Original Study

The Efficacy and Safety of Preoperative Chemotherapy With Triweekly Abraxane and Cyclophosphamide Followed by 5-Fluorouracil, Epirubicin, and Cyclophosphamide Therapy for Resectable Breast Cancer: A Multicenter Clinical Trial

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Abstract

Tri-weekly Abraxane has better outcomes than tri-weekly Cremophor-based taxol, and cyclophosphamide combined with taxane shows an enhanced antitumor effect. We showed excellent efficacy and safety of preoperative chemotherapy with TRI-ABC (tri-weekly Abraxane and cyclophosphamide) followed by FEC (5-fluorouracil, epirubicin and cyclophosphamide) for resectable breast cancer. Further clinical studies should be conducted to compare the tri-weekly Abraxane and cylophosphamide regimen with conventional taxane regimens.

Background: It has been reported that tri-weekly Abraxane therapy has better outcomes in recurrent breast cancer than tri-weekly Cremophor-based taxol therapy, and that cyclophosphamide combined with taxane shows an enhanced antitumor effect. We conducted a phase II clinical trial of preoperative chemotherapy with a combination of TRI-ABC. **Patients and Methods:** From September 2011 to September 2013, 4 cycles of preoperative chemotherapy with TRI-ABC followed by 4 cycles of FEC were administered in patients with resectable breast cancer. In patients with HER2-positive breast cancer, tri-weekly Trastuzumab was administered with TRI-ABC. The primary end point was the pathological complete response (pCR) rate in the breasts and lymph nodes. **Results:** The treatment outcomes and safety were evaluated in 54 patients who received at least 1 dose of chemotherapy. All patients underwent radical surgery, and the overall pCR rate of 37% (20 of 54) was achieved. The pCR rates according to each subtype were 8% (2 of 24) in hormone receptor (HR)-positive HER2-negative breast cancer, 56% (5 of 9) in HR-positive HER2-positive breast cancer, 63% (5 of 8) in HR-negative HER2-positive breast cancer, and 62% (8 of 13) in triple-negative breast cancer. Multivariate analysis revealed that HR negativity and HER2 positivity were predictive factors of pCR. Clinical response was observed in 49 patients (91%). The safety profile was acceptable. **Conclusion:** Preoperative chemotherapy with TRI-ABC followed by FEC showed high efficacy and excellent safety. Further clinical studies should be conducted to compare the efficacy of TRI-ABC followed by FEC with conventional taxane–anthracycline regimens.

Clinical Breast Cancer, Vol. 15, No. 2, 110-6
Keywords: Abraxane, Breast cancer, Cyclophosphamide, Preoperative chemotherapy

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Submitted: Jul 7, 2014; Accepted: Sep 25, 2014; Epub: Oct 2, 2014

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1526-8209/$ - see frontmatter
http://dx.doi.org/10.1016/j.clbc.2014.09.010

Introduction

Administration of anthracycline followed by taxane is the standard preoperative chemotherapy for breast cancer, and trastuzumab is concurrently administered in HER2-positive ($HER2^+$) breast cancer.[1-4] For patients who attain a pathological complete response (pCR) after preoperative chemotherapy, long-term prognosis is favorable.[5,6] Therefore, to improve pCR rates, several new chemotherapy regimens are being considered. These include dose-dense therapy and chemotherapy with agents that do not show cross-tolerance, including capecitabine, gemcitabine, carboplatin, and bevacizumab.[7-13]

Abraxane (*nab*-paclitaxel) is a human albumin-bound formulation of paclitaxel nanoparticles of 130 nm in size. It is a novel taxane formulation developed to avoid side effects, such as neuropathy and allergic reactions, caused by Cremophor/ethanol found in conventional Cremophor—paclitaxel formulations. Abraxane characteristically shows a strong antitumor effect because of its enhanced vascular permeability, resulting from it being bound to albumin, providing a higher intratumor paclitaxel concentration than that obtained with Cremophor-based paclitaxel.[14-16] To date, clinical trials on recurrent breast cancer with metastasis have shown that Abraxane treatment shows better outcomes than Cremophor-based paclitaxel or docetaxel treatment, and a phase III trial demonstrated that tri-weekly Abraxane was superior to Cremophor-based paclitaxel in terms of overall survival, progression-free survival, and safety.[17]

