Epirubicin and Cyclophosphamide Followed by Docetaxel as Primary Systemic Chemotherapy 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 (EC) followed by docetaxel as primary systemic chemotherapy (PST) in locally advanced breast cancer. Patients and Methods: In this phase II trial, 46 patients with locally advanced breast cancer (T>3 cm or N>1) received epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks for four cycles, followed by docetaxel (70 mg/m^2) every 3 weeks for four cycles. Primary endpoints were pathological and objective response in the breast and axilla, and toxicities. Results: The clinical response rate was 80.4% (95% confidence interval, 68.9-91.9%). Pathological response evaluation revealed 6 complete responses (CR: 13.0%). Patients with ER-negative tumors had a significantly higher rate of pathological CR than the others (33.3% vs. 3.2%; p=0.0105). Febrile neutropenia occurred in 4 patients (8.7%). Conclusion: EC followed by docetaxel is an active and well-tolerated treatment as PST for locally advanced breast cancer.*

Primary systemic chemotherapy (PST) is now widely used as the treatment of patients with operable as well as inoperable breast cancer (1-5). National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial clarified that preoperative chemotherapy never shortens survival time compared with postoperative chemotherapy (6). This trial also demonstrated that pathological tumor response was predictive of overall survival, suggesting that preoperative chemotherapy would take advantage of controlling micrometastasis and drug delivery to cancer cells. Thus, PST is now considered to be standard therapy for the treatment of high-risk breast cancer.

It is clear that the anthracyclines are the most standard and active drugs for breast cancer. Anthracycline-based regimens include doxorubicin and cyclophosphamide (AC), epirubicin and cyclophosphamide (EC), and 5-fluorouracil, epirubicin and cyclophosphamide (FEC). Although anthracycline-based preoperative chemotherapy showed a good response rate, a pathological complete response (pCR) rate was not achieved (6-9).

In an attempt to achieve a superior response rate as a surrogate endpoint, the taxanes have been added to anthracycline-containing regimens. Docetaxel, the semisynthetic taxoid, has been shown in several studies to be effective both in pretreated and treated disease (10-13). Furthermore, the combination of anthracycline plus taxane was demonstrated to have a superior clinical effect over conventional anthracycline-based regimens in metastatic and locally advanced breast cancer (3-19).

The polychemotherapy of anthracyclines and taxanes is divided into two methods, combination and sequential. In the German Preoperative Adriamycin Docetaxel Study Group (GEPARDUO) trial, the pCR rate was 14.3% in the sequential arm and 7.0% in the combination arm ($p<0.001$) (20). According to the recommendation of the data monitoring committee, recruitment to the study was ceased due to the significant difference in pCR rates observed between the treatment arms (21). This study indicated the superiority of sequential chemotherapy over combination one. Another sequential setting of AC followed by docetaxel (AC-T), the NSABP B-27 trial, has finished (22). In the preoperative AC-T arm, the pCR rate was 26.1% and 18.9% of these patients had no evidence of cancer in the breast, while another 7.2% had noninvasive cancer (23).

We chose epirubicin, which is less cardiotoxic than doxorubicin, as an anthracycline and docetaxel as a taxane for sequential chemotherapy. Furthermore, cyclophosphamide is added to epirubicin in order to enhance the effect of

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anthracycline. We designed a phase II trial with patients receiving preoperative epirubicin and cyclophosphamide (EC) followed by docetaxel for locally advanced breast cancer to determine the activity and toxicity of this regimen. This is the first report of sequential EC and docetaxel as PST in breast cancer.

Patients and Methods

Endpoints. In this single-center, phase II trial, the primary endpoints of the study were the pathological and objective response in the breast and axilla, and toxicities. Secondary endpoints involved the rate of breast-conserving surgery and the 5-year overall survival (OS) and disease-free survival (DFS) rate.

