Table 4. Grade of Skin Adverse Reactions by Institution

Phase	Garde	Institution				Total (n = 284)	Institutional difference
		A (n = 66)	B (n = 90)	C (n = 64)	D (n = 64)		*p*-value (KW Test*)
Acute:	0	5 (7%)	8 (9%)	9 (14%)	1 (2%)	23 (8%)	<0.0001
0 to 3 months	1	51 (77%)	42 (47%)	44 (69%)	34 (53%)	171 (60%)	
	2	10 (15%)	35 (39%)	10 (16%)	26 (41%)	81 (29%)	
	3	–	5 (6%)	1 (2%)	3 (5%)	9 (3%)	
Late:	0	17 (26%)	79 (88%)	54 (84%)	16 (25%)	166 (59%)	<0.0001
3 months	1	49 (74%)	11 (12%)	9 (14%)	28 (44%)	97 (34%)	
	2	–	–	1 (2%)	17 (27%)	18 (6%)	
	3	–	–	–	3 (5%)	3 (1%)	
Late:	0	48 (73%)	86 (96%)	62 (97%)	59 (92%)	255 (90%)	<0.0001
6 months	1	18 (27%)	4 (4%)	2 (3%)	4 (6%)	28 (10%)	
	2	–	–	–	1 (2%)	1 –	
	3	–	–	–	–	–	

*KW: Kruskal-Wallis test

Statistical Analysis

We dichotomized skin reactions into an acute phase (grades 2 and over) and a late phase (grade 1 and over). For univariate analysis of associations between response and baseline characteristics or treatment details, we used Fisher's exact test for binary variables and the Cochran-Armitage test for ordinary variables. We substituted the c^2 test for the Fisher exact test when the number of categories was large and caused computational difficulties.

We performed logistic regression to construct a model with multiple factors for the prediction of responses. We used a backward selection procedure to eliminate non-significant factors. The initial set of variables comprised all factors that displayed significant univariate association with the responses and had less than 10 missing values.

Results

Adverse Skin Effects; Clinical Radiosensitivity

Table 4 shows skin reactions by phase and institution. All but 23 patients displayed acute phase effects, and the institutions were identified as a factor associated with adverse effects ($p < 0.0001$).

The incidence of grade 1 reactions decreased rapidly with time, but considerable inter-institutional differences were apparent. Inter-institutional differences were also observed for grade 2+ skin reactions in the early phase and at 3 months.

Univariate Analysis

Univariate analysis of associations between treatment details and baseline characteristics with skin reactions identified operative procedure ($p = 0.0056$), photon energy ($p = 0.0032$), smoking habits ($p = 0.0017$), and use of an immobilization device ($p = 0.0040$) as risk factors for grade 2+ skin reactions at less than 3 months (Table 5). Smokers had a higher incidence of grade 2+ skin reactions in the acute phase ($p = 0.0017$). At 3 months, the following factors were associated with grade 1+ adverse skin effects: operative procedure ($p = 0.047$), photon energy ($p = 0.0002$), use of a multileaf collimater (MLC) ($p < 0.0001$), use of a wedge filter ($p < 0.0001$), and use of an immobilization device ($p < 0.0001$). A bolus was used in 13 patients at institution A. In 11 of 13 patients, radiotherapy was performed with 10-MV photon. Five of 13 patients developed grade 2+ skin reaction in the early phase. At 3 months, nine of 13 were scored as grade 1. Though use of a bolus was not associated with grade 1+ skin reactions at 3 months at institution A (66 patients), there was a weak association between the use of a bolus and skin reactions in 284 patients ($p = 0.035$). At 6 months, the factors associated with grade 1+ adverse skin effects were use of an MLC ($p = 0.0020$) and use of an immobilization device ($p < 0.0001$). Unilateral vs. bilateral breast cancer, administration of intravenous chemotherapy, and

Table 5. Univariate Analysis of Baseline Characteristics and Treatment Details with Acute Skin Reactions with Grade 2+

Factors	Institution									
	A		B		C		D		Total	
	number of patients	number of patients with grade 2+	number of patients	number of patients with grade 2+	number of patients	number of patients with grade 2+	number of patients	number of patients with grade 2+	number of patients	number of patients with grade 2+
Smokng habbit: CA*	$p=0.2275$		$p=0.0003$		$p=0.3749$		$p=0.9453$		$p=0.0017$	
Yes	8	2	14	12	2	1	4	2	28	17 (61%)
Quit	1	2	4	3	2	–	10	4	17	7 (41%)
Never	24	6	71	25	38	6	50	23	183	56 (31%)
Surgery: FE*	$p=0.4963$		$p=0.0104$		$p=0.6460$		$p=0.4603$		$p=0.0056$	
Quadrantectomy	61	9	18	11	9	2	1	1	89	23 (26%)
Partial exision	3	1	58	19	55	9	62	28	178	57 (32%)
Tumorectomy	–	–	1	1	–	–	–	–	1	1
Others	1	0	11	8	–	–	–	–	12	8
Photon energy: CA*	$p=0.0031$		$p=0.4529$		–		$p=0.2751$		$p=0.0032$	
Photon-linac 4	52	5	5	3	64	11	62	28	183	47 (26%)
Photon-linac 6	–	–	84	36	–	–	1	1	85	37 (44%)
Photon-linac 10	11	5	–	–	–	–	–	–	11	5 (46%)
Immobilization device: FE*	–		$p=1.0000$		–		–		$p=0.0040$	
Yes	–	–	87	39	64	11	64	29	215	79 (37%)
No	60	10	3	1	–	–	–	–	63	11 (18%)

*CA: Cochran-Armitage test, FE: Fisher's Exact test

hormone therapy did not have statistically significant univariate associations in the study patients.

Logistic Regression Analysis

We performed logistic regression modeling to evaluate the influence of multiple risk factors on the risk of developing clinical radiosensitivity. We included factors significantly ($p < 0.05$) associated with clinical radiosensitivity and less than 10 missing data for the initial set of variables and then applied a backward variable selection procedure.

Institution, operative procedure, and photon energy for whole breast irradiation were associated with acute adverse effects, but at 3 months, only the institution remained as a risk factor (Table 6).

Discussion

We studied 284 breast cancer patients who had received breast-conserving surgery and radiotherapy for associations between 45 clinical factors and adverse skin effects as a measure of radiosensitivity. In this study, all four institutions had clinically radiosensitive patients (Table 4).

Risk factors associated with breast cancer include number of pregnancies or births, age at menarche or menopause (estrogen exposure)[21, 22], and family history of breast cancer[23]. None of those factors were significantly associated with adverse effects of radiotherapy in the present study. Diabetes mellitus[24] and collagen disease[25, 26] are known as risk factors for adverse irradiation effects. This study included 11 patients with diabetes mellitus and 5 with collagen disease. Significant univariate association was not revealed between adverse skin effects and these conditions in this study. Eleven patients had bilateral breast cancer, and each had been diagnosed with cancer in the contralateral breast prior to the present diagnosis. Skin reaction severity was the same among those patients as among patients with unilateral breast cancer.

In institution A, 9 (15%) of the 61 patients who received quadrantectomy developed grade 2+ skin reactions, while in institution B, 11 (61%) of the 18 patients who received quadrantectomy developed 2+ skin reactions, indicating that the pro-

Table 6. Final Logistic Models after Backward Variable Selection for Each Phase

Response variable	Explanatory variable	*p*-value	Category	Odds Ratios (95%C.I.)
Acute:				
0 to 3 months	Institution	0.0002	B vs A	9.2 (1.2, 71.9)
Skin reaction with Grade 2+			C vs A	3.7 (1.0, 13.8)
			D vs A	16.1 (4.2, 62.3)
	Breast-conserving Surgery	0.0099	Bq* vs Bp*	3.0 (1.3, 7.0)
			Others vs Bp*	5.1 (1.2, 21.3)
	Photon energy level	0.0143	6-MV vs 4-MV	1.1 (0.2, 6.5)
			10-MV vs 4-MV	11.3 (2.2, 57.3)
Late:				
3 months				
Skin reaction with Grade 1+	Institution	<0.0001	B vs A	0.1 (0.0, 0.1)
			C vs A	0.1 (0.0, 0.2)
			D vs A	1.2 (0.5, 2.8)
Late:				
6 months				
Skin reaction with Grade 1+	Institution	<0.0001	B vs A	0.2 (0.0, 0.5)
			C vs A	0.1 (0.0, 0.5)
			D vs A	0.3 (0.1, 0.9)

*Bq: Quadrantectomy, Bp: Partial exision

cedure might not represent a significant risk factor.

