as indicated clinically. Patients who received at least one cycle of treatment were considered evaluable for toxicity and response. Toxicity was evaluated using National Cancer Institute's Common Toxicity Criteria version 2.0. To evaluate tumor size, either computed tomography (CT) or magnetic resonance imaging (MRI) were performed every 2 cycles. Clinical tumor response was evaluated according to response evaluation criteria in solid tumors (RECIST) version 1.0 and based on image study result after 4 cycles of TXP treatment. Bidimensional measurement of the lesions was also performed in every patient to get data for tumor evaluation according to World Health Organization (WHO) criteria. Surgery with curative intent was performed if the tumor was considered operable and radiotherapy was administered post-surgically [30]. A pCR was defined as either the disappearance of both primary lesion and axillary metastasis or the presence of breast in situ carcinoma only without invasive tumor or tumor cells in the lymph nodes. Adjuvant chemotherapy was administered at the discretion of the physician in charge. For patients with tumor progression after chemotherapy or with stable disease after 4 cycles of protocol treatment, second-line chemotherapy regimens followed by surgery or surgery followed by adjuvant chemotherapy were initiated at the discretion of the physician in charge.

Statistics

Simon's optimal two-stage design was used to estimate number of patients needed for this phase II trial [31].

The combination protocol of docetaxel/cisplatin/capecitabine was considered non-effective (unsatisfactory) if the proportion of response was <60% (because the response rate is inferior to standard chemotherapy AC in historical review) and was considered worthy of further study if the proportion of responses was ≥80%. With type 1 and type 2 errors of 0.05 and 0.1, respectively, this design called for 26 patients for the first stage. If ≤14 objective responses were observed, then the study would be terminated. Otherwise, a total of 40 evaluable patients would ultimately be entered into the study. The treatment would be rejected if ≤26 objective responses were observed in the 40 patients. Objective response rate were summarized using descriptive statistics. Safety data were summarized with descriptive statistics in the population of patients that received study drug. The actual PFS was calculated from the first date of chemotherapy to the date of first objective documentation of disease recurrence, and OS was calculated from the first day of treatment to the date of death. OS and disease free survival (DFS) were estimated using the product-limit method of Kaplan–Meier. Log-rank test was used to compare overall survival and disease free survival between patients with pCR/near pCR versus patients without pCR/near pCR. Statistical analysis was performed using SPSS for Windows (SPSS Inc., Chicago, IL).

Results

Between May 2004 and January 2006, 42 women diagnosed with LABC were enrolled. Median patient age was 48.5 years (range 31–66 years, Table 1). All 42 patients completed at least 3 cycles of treatment and were included in the safety analysis. A total of 216 cycles with a median of 5 cycles per patient (range 3–6 cycles) of TXP neoadjuvant therapy were administered. As summarized in Table 2 describing treatment-related toxicities, hematological toxicity was generally manageable. Grade 3/4 neutropenia occurred in 58.6% of the cycles without the occurrence of any febrile neutropenia. Non-hematological toxicity was generally mild except grade 3 hand-foot syndrome occurred in 5.6% of the treatment cycles. Neurotoxicity consisted of paresthesia over the extremities in 14 patients and grade 2 hearing loss in one patient. Other toxicities were generally mild. The protocol was discontinued in only one patient after six courses of treatment due to persistent grade 2 leukopenia. In total, 39 (93%) patients were maintained at designed chemotherapy dose through four cycles. The median relative dose intensities were 0.96, 0.94, and 0.96 for docetaxel, capecitabine, and cisplatin, respectively. Two patients received only 3 cycles of TXP treatment before tumor resection because of patients' request for early operation.

Table 1 Clinical characteristics of enrolled patients ($n = 42$)

	n (range or %)
Median age, years	48.5 (31–66)
Median tumor size, cm	6.8 (2.7–15)
Hormone receptor	
ER + or PR+	21 (50%)
ER−/PR−	21 (50%)
Her2/neu	
~0–2+	35 (83.3%)
3+	7 (16.7%)
Clinical nodal status	
Positive	29 (69%)
Negative	13 (31%)
Stage	
IIIa	22 (53.4%)
IIIb	20 (47.6%)

ER estrogen receptor, *PR* progesterone receptor

Clinical response

All 42 patients were evaluable for tumor response to TXP. Of these, 22 completed 6 cycles of TXP, 5 patients completed 5 cycles, 13 patients completed 4 cycles, and 2 patients completed 3 cycles. The overall clinical response rate (partial response plus complete response after 4 cycles of TXP treatment, according to CT or MRI) was 97.6% according to RECIST and 100% according to WHO

