Phase II Trial of Preoperative Chemotherapy for Breast Cancer: Japan Breast Cancer Research Network (JBCRN)-02 Trial

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Abstract. *Background: Neoadjuvant chemotherapy (NAC) is one of the main strategies for patients with locally advanced breast cancer. In our previous study, biological markers such as estrogen receptor (ER), progesterone receptor (PgR), and HER2 were essential predictors of the effectiveness of NAC to help individualize treatment. This study examined the effect of NAC on the disease-free survival (DFS) of breast cancer patients. Furthermore, the study was expanded by adding Ki-67 as a biological marker, and examined the correlation between Ki-67 and the prognosis. Patients and Methods: Between September 2005 and September 2007, 43 patients with breast cancer received NAC and surgery. Four cycles of DC (doxorubicin: 60 mg/m^2, and cyclophosphamide: 500 mg/m^2) were administered intravenously (i.v.) on day 1 every 21 days, followed by 12 cycles of paclitaxel i.v. (80 mg/m^2) every 7 days, prior to surgery. The primary endpoint was the pathological complete response (pCR) rate and the secondary endpoint was DFS; the pCR rate was estimated for each groups stratified by the presence or absence of different factors (PcR, ER/PgR, and Ki-67). Results: The clinical response (cCR+cPR) rate was 81.0%, and the pCR rate was 25.6%. The pCR rate was 75, 50, 9 and 0% in HER2$^+$/ER$^-$, HER2$^+$/ER$^+$, HER2$^-$/ER$^-$, and HER2$^-$/ER$^+$ patients, respectively. The 4-year DFS rate was estimated at 78% for all patients. The HER2 status was an independent predictor of pathological complete response (pCR). The DFS rate of patients with lower Ki-67 values (<15%) was higher than that of patients with higher Ki-67 values (≥15%). The treatment-related adverse events were manageable: the majority were mild, but five patients experienced grade 3 (neutropenia and sensory neuropathy) adverse events. Conclusion: DC followed by weekly paclitaxel is an active and manageable preoperative regimen for breast cancer patients. HER2 overexpression may be a good predictive marker of pCR, and the Ki-67 value after NAC may be a prognostic factor for DFS.*

Neoadjuvant chemotherapy (NAC) has emerged as a promising step forward in the management of locally advanced breast cancer. When administered before surgery, chemotherapy may induce tumor shrinkage, facilitate surgery, and increase the breast-conserving surgery rate (1-3).

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-27 demonstrated that compared to preoperative DC alone, the addition of sequential docetaxel doubled the pathological complete response (pCR) rate, increased the clinical complete response (cCR) rate, and increased the proportion of patients with negative axillary nodes (3-5). Some studies demonstrated that patients with pCR to chemotherapy had a good prognosis (1-5). Therefore the pathological response is an important prognostic parameter that can be used as a surrogate parameter for clinical outcomes. Furthermore, preoperative systemic therapy administering molecular targeted therapies, such as trastuzumab (Herceptin), and new hormone blockers, such as aromatase inhibitors, have been added to these regimens for the past 10 years (6). However pathological response cannot be accurately predicted.

In our previous study, biological markers such as estrogen receptor (ER), progesterone receptor (PgR), and HER2 were essential predictors of the effectiveness of NAC to help individualize treatment (7). This study examined the effect of NAC on the disease-free survival (DFS) of breast cancer

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Table I. *Response criteria used in the present study.*

Grade 0 (negative)	Almost no changes in post-treatment cancer cells.
Grade 1 (slight)	
1a (mild)	Slight changes observed in cancer cells regardless of lesion size.
	Significant changes observed in <1/3 of cancer cells.
1b (moderate)	Significant changes observed in 1/3 to <2/3 of cancer cells.
Grade 2 (significant)	Significant changes observed in approximately ≥2/3 of cancer cells.
Grade 3 (complete)	All cancer cells necrotize or disappear, replaced with granuloma-like tissues or focal fibrosis.

patients. In addition, we expanded the study by adding Ki-67 as a biological marker. We conducted a multicenter prospective neoadjuvant trial with four cycles of doxorubicin and cyclophosphamide (DC) followed by twelve cycles of paclitaxel for breast cancer patients to investigate the relationship between pathological effect and survival. Clinical response, the rate of breast-conserving surgery (BCS), some factors, and safety were also evaluated.

