Efficacy of doxifluridine combined with weekly paclitaxel therapy in the treatment of advanced or recurrent breast cancer: results of the JMTO BC01 phase II trial

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We conducted a phase II study to determine the availability and safety of combination chemotherapy with weekly paclitaxel and doxifluridine (a capecitabine metabolite) in the treatment of advanced or recurrent breast cancer. Patients were treated with a combination chemotherapy regimen: doxifluridine was orally administered at 800 mg/day for 14 days, followed by a 7-day washout period. Paclitaxel was given intravenously on days 1 and 8 at 80 mg/m^2 for 1 h, followed by a 1-week washout period. This 3-week cycle of therapy was repeated as long as possible (at least eight cycles) until the progression of the tumor and drug-related adverse effects were no longer observed. From May 2003 to December 2005, 26 patients were enrolled in the study. The overall response rate was 53.8% (95% confidence interval, 33.4–73.4%). The clinical benefit rate, including long-term no change, was 65.4% (95% confidence interval, 44.3–82.8%). Time to progression and survival time were 297 and 1182 days, respectively, for the 26 enrolled patients. No severe toxicities were observed. Grade 3/4 leucopenia in three patients, neutropenia in five patients, increased serum creatinine in three patients, hypercalemia in one patient, hypocalcemia in one patient, nausea/vomiting in two patients, and diarrhea in one patient. The good response rate and long time to progression and overall survival time of this doxifluridine combined with weekly paclitaxel therapy indicate its potential as a first-line or second-line treatment for advanced or recurrent breast cancer patients.
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Introduction

It is often impossible to achieve a cure in the treatment of advanced and recurrent breast cancer, even when the patient responds to chemotherapy. Nevertheless, chemotherapy has now been established as a standard treatment modality, which plays an important role in alleviating cancer symptoms and improving the patients' quality of life [1].

The response rate of advanced and recurrent breast cancer to chemotherapy is comparatively high. The following combination chemotherapies are available: cyclophosphamide (CPA), methotrexate, 5-fluorouracil (5-FU) treatment using CPA, methotrexate, and 5-FU; CAF treatment using CPA, adriamycin, and 5-FU; AC therapy with CPA and adriamycin); and recently approved taxanes, including paclitaxel and docetaxel [2]. In recent years, the US FDA has approved the use of an oral FU, capecitabine, [3] for the treatment of taxane-refractrory breast cancer. In Japan, doxifluridine, an intermediate metabolite of capecitabine, has already been approved for use, and Niitani *et al.* [4] found the drug to be useful in the treatment of solid tumors, including breast cancer. Doxifluridine is a prodrug that is converted to 5-FU as a result of activation by dThdPase [5]. dThdPase is more abundant in tumor tissues than in normal tissues.

Paclitaxel is extracted from the needle leaves of the Western yew or Pacific yew trees (*Taxus brevifolia*), and it arrests the cell cycle in the G2/M phase by promoting microtubule assembly. The mechanism of action of the drug is different from that of conventional anticancer drugs, and a favorable response is expected when used in combination with other anticancer drugs [6,7]. Several years ago, Sawada *et al.* [8] conducted fundamental studies and demonstrated the specific induction of dThdPase activity in tumor tissues after the administration of various anticancer agents, including paclitaxel. In addition, Cook *et al.* [9] reported that, in relation to tumors showing the specific induction of a ThdPase,

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the combination therapy with paclitaxel and doxifluridine showed a strong synergistic activity that has not been seen with the use of other drugs.

On the basis of the findings of these fundamental studies, Okamoto *et al.* [10] performed a pilot study to further assess the efficacy of combined paclitaxel and doxifluridine and thereby showed a synergic effect of this therapy in the clinical setting. This study was also designed to investigate the efficacy and safety of combined therapy with doxifluridine and paclitaxel in the treatment of advanced or recurrent breast cancer. The efficacy and clinical significance of this combination chemotherapy for breast cancer are discussed.

Patients and methods

Patients

The patients enrolled in this study had either advanced or recurrent breast cancer, in which the primary lesion was histologically or cytologically found to be a carcinoma. In addition, the patients met the following inclusion criteria: (i) previous treatment discontinued at least 4 weeks before the study, in principle, except for prior treatment with a biological response modifier, hormonal preparation, etc., thus requiring a washout period of at least 2 weeks, (ii) a performance status (PS) of 0–2, (iii) expected to survive for at least 3 months, (iv) had adequate hematological, hepatic, renal, and cardiac function (WBC, 4000–10 000/μl; neutrophil count, >2000/μl; platelet count, $>100\,000$/μl; Hb, >9.5 g/dl; aspartate aminotransferase and alanine aminotransferase, <1.5 times the upper normal limit; Al-P, >2.5 times the upper normal limit; total bilirubin, <1.5 mg/dl; and serum creatinine, <1.2 mg/dl), (v) aged 20 years and above, (vi) had measurable or evaluable lesions, and (vii) provided informed consent.