Tamoxifen treatment during radiotherapy enhances the risk of radiation-induced lung fibrosis[28], but we noted no relationship between tamoxifen treatment and adverse skin effects among the 123 patients in this study who received tamoxifen (data not shown).

Radiotherapy factors associated with various secondary effects include total dose, total number of fractions, total duration of treatment, size of radiation field, and combination with boost irradiation[29]. Habibollahi, *et al.* measured doses at several points over the irradiated breast using thermoluminescent dosimetry in 51 patients treated using breast-conservation techniques, including tumor site implantation with iridium-192 wires to give a boost dose followed by external beam therapy. Skin dose was reportedly unrelated to development of skin pigmentation, edema or fibrosis[30]. More recent protocols for breast-conserving surgery included relatively uniform radiotherapy (such as a 50 Gy total dose for the whole breast using 2 Gy fractions over 5 weeks of treatment), and that might be another reason why the total dose, total number of fractions and total duration of treatment were not identified in this study, in which most patients were treated with a uniform protocol.

Higher energy machines increase the depth of the 100% isodose and decrease the size and magnitude of hot spots on the irradiated skin. In the present study, the use of a 10-MV linear accelerator was associated with a higher incidence of adverse effects (Table 5). A 10-MV linear accelerator was used in only one institution. In practice, a significant dose is given to the skin due to scattered radiation from the treatment machine[31]. This comes from interactions of the photon beam with the collimator and beam-modifying devices, and it varies with the design of the linear accelerator. Sixel and Podgorsac also investigated the depth of maximum dose (Dmax) for megavoltage x-rays. Dmax represented a function of beam energy and field size for 6-, 10-, and 18-MV x-ray beams with field sizes ranging from small to very large[32]. In our study, the field size for most patients was 100-200 cm^2, and it was not associated with adverse effects (data not shown).

It was not expected that modalities for patient-benefit, such as MLCs and immobilization devices, would be significantly associated with adverse effects. Use of an MLC has been reported to increase surface dose relative to an open field, by about 6%[33]. Dose inhomogeneity is related to the complex 3-dimensional shape of the breast, with

various distances between the beam entry and exit points, between source and skin, and the presence of tissues of varying radiological density. Inhomogeneous dose distribution is believed to result in areas of increased dose/fraction and leads to poor cosmesis[34]. In this study, immobilization devices were also associated with adverse effects. Immobilization devices prevent patients from changing position and improve the accuracy and reproducibility of results[35] so that inhomogeneity of dose distribution caused by patient set-up errors is reduced. It should be noted that patients at institutions A and D were irradiated without a MLC, and only patients at institution A were irradiated without an immobilization device.

Finally, we found that the risk of skin reactions to radiotherapy was highly dependent on the institution at which the patient was treated. That may have been due to the different treatment techniques used at the institutions (Table 3). Each institution showed different preferences in treatment techniques, such as operative procedures, magnitude of photon energy, and use of MLCs, immobilization devices and wedge filters. Analysis of genetic factors associated with adverse effects would be possible by stratifying patients according to institution. Selection of eligible institutions, where treatment modalities are employed, would also be possible when planning such a study.

Logistic regression analysis (Table 6) indicated that the risk factors we detected did not fully explain inter-patient differences in skin response. After we stratified according to these risk factors, we still observed substantial variations in the frequency of skin reactions between patients. This supports previous conclusions on the importance of genetic factors in normal tissue response of breast cancer patients[15-17] and suggests the need for investigation of the genetic factors related to individual radiosensitivity.

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Case Report

Two Cases of Adenoid Cystic Carcinoma: Preoperative Cytological Findings were Useful in Determining Treatment Strategy

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Adenoid cystic carcinoma (ACC) of the breast is a rare variant of breast malignancy and is known to have an excellent prognosis. We report two cases of ACC diagnosed by preoperative fine-needle aspiration cytology (FNAC), which proved to be very useful in determining the appropriate treatment. The patients were a 57-year-old woman (case 1) and a 71-year-old woman (case 2). On physical examinations and imaging studies both tumors were recognized as lobulated tumors that measured 3.0 × 2.3 cm (case 1) and 3.9 × 3.4 cm (case 2) respectively. FNAC materials showed clusters of malignant cells surrounding globules of mucus, therefore, ACC was diagnosed. Considering the characteristics of ACC, breast-conserving surgeries with axillary dissection and adjuvant radiotherapy were performed instead of primary chemotherapy or mastectomy. Histologically, a distinctive biphasic pattern was observed that consisted of true laminae and pseudocystic spaces. Tumor sizes were 4.0 × 3.3 cm (case 1) and 4.6 × 3.8 cm (case 2), respectively, and surgical margins were negative on microscopic examination. Lymph node metastasis was not present in either case. Even though ACC is very rare, preoperative diagnosis can be made based on its characteristic features. Preoperative diagnosis is extremely useful for determining appropriate treatment.

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Key words: Adenoid cystic carcinoma, Fine needle aspiration cytology

Adenoid cystic carcinoma (ACC) of the breast is rare, accounting for approximately 0.1% of all breast carcinomas. It has a more favorable prognosis than most other forms of breast cancer. Because of its excellent prognosis, it has been suggested that good local control could be obtained with either partial resection and radiation or simple mastectomy. Recently we encountered two cases of large size ACC, both of which were diagnosed by FNAC and treated with breast-conserving surgery and radiotherapy.

Case Report

Case 1

The patient was a 57-year-old postmenopausal woman who presented with a right breast mass on breast cancer screening. On physical examination the tumor was located at the boundary between both outer quadrants of the right breast. Palpation revealed that it was mobile, elastic hard and had clear margins. Mammmography revealed however, a mass with partially indistinct margins (Fig 1). The mass was a hypoechoic, lobulated solid tumor measuring 3.0 × 2.3 cm on ultrasonography (US) (Fig 2). Computed tomography (CT) showed enhanced breast tumor and a round shaped axillary lymph node suggesting metastasis of the carcinoma (Fig 3). Magnetic resonance (MR) mammography revealed early enhancement following injection of gadolinium diethylenetriamine-pentaacetic acid (Gd-DTPA), suggesting malignant neoplasm (Fig 4). FNAC of the tumor demonstrated clusters of malignant cells surrounding globules of mucus. The cytological findings were suggestively of a malignant tumor, most probably an ACC tumor. Thus, preoperative T2N1M0, stage IIB (TNM Stage classification, General Rules for Clinical and Pathological Recording of Breast Cancer, The Japanese Breast Cancer Society) was diagnosed,

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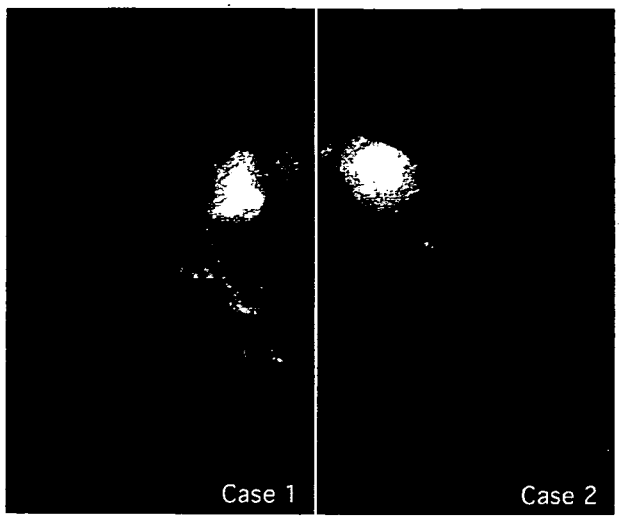

Fig 1. Case 1: Mammography demonstrated a tumor with an indistinct margin and lobule-shaped, high-density nodules without microcalcification or spicula formation. Case 2: Mammography demonstrated a high-density mass with a distinct margin; neither microcalcification nor spicula formation were observed.

