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Docetaxel Followed by Fluorouracil/Epirubicin/Cyclophosphamide as Neoadjuvant Chemotherapy for Patients with Primary Breast Cancer

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Objective: This multicenter, open-label, single-arm, Phase II study assessed the efficacy of a neoadjuvant chemotherapy with docetaxel (75 mg/m^2 q3w) followed by 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2 q3w in patients with early-stage breast cancer.

Methods: Women with resectable breast cancer (T1c–3 N0 M0 or T1–3 N1 M0) were enrolled. Before surgery, patients received four cycles of docetaxel followed by four cycles of 5-fluorouracil, epirubicin, and cyclophosphamide. The primary endpoint was the pathological complete response (pCR) rate defined for the breast alone, assessed by a central review committee. Secondary endpoints included clinical response and safety.

Results: One hundred and thirty-seven patients were enrolled. Of the 132 patients assessable for pathologic response, 23% (95% confidence interval, 16–31%) experienced a pathological complete response and 6% (95% confidence interval, 3–12%) had a near pathological complete response (few remaining cancer cells), resulting in a quasi-pathological complete response of 29% (95% confidence interval, 21–37%). Clinical response rate following the initial docetaxel regimen was 64%. The overall clinical response rate after completion of 5-fluorouracil, epirubicin, and cyclophosphamide was 79%; breast-conserving surgery was performed in 79% of patients. More patients with triple-negative disease (estrogen/progesterone receptors negative; human epidermal growth factor 2 negative) experienced a pathological complete response [14/29, (48%); 95% confidence interval, 29–68%] versus those with other molecular subtypes. The safety profile was acceptable.

Conclusions: Eight cycles of neoadjuvant chemotherapy—docetaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide—are tolerable and conferred high rates of pathological complete response and breast-conserving surgery. Patients with triple-negative disease were more likely to achieve pathological complete response versus other subtypes, suggesting that selecting appropriate neoadjuvant chemotherapy based on molecular subtype could be possible.

Key words: breast neoplasms – neoadjuvant therapy – FEC protocol – docetaxel

INTRODUCTION

Neoadjuvant chemotherapy has been widely used for patients with operable breast cancer to increase the chance of breast conservation (1–7). Furthermore, response to neoadjuvant treatment can provide important information on long-term survival outcomes. Pathological complete response (pCR) in the breast and axillary lymph nodes predicts a favorable prognosis, whereas a lack of pCR in the breast and node-positive status do not (6,7). This implies the possibility of tailoring subsequent treatment according to the response to initial treatment (7–12). In addition, correlative studies of tumor samples before and after treatment may provide information on markers that could predict response or resistance to treatment (13–16).

Results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-18 trial demonstrated the impact of neoadjuvant chemotherapy in patients with operable early-stage breast cancer (17). The protocol-specified anthracycline-containing regimen—four cycles of doxorubicin and cyclophosphamide (AC)—resulted in an increased likelihood of breast-conserving surgery (BCS) compared with no neoadjuvant chemotherapy. The study established pCR as a prognostic marker for long-term disease-free survival (DFS) and demonstrated that there was no difference in survival if chemotherapy was administered before or after surgery. Subsequent studies, such as the Aberdeen trial, have demonstrated the benefit of the sequential addition of taxanes to neoadjuvant anthracycline regimens (5). The NSABP Protocol B-27 trial demonstrated that, compared with neoadjuvant AC alone, the addition of sequential docetaxel doubled the pCR rate, increased the clinical complete response rate (RR) and increased the proportion of patients with negative axillary nodes (7–18).

We previously conducted a Phase II study to evaluate the clinical and pathological response and safety of the FEC regimen (5-fluorouracil, epirubicin and cyclophosphamide) followed by docetaxel as neoadjuvant chemotherapy in Japanese women with early-stage breast cancer [Japan Breast Cancer Research Group (JBCRG) 01 trial]. The results of this study have been reported previously (19). Although the pCR rate was 16% and BCS was possible for 85% of patients, there were some safety concerns, with 18% of patients experiencing febrile neutropenia and 41% of patients experiencing Grade 1/2 peripheral edema (no Grade 3/4 events observed) following the docetaxel regimen (unpublished data). Disease progression occurred in 6% of patients after the completion of all planned treatment (unpublished data).

In an effort to achieve a higher pathological RR with an improved safety profile, we decided to evaluate the efficacy and safety of docetaxel followed by FEC (JBCRG 03 trial)—the reverse of the sequence of chemotherapy used in the JBCRG 01 trial (19). The clinical and pathological effects and the toxicity profile of this regimen are presented here, and the results of predictive marker analyses are discussed.

PATIENTS AND METHODS

Patient Eligibility

This was a multicenter, open-label, single-arm, Phase II study that recruited patients via central registration. Japanese women aged 20–59 years with histologically proven early-stage breast cancer (T1c–3 N0 M0 or T1–3 N1 M0) were enrolled. No prior chemotherapy, radiotherapy, hormonal therapy or immunotherapy was allowed. Other inclusion criteria were Eastern Cooperative Oncology Group performance status 0–1; white blood cell count 4000–12 000/mm^3; neutrophil count $\geq$ 2000/mm^3; platelet count $\geq$ 100 000/mm^3; hemoglobin $\geq$ 9.5 g/dl; serum bilirubin $\leq$ 1.25 times upper limit of normal (ULN); creatinine $\leq$ 1.5 times ULN and aspartate aminotransferase and alanine aminotransferase $\leq$ 1.5 times ULN. Patients with congestive heart failure or left ventricular ejection fraction $\leq$60% were excluded. 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; brain metastasis; peripheral neuropathy; history of edema with severe drug allergy; or previous long-term corticosteroid therapy. Pregnant or lactating women were excluded. Mammography, ultrasonography, magnetic resonance imaging or computed tomography was used to assess the presence of tumors. Baseline evaluations included complete blood cell and platelet count, routine blood chemistry and liver function tests, chest X-ray, bone scan, electrocardiogram and echocardiogram.

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

Treatment

Four cycles of docetaxel (75 mg/m^2) administered intravenously (i.v.) every 21 days were followed by four cycles of FEC (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2) administered i.v. on Day 1 every 21 days before surgery. Premedication was administered based upon each physician's decision to prevent edema, nausea and allergic reactions (e.g. dexamethasone 12 mg i.v. and/or granisetron 4 mg i.v. on Day 1, and oral dexamethasone 8 mg on Days 2 and 3 of docetaxel treatment; dexamethasone 24 mg i.v. on Day 1 and oral dexamethasone 8 mg on Days 2–6 with the FEC regimen). Administration of granulocyte colony-stimulating factor and antibiotics was left to the judgment of each investigator.

Clinical Response Assessment

Tumor assessments were performed within 4 weeks before docetaxel treatment, after completion of docetaxel treatment

and before surgery. Tumor response was assessed using the modified Response Evaluation Criteria in Solid Tumors guidelines (in which confirmatory scans/assessments were not required due to the timing of surgery), for patients who had measurable lesions.

Central Pathologic Assessment

Hematoxylin and eosin-stained slides were prepared from core needle biopsy and surgical specimens from the primary tumor. All surgical specimens were cut in 5 mm interval and all surfaces were microscopically examined in each institution. Pathological response of chemotherapy was assessed by a central review committee consisting of three pathologists who used criteria established by the Japanese Breast Cancer Society. pCR was defined as necrosis and/or disappearance of all tumor cells, and/or the replacement of cancer cells by granulation and/or fibrosis. If only ductal components remained, the pathological response was described as a pCR. Near pCR was defined as extremely high grade marked changes approaching a complete response, with only a few remaining isolated cancer cells (19). Quasi-pCR (QpCR) was the total of both pCR and near pCR. The central review committee evaluated the pathological responses independently from local pathologists. This committee was blinded to the local pathologists' reports. Patients who did not have surgery because of disease progression were considered not to have a pCR.

Hormone Receptor and Human Epidermal Growth Factor 2 Overexpression

Estrogen receptor (ER) and progesterone receptor (PgR) status was determined by immunohistochemistry (IHC) before docetaxel treatment at each participating institute.In general, tumors with more than 10% positively stained tumor cells were classified as positive for ER and PgR. The human epidermal growth factor 2 (HER2) status of the tumor was also determined at each institute by IHC or by fluorescence *in situ* hybridization (FISH) analysis. HER2-positive tumors were defined as those scoring 3+ with IHC staining or testing positive by FISH. HER2-negative tumors were defined as those scoring 0–1+ with IHC or scoring 2+ with IHC and testing negative by FISH.

