

Differential Response of Triple-Negative Breast Cancer to a Docetaxel and Carboplatin-Based Neoadjuvant Treatment

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BACKGROUND: In this study, the authors evaluated whether a pathologic complete response (pCR) or a clinical complete response (cCR) to neoadjuvant treatment in patients with locally advanced breast cancer differed among the 3 subtypes of breast cancer: triple-negative breast cancer (TNBC), human epidermal growth factor receptor 2 (HER2)-positive breast cancer, and hormone receptor-positive/HER2-negative breast cancer. Whether a cCR or a pCR was correlated with fewer recurrences and better survival also was investigated. **METHODS:** Patients with stage II/III breast cancer received 4 cycles of neoadjuvant docetaxel and carboplatin (TC) every 3 weeks. Patients with HER2-positive tumors were randomized to receive either additional weekly trastuzumab preoperatively or TC alone. Postoperatively, all patients received 4 cycles of TC, and all HER2-positive patients received a total of 52 weeks of trastuzumab. The recurrence-free survival (RFS) and overall survival (OS) rates at 2 years were reported. **RESULTS:** Seventy-four patients were enrolled, including 11 patients with TNBC, 30 patients with HER2-positive tumors, and 33 patients with hormone receptor-positive/HER2-negative tumor. The cCR rates were 45.4%, 50% and 40.6% in TNBC, HER2-positive, and hormone receptor-positive/HER2-negative groups, respectively. The pCR rate for the entire group was 26.8%, and patients with TNBC had the best response (54.6%) followed by patients with HER2-positive tumors (24.1%) and patients with hormone receptor-positive/HER2-negative tumors (19.4%; $P = .0126$). The pCR rate for patients with HER2-positive tumors improved from 7% to 40% if trastuzumab was added ($P = .08$). Infiltrating ductal cancer, TNBC, negative estrogen receptor and/or progesterone receptor status, tumor classification predicted a pCR ($P \leq .05$). Multivariate analysis using a logistic regression test indicated that tumor type was an independent predictor. The RFS rate for patients who did versus patients who did not achieve a pCR was 93.8% versus 78.4% at 2 years, respectively, and 83.3% versus 58% at 3 years, respectively ($P = .1227$); whereas, for patients who did versus patients who did not achieve a cCR, the RFS rate was 80.9% versus 83.9%, respectively, at 2 years and 65% versus 64.3%, respectively, at 3 years ($P = .999$). **CONCLUSIONS:** The current results indicated that the TC combination is promising for the treatment of TNBC. The addition of trastuzumab to TC improved the pCR rate significantly in patients with HER2-positive breast cancer. *Cancer* 2010;000:000-000. © 2010 American Cancer Society.

KEYWORDS: locally advanced breast cancer, triple-negative breast cancer, neoadjuvant chemotherapy, docetaxel, carboplatin, trastuzumab.

Prospective, randomized clinical trials repeatedly have demonstrated a significant survival advantage from postoperative adjuvant chemotherapy for patients with breast cancer.^{1,2} However, patients with locoregionally advanced breast cancer frequently receive neoadjuvant (preoperative) chemotherapy as a first-line treatment. The survival outcome achieved with neoadjuvant chemotherapy reportedly was at least equivalent to³⁻⁵ or better than the outcome achieved with conventional postoperative chemotherapy.⁶ Although the survival benefit of neoadjuvant versus postoperative systemic treatment is yet to be defined, it has been demonstrated clearly that neoadjuvant chemotherapy can downstage tumors to

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facilitate breast-conservation surgery⁶⁻⁸ in some patients and can improve resectability in others. Most important, patients who achieve a pathologic complete response (pCR)^{3,8-11} have better long-term survival than patients who achieve a lesser response. Not only is response to neoadjuvant chemotherapy clinically important, it also provides a research opportunity to study the molecular basis of differential tumor responses.

Because of the heterogeneous nature of breast cancer, clinical outcomes with the same treatment vary widely even among patients with breast cancer of identical stage and histology. In recent years, gene expression studies have identified 5 subtypes of breast cancer: luminal A, luminal B, basal-like, normal-like, and human epidermal growth factor receptor 2 (erbB2 or HER2)-positive,¹²⁻¹⁴ all of which have distinct clinical outcomes and require different treatment considerations. In the current study, we investigated tumor responses to a neoadjuvant regimen consisting of docetaxel and carboplatin (TC) with trastuzumab (TCH) or without trastuzumab in patients with stage II/III breast cancer.