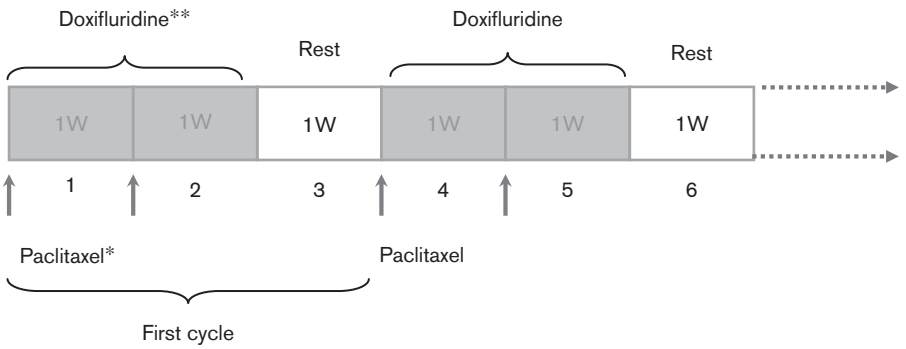
The patients were excluded from the study if they met any of the following criteria: a history of previous treatment with doxifluridine; a history of hypersensitivity to paclitaxel or polyoxyethylene castor oil; any serious concurrent conditions; a fever associated with a possible infection; any peripheral nervous symptoms; symptomatic brain metastasis; active double cancer; pregnant or possibly pregnant women or lactating mothers; interstitial pneumonia or pulmonary fibrosis; pleural effusion, ascites, or pericardial effusion requiring treatment; and any other patients considered not eligible for the study as assessed by the investigators.

Study procedures

Thirty patients with advanced or recurrent breast cancer met the inclusion criteria and were thus enrolled in the study that was mainly conducted by facsimile transmission during the period from May 2003 to December 2005. These patients were treated with a combination chemotherapy regimen: doxifluridine was orally administered at 800 mg/day for 14 days, followed by a 7-day washout period. Paclitaxel was given intravenously on days 1 and 8 at 80 mg/m^2 for 1 h, followed by a 1-week washout period. This 3-week cycle of therapy was repeated as long as possible (at least eight cycles) until the progression of the tumor and drug-related adverse effects were no longer observed (Fig. 1).

The primary endpoint was an antitumor effect of the combined therapy, and the secondary endpoints were treatment completion rate, time to progression (TTP), safety, and survival time. The clinical effect was evaluated in accordance with the General Rules for Clinical and Pathological Recording of Breast Cancer in the Guideline for Treatment of Breast Cancer, 14th

Fig. 1



*Paclitaxel was administered at 80 mg/m^2 on days 1and 8 by intravenous infusion over 1h.
**Doxifluridine was administered orally at 800 mg/day on days 1–14. One course lasted 3 weeks and the regimen was repeated as many cycles as possible.

Administration schedule for combination chemotherapy using paclitaxel and doxiflutidine.

Edition; edited by the Japanese Breast Cancer Society. Both the measurement of measurable lesions and the evaluation of evaluable lesions were performed objectively on the basis of image findings using radiographs, computed tomography scans, MRI, etc., and extracorporeal measurements. Whenever possible, the same method was repeated for all measurements and evaluations in a patient. TTP was defined as the time from the start of therapy until the first evidence of disease progression. The safety profile of the combination chemotherapy was assessed according to the Japanese Clinical Oncology Group version of the NCI-Common Toxicity Criteria version 2.0. Each patient was followed up either until death or for 3 years.

Evaluation of parameters and statistical analysis

The following background characteristics for the eligible patients were evaluated: age, PS, tumor type (invasive ductal carcinoma or not), disease stage at initial examination, disease status (progression or recurrence), estrogen and progesterone receptor test, etc.

The clinical effect of the therapy was assessed from 4 weeks after the start of therapy, and the categories used were complete response, partial response, no change (NC), and progressive disease. An NC which continued for 24 weeks or more was defined as a long-term NC. A multivariate analysis was performed for patient background characteristics to identify any influence on the therapeutic effect, using a logistic regression analysis. TTP and survival time were calculated using the Kaplan–Meier method.