Surgery and Radiotherapy

Following chemotherapy and clinical assessment of response, patients underwent surgery. If the tumor was too large or invasive for BCS, a modified radical mastectomy was recommended. Careful pathological assessment of tumor margins was performed in accordance with the Japanese Breast Cancer Society criteria (20). Sentinel lymph node biopsy was performed to confirm disease stage or to avoid surgical axillary dissection. Autologous or heterologous reconstructive surgery was performed depending on the patient's requirements and health status. All patients who underwent BCS were given standard radiotherapy to the remaining ipsilateral breast tissue after surgical recovery. For patients diagnosed as sentinel node negative and thus not requiring axillary dissection; radiotherapy to the axilla was allowed.

Toxicity and Dose Modification

Toxicities were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3) throughout treatment with docetaxel and FEC before surgery. Treatment could be postponed for a maximum of 2 weeks only for severe toxicity. If the adverse event (AE) did not improve during this period, chemotherapy was discontinued and surgery was recommended. Dose reductions were permitted for docetaxel from 75 to 60 mg/m^2 and for epirubicin from 100 to 75 mg/m^2 in cases of febrile neutropenia or Grade 3/4 non-hematologic toxicities, except for nausea, vomiting and fatigue.

Statistical Methods

The primary endpoint was the pCR rate. Before the initiation of the current study, the pCR rate for non-taxane anthracycline regimens ranged from 12.8% (NSABP Protocol B-27) (18) to 15.4% (Aberdeen trial) (5). Previously, we had conducted JBCRG01 trial to evaluate the pCR rate defined for breast disease (19). Therefore, in order to detect improvement in the pCR rate in the same definition of our previous study, a sample of 119 patients was required according to binominal distribution, with a one-sided threshold pCR rate of 12%, an expected pCR rate of 22%, an α error of 5% and a β error of 10%. The target number of patients for recruitment was therefore 119, so assuming that 5% of patients would not be evaluable, we planned to enroll 130 patients. Secondary endpoints included safety, clinical RR, rate of BCS, DFS, overall survival and a subset analysis according to biomarkers. Pathological and clinical RRs were calculated with 95% confidence intervals (95% CIs), with each complete RR based on a binominal distribution. Pathological response was evaluated by hormone receptor status and HER2 status. A multiple logistic regression analysis was performed to examine which factors (menopausal status, tumor size, ER and PgR status, HER2 status and clinical response to docetaxel and FEC) were associated with pCR and QpCR.

RESULTS

Patients Characteristics and Treatment

Enrollment took place from October 2005 through October 2006. One hundred and thirty-seven patients were enrolled. Two patients did not receive study treatment because of early withdrawal of consent; therefore, 135 patients were evaluable for safety and clinical response. These evaluable

Table 1. Patients' characteristics

Characteristic	Value[a]
Number of evaluable[b] patients	135
Age (years)	
Median	46
Range	24–62
Performance status, *n* (%)	
0	133 (99)
1	2 (1)
Menopausal status, *n* (%)	
Premenopausal	94 (70)
Postmenopausal	41 (30)
Clinical tumor stage, *n* (%)	
T1	13 (10)
T2	98 (73)
T3	24 (18)
Clinical nodal stage, *n* (%)	
N0	62 (46)
N1	73 (54)
ER status, *n* (%)	
Positive	86 (64)
Negative	46 (34)
Unknown	3 (2)
PgR status, *n* (%)	
Positive	63 (47)
Negative	70 (52)
Unknown	2 (1)
HER2 status,[c] *n* (%)	
0	21 (16)
1+	63 (47)
2+	20 (15)
3+	31 (23)

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor.
[a]Percentages may not add up to 100% because of rounding.
[b]Number of patients evaluable for safety and clinical response.
[c]Evaluated by immunohistochemistry.

patients included two patients aged 60 and 62 years (included because their age was not considered to influence the evaluation). Two patients were lost to follow-up before surgery, thus 133 patients were evaluable for surgical response. A total of 132 patients were evaluable for pathological response; one patient was excluded owing to lack of confirmation of invasive carcinoma (following the pathologic central review) due to inadequate samples from core needle biopsy before study treatment.

The patient characteristics are summarized in Table 1. Thirty patients (22%) had triple-negative disease, defined as ER-negative, PgR-negative and HER2-negative primary breast cancer, including one patient who was lost to follow-up before surgery.

Overall, 98 patients (73%) completed the planned eight cycles of treatment without dose reductions or study discontinuation. A total of 115 (85%) and 106 (82%) patients completed all four planned treatment cycles of docetaxel and FEC, respectively; dose reductions were necessary in 9 (7%) and 17 (13%) patients, respectively. The majority of the dose reductions were attributable to toxicities, particularly febrile neutropenia during treatment with FEC (10 versus 2 patients during docetaxel treatment). Dose reductions due to neutropenia were required by three patients each during the docetaxel and FEC regimens. Eleven (8%) and six patients (5%), respectively, discontinued treatment during docetaxel and FEC therapy because of toxicities (five patients discontinued during both regimens) or disease progression (six patients during docetaxel and one patient during FEC). The mean dose intensities were 24.2 and 30.3 mg/m^2/week for docetaxel and epirubicin, respectively.

Toxicities

The incidence of treatment-related AEs is summarized in Table 2. Neutropenia was the most common Grade 3/4 treatment-related AE and was observed in 44% and 60% of patients during docetaxel and FEC therapy, respectively. Overall, 67% and 15% of patients experienced at least one episode of Grade 3/4 neutropenia or febrile neutropenia, respectively. For non-hematologic toxicities of any grade, rash, sensory neuropathy, edema, muscle pain and joint pain occurred more frequently during docetaxel treatment than with FEC. Conversely, the frequency of gastrointestinal symptoms, such as nausea, vomiting and anorexia, was higher with FEC than with docetaxel. The frequency of Grade 1/2 peripheral edema was similar during exposure to docetaxel (33%) and FEC (29%); no patient had Grade 3/4 edema. Grade 3/4 non-hematologic toxicities, including gastrointestinal disturbances, were infrequent during both docetaxel and FEC. No fatal AEs were reported.

Clinical Response to Treatment

The overall clinical RR was 79% (106/135; 95% CI, 71–85%), with a clinical complete RR of 21% (29/135), a partial RR of 57% (77/135) and a disease progression rate of 5% (7/135). The clinical RR following the initial docetaxel regimen was 64%. The clinical responses to treatment with docetaxel followed by FEC according to response to initial docetaxel are shown in Table 3. Eight of the 135 patients (6%) progressed during docetaxel administration; 2 of 135 patients (1%) had disease progression during FEC. Of the 30 patients with triple-negative disease, 7 patients were observed to have disease progression following docetaxel treatment. One of the 17 patients with ER-positive, PgR-negative and HER2-negative tumors had disease

Table 2. Treatment-related adverse events

Adverse event, *n* (%)	DOC ($n = 135$)		FEC ($n = 29$)		Overall ($n = 35$)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Non-hematologic toxicities						
Infection with neutropenia	6 (4)	2 (1)	3 (2)	2 (2)	9 (7)	4 (3)
Fever	15 (11)	0	13 (10)	1 (1)	22 (16)	1 (1)
Infection (other)	3 (2)	1 (1)	2 (2)	0	4 (3)	1 (1)
Fatigue	82 (61)	0	84 (65)	2 (2)	98 (73)	2 (1)
Nausea	52 (39)	1 (1)	102 (79)	3 (2)	108 (80)	4 (3)
Vomiting	19 (14)	1 (1)	51 (40)	3 (2)	61 (45)	4 (3)
Anorexia	53 (39)	1 (1)	86 (67)	2 (2)	91 (67)	2 (1)
Stomatitis	50 (37)	1 (1)	51 (40)	0	68 (50)	1 (1)
Diarrhea	39 (29)	1 (1)	20 (16)	0	46 (34)	1 (1)
Phlebitis	2 (1)	1 (1)	2 (2)	0	4 (3)	1 (1)
Alanine aminotransferase	36 (27)	0	50 (39)	2 (2)	57 (42)	2 (1)
Aspartate aminotransferase	19 (14)	0	34 (26)	1 (1)	40 (30)	1 (1)
Nail changes	2 (1)	0	33 (26)	1 (1)	33 (24)	1 (1)
Weight loss	5 (4)	0	6 (5)	1 (1)	8 (6)	1 (1)
Creatinine	4 (3)	1 (1)	6 (5)	0	7 (5)	1 (1)
Edema	44 (33)	0	37 (29)	0	55 (41)	0
Hematologic toxicities						
Neutropenia	60 (44)	59 (44)	91 (71)	77 (60)	100 (74)	91 (67)
Leukopenia	69 (51)	50 (37)	101 (78)	66 (51)	108 (80)	76 (56)
Thrombocytopenia	13 (10)	0	28 (22)	2 (2)	31 (23)	1 (1)
Anemia	66 (49)	0	99 (77)	1 (1)	106 (79)	1 (1)
Febrile neutropenia	9 (7)	9 (7)	15 (12)	15 (12)	20 (15)	20 (15)

DOC, docetaxel; FEC, 5-fluorouracil, epirubicin and cyclophosphamide.

