Neoadjuvant Epirubicin/Docetaxel (ET) Concomitant Chemotherapy for Primary Breast Cancer with Tumor Diameter ≥3.1 cm: Results of the Kyushu ET Therapy Phase II Trial

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Abstract. *Aim: Neoadjuvant epirubicin/docetaxel (ET) combination chemotherapy was administered to breast cancer patients in order to investigate their clinical and pathological response. Moreover, the breast-conserving surgery (BCS) rate, disease-free (DFS) and overall survival (OS), safety profile and the correlation of biological markers were investigated. Patients and Methods: Out of the 46 enrolled patients, 45 patients were analyzed for clinical response, and 40 patients were examined for pathological response. Estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor type2 (HER2) expression were examined immunohistologically. Results: The median tumor size was 4.5 cm in diameter. Complete (CR) and partial responses were seen in 3 and 30 patients, respectively. A pathological CR was achieved in 4 patients and correlated with ER and PgR negativity. Moreover, BCS was performed on 16 patients. The 5-year cumulative DFS was 60.7% and OS was 91.8%. Conclusion: ET therapy is clinically effective with a pathological CR rate of 10% for patients with a large tumor, and should be considered as a neoadjuvant treatment option.*

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Key Words: Breast cancer, epirubicin, docetaxel, neoadjuvant chemotherapy, ER-negative, PgR-negative.

Recent advances in drug therapy and biological research on breast cancer have shown an important role of systemic therapy in breast cancer. Prolonged survival was reported by the Early Breast Cancer Trialists' Collaborative Group of patients with early breast cancer who were treated with systemic therapy (1). Hormone-dependent breast cancer responds well to endocrine therapy, while chemotherapy and anti-(HER2) therapy are also effective treatment options. Neoadjuvant chemotherapy (NAC) has been used for patients with locally advanced breast cancer

since the 1970s and has led from irresectable to resectable tumor-state in some patients. Based on this result, randomized controlled trials were performed using NAC for patients with even further early-stage disease, which was potentially resectable at the time of diagnosis.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 (2, 3) was the first clinical study in which NAC was determined to be one of the treatment choices for early-stage breast cancer. When doxorubicin and cyclophosphamide (AC) treatment was administered before surgery, pathological complete response (pCR) was found in 13% of patients and the rate of breast-conserving surgery (BCS) appeared to be high for patients treated before surgery, compared to those treated after surgery. Although there was no significant difference in disease-free survival (DFS) and overall survival (OS), prognosis of patients with pCR was superior to those with non-pCR. In the clinical trial NSABP B-27 (4), AC was compared with AC followed by docetaxel. The latter gave rise to significantly more patients who achieved pCR and a favorable prognosis, indicating an add-on effect of docetaxel. Thus, the aim of neoadjuvant therapy is to obtain pCR, as well as to increase the rate of BCS. It was also found that concomitant use of AC and docetaxel (TAC) resulted in a high response rate with an acceptable toxicity. In early 2000, we undertook a phase I study using a combination of epirubicin and docetaxel (ET) and the recommended dose for phase II study was determined to be 60 mg/m^2 docetaxel and 60 mg/m^2 epirubicin. This study investigated the efficacy, adverse events and prognosis when ET therapy was used as NAC.

Patients and Methods

Patients. This study involved patients who had stage II and III primary breast cancer with a tumor diameter ≥3.1 cm and who received no prior treatment for breast cancer. The inclusion criteria were i) stage II-III primary breast cancer, excluding patients with metastasis to supraclavicular lymph nodes; ii) tumor diameter ≥3.1 cm measured by an imaging study; iii) no previous chemotherapy, radiotherapy, endocrine therapy or immunotherapy; iv) performance status (PS) of 0-1; v) measurable lesions; vi) adequate hematological, hepatic, renal and cardiac function *i.e.* white blood cell count (WBC) ≥4,000/μl and ≤10,000/μl, neutrophil count≥2,000/μl, platelet count ≥ 100,000/μl, Hb ≥9.5g/dl, asparate aminotransferase (AST), alanine aminotransferase (ALT) ≤ two-fold the standard institutional upper limit, total bilirubin ≤1.5 mg/dl, serum albumin ≥3.0 g/dl, serum creatinine within the institutional standards, ECG was within the institutional standards, and ejection fraction (EF) ≥50%; vii) age ranging from 20 to 75 years, and viii) written informed consent.