Patients. Patients with histologically diagnosed invasive breast cancer by core-needle biopsy of the T2-4 (>3 cm) or N1-3 categories of the International Union Against Cancer (UICC) staging system (24) were included in this study. Eligible patients were age <75 years, had a performance status of 0 to 1 according to the Eastern Cooperative Oncology Group scale, and had adequate organ functions [WBC count ≥4,000/mm^3 and ≤12,000/mm^3; absolute neutrophil count ≥2,000/mm^3, platelet count ≥100,000/mm^3, hemoglobin level ≥9.5 g/dl, transaminase level ≤1.5 x upper limit of normal value (ULNV), total-bilirubin level ≤1.25 x ULNV, serum creatinine level ≤1.5 x ULNV, and left ventricular ejection fraction (LVEF) ≥60%]. Patients with inflammatory or bilateral breast cancer were excluded. All patients provided written informed consent.

Treatment. Each patient was to receive four cycles of EC followed by four cycles of docetaxel; cycles were repeated every 3 weeks for eight cycles. EC consisted of 90 mg/m^2 epirubicin intravenously (*i.v.*) and 600 mg/m^2 cyclophosphamide *i.v.* on day 1. Docetaxel was administered at 70 mg/m^2 over 1 hour. Premedication consisted of 16 mg dexamethasone, 20 mg famotidine, an intravenous 5-HT3 antagonist at a standard dose immediately *i.v.* before chemotherapy. Granulocyte-colony stimulating factor (G-CSF) could be used in patients with febrile grade 3 to 4 leucopenia or grade 4 neutropenia. All patients treated with breast-conserving surgery received whole-breast irradiation.

Assessment of response and toxicity. Objective responses were defined clinically for the primary endpoint of this study (25) and evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST). A complete response (CR) was defined as the complete disappearance of all known disease. A partial response (PR) was defined as a >30% decrease in the sum of longest diameters of all target lesions and progressive disease (PD) as an increase of >20% in the sum of the longest diameters of all target lesions.

Pathological responses were graded as follows (26). Grade 0, no response: no histological change in the cancer cells after treatment; grade 1a, mild response: mild changes in cancer cells regardless of the area, or marked changes in less than one third of the cancer cells; grade 1b, moderate response: marked change in one third or more but less than two thirds of tumor cells; grade 2, marked response: marked change in two thirds or more of tumor cells including residual cancer cells only *in situ*; grade 3, complete response: necrosis or disappearance of all tumor cells. pCR was defined as no evidence of residual invasive cancer, either in the breast and axillary lymph nodes. Therefore, pCR in this study was made up of all grade 3 responders and a part of grade 2 ones.

Toxicity was 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. Blood cell count was also repeated on day 8 of each cycle. To describe toxicity, the Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) were applied (27).

Statistical analysis. It was determined that the expected rate of pCR in the trial was 25%, and the sample size was calculated using the Simon method, with a type I error of 5% and a study power of 80%. The target enrollment was estimated to be 40 evaluable patients. The association of pCR with immunohistochemical staining of ER, PgR and HER2 was analyzed with Chi-square test.

Results

Forty-six patients who were referred to the Tokyo Women's Medical University Medical Center East were enrolled from January 2003 to December 2005. The clinical characteristics of patients and tumor are shown in Table I. The median age of the patients was 55 years (range, 38-75 years). Two-thirds of the women were menopausal. Overall, 343 cycles (93.2%) of treatment were administered; 181 cycles (98.4%) of EC and 162 cycles (88.0%) of docetaxel were performed. Treatment was interrupted before its planned completion in 8 patients due to PD in 1 patient after the first cycle, allergic reaction to docetaxel in 1 patient, grade 3 nonhematological toxicities in 1 patient after the fifth cycle and patient refusal in 4 patients. Thirteen patients required G-CSF support according to protocol rules. Surgery was performed for almost all patients except one who refused surgery after chemotherapy with clinical evidence of complete response, and breast conserving surgery was undergone in 27 patients (60.0%). Clinical CRs were observed in 9 patients and PRs were observed in 28 patients (Table II). The clinical response rate was 80.4% (95% confidence interval, 68.9-91.9%).