Table 3. Clinical response to DOC followed by FEC according to response to initial DOC treatment ($n = 135$)

Clinical response,[a] *n* (%)	Total[b]	Responder	Non-responder
Response to DOC			
Responder	87 (64)	79 (58)	8 (6)
Non-responder	48 (36)	27 (20)	21 (16)

[a]Overall response was confirmed after completion of chemotherapy in comparison with before docetaxel treatment.
[b]Percent value of each column was calculated by dividing by the total number of the evaluable patients ($n = 135$).

progression; while of the 53 patients with ER-positive, PgR-positive, and HER2-negative tumors and of the 9 patients with ER-positive, PgR-positive, and HER2-positive tumors, no patient had disease progression during docetaxel treatment. Among those with triple-negative disease, the majority of patients with disease progression after initial docetaxel were premenopausal [6/7 patients (86%)] and had solid-tubular carcinoma which characterized by solid cluster of cancer cells with expansive growth forming sharp borders [4/7 patients (57%)], as assessed using the Japanese Breast Cancer Society histological classification of breast tumors (21) (Table 4). Excluding the differences outlined above, there were no differences between patient and tumor characteristics for those with progressive disease versus non-progressive disease.

Twenty-seven of 48 non-responders to docetaxel (56%) had a response to FEC treatment; however, 8 of 87 responders to docetaxel (9%) showed no improvement in response with FEC treatment. Following chemotherapy, BCS was performed for 105 of 133 assessable patients (79%).

Pathological Response and Predictive Factors to Treatment

The primary endpoint—pCR rate—was 23% (95% CI, 16–31%). A near pCR rate of 6% (95% CI, 3–12%) resulted

Table 4. Clinical and pathologic characteristics of triple-negative breast cancer[a] for patients with progressive disease versus patients without progressive disease, following initial docetaxel therapy

Characteristic	Without PD	PD
No. of evaluable patients	23	7
Age, years		
Median	43	46
Range	(30–62)	(29–53)
Menopausal status, *n* (%)		
Premenopausal	15 (65)	6 (86)
Postmenopausal	8 (35)	1 (14)
Tumor stage		
T1	2 (9)	0
T2	14 (61)	5 (71)
T3	7 (30)	2 (29)
Nodal stage, *n* (%)		
N0	13 (57)	3 (43)
N1	10 (43)	4 (57)
Tumor type, *n* (%)		
Solid-tubular carcinoma	6 (26)	4 (57)
Papillotubular carcinoma	5 (22)	3 (43)
Scirrhous carcinoma	3 (13)	0
Unspecified invasive carcinoma	9 (39)	0

PD, progressive disease.
[a]Triple-negative tumors were defined as ER-negative, PgR-negative and HER2-negative primary breast cancer.

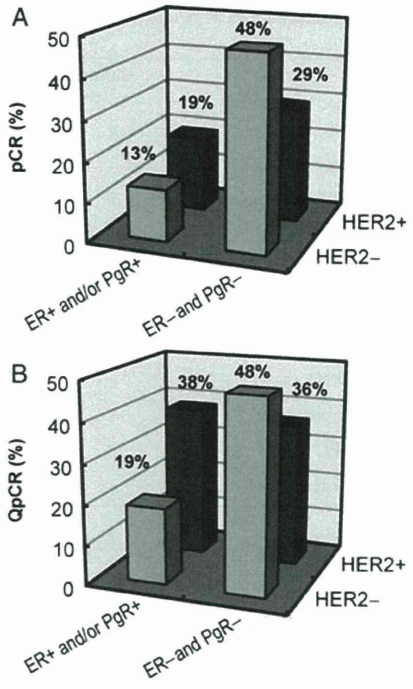

Figure 1. (A) Relationship between pCR versus HER2 and ER/PgR status following DOC and FEC ($n = 129$). (B) Relationship between QpCR versus HER2 and ER/PgR status following DOC and FEC ($n = 129$). Three patients were excluded from evaluable patients for pathologic response ($n = 132$) because of their unknown hormone receptor status. There were no near pCR case observed in triple-negative (ER−, PgR− and HER2−) diseases. DOC, docetaxel; ER, estrogen receptor; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; HER2, human epidermal growth factor receptor 2; pCR, pathologic complete response; PgR, progesterone receptor; QpCR, quasi-pathologic complete response.

in a QpCR rate of 29% (95% CI, 21–37%) when combined with the pCR. Pathological response of each subset population according to their hormone receptor and HER2 status is summarized in Fig. 1A and B. Patients with triple-negative disease had the highest pCR rate of 48% (95% CI, 29–68%). Near pCR was not observed in triple-negative disease. Patients with HER2-positive, ER-negative and PgR-negative tumors had a pCR rate of 29% (95% CI, 8–58%) and a QpCR rate of 36% (95% CI, 13–65%); patients with HER2-positive and ER-positive and/or PgR-positive tumors had a pCR rate of 19% (95% CI, 4–46%) and a QpCR rate of 38% (95% CI, 15–65%). Patients with HER2-negative and ER-positive and/or PgR-positive tumors had the lowest pCR and QpCR rates (13%; 95% CI, 6–23% and 19%; 95% CI, 10–30%, respectively). One of the seven patients who experienced clinical disease progression with initial docetaxel treatment had a QpCR following FEC.

The relationship between tumor pathological feature and pCR rate is shown in Table 5. The only variable found to be significantly associated with a pCR after docetaxel treatment was ER status.

Survival outcomes will be reported when the 5-year follow-up has been completed for this study.

DISCUSSION

This is the first report to evaluate the effectiveness of an initial docetaxel regimen for neoadjuvant therapy of Japanese patients with early-stage breast cancer. An additional component of the study was to analyze the data according to hormone receptor and HER2 status. Recently, Wildiers et al. (22) reviewed four adjuvant trials which had demonstrated the taxane-first regimens were favorable in terms of the relative drug dose intensity achieved. Also they mentioned larger non-randomized adjuvant studies for a series of 284 patients who first received three cycles of FEC followed by three cycles of docetaxel, the mean relative dose intensity was 91% for FEC and 76% for docetaxel, whereas in another series of 378 patients who received three cycles of docetaxel followed by four cycles of EC (epirubicin plus cyclophosphamide), a median docetaxel dose intensity of 100% was achieved. Therefore, they concluded such data suggest that the administration of a taxane first, followed by an anthracycline, may be preferable in line with the Norton–Simon hypothesis (23). In the JBCRG 01 study, the largest study to date to evaluate neoadjuvant chemotherapy in this patient population, the clinical and pathological responses

Table 5. Predictive variables for pCR before and following chemotherapy

Variables	Before treatment			After DOC			After FEC following DOC		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Menopausal status: pre (versus post)	1.5	0.94–2.40	0.0923	1.52	0.94–2.47	0.0867	1.42	0.87–2.31	0.1575
Tumor size: ≥3 cm (versus <3 cm)	1.51	0.94–2.41	0.0881	1.45	0.90–2.34	0.1266	1.56	0.96–2.52	0.0724
ER: negative (versus positive)	0.58	0.32–1.03	0.0650	0.51	0.28–0.95	0.0331	0.58	0.32–1.05	0.0709
PgR: negative (versus positive)	0.66	0.34–1.28	0.2211	0.72	0.37–0.95	0.3408	0.65	0.33–1.27	0.2083
HER2: 3+ (versus <3+)	1.32	0.76–2.28	0.3251	1.41	0.80–2.47	0.2360	1.39	0.80–2.41	0.2445
Clinical response to DOC									
Response (versus no response)	—	—	—	0.64	0.38–1.07	0.0875	—	—	—
Clinical response to FEC following DOC									
Response (versus no response)	—	—	—	—	—	—	0.58	0.29–1.14	0.1160

