

The Combination of Epirubicin plus Docetaxel as Neoadjuvant Chemotherapy in Locally-advanced Breast Cancer

AKIRA HIRANO^{1*}, TADAO SHIMIZU^{1*}, HIROSHI IMAMURA¹, OSAMU WATANABE¹, JUN KINOSHITA¹, TOSHIHIRO OKABE¹, KIYOMI KIMURA¹, MARI KAMIMURA¹, KAORU DOMOTO¹, MOTOHIKO AIBA² and KENJI OGAWA¹

¹Department of Surgery and ²Department of Surgical Pathology, Tokyo Women's Medical University Daini Hospital, Tokyo 116-8567, Japan

Abstract. *Background:* The purpose of this study was to evaluate the activity and toxicity of epirubicin plus docetaxel as neoadjuvant chemotherapy for locally advanced breast cancer. *Patients and Methods:* In this single-center, phase II trial, twenty-one patients with locally advanced breast cancer ($T>3$ cm or $N>1$) received epirubicin (70 mg/m^2) and docetaxel (60 mg/m^2) on Day 1 of each cycle for up to 6 cycles. *Results:* Clinically complete responses (CR) were observed in 5 patients and partial responses were observed in 14 patients. The clinical response rate was 90.5% (95% confidence interval, 78.0-99.9). Eleven patients (52.4%) underwent breast conserving surgery. Pathological response evaluation revealed 2 CR (9.5%). Grade 4 neutropenia was recorded in 81.0% of the patients and febrile neutropenia occurred in 1 patient. *Conclusion:* The combination of epirubicin plus docetaxel was an active and well-tolerated treatment for locally-advanced breast cancer.

Many studies have indicated that adjuvant chemotherapy was active for breast cancer and prolonged the survival time of patients (1, 2). The famous National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial clarified that pre-operative chemotherapy never shortens survival time compared with post-operative chemotherapy (3).

This trial also demonstrated that pathological tumor-response was a predictor of overall survival, suggesting that pre-operative chemotherapy would take advantage of controlling micrometastasis and drug-delivery to cancer cells. Thus, neoadjuvant (primary) chemotherapy is now considered

the standard therapy for the treatment of locally-advanced breast cancer.

It is clear that the anthracyclines are the most standard and active drugs for breast cancer. Combination chemotherapy is associated with higher response rates than single-agent treatment in metastatic breast cancer. Anthracycline-based regimens include doxorubicin and cyclophosphamide, epirubicin and cyclophosphamide and doxorubicin, cyclophosphamide and 5-Fluorouracil. Although anthracycline-based pre-operative chemotherapy showed a good response rate, a complete pathological response (pCR) rate was not achieved (3-6).

In an attempt to achieve a superior response rate as a surrogate end-point, many new drugs have been investigated. In the 1990s, the taxanes emerged as novel chemotherapeutic agents. Docetaxel, the semi-synthetic taxoid, has been shown in several studies to be effective both in pre-treated and treated disease (7-10). Furthermore, the combination of anthracycline plus taxane was demonstrated to be a superior clinical effect than conventional anthracycline-based regimens in metastatic breast cancer (11).

We expected that the combination of anthracyclines plus taxanes would show a higher response-rate as primary chemotherapy. Several trials indicated that the polychemotherapy of anthracycline plus docetaxel is an effective regimen of neoadjuvant chemotherapy (12-14). Epirubicin, which is less cardiotoxic than doxorubicin, was the anthracycline selected and docetaxel was the taxane selected for this combination chemotherapy. We designed a phase II trial with patients receiving neoadjuvant epirubicin plus docetaxel for locally-advanced breast cancer to determine the efficacy and toxicity of this regimen.

Patients and Methods

Study design. In this single-center, phase II trial, the primary end-point of the study was the rate of objective response evaluated by clinical examination, and secondary end-points were pathological response in the breast and axilla, breast-conserving rate and toxicities.

*Both authors contributed equally to this work.

Correspondence to: Kenji Ogawa, MD, 2-1-10 Nishiogu, Arakawa-ku, Tokyo 116-8567, Japan. Tel: +81-3-3810-1111, Fax: +81-3-3894-5493, e-mail: ogawasu@dnh.twmu.ac.jp

Key Words: Breast cancer, neoadjuvant chemotherapy, epirubicin, docetaxel.