Because of the association of serious cardiotoxicities and leukemia with anthracyclines,¹⁵ nonanthracycline-based chemotherapeutic agents have been evaluated for their roles in the treatment of breast cancer. Taxanes have emerged as the most effective alternative to doxorubicin. Docetaxel had activity in both anthracycline-sensitive and anthracycline-resistant patients¹⁶⁻¹⁹ and was at least as effective as doxorubicin in a randomized phase 3 study.²⁰ In addition, 6 major prospective, randomized clinical trials that included at least 1000 patients in each trial also demonstrated the superior efficacy of taxanes compared with anthracycline-based regimens.²¹⁻²⁶ In the US Oncology 9735 study,²⁶ 1016 patients with lymph node-positive breast cancer and high-risk, lymph node-negative breast cancer were randomized to receive 4 cycles of doxorubicin and cyclophosphamide (AC) (doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m²) or TC (docetaxel 75 mg/m² and cyclophosphamide 600 mg/m²). After a median follow-up of 66 months, the results indicated that TC was superior to AC in terms of both disease-free survival (86% vs 80%; hazard ratio [HR], 0.67) and overall survival (OS) (90% vs 87%; HR, 0.76). At 7 years, the TC group had a statistically better disease-free survival rate compared with the AC group (81% vs 75%) and a better OS rate (87% vs 82%). The incidence of febrile neutropenia was higher in the TC group, whereas nausea and vomiting were more severe in the AC group. A docetaxel-based regimen without doxorubicin also demon-

strated efficacy in patients with HER2-positive cancer. In the Breast Cancer International Research Group 006 study,²⁷ patients with HER2-positive disease were randomized into 3 groups: 4 cycles of AC followed by docetaxel, 4 cycles of AC followed by trastuzumab and docetaxel, or 6 cycles of TCH. After 4 years, patients who received trastuzumab in addition to chemotherapy had better disease-free survival than patients who received AC alone. There was no significant therapeutic difference between the doxorubicin, cyclophosphamide, docetaxel, and trastuzumab (ACTH) group and the TCH group among patients with HER2-positive breast cancer. The 4-year disease-free survival rates were 83%, 82%, and 77% for the ACTH, TCH, and AC groups, respectively.²⁷ Taken together, docetaxel was effective in all subgroups of patients with breast cancer who had different hormone receptor status and HER2 status. Thus, docetaxel was selected in our study as part of the neoadjuvant regimen for the treatment of patients with large, nonmetastatic breast cancer.

In considering another drug, we chose carboplatin as the second agent. Preclinical studies indicated that, when given together with trastuzumab, platinum salts had a synergistic antitumor effect both in vitro and in vivo.^{28,29} Platinum salts, when used as third-line treatment, demonstrated a response rate of only 10%. However, when platinum salts were combined with other drugs and used as first-line treatment, the response rates were as high as 50%. It was demonstrated that platinum caused interstrand DNA cross-linking, which cannot be repaired effectively in triple-negative breast cancer (TNBC) associated with mutation of the breast cancer 1 gene *BRCA1*. Therefore, TC with or without trastuzumab was chosen for patients with large primary breast cancer.

MATERIALS AND METHODS

Patients

Between 2002 and 2007, 74 patients who had a tissue-proven diagnosis of T2, T3, or T4 breast carcinoma with any lymph node status and without distant metastasis were enrolled onto an institutional review board-approved neoadjuvant study evaluating tumor response induced by TC in patients with HER2-negative breast cancer and TC with or without trastuzumab in HER2-positive cancer. Baseline estrogen receptor (ER) and progesterone receptor (PgR) status determined by immunohistochemical (IHC) staining and HER2 status determined by fluorescent in situ hybridization (FISH)

were required for all patients. Patients who had a previous cancer diagnosis or who had received any of the study drugs in the past were excluded.

All patients were required to have breast examinations and mammography for tumor assessment before and after neoadjuvant treatment. Breast magnetic resonance imaging (MRI) studies were optional when tumor size assessed by both modalities was similar and were required if the findings were discordant. Baseline positron emission tomography (PET)/computed tomography scans and bone scans were required. Tumor tissues at baseline and at definitive surgery after neoadjuvant treatment were collected for molecular analysis of drug susceptibility.

Treatment

Docetaxel (75 mg/m²) and carboplatin (area under the receiver operating characteristic curve = 6) were administered every 3 weeks for 4 cycles both before and after definitive surgery in all patients. Patients who had HER2-amplified tumors were randomized to receive neoadjuvant chemotherapy alone (15 patients) and chemotherapy plus weekly trastuzumab (4 mg/kg followed by 2 mg/kg; 15 patients) before surgery. Patients with HER2-positive disease who were randomized to receive preoperative chemotherapy alone received a total of 52 weeks of trastuzumab postoperatively, and patients who were randomized to receive neoadjuvant TCH received trastuzumab both preoperatively and postoperatively for a total 52 weeks of trastuzumab. The trastuzumab dosing was changed from weekly to every 3 weeks (6 mg/kg) once chemotherapy was complete.