The exclusion criteria included history of hypersensitivity to the investigational drugs; serious complications, including active infection, peripheral neuropathy, pleural or pericardial effusion that required treatment; other active cancer, male breast cancer; women who were breast-feeding; edema, hydrocephalus, interstitial pneumonia or pulmonary fibrosis that required steroid treatment; a history of mental illness or active mental disorders; or ineligiblity to participate in this study, as judged by the investigators.

Tumor status and response criteria. Prior to the ET therapy, the tumor size and the status of lymph nodes were evaluated by an imaging study. Surgery was performed after four courses of ET, and lymph nodes were examined pathologically and were compared with those seen before ET. Before ET, tissue samples were also collected by needle biopsy to determine invasive carcinoma. They were also immunostained to assess estrogen receptor (ER), progesterone receptor (PgR), and HER2 status. Hormone receptor was determined to be positive if more than 10% of tumor cells were positively stained. HER2- and HER1+ were classified as HER2 negative; and HER2, 3+, or 2+ with positive immunofluorescence *in situ* hybridization (FISH) were determined as being HER2 positive.

Response evaluation criteria in solid tumors (RECIST) were used to evaluate the treatment response to the primary tumor (5), and the pathological response was assessed by the criteria of the Japanese Breast Cancer Society (6). The latter was classified from grade 0 to 3. Grade 3 pathological response was determined when complete disappearance of cancer cells was obtained. Grade 2 response was degeneration or necrosis in two thirds or more in the tumor and few remaining invasive tumor cells (near pCR), while grade 1 was slight response, and grade 0 was no response (non-pCR). Patients with grades 2 and 3 were determined to be pathological responders. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (version 2) (7).

In this study, primary endpoints were clinical response, pathological response and rate of BCS. Secondary endpoints were DFS, OS, and safety profile.

Treatment. The treatment consisted of intravenous injection of 60 mg/m^2 epirubicin and 60 mg/m^2 docetaxel, and both were administered every three weeks for a total of four cycles. To prevent chemotherapy-induced nausea, vomiting and edema, dexamethasone and 5-hydroxytryptamine 3 (5HT3) receptor antagonists were used in the each institutional protocol. Three to four weeks after the fourth cycle of ET, breast surgery was offered to the patient.

Statistical considerations. Enrollment for this study started in July 2002 and ended in May 2004. The follow-up period began in 2004 and ended in 2009 and the data were collected in 2010. More than 30 patients were needed, including drop-out patients, by using Simon Minimax Design when the expected response rate was 90% and the lower limit of response was 70%, with an α error of 0.05 and β error of 0.2. DFS and OS after the start of treatment were determined by the Kaplan-Meier method.

Results

Patients' background factors and surgical results. Forty-six patients were enrolled in this study from July 2002 to May 2004. The median observation period was 69.2 months. One patient withdrew her consent midway through this study. Thus, it was possible to analyze data for a total of 45 patients for efficacy. Among these 45 patients, pathological response was evaluated in 40 patients who underwent surgery.

The background characteristics of the 46 patients are shown in Table I. Age distribution was 29-75 years, with a median age of 47. Twenty-nine patients were premenopausal. PS was 0 in 45 patients. The median tumor diameter before

treatment was 4.5 cm and 14 patients had a large tumor, with a maximum diameter ≥5.0 cm. The median tumor diameter after treatment was 2.5 cm and one patient remained with a tumor of diameter ≥5.0 cm; tumors showed significant shrinkage upon NAC treatment ($p<0.0001$). Before treatment, lymph node metastasis was found in 29 (63.0%) patients and histological examination at surgery showed no lymph node metastasis in 19 (41.3%) patients. Histologically, 38 patients had invasive ductal carcinoma (IDC), while two had invasive lobular carcinoma (ILC).