Table 1 Patient characteristics

Characteristics	Number of patients	%
No. of enrolled patients	26	
No. of eligible patients	26	
Age (years)		
Median (range)	54	(39–71)
Performance status		
0	20	76.9
1	4	15.4
<2	2	7.7
Prior therapy		
Yes	26	
No	0	
Prior chemotherapy (including as adjuvant therapy)		
Anthracycline	5	19.2
Anthracycline + taxanes	6	23.1
CMF or FU derivatives	7	26.9
Hormones	8	30.1
Histopathologic type		
Invasive ductal carcinoma	24	92.3
Unknown	2	7.7
Estrogen receptor status		
Positive	15	57.7
Negative	8	30.8
Unknown	3	11.5
Progesterone receptor status		
Positive	12	46.2
Negative	10	38.5
Unknown	4	15.4

CMF, cyclophosphamide; FU, fluorouracil.

Table 2 Clinical effect of combination chemotherapy using paclitaxel and doxifluridine

CR	PR	Long NC	NC	PD	NE	RR (%)
2	12	3	4	2	3	53.8% (14/26) 95% CI [33.4–73.4%]

CI, confidence interval; CR, complete response; NC, no change; NE, not evaluated; PD, progressive disease; PR, partial response.

Results

Patient background characteristics

Table 1 shows that a total of 26 patients were enrolled in the study during the recruitment period between May 2003 and December 2005. All these patients were eligible for the study and included in the final analysis. Patients were between 39 and 71 years, with a median age of 54.0 years. At the start of this study, 20 patients had a PS of 0, and 24 patients had invasive ductal carcinoma. The disease stage was stage I in four patients, stage II in 12 patients, stage III in five patients, and stage IV invasive ductal carcinoma in five patients. Fifteen patients were positive, eight were negative, and three were unknown for the estrogen receptor. Twelve patients were positive, 10 were negative, and four were unknown for the progesterone receptor.

Response rate

The clinical responses of the 26 eligible patients are shown in the Table 2. Two patients achieved complete response and 12 patients partial response, whereas seven patients were assessed as NC and two patients as progressive disease. Of the seven patients assessed as NC, however, three were rated as long-term NC. The responses could not be evaluated in three patients. The response rate was therefore 53.8% (95% confidence interval, 33.4–73.4%). The clinical benefit rate including long-term NC, which may contribute to a prolongation of the survival time, was 65.4% (95% confidence interval, 44.3–82.8%). The median of response duration for cases including long-term NC was 79.5 days.

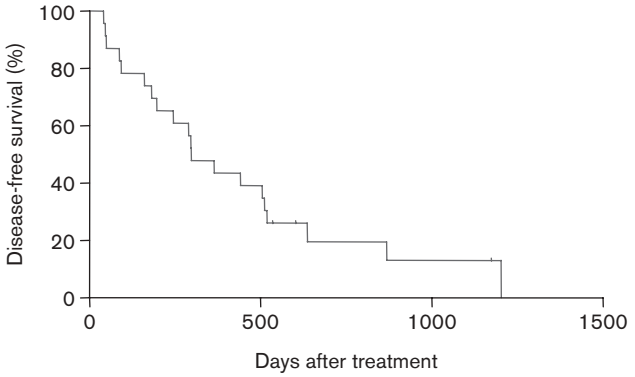
Time to progression and survival time

Figures 2 and 3 show that median of the secondary endpoints, TTP and survival time, to be 297 days and 1182 days, respectively, for the 26 enrolled patients.

Toxicity

Grade 3 or higher adverse events reported in this study are shown in Table 3. The following common adverse events were reported in the 26 enrolled patients: leucopenia in three, neutropenia in five, increased serum creatinine in three, hypercalemia in one, hypocalcemia in one, nausea/vomiting in two, and diarrhea in one.

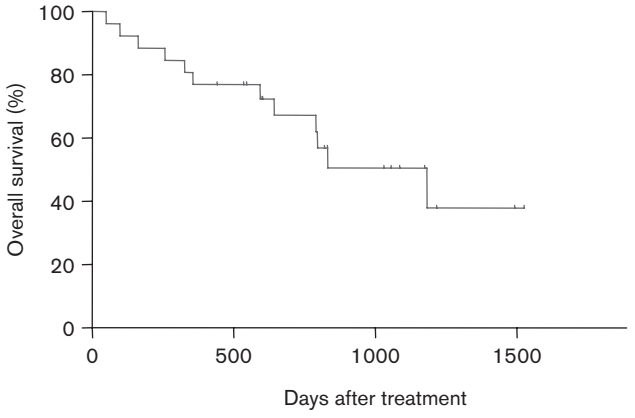
Fig. 2



Median: 297 days (95% confidential interval, 180–414 days)

Time to progression.