Patients and Methods

This multicenter, open-label, single-arm, phase II study was conducted in women aged 20 to 69 years with previously untreated unilateral carcinoma of the breast (T2-3, N0-1, M0). Patients with bilateral, locally advanced, or metastatic disease were excluded. Other eligibility criteria included: Eastern Cooperative Oncology Group performance status 0 to 1; adequate bone marrow reserve (absolute neutrophil count (ANC) >2,000/mm^3, platelet count >100,000/mm^3), and adequate renal (serum creatinine <1.5 times upper normal limit) and hepatic function (total bilirubin <2 times upper normal limit); left ventricular ejection fraction (LVEF) within normal limits based on echocardiographic (ECG) assessment. Patients were excluded from the study if they had any history of another neoplasm. All patients gave written informed consent before their participation in the trial. The study was conducted in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by the Institutional Review Boards at all participating centers, and written informed consent was obtained from all patients prior to the study.

Four cycles of DC (doxorubicin: 60 mg/m^2 and cyclophosphamide: 500 mg/m^2) administered intravenously (*i.v.*) on day 1 every 21 days were followed by 12 cycles of paclitaxel *i.v.* (80 mg/m^2) every 7 days, prior to surgery. Treatment was continued in the absence of unacceptable toxicity. Premedication 30 min prior to paclitaxel administration consisted of *i.v.* ranitidine (50 mg), and *i.v.* dexamethasone (20 mg), and oral diphenhydramine (50 mg). Prophylactic hematologic growth factor support was prohibited before the second course of treatment.

The disease status was confirmed by physical examination, mammography, and breast ultrasonography and a core or fine-needle biopsy for histopathological diagnosis. During treatment, white blood cell count was repeated weekly. Biochemistry tests were performed after courses 2 and 4, and cardiac monitoring comprised an ECG after course 4 and LVEF measurement after courses 2 and 4, or after study discontinuation. Adverse events were evaluated according to CTC grades.

Treatment was to be postponed for a maximum of 2 weeks for severe toxicity. If toxicity did not improve during this period, chemotherapy was discontinued and surgery was recommended. Dose reductions of doxorubicin from 60 to 40 mg/m^2, cyclophosphamide from 600 to 400 mg/m^2, and paclitaxel from 80 to 60 mg/m^2 were permitted in cases of febrile neutropenia and grade 3 or 4 non-hematological toxicities except for nausea, vomiting, and fatigue. Following chemotherapy and clinical assessment of the response, patients underwent surgery. If the tumor was too large or invasive for BCS, modified radical mastectomy was recommended. Sentinel lymph node biopsy was not performed to confirm the disease stage.

Assessment of response to therapy. A physical examination was performed and the performance status was assessed on day 1 of each course. Tumor assessment involved a physical examination before, during, and after every course and breast ultrasonography after 4 courses of DC regimen; the appearance of any new lesion was documented. The primary endpoint was to determine the rate of pCR induced by primary chemotherapy and assessment of the pathological response as an independent predictor of DFS. The pathological response was classified according to the criteria in Table I.

The clinical response of bidimensionally measurable and assessable disease was classified as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to WHO criteria. CR was defined as the disappearance of all clinical evidence of the tumor; PR was defined as a 50% or more reduction in the sum of the products of measured lesions, or an estimated decrease in the tumor size of at least 50%, without the appearance of new lesions; SD was defined as a decrease in the lesion size of less than 50% for the sum of the products of measured lesions, or an estimated decrease of less than 50% and increase of less than 25%, without the appearance of new lesions. Any measured or estimated increase greater than 25% or the appearance of new lesions was defined as PD. The clinical response was defined as the sum of CRs and PRs. Surgery was to be performed less than 4 weeks after the last chemotherapy course.