CI, confidence interval; OR, odds ratio; pCR, pathologic complete response.

and safety of FEC followed by docetaxel were investigated (19). The eligibility criteria, treatment dose and distribution of patient characteristics (menopausal status, tumor stage, hormone receptor status and HER2 status) studied in the JBCRG 01 trial were similar to those investigated in the present JBCRG 03 study (19). The incidences of Grade 3/4 neutropenia and febrile neutropenia observed in the current study were similar to those reported in the JBCRG 01 trial (19). However, the rate of Grade 1/2 edema during docetaxel treatment was lower in the present study (33%) than in the JBCRG 01 study (41%), suggesting that docetaxel might be better tolerated when given up front than when administered after completion of prior chemotherapy. Further studies are warranted to assess quality of life and the incidence of edema in order to confirm the effect of administering docetaxel as the initial therapy.

Many different neoadjuvant chemotherapy schedules and dose regimens are used in clinical practice. The NSABP Protocol B-18 trial, which compared AC treatment before and after surgery, reported no difference in DFS between the two approaches (17). However, the rate of BCS was greater with neoadjuvant AC chemotherapy, and the prognosis of patients who obtained a pCR was also better with this treatment regimen (17). Several other regimens have been evaluated in an effort to increase the pCR rate. The addition of a taxane to an anthracycline-containing regimen has been shown to improve the pCR and clinical RRs (5,18). Furthermore, excellent results have been reported by the MD Anderson Cancer Center using a regimen of paclitaxel plus trastuzumab followed by FEC plus trastuzumab in patients with operable breast cancer and HER2 overexpression (24). However, few studies have evaluated initial taxane therapy followed by an anthracycline-containing regimen in this indication (24). Thus, it was decided to evaluate such a reverse regimen and to analyze the findings according to molecular subtypes. Importantly, the primary endpoint—pCR rate—achieved in the present study was 23% (95% CI, 16–31%), far exceeding our estimate of 12% (19). Even though the pCR rate here cannot be directly compared with the results from the JBCRG 01 trial (pCR rate: 12%, QpCR rate: 25%), the pCR rate from this study is a favorable result considering the similar patient characteristics in both trials (19).

The overall clinical RR of 79% was similar to that reported in the JBCRG 01 trial (74%) (19). Furthermore, the clinical RR following the initial docetaxel regimen was 64%, similar to the clinical response following the initial FEC regimen in the JBCRG 01 trial (61%) (19). The clinical RR following the initial docetaxel regimen, however, is lower in this study than those reported in other studies (71.7–85%) (25,26). It could be hypothesized that the clinical response might be influenced by the lower dose of docetaxel used in this study (75 mg/m^2) compared with the 100 mg/m^2 dose used in previous studies (25,26).

The rate of BCS observed in our study (79%) was similar to that reported in the JBCRG 01 trial (85%) (19). Unfortunately, the overall disease progression rate (5%) was not lowered by the use of docetaxel followed by FEC in this study, and was similar to that seen in the JBCRG 01 trial (6%) (19).

Although 7 of the 29 patients with triple-negative disease had disease progression during the initial docetaxel regimen, 14 of the 22 patients without disease progression (64%) achieved a QpCR. This QpCR rate is markedly higher compared with previous findings (27).

Our results indicate that if patients with triple-negative disease who experienced disease progression following initial docetaxel therapy were excluded, the pCR rate for this group of patients would have been higher. We thus compared the clinical and pathological characteristics between patients with triple-negative disease who experienced disease progression following the initial docetaxel regimen with those who did not have disease progression. However, no

significant differences in patient or tumor characteristics were seen between these patient groups. It was noted, however, that six of seven premenopausal patients (86%) and four of seven patients (57%) with solid-tubular carcinoma had disease progression following docetaxel therapy. Given the high incidence of disease progression among patients with triple-negative disease who had solid-tubular subtype tumors, this phenotype could be used in future studies to predict which patients are more likely to experience progressive disease following docetaxel therapy. Accordingly, the identification of patients with hormone receptor-positive and HER2-negative disease would also enable the selection of patients who are more likely to benefit from neoadjuvant chemotherapy. Thus, studying patients' molecular subtypes, and selecting appropriate chemotherapy regimens accordingly, has the potential to provide superior results to those of the JBCRG 03 trial.

Recently, it has been shown that basal-like breast cancer defined by five biomarkers [epidermal growth factor receptor (EGFR), cytokeratin 5/6 (CK5/6), ER, PgR and HER2 status] provides a more specific definition of basal-like breast cancer that predicts survival better than the triple-negative phenotype (27,28). In patients treated with anthracycline-based chemotherapy, tumors found to be positive for the basal markers corresponded to a cohort of patients with a significantly worse outcome (29). Thus in future trials, it may be beneficial to assess EGFR and CK5/6 status in patients with triple-negative disease to help predict patient survival.

Interestingly, the pCR rate (27%) following neoadjuvant chemotherapy in patients with HER2-negative breast cancer was higher in this study than in the JBCRG 01 study (14%), suggesting that this subpopulation may benefit from initial docetaxel treatment. Conversely, a lower QpCR rate was observed in HER2-positive patients (37%) in this study than in the JBCRG 01 trial (52.8%). This suggests that initial anthracyclines may be required for HER2-positive disease. A study by Buzdar et al. (24) reported that a high pCR rate of 60% was observed in patients with HER2-positive disease treated with the combination of paclitaxel plus trastuzumab followed by FEC plus trastuzumab, indicating that the HER2-positive population in the current study may have benefited further from concomitant trastuzumab therapy. These findings demonstrate the benefit of selecting the most effective chemotherapy regimen according to each patient's molecular subtype and initial response to neoadjuvant treatment.

One limitation of the study was that HER2-positive patients were not treated with trastuzumab, which has been shown to improve outcomes in patients with HER2-overexpressing breast cancer (24). Further studies investigating optimal treatment regimens for different molecular subtypes should include concurrent trastuzumab for patients with the HER2-positive phenotype.

In conclusion, docetaxel followed by FEC as neoadjuvant chemotherapy is a tolerable and effective regimen for patients with early-stage breast cancer. In addition, a high pCR rate made this regimen particularly promising in patients with triple-negative breast cancer. In the future, selection of a neoadjuvant chemotherapy regimen for operable breast cancer may be possible based on molecular subtype.

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Conflict of interest statement

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Randomized Phase II Study of Primary Systemic Chemotherapy and Trastuzumab for Operable HER2 Positive Breast Cancer

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Abstract

Primary systemic therapy for patients with HER2$^+$(human epidermal growth factor receptor 2 positive) breast cancer may be improved by adding trastuzumab to chemotherapy. This randomized phase II trial compared 2 chemotherapy regimens comprising FEC (5-fluorouracil/epirubicin/cyclophosphamide), trastuzumab and either PH (paclitaxel) or DH (docetaxel) in 102 patients. FEC-PH and FEC-DH achieved high pathologic complete response rates. Breast conserving surgery was possible in more patients in the paclitaxel arm.