Table 2 Chemotherapy toxicity

Toxicity	Grade* (%)			
	1	2	3	4
Leukopenia	34 (15.8)	45 (45.1)	52 (24.3)	3 (1.4)
Neutropenia	21 (9.8)	37 (17.2)	65 (30.2)	61 (28.4)
Thrombocytopenia	12 (5.6)	1 (0.5)	0	0
Anemia	75 (34.9)	46 (21.4)	2 (0.9)	0
Infection	1 (0.5)	1 (0.5)	1 (0.5)	0
Fever	10 (4.7)	0	0	0
Stomatitis	35 (16.3)	11 (5.1)	0	0
Diarrhea	26 (12.1)	8 (3.7)	0	0
Nausea	114 (53.0)	8 (3.7)	0	0
Vomiting	56 (26.0)	10 (4.7)	1 (0.5)	0
Alopecia	121 (56.3)	58 (27.0)	0	
Nephrotoxicity	26 (12.1)	1 (0.5)	0	0
Nail change	79 (36.7)	12 (5.6)	0	0
Hand-foot-S	52 (24.2)	26 (12.1)	12 (5.6)	0
Neurotoxicity	32 (14.9)	3 (1.4)	0	0
Edema	5 (2.4)	6 (2.8)	0	0

* Values are reported as the total number of events in all cycles (%)

criteria. Six patients (14.3%) achieved pCR and an additional 5 patients (11.9%) achieved near pCR. The near pCR group included patients who had residual tumor burden equal to the residual T1a using the AJCC staging system 6th edition (i.e., residual tumor <5 mm) noted during the pathological review. Among the 22 patients who completed 6 cycles of TXP, 6 achieved pCR (27.3%) whereas no pateints who received <6 cycles ($n = 20$) achieved pCR.

Estrogen receptor (ER) status in relation to pCR was also examined. Of the 21 patients with a negative ER status, 5 patients achieved pCR (23.8%) while the remaining 21 ER positive patients, only one achieved pCR (4.7%). Of 7 patients with human epidermal growth factor receptor 2 (HER2) overexpression, 2 patients achieved pCR (28.5%).

Post-operatively, more than half of the patients were administered adjuvant chemotherapy including anthracycline-containing regimens in 23 patients and a combination of cyclophosphamide, methotrexate, and fluorouracil in 3 patients. In addition, one patient received adjuvant tamoxifen alone. Tamoxifen was also prescribed in 21 ER positive patients after the completion of adjuvant chemotherapy. The majority of patients ($n = 40$) also received adjuvant radiotherapy.

Median follow-up for this study population was 58 months (range 12–68 months). Disease progression occurred in 13 patients with local recurrence in three patients and distant metastasis in 11 patients (one patient had both local and distant metastases). Among the 14 patients with pCR or near pCR, only 1 had disease recurrence (7.1%) during the follow-up period. In the 28 patients without pCR/near pCR, 11 patients had disease recurrence (39.3%). The DFS and OS for patients with pCR/near pCR versus patients without pCR/near pCR have been illustrated in Fig. 1a and b. The 5-year DFS was 89.5% vs. 41.1%, respectively ($P = 0.014$ by the log-rank test). Five-year OS was 100% vs. 82.3% ($P = 0.126$ by the log-rank test), respectively.

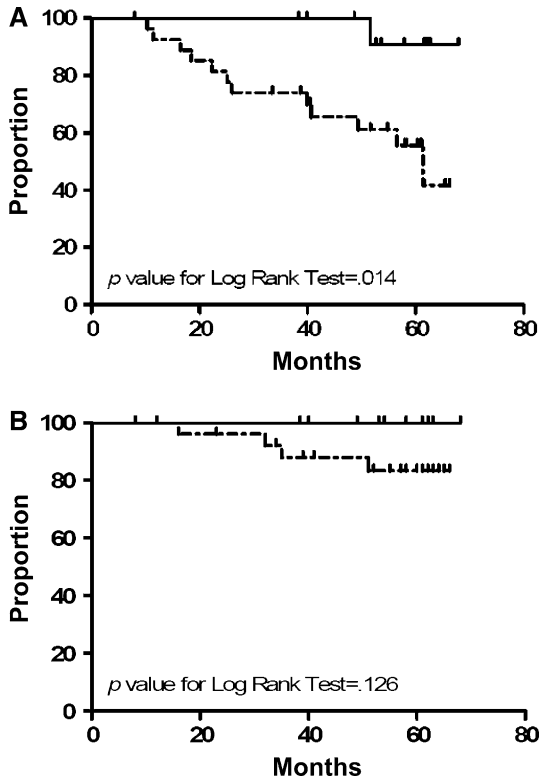

Fig. 1 Kaplan-Meier curves for **a** PFS and **b** OS in patient with pCR/near pCR (*solid line*) versus patient without pCR/near pCR (*dot line*)

Discussion

In this study, TXP proved to be an effective regimen with very high clinical response rate in patients diagnosed with LABC. Although the overall pCR rate was not remarkable compared with other regimens, patients who completed 6 cycles of TXP neoadjuvant chemotherapy had a pCR rate comparable to those reported in other studies focusing on stage III LABC. Of note, no prophylactic G-CSF and/or antibiotics was allowed in this protocol making it particularly impressive that no fever > grade 2 and no febrile neutropenia was observed in this cohort of patients. This might due to the rapid recovering of neutrophil counts in this patient population. Thus, the TXP regimen described herein appears to provide excellent treatment results with only limited bone marrow toxicity. Since the potential for curing LABC is relatively slim compared to early stage breast cancer, it is therefore desirable to establish a regimen with low toxicity and high clinical response for managing LABC.