Tumor Response

Clinical responses were rated according to the Response Evaluation Criteria in Solid Tumors.³⁰ Clinical tumor size was assessed in 2-dimensional measurement by 1) physical examination, 2) mammography, and 3) MRI. In patients with inflammatory breast cancer (IBC), when a dominant mass was not present, the area of diffuse swelling and skin change was measured. The clinical response was assigned into 5 groups: complete response (CR), partial response (PR), marginal response, stable disease (SD), and disease progression. Pathologic response of the primary tumor was assigned into 2 groups: pathologic CR (pCR) (defined as no evidence of residual invasive disease in mastectomy or lumpectomy specimen) or non-pCR. The primary endpoints of the study were clinical and pathologic response to the treatment and toxicity associ-

ated with that treatment. Secondary endpoints were recurrence-free survival (RFS) and OS.

Statistical Analysis

Continuous variables were summarized with means and standard deviations. Kappa statistics were computed to assess response category agreement beyond chance between physical examination versus mammography or MRI. Chi-square tests and their exact small sample size *P* values were computed for comparing proportions. Student *t* tests were used to compare continuous variables between 2 groups. Backward stepwise logistic regression was used to identify the independent predicting variables for pCR. Survival curves were estimated using the Kaplan-Meier method and were compared in log-rank tests.

Toxicity Assessment

Toxicity after 4 cycles of neoadjuvant therapy was evaluated according to the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, which includes constitutional symptoms; allergic reactions; and cardiovascular, skin, gastrointestinal, hematologic, hepatic, renal, neurologic, metabolic, and infectious conditions.

RESULTS

Demographic and toxicity data obtained during neoadjuvant treatment are reported for all 74 enrolled patients. One patient with bilateral disease was excluded from all analyses, and 2 patients who did not undergo surgery were excluded from the analysis for pathologic response. Seventy-three patients were included in the analysis of clinical response, and 71 patients were included in the pathologic response analysis. Forty-four patients had HER2-negative disease, and 30 patients had HER2-positive disease. All 44 patients with HER2-negative disease and 15 patients with HER2-positive disease were randomized to receive neoadjuvant TC, and the other 15 HER2-positive patients received TCH.

Patient Characteristics

The patients and their tumor characteristics are summarized in Table 1. Fifty-eight patients (79.5%) had infiltrating ductal cancer (IDC), and 9 patients (12.3%) had infiltrating lobular cancer. Eighty-one percent of patients had T3/T4 tumors, including 11 patients with IBC. The mean tumor size for the group was 7.75 cm (7.64 cm in patients with TNBC, 7.78 cm in patients with HER2-

Table 1. Patient and Tumor Characteristics at Baseline^a

Characteristic	No. of Patients (%)
Race	
White	46 (62.2)
Black	6 (8.1)
Hispanic	10 (13.5)
Asian	12 (16.2)
Age, y	
Mean [range]	49.6 [29-84]
<50	39 (52.7)
≥50	35 (47.3)
Mean tumor size on PE, cm ^a	7.75
Tumor classification^a	
T2	14 (19.2)
T3	42 (57.5)
T4	17 (23.3)
Clinical lymph node status^a	
N0	32 (44.4)
N1-N3	40 (55.6)
Nx	1
Histologic type^a	
Infiltrating ductal	58 (79.5)
Infiltrating lobular	9 (12.3)
Others	6 (8.2)
Breast cancer subtype^a	
TNBC	11 (15.1)
HER2+	30 (41.1)
Hormone receptor+/HER2-	32 (43.8)

PE indicates physical examination; TNBC, triple-negative breast cancer; HER2+, human epidermal growth factor receptor 2-positive, HER2-, human epidermal growth factor receptor 2-negative.

^aN=73. (Note that the analysis excluded 1 patient who had bilateral disease.)

positive disease, and 7.76 cm in patients with hormone receptor-positive/HER2-negative disease). Initially, none of these patients were considered candidates for breast-conservation surgery.

Of the 73 patients who were included in the clinical response analysis, 11 patients (15.1%) had TNBC, 30 patients (41.1%) had HER2-positive breast cancer, and 32 patients (43.8%) had hormone receptor-positive/HER2-negative breast cancer.