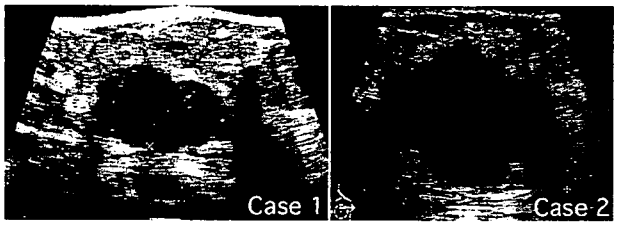

Fig 2. Ultrasonography showed lobulated, hypoechoic tumors with well-defined borders in both cases.

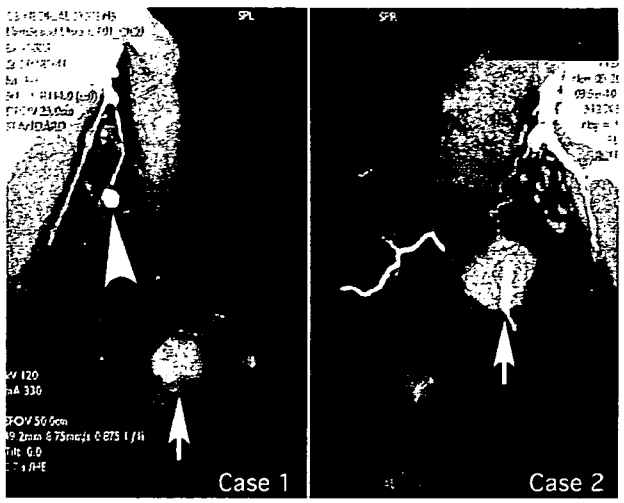

Fig 3. Three-dimensional CT revealed enhancing tumors (arrows) and an enhancing round shaped axillary lymph node (arrow head in case 1) suggesting metastasis.

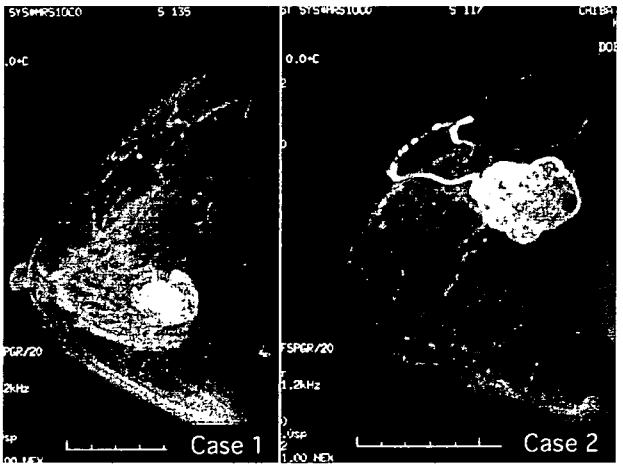

Fig 4. MR mammography showed breast tumors. Early enhancement was demonstrated suggesting malignancy. In case 1 the border of the tumor was poorly defined, however in case 2 the tumor showed strong peripheral enhancement.

which is usually treated with primary chemotherapy or mastectomy with axillary lymph node dissection. However, based on the cytological findings, breast-conserving surgery with axillary dissection was performed. The cut surface of the tumor was solid and yellow-white in color (Fig 6). Histologically, the tumor cells formed various arrangements including cribriform, tubular and trabecular nests, and extended 4.0 × 3.3 × 1.6 cm as an invasive lesion. The tumor showed a distinctive biphasic pattern consisting of both true laminae and pseudocystic spaces that contained mucous material (Fig 7-A, B). Immunohistochemically, the epithelial cells forming the true ducts were reactive to cytokeratin (Fig 7-C), and the myoepithelial cells surrounding the pseudocystic spaces were reactive to vimentin and α-smooth muscle actin (Fig 7-D). Materials in the true duct were reactive to carcinoembryonic antigen (CEA), while the contents of the pseudocysts were not (Fig 7-E). Pseudocyst contents were stained by Alcian blue but not Periodic acid Schiff (PAS) (Fig 7-F). The surgical margin was negative for cancer cells and no metastasis was observed in twenty-five axillary lymph nodes. Mild lymphatic and venous invasion were evident. Immunohistochemically, estrogen receptor (ER) and progesterone receptor (PgR) were negative and the Hercep Test score was 0. Postoperatively the patient was treated with CMF chemotherapy and radiotherapy. There has been no tumor recurrence within the first year following treatment.

Fig 5. FNAC findings of case 2. A: FNAC material contains round and branching multilayered clusters of cohesive, small, uniform epithelial cells and mucoid globules. (Papanicolaou stain). B: High-power view of A in another field showing globule of mucous surrounded by epithelial cells with little cytoplasm and small hyperchromatic nuclei (Papanicolaou stain).

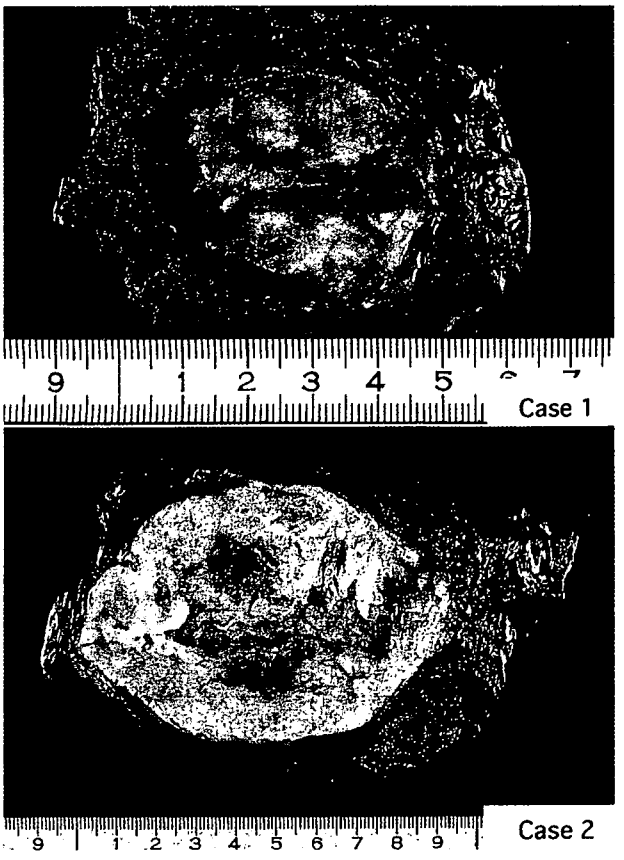

Fig 6. The cut surface of the tumors. Case 1: The tumor had a solid, yellow-white surface. Case 2: The cut surface of the tumor was yellow-white in color and contained cystic lesions.

Case 2

The patient was a 71-year-old postmenopausal woman who noticed a left breast mass. She visited another hospital and was referred to our institution for treatment. On physical examination, a hard tumor was found in the upper lateral quadrant. The tumor was mobile with clear margins and no axillary lymph nodes were palpable. Mammography demonstrated a well-circumscribed, lobulated, dense mass (Fig 1). US showed a heterogeneous lobulated tumor that measured 3.9 × 3.4 × 3.4 cm (Fig 2). On CT, the tumor showed a clear margin and no axillary lymph node swelling was apparent (Fig 3). Strong peripheral enhancement of the tumor was observed on MR mammography (Fig 4). FNAC samples of the tumor showed clusters of atypical cells surrounding globules of mucus (Fig 5). Malignant neoplasm was diagnosed suggestive of ACC. Core needle biopsy (CNB) was performed for further diagnosis. The CNB specimen showed cribriform and solid arrangements of monotonous tumor cells that had hyperchromatic nuclei and a small amount of cytoplasm. Mucous material was observed in the true ducts. Based on these findings the tumor was suspected as ACC, T2N0M0, stage IIA (TNM Stage classification, General Rules for Clinical and Pathological Recording of Breast Cancer, The Japanese Breast Cancer Society). Breast-conserving surgery with axillary dissection was performed. The tumor showed a yellow-white cut surface with cystic lesions (Fig 6). Histologically, the tumor cells formed cribriform and solid arrangements, and lumina containing mucous material were observed. Immunohistochemically, some of the lumina were surrounded by epithelial cells that were reactive to cytokeratin and others were surrounded by myoepithelial cells that were reactive to vimentin. Materials in the true ducts and pseudocysts were reactive to CEA and Alcian blue respectively. Based on these findings, the ACC was diagnosed. The tumor size was 4.6 × 3.8 cm, and the surgical margin was negative for tumor cells. Both ER and PgR were negative, and the Hercep score was 0. No metastasis was observed in thirty axillary lymph nodes. The patient received postoperative radiotherapy. No recurrence has been recognized 1 year after surgery.