Where possible, breast-conserving methods were carried out, taking into account the residual tumor size after chemotherapy, and esthetics. After a complete clinical response to chemotherapy, when feasible, a wide surgical excision was performed to remove the tumor with free margins without deforming the breast. Postoperative irradiation was delivered to the breast and regional lymph nodes according to local practices. After chemotherapy, a mastectomy was carried out if the initial multifocal disease could not be removed by a single wide excision or if an extensive area of radiological microcalcifications did not regress with chemotherapy (even though a cCR had been achieved). Hormonal treatment with tamoxifen was given to all patients with ER$^+$ tumors, and any additional chemotherapy was administered at the discretion of the investigator. Follow-up was performed every 4 months for the first 2 years, thereafter every 6 months, and once a year after 5 years. A total of 43 assessable patients were enrolled in the study.

Table II. *Patient characteristics, n (%).*

Stage	1	2 (4.7%)
	2a	10 (23.3%)
	2b	17 (39.5%)
	3a	6 (14.0%)
	3b	3 (7.0%)
	3c	5 (11.6%)
Tumor size (mm)	<20	4 (9.3%)
	20 +	39 (90.7%)
ER	Positive	28 (65.1%)
	Negative	15 (34.9%)
PgR	Positive	25 (58.1%)
	Negative	18 (41.9%)
HER2	0	19 (44.2%)
	1+	5 (11.6%)
	2+	5 (11.6%)
	3+	14 (32.6%)
Pathological grade	1	15 (34.9%)
	2	24 (55.8%)
	3	3 (7.0%)
	Unknown	1 (2.3%)
Lymph-node status	0	27 (62.8%)
	1-3	9 (20.9%)
	4+	5 (11.6%)
	Unknown	2 (4.7%)

Table III. *Prediction of pCR (G3) by logistic regression.*

Factors	% pCR	Statistics	Univariate analysis	Multivariate analysis
Age				
<50 years	23.8% (5/21)	OR	1.19	1.80
≥50 years	27.3% (6/22)	*P*-value	1.000	1.000
Tumor size				
<30 mm	0.0% (0/7)	OR	3.92	3.82
≥30 mm	30.6% (11/36)	*P*-value	0.209	0.288
ER				
–	40.0% (6/15)	OR	2.98	1.19
+	17.9% (5/28)	*P*-value	0.225	1.000
PgR				
–	38.9% (7/18)	OR	3.24	0.93
+	16.0% (4/25)	*P*-value	0.180	1.000
HER2				
2+	6.9% (2/29)	OR	21.72	21.07
3+	64.3% (9/14)	*P*-value	<0.001	0.003
Clinical response				
SD+PD	11.1% (1/9)	OR	3.26	3.17
CR+PR	29.4% (10/34)	*P*-value	0.510	0.762

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; OR: odds ratio.

Histopathological examination. Pretreatment diagnosis was established by our pathologists using samples from core needle biopsy. The items investigated were the presence or absence of lymph node metastasis, nuclear grade, ER/PgR status, and HER2. Recent data suggest that several biological markers, especially Ki-67, may have the potential to predict the effectiveness of NAC with anthracycline and taxane. Therefore, we performed a post-hoc analysis of outcomes according to Ki-67. Immunostaining of ER, PgR, Ki-67, and HER2 was conducted as previously described (8). The positive cell rates for ER/PgR were determined by Immunohistochemistry. An assessment value of 10% or higher was rated as positive. Proliferative activity was determined by immunostaining for Ki-67 antibody (Dako, Tokyo, Japan). The fraction of proliferating cells was based on a count of at least 500 tumor cells. The Ki-67 values were expressed as the percentage of positive cells in each case.