Clinical and Pathologic Response to Neoadjuvant Chemotherapy

Of the 73 patients who were evaluated for clinical response, only 39 had evaluable mammography, 32 patients had false-negative or nonevaluable mammography, and 2 patients could not undergo mammography because of the advanced nature of T4 breast cancer. Fifty-six patients had MRI studies obtained both at baseline and at the end of neoadjuvant treatment. Thirty-three

Table 2. Clinical Tumor Response at the End of Neoadjuvant Treatment Measured by Physical Examination and Breast Imaging Studies

Response	No. of Patients (%)		
	Physical Examination	Mammogram	MRI
CR	33 (45.2)	18 (46.2)	10 (17.9)
PR	34 (46.6)	11 (28.2)	28 (50)
MR	3 (4.1)	5 (12.8)	12 (21.4)
SD	3 (4.1)	5 (12.8)	6 (10.7)

MRI indicates magnetic resonance imaging; CR, complete response; PR, partial response; MR, marginal response; SD, stable disease.

patients (45.2%) had a clinical CR (cCR), and 34 patients (46.6%) had a clinical PR on clinical examination (Table 2). Of the 39 patients who had evaluable mammography studies, 18 patients (46.2%) had a mammographic CR. Of the 56 patients who had MRI studies, 10 patients (17.9%) had an MRI CR. When the 2 breast-imaging modalities were compared with clinical examination, there was no agreement beyond chance (mammography: $\kappa = 0.07$ [$P = .175$]; MRI: $\kappa = 0.15$ [$P = .0876$]) (Table 3). The sample size for the kappa test in this study was not sufficiently large; therefore, the P values should be interpreted with caution.

The mean tumor size of the entire group was decreased from 7.75 cm at baseline to 2.20 cm after neoadjuvant treatment on clinical examination. Thirty-one patients (43.7%) underwent lumpectomy, and 40 patients underwent mastectomy (56.3%). Twenty-eight patients (39.5%) underwent sentinel lymph node biopsy (7 patients at baseline and 21 patients after neoadjuvant treatment), and 43 patients (60.5%) underwent axillary lymph node dissection.

Seventy-one patients underwent definitive cancer surgery and had their tumor response evaluated pathologically. Nineteen of 71 patients (26.8%) had pCR of the invasive breast cancer, including 6 patients with TNBC, 7 patients with HER2-positive cancers, and 6 patients with hormone receptor-positive/HER2-negative breast cancer (pCR rates: 54.6%, 24.1%, and 19.4%, respectively) (Fig. 1). In the HER2-positive group, the pCR rate was 40% when trastuzumab was administered with 4 cycles of TC and 7.1% if only chemotherapy was received preoperatively. The patients with TNBC who received TC and the patients with HER2-positive cancer who received preoperative TCH had a statistically significant advantage of achieving pCR with the regimen (Fig. 1). Because the mean baseline tumor size was similar for the 3 subgroups,

Table 3. Tumor Response Assessment Measured by Physical Examination, Breast Mammography, and Magnetic Resonance Imaging

Response by PE	Response by Mammogram ^a				Response by MRI ^b			
	CR	PR	MR/SD	Total	CR	PR	MR/SD	Total
CR	11	6	2	19	8	10	5	23
PR	6	4	7	17	2	15	11	28
MR/SD	1	1	1	3	0	3	2	5
Total	18	11	10	39	10	28	18	56

MRI indicates magnetic resonance imaging; PE, physical examination; CR, complete response; PR, partial response; MR, marginal response; SD, stable disease.

^a There was no significant agreement between PE and mammogram evaluations (kappa, 0.07 ± 0.11 ; $P = .1751$).

^b There was no significant agreement between PE and MRI evaluations (kappa, 0.15 ± 0.09 ; $P = .0876$).

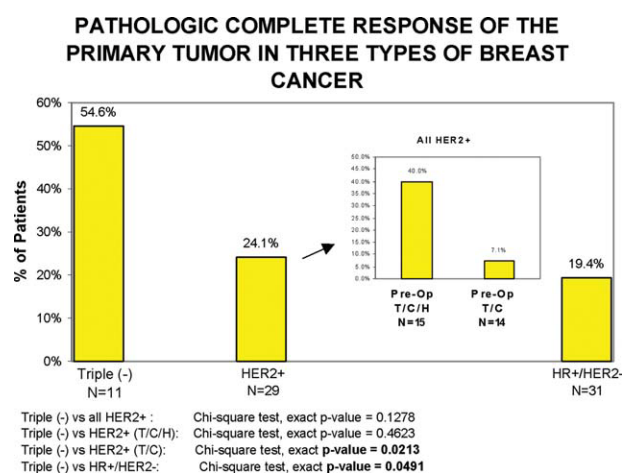


Figure 1. Pathologic complete response of the primary tumor is illustrated for 3 types of breast cancer. Pre-Op indicates preoperative; T, docetaxel; C, carboplatin; H, trastuzumab; Triple (-), triple-negative breast cancer; HER2+, positive for human epidermal growth receptor 2; HR+, positive for hormone receptors (estrogen receptor and progesterone receptor).

we determined that tumor size was not responsible for the differences in pathologic complete tumor response observed in the 3 subtypes of breast cancer.