For clinical trials, pCR is frequently considered as a surrogate marker for favorable long-term prognosis. Multiple clinical trials have shown that patients who achieve pCR after neoadjuvant chemotherapy have improved survival benefits. In patients that do not receive concomitant targeted therapy (such as trastuzumab in HER2-positive patients), clinical studies with neoadjuvant chemotherapy protocols reported pCR rates between 10% and 36% using different chemotherapy combinations [32]. Some of those studies also identified additional factors that might affect pCR. Lower-stage cancer (stage II vs. III), patients with ER-negative tumors, and study arms with more cycles (6–8 cycles vs. 4 cycles) have higher pCR rates. For example, in the phase III neoadjuvant GEPARDUO study, the pCR rate was 7% in patients who underwent four cycles of doxorubicin 50 mg/m^2 plus docetaxel 75 mg/m^2 every 14 days for with filgrastim support and the pCR rate was 14,3% in patients receiving doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 21 days followed by docetaxel 100 mg/m^2 every 21 days for four cycles each (i.e., a total of 8 cycles) [33]. The TXP regimen described in this study

Table 3 Capecitabine-based neoadjuvant combinations for treating breast cancer

	No. of patients	Stages	Tumor response (%)			References
			Overall	cCR	pCR	
Capecitabine (1,250) day 1–14; Docetaxel (75) on day 1	32	III	78	16	21	[16]
Capecitabine (937.5–1,000) day 2–15; Docetaxel (60–75) on day 1	29	III	90	31	7	[17]
Capecitabine (1,000) day 1–14; Docetaxel (75) on day 1	103	II/III	84	5	15	[18]
Capecitabine (1,000) day 5–21; Docetaxel (36) day 1, 8, and 15 of a 28-day cycle	26	II/III	NA	NA	26.9	[35]
Cisplatin (75) day 1 Docetaxel (75) day 1	57	II/III	NA	NA	20	[36]
Capecitabine (625) day 5–18; Docetaxel (30) on day 1, day 8, day 15 Carboplatin (AUC = 2) on day 1, 8, and 15; every 28 days	24	III	93	62	17	[37]
Capecitabine (900) day 1–14; Docetaxel (60) on day 1 Cisplatin (50) on day 1	42	III	98	12	14	*

* Present study

had a pCR rate of 14.3% after only 4–6 cycles of treatment, a rate comparable to other reported pCR rates. Reason(s) for a lack of pCR achievement in patients receiving less than 6 cycles of TXP remains unexplored.

Hudis et al. noted that there are three distinct subsets of patients for whom pre-operative therapy is justified: those with locally advanced inoperable disease; those with large tumors necessitating mastectomy yet a concomitant desire for breast conservation; and, those participating in clinical trials [34]. For the first two subsets, the primary objective of neoadjuvant therapy is to decrease tumor size to allow or facilitate surgical treatment. Therefore, regimens with high response rates are important. In the study described herein, the RECIST response rate was selected as the primary endpoint instead of pCR rate. In this study, the TXP protocol provided excellent treatment results with a 97.6% clinical response rate according to the RECIST criteria after only 4 cycles. Together with the limited toxicity despite lack of prophylaxis G-CSF support suggests that this regimen could be a reasonable choice for the clinical care of LABC patients.

Several groups have studied the activity of anthracycline-free, capecitabine/docetaxel-based or docetaxel/platinum-based neoadjuvant regimens for breast cancer. These results have been summarized in Table 3. Five studies used capecitabine/docetaxel combinations to achieve clinical response rates ranging from 79 to 90% and pCR rates from 10 to 27% [16–18, 35]. One study used cisplatin/docetaxel combinations to achieve a pCR rate of 20%. [36]. Two studies, including the present study, used triple chemotherapy with docetaxel/capecitabine/and a docetaxel/platinum-based drug and resulted in clinical response rates ranging from 76 to 97% and pCR rates from 14 to 17% [37, 38]. There are no studies currently published that directly compare clinical outcomes between capecitabine/docetaxel-based doublets neoadjuvant regimens and triple regimens. Several studies employing anthracycline-containing regimens plus capecitabine/docetaxel-based or docetaxel/platinum-based neoadjuvant regimens for breast cancer are reported. in these studies, the pCR rates ranged from 8.3 to 25% [39–42]. Currently, patients with HER2 overexpressing tumors are candidates for targeted therapy (i.e., anti-HER agents) in the neoadjuvant setting. Seven of our patients did fall into this category, but anti-HER2 treatment was not standard treatment during this study period.

In conclusion, combination neoadjuvant chemotherapy with the TXP regimen resulted in substantial clinical and pathological response rates. The protocol was well tolerated and had a good safety profile in treating patients with LABC without the use of prophylactic G-CSF or antibiotics.

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