Looking at the distribution of the biological markers, 28 patients had tumors that were positive for ER with a positive rate of 62.2%. PgR was positive in 22 patients (48.9%). HER2 expression was negative in 20, 1+ in 9, 2+ in 2, and 3+ or FISH-positive in 12 patients, with an overall positive rate of 26.1%.

Excluding one patient who rejected treatment, surgery was performed on 45 patients. Total mastectomy was performed on 29 and BCS on 16 (35.5%) patients. Out of the 46 patients, 42 completed four cycles of neoadjuvant ET treatment; the remaining four were unable to finish four cycles of ET because of progression of their disease (PD), allergic reaction and treatment rejection by the patient. The dose intensity (DI; mg/m^2/week) had a median value of 20 mg (16.0-20.7 mg) and the relative dose intensity (RDI) had a mean of 96.4% and median of 100% (Table I).

Clinical response to ET treatment. The clinical response of the primary tumor is shown in Table II. Clinical CR and partial response was seen in three (6.7%) and in 30 (66.7%) patients, respectively, and thus the overall response rate was 73.3%. With regards to the factors that correlated with this response, there was no clear relation with the tumor diameter or with menopausal status. It seems that ER-negative tumors clearly responded well to ET and many patients with PgR-negative and HER2-positive tumors tended to respond to ET (Table II).

Pathological response to ET treatment. The pathological response was pCR in four (10%) patients, and grade 2 that was determined to be near pCR in 12 (30%) patients, as shown in Table III. The factors that correlated with the pathological response appeared to be ER and PgR status. The number of patients that responded well to ET when the tumor was negative for both hormone receptors was significantly high. In contrast, menopausal status, tumor size and HER2 status had no clear correlation to tumor response (Table III).

Effect of ET treatment on prognosis. Figures 1 and 2 show DFS and OS of the patients who received neoadjuvant ET therapy. The 5-year cumulative DFS rate was 60.7% (Figure 1), and the cumulative OS rate was 91.8% (Figure 2).

Table I. *Patients' characteristics*.

Characteristic	Number	Percentage
Total no. of patients	46	
Median age at diagnosis years (range)	47 (29-75)	
Performance status		
0	45	97.8
1	1	
Menopausal status		
Pre-	27	58.7
Post-	19	
Clinical stage		
IIA	12	26.1
IIB	9	19.6
IIIA	16	34.8
IIIB	9	19.6
Tumor size (diameter)		
Pre-treatment median=45 mm		
≤5 cm	31	67.4
>5 cm	14	
Unknown	1	
Post-treatment median=25 mm*		
≤5 cm	44	95.7
>5 cm	1	
Unknown	1	
Nodal status		
Pre-treatment		
N0	17	37.0
N1	22	
N2	7	
Post-treatment		
N0	19	41.3
N+	25	
Unknown	2	
Histological type		
Invasive ductal carcinoma	44	95.7
Invasive lobular carcinoma	2	
ER of the primary tumor		
Positive	28	60.9
Negative	15	
Unknown	3	
PgR of the primary tumor		
Positive	22	47.8
Negative	21	
Unknown	3	
HER2 of the primary tumor		
0	20	
1+	9	
2+	2	
Positive$^+$	12	26.1
Unknown	3	
Surgery		
Total mastectomy	29	63.0
BCS	16	
Not performed	1	
Treatment		
Completed 4 cycles	42	
Discontinuation	4 (PD, allergy, refusal)	
DI (mg/m^2/week) Median (range)	20 (16.0-20.7)	
RDI		
Mean	96.4	
Median	100	

DI: Dose-intensity; RDI : relative DI; BCS: breast-conserving surgery; $^+$3+ or 2+/FISH-positive. *$p<0.0001$.