Furthermore, it has been reported that when combined with cyclophosphamide, taxane formulations exhibit a strong antitumor effect and enhanced safety. When treating early-stage breast cancer, taxotere and cyclophosphamide chemotherapy has been shown to prolong the survival, compared with doxorubicin (Adriamycin) and cyclophosphamide (AC) chemotherapy, while avoiding the risk of cardiotoxicity caused by anthracyclines.[18-20] Clinical trials using Abraxane—cyclophosphamide combination chemotherapy as adjuvant therapy to treat early-stage breast cancer have been conducted; they revealed that hematotoxicity is mild and the ratio of patients who completed treatment is high, with few Grade 3 or Grade 4 side effects.[21]

On the basis of these reports, it is expected that better pCR rates in preoperative chemotherapy with the combination of tri-weekly Abraxane and cyclophosphamide can be obtained. However, reports on clinical trials of tri-weekly Abraxane to treat early breast cancer are limited and its efficacy is yet to be elucidated. Moreover, there are no reports of preoperative chemotherapy using TRI-ABC (tri-weekly Abraxane combined with cyclophosphamide). Therefore, we conducted a multicenter single-arm phase II trial to examine the efficacy and safety of preoperative chemotherapy with TRI-ABC.

Patients and Methods

Patient Eligibility

This was a multicenter, single-arm, phase II study that recruited patients via central registration. Women aged 20 to 70 years with histologically proven operable breast cancer (T1c3N02M0) were enrolled. No previous chemotherapy, radiotherapy, hormonal therapy, or immunotherapy was allowed. Patients were required to have Eastern Cooperative Oncology Group performance status of 0 or 1, measurable disease, adequate bone marrow, renal, and hepatic function, and a baseline cardiac scan or echocardiogram within the normal range for the institution. Patients were also excluded if they had confirmed infection; serious concomitant illness such as severe cardiovascular disease, uncontrolled diabetes, malignant hypertension or hemorrhagic disease; active concomitant malignancy; peripheral neuropathy; history of edema with severe drug allergy; or previous long-term corticosteroid therapy. Pregnant or lactating women were excluded. All patients underwent staging evaluation that included imaging of the chest and abdomen and bone scan (positron emission tomography imaging was permitted as an alternative to computed tomography and bone scan). All tumors were tested locally for estrogen receptor (ER), progesterone receptor (PgR), and HER2 status. ER and PgR status was determined using immunohistochemistry (IHC) before treatment and tumors with $> 1\%$ positively-stained tumor cells were classified as positive for ER and PgR. Hormone receptor (HR) was classified as positive when tumor cells were positive for ER and/or PgR. HER2 status of the tumor was determined using IHC and/or fluorescence in situ hybridization (FISH) analysis and $HER2^+$ tumors were defined according to IHC scoring of 3 + or gene amplification using FISH.

