A Phase II Study of Epirubicin and Cyclophosphamide Followed by Weekly Paclitaxel with or without Trastuzumab as Primary Systemic Therapy in Locally Advanced Breast Cancer

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Abstract. *Background: The aim of this study was to evaluate the activity and toxicity of epirubicin and cyclophosphamide followed by weekly paclitaxel with or without trastuzumab as primary systemic therapy in locally advanced breast cancer. Patients and Methods: Patients with T2-4 (>3 cm) or N1-3 breast cancer received epirubicin (100 mg/m^2) and cyclophosphamide (600 mg/m^2) every three weeks for four cycles followed by paclitaxel (80 mg/m^2) every week for twelve cycles. Trastuzumab (initially 4 mg/kg, then 2 mg/kg) was added to paclitaxel in HER2-positive patients. The primary endpoint was the pathological complete response (pCR) rate in the breast and axilla, and secondary endpoints were the breast-conserving rate and toxicity. Results: Forty-three patients were enrolled into this study and 3 patients withdrew. The pCR rate was 20.0% (95% confidence interval, 10.5-34.8%). Patients with HER2-positive tumours had a significantly higher pCR rate than the others (62.5% vs. 9.4%; p=0.0008). Twenty-four patients (60.0%) underwent breast-conserving surgery. Grade 4 neutropenia was recorded in 30.0% of the patients, and febrile neutropenia occurred in 7 patients (17.5%). Conclusion: Epirubicin and cyclophosphamide followed by weekly paclitaxel, either with or without trastuzumab, was an active and well-tolerated treatment for locally advanced breast cancer.*

Primary systemic chemotherapy (PST) has been evaluated in a number of studies and widely used as the standard treatment for patients with operable breast cancer (1, 2). The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial is a landmark trial, which has already established that preoperative chemotherapy in patients with operable early breast cancer is as effective as postoperative chemotherapy with the same regimen in terms of disease-free survival (DFS) or overall survival (OS) (3). Furthermore, preoperative chemotherapy with four cycles of doxorubicin (adriamycin) and cyclophosphamide (AC) has been reported to result in an increased probability of breast-conserving surgery in comparison to postoperative chemotherapy (3). This trial also demonstrated that a pathological complete response (pCR) was predictive of DFS or OS, suggesting that preoperative chemotherapy would have the advantage of controlling micrometastasis and drug delivery to cancer cells. Therefore, PST is now considered to be standard therapy, and the anthracyclines are the most common and active chemotherapy drugs for breast cancer. Although anthracycline-based preoperative chemotherapy has shown a good response rate in several studies, the pCR rate has been shown to be unsatisfactory (3-6). The sequential use of taxanes to preoperative anthracycline regimens has demonstrated a benefit in some trials (7-9). The NSABP B-27 trial demonstrated that the addition of four cycles of docetaxel after preoperative AC increases the clinical complete response rate, clinical overall response rate and pCR rate in comparison to preoperative AC alone (9, 10). However, that trial demonstrated that the addition of preoperative or postoperative taxane after preoperative AC does not significantly affect OS and slightly improves DFS. Although, a prospective study demonstrated that single-agent tri-weekly paclitaxel as neoadjuvant therapy has tumour activity comparable to the combination of fluorouracil, doxorubicin and cyclophosphamide (11), 12 weekly cycles of paclitaxel at low dose was superior to 4 cycles of tri-weekly paclitaxel when administered sequentially with anthracycline-based chemotherapy in the metastatic or adjuvant setting (12, 13). The pCR rate was significantly higher for weekly paclitaxel in comparison to tri-weekly paclitaxel (28.2% *vs.* 15.7%, p=0.02) (14) in a neoadjuvant setting with the sequential administration of fluorouracil, doxorubicin and cyclophosphamide.

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Trastuzumab is effective for patients with advanced HER2-positive breast cancer. At least one year of trastuzumab with chemotherapy significantly improves DFS or OS in an adjuvant setting (15, 16). There are some phase II studies reporting the use of trastuzumab in a preoperative setting. Buzdar *et al*. reported a randomised trial comparing neoadjuvant chemotherapy for operable HER2-positive breast cancer with or without administration of trastuzumab (17). A total of 26% of the 42 randomised patients in the chemotherapy arm (four cycles of paclitaxel followed by four cycles of fluorouracil, epirubicin and cyclophosphamide (FEC)) achieved pCR in comparison to 65.2% in the trastuzumab (simultaneously for 24 weeks) plus chemotherapy arm (p=0.016) (17). However, cardiac dysfunction was observed in approximately 30% of the trastuzumab arm with no significant difference, and, therefore, cardiac safety should be assessed in the future.