Background: In primary systemic therapy in patients with human epidermal growth factor receptor 2 positive (HER2$^+$) breast cancer, improvements in pathologic complete response (pCR) rate have been achieved by administering trastuzumab. **Patients and Methods:** Patients with stage II or IIIA HER2$^+$ operable breast cancer were randomly assigned to receive four 3-weekly cycles of FEC (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2) followed by 4 cycles of 3-weekly trastuzumab (8 mg/kg week 1 and then 6 mg/kg) with either 12 weekly doses of paclitaxel 80 mg/m^2 (FEC-PH) or 4 cycles of 3-weekly docetaxel 75 mg/m^2 (FEC-DH). **Results:** Between March 2007 and June 2008, 102 patients were enrolled. Forty-nine patients receiving FEC-PH and 47 receiving FEC-DH were assessable for efficacy and safety. Eighty-four patients completed treatment and underwent surgery. There was no significant difference in the pCR rate between the 2 groups (46.9% [95% CI, 33.7%-60.6%] with FEC-PH vs. 42.6% [95% CI, 29.5%-56.8%] with FEC-DH; $P = .67$). Analysis by hormone receptor (HR) status showed pCR rates of 54.2% (32/59) in HR$^-$ tumors and 29.7% (11/37) in HR$^+$ tumors ($P = .02$). Among HR$^-$ tumors, the pCR rates were 65.4% and 45.5% in patients treated with FEC-PH and FEC-DH, respectively ($P = .13$). **Conclusions:** There was no significant difference in pCR rate between FEC-PH and FEC-DH. Both regimens achieved higher pCR rates in HR$^-$ than HR$^+$ breast cancer, and there was a trend toward higher pCR in HR$^-$ tumors with FEC-PH compared with FEC-DH. Further investigation is warranted to explore the relationship between efficacy and HR status.

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Introduction

Primary systemic therapy (PST) is regarded as one of the standard therapies for locally advanced breast cancer and selected patients with operable disease to facilitate breast conservation.[1–4] Patients achieving pathologic complete response (pCR) in the primary lesion and with no residual tumor in axillary nodes after PST have longer recurrence-free survival than those without pCR.[4–6] Consequently, pCR is commonly used as a surrogate for long-term outcome when evaluating novel chemotherapy regimens. Currently, sequential regimens, including an anthracycline followed by either weekly paclitaxel or 3-weekly docetaxel are commonly used to achieve high pCR rates.[3,7]

Trastuzumab plays an important role in therapy for human epidermal growth factor receptor 2 (HER2) positive ($HER2^+$) breast cancer, and its efficacy has been proven in both the adjuvant[8-10] and the metastatic[11,12] settings. In the neoadjuvant setting, improvements in the pCR rate have been achieved by administering trastuzumab with PST in patients with $HER2^+$ breast cancer. In a randomized trial that compared chemotherapy with or without trastuzumab, the trastuzumab-containing regimen improved the pCR rate (65.2% vs. 26.3%; $P = .002$).[13] A second randomized trial, the neoadjuvant herceptin (NOAH), showed a higher pCR rate with the combination of chemotherapy and trastuzumab than chemotherapy alone (39% vs. 20%; $P = .002$).[14] In addition, single-arm trials that evaluated the combination of chemotherapy and trastuzumab as PST showed high pCR rates.[15–20] Recently, it was reported that patients who achieve pCR have longer survival compared with those who do not achieve pCR, even in a $HER2^+$ population.[21,22] It is possible, therefore, that pCR could be considered to be a surrogate marker for the efficacy of PST, even in patients with $HER2^+$ breast cancer, although definitive evidence is required to confirm this proposition. Based on these data, we conducted a randomized phase II trial to compare pCR rates achieved with FEC (5-fluorouracil/epirubicin/cyclophosphamide) followed by weekly paclitaxel plus trastuzumab and FEC followed by 3-weekly docetaxel plus trastuzumab as PST for $HER2^+$ breast cancer.

Patients and Methods

Patient Eligibility

Eligible patients had previously untreated, unilateral, histologically confirmed, invasive, noninflammatory breast carcinoma. Histologic confirmation of invasive cancer was performed by core needle biopsy (CNB). $HER2^+$ was defined as a score of 3+ by immunohistochemistry or a HER2 gene copy-chromosome 17 ratio of ≥2.0 by fluorescence in situ hybridization. Patients with a tumor ≥2 cm at the largest dimension by ultrasonography or <2 cm with axillary lymph node metastasis clinically diagnosed as positive were eligible (clinical stage II and IIIA). Patients with axillary nodes enlarged by >1 cm at the largest dimension according to ultrasonography were considered node positive without the need for confirmatory biopsy. Patients with T4N3 (supraclavicular lymph node), or distant metastatic disease (M1) were excluded from the study.

Other requirements were age between 18 and 65 years, ECOG (Eastern Cooperative Oncology Group) performance status 0 to 2, adequate bone marrow function (absolute granulocyte count ≥1500/mm^3 and platelet count ≥100,000/mm^3), liver function (total bilirubin level ≤1.5 mg/dL and liver transaminase levels [aspartate aminotransferase and alanine aminotransferase] ≤60 IU/L), and renal function (serum creatinine level ≤1.5 mg/dL). Patients with a history of ischemic cardiac disease and cardiomyopathy or a left ventricular ejection fraction (LVEF) <60% according to echocardiogram were excluded. Patients with clinically negative axillary lymph nodes had the option of undergoing pretreatment sentinel lymph node biopsy (SLNB). The study was approved by institutional review boards and was conducted in accordance with the Declaration of Helsinki. All the patients provided written informed consent.

Study Design and Preoperative Systemic Therapy

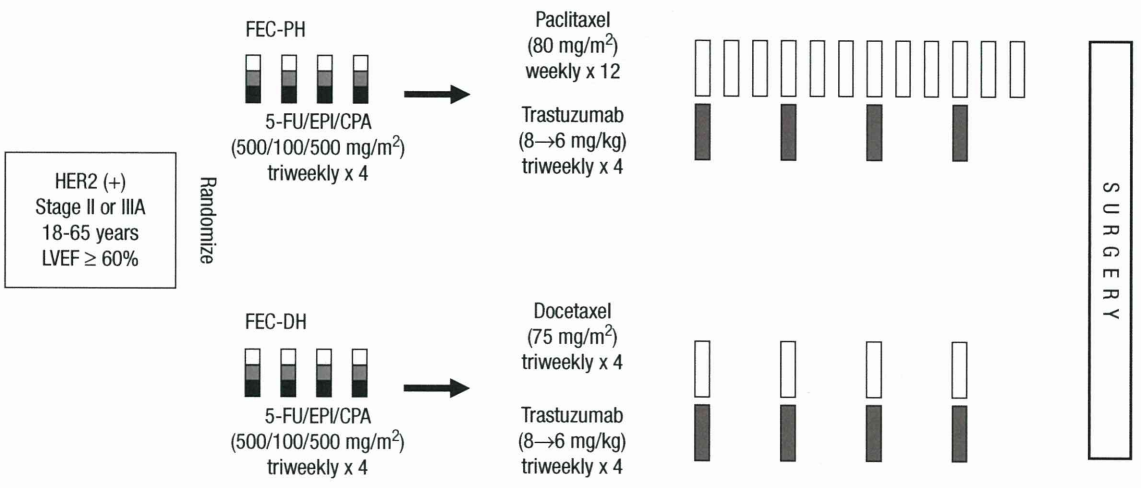
Patients were randomly assigned to receive either FEC followed by the combination of paclitaxel and trastuzumab (FEC-PH) or FEC followed by the combination of docetaxel and trastuzumab (FEC-DH). The dose and schedule of FEC and docetaxel were selected based on efficacy and safety data from our previously reported study of PST.[23,24] FEC consisted of 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 administered by intravenous (I.V.) infusion on day 1 every 3 weeks for 4 cycles (Figure 1). Paclitaxel was administered at 80 mg/m^2 I.V. over 1 hour on days 1, 8, and 15 every 3 weeks for 4 cycles. Docetaxel was administered at 75 mg/m^2 I.V. over 1 hour on day 1 every 3 weeks for 4 cycles. In both arms, trastuzumab was administered at a dose of 8 mg/kg I.V. over 90 minutes on day 1 of the first cycle and subsequent doses were administered at a dose of 6 mg/kg over 30 minutes every 3 weeks for a total of 4 cycles.

If a patient developed grade ≥3 febrile neutropenia, thrombocytopenia <25,000/mm^3, or grade ≥3 nonhematologic toxicity, then the doses of epirubicin and docetaxel were reduced by 25% and 20%, respectively, in subsequent cycles. The dose of paclitaxel was reduced by 25% in subsequent cycles if a patient developed grade 3 neurotoxicity. Before administration of the following cycle of FEC or docetaxel, the patients were required to have a granulocyte count ≥1500/mm^3, platelet count ≥75,000/mm^3, and no nonhematologic toxicity of grade >2 (excluding alopecia). Before administration of the next cycle of paclitaxel, the patients were required to have a granulocyte count ≥1000/mm^3, platelet count ≥75,000/mm^3, and no nonhematologic toxicity of grade >2 (excluding alopecia). If toxicity did not improve within 2 weeks, then chemotherapy and trastuzumab were discontinued and surgery was recommended.