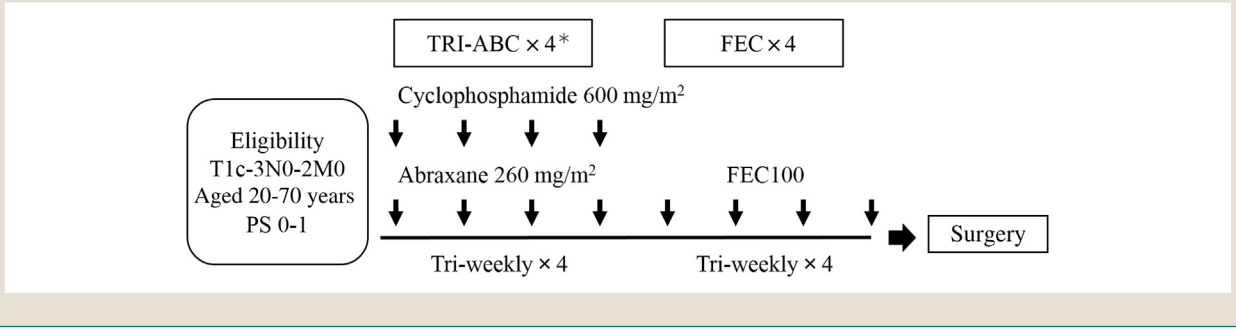
The local ethics committee or institutional review board approved the study at each institution. All patients gave written informed consent to participate. The protocol (UMIN 000007180) was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Treatment

Study design is shown in Figure 1. Each patient received Abraxane 260 mg/m^2 and cyclophosphamide 600 mg/m^2 intravenously tri-weekly (TRI-ABC) for 4 cycles. Three to 4 weeks after the last TRI-ABC cycle, FEC (5-fluorouracil, epirubicin and cyclophosphamide) was administered at the following doses: 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 on a tri-weekly schedule for 4 cycles. Patients with $HER2^+$ breast cancer were administered concomitant tri-weekly trastuzumab with TRI-ABC; trastuzumab was suspended during FEC treatment. Trastuzumab 8 mg/kg was given as a loading dose followed by 6 mg/kg tri-weekly.

TRI-ABC was withheld for any toxicity of Grade ≥ 2 on the planned day of therapy except for Grade 2 sensory peripheral neuropathy. If a patient developed Grade 3 febrile neutropenia, the dose of Abraxane could be reduced. Grade 4 infections or Grade 3 thrombocytopenia required a dose reduction. Grade ≥ 3 non-hematologic toxicity required a dose reduction. Similar dose modifications were used for the FEC portion of the program. Treatment could be postponed for a maximum of 3 weeks only for severe toxicity. If the adverse events did not improve during this period, chemotherapy was discontinued and surgery was recommended. Dose reductions for TRI-ABC were permitted for Abraxane from 260 to 220 mg/m^2, and cyclophosphamide from 600 to 500 mg/m^2. A second dose reduction was allowed to Abraxane 175 mg/m^2, cyclophosphamide 400 mg/m^2 if severe adverse events occurred after the first dose reduction, and for epirubicin from 100 to 75 mg/m^2 in cases of febrile neutropenia or Grade 3/4 non-hematologic toxicities. Doses of epirubicin were reduced to 75 mg/m^2 as first dose reduction and to 50 mg/m^2 after the first dose reduction. Trastuzumab was to be continued if chemotherapy was delayed.

Figure 1 Study Design



Abbreviation: FEC = 5-Fluorouracil, Epirubicin, and Cyclophosphamide. *Trastuzumab Was Administered 3 Times per Week Concomitant With Abraxane and Cyclophosphamide 3 Times per Week (TRI-ABC) in $HER2^+$ Patients.

Patients received prophylactic antiemetic therapy according to standard guidelines, as moderately emetogenic chemotherapy for TRI-ABC and highly emetogenic chemotherapy for FEC. The use of granulocyte colony-stimulating factors was left to the discretion of the treating physician, however the routine prophylactic use of pegfilgrastim was not allowed in this trial.

Treatment After Chemotherapy

Surgery was performed after completion of neoadjuvant chemotherapy and clinical assessment of response. Choice of definitive curative surgery was at the discretion of the surgeon. Axillary lymph node dissection was required if axillary node metastasis was pathologically positive before neoadjuvant treatment. Sentinel node biopsy could be substituted for axillary lymph node dissection in cases of clinical node-negative status before neoadjuvant treatment. Radiation therapy of the breast was required for breast-conserving therapy, and regional nodal irradiation was recommended after mastectomy and if the patient presented with nodal involvement before treatment. Endocrine therapy after surgery for receptor-positive patients was required for a minimum of 5 years, and the choice of agents was determined by the investigator. Patients with $HER2^+$ disease continued trastuzumab at tri-weekly intervals for a total of 1 year.