Discussion

Adenoid cystic carcinoma (ACC) of the breast is one of the rarest forms of primary breast cancer, accounting for approximately 0.1% of all breast carcinomas. Frequently, palpation reveals a mobile tumor with clear margins that is often difficult to distinguish from fibroadenoma. On diagnostic imaging studies, ACC also has some features sug-

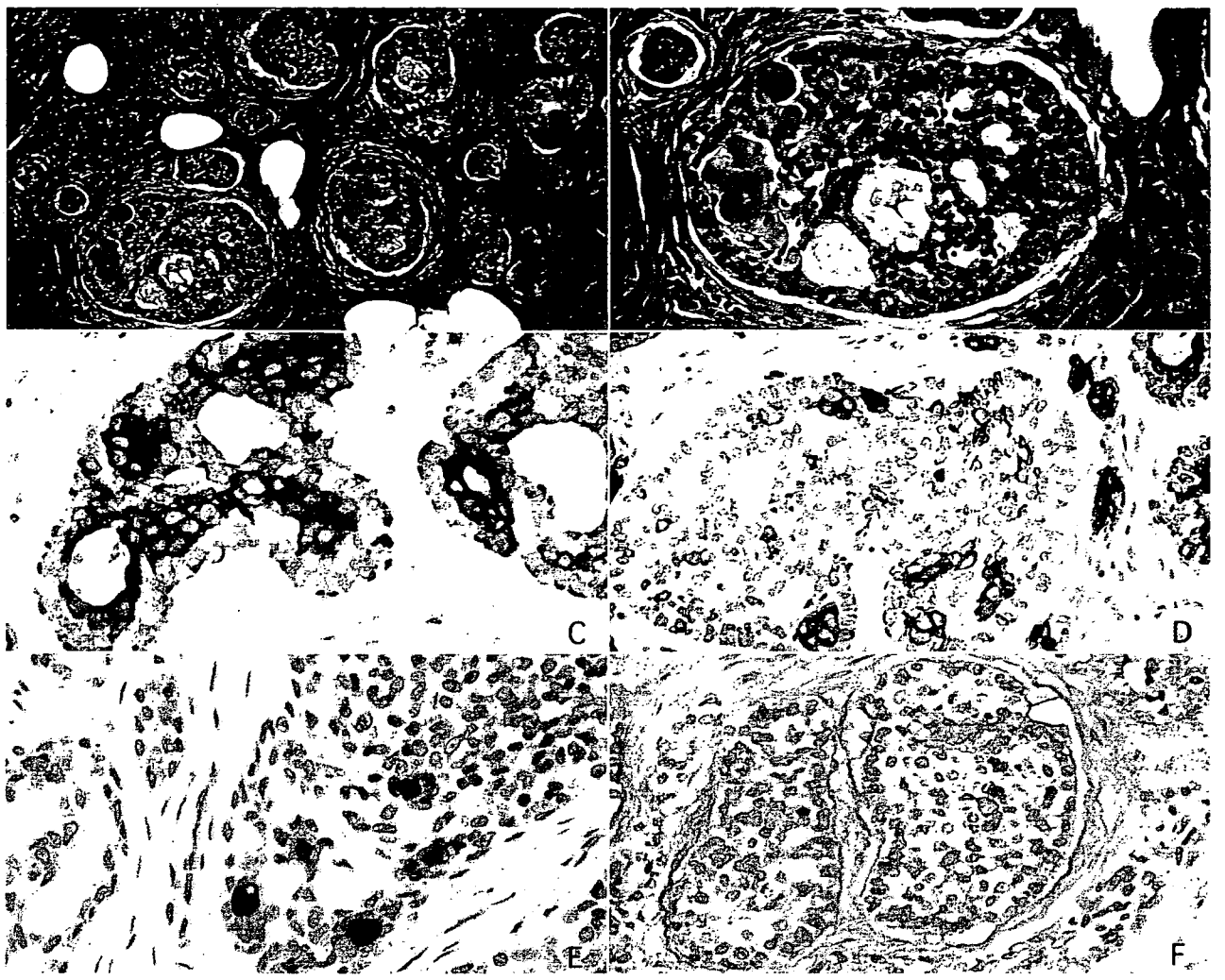

Fig 7. Histological findings in case 1. A: Low-power view revealed cribriform and tubular arrangements of cells (H&E stain). B: High-power view showed a biphasic pattern of tumor cells and both true laminae and pseudocystic spaces (H&E stain). C: Cytokeratin staining was positive in the cells forming true lamina. D: α-smooth muscle actin staining was positive in the cells surrounding the pseudocysts. E: Materials in the true duct were reactive to CEA. F: Contents of pseudocysts stained with Alcian blue.

gestive of fibroadenoma. The average tumor size has been reported as 2 to 3 cm in diameter and tumor growth is thought to be slow[1-4].

The prognosis for patients with ACC is good. Arpino *et al.*[1] reported that the 5-year disease free survival rate in their 28 cases was 100% despite different treatment strategies. Axillary lymph node metastasis is extremely uncommon, with only 0.8% (1 of 120 cases)[5], 1.7% (4 of 182 cases)[1] and 6.7% (1 of 15 cases; micrometastases detected on immunohistochemical staining)[2] of ACC patients reported lymph node positive in the literature.

The incidence of local recurrence after excision is also reported to be low. Arpino *et al.*[1] reported a recurrence rate of 7.7%, interestingly none of the patients with local recurrence had received adjuvant radiotherapy. They also reported that no local recurrence was described in the group of patients who had received adjuvant radiotherapy. The biological features of ACC have been studied using immunohistology and DNA flow cytometry. These studies showed that ACC has low proliferative activity which may account for the low recurrence rate. Based on these findings, lumpectomy and radiation or simple mastectomy is thought to have a chance to achieve adequate local control of nearly all tumors[1, 2]. Estrogen and progesterone receptors usually are absent in ACC[1]. Consideration of these features is of paramount importance when determining appropriate adjuvant treatment.

Histologically, ACC has a distinctive biphasic pattern that consists of true laminae and pseudo-

cystic spaces. True glands are lined by epithelial cells and pseudocysts are lined by myoepithelial cells. Immunohistologically, the biphasic pattern can be confirmed with anti-cytokeratin and anti-vimentin antibodies or smooth muscle actin antibody. True lumina contain PAS-staining and CEA-reactive mucous and pseudocysts contain Alcian blue-staining mucous[4,6].

Cytologically, the tumor shows a typical pattern; globules of mucous surrounded by epithelial cells with little cytoplasm and small hyperchromatic nuclei. Despite the low frequency of ACC tumors, the specific features of these tumors suggest that diagnosis by preoperative FNAC is possible. As prognosis is good, preoperative diagnosis is important in the determination of suitable treatment[7-9].

Both tumors we have reported were evaluated as T2. CT investigation of the case 1 tumor revealed round and well enhanced axillary lymph nodes which are regarded as metastatic nodes according to some authors' criteria[10,11]. Although primary chemotherapy is usually performed in such cases, diagnosis of the tumor as ACC meant that chemotherapy was not required. Furthermore, tumors requiring mastectomy tend to be selected by size. Although these tumors were 3.0 cm and 3.9 cm in diameter, breast-conserving surgery with adjuvant radiotherapy was chosen based on the preoperative diagnosis of ACC. In both cases we performed axillary lymph node dissection after informed consent instead of sentinel node biopsy because of the preoperative CT findings (case 1) and the large tumor sizes (cases 1 & 2). Axillary node involvement was not found in either case. These results are consistent with other reported cases of ACC. Thus, preoperative diagnosis based on FNAC findings was very useful in determining the appropriate treatment strategies for these patients.

In conclusion, we report two cases of ACC tumors >4 cm in diameter that were treated with breast-conservative surgery and adjuvant radiotherapy based on preoperative FNAC findings.