Pathological response evaluation showed 6 pCRs (13.0%): 4 patients were grade 3 responders with the complete disappearance of tumor cells both in breast and axillary nodes, 2 patients were grade 2 responders with the complete disappearance of invasive tumor cells and residual cancer cells only *in situ*. Pathological complete responses according to ER, PgR and HER2 status are shown in Table III. Patients with ER-negative tumors had a significantly higher rate of pathological CR than the others (33.3% *vs.* 3.2%; p=0.0105), as did patients with HER2-positive tumors (40.0% *vs.* 5.6%; p=0.0151).

The adverse events that were shown in more than one patient are summarized in Table IV. Grade 4 neutropenia was recorded in 24 patients (52.2%), and febrile neutropenia

Table I. *Clinical and tumor characteristics of 46 patients.*

	No. of patients	%
Age, years		
Median	55	
Range	38-75	
Menopausal status		
Premenopausal	16	34.8
Postmenopausal	30	65.2
Tumor status		
T1	3	6.5
T2	35	76.1
T3	2	4.3
T4	6	13.0
Nodal status		
N0	12	26.1
N1	27	58.7
N2	4	8.7
N3	3	6.5
Clinical stage		
IIA	12	26.1
IIB	24	52.2
IIIA	3	6.5
IIIB	4	8.7
IIIC	3	6.5
Hormone receptor status		
ER and PgR both positive	26	56.5
ER or PgR positive	5	10.9
ER and PgR both negative	15	32.6
HER2 status (Herceptest)		
3+	10	21.7
2+	12	26.1
0-1+	24	52.2

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

	No. of patients	%
Clinical response		
CR	9	19.6
PR	28	60.9
SD	7	15.2
PD	2	4.3
Overall response rate		80.4
Pathological response		
Grade 3	4	8.7
Grade 2	16	34.8
Grade 1b	6	13.0
Grade 1a	17	37.0
Grade 0	2	4.3

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

occurred in 4 (8.7%). Grade 1-2 anemia was recorded in 80.4% and grade 3 thrombocytopenia was recorded in one patient. There were no toxicities recorded for the heart, lungs or kidneys. Grade 3 liver dysfunction (AST and ALT) was recorded in one patient. All patients had grade 2 alopecia. Grade 1-2 nausea was experienced by 41.3% and vomiting was experienced by 17.4% of the patients. Grade 1-2 fatigue was experienced by 30.4%. Sensory neuropathy was recorded in 32.6% . Only one patient had dyspnea (grade 3).

Table III. *Pathological complete responses according to ER, PgR and HER2 status.*

	No. of patients	pCR rate (%)	*p*-Value
ER			
Negative (n=15)	5	33.3	
Positive (n=31)	1	3.2	0.0105
PgR			
Negative (n=20)	6	30.0	
Positive (n=26)	0	0.0	0.0041
HER2			
3+ (n=10)	4	40.0	
(IHC)			
0~2+ (n=36)	2	5.6	0.0151

Discussion

Several trials indicated that the polychemotherapy of anthracycline plus docetaxel is an effective regimen of neoadjuvant chemotherapy (15-18). In order to assess the activity and toxicity of the combination chemotherapy of anthracycline and taxane as PST, we had performed a phase II trial of ET (epirubicin plus docetaxel) in 2002 (28). The results of this trial demonstrated that the pCR rate was 9.5% and the rate of breast-conserving surgery was 52.4% . We expected that the sequential anthracyclines and taxanes would provide a higher response rate than the combination as primary chemotherapy and consequently planned this phase II trial.

