Original Article

Radiotherapy with Concurrent Docetaxel for Advanced and Recurrent Breast Cancer

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Background: Docetaxel has shown remarkable radiosensitizing properties *in vitro*. In this study we investigated whether the addition of docetaxel to radiotherapy enhanced tumor response in patients with advanced or recurrent breast cancer.

Methods: A total of 35 patients were enrolled in this study. Docetaxel was administered concurrently during radiotherapy. Radiation doses were 54 to 69 Gy (median 60 Gy). In those enrolled through January 2000, docetaxel 40 mg/m^2 was administered biweekly (once every two weeks), with subsequent dose adjustments based on tolerance and bone marrow and liver function. Beginning in February 2000, a weekly docetaxel schedule was used instead. This new regimen was based on data suggesting reduced myelosuppression with this regimen. The weekly dose rate was 20 mg/m^2, with dose reductions for impaired organ function.

Results: All patients were evaluated for toxicity and response and a total of 40 irradiated sites were evaluated for local response. The overall response rate of irradiated sites was 95% and the CR rate was 68%. CR and PR were achieved in 40%, 37% of patients, respectively. Acute toxicities were tolerated by most patients: 17% had Grade 3-4 neutropenia, 6% had Grade 3-4 radiation dermatitis, and 3% had Grade 3-4 pneumonitis.

Conclusion: The combination of docetaxel with radiotherapy is an active and safe regimen in patients with inoperable advanced or recurrent breast cancer. We determined the recommended dose of docetaxel with concomitant radiotherpy to be 20 mg/m^2 weekly for a Phase II study. Further study is necessary to assess the impact of this treatment on long-term outcome.

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Key words: Breast cancer, Docetaxel, Concurrent chemotherapy, Radiotherapy

Radiotherapy treatment in combination with chemotherapy has been used to increase treatment response in patients with breast cancer. In patients with unresectable tumor, radiotherapy is the most effective treatment modality for local control. On the other hand, chemotherapy and hormonal therapies are important in advanced and recurrent cases for systemic disease control. Radiotherapy with concurrent chemotherapy aimed at improving local control and systemic therapies have focused on novel agents with cytotoxic activity and radiation sensitizing potential in breast cancer.

The taxoids, including docetaxel and paclitaxel, stabilize microtubules. This leads to cell cycle arrest in the radiosensitive G2/M phase of the cell cycle[1-4]. *In vitro* studies demonstrated that paclitaxel enhanced radiation effects in epithelial and hematologic tumor cell lines[3]. Other preclinical

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Abbreviations:
CR, Complete response; PR, Partial response; CT, Computed tomography; MRI, Magnetic resonance imaging; SD, Stable disease; PD, Progressive disease; n_s, Number of site

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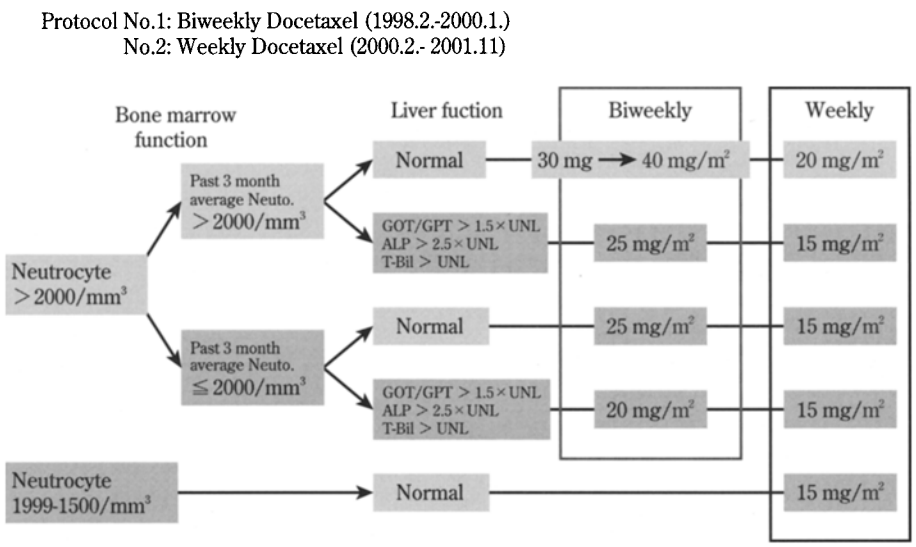

Fig 1. Docetaxel with concurrent radiotherapy for patients with breast cancer: Treatment protocol for docetaxel. Neutro, Neutrophil; AST, Aspartate transaminase; ALT, Alanine transaminase; ALP, Alkaline phosphatase; UNL, Upper normal limit; T-bil, Total bilirubin.

studies further illustrated the radiosensitizing effects of taxoids on tumor-cell lines. Docetaxel exhibited an effect 10 times higher than that of paclitaxel at equimolar concentrations[1].