It was determined that the expected rate of objective response in the trial was 90% 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 17 evaluable patients.

Patients. Women referred to the Tokyo Women's Medical University Daini Hospital, Japan, with histologically-diagnosed breast cancer that fell into the T2 (>3 cm), T3, T4a-c or N1-3 categories of the International Union Against Cancer (UICC) staging system (15), were eligible if they were age ≤ 75 years, had a performance status of 0 to 2 according to the Eastern Cooperative Oncology Group scale and had adequate organ function (*i.e.*, WBC count $\geq 4,000/\text{mm}^3$ and $\leq 12,000/\text{mm}^3$, absolute neutrophil count $\geq 2,000/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, hemoglobin level $\geq 9.5\text{ g/dl}$, transaminase level $\leq 1.5 \times$ upper limit of normal value (ULNV), alkaline phosphates level $\leq 2.5 \times$ ULNV and bilirubin level $\leq 1.5 \text{ mg/dl}$). Patients with inflammatory breast cancer were excluded. Written informed consent was obtained from all patients.

Treatment. The patients received 4 to 6 cycles of epirubicin 70 mg/m^2 over 20 min followed by docetaxel 60 mg/m^2 for more than 1 h every 21 days. Pre-medication consisted of dexamethasone (8 mg) and famotidine (20 mg), an intravenous 5-HT₃ antagonist at a standard dose immediately before starting chemotherapy. Granulocyte-colony stimulating factor (G-CSF) could be used in patients with febrile Grade 3 to 4 leucopenia or Grade 4 neutropenia. Radiation therapy was also given to patients undergoing breast-conserving surgery.

Assessment of response and toxicity. Objective responses were defined clinically for the primary end-point of this study. A complete response (CR) was defined as the complete disappearance of all known disease. A partial response (PR) was defined as a $\geq 50\%$ decrease in the sum of the products of the perpendicular diameters of all measurable lesions, and progressive disease (PD) as an increase of $\geq 25\%$ in the size of 1 or more measurable lesions.

The pathological responses were graded as follows (16): Grade 0, no histological change in the cancer cells; Grade 1a, mild cellular injury in a proportion of the cancer cells, or severe cellular injury or replacement of less than 1/3 of the cancer cells by fibroblasts, histiocytes or fibrosis; Grade 1b, severe cellular injury or replacement of 1/3 to 2/3 of the cancer cells; Grade 2, severe cellular injury or replacement of 2/3 or more of the cancer cells including residual cancer cells only *in situ*; Grade 3, no cancer cells, necrotic or non-viable residual cancer cells. pCR was defined as no evidence of invasive malignancy in the breast or lymph nodes. Therefore, pCR was made up of Grade 3 and a part of Grade 2.

Toxicity was assessed through clinical examination at baseline and before each drug administration. Laboratory tests, including a complete biochemical routine and a complete blood cell count, were performed at the baseline and at the end of each cycle. A blood cell count was also repeated on day 7 of each cycle. To describe toxicity, the Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) were applied (17).

Results

The clinical characteristics of the 21 female patients are shown in Table I. The median age of the patients was 54 years (range, 26-66 years). Two-thirds of the women were menopausal and

Table I. Clinical characteristics of 21 patients.

Age	No. of patients (%)	
	Median	Range
Initial tumor category		
T2	11	(52.3)
T3	6	(28.6)
T4b	3	(14.3)
T4c	1	(4.8)
Initial lymph node category		
N0	8	(38.1)
N1	11	(52.3)
N2	1	(4.8)
N3	1	(4.8)
Menopausal status		
pre-menopausal	7	(33.3)
post-menopausal	14	(66.7)
Stage of disease		
IIA	5	(23.8)
IIB	7	(33.3)
IIIA	4	(19.0)
IIIB	4	(19.0)
IIIC	1	(4.8)
Hormone receptor status		
ER and PgR both positive	6	(28.6)
ER or PgR positive	3	(14.3)
ER and PgR both negative	12	(57.1)
HER2 (Herceptest)		
3+	7	(33.3)
2+ ~ 0	14	(66.7)