Response and Toxicity Assessments

Tumor assessments were performed after completion of FEC treatment and before surgery. Clinical response was assessed using computed tomography and/or magnetic resonance imaging in accordance with modified Response Evaluation Criteria in Solid Tumors guidelines. pCR was defined as necrosis and/or disappearance of all tumor cells, and/or the replacement of cancer cells by granulation and/or fibrosis in the surgical breast specimen and axillary lymph node. If only intraductal components remained, the pathological response was described as a pCR. All patients who received any chemotherapy were evaluated for safety. Adverse events for laboratory and nonlaboratory toxicities were summarized according to regimen of therapy using the Common Toxicity Criteria of the National Cancer Institute for Adverse Events, version 3.0.

Statistical Methods

The primary end point was the pCR rate. A sample of 50 patients was required according to binominal distribution, with a 1-sided threshold pCR rate of 20%, an expected pCR rate of 35%, an α error of 5%, and a β error of 20%. Assuming that some patients would not be evaluable, we planned to enroll 55 patients. Secondary end points included pathological response, safety, clinical response rate (RR), rate of breast-conserving surgery, and disease-free survival. Pathological and clinical RRs were calculated with 95% confidence intervals (CIs), with each complete RR based on a binominal distribution. Pathological response was evaluated according to HR status and HER2 status. A multiple logistic regression analysis was performed to examine which factors (menopausal status, tumor size, nodal status, Grade, and ER, PgR, and HER2 status) were associated with pCR. Data were analyzed using the Statistical Package for the Social Sciences version 10.5 (SPSS Inc, Chicago, IL).

Results

Patient Characteristics

Between September 2011 and September 2013, 55 patients with operable breast cancer who met eligibility criteria were enrolled in this trial. Baseline clinicopathological characteristics of the 55 patients are summarized in Table 1. The median age was 49 years (range, 31-68 years). All patients were diagnosed to have invasive breast cancer according to needle biopsy. Involvement of axillary lymph node (N+) was confirmed using fine-needle aspiration cytology or histological examination in 26 patients (47%). The stage distribution included 7 patients (13%) with I, 23 patients (42%) with IIA, 9 patients (16%) with IIB, and 16 patients (29%) with IIIA disease. ER and/or PgR were positive in 35 patients (64%) and were negative in 20 patients (36%), and HER2 was positive in 17 patients (31%). The subtype defined according to HR and HER2 status was 24 patients (44%) $HR^+/HER2^-$; 10 patients (18%) $HR^+/HER2^+$; 8 patients (15%) $HR^-/HER2^+$, and 13 patients (24%) $HR^-/HER2^-$ subtype.

Compliance and Safety

Fifty-five patients were initiated into protocol therapy. One patient withdrew from the study before receiving study drug; thus, 54 patients were included in the safety and response analyses. All patients completed 4 cycles of TRI-ABC. Dose reductions and dose delays of $\geq$ 1 week for TRI-ABC were required in 3 (6%) and 9 (18%) of 54 patients, respectively. The mean dose intensity based

Table 1 Patient Characteristics (n = 55)

Characteristic	Value
Age, Years	
Median	49
Range	31-68
Performance Status = 0	55 (100)
Menopausal Status	
Premenopausal	33 (60)
Postmenopausal	22 (40)
Clinical Tumor Stage	
T1	11 (20)
T2	36 (65)
T3	8 (15)
Clinical Nodal Stage	
N0	29 (53)
N1	14 (26)
N2	12 (22)
Clinical Stage	
I	7 (13)
IIA	23 (42)
IIB	9 (16)
IIIA	16 (29)
Histologic Type	
Infiltrating ductal carcinoma	52 (95)
Invasive micropapillary carcinoma	3 (5)
Grade	
1	5 (9)
2	16 (29)
3	36 (66)
ER Status	
Positive	34 (62)
Negative	21 (38)
PgR Status	
Positive	22 (40)
Negative	33 (60)
HER2 Status	
Positive	17 (31)
Negative	38 (69)
Subtype	
$HR^+/HER2^-$	24 (44)
$HR^+/HER2^+$	10 (18)
$HR^-/HER2^+$	8 (15)
$HR^-/HER2^-$	13 (24)