In univariate analyses using chi-square tests (Table 4), TNBC, ER-negative status, PgR-negative status, ER-negative/PgR-negative status, and IDC were predictors of a pCR to the neoadjuvant regimen used in this study for patients who had large breast cancers. Tumor (T) classification and the addition of trastuzumab to the regimen for patients who had HER2-positive disease had a trend toward a favorable effect on the pCR rate. T4 tumors were associated with a low rate of pCR. In total, 17 patients had T4 disease, including 11 patients with T4d disease. The only patient who achieved a pCR after 4 cycles of neoadjuvant treatment had T4d TNBC. A multivariate logistic regression with backward stepwise selec-

tion was used to simultaneously correlate clinical and pathologic factors with pCR ($P \leq .05$). Age, ER status, PgR status, T classification, tumor histologic type, and TNBC were retained in the model as significant factors. IDC tumor type was the most significant factor correlated with pCR. The exact odds ratio estimated for IDC versus all others was 8.47 (95% confidence interval, 1.2–22.5; $P = .0219$).

When the pathologic tumor response was examined among 71 evaluable patients, 19 patients had no residual invasive cancer. The median pathologic residual tumor size was 2.2 cm, which was the same as the size on clinical assessment by physical examination. Of the 19 patients who achieved a pCR, 11 patients had no evidence of either invasive disease or ductal carcinoma in situ (DCIS), and 8 patients had only residual DCIS.

Thirty-five of 71 patients (49.3%) had pathologic positive lymph node status (N), including with 16 patients (22.5%) N1 disease, 13 patients (18.3%) with N2 disease, and 6 patients (8.5%) with N3 disease. The status of lymph node metastasis after neoadjuvant treatment was proportionate to the extent of residual disease present in the breast. Of the 11 patients who had no residual invasive or in situ disease, all had N0 lymph node status. Of the 8 patients who had residual DCIS, 4 patients had positive lymph nodes (N1 in 2 patients and N2 in 2 patients). Although we do not expect chemotherapy to affect DCIS, the presence of DCIS seems to be correlated with an incomplete lymph node response. Of the 52 patients who had residual invasive breast disease, 31 patients had positive lymph node disease (N1 in 14 patients, N2 in 11 patients, and N3 in 6 patients) (Table 5).

The cCR rates among patients with TNBC, HER2-positive tumors, and hormone receptor-positive/HER2-negative tumors were 45.4% (5 of 11 patients), 50% (15 of 30 patients), and 40.6% (13 of 32 patients), respectively. The similarity in the cCR rate for the 3 subgroups

Table 4. Clinicohistologic Predictors of a Pathologic Complete Response

Variable	No. of Patients (%)		P
	pCR, N=19	No pCR, N=53	
Age, y			
Mean±SD	51.4±11.6	49.0±10.2	.4108 ^a
Median [range]	51 [34-84]	48.5 [29-76]	
<50	8 (22.2)	28	.3810 ^b
≥50	11 (31.4)	24	
ER status			
Negative	11 (44)	14	.0156 ^b
Positive	8 (17.4)	38	
PgR status			
Negative	14 (36.8)	24	.0395 ^b
Positive	5 (15.2)	28	
ER and PgR status			
Both negative	9 (39.1)	14	.0116 ^c
One negative	7 (41.2)	10	
Both positive	3 (9.7)	28	
HER2 status			
Negative	12 (28.6)	30	.6783 ^b
Positive	7 (24.1)	22	
Tumor classification			
T2	5 (35.7)	9	.0509 ^c
T3	13 (32.5)	27	
T4	1 (5.9)	16	
T2	5 (35.7)	9	.3983 ^b
T3-T4	14 (24.6)	43	
Tumor type			
IDC only	19 (33.3)	38	.0148 ^b
All others	0 (0)	14	
ILC only	0 (0)	9	.1007 ^b
All others	19 (30.6)	43	
Triple negative			
Yes	6 (55)	5	.0126
All others: TC			
No	7 (15.6)	38	
Trastuzumab: FISH-positive only			
No	1 (7.1)	13	.0801 ^b
Yes	6 (40)	9	

pCR indicates pathologic complete response; SD, standard deviation; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; TC, docetaxel and carboplatin; FISH, fluorescence in situ hybridization..

^a T test.

^b Chi-square test (an exact P value was used for small expected counts).