one-third was not. In total, 86 cycles of treatment were administered. The treatment was interrupted before its planned completion in 3 patients due to no change in 2 patients after the third cycle and patient refusal with clinical evidence of complete response in 1 patient after the third cycle. Eleven patients required G-CSF support according to the protocol rules. Surgery was performed for all patients and breast conservation in 11 patients (52.4%). Clinical CRs were observed in 5 patients and PRs were observed in 14 patients (Table II). The clinical response rate was 90.5%. Pathological response evaluation showed 2 pCRs (9.5%): 2 patients were Grade 3 responses with the complete disappearance of invasive and non-invasive tumors in breast and lymph nodes. There was a Grade 2 response with the complete disappearance of invasive tumor, but there were residual tumors in the intraductal areas and lymph nodes observed in 1 patient.

The adverse events that were shown in more than 1 patient are summarized in Table III. Grade 4 neutropenia was recorded in 17 patients (81.0%) and febrile neutropenia occurred in 1 patient (4.8%). Grade 1-2 anemia was recorded in 76.2% and Grade 1-2 thrombocytopenia was recorded in 23.8%. There were no toxicities recorded for the liver, lungs

Table II. Objective results of main tumor.

	No. of patients (%)
Clinical response	
CR	5 (23.8)
PR	14 (66.7)
NC	2 (9.5)
PD	0 (0)
Pathological response	
Grade 3	2 (9.5)
Grade 2	8 (38.1)
Grade 1b	4 (19.0)
Grade 1a	6 (28.6)
Grade 0	1 (4.8)

CR=complete response; PR=partial response; NC=no change; PD=disease progression.

or kidneys. All patients had Grade 2 alopecia. Grade 1-2 nausea was experienced by 14.3% and vomiting was experienced by 9.5% of the patients. Fatigue (Grade 1) was experienced by 9.5%. Only 1 patient had diarrhea (Grade 3).

Discussion

The clinical response rate (CRR) of this trial was 90.5%. It was higher than with the other anthracycline-based regimen (CRR: 49% to 83%) (3-6) and similar to the data from combination of anthracyclines and taxanes (11, 13, 14). Among patients with negative hormone-receptors and positive HER2, primary chemotherapy was more effective and had a higher pCR rate (12).

ER and PgR were both negative in 2 pCR cases and HER2 was overexpressed in 1 pCR case. These factors could predict a good response to chemotherapy. Although there is a tendency that the observation of pCR is rare among patients with positive hormone-receptors or negative HER2, these factors do not become negative prognostic markers indicating termination of the anthracycline/taxane chemotherapy. Thus, novel negative prognostic markers are needed in order to predict any PD cases and to avoid unnecessary chemotherapy.

The breast conservative rate of this study was 52.4%, and is consistent with the data reported in extended studies that employed other novel regimens, such as doxorubicin plus docetaxel (13, 18).

Myelosuppression was severe but reversible toxicity was achieved in the present study. Neutropenia was frequent and Grade 4 neutropenia was recorded in 17 patients (81.0%). Neither neurosensory symptoms nor cardiotoxicity were observed.

In other trials combining epirubicin and docetaxel, the recommended dose of epirubicin (E)/docetaxel (T) was E: 75 mg/m², T: 75-80 mg/m² and dose escalation did not improve the response rate (19). The recommended dose of

Table III. Hematological and non-hematological toxicities.

Toxicities	No. of patients (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Neutropenia	0 (0.0)	0 (0.0)	4 (19.0)	17 (81.0)
Leucopenia	0 (0.0)	6 (28.6)	8 (38.1)	7 (33.3)
Anemia	6 (28.6)	10 (47.6)	0 (0.0)	0 (0.0)
Thrombocytopenia	4 (19.0)	1 (4.8)	0 (0.0)	0 (0.0)
Non-hematological				
Alopecia	0 (0.0)	21 (100)		
Nausea	1 (4.8)	2 (9.5)	0 (0.0)	0 (0.0)
Vomiting	1 (4.8)	0 (0.0)	1 (4.8)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)
Fatigue	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)
Mucositis	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

docetaxel as a single agent for Japanese women was 60-70 mg/m² (20) and the addition of epirubicin accelerated the myelosuppression. Therefore, the docetaxel dose in combination was reduced to 60 mg/m² in this study. Despite dose-reduction, a higher clinical response-rate was obtained in this study. There was a good clinical response, but the pCR rate (9.5%) was not as high as other anthracycline-based regimens (3-6).