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Original Article

Combination Docetaxel and Trastuzumab Treatment for Patients with HER-2-Overexpressing Metastatic Breast Cancer: A Multicenter, Phase-II Study

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Background: Pre-clinical and clinical studies indicate that a combination of docetaxel and trastuzumab may effectively treat patients with human epidermal growth factor receptor-2 (HER-2) overexpressing metastatic breast cancer. We evaluated the efficacy and safety of this combination in a multicenter, open-label phase II study in Japan.

Methods: Women with metastatic breast cancer whose tumors overexpressed HER-2, as assessed by immunohistochemistry and by fluorescence *in situ* hybridisation, received 2 to 6 cycles of docetaxel (70 mg/m^2, every 3 weeks) and trastuzumab (4 mg/kg loading dose, 2 mg/kg weekly thereafter). The primary endpoint was tumor response. Secondary endpoints were time to disease progression and adverse events.

Results: Of the 40 women enrolled in the study, 27 (68%) completed 6 cycles of treatment. Three patients discontinued the study before the second cycle. Median follow-up was 20.8 months (range, 0.6 to 30.9 months). The overall response rate was 65% (26/40; 95% CI, 48% to 79%). The median time to progression was 6.8 months (range, 0.6 to 21.2 months). Of the 40 patients, 35 (88%) had grade 3 or 4 leukopenia, and 33 (83%) had grade 3 or 4 neutropenia. Most instances of leukopenia and neutropenia were manageable by reducing the dose of docetaxel or by treatment with granulocyte colony-stimulating factor. In 4 patients, left ventricular ejection fraction decreased by more than 10% from baseline.

Conclusions: The combination of docetaxel and trastuzumab was as effective as reported in other similar studies and was well tolerated in these patients.

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Key words: Clinical trial, Phase II, Metastatic breast cancer, Docetaxel, Trastuzumab

Breast cancer is one of the leading causes of death in women, despite advances in treatment. Metastatic relapse is still common, and survival of patients with metastatic breast cancer remains poor[1]. For patients with advanced breast cancer whose tumors express the estrogen or progesterone receptor, endocrine therapy is the first-line treatment and extends survival[2, 3]. For patients with receptor-negative cancers or those whose disease has become resistant to endocrine therapy, chemotherapy is the first-line treatment. Anthracyclines are the standard chemotherapeutic agents for metastatic breast cancer[4]. However, some patients do not respond to anthracycline therapy, and anthracyclines have severe toxic effects, especially on the heart.

Docetaxel is a semisynthetic taxoid derived

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Abbreviations:
HER-2, Human epidermal growth factor receptor-2; IHC, Immunohistochemistry; FISH, Fluorescence *in situ* hybridisation; LVEF, Left ventricular ejection fraction; IV, Intravenously; NCI-CTC, National cancer institute common toxicity criteria; G-CSF, Granulocyte colony-stimulating factor; ECOG, Eastern cooperative oncology group

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from the European yew tree, *Taxus baccata*[5]. It is one of the most active chemotherapeutic agents for treating patients with metastatic breast cancer. Docetaxel is effective both as first-line treatment[6,7] and as second-line treatment for patients who have received anthracycline- or an alkylating agent-containing chemotherapy[8,9]. Docetaxel is the only drug to have shown superiority over single-agent anthracycline therapy as well as combination regimens in the metastatic setting[10].

Trastuzumab is a humanised monoclonal antibody directed against the human epidermal growth factor receptor-2 (HER-2) protein. HER-2 overexpression is associated with short survival in breast cancer[11,12], and thus trastuzumab is used to treat these patients. Trastuzumab is effective as a single agent and in combination with chemotherapy. The combination of trastuzumab and doxorubicin plus cyclophosphamide has a high response rate and improves survival but can cause severe cardiac dysfunction[13]. As a result, new combinations of trastuzumab and chemotherapeutic agents are being considered.

A pre-clinical study showed a beneficial interaction between docetaxel and trastuzumab[14], and several phase II clinical studies showed that the combination of docetaxel and trastuzumab may also be effective[15-18].

To evaluate the efficacy and safety of the combination of 3-weekly docetaxel and weekly trastuzumab in patients with HER-2-overexpressing metastatic breast cancer, we conducted an open-label, multicenter phase-II study. A previous article reported the results of the interim analysis (median follow-up was 14.3 months [range, 0.6 to 23.0])[19]. This paper reports the final results.

Patients and Methods

Patients

Women with histologically confirmed metastatic breast cancer whose tumors overexpressed HER-2 were eligible for the study. HER-2 status was confirmed by immunohistochemistry (IHC) and by fluorescence *in situ* hybridisation (FISH). Patients with tumors graded with an IHC score of 3+, or an IHC 2+ and FISH-positive for HER-2 were enrolled. Other eligibility criteria were: Eastern Cooperative Oncology Group performance status of 0 to 2; age between 20 and 75 years; measurable disease (a tumor more than 10 mm in one dimension); a life expectancy of at least 3 months; at least 2 weeks after any chemotherapy; hemoglobin greater than 9 g/dL; a white blood cell count between 4,000/mm^3 and 12,000/mm^3; a neutrophil count greater than 2,000/mm^3; a platelet count greater than 100,000/mm^3; a serum bilirubin within the normal range; aspartate aminotransferase and alanine aminotransferase less than 100 IU/L; and serum creatinine less than or equal to 1.5 times the upper normal limit.

Pregnant women or women who might be pregnant were excluded from the study. Prior docetaxel or trastuzumab treatment was not allowed. The cumulative dose of anthracycline derivatives would not exceed 360 mg/m^2 (converted into the dose of doxorubicin). Other exclusion criteria included contralateral breast cancer, uncontrolled concomitant disease, active concomitant malignancy, a history of myocardial infarction or clinically important cardiovascular disease, a left ventricular ejection fraction (LVEF) less than 50% or below the upper limit of normal, New York Heart Association functional classification II to IV, suspected infection with fever, motor paralysis or peripheral neuropathy; pleural or pericardial effusion that required treatment, symptomatic brain metastasis, edema of grade 2 or higher, interstitial pneumonia or lung fibrosis, or allergy to polysorbate 80.

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the institutional review board of each participating center (Participating centers are listed in the Appendix). All patients gave written informed consent.

Study Design

This was a multicenter, open-label, single-arm, phase-II study. Combination treatment of docetaxel and trastuzumab was given in 3-week cycles. Patients received docetaxel every 3 weeks and trastuzumab every week. In each cycle, 70 mg/m^2 docetaxel was administered intravenously (i.v.) over 60 minutes. Trastuzumab (2 mg/kg) was administered IV over 90 minutes, with the exception of the first treatment. In the first treatment (day 1 of the first cycle), a loading dose of 4 mg/kg trastuzumab was administered i.v. over 90 minutes. In the first cycle, docetaxel was administered on day 2, and trastuzumab was administered on days 1, 8, and 15. After the first cycle, docetaxel was administered on day 1, and trastuzumab was administered on days 1, 8, and 15 of each cycle.

Patients received 2 to 6 cycles of combination treatment unless disease progression or unacceptable toxicity was observed.

If any of the following adverse effects were observed, docetaxel was withheld until recovery was confirmed: a white blood cell count below 3,000/mm^3; a neutrophil count below 1,500/mm^3; neuropathy of grade 2 or more; edema of grade 2 or more; and liver or renal dysfunction of grade 2 or more. These toxicities were classified according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC). The dose of docetaxel could be reduced to 60 mg/m^2 if investigators considered it necessary. The dose of trastuzumab could not be modified. Pre- and postmedication with dexamethasone was optional. Investigators were allowed to administer granulocyte colony-stimulating factor (G-CSF) if leukopenia or neutropenia of grade 4 or grade 3 with fever (>38℃) was observed.

The primary endpoint was tumor response classified according to the Response Evaluation Criteria in Solid Tumors[20]. The secondary endpoints were time to disease progression and adverse events. Adverse events were assessed according to the NCI-CTC (version 2, as translated into Japanese by the Japan Clinical Oncology Group).

Statistical Methods

The sample size calculation was based on an estimated overall response rate of 70%. To achieve an overall response rate of at least 50%, we planned to enroll 40 patients. This sample size was calculated using Simon's minimax design[21]. Time to disease progression was calculated from the date of the first treatment until disease progression or death and was analysed using the Kaplan-Meier method.