Therapy After Preoperative Chemotherapy

Patients who were considered candidates for breast-conserving therapy (BCT) were offered lumpectomy. Patients who refused or were considered inappropriate for BCT received total mastectomy. Axillary lymph node dissection (AxLND) was mandatory, except in the patients diagnosed with nonmetastatic disease by SLNB before PST. Surgery was performed within 8 weeks after completion of preoperative chemotherapy. All the patients who underwent BCT received whole-breast irradiation. After completion of preoperative chemotherapy and surgery, the patients with hormone receptor (HR) positive (HR^+) disease received adjuvant endocrine therapy. After completion of local therapy, adjuvant trastuzumab was administered every 3 weeks for up to 1 year. The patients with HR^+ breast cancer received adjuvant trastuzumab in combination with endocrine therapy.

Figure 1 Study Regimen



Study Evaluation and Criteria

The HER2 status of a CNB was determined by immunohistochemistry and/or fluorescence in situ hybridization performed in each institution (no central review) before study enrollment. After completion of PST, resected specimens and CNB specimens were evaluated centrally by 3 breast pathologists (H.T., F.A. and M.K.). The pCR was defined as the absence of viable invasive tumor in both the breast and the axillary nodes. Patients with residual ductal carcinoma in situ (DCIS) in breast tissue and no viable invasive tumor in the axillary nodes also were classified as having pCR. Clinical response was evaluated by palpation after each cycle by using the response evaluation criteria in solid tumors.[25]

All adverse events were evaluated according to the CTCAE (Common Terminology Criteria for Adverse Events) v3.0.[26] Infusion reactions were defined by the occurrence of the following symptoms during infusion or within 24 hours after starting trastuzumab: pyrexia, chills, nausea, vomiting, pain, headache, cough, dyspnea, dizziness, rash, pruritus, general malaise, skin eruption, and decrease in blood pressure.

Endpoints and Statistical Analysis

The primary endpoint was the pCR rate. The secondary endpoints were disease-free survival, clinical response rate, breast conservation rate, and safety. In this report, disease-free survival is not reported because of the short follow-up. Analyses of efficacy and safety were performed in the intent-to-treat (ITT) population. The ITT population comprised subjects fulfilling the study inclusion criteria who had received at least one dose of study chemotherapy. The per-protocol population comprised ITT subjects who had undergone surgery in this study without serious violations of the inclusion criteria. As sensitivity analysis, the pCR rates among the per-protocol population were calculated. By assuming a difference in the pCR rate between the 2 groups of 10% and an expected baseline pCR rate of 30%, a sample size of 49 patients in each treatment group was necessary to demonstrate a higher pCR rate with a probability of 85%. The target number of patients was considered to be 100 patients to allow for patient dropout. The pCR was compared between 2 groups by using the χ^2 test. P values $<.05$ were considered statistically significant.

Results

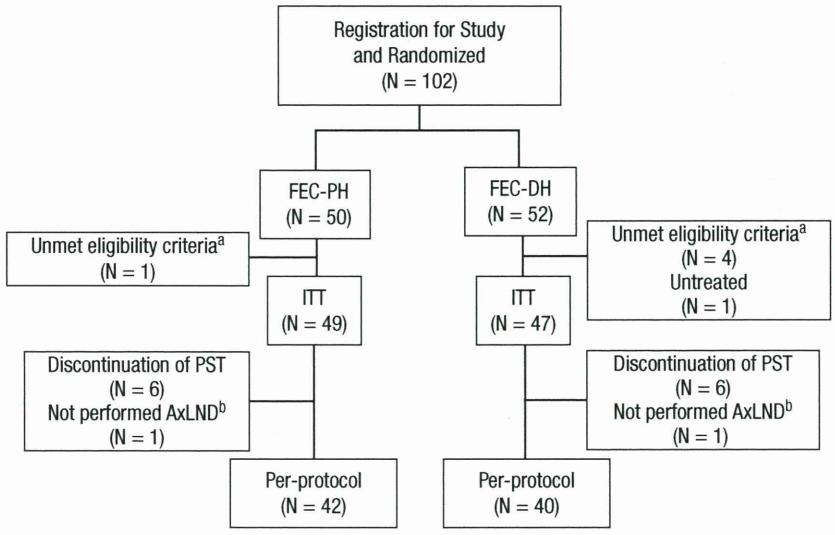
Patient Characteristics

Between March 2007 and June 2008, 102 patients were enrolled in this study. Of these, 49 patients receiving FEC-PH and 47 receiving FEC-DH were evaluable in the ITT population. According to central review, 4 patients were considered ineligible (2 patients not $HER2^+$, 1 not evaluable for HER2 status, 1 with noninvasive carcinoma in the CNB specimen). One patient had an aneurysm of the thoracic aorta immediately after the first cycle of FEC, discontinued FEC, and, therefore, was considered ineligible. One patient did not receive PST because of persistent hypertension (Figure 2).

The characteristics of the ITT population are shown in Table 1. Distribution of tumor size was similar in the 2 treatment groups. The proportion of patients with clinically diagnosed axillary node-positive tumors was higher in the FEC-DH arm. Approximately two-thirds of patients had HR^- tumors, with a slightly higher representation in the FEC-DH than in the FEC-PH arm.

One patient in the FEC-DH arm was considered not evaluable for pathologic response by central review because she had not undergone AxLND or SNLB before PST and had DCIS in the breast after surgery. Eighty-four patients received surgery after completion of PST. The HR and HER2 status of the breast tumors were not reassessed after surgery. Twelve of 72 patients who received AxLND had lymph-node metastases. Two patients did not undergo either AxLND or SLNB before PST. Therefore, 82

Figure 2 Consort Diagram



[a]Three Cases Were Human Epidermal Growth Factor Receptor 2 Negative ($HER2^-$) by Central Review. [b]Axillary Node Dissection.

patients (42 in the FEC-PH arm and 40 in the FEC-DH arm) were evaluated in the per-protocol population (Figure 2).

Treatment Exposure

Ninety-one (94.8%) of 96 patients completed 4 cycles of FEC. Four patients discontinued FEC due to adverse events, and one patient discontinued due to disease progression after 2 cycles of FEC. Among patients who completed 4 cycles of FEC, 3 discontinued PH (grade 3 neurotoxicity in 2 patients; suicide in 1 patient) and 4 discontinued DH (adverse events in 2 patients; disease progression after 1 cycle in 1 patient; refusal in one patient). Thus, 43 of 49 patients (87.8%) in the FEC-PH arm and 41 (87.2%) of 47 patients in the FEC-DH arm completed PST.

Efficacy

In the ITT population, 23 (46.9%) of 49 patients receiving FEC-PH and 21 (44.7%) of 47 patients receiving FEC-DH achieved a pCR according to central pathologic review. The difference between FEC-PH and FEC-DH is 2.3% (95% confidence interval [CI], −17.7% to 22.2%; $P = .82$). The pCR rates were 54.8% with FEC-PH and 50.0% with FEC-DH in the per-protocol population. The difference is 4.8% (95% CI, −16.8% to 26.4%; $P = .67$). The difference between the 2 arms were <10%. The pCR rate included 24 patients with DCIS in the breast (10 in the FEC-PH arm and 14 in the FEC-DH arm). No patients with pCR in the breast had persistent nodal carcinoma. The pCR rates according to institutional review were 44.9% (22/49) in the FEC-PH arm and 36.2% (17/47) in the FEC-DH arm; 4 patients who were diagnosed with residual invasive carcinoma in the breast by institutional review were assessed as pCR with DCIS by central review.

Subpopulation analysis according to HR status showed pCR rates of 54.2% (32/59) in HR^- tumors and 29.7% (11/37) in HR^+ tumors ($P = .02$). The pCR rates in patients with HR^+ tumors were 26.1% with FEC-PH and 35.7% with FEC-DH ($P = .54$) (Figure 3). In patients with HR^- tumors, the pCR rates for FEC-PH and FEC-DH were 65.4% and 45.5%, respectively ($P = .13$) (Figure 3). The clinical response rates by palpation were 79.6% in the FEC-PH arm and 76.6% in the FEC-DH arm, respectively (Table 2). Eighty-four patients received surgery. Seventy-two of these 84 patients received adjuvant trastuzumab. BCT was possible in 35 patients (71.4%) in the FEC-PH arm and 27 (57.4%) in the FEC-DH arm.