The polychemotherapy of anthracyclines and taxanes is divided into 2 methods, combination and sequential. In the GEPAR-DUO trial, the pCR rate was 14.1% in the sequential arm and 7.1% in the combination arm ($p<0.01$) (21). 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 (22). The results of the study suggested the priority of sequential chemotherapy, however, another ongoing trial, NSABP-B27, could not prove the hypothesis that improving the pCR rate might produce a direct survival benefit (23). Thus, we cannot conclude that the sequential regimen is superior to the combination until evidence of a survival benefit is indicated.

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

References

- 1 Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 352: 930-942, 1998.
- 2 Bonadonna G, Brusamolino E, Valagussa P, Rossi A, Brugnatelli L, Brambilla C, De Lena M, Tancini G, Bajetta E, Musumeci R and Veronesi U: Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294: 405-410, 1976.

- 3 Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, Wickerham DL, Begovic M, DeCillis A, Robidoux A, Margolese RG, Cruz AB Jr, Hoehn JL, Lees AW, Dimitrov NV and Bear HD: Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 16: 2672-2685, 1998.
- 4 Belembaogo E, Feille V, Chollet P, Cure H, Verrelle P, Kwiatkowski F, Achard JL, Le Bouedec G, Chassagne J and Bignon YJ: Neoadjuvant chemotherapy in 126 operable breast cancers. *Eur J Cancer* 28A: 896-900, 1992.
- 5 van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vanderveiden C, Duchateau L and Cooperating investigators: Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. *J Clin Oncol* 19: 4224-4237, 2001.
- 6 Kuerer HM, Newman LA, Smith TL, Ames FC, Hunt KK, Dhingra K, Theriault RL, Singh G, Binkley SM, Sneige N, Buchholz TA, Ross MI, McNeese MD, Buzdar AU, Hortobagyi GN and Singletary SE: Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol* 17: 460-469, 1999.
- 7 Fumoleau P, Chevallier B, Kerbrat P, Krakowski Y, Misset JL, Maugard-Louboutin C, Dieras V, Azli N, Bougnon N, Riva A and Roche H: A multicentre phase II study of the efficacy and safety of docetaxel as first-line treatment of advanced breast cancer: report of the Clinical Screening Group of the EORTC. *Ann Oncol* 7: 165-171, 1996.
- 8 Amat S, Bougnoux P, Penault-Llorca F, Fetissof F, Cure H, Kwiatkowski F, Achard JL, Body G, Dauplat J and Chollet P: Neoadjuvant docetaxel for operable breast cancer induces a high pathological response and breast-conservation rate. *Br J Cancer* 88: 1339-45, 2003.
- 9 Sjstrom J, Blomqvist C, Mouridsen H, Pluzanska A, Ottosson-Lonn S, Bengtsson NO, Ostentad B, Mjaaland I, Palm-Sjovall M, Wist E, Valvere V, Anderson H and Bergh J: Docetaxel compared with sequential methotrexate and 5-fluorouracil in patients with advanced breast cancer after anthracycline failure: a randomised phase III study with crossover on progression by the Scandinavian Breast Group. *Eur J Cancer* 35: 1194-201, 1999.
- 10 Nabholz JM, Senn HJ, Bezwoda WR, Melnychuk D, Deschenes L, Douma J, Vandenberg TA, Rapoport B, Rosso R, Trillet-Lenoir V, Drbal J, Molino A, Nortier JW, Richel DJ, Nagykalnai T, Siedlecki P, Wilking N, Genot JY, Hupperets PS, Pannuti F, Skarlos D, Tomiak EM, Murawsky M, Alakl M and Aapro M: Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 Study Group. *J Clin Oncol* 17: 1413-1424, 1999.
- 11 Bonnerterre J, Dieras V, Tubiana-Hulin M, Bougnoux P, Bonnerterre ME, Delozier T, Mayer F, Culin S, Dohoulo N and Bendahmane B: Phase II multicentre randomised study of docetaxel plus epirubicin vs. 5-fluorouracil plus epirubicin and cyclophosphamide in metastatic breast cancer. *Br J Cancer* 91: 1466-1471, 2004.