Results

Between March 2002 and May 2003, 40 patients were enrolled in this study. Of these, 1 was later determined to have been ineligible because her white blood cell and neutrophil counts at enrollment were below the eligibility criteria (2,600/mm^3, 1,432/mm^3, respectively). However, this patient completed 6 treatment cycles. Another patient was withdrawn from the study before receiving docetaxel because a brain metastasis was found after the first trastuzumab treatment. Two other patients discontinued the study after the first cycle because of adverse events (disseminated intravascular coagulation and ischemic heart disease). We suspect that disseminated intravascular coagulation may have been caused by multiple bone metastases. The other patient who discontinued the study had palpitations and grade 1 myocardial ischemia. The patient could have received 8 cycles of docetaxel after she was taken off protocol.

Table 1. Baseline Characteristics of 40 Women with HER-2-Overexpressing Metastatic Breast Cancer Treated with a Combination of Docetaxel and Trastuzumab in an Open-Label Phase II Study

Characteristic	Patients (n = 40)
Median (range) Age, years	57.5 (32 to 73)
ECOG Performance Status, n (%)	
0	25 (63)
1	11 (28)
2	4 (10)
Metastatic sites, n (%)	
1	20 (50)
2	12 (30)
3	5 (13)
>4	3 (8)
Prior Chemotherapy, n (%)	
Anthracycline-based	16 (40)
Non-anthracycline-based	17 (43)
Postmenopausal, n (%)	29 (73)
Receptor status	
Estrogen receptor positive	8 (20)
Progesterone receptor positive	10 (25)

ECOG = Eastern Cooperative Oncology Group

These 4 patients were included in the intention-to-treatment analysis. Thus, all analyses included data from the 40 enrolled patients. Median follow-up was 20.8 months (range, 0.6 to 30.9 months). The dose of docetaxel was reduced in 6 patients because of adverse events, such as edema, neutropenia, and pneumonia. Twenty-seven patients (69%) completed 6 cycles of treatment. The median relative dose intensity of docetaxel was 98.8% (range, 0 to 101.6%).

Half the patients had more than one metastatic site (Table 1). The distribution of metastatic sites was as follows: 26 were in soft tissue (primary 5, lymph node 15, skin 6); 33 were visceral (lung 17, liver 13, pleura 2, adrenal 1); and 12 were in bone. Most patients (83%) had undergone chemotherapy; only 1 had received radiotherapy. The IHC score of the tumors was 3+ in 39 patients. In the remaining patient, the IHC score was 2+, and

Table 2. Tumor Responses in 40 Women with HER-2-Overexpressing Metastatic Breast Cancer Treated with a Combination of Docetaxel and Trastuzumab

Response	Patients n (%)
Overall Response	26 (65)*
Complete Response	7 (18)
Partial Response	19 (48)
Stable Disease	7 (18)
Progressive Disease	1 (3)
Not Evaluable	6 (15)†

*95% Confidence Interval, 48% to 79%
†Includes 1 patient who withdrew before receiving docetaxel because a brain metastasis was found after the first trastuzumab treatment; 2 patients who discontinued after the first cycle because of adverse events. According to the RECIST Guidelines, 3 patients were judged not to have measurable lesions which were supposed to have at least one dimension ≧2.0 cm by conventional techniques or ≧1.0 cm by spiral CT.

HER-2 positivity was confirmed by FISH. Estrogen-receptor positive tumors were found in 8 patients (20%), and progesterone-receptor positive tumors were found in 10 (25%).

The overall response rate was 65% (95% CI, 48% to 79%): 7 patients (18%) had complete response, and 19 (48%) had partial response (Table 2). The median time to disease progression was 6.8 months (range, 0.6 to 21.2 months; Fig 1). The median overall survival was 20.9 months (range, 0.6 to 30.9 months).

Leukopenia and neutropenia were the most common hematological toxicities (Table 3): 35 patients (88%) had grade 3 or 4 leukopenia, and 33 (83%) had grade 3 or 4 neutropenia. In 3 patients, the dose of docetaxel was reduced because of neutropenia. Thirteen patients (33%) were treated with G-CSF because of leukopenia or neutropenia. Leukopenia or neutropenia did not result in treatment discontinuation.

The most common nonhematological toxicities were anorexia, peripheral neuropathy, and rash (Table 3). The majority of these were mild (grade 1 or 2). Because of grade 2 edema, 2 patients reduced the dose of docetaxel according to the study design. Three others discontinued the treatment (2 after 4 cycles, and 1 after 5 cycles). These three patients developed progressive disease, and then discontinued the protocol. In 4 patients, LVEF decreased by more than 10% from the baseline value. Two others discontinued the treatment because of chest pain and cardiac ischemia.

Discussion

This study showed that the combination of docetaxel and trastuzumab is a promising new regimen in women with HER-2-overexpressing metastatic breast cancer. The overall response rate was 65%, which is similar to that reported in other docetaxel-trastuzumab combination studies[15-18]. In our study, 7 patients (18%) responded completely. Esteva *et al.*[15], Raff *et al.*[16], and Tedesco *et al.*[17], using weekly docetaxel (35, 33 to 40, and 35 mg/m^2, respectively), reported complete responses in 0% (0/30), 0% (0/17), and 8% (2/26) of their patients, respectively. Montemuo *et al.*[18], using 3-weekly docetaxel (75 mg/m^2), reported complete responses in 17% (7/42) of their patients. These 4

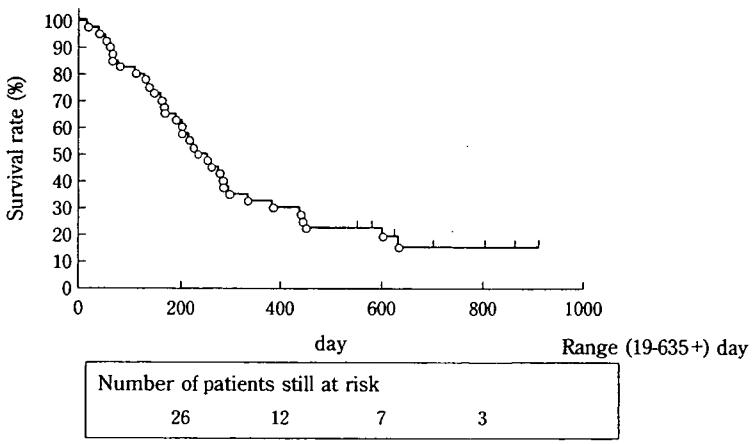

Fig 1. The cumulative probability of freedom from disease progression. Time to progression was calculated from the date of the first treatment until disease progression or death.

Table 3. Frequency of Adverse Events among 40 Women with HER-2-Overexpressing Metastatic Breast Cancer Treated with a Combination of Docetaxel and Trastuzumab

Adverse Event	Number of Adverse Events by Grade*				Number (%) of Patients Experiencing Grade 3 or 4 Adverse Events
	1	2	3	4	
Hematologic					
Leukopenia	1	1	26	9	35 (88)
Neutropenia	0	1	9	24	33 (83)
Febrile neutropenia	0	0	6	0	6 (15)
Thrombocytopenia	2	0	1	0	1 (3)
Hemoglobin decrease	10	11	0	1	1 (3)
Nonhematologic					
Weight gain	0	1	2	0	2 (5)
Anorexia	19	2	1	0	1 (3)
Peripheral neuropathy	11	10	1	0	1 (3)
Fever	14	1	1	0	1 (3)
Rash	13	8	1	0	1 (3)
Edema	13	11	0	0	0 (0)
Cardiac left ventricular function	4	0	0	0	0 (0)

*National Cancer Institute Common Toxicity Criteria

studies used the same dose of trastuzumab that we used (4 mg/kg/week, loading; 2 mg/kg/week thereafter). Given these results, 3-weekly docetaxel may be more effective than a weekly regimen, although we cannot draw any conclusions from comparing the results of small, open-label, phase-II studies.

The combination was well tolerated. The most common hematological toxicities were leukopenia and neutropenia. The incidence of grade 3 or 4 neutropenia was higher than that reported in the weekly docetaxel-trastuzumab combination studies[15-17], suggesting that weekly docetaxel may have fewer hematological toxicities (we could not compare the incidence rate of leukopenia because some studies did not report those data). However, most cases of leukopenia and neutropenia were manageable by reducing the dose of docetaxel or treatment with G-CSF. Neither leukopenia nor neutropenia led to treatment discontinuation.