Safety

Grade 3/4 neutropenia was observed in 28.1% of 96 patients who received FEC, and 11 patients (11.5%) developed febrile neutropenia (Table 3). Adverse events that lead to hospitalization were reported in a total of 8 patients during FEC; 3 of these discontinued FEC. During the taxane phase, peripheral neurotoxicity was more common with PH than DH, whereas grade 3/4 neutropenia, febrile neutropenia, peripheral edema, and grade 1/2 mucositis and/or stomatitis were more common with DH than with PH. One patient developed grade 3 peripheral edema after 2 cycles of DH and stopped chemotherapy.

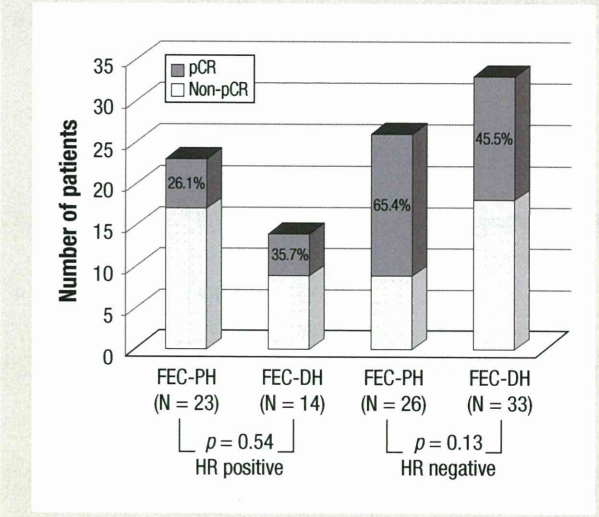
Cardiac events were observed in 4 patients. Two patients who received PH and 1 patient who received DH experienced grade 1 supraventricular arrhythmia. One patient developed grade 3 left ventricular systolic dysfunction with shortness of breath on exertion immediately after completion of 4 cycles of PH, accompanied by a decrease in LVEF to 39%. She had no history of cardiovascular disease but had received diuretic and beta-blocker

Table 1 Patient Characteristics

	FEC-PH (n = 49)	FEC-DH (n = 47)
Median Age (Range), y	51 (34-65)	53 (28-63)
Clinical Stage, No. (%) Patients		
IIA[a]	21 (42.9)	16 (34.0)
IIB	19 (38.8)	22 (46.8)
IIIA	9 (18.4)	9 (19.1)
Tumor, No. (%) Patients		
T1	1 (2.0)	1 (2.1)
T2	38 (77.6)	34 (72.3)
T3	10 (20.4)	12 (25.6)
Axillary Lymph Node-Positive Determination, No. (%) Patients		
Ultrasonography	27 (55.1)	33 (70.2)
SLNB	5 (10.2)	2 (4.3)
HER2 Status, No. (%) Patients		
IHC 3+	43 (87.8)	43 (91.5)
IHC 2+/FISH +	6 (12.2)	4 (8.5)
Hormone Receptor Status No. (%) Patients		
ER+/PgR+	12 (24.5)	4 (8.5)
ER+/PgR−	1 (20.4)	10 (21.3)
ER−/PgR+	1 (2.0)	0 (0)
ER−/PgR−	26 (53.1)	33 (70.2)

Abbreviations: DH = docetaxel; ER = estrogen receptor; FEC = 5-fluorouracil/epirubicin/cyclophosphamide; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; PgR = progesterone receptor; PH = paclitaxel; SLNB =sentinel lymph node biopsy.
[a] Including patients with tumor 2 cm in greatest dimension (T1c) and N0.

Figure 3 Pathologic Results According to Hormone Receptor (HR) Status. The Left Side Shows Pathologic Complete Response (pCR) in Patients With HR+ Disease and the Right Side Shows pCR in Those With HR− Disease



therapy for left ventricular systolic dysfunction. After 2 months, her symptoms had resolved with treatment, and she underwent BCT. Her LVEF had recovered to 58% one year after completion of PST. Four patients with adverse events were hospitalized during the trastuzumab plus taxane phase (1 patient received PH and 3 received DH). All remaining 84 patients who completed PST underwent surgery.

Twenty-nine (31.9%) of 91 patients who received trastuzumab plus taxane experienced infusion reactions during the first cycle of trastuzumab (14 patients with PH and 15 with DH). Among patients with infusion reactions, rigors and/or chills, fever, and pain were commonly observed; all events were grade 1 or 2. Eight (27.6%; 8.8% of all patients receiving trastuzumab plus taxane) of 29 patients who experienced infusion reactions during the first cycle of trastuzumab experienced a further infusion reaction during a later cycle.

Discussion

This study showed high pCR rates (46.9% with FEC-PH and 42.6% with FEC-DH) and that 62 (73.8%) of 84 patients undergoing surgery were able to receive BCT. The results of this study are consistent with the high pCR rates reported in previous trials that evaluated the combination of chemotherapy and trastuzumab as PST.[13–20,27] However, there was no significant difference in pCR rates between the 2 treatment groups. There was a trend to a higher rate of BCT with FEC-PH compared with FEC-DH, but the difference was not statistically significant. The small sample size may explain the lack of significant difference between the regimens.

The pCR rates were significantly higher in HR− tumors than in HR+ tumors with both treatments. This result is consistent with findings from several other studies of trastuzumab combined with anthracycline- and nonanthracyline-based regimens, including NOAH (concurrent anthracycline/taxane)[14] NeoSphere (docetaxel),[28] and NeoALTTO (paclitaxel).[29] Analysis of the data from these studies suggests that patients with HER2+ and HR− disease will obtain greatest benefit from a trastuzumab-containing chemotherapeutic regimen. Although other findings, reported by Peintinger et al[30] and Buzdar et al[13] contrast with results from NOAH, NeoSphere, NeoALTTO and the present study, the larger studies have demonstrated higher pCR rates in HR− than HR+ breast cancer after trastuzumab-based regimens. Moreover, after the initial conclusions from Buzdar[13] and Peintinger,[30] additional data from the M.D. Anderson group demonstrated a statistically higher pCR rate in HR− than HR+ breast cancer (61.1% vs. 38.9%, respectively). Recently, von Minckwitz et al[31] presented data from a meta-analysis of 7 trials (n = 6377) of neoadjuvant therapy, including anthracyclines and taxanes with or without trastuzumab, that showed that pCR is a surrogate for survival in patients with HER2+ HR− breast cancer but not in those with HR+ disease. It is also relevant to note that, in large trials of adjuvant therapy, prognosis is not different between HR− and HR− tumors.[8–10] Therefore, longer follow-up is required in the setting of PST before definitive conclusions can be made about the importance of HR status and therapeutic outcomes. Further clinical and translational

Table 2 Clinical and Pathologic Response Rates

	FEC-PH (n = 49)		FEC-DH (n = 47)	
	No. Patients	%	No. Patients	%
Completion of PST	43	87.8	41	87.2
Clinical Response by Palpation[a]	39	79.6	36	76.6
CR	30	–	28	–
PR	9	–	8	–
SD	0	–	2	–
PD	1	–	1	–
Breast Surgery	43	87.8	41	87.2
Mastectomy	8	–	14	–
BCT	35	71.4	27	57.4
AxLND	36	–	36	–
Lymph Nodes (Pathologic)				
Negative	32	–	28	–
Positive	4	–	8	–
SLNB Without AxLND[b]	6	–	4	–
Pathologic CR[c] ITT	23	46.9	20	42.6
Per protocol	23/43	53.5	20/40	50.0
DCIS in Breast	10	–	14	–

Abbreviations: AxLND = axillary lymph node dissection; BCT = breast conserving therapy; CR = complete response; DCIS = ductal carcinoma in situ; DH = docetaxel; FEC = 5-fluorouracil/epirubicin/cyclophosphamide; PD = progressive disease; PH = paclitaxel; PR = partial response; PST = preoperative systemic therapy; SD = stable disease; SLNB = sentinel lymph node biopsy.