- 12 Bear HD, Anderson S, Brown A, Smith R, Mamounas EP, Fisher B, Margolese R, Theoret H, Soran A, Wickerham DL and Wolmark N: The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 21: 4165-4174, 2003.
- 13 Ganem G, Tubiana-Hulin M, Fumoleau P, Combe M, Misset JL, Vannetzel JM, Bachelot T, De Ybarlucea LR, Lotz V, Bendahmane B and Dieras V: Phase II trial combining docetaxel and doxorubicin as neoadjuvant chemotherapy in patients with operable breast cancer. *Ann Oncol* 14: 1623-1628, 2003.
- 14 de Matteis A, Nuzzo F, D'Aiuto G, Labonia V, Landi G, Rossi E, Mastro AA, Botti G, De Maio E and Perrone F: Docetaxel plus epidoxorubicin as neoadjuvant treatment in patients with large operable or locally advanced carcinoma of the breast: a single-center, phase II study. *Cancer* 94: 895-901, 2002.
- 15 Wittekind CH: Breast Tumours. In: TNM Classification of Malignant Tumours Sixth ed., Wiley-Liss, New York, USA, pp. 131-141, 2002.
- 16 Kurosumi M, Akiyama F, Iwase T, Motomura K, Okazaki M and Tsuda H: Histopathological criteria for assessment of therapeutic response in breast cancer. *Breast Cancer* 1: 1-2, 2001.
- 17 National Cancer Institute: Common Treatment Criterion for Adverse Event Version 3.0. Dec.12, 2003. <http://ctep.info.nih.gov/reporting/ctcnew.html>
- 18 Matsuo K, Fukutomi T, Watanabe T, Hasegawa T, Tsuda H and Akashi-Tanaka S: Concordance in pathological responses to neoadjuvant chemotherapy between invasive and noninvasive components of primary breast carcinomas. *Breast Cancer* 9: 75-81, 2002.
- 19 Pagani O, Sessa C, Martinelli G, Crivellari D, Buonadonna A, Thurlimann B, Hess D, Borner M, Bauer J, Zampino G, Zimatore M, Grafeo R, Riva A and Goldhirsch A: Dose-finding study of epirubicin and docetaxel as first-line chemotherapy in patients with advanced breast cancer. *Ann Oncol* 10: 539-545, 1999.
- 20 Adachi I, Watanabe T, Takashima S, Narabayashi M, Horikoshi N, Aoyama H and Taguchi T: A late phase II study of RP56976 (docetaxel) in patients with advanced or recurrent breast cancer. *Br J Cancer* 73: 210-216, 1996.
- 21 Jackisch C, von Minckwitz G, Raab G, Schuette M, Blohmer JU, Hilfrich J, Gerber B, Costa S, Merkle E, Eidtmann H, Lampe D, DuBois A, Tulusan AH, Caputo A and Kaufmann M: Primary endpoint analysis of the Geparduo-study-preoperative chemotherapy (PCT) comparing dose-dense *versus* sequential adriamycin/docetaxel combination in operable breast cancer (T2-3, N0-2, M0). San Antonio Breast Cancer Symposium 2002. Abst #152.
- 22 Jackisch C, von Minckwitz G, Eidtmann H, Costa SD, Raab G, Blohmer JU, Schutte M, Gerber B, Merkle E, Gademann G, Lampe D, Hilfrich J, Tulusan AH, Caputo A and Kaufmann M: Dose-dense biweekly doxorubicin/docetaxel *versus* sequential neoadjuvant chemotherapy with doxorubicin/cyclophosphamide/docetaxel in operable breast cancer: second interim analysis. *Clin Breast Cancer* 3: 276-280, 2002.
- 23 Bear HD, Anderson S, Smith RE, Robidoux A, Kahlenberg MS, Margolese RG, Dakhil SR, Pajon ER, Hoehn JL, Mamounas EP, Geyer CE, Julian TB and Wolmark N: A randomized trial comparing preoperative (preop) doxorubicin/cyclophosphamide (AC) to preop AC followed by preop docetaxel (T) and to preop AC followed by postoperative (postop) T in patients with operable carcinoma of the breast: results of NSABP B-27. San Antonio Breast Cancer Symposium 2004. Abst #26.

Received October 3, 2005

Accepted November 25, 2005