Although in Europe and the United States the standard dose of docetaxel is 100 mg/m^2, the recommended dose of docetaxel for Japanese women is 60-70 mg/m^2 (29). Therefore, the dose of docetaxel was decided at 70 mg/m^2 in this study. Despite the lower dose of docetaxel as compared with other countries, a high clinical response rate (80.4%) was obtained in this study. Thus, this dose is recommended for Japanese women. However, the pCR rate (13.0%) was not as high as other anthracycline-based regimens (3.7%-13%) (5-8). Although the difference in pCR rate between these two trials was not significant, the pCR rate of this trial was higher than the rate with ET (13.0% *vs*. 9.5%) and a tendency of superiority of the sequential therapy to the combination one was observed.

In comparison with B-27 trial, the overall pCR rate of this trial was inferior. However, among patients with negative ER, the pCR rate was higher than in the B-27 trial (33.3% *vs*.

Table IV. *Hematological and nonhematological toxicities.*

Toxicity	No. of patients (%)							
	Grade 1		Grade 2		Grade 3		Grade 4	
Hematological								
Neutropenia	2	(4.3)	7	(15.2)	10	(21.7)	24	(52.2)
Leukopenia	2	(4.3)	13	(28.3)	17	(37.0)	12	(26.1)
Anemia	18	(39.1)	19	(41.3)	1	(2.2)	1	(2.2)
Thrombocytopenia	1	(2.2)	0	(0)	1	(2.2)	0	(0)
Nonhematological								
Alopecia	0	(0)	46	(100)				
Nausea	18	(39.1)	1	(2.2)	0	(0)	0	(0)
Vomiting	2	(2.2)	5	(10.9)	1	(2.2)	0	(0)
Dyspnea	0	(0)	0	(0)	1	(2.2)	0	(0)
Fatigue	12	(26.1)	2	(4.3)	0	(0)	0	(0)
Taste alteration	11	(23.9)	5	(10.9)				
Mucositis	8	(17.4)	1	(2.2)	1	(2.2)	0	(0)
Sensory neuropathy	13	(28.3)	1	(2.2)	1	(2.2)	0	(0)
AST	2	(4.3)	1	(2.2)	1	(2.2)	0	(0)
ALT	6	(13.0)	2	(4.3)	1	(2.2)	0	(0)

AST: Asparatate Aminotransferase; ALT: Alanine Aminotransferase.

22.8%). In general, primary chemotherapy shows a more effective and higher pCR rate for patients negative for hormone receptors, than these positive for hormone receptors (20, 23). In fact, patients with hormone-negative tumors had a significantly higher rate of pCR (Table IV). These factors could predict a good response to chemotherapy. Although there is a tendency that the observation of pCR is rare among patients with hormone receptor-positive or HER2 negative-tumors, these factors would not become negative prognostic markers that would indicate giving up the anthracycline/taxane chemotherapy. Thus, we need novel negative prognostic markers in order to predict any PD cases and avoid unnecessary chemotherapy.

The breast conservative rate of this study was 60.0% . The rate was consistent with the data reported in extended studies that employed other novel regimens, such as AC followed by docetaxel (23).

Myelosuppression was severe but reversible toxicity was achieved in the present study. Neutropenia was frequent and grade 4 neutropenia was recorded in 24 patients (52.2%). Neither motor neuropathy nor cardiotoxicity were seen however.

The GEPARDUO study suggested the superiority of sequential chemotherapy, however, the B-27 trial could not prove the hypothesis that improving the pCR rate might produce a direct survival benefit (22). Thus, we cannot conclude that preoperative chemotherapy is superior to adjuvant chemotherapy until the evidence of survival benefit is provided.

We have not yet conclusively determined which taxane is more effective for breast cancer, docetaxel or paclitaxel. Molecular targeting drugs are hoped to improve the prognosis of postoperative and preoperative breast cancer. Buzdar *et al*. reported the surprisingly higher pCR rate after primary systemic therapy with trastuzumab, paclitaxel and FEC in HER2-positive breast cancer (30). In order to achieve a higher rate of pCR as a surrogate endpoint, a new trial adding trastuzumab should be explored.

Conclusion

In conclusion, the sequential setting of epirubicin and docetaxel was an active and well-tolerated treatment for locally advanced breast cancer.

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