Epirubicin, which is less cardiotoxic than doxorubicin (18), was selected as an anthracycline and paclitaxel as a taxane for sequential chemotherapy. This study describes a phase II trial with patients receiving preoperative epirubicin and cyclophosphamide (EC) followed by weekly paclitaxel plus trastuzumab for locally advanced breast cancer to determine the activity and toxicity of this regimen.

Patients and Methods

Patient eligibility. Patients with invasive breast cancer that was histologically diagnosed by a core needle biopsy as T2-4 (>3 cm) or N1-3 by the International Union Against Cancer (UICC) staging system (19) were eligible for this study. All patients receiving PST had to have measurable disease and to have not received local therapy for their cancer. Patient eligibility criteria were: age >20 years, performance status of 0 to 1 according to the Eastern Cooperative Oncology Group scale, and adequate organ functions, namely, white blood cell count ≥4,000/mm^3, absolute neutrophil count ≥2,000/mm^3, haemoglobin ≥10.0g/dl, platelet count ≥100,000/mm^3, bilirubin 1.5 mg/dl, transaminase level ≤ two times the upper limit of healthy, serum creatinine ≤1.5 mg/dl and left ventricular ejection fraction (LVEF) ≥60%. Patients with severe organ failure, an allergy to alcohol, central nervous system disease and inflammatory or bilateral breast cancer were excluded. All patients provided their written informed consent.

Assessment of hormone receptor and HER2 overexpression. The estrogen receptor (ER) status and progesterone receptor (PgR) status of tumour samples collected by a core needle biopsy were determined by immunohistochemical analysis. Tumours with >10% positively stained cancer cells were classified positive for ER and PgR. HER2 status was assessed using the DAKO HercepTest Kit (Dako Denmark, Glostrup, Denmark) or fluorescence *in situ* hybridisation analysis. HER2-positive tumours were defined as 3+ by HercepTest or positive by fluorescence *in situ* hybridisation.

Treatment. Each patient received four cycles of epirubicin and cyclophosphamide (EC) therapy followed by 12 cycles of weekly paclitaxel. The patients with HER2-positive breast cancer received trastuzumab on the same day of paclitaxel administration. EC was administered at a dose of 100 mg/m^2 epirubicin intravenously (*i.v.*) and 600 mg/m^2 cyclophosphamide *i.v.* on day 1; the cycles were repeated every 21 days for cycles. Paclitaxel was administered at 80 mg/m^2 IV weekly for 12 cycles. The patients were pre-medicated with 16 mg dexamethasone, 20 mg famotidine, and an *i.v.* 5-HT$_3$ antagonist at a standard dose immediately prior to chemotherapy. Patients received diphenhydramine 50 mg *i.v.* before paclitaxel infusion. Trastuzumab was administered at a dose of 2 mg/kg (initially 4 mg/kg) *i.v.* Granulocyte-colony stimulating factor (G-CSF) was used in patients with febrile grade 3 to 4 leucopenia or grade 4 neutropenia. The clinical response was evaluated after chemotherapy, and patients underwent surgery. Patients who were considered appropriate candidates for breast-conserving treatment were offered a partial mastectomy. All patients treated with breast-conserving surgery underwent whole-breast irradiation.

Endpoints. The primary endpoint of this single-centre, phase II trial was the pCR rate in the breast and axilla. Secondary endpoints involved the rate of breast-conserving surgery and the determination of toxicity.

Assessment of response and toxicity. Clinical responses were evaluated according to the response evaluation criteria in solid tumours (RECIST) (20) using computed tomography. Pathological responses were evaluated based only on histological changes in the invasive area, and were graded as follows (21): Grade 0: no histological change in the cancer cells after treatment; grade 1a: mild changes in cancer cells regardless of the extent and/or marked changes in less than one-third of cancer cells; grade 1b: marked change in one-third or more but less than two-thirds of cancer cells; grade 2a: marked changes in two-thirds or more of tumour cells with apparent remaining cancer cells; grade 2b: marked changes approaching a complete response with only a few remaining cancer cells and finally, grade 3: necrosis and/or disappearance of all tumour cells, and/or replacement of cancer cells by granulation and/or fibrosis. The pCR was defined as no evidence of residual invasive cancer, either in the breast or in the axillary lymph nodes. Therefore, pCR in this study included all grade 3 responders with or without a ductal component.