Data are presented as n (%) except where otherwise stated.
Abbreviations: ER = estrogen receptor; HR = hormone receptor; PgR = progesterone receptor.

on the planned number of cycles was 99.6%. All 54 patients received at least 1 dose of FEC, and 50 (93%) completed 4 cycles. One patient discontinued FEC treatment because of progressive disease, and 3 patients discontinued FEC treatment for toxicity (1 patient after the first cycle, 1 after 2 cycles, and 2 after 3 cycles). Dose reductions and dose delays of ≥ 1 week for FEC were required in 7 (15%) and 16 (30%) of 54 patients, respectively. The mean dose intensity based on the planned number of cycles was 93.8%. Fifty of 54 (93%) patients who were initiated with therapy completed all planned chemotherapy and underwent curative surgery. All patients with $HER2^+$ disease were administered trastuzumab in combination with TRI-ABC.

In Table 2, Grade 2 to 4 adverse events that occurred in patients during TRI-ABC and FEC treatment are shown. During TRI-ABC treatment, the most frequent Grade 2 nonhematological toxicities were sensory neuropathy (46%), myalgia (19%), rash (11%), and fatigue (7%). Grade 3 toxicities included myalgia (4%), and sensory neuropathy (2%). Grade 3 to 4 hematological toxicities were neutropenia (31%) and febrile neutropenia (6%). One patient experienced a Grade 3 increase of alanine aminotransferase. There was no apparent heart toxicity among patients who were administered trastuzumab. During FEC treatment, important frequent nonhematologic Grade 2/3 toxicities were nausea (41%) and fatigue (17%). Grade 3 to 4 hematological toxicities were neutropenia (22%) and febrile neutropenia (19%).

All patients underwent definitive curative surgery for primary breast cancer and had complete pathological evaluations of resected specimens. Breast-conserving surgery was performed for 27 of 54 assessable patients (50%).

Clinical and Pathologic Assessments of Response

A pCR in breast and lymph node was observed in 20 of 54 patients (37%; 95% CI, 24%-50%), which met the primary end point of this study. The rate of pCR in the breast was 38% (21 of 54). In patients with axillary lymph node (AxLN) proven metastasis, the rate of pCR in the AxLNs was 44% (11 of 25). Pathological complete response in breast and axillary lymph node in each subtype is shown in Table 3. The rate of pCR in breast and AxLN according to HR status and HER2 status were 8% (2 of 24) in patients with $HR^+/HER2^-$ disease, 56% (5 of 9) in patients with $HR^+/HER2^+$ disease, 63% (5 of 8) in patients with $HR^-/HER2^+$ disease and 62% (8 of 13) in patients with $HR^-/HER2^-$ (triple negative) tumors. The cohort of women with disease except for $HR^+/HER2^-$ disease had a pCR rate of 60% (18 of 30). The relationship between clinicopathological features and pCR rate is shown in Table 4. The variables found to be significantly associated with a pCR in a multiple logistic regression analysis were HR status (negative vs. positive; hazard ratio, 11.9; 95% CI, 2.8-52.6; $P = .001$) and HER2 status (positive vs. negative; hazard ratio, 6.8; 95% CI, 1.5-32.0; $P = .015$).