Table II. *Clinical response to neoadjuvant epirubicin/docetaxel (ET) treatment and clinicopathological factors.*

	Response, n (%)				
	CR	PR	SD/PD	Total	Chi-value
Menopausal status					
Pre-	3 (10.3)	18	7/1	29	
Post-	0	12	4/0	16	0.38
Tumor size (cm)					
≤5.0	1 (3.2)	22	7/1	31	
>5.0	2 (14.3)	8	4/0	14	0.35
ER status					
–	3 (20)	7 (46.7)	4/1	15	
+	0	22 (78.6)	6/0	28	0.02
Unknown	0	1	1/0	2	
PgR status					
–	3 (13.6)	11 (54.5)	6/1	21	
+	0	18 (83.3)	4/1	22	0.06
Unknown	0	1	1/0	2	
HER2 status					
–, 1+	1 (3.4)	18 (62.1)	9/1	29	
2+, 3+	2 (14.3)	11 (78.6)	1/0	14	0.09
Unknown	0	1	1/0	0	
Total	3 (6.7)	30 (66.7)	11/1	45	

ER: Estrogen receptor, PgR: progesterone receptor; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Table III. *Pathological Response to ET treatment and clinico-pathological factors*

Grade	3: pCR	2: Near pCR	1b/1a/0: Non-pCR	Total	Chi-Value
Menopausal status					
Pre-	2 (7.7)	8 (30.8)	3/11/2	26	
Post -	2 (14.3)	4 (28.6)	0/4/4	14	0.80
Tumor Size					
≤5.0	3 (10.3)	8 (27.6)	2/11/5	29	
5.0<	1 (9.1)	4 (36.4)	1/4/1	11	0.86
ER status					
–	2 (13.3)	8 (53.3)	1/3/1	15	
+	2 (8.7)	3 (13.0)	1/12/5	23	0.016
Unknown	0	1	1/0/1	3	
PgR status					
–	2 (10)	10 (50)	2/5/1	20	
+	2 (11.1)	1 (5.6)	0/10/5	18	0.009
Unknown	0	1	1/0/0	2	
HER2 status					
–, 1+	4 (16.0)	6 (24.0)	1/9/5	25	
2+, 3+	0	5 (38.5)	1/6/1	13	0.26
Unknown	0	1	1/0/0	2	
Total		4 (10)	12 (30)	3/15/6	40

ER: Estrogen receptor, PgR: progesterone receptor, pCR: pathological complete response, ( ):%.

Adverse events. A summary of adverse events (AEs) associated with ET prior to surgery is shown in Table IV. Grade 3 and 4 hematological toxicities were leukopenia, neutropenia and febrile neutropenia. In addition, abnormal AST and ALT values were seen in one patient. The non-hematological toxicities were fatigue, nausea, vomiting, anorexia, and constipation (Table IV).

Discussion

The aim of NAC is to achieve pCR and to improve the rate of BCS after reduction of tumor volume. However, as far as adverse events of NAC are considered, they are sometimes quite harmful to the patients. Therefore, treatment regimens must be selected depending on the aim of treatment and on the patients' preference. The ET treatment used in this study is a concomitant use of anthracycline and taxane. The clinical response was 73.3% and pCR was 10%, while the incidence of significant adverse events such as febrile neutropenia was 17.4%.