Toxicities were assessed through clinical examination at baseline and before each cycle of chemotherapy. Laboratory tests, including a complete biochemical routine and a complete blood cell count, were performed on day 1 of each cycle. The blood cell count was also repeated on day 8 of each cycle. LVEF was determined at baseline, after 12 weeks of neoadjuvant EC and after neoadjuvant paclitaxel with or without trastuzumab. The Common Terminology Criteria for Adverse Events version 3.0 (22) were applied to describe toxicities.

Statistical analysis. The expected rate of pCR in this trial was calculated to be 25%, and the sample size was calculated using Simon's method (23), with a type I error of 5% and a study power of 80%. The target size for patient enrolment was estimated to be 40 evaluable patients. The association of pCR with immunohistochemical staining of ER, PgR and HER2 was analysed with the chi-square test. Analyses were performed with JMP (version 6.1, SAS Institute Inc.).

Results

A total of 43 patients who were referred to the Tokyo Women's Medical University Medical Center East were enrolled from January 2006 to February 2008. Three patients withdrew, while 40 patients were assessed for safety and

Table I. *Clinical and tumor characteristics of 40 patients evaluated in the study.*

	No. of patients	%
Age, years		
Median	59	
Range	36-74	
Menopausal status		
Premenopausal	13	32.5
Postmenopausal	27	67.5
Tumour status		
T1	1	2.5
T2	27	67.5
T3	4	10.0
T4	8	20.0
Nodal status		
N0	5	12.5
N1	30	75.0
N2	5	12.5
Clinical stage		
IIA	5	12.5
IIB	21	52.5
IIIA	6	15.0
IIIB	8	20.0
Hormone receptor status		
ER and PgR, both positive	22	55.0
ER- or PgR-positive	8	20.0
ER and PgR, both negative	10	25.0
HER2 status (Herceptest)		
3+	8	20.0
2+	0	0
0,1+	32	80.0

Table II. *Objective responses of breast and axilla.*

	No. of patients	%
Clinical response		
CR	7	17.5
PR	30	75.0
SD	3	7.5
PD	0	0
Overall response rate		92.5
Pathological response		
Grade 3	8	20.0
Grade 2b	2	5.0
Grade 2a	11	27.5
Grade 1b	11	27.5
Grade 1a	7	17.5
Grade 0	1	2.5

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

Table III. *Pathological complete response (pCR) according to ER, PgR and HER2 status.*

	No. of patients	pCR rate (%)	*p*-Value
ER and PgR, both positive (n=22)	1	4.6	
ER- or PgR-positive (n=8)	1	12.5	0.0011
ER and PgR, both negative (n=10)	6	60.0	
HER2-			
Positive (n=8)	5	62.5	0.0008
Negative (n=32)	3	9.4	

evaluated for clinical and pathological assessment. The clinical characteristics of patients and tumour are shown in Table I. The median age of the patients was 59 years (range, 36-74 years). Two-thirds of the women were menopausal. Approximately one third of the patients had T3 or T4 breast cancer. Thirty-five patients had clinically detectable axillary lymphadenopathy. The hormone receptor status and HER2 status as determined by immunohistochemical analysis are shown in Table I. The percentage of patients with hormone-positive breast cancer was 75%, while 20% of the tumours were HER2-positive.

Overall, 614 cycles (95.9%) of treatment were administered; 159 cycles (99.4%) of EC and 455 cycles (94.8%) of paclitaxel were performed. For eight patients that had HER2-positive cancer all cycles of trastuzumab were performed. Thirty-four patients (85%) completed all four cycles of EC and twelve cycles of paclitaxel. Among these patients, 31 completed therapy without dose modifications. One patient discontinued EC and paclitaxel treatment due to their request for early surgery. Five patients discontinued paclitaxel due to toxicities (three patients with grade 3 sensory neuropathy and two patients with febrile neutropenia). Seven patients required G-CSF support according to protocol rules. Surgery was performed for all patients, and 24 patients underwent breast-conserving surgery (60.0%).

Clinical CRs were observed in seven patients and PRs were observed in 30 patients (Table II). The overall clinical response rate was 92.5% (95% confidence interval (CI), 80.1-97.4%). The pathological response evaluation showed eight pCRs (20.0%: 95% CI, 10.5-34.8%): six patients were grade 3 responders with the complete disappearance of tumour cells both in breast and axillary nodes, two patients were grade 3 responders with the complete disappearance of invasive tumour cells and residual cancer cells only *in situ*. Table III shows pCRs according to ER, PgR and HER2 status. Patients with both ER- and PgR-negative tumours had a significantly higher rate of pCR than the others (60.0% *vs*. 4.6%, 12.5%; p=0.0011), as did patients with HER2-positive tumours (62.5% *vs*. 9.4%; p=0.0008).