Fig. 3



Median: 1182 days (95% confidential interval, 631–1733 days)

Overall survival.

Discussion

In the treatment for advanced and recurrent breast cancer, taxanes including paclitaxel are used as the second-line chemotherapy in patients previously treated with anthracyclines or other drugs. Trials have been performed to use these taxanes with a weekly regimen to increase the drug intensity and reduce drug-related adverse reactions. Seidman *et al.* [11] conducted a phase II clinical trial of weekly paclitaxel treatment in anthracycline-resistant breast cancer patients and showed a satisfactory response rate of 53%. Perez *et al.* [12] reported a response rate of 21.5% from their clinical trial of paclitaxel given at 80 mg/m^2 weekly in patients previously treated with anthracyclines or taxanes. In addition, a response rate of 38% was obtained in elderly patients with metastatic breast cancer in a study conducted by Ten Tije *et al.* [13].

Table 3 Grade 3 and 4 toxicity of combination chemotherapy using paclitaxel and doxifluridine

Toxicity $n=26$	Grade 3	Grade 4	Grade 3 and 4	%
Leukocytes	2	1	3	11.5
Neutrophils	5		5	19.2
Creatinine	1	2	3	11.5
Hypercalemia		1	1	3.8
Hypercalcemia		1	1	3.8
Diarrhea	1		1	3.8
Nausea/vomiting	2		2	7.7
Anorexia	1		1	3.8
Neurotoxicity	1		1	3.8
Abdominal pain	2		2	7.7
Others	1		1	3.8

In contrast, Ishikawa *et al.* [14] performed a laboratory study using a human cancer xenograft model and demonstrated that the ratio of thymidine phosphorylase (TP), which is specifically abundant in tumor cells, to dehydropyrimidine dehydrogenase, a 5-FU-metabolizing enzyme abundant in the liver, positively correlates the tumor susceptibility to doxifluridine, an intermediate metabolite of capecitabine. The concurrent use of doxifluridine with chemotherapy or radiation therapy, which increases the intratumoral TP-to-dehydropyrimidine dehydrogenase ratio, may be considered as a strategy to enhance the drug's susceptibility. Endo *et al.* [15] reported that paclitaxel upregulated the intratumoral TP in human mammary cancer MX-1 cell line. In addition, Sawada *et al.* [8] showed that paclitaxel combined with doxifluridine produced a synergistic effect in comparison with paclitaxel administered alone. Although Fujimoto-Ouchi *et al.* tried to identify the optimal administration schedule in combination therapy with docetaxel and capecitabine in human cancer xenograft models. The most potent and synergistic activity was observed when docetaxel was given on day 8 [16]. Nishimura *et al.* reported phase II trial on the combination therapy of docetaxel on day 8 of doxifluridine in advanced or recurrent breast cancer. The overall response rate was 41% and the median TTP was 295 days [17].

This clinical study was conducted using this combination therapy based on the laboratory and basic research and demonstrated that the combination therapy used as the second-line or third-line therapy produced a response rate of 53.8% for patients previously treated with anthracyclines. This response rate was comparable with that of 48% from a phase II study conducted by Panday *et al.* [18] using paclitaxel at 80 mg/m^2 weekly in combination with doxorubicin, 51% in another phase II trial documented by Köhler *et al.* [19] using paclitaxel at 80 mg/m^2 weekly in combination with epirubicin [19], as

well as those reported by Schwonzen *et al.* [20], and Fulfaro *et al.* [21].

Except for neutropenia, which occurred in 19% of the patients, and was the only adverse event comparable with those reported in other studies, grade 3 or greater adverse drug reactions were lower in incidence, and therefore did not interfere with continuation of the combination therapy, in comparison with those from other studies, such as 13% for leucopenia and 16% for neutropenia reported by Panday *et al.* [18], 30% for neutropenia and 72% for alopecia reported by Köhler *et al.* [19].

Furthermore, this study showed favorable results regarding the secondary endpoints, including a median TTP of 283 days and a median overall survival of as long as 3 years and 3 months, thus suggesting the efficacy of weekly paclitaxel therapy combined with doxifluridine for the treatment of either advanced or metastatic breast cancer.

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