The overall clinical RR was 91% (49 of 54; 95% CI, 83%-99%), including clinical complete response in 25 patients (46%) and partial response in 24 patients (44%). Three patients (6%) achieved clinical stable disease and progressive disease was recognized in 2 (4%) patients during FEC treatment; both patients had triple-negative disease and were observed to have disease progression after clinical partial response with TRI-ABC treatment. The overall clinical RR after the initial TRI-ABC was 70% (38 of 54), including clinical complete response in 10 patients (19%) and partial response in 28 patients (52%). Figure 2 depicts maximum tumor reduction ratio as a waterfall plot. Survival outcomes will be reported when the 5-year follow-up has been completed for this study.

Table 2 Treatment-Related Adverse Events

	TRI-ABC (n = 54)						FEC (n = 54)					
	Grade 2		Grade 3		Grade 4		Grade 2		Grade 3		Grade 4	
Adverse Event	n	%	n	%	n	%	n	%	n	%	n	%
Hematologic												
Febrile neutropenia	0	0	3	6	0	0	0	0	10	19	0	0
Neutropenia	5	9	11	20	6	11	6	11	6	11	6	11
Anemia	0	0	0	0	0	0	8	15	0	0	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0	0	0	0	0
Aspartate aminotransferase	2	4	0	0	0	0	1	2	0	0	0	0
Alanine aminotransferase	2	4	1	2	0	0	1	2	0	0	0	0
Nonhematologic												
Fatigue	4	7	1	2	0	0	9	17	2	4	0	0
Neuropathy	25	46	1	2	0	0	1	2	0	0	0	0
Myalgia	10	19	2	4	0	0	4	7	0	0	0	0
Nausea	3	6	0	0	0	0	22	41	3	6	0	0
Rash	6	11	1	2	0	0	0	0	0	0	0	0

Abbreviations: FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; TRI-ABC = Abraxane and cyclophosphamide 3 times per week.

Discussion

Chemotherapy before surgery for breast cancer is performed to facilitate curative resection of locally advanced breast cancer and breast-conserving surgery for early-stage breast cancer.[6] In addition to these surgical objectives, preoperative chemotherapy for breast cancer is also performed to evaluate the sensitivity to pharmacotherapy. In patients with pCR after preoperative breast cancer chemotherapy, long-term prognosis is favorable; therefore, pCR has been established as a surrogate marker of long-term prognosis.[5,6] Because an improvement in pCR rates is believed to improve long-term prognosis, new treatment regimens have been studied to attain a higher pCR rate. To date, studies have examined dose-dense therapy and the combination of agents, such as capecitabine, gemcitabine, carboplatin, and bevacizumab, with the standard preoperative chemotherapy with anthracyclines and taxanes.[7-13] Although these regimens generally tend to increase the pCR rate, they also increase the incidence of serious adverse events and there have been no reports indicating that they improve long-term prognosis; therefore, no new treatment regimens showing better efficacy and safety than the existing standard treatments have been established.

Here, we conducted a multicenter single-arm phase II clinical trial of preoperative chemotherapy (TRI-ABC with FEC) using tri-weekly Abraxane combined with cyclophosphamide followed by FEC treatment to further increase the pCR rate than conventional anthracycline and taxane-based therapies. In a phase III clinical trial comparing Abraxane and conventional standard taxanes to treat recurrent breast cancer patients with metastasis, it was demonstrated that tri-weekly Abraxane therapy had superior outcomes compared with Cremophor-based paclitaxel, a conventional taxane formulation.[17] However, in a phase II trial, it was suggested that weekly Abraxane was more effective than tri-weekly docetaxel,[22] whereas in a phase III trial, the combination of Abraxane and bevacizumab did not show better outcomes compared with weekly Cremophor-based paclitaxel therapy.[23] Therefore, Abraxane has not been established as a standard treatment. On the basis of the studies described herein, tri-weekly administration of Abraxane at a dose of 260 mg/m^2 was approved as the standard regimen, and we adopted preoperative chemotherapy including tri-weekly Abraxane treatment.