The haematological toxicities that were shown in more than one patient are summarised in Table IV. Grade 4 neutropenia was recorded in 12 patients (30.0%), and febrile

Table IV. *Haematological and non-haematological toxicities (N=40).*

Toxicity	No. of patients (%)							
	Grade 1		Grade 2		Grade 3		Grade 4	
Haematological toxicity								
Neutropenia	6	(15.0)	8	(20.0)	8	(20.0)	12	(30.0)
Febrile neutropenia	0	(0)	0	(0)	0	(0)	7	(17.5)
Leukopenia	6	(15.0)	17	(42.5)	13	(32.5)	2	(5.0)
Anaemia	16	(40.0)	11	(27.5)	2	(5.0)	0	(0)
Thrombocytopenia	3	(7.5)	1	(2.5)	0	(0)	0	(0)
Non-haematological toxicity								
Alopecia	0	(0)	40	(100)				
Nausea	20	(50.0)	7	(17.5)	1	(2.5)		
Vomiting	7	(17.5)	1	(2.5)	6	(15.0)		
Constipation	9	(22.5)	0	(0)	0	(0)		
Diarrhoea	4	(10.0)	0	(0)	0	(0)		
Stomatitis	12	(30.0)	0	(0)	0	(0)		
AST	9	(22.5)	2	(5.0)	1	(2.5)		
ALT	9	(22.5)	1	(2.5)	3	(7.5)		
Anorexia	12	(30.0)	1	(2.5)	0	(0)		
Fatigue	6	(15.0)	0	(0)	0	(0)		
Taste alteration	9	(22.5)	2	(5.0)	0	(0)		
Sensory neuropathy	18	(45.0)	3	(7.5)	3	(7.5)		
Skin change	3	(7.5)	0	(0)	0	(0)		
Nail change	12	(30.0)	0	(0)	0	(0)		
Oedema	3	(7.5)	4	(10.0)	0	(0)		
Weight loss	2	(5.0)	1	(2.5)	0	(0)		
Headache	7	(17.5)	0	(0)	0	(0)		
LVEF	0	(0)	1	(2.5)	0	(0)		

AST: Aspartate aminotransferase; ALT: alanine aminotransferase; LVEF: left ventricular ejection fraction.

neutropenia occurred in seven (17.5%). Grade 3 anaemia was recorded in two patients (5.0%) and no grade 3 thrombocytopenia occurred. The most common non-haematological toxicity was grade 2 alopecia, occurring in all patients (Table IV). No patient experienced grade 4 non-haematological toxicity. Grade 3 non-haematological toxicities with more than 5% incidence included vomiting (15.0%), ALT (7.5%) and sensory neuropathy (7.5%). Grade 1-2 sensory neuropathy was experienced by 52.5% of the patients. One patient with an HER2-negative tumour had grade 2 LVEF, which declined from 64% to 55% post-EC, then to 41% after chemotherapy.

Discussion

This phase II study sought to examine the activity and toxicity of preoperative EC followed by weekly paclitaxel plus trastuzumab for locally advanced breast cancer. This study of 40 Japanese patients demonstrated high overall responses in 92.5% of patients and pCR in 20.0% of tumours. In particular, pCR was frequently observed in 62.5% of patients with HER2-positive breast cancer. There were no significant differences in the types and grades of toxicity from treatment with EC or paclitaxel without trastuzumab (3, 12, 13).

Trastuzumab treatment has become the standard of care for HER2-positive breast cancer. Trastuzumab, as a single agent or in combination with standard chemotherapy, shows a favourable outcome for metastatic breast cancer overexpressing HER2 (24, 25). The addition of trastuzumab after chemotherapy in patients with HER2-positive breast cancer is a more active treatment in the adjuvant setting (15, 16), and it is possible that it is able to increase the pCR rate in the neoadjuvant setting. A number of phase II studies have evaluated PST with trastuzumab plus various non-doxorubicin containing cytotoxic therapies, because a therapy with simultaneous combination of doxorubicin and trastuzumab is associated with cardiac toxicity (26). The pCR rates in those studies range from 18% to 54% (27-30). In contrast, Buzdar *et al*. (17) reported that the pCR rate in the neoadjuvant setting is 65.2% for patients treated with trastuzumab plus chemotherapy in comparison to 26% for patients treated with chemotherapy alone in stage II to IIIA disease. In that study (17), simultaneous weekly trastuzumab was administered for