^c Cochran-Armitage test for trend.

and the overestimated cCR rates in 2 of the 3 subgroups suggested that a cCR could not be used to predict a pCR. Furthermore, imaging studies that identified a cCR missed the majority of pCRs. When we cross-tabulated the results for pCR versus surgery type (lumpectomy or

Table 5. Pathologic Lymph Node Status According to Primary Tumor Response

Lymph Node Status	No. of Patients (%)		
	No Residual Disease, N=11	DCIS Only, N=8	Residual Invasive Disease, N=52
N0	11 (100)	4 (50)	21 (40.4)
N1	—	2 (25)	14 (26.9)
N2	—	2 (25)	11 (21.2)
N3	—	—	6 (11.5)

DCIS indicates ductal carcinoma in situ.

mastectomy), we observed that patients who achieved a pCR were more likely to undergo lumpectomy compared with patients who did not achieve a pCR (63.2% vs 36.5%, respectively; $P = .045$).

Toxicity

All 74 enrolled patients completed prescribed neoadjuvant treatment for which toxicity is reported. The 5 most frequently observed adverse effects for the entire group, including those who received TCH, were similar. The incidence for all patients was as follows: alopecia, 89.2%; fatigue, 87.8%; nausea, 79.7%; anemia, 71.6%; and leukopenia, 62.2%.

No deaths were associated with the study treatment. Grade 3/4 toxicity other than hematologic toxicities, such as neutropenia (43%), leukopenia (17.6%), lymphopenia (5%), and febrile neutropenia (4%), were rare. Grade 3 docetaxel hypersensitivity was noted in 4% of patients, and all other grade 3/4 adverse events occurred in <2% of patients. The types of grade 3/4 events observed in the TC group versus the TCH group were similar; however, the frequency of grade 3/4 leukopenia, lymphopenia, and febrile neutropenia was higher in the TCH group than in the TC group.

Peripheral neuropathy is a unique side effect of taxanes. In the current study, 4 patients (5.5%) experienced grade 1/2 peripheral neuropathy, and 12 patients (16.2%) had grade 1 tingling and/or paresthesia.

Cardiotoxicity, which is a concern in the adjuvant use of trastuzumab for treating breast cancer, was evaluated mainly by left ventricular ejection fraction (LVEF) using either echocardiograms or multiple-gated acquisition scans at baseline and postneoadjuvant treatment and after completing all 52 weeks of trastuzumab treatment. Of the 74 patients who were treated, 6 patients (8.1%) had a reduction in the LVEF between 10% and 15% from baseline, including 4 of 59 patients who received chemotherapy alone (6.8%) and 2 of 15 patients who received

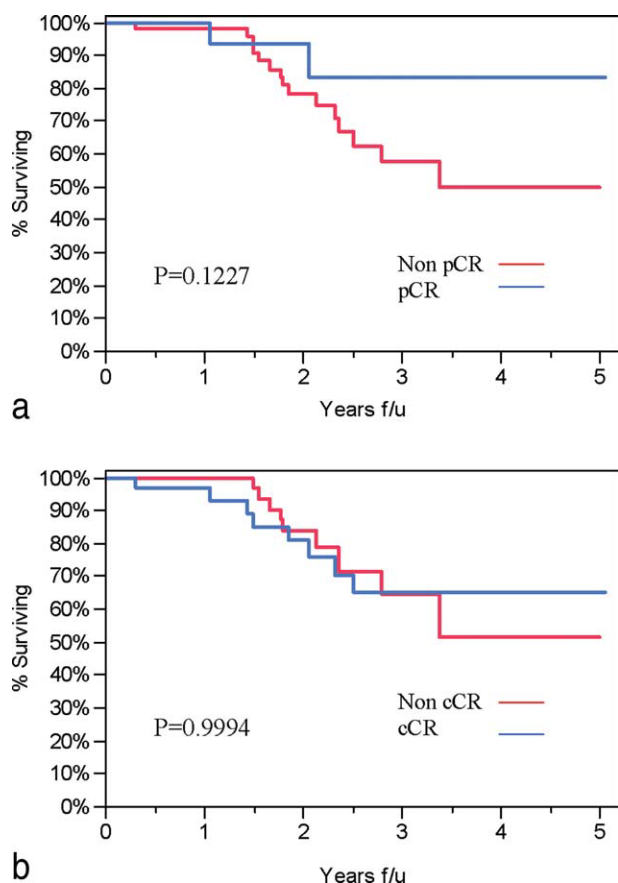


Figure 2. The effects of a pathologic complete response (pCR) and a clinical complete response (cCR) on recurrence-free survival are illustrated (f/u indicates follow-up). (a) Unadjusted recurrence-free survival is illustrated according to pCR status. (b) Unadjusted recurrence-free survival is illustrated according to cCR status.

TCH (13.3%). None of those patients had a decrease in LVEF below the normal limit of 55% to 60%.