Considering the efficacy mentioned above, we conclude that 3-weekly docetaxel regimen has an acceptable risk-benefit ratio in these patients.

Cardiotoxicity is a major concern of trastuzumab therapy. A decrease in LVEF was observed in 4 patients, and 2 others discontinued the treatment because of adverse cardiac events. One of these patients had chest pain (described as a constricted feeling in the chest), suggesting the possibility of pulmonary congestion secondary to cardiac dysfunction. Although no grade 3 cardiotoxicity was reported in this study, we recommend periodic cardiac monitoring during trastuzumab-docetaxel combination treatment. The other nonhematological toxicities were generally mild, and most were classified as grade 1 or 2.

The study was designed to withhold docetaxel until recovery from edema of grade 2 or more was confirmed. Docetaxel-induced fluid retention may confuse the clinical picture, by making congestive heart failure, which is one of the most serious toxicities to be associated with trastuzumab-based therapy, difficult to diagnose.

In conclusion, combination therapy with 3-weekly docetaxel and weekly trastuzumab is effective and well tolerated in patients with HER-2-overexpressing metastatic breast cancer. Further study will be needed to confirm the effectiveness of this combination in the metastatic setting.

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● 原 著

HER 2過剰発現を呈する進行乳癌に対するDocetaxelとTrastuzumab併用による術前化学療法の検討

—JECBC 02 Trial—

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Multicenter Phase II Trial of Thrice-Weekly Docetaxel and Weekly Trastuzumab as Preoperative Chemotherapy in Patients with HER 2-Overexpressing Breast Cancer—Japan East Cancer Center Breast Cancer Consortium (JECBC) 02 Trial:

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Summary

The efficacy and safety of combination therapy of 4 cycles with docetaxel 70mg/m^2 every 3 weeks and trastuzumab as primary chemotherapy for operable breast cancer was determined in 21 patients (pts) by assessing the pathological complete response (pCR) rate, clinical response rate (RR), breast conservation surgery (BCS) rate and toxicities. To date, 19 pts have completed surgery. The pCR rate was 21% [95% CI 6%-46%]. The overall RR was 90% [95% CI 67%-99%], with 5 CR, 12 PR, 2 SD and 0 PD. Grade 3 or 4 adverse events were leukopenia 48%, neutropenia 67%, hemoglobin 5%, and febrile neutropenia 10%. All non-hematological toxicities were mild and manageable.

The pCR rate is not as low as that achieved in previous international studies. The combination of docetaxel and trastuzumab was a well-tolerated and very active regimen for the treatment of patients with HER 2-overexpressing operable breast cancer. This regimen promises to be one of the leading future treatments for progressive breast cancer. **Key words:** Breast cancer, Docetaxel, Trastuzumab, Neoadjuvant

要旨 HER 2過剰発現を呈する進行乳癌症例21例に対し，docetaxel 70 mg/m^{2}を3週間隔とtrastuzumab初回投与4 mg/kg，2回目以降は2 mg/kgを1週間隔の併用療法を行い，3週を1コースとして4コース投与後手術を行うこととし，組織学的効果，抗腫瘍効果，乳房温存術施行率および安全性を検討した。手術を終了している19例中，組織学的効果は21%，抗腫瘍効果は，CR 5例，PR 12例，SD 2例，PD 0例の90%であった。grade 3以上の有害事象として白血球減少が48%，好中球減少が67%，ヘモグロビン減少が5%，発熱性好中球減少が10%であった。その他のgrade 3以上の非血液毒性は発

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現しなかった。docetaxel と trastuzumab の併用療法は海外試験の組織学的効果と遜色ない結果が得られた。また，高い抗腫瘍効果を示し，副作用も重篤なものは認められず忍容可能であったことから，今後の進行乳癌の治療の一つとして期待される。

はじめに

乳癌は比較的早期から潜在的微小転移を形成するため，外科療法，放射線療法などの局所療法のみでは制御不可能な場合が多い。このため，術前・術後化学療法，内分泌療法など全身療法が導入され，最近その重要性がさらに増してきている。NSABP B 18 study では乳癌の標準治療とされている doxorubicin/cyclophosphamide (60/600) を用い，術前・術後化学療法の比較が行われ pathological CR (pCR) が得られた症例のみ生存期間，無病生存期間とともに明らかな予後改善効果が認められている[1]。このことより現在では術前化学療法として高い pCR を得られる薬剤，投与方法が検討されている。HER 2 過剰発現を呈する乳癌に対しては，HER 2 選択的治療方法として投与される trastuzumab は単剤よりも他の化学療法剤との併用においてより有用性が認められているが，anthracycline 系薬剤と併用した場合，心毒性の発現率が上昇することが海外の臨床試験の成績から報告されている[2]。また，docetaxel は転移性乳癌に対して anthracycline と同等以上の効果が認められていることから，trastuzumab との併用においてもその有用性が期待され，① 前臨床試験において相乗効果が報告されていること[3]，② anthracycline 系薬剤と trastuzumab との併用時における心毒性が回避できる可能性があること，③ 海外で高い有用性が報告されていること[4]などから，われわれは docetaxel と trastuzumab を併用した臨床試験を実施してきた。その結果，78%と高い抗腫瘍効果を報告した[5]。さらに，海外では Marty らが HER 2 過剰発現の転移性乳癌症例において，docetaxel 単剤群の生存期間は 13 か月，docetaxel と trastuzumab 併用群では 24 か月と生存期間の延長を報告している[6]。

近年，癌の治療は personalized あるいは tailored medicine として個別化の重要性が唱えられている。年齢，性別はもとより患者個人あるいは癌細胞がもつ特性によって治療法，たとえば治療に用いる薬剤や投与量など考慮する傾向にある。また，ターゲティング治療という面から考えるとホルモン受容体陽性の患者において tamoxifen などのホルモン療法が第一選択薬であるように，HER 2 過剰発現の症例には trastuzumab をより早い段階で投与することで高い抗腫瘍効果が期待でき，術前化学療法としての投与が現在探られているところである。以上のことから，より早期の段階で化学療法との併用療法を行うことでさらなる効果が期待できる。われわれは進行乳癌症例を対象に docetaxel と trastuzumab の併用臨床試験を計画し，その組織学的効果，抗腫瘍効果，乳房温存術施行率および安全性を検討した。

I. 対象と方法

1. 対象症例

HER 2 過剰発現を呈する進行乳癌のうち，以下の基準を満たす症例を対象とした。① 組織学的に進行乳癌と診断された 3 cm 以上の原発巣もしくはリンパ節転移陽性の症例，② 原発巣あるいは対象病変の乳癌組織において免疫組織化学的方法 (IHC 法) により HER 2 蛋白の過剰発現が確認されたスコア 3+の症例，③ performance status (PS) が 0～1 の症例，④ 登録時に 20 歳以上 75 歳未満の症例，⑤ 乳癌に対する先行治療として化学療法，放射線療法，内分泌療法，免疫療法が行われていない症例，⑥ 画像診断などの客観的検査により，測定可能病変を有する症例，⑦ 主要臓器の機能が十分に保持されており，以下の基準を満たす症例。ヘモグロビン 9.0 g/dL 以上，白血球数 4,000/mm³以上 12×10³/mm³以下，好中球数 2,000/mm³以上，血小板数 10×10⁴/mm³以上，血清総ビリルビン値: 施設基準値上限以下，AST および ALT 100 IU/L 未満，血清クレアチニン値: 施設基準値上限 1.5 倍以下，そして ⑧ 本試験の説明を十分に受け，本人の文書による同意を得られた症例とした。

また，以下に該当した症例を除外基準とした。① 本治療に支障を来す恐れのある薬剤アレルギーの既往のある症例，② 男子乳癌あるいは両側乳癌の症例，③ コントロールできない重篤な合併症のある症例，④ 活動性の重複癌 (無病期間 5 年未満) を有する症例，⑤ 心筋梗塞の既往，あるいは臨床上問題となる心臓血管系疾患を有する症例，⑥ 心エコー図により左室駆出率 (LVEF) が 50% 未満または施設基準値以下の症例，⑦ NYHA 分類が II，III，IV度といった循環器系疾患を有する症例，⑧ 発熱を伴った感染の疑いのある症例，⑨ 運動麻痺あるいは末梢神経障害のある症例，⑩ 治療を要する胸水，または心嚢液貯留のある症例，⑪ 症状を有する脳転移のある症例，⑫ 妊娠または妊娠している可能性のある症例，⑬ grade