Statistical analysis. The primary endpoint was the pCR rate of the treatment. Pathological response grades were stratified by tumor and nodal staging, patient age, and clinical response. Secondary endpoints included predictors for pCR, DFS, the rate of breast-conserving surgery, and safety. A 10-30% pCR rate was reported based on histopathology in preoperative anthracycline plus taxane (PTX) chemotherapy regimens. The required number of patients was calculated as 41, using a 25% expected efficacy rate, 10% threshold efficacy rate, two-sided alpha level of 0.05, and 80% power for the statistical analysis of the primary endpoint for this sequential combination chemotherapy. Analyses were performed with JMP (version 9; SAS Institute Inc., Tokyo, Japan).

Results

Patient characteristics. Between April 2004 and March 2007, 43 patients were prospectively enrolled. The characteristics of the study population are presented in Table II. The median age was 50 (range: 20-69) years. The majority of patients had T2 tumors.

Efficacy of NAC. The patients were evaluable regarding their response and toxicity. Clinical responses were rated as cCR in 9 patients (22%), cPR in 25 patients (59%), and cSD in 9 patients (19%). The pCR was seen in 25.6%. Breast-conserving surgery was achieved in 58% of all 43 patients. Furthermore, multiple logistic regression analysis was performed to examine factors including menopausal status, tumor size, ER status, PgR status, HER2 status, and clinical response (Table III). Multivariate analysis showed that the HER2 status was an independent predictive factor of pCR. The pCR rates stratified by HER2 and ER are shown in Figure 1. The pCR rate was 75%, 50%, 9% and 0 % in HER2$^+$/ER$^-$, HER2$^+$/ER$^+$, HER2$^-$/ER$^-$, and HER2$^-$/ER$^+$ patients, respectively.

The estimated 4-year DFS was 78% for all patients. Patients who achieved pCR did not show an improved DFS compared to those without pCR (log-rank test, *p*<0.05, Figure 2). Because of evidence that Ki-67 may be useful to evaluate the neoadjuvant setting (8, 9), we evaluated the influence of the Ki-67 status and pCR. This analysis should be regarded as exploratory, because it was not prespecified. As a result, the DFS rate of patients with lower (<15%) Ki-67 values was higher than that of patients with higher (≥15%) Ki-67 values.

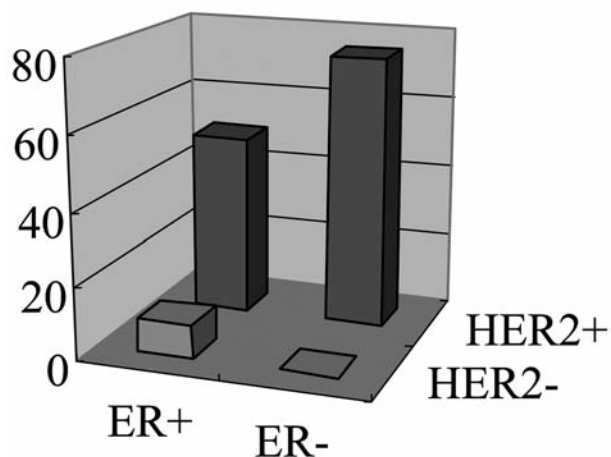The toxicities were manageable and the safety profile is summarized in Table IV. Dose reduction and interuption due

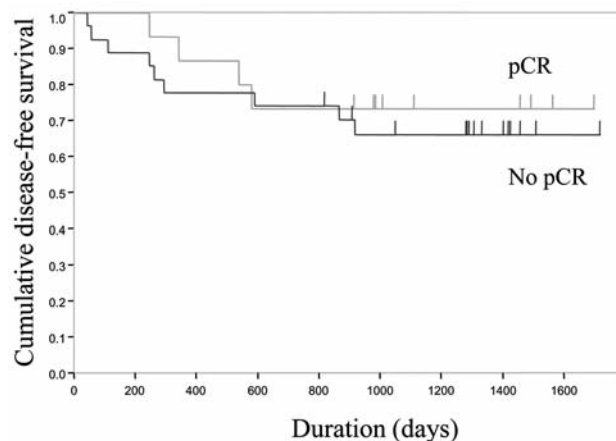Figure 1. *Relationship between pCR and HER2/ER status.*

Figure 2. *Relationship of pCR and non-pCR to disease-free survival.*

to toxicities did not occur during treatment. The most common toxicity was nausea, which was observed in 62.8% of patients during DC treatment and 33% of patients during paclitaxel treatment. Grade 3-4 nausea was not seen in either treatment. Grade 3 neutropenia was reported in 2.3% and 7.1% of patients during treatment with DC and paclitaxel, respectively.