Of all 74 treated patients, 1 patients (1.3%) had worsening hypertension that exceeded her baseline condition, 4 patients (5.4%) had tachycardia, 7 patients (10.8%) reported chest pain, and 6 patients (10.6%) had swelling that may have been associated with cardiovascular events. Edema, tachycardia, dyspnea, and chest pain were slightly more frequent in the 15 patients who received neoadjuvant TCH. No significant cardiotoxicity was observed in any patient, regardless of trastuzumab administration.

Follow-Up and Survival Data

Follow-up data were available for all patients. The median follow-up was 1.9 years. Local recurrences developed in 2 patients, distant recurrences developed in 13 patients, and

1 patient had both local and distant recurrences. Seven patients died of recurrent disease, and 1 patient who achieved a pCR died of a cause unrelated cancer.

The RFS for patients who achieved a pCR versus patients who did not achieve a pCR was 93.8% versus 78.4%, respectively, at 2 years and 83.3% versus 58%, respectively, at 3 years ($P = .1222$). For patients who achieved a cCR versus patients who did not achieve a cCR, the RFS rate was 80.9% versus 83.9%, respectively, at 2 years and 65% versus 64.3%, respectively, at 3 years ($P = .999$). Figure 2a,b provides the RFS curves according to pCR and cCR. The RFS probabilities were better in the pCR group than the in non-pCR group, and the differences approached statistical significance ($P = .1227$).

Within the subgroup of patients with HER2-positive tumors, the estimated survival rate was determined according to the type of neoadjuvant treatment received: TCH versus TC. The log-rank test was used to compare survival curves between these 2 groups of patients. Although the RFS rate seemed slightly better in the neoadjuvant TCH group, the OS and RFS rates were statistically similar between the 2 groups ($P = .5055$ and $P = .1752$, respectively). This finding was not surprising, because both groups received identical total doses of TC and trastuzumab.

DISCUSSION

In this study, neoadjuvant treatment consisting of TC with or without trastuzumab was effective in treating breast cancer of all types. This regimen achieved a 45.2% cCR rate and a 46.6% PR rate in 73 patients who had advanced breast cancer. Forty-four percent of these patients were able to undergo lumpectomy for treatment, which initially was deemed impossible. In the remaining 56% of patients, mastectomy was chosen because of the significant amount of residual disease, patient preference, or surgeon recommendation. A tumor-free surgical margin was achieved in all patients. Clinical assessment of the breast tumor size, although not useful for predicting survival outcome, was important in deciding the type of surgery for local treatment.

Compared with pathologic tumor response, clinical assessment by physical examination or mammography frequently overestimated the response. At the same time, the pCRs also were missed on clinical assessment, especially by MRI. Of all the clinical assessments, mammography was the least dependable in assessing large breast cancers both before and after neoadjuvant chemotherapy.

Table 6. Neoadjuvant Trials

Trial	No. of Patients	Tumor Classification/ Staging	Mean/Median Tumor Size, cm	Neoadjuvant Regimen	pCR Rate	Clinical Response Rate
Current report	74	T2-T4, any N (HER2- and HER2+)	Mean, 7.75	TC×4; HER2+ patients randomized to receive preoperative TC or TCH	Overall, 26.8%; TNBC, 54.1%; HR+/HER2-, 19.4%; HER2+ and TCH, 40%; HER2+ and TC, 7.1%	cCR, 45.2%; cPR, 46.6%
Coudert et al, 2006 ³²	33	T2, T3; N0-N2; stage II-III; non-T4d (HER2+)	Mean, 4.6	D×6 plus H	36%	cCR, 73%; cPR, 23%
Coudert et al, 2007 ³³	70	T2, T3; N0-N2; stage II-III; non-T4d (HER2+)	Mean, 4.5	TCH×6	39%	cCR, 85%; cPR, 10%
Gianni et al, 2007 ³⁴	228	T3N1, T4, or any T, N2-N3 (HER2- and HER2+)	Median, 5.5	AT×3, then T×4, then CMF×3; HER2+ patients randomized with or without concurrent H	HER2+ patients, 43% (chemo and H) vs 23% (chemo alone); HER2- patients, 17%	ORR, 81% (chemo and H) vs 73% (chemo alone)
Von Minckwitz et al, 2008 ³⁵	2072	HER2- and HER2+	Not provided	TAC×2; if CR or PR, then randomized to TAC×4 or NX×6; if no response, then randomized to TAC×4 or NX×4	Overall, 18.6%; TNBC, 60%; HR+/HER2-, 9%; HER2+, 17.6%	Not provided
Bear et al, 2003 ³⁶	2411	With LN: any T (T1-T3), N1, M0; without LN: tumor >1 cm to T3; N0-N1; M0	Mean, 4.5	Randomized to AC×4 vs AC×4, then D×4 vs AC×4, then postoperative D×4	26.1% (for 8 cycles) vs 13.7% (for 4 cycles)	ORR (cCR and cPR) similar between the 3 groups; cCR, 40.2% (Arm I), 38.4% (Arm II), 40% (Arm III)
Buzdar et al, 2005 ³⁷	42	T1-T4; N0-N2; stage II-IIIa; non-T4d (HER2+)	Not provided	Randomized to T×4, then FEC×4 with or without concurrent H	65.2% vs 26.3% (H and chemo vs chemo alone)	cCR, 86.9% vs 47.4% (H and chemo vs chemo alone)