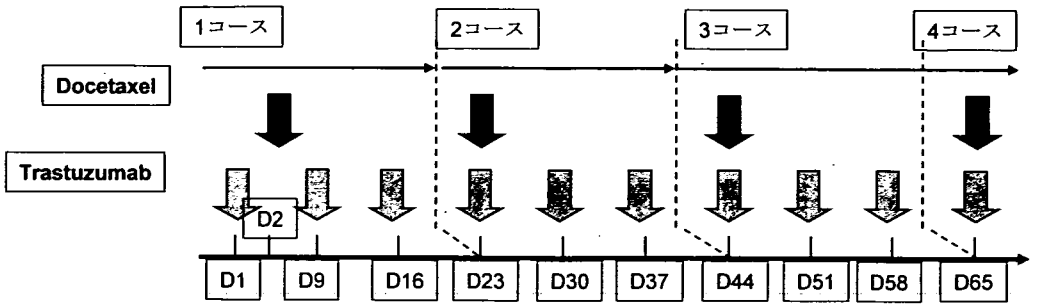

図 1 試験デザイン
docetaxel 70 mg/m²を3週間隔で1時間以上かけて点滴静注し，trastuzumab初回投与時4 mg/kg，2回目以降は2 mg/kgを1週間隔で90分かけて点滴静注する。3週間を1コースとし4コース施行する

表 1 患者背景（n=21）

年齢（y）（range）	54（33～69）	腫瘍径	
ECOG PS		中央値（mm）（range）	54（13～150）
0	18（86%）	～30 mm	2（10%）
1	3（14%）	30～50 mm	5（24%）
組織型		50～70 mm	9（43%）
乳頭腺管癌	4（19%）	70～100 mm	2（10%）
充実腺管癌	9（43%）	100 mm～	3（14%）
硬癌	8（38%）	閉経	
		前	8（38%）
		後	13（62%）
		ER	
		+/−	3（14%）/18（86%）
		PgR（不明1例）	
		+/−	0（0%）/20（95%）

2以上の浮腫のある症例，⑭間質性肺炎あるいは肺線維症のある症例，⑮ポリソルベート80含有製剤に対して過敏症の既往のある症例，⑯精神疾患既往，または治療中の症例，そして⑰その他として試験担当医師が不適切と判断した症例とした。

2．投与方法

上記選択基準を満たす進行乳癌患者に対してdocetaxelは70 mg/m²を3週間隔で1時間以上かけて点滴静注し，trastuzumabは初回投与時には4 mg/kgを，2回目以降は2 mg/kgを1週間隔で90分かけて点滴静注した。3週間を1コースとして4コースまで投与後手術をすることとした（図1）。trastuzumabとdocetaxelは原則同日投与とするが，初回投与時のみtrastuzumabを1日目に，docetaxelを2日目に投与することとした。primary endpointは組織学的効果，抗腫瘍効果，secondary endpointは乳房温存術施行率，安全性（有害事象）とした。

3．評価方法

抗腫瘍効果は固形がんの治療効果判定のためのRECIST（New Guidelines to Evaluate the Response to Treatment in Solid Tumors）ガイドラインに準じて評価した。組織学的効果は「乳癌の組織学的効果判定基準（乳癌学会・編：乳癌取扱い規約，第14版）」に従って評価した。また，安全性はNCI-Common Toxicity Criteria Ver. 2.0の日本語訳JCOG版に基づいて評価した。

II．結 果

1．対象症例の背景因子

症例の集積は2004年7月から2005年2月まで中央登録方式にて行った。

HER2過剰発現を呈する進行乳癌症例は21例登録された。年齢は中央値54歳（33～69歳）で，腫瘍径の中央値は54 mm（13～150 mm）であった。治療開始時の全身状態はPS 0：18例，PS 1：3例であった。ホルモン受容体についてはER陽性3例，ER陰性18例，PgR陽性0例，PgR陰性20例，不明1例であった。閉経状況は閉経前8例，閉経後13例であった（表1）。

2．組織学的効果・抗腫瘍効果

21例の登録症例のうち，肝転移を有する症例に対しては，全身治療を先行するという患者の希望を優先し，手術を施行しなかった。手術を実施した19例に対し中央病

理判定を実施し，組織学的効果を判定した。Grade 3: 4例，Grade 2: 7例，Grade 1: 8例となり組織学的完全寛解（pCR）は21%であった（表2）。pCRを得られた試験前腫瘍径は80，52，26，19 mmの4例であった。抗腫瘍効果は判定委員会を実施し，CR 5例，PR 12例，SD 2例，PD 0例となり，90%（95%信頼区間67～99%）であった（表3）。

3．乳房温存施行率

登録時の予定術式と4コース終了後の実施術式を調査した結果，登録時に乳房切除予定であった15例のうち9例，60%の症例に乳房温存術が実施された（表4）。

4．有害事象

登録症例21例について，grade 3以上の有害事象として白血球減少48%，好中球減少67%，ヘモグロビン減少5%，発熱性好中球減少10%であった。また，頻度の多い有害事象として爪の変化や全身倦怠感，発疹などがみられたがgrade 3以上の毒性の発現はなかった（表5）。また，すべての症例において心毒性も認められなかった。

表2 組織学的効果（n=19）

Response	Case (%)
Grade 3	4 (21)*
Grade 2	7 (37)
Grade 1	8 (42)
Grade 0	0 (0)

*95% CI: 6～46（%）

表3 抗腫瘍効果（n=19）

Clinical response	Case (%)
ORR	17 (90)*
CR	5 (26)
PR	12 (63)
SD	2 (11)
PD	0

*95% CI: 67～99（%）

浮腫，好中球減少などの副作用に対する予防としてdexamethasoneを使用した症例は11例（53%）であり，G-CSFが投与された症例は9例（43%）であった。また，すべての症例で予定された投与コースである4コースが完遂できた。

III．考　察

個別化治療に期待が高まるなか，HER 2過剰発現を呈する転移性乳癌に対しdocetaxelとtrastuzumabの併用療法で高い抗腫瘍効果と安全性を認めたことを報告している[5]。今回，われわれは術前化学療法としてdocetaxelとtrastuzumabの併用療法を実施したところ，pCRは21%，抗腫瘍効果は90%の結果を得た。術前腫瘍径の中央値は54 mmであり，pCRを得られた症例に80 mmの症例を含んでいた。また，登録時乳房切除予定であった15症例のうち9例（60%）に温存手術が実施された。また，腫瘍径の大きい腫瘍からpCRが得られていることなどから本試験の有用性は高いと考えられる。海外で発表されている本併用療法の成績はpCRが15～31%，抗腫瘍効果は70～91%であり[7]，これらの成績と比較しても遜色ない結果であった。安全性の面でもすべての症例で4コース完遂できていること，好中球減少，白血球減少についても適切な支持療法を使用することにより，管理可能であったことから安全性も確認された。trastuzumabにより発現の可能性のある心毒性についても経験しなかった。以上のことより，HER 2過剰発現を呈する進行乳癌に対し，docetaxelとtrastuzumab併用療法

表4 予定術式と実施術式（n=19）

		実施術式	
		乳房切除術	乳房温存術
予定術式	乳房切除術	6	9
	乳房温存術	2	2

表5 有害事象（n=21）

	grade					
	grade 1	grade 2	grade 3	grade 4	≥ grade 1 (%)	≥ grade 3 (%)
ヘモグロビン減少	8	4	1	0	13 (62)	1 (5)
血小板減少	3	0	0	0	3 (14)	0 (0)
好中球減少	2	2	4	10	18 (86)	14 (67)
白血球減少	0	7	8	2	17 (81)	10 (48)
発熱性好中球減少	0	0	2	0	2 (10)	2 (10)
爪の変化	12	1	0	0	13 (62)	0 (0)
全身倦怠感	10	4	0	0	14 (67)	0 (0)
発疹	8	5	0	0	13 (62)	0 (0)
浮腫	5	0	0	0	5 (24)	0 (0)