24 cycles in combination with FEC for four cycles and tri-weekly paclitaxel for four cycles. Only 12 weekly cycles of trastuzumab were administered in combination with weekly paclitaxel to avoid the cardiac toxicity, and the pCR rate was 62.5% in HER2-positive patients. Therefore, trastuzumab is absolutely essential to achieve a higher pCR rate of PST for HER2-positive breast carcinoma, but should not be administered in combination with anthracycline containing regimens. However, the pCR rate of HER2-negative tumours was 9.4%. A phase II trial of epirubicin plus docetaxel (ET) was conducted in 2002 (31), while that of EC followed by docetaxel was performed in 2008 (32). Those trials demonstrated that pCR is 7.1% and 5.6% in patients with HER2-negative tumours, which is significantly low in comparison to those with HER2-positive tumours. Furthermore, several studies for PST demonstrated that the pCR rate for patients with ER-negative tumours is remarkably high in comparison to ER-positive tumours (31, 32). It is likely that ER-negativity or HER2-positivity of tumours will predict pCR. PST will be also required for improved prognosis for patients with those types of tumours. However, the pCR does not have prognostic significance in patients with ER-positive tumours (33) and alternative approaches such as neoadjuvant endocrine therapy are required for patients with ER-positive and HER2-negative phenotype tumours.

The possibility of breast-conserving surgery for locally advanced breast cancer is considered to be another important advantage of PST (1, 9). The breast-conservation rate, which was a secondary endpoint of this study, at 60.0% was almost as high as the breast conservation rates of previous phase II trials (54% in ET, 60% in EC followed by docetaxel) (31, 32). The frequency of successful breast-conservation in NSABP B-27 (9) was similar among the patients who received preoperative AC only and those who received both AC and docetaxel (61.6% *vs*. 63.7%; p=0.33). It is unlikely that any regimen of PST with more than 80% clinical response will increase the breast-conservation rate. Therefore, additional taxane would be unnecessary in PST for patients with ER-positive and HER2-negative phenotype tumours with superior prognosis with regard to the breast-conservation rate.

Neutropenia was the most common toxicity. Grade 4 neutropenia was recorded in 12 patients (30.0%) and febrile neutropenia occurred in seven (17.5%). The incidence of grade 4 neutropenia was less than that observed in previous phase II trials (81% in ET, 52% in EC followed by docetaxel) (31, 32). Although no patient experienced grade 4 non-haematological toxicity, grade 3 sensory neuropathy was experienced by 7.5% of the patients and grade 1-2 was observed in 52.5%. Green *et al*. (14) reported that paclitaxel administered at a low dose of 80 mg/m^2 was well tolerated, with a reduced risk of neutropenic fever and grade 3 neuropathy in comparison to paclitaxel administered once every three weeks. Furthermore, patients receiving weekly paclitaxel had a higher pCR rate than patients with once-every-three-weeks paclitaxel.

The simultaneous combination of doxorubicin and trastuzumab results in a high rate of cardiac toxicity (26). Although epirubicin has a dose-dependent response in the adjuvant setting, administration of FEC100, using 100 mg/m^2 epirubicin per cycle, results in a significantly improved 10-year survival in comparison to FEC50, using epirubicin 50 mg/m^2 (34). Buzdar *et al*. (17) selected FEC75 as a safe compromise between efficacy and cardiac safety because concurrent trastuzumab administration was planned. However, cardiac dysfunction was observed in approximately 30% of the trastuzumab arm with no significant difference. In the present study EC was selected using 100 mg/m^2 epirubicin, and no decline in the LVEF was detected in patients with HER2-positive tumours. However, one patient with a HER2-negative tumour had grade 2 LVEF which declined from 64% to 55% post-EC and then to 41% after chemotherapy. Only 12 cycles of trastuzumab combined with weekly paclitaxel achieved a similar high pCR rate. Therefore, concurrent epirubicin and trastuzumab should be avoided for cardiac safety.

In conclusion, EC followed by weekly paclitaxel with or without trastuzumab was an active and well-tolerated treatment for locally advanced breast cancer. The neoadjuvant administration of this regimen may also be a possible treatment, especially for patients with HER2-positive tumours. A randomised phase III trial is currently underway (American College of Surgeons Oncology Group Z1041) to compare a neoadjuvant regimen of FEC75 followed by paclitaxel plus trastuzumab with a neoadjuvant regimen of paclitaxel plus trastuzumab followed by FEC75 plus trastuzumab in patients with HER2-positive operable breast cancer.

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