Discussion

Our study demonstrates that DC followed by paclitaxel is a promising NAC regimen for patients with breast cancer not amenable to conservative surgery. In other studies, the regimen of three cycles of 5-fluorouracil plus epirubicin plus cyclophosphamide followed by three cycles of docetaxel at 100 mg/m^2 led to the favorable result of an 18% risk reduction in DFS and 27% risk reduction in overall survival. However, in Japan, the standard dose of docetaxel is 75 mg/m^2. Therefore, we selected DC followed by weekly paclitaxel, and showed that the actual 4-year DFS rate of 78% was similar to the results of other studies (1-5). Unfortunately, there was no significant improvement in DFS regardless of the existence of pCR, possibly because this was not a large study. However, the DFS rate of patients with lower Ki-67 values (<15%) was higher than that of patients with higher values (≥15%).

Regarding toxicity, there were no severe toxic effects as compared with other recent studies (1-5). In terms of the incidence of febrile neutropenia, it was lower than that of other studies. (1-5). This confirms that DC followed by weekly paclitaxel as the neoadjuvant setting is appropriate for Japanese women.

In addition, we investigated ER, PgR, HER2, and Ki-67. We found that the pCR rate was the highest in patients who were ER$^-$/HER2$^+$. pCR was significantly associated with

Table IV. *Treatment-related toxicities reported by patients in the study.*

Toxicity	DC (N=43)		Paclitaxel (N=42)	
	All grades	Grade 3+	All grades	Grade 3+
Neutropenia	17 (39.5%)	1 (2.3%)	17 (40.5%)	3 (7.1%)
Nausea	27 (62.8%)	0 (0.0%)	14 (33.3%)	0 (0.0%)
Vomiting	19 (44.2%)	0 (0.0%)	7 (16.7%)	0 (0.0%)
Hair loss	19 (44.2%)	0 (0.0%)	7 (16.7%)	0 (0.0%)
Stomatitis	8 (18.6%)	0 (0.0%)	1 (2.4%)	0 (0.0%)
Peripheral neuropathy	4 (9.3%)	0 (0.0%)	24 (57.1%)	2 (4.8%)
Subungual bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hand–foot syndrome	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)
Diarrhea	0 (0.0%)	0 (0.0%)	2 (4.8%)	0 (0.0%)

HER2 positivity based on multivariate analysis. Furthermore, in the present study, a higher pCR was often found in patients with tumors with a higher Ki-67 value, and there was no pathological responder in cases with Ki-67 <15% (data not shown). Regarding breast cancer subtypes, Ki-67 values were higher in patients with triple-negative tumors (10-13). These tumors respond more frequently to a neoadjuvant setting. On the other hand, ER$^+$ and/or PgR$^+$ tumors had lower Ki-67 values (10-13). These tumors respond more frequently to endocrine therapy. Therefore, clarifying the proliferative activity may be important for the treatment of breast cancer.

HER2 overexpression was suggested to be a predictor of the sensitivity to anthracycline chemotherapy (12). Indeed, in this study, HER2 was the only predictive factor for pCR. However, in the present study, trastuzumab was not administered to patients with HER2-overexpressing tumors because its use in such a setting has not yet been approved in

Japan. Recently, trastuzumab was found to significantly improve the prognosis and response to chemotherapy in such patients; the pCR rate was significantly higher in patients who were treated with trastuzumab (15-17). The relationship between HER2 overexpression and the response to chemotherapy with trastuzumab needs future investigation.

In conclusion, DC followed by weekly paclitaxel is safe, feasible, and effective as a preoperative adjuvant chemotherapy for Japanese women with breast cancer.

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