In addition, it has been reported that combination chemotherapy with taxanes and cyclophosphamide exhibits a potent antitumor effect. Combination chemotherapy using docetaxel with cyclophosphamide prolongs overall survival more than AC therapy and is recognized as the standard adjuvant chemotherapy regimen.[18,19] On the basis of reports indicating that tri-weekly Abraxane has superior tolerability than tri-weekly docetaxel and that Abraxane—cyclophosphamide combination chemotherapy is safe, we assumed that TRI-ABC would exhibit equal or greater safety and tolerability. Hence, we adopted preoperative combination chemotherapy with TRI-ABC, with a tri-weekly Abraxane dose of 260 mg/m^2 and a cyclophosphamide dose of 600 mg/m^2.

The present clinical study confirmed the efficacy and safety of preoperative TRI-ABC with FEC. First, it was confirmed that TRI-ABC with FEC exhibited good antitumor effect and resulted in a pCR rate of 37%, which exceeded the target value determined beforehand. A particularly potent antitumor effect was observed in chemotherapy-sensitive subtypes, with a pCR rate of 59% in HER2$^+$ breast cancer and 62% in triple-negative breast cancer

Table 3 Pathological Complete Response in Breast and Axillary Lymph Node (n = 54) in Each Subtype

Subtype	n (%)
HR$^+$/HER2$^-$	2/24 (8)
HR$^+$/HER2$^+$	5/9 (56)
HR$^-$/HER2$^+$	5/8 (63)
HR$^-$/HER2$^-$	8/13 (62)
Total	20/54 (37); 95% CI, 24%-53%

Abbreviation: HR = hormone receptor.

Table 4 Predictive Variables for pCR Before Chemotherapy

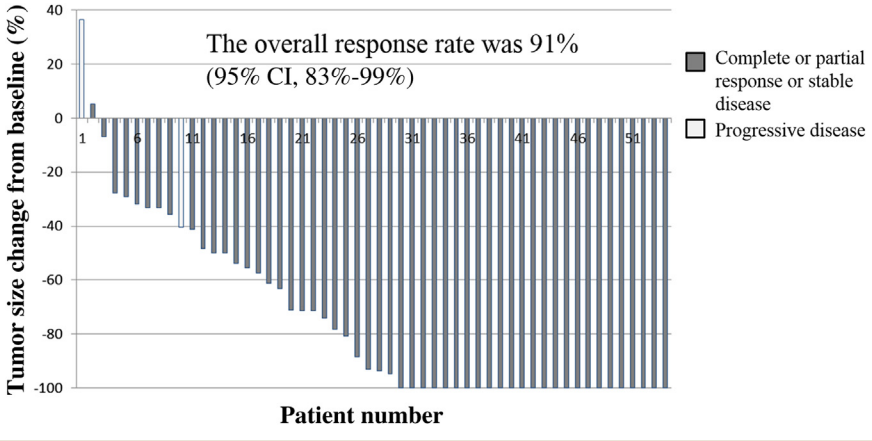
Variable	HR (95% CI)	*P*
Univariate Analysis		
Menopausal status: post- versus premenopausal	0.5 (0.2-1.8)	.31
Clinical tumor stage: II and III versus I	0.9 (0.2-3.5)	.83
Clinical nodal status: positive versus negative	0.8 (0.3-2.5)	.72
Grade: 3 versus 1 and 2	1.3 (0.4-4.2)	.69
ER: negative versus positive	9.0 (2.5-32.3)	.001
PgR: negative versus positive	5.5 (1.6-18.9)	.007
HER2: positive versus negative	4.7 (1.4-16.2)	.015
Multivariate Analysis		
Menopausal status: post- versus premenopausal	0.5 (0.1-2.2)	.38
Clinical tumor stage: II and III versus I	0.9 (0.1-5.9)	.83
Clinical nodal status: positive versus negative	0.8 (0.2-4.0)	.79
Grade: 3 versus 1 and 2	1.1 (0.2-5.4)	.9
ER: negative versus positive	11.9 (2.8-52.6)	.001
PgR: negative versus positive	1.1 (0.2-7.3)	.92
HER2: positive versus negative	6.8 (1.4-32.1)	.015

Abbreviations: ER = estrogen receptor; HR = hazard ratio; PgR = progesterone receptor.