[a] Including 7 patients not evaluable for response (4 in the FEC-PH group and 3 in the FEC-DH group).

[b] SLNB was performed before PST.

[c] Including one patient not evaluable for pathologic response in the FEC-DH group.

research on the interaction between HR status, HER2 status, and pCR is warranted.

In the NOAH trial, the addition of trastuzumab to preoperative chemotherapy and postoperative trastuzumab for 52 weeks improved disease-free survival relative to chemotherapy alone (71% vs. 56% at 3 years; $P = .006$).[14] It remains to be determined whether the addition of postoperative trastuzumab will further improve disease-free and overall survival in patients who have achieved a pCR with sequential anthracycline and taxane plus trastuzumab. However, longer survival has been demonstrated in patients achieving pCR compared with those not achieving pCR, even in the $HER2^+$ subgroup,[21,22] although it may be different in patients with HR^- and HR^+ breast cancer, and needs to be viewed cautiously.

In studies with trastuzumab and nonanthracycline-containing regimens (eg, combination of taxane and platinum), pCR rates have ranged from 17% to 76%.[16–20] Studies of preoperative concurrent anthracycline and taxane with trastuzumab (for 12-24 weeks) have shown pCR rates of 38%-66%.[13–15] Results of these studies suggest that concurrent anthracycline and trastuzumab has a considerable antitumor effect, although, cardiotoxicity remains a concern with this regimen. A review of the medical literature provides reassurance that the cardiac toxicity of concurrent trastuzumab and anthracycline is acceptable and manageable.[13–15] The dose of anthracycline is an important factor in cardiac safety. In the current study, the dose of anthracycline (epirubicin 100 mg/m^2 for 4 cycles was higher than in previous studies that used doxorubicin (60 mg/m^2 for 3 cycles) or epirubicin (75 mg/m^2 for 4 cycles). Therefore, cardiotoxicity may be avoided by reducing the dose of anthracycline when used in combination with trastuzumab. Sequential administration of trastuzumab after anthracycline, as used in the present study, is also an appropriate approach to reduce the risk of cardiotoxicity. However, it might relate to an administration order of anthracycline and taxane, not concurrent administration of anthracycline and trastuzumab, because concurrent administration of anthracycline and trastuzumab has less cardiotoxicity in the report by Buzder et al.[13] Longer follow-up is required to further evaluate the cardiac safety profile of anthracyline-trastuzumab PST to determine a preferable method; dose reduction or sequential administration, including an administration order of anthracycline and taxane.

Twelve (12.5%) of 96 patients in our study did not complete PST. The major reasons for discontinuation of PST were chemotherapy-related adverse events. One patient in the FEC-PH group experienced grade 3 left ventricular systolic dysfunction. A limitation of this study was the evaluation of LVEF by echocardiogram only at study entry and completion of surgery if patients showed no symptoms of left ventricular failure. Experience of cardiotoxicity in this study suggests that LVEF by echocardiogram should be monitored at completion of FEC and again at completion of trastuzumab plus taxane therapy. Long-term follow-up of cardiotoxicity is required for patients in this study who received preoperative and adjuvant trastuzumab.

Because FEC-PH and FEC-DH demonstrated similar efficacy overall, differences in safety profile are important in determining the most appropriate PST regimen to offer to candidates for BCT. Paclitaxel was associated with an increased incidence of peripheral neuropathy, whereas use of docetaxel produced greater neutropenia, febrile neutropenia, peripheral edema, and mucositis. The choice of PST, therefore, should be individualized according to patient characteristics and preferences. Although analysis of data suggested a possible advantage for paclitaxel in terms of higher pCR in the subgroup of patients with HR^- disease and a higher rate of BCS, the differences were not statistically significant.

Conclusion

FEC, followed by concurrent trastuzumab with taxane (weekly paclitaxel or 3-weekly docetaxel), seems active and feasible as PST for $HER2^+$breast cancer. There was no significant difference in pCR rate between FEC-PH and FEC-DH, although there was a trend to a higher rate of pCR with the paclitaxel-containing regimen in patients with HR^- breast cancer. Whether this trend is clinically significant is not yet known. Long-term follow-up of patients in this study treated with preoperative and adjuvant trastuzumab will provide further information on cardiac safety and disease-free survival.

Randomized comparisons of PST regimens, comprising various permutations of anthracyclines, taxanes, and platinum administered with concurrent and/or sequential trastuzumab, together with long-term follow-up of cardiac safety and disease-free

Table 3 Adverse Events During Primary Systemic Therapy (NCI CTCAE version 3.0 grading)

Toxicity	FEC-PH (grade, %)				FEC-DH (grade, %)			
	FEC (n = 49)		PH (n = 46)		FEC (n = 47)		DH (n = 45)	
	All	3/4	All	3/4	All	3/4	All	3/4
Hematologic								
Neutropenia	46.9	28.6	39.1	2.2	36.2	27.7	15.6	8.9
Febrile neutropenia	12.2	12.2	0	0	10.6	10.6	6.7	6.7
Anemia	44.9	2.0	54.3	0	44.7	0	55.6	2.2
Thrombocytopenia	4.1	0	0	0	8.5	0	2.2	0
Nonhematologic								
Anorexia	46.9	2.0	8.7	0	40.4	0	17.8	0
Nausea/vomiting	87.8	2.0	21.7	0	91.5	0	24.4	0
Vomiting	44.9	4.1	15.2	0	65.9	6.4	15.6	0
Diarrhea	12.2	0	30.4	0	19.1	0	35.6	0
Mucositis and/or stomatitis	53.1	0	19.6	0	61.7	0	57.8	0
Taste alteration	38.8	–	41.3	–	44.7	–	53.3	–
Fatigue	49.0	0	50.0	0	68.1	2.1	64.4	0
Peripheral neurotoxicity	4.1	0	95.7	4.3	8.5	0	51.1	0
Arthralgia and/or myalgia	0	0	39.1	0	0	0	42.2	0
Peripheral edema	6.1	0	39.1	0	12.8	0	62.2	2.2
Infection	6.1	0	6.5	0	8.5	0	13.3	0
Elevated AST, ALT	38.8	2.0	47.8	0	25.5	0	31.1	0
Arrhythmia	0	0	4.3	0	2.1	0	2.2	0
Left ventricular dysfunction	0	0	2.2	2.2	0	0	0	0
Hyperglycemia	0	0	0	0	0	0	2.2	2.2
Nail changes	63.3	–	73.9	–	51.1	–	60.0	–
Skin rash	16.3	0	21.7	0	4.3	0	26.7	0
Infusion reaction	–	–	30.4	0	–	–	33.3	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; FEC = 5-fluorouracil/epirubicin/cyclophosphamide; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = progressive disease; PH = paclitaxel.

survival are required before definitive recommendations can be made for patients with HER2$^+$ breast cancer.

Clinical Practice Points

- PST is a standard management option for patients with operable breast cancer and can facilitate breast conservation.
- The addition of trastuzumab to primary systemic chemotherapy achieves a high rate of pCR in patients with HER2$^+$ breast cancer, but the optimal treatment regimen has not yet been defined.
- Concurrent use of trastuzumab and anthracycline-based therapy must be used with caution because of the potential risk for cardiac toxicity.
- Preoperative treatment regimens comprising FEC followed by either trastuzumab and paclitaxel or trastuzumab and docetaxel were similarly effective in patients with HER2$^+$ breast cancer and both achieved high rates of pCR.
- The pCR rates were higher in patients with HR$^-$ tumors than in those with HR$^+$ disease.
- The paclitaxel-containing regimen showed a trend to a higher pCR rate in patients with HR$^-$ tumors and a higher rate of breast conserving surgery compared with the docetaxel-containing regimen.
- Sequential use of trastuzumab-taxane after FEC was generally well tolerated, although cardiac safety remains an important consideration. It is important that LVEF is monitored at study entry, at the completion of FEC, and again at the completion of trastuzumab-taxane combination therapy.

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registration-directed trial in accordance with the Good Clinical Practice guideline (Enforcement Regulation No. 106 of the MHLW (revised GCP) dated May 15, 2003), which is laid down by the revised Pharmaceutical Affairs Act in Japan (No. 96 of the MHLW dated on 31 July 31, 2002).

Disclosure

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

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