To determine whether concomitant therapy or sequential treatment should be applied to patients with early breast cancer, a comparison between two treatments was made in the phase III Gepar Duo trial (8), which used a dose-dense combination therapy of doxorubicin at 50 mg/m^2 plus docetaxel at 75 mg/m^2 every 14 days for four cycles with filgrastim support, and treatment with AC followed by docetaxel (doxorubicin at 60 mg/m^2 plus cyclophosphamide at 600 mg/m^2, every 21 days, followed by docetaxel at 100 mg/m^2 every 21 days for four cycles). Clinical response in the sequential arm was 78.6% and that of the concomitant treatment arm was 68.6%, showing a significant difference (p<0.001). However, there was no significant difference in the pCR rate (14.3% *versus* 7.0%). The rate of BCS in the concomitant treatment arm was 58.1%, and the sequential arm gave rise to a rate of 63.4% (p=0.05). It is reported that achievement of pCR is attributed to the following factors: sequential therapy, high tumor grade, and negative hormone receptor status. In the same ET regimen, which consisted of high dose epirubicin and docetaxel with 75 mg/m^2 for each drug, the clinical response and pCR were found to be 72% and 11%, respectively (9). The pCR rate reported in another trial (10) was 7.7% and 18.6% for patients who received three and six cycles of epirubicin and docetaxel (both at 75 mg/m^2) combination, respectively. Moreover, docetaxel (75 mg/m^2) plus high-dose epirubicin (120 mg/m^2) led to a pCR of 18% in patients with locally advanced and inflammatory breast cancer (11). Our study agrees with the results of these authors, although doses of ET were lower.

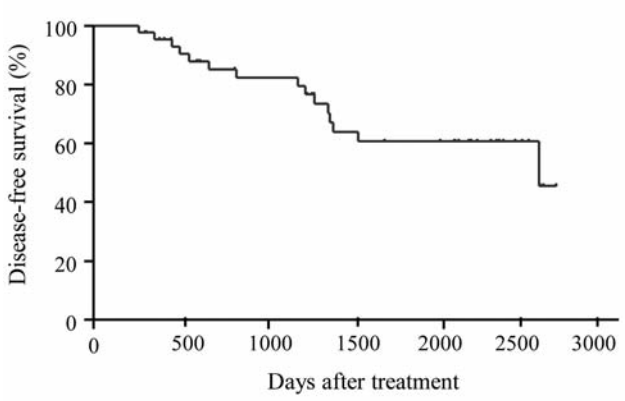

Figure 1. *Disease-free survival after treatment of the 45 enrolled patients. The 5-year cumulative disease-free survival rate after treatment was 60.7%.*

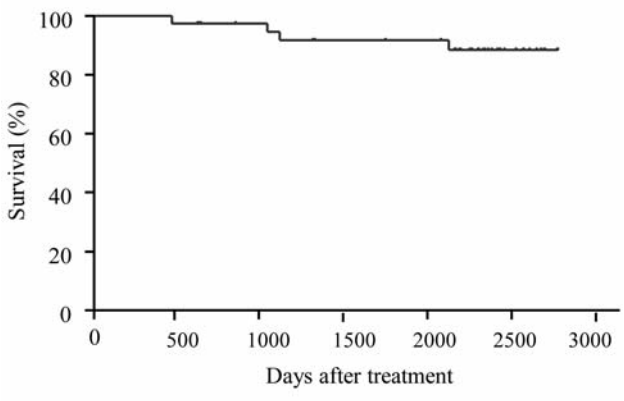

Figure 2. *Overall survival after treatment of the 45 enrolled patients. The cumulative overall survival rate after treatment was 91.8%.*

Table IV. *Hematological and non-hematological toxicities due to epirubicin and docetaxel concomitant chemothrapy for breast cancer.*