pCR indicates pathologic complete response; HER2-, human epidermal growth factor receptor 2-negative; HER2+, human epidermal growth factor receptor 2-positive; TC, docetaxel and carboplatin; TCH, docetaxel, carboplatin, and trastuzumab; TNBC, triple-negative breast cancer; HR+, hormone receptor-positive; cCR, clinical complete response; cPR, clinical partial response; D, docetaxel; H, trastuzumab; AT, doxorubicin and paclitaxel; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; chemo, chemotherapy; ORR, overall response rate; TAC, docetaxel, doxorubicin, and cyclophosphamide; CR, complete response; PR, partial response; NX, vinorelbine and capecitabine; . LN, lymph node; AC, doxorubicin and cyclophosphamide; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide.

Forty-seven percent of all mammography studies fell into the nonevaluable category because of false-negative findings or nonmeasurable nature of the mammography findings. Of the patients who had measurable disease on mammography, the tumor size frequently did not match the size noted during the other clinical assessment at the beginning and during the pathologic measurement at the end.

Although clinical assessment of primary tumor size suffered from imperfect measurement, clinical assessment for lymph node metastasis was even more difficult. Negative axilla predicted by clinical examination and PET scans at the end of neoadjuvant treatment more frequently was incorrect than correct in predicting pathologic lymph node stage. The pathologic lymph node status was predicted better by the baseline evaluation.³¹ Our results suggested that patients with clinically positive lymph nodes at baseline frequently had pathologically proven metastasis after neoadjuvant treatment, even when the clinical examination and PET scan results converted to normal. Thus, surgical staging of the lymph nodes cannot be spared even in women with negative axillae at the end of neoadjuvant treatment and especially in those who present initially with suspicious lymph nodes. In this study, patients who achieved a pCR of the primary tumor for both invasive disease and DCIS had no lymph node involvement. Although residual DCIS in the breast was not expected to reflect the efficacy of chemotherapy, patients who had residual DCIS had lymph node involvement, although the involvement was limited and infrequent. Not achieving a pCR of the primary tumor was associated with more extensive lymph node involvement in patients with advanced disease.

It is well known that neoadjuvant chemotherapy induces various degrees of tumor response in patients with similar disease stage and tumor histology. Our current results suggest that negative hormone receptor status (either ER, or PgR, or both), ductal histology, and TNBC predict a better chance of achieving a pCR after TC. The overall pCR rate was 26.8%, including 81% with T3/T4 breast cancer and 11 patients with IBC. Our study included patients with significantly larger and more advanced cancer compared with other series reported in the literature (Table 6). For HER2-positive tumors, adding trastuzumab to chemotherapy predicted a better chance of achieving pCR. In our study, a pCR was achieved by 55% of patients with TNBC, by 40% of patients with HER2-positive cancer who received simultaneous chemotherapy and trastuzumab, by 7% of patients

with HER2-positive breast cancer who received chemotherapy alone, and by 19% of patients with hormone receptor-positive/HER2-negative breast cancer. The pCR rates achieved in this study were comparable to the best results reported in the literature.^{33,35,36,38-40} In reviewing the representative neoadjuvant trials, significant differences in tumor stage, in the number of cycles used in preoperative treatment, and in the definition of pCR are noted among these studies. In our study, approximately 81% of patients had T3-T4 disease, including a significant number with IBC compared with other trials, in which the patients mainly had smaller tumors and T4 disease was excluded. When the mean or median tumor size was available for comparison, our patients also had significantly larger tumors than the patients in other reports. In our study, only 4 cycles of neoadjuvant therapy were given as opposed to ≥ 6 cycles reported by all others. These differences may have contributed to the differences in the reported pCR rates. Therefore, comparisons of the results from different trials can be difficult.

The superior pCR rate observed in the patients with TNBC in our study suggests that TC is among the most effective first-line treatments for these patients. Additional studies in patients with TNBC will be required to confirm the effectiveness of this regimen and to explore additional targeted therapy for further improvement. Emerging studies identifying molecular markers that profile the success of drug treatment will be extremely important in improving tumor classification and patient selection, and the pCR rate can be used as a surrogate marker to evaluate more treatments.^{41,42}

CONFLICT OF INTEREST DISCLOSURES

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