(TNBC). It has been reported that in clinical studies of preoperative chemotherapy using other anthracyclines and taxanes, these chemotherapy-sensitive breast cancer subtypes had a pCR rate of 40% to 50%[4,10,24]; thus, the pCR rate attained in our study was equal to or greater than that in the past reports. A meta-analysis of preoperative chemotherapy revealed that in chemotherapy-sensitive breast cancer subtypes, pCR is a surrogate marker of long-term prognosis,[24,25] and we believe that the clinical significance of the high pCR rate attained in these subtypes is great. Furthermore, cytoreduction was achieved in many patients (91%), and we believe that a good antitumor effect was demonstrated, improving the rate of breast conservation and complete tumor resection.

Second, it was verified that TRI-ABC with FEC showed a good safety profile. All patients completed 4 cycles of TRI-ABC therapy, and most patients successfully received treatment at the planned dosage. Patients were expected to have severe hematotoxicity caused by TRI-ABC, and Grade 3 or Grade 4 neutropenia was observed in 31% of patients. However, febrile neutropenia was observed in only a few patients (6%), and bone marrow function was restored rapidly. Moreover, although approximately 50% of patients exhibited Grade 2 peripheral neuropathy, we were able to continue the treatment in most patients, with a few patients requiring a dosage reduction or discontinuation of the treatment. Marked cardiotoxicity was not observed in $HER2^{+}$ breast cancer patients treated with additional Trastuzumab. On the basis of these findings, we believe that TRI-ABC with FEC has excellent safety in patients with resectable breast cancer. Considering the safety of the outcomes demonstrated here, we believe that

Figure 2 Waterfall Plot of Largest Tumor Size Reduction From Baseline



TRI-ABC with FEC should be considered as an option for the standard adjuvant chemotherapy in patients with resectable breast cancers.

Our study has 2 limitations. First, the present study was a single-arm phase II trial with a relatively small subject sample; a randomized controlled trial with a larger subject sample should be conducted to confirm its results. Second, long-term outcomes were not obtained, and studies with longer follow-up should be conducted in the future.

Conclusion

To our knowledge, this is the first report to describe the outcomes of preoperative chemotherapy with TRI-ABC followed by FEC for resectable breast cancer. In the present study we were able to achieve a pCR rate of 37% using this regimen, which exceeded the target value of 35%. Furthermore, there were no particular concerns regarding safety of the regimen in the present study. On the basis of our results, we recommend that further studies of adjuvant chemotherapy including Abraxane in patients with resectable breast cancer should be conducted.

Clinical Practice Points

- Tri-weekly administration of Abraxane at a dose of 260 mg/m^2 was presently approved as the standard regimen and dose for breast cancer, and combination with taxane and cyclophosphamide is regarded as a preferred regimen with an enhanced antitumor effect. However, there is lack of evidence of tri-weekly Abraxane and cyclophosphamide-based preoperative chemotherapy for resectable breast cancer.
- With these findings, we conducted phase II clinical trial of preoperative chemotherapy using TRI-ABC followed by FEC for resectable breast cancer.
- In this study, TRI-ABC with FEC showed high efficacy with a pCR rate of 37% which exceeded the target value of 35% determined beforehand, and a potent antitumor effect was observed in chemotherapy-sensitive subtypes, with a pCR rate of 59% in HER2$^+$ breast cancer and 62% in TNBC. In addition, no particular concerns regarding safety of the regimen occurred in the present study.
- On the basis of this study, further clinical studies should be conducted to compare the efficacy of TRI-ABC followed by FEC with conventional taxane—anthracycline regimens.

Disclosure

The authors have stated that they have no conflicts of interest.

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