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3-4	
Hematological toxicities						
Anemia	21	11	0	0	0	
Thrombocytopenia	13	0	0	0	0	
Leukocytopenia	3	6	19	13	32	69.6%
Neutropenia	2	1	8	26	34	73.9%
Febrile neutropenia	0	0	8	0	8	17.4%
Fever	5	3	7	0	7	15.2%
Elevated AST	14	0	1	0	1	2.2%
Elevated ALT	12	6	0	1	1	2.2%
Elevated Alb	10	0	0	0	0	
Elevated Al-p	3	0	0	0	0	
Hyperbilirubinemia	3	0	0	0	0	
Elevated creatinine	2	0	0	0	0	
Elevated CPK	3	1	0	0	0	
Hypocalcemia	3	0	0	0	0	
Hyperkalemia	3	1	0	0	0	
Hypokalemia	3	0	0	0	0	
Hypernatremia	3	0	0	0	0	
Hyponatremia	2	0	0	0	0	
Non-hematological toxicities						
Fatigue	23	5	2	0	2	4.3%
Edema	2	0	0	0	0	
Acute reaction	2	1	0	0	0	
Vomiting	11	5	2	0	2	4.3%
Nausea	21	12	1	0	1	2.2%
Diarrhea	7	3	0	0	0	
Oral cavity	8	2	0	0	0	
Anorexia	22	8	4	0	4	8.7%
Alopecia	2	33	0	0	0	
Skin	1	3	0	0	0	
Constipation	10	4	2	0	2	4.3%
Peripheral neurotoxicity	1	0	0	0	0	

AST: Asparate aminotransferase; ALT: alanine aminotransferase; Alb: albumin; Al-p: alkaline phosphatase; CPK: creatine phosphokinase.

As for BCS, the rate of BCS was low, reaching 35.6% in our study. It is apparent that BCS was rarely performed in Japan, especially for tumors larger than 3.1 cm, when this study was started in early 2002. BCS was not a common practice even for patients with tumors that became small enough to be suitable for BCS after neoadjuvant chemotherapy. Currently sequential treatment with an anthracycline, followed by a taxane is also being used as a standard therapy in many institutions, but decision making is commonly based on the informed consent of patients concerning efficacy, adverse events and the treatment period.

The most important point to consider when one is selecting the modality of treatment is whether an efficacy can be predicted or not. In the ET therapy, ER negativity was found to be significantly correlated with clinical response, while a marginal difference was seen in regard to PgR and HER2 status. In addition, negative ER and PgR status led to the highest pCR. Several immunohistochemical markers and gene expression profiles have been tested for their predictive value in the neoadjuvant setting. Several NAC studies (12, 13) have demonstrated that patients with ER-negative tumors are more likely to achieve pCR than those with ER-positive tumors. Other factors that have been associated with response to NAC are invasive lobular carcinoma, p53 and Ki-67 expression (14-17).

The ET regimen used in this study produced a 5-year OS rate of 91.8%, which appeared to be very good considering the study patients who had large primary tumors. The prognosis of patients who were able to achieve pCR was favorable, while for patients with residual tumors, the prognosis is known to be dependent on the tumor biology (12, 18, 19). Moreover, the status of lymph node metastasis after treatment was also reported to be a significant factor (3, 18-20). In the present study, lymph node metastasis was seen in 63% of the patients before treatment, while it was slightly reduced to 56.8% (n=25) of patients, after treatment.

The AEs commonly experienced in this study were hematological toxicities but manageable. This translates into the high mean and median RDI, which were up to 96.4% and 100% respectively, indicating that the chemotherapy completion rate and the DI were high. With regard to AEs and treatment regimen, the incidence of AEs was reported to be much higher with concomitant use of antineoplastic agents than in sequential therapy (8). In the GEICAM-9903 study (21), febrile neutropenia appeared to be less commonly seen in the anthracycline followed by taxane arm (29.3% of patients), as compared with the concomitant therapy arm (47.8%; p=0.02). In addition, asthenia, diarrhea, and fever also occurred more frequently in the concomitant therapy arm. The doses used in that study were 50 mg/m^2 of doxorubicin and 75 mg/m^2 of docetaxel. In our study, febrile neutropenia was observed in 17.4% of patients, which was much lower than that seen in the concomitant regimen, in the GEICAM-9903 study.

In conclusion, the ET regimen produced a high clinical response, associated with a pCR of 10% and a BCS rate of 35.6%. The prognosis after the treatment was good, with 5-year OS of 91.8%. Most importantly, AEs were also easily manageable indicating that ET can be considered as a valuable treatment option in the neoadjuvant treatment setting for patients with primary breast cancer.

Conflict of Interest

None of the Authors have any conflict of interest.

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