The purpose of this study is to investigate the efficacy of radiotherapy with docetaxel for patients with advanced and recurrent breast cancers.

Materials and Methods

Eligibility

Patients eligible for this study had histologically documented malignant neoplasm of the breast with a locally advanced breast tumor or a recurrent tumor requiring localized radiotherapy treatment. Other criteria included bone marrow function tolerance with a neutrophil count $> 1,500/\mu L$, life expectancy of more than 3 months, and absence of infection or severe respiratory complications. Before treatment began, all patients underwent uniform staging and preparatory procedures including CT scan and/or MRI of the head, neck, chest and abdomen, along with bone scintigraphy. Written informed consent on treatment methods, expected results, and potential adverse effects was obtained before treatment.

Chemotherapy

From February 1998, docetaxel was initially administered biweekly (once every 2 weeks) along with radiotherapy. The docetaxel dose used was based upon the patient's bone marrow and liver function in the preceding 3 months. The regimen is shown in Fig 1 as Protocol No. 1. Patients with normal bone marrow and liver function tests received an initial docetaxel dose at the rate of 30 mg/m^2 once every 2 weeks for two treatment courses, followed by a 1-week rest. Normal levels were characterized by neutrophil counts $> 2,000/\mu L$ for the previous 3 months, aspartate transaminase/alanine transaminase (AST/ALT) $> 1.5\times$ the upper normal limit (UNL), alkaline phosphatase (ALP) $> 2.5\times$ UNL, and total bilirubin $<$ UNL. Docetaxel was diluted in a solution of 250 mL 5% glucose and infused over 1 hour before the patient underwent radiotherapy. Medications prior to treatment to prevent hypersensitivity reactions were not used routinely. Only patients in whom a previous allergic reaction had occurred were gives such medication. The initial dose was 30 mg/m^2. After confirming patient tolerance in two patients, doses were increased up to a maximum rate of 40 mg/m^2. In the case of poor bone marrow or liver function, the docetaxel dose was decreased to 25 mg/m^2 if either function was abnormal and to a rate of 20 mg/m^2 if both the liver and bone marrow functions were abnormal. These dose reductions were based on a standard schedule established in the Phase II study[5] and on the Japanese dose administration standards[6]. In February 2000, the docetaxel administration was changed from biweekly to weekly based on

published reports of less severe hematologic adverse effects[7-10]. Mauer *et al.* conducted a study of weekly docetaxel with concomitant chest radiotherapy and suggested a docetaxel dose of 20 mg/m^2 for the Phase I trials[11]. As shown in Fig 1, Protocol No. 2, patients with normal bone marrow and liver function received 20 mg/m^2 docetaxel per week for 3 courses, followed by a 1-week rest. Patients with reduced bone marrow or liver function or with a neutrophil count between 1,500/μL and 2,000/μL, received a 15 mg/m^2 dose.

Radiotherapy

Radiation therapy with 4-MV photon beams was carried out in 2 Gy fractions, 5 times a week. The electron beam radiation therapy schedule was 3 Gy per fraction, 3 times a week. Total radiation doses were determined by radiation response and irradiated normal tissue volume. In principle, patients with advanced primary tumors, even with distant metastases, received radical radiotherapy doses for local control. Lesions such as bone metastasis which were irradiated with palliative intent were excluded from the analysis. Radiotherapy was delivered to the whole breast and ipsilateral axillary regions with tangential photon beams for the primary breast tumor. Electron beam radiotherapy was delivered to recurrent chest wall tumors with more than a 2-cm margin. For parasternal and/or supraclavicular lymph node metastases, radiotherapy was delivered with a single anterior beam.

Treatment Evaluation

All patients underwent serial clinical examinations during their evaluations for tumor response and acute toxic reactions. Tumor response was assessed by physical examination and CT and/or MRI. A complete response (CR) was defined as the complete clinical and radiological disappearance of the tumor. A partial response (PR) was characterized as a reduction by at least 50% of the product of the longest perpendicular diameters of the most easily measurable or largest tumor mass within the irradiation field. A partial response also required that there was no growth of other lesions and no new lesions over at least 28 consecutive days. Stable disease (SD) was characterized as a reduction of less than 50% or a progression of less than 25%. Progressive disease (PD) was characterized as a progression of more than 25%.

Acute and subacute toxicities were assessed weekly and graded according to the National Cancer Institute common toxicity criteria version 2. All patients were checked with a hematological profile including blood count, serum creatinine and liver enzyme tests at least once a week. Late treatment-related toxicities were graded according to the RTOG/EORTC Late Effect Normal Tissue (LENT) scores[12]. Four weeks after the end of treatment, reevaluations were scheduled followed by physical examination at least every month. CT and/or MRI scans were scheduled at least every 6 months.

The statistical analysis of survival was calculated using the Kaplan-Meier method.

Table 1. Patients' Characteristics

No. of analyzed cases	35
Age (year)	27-82 (median 58)
States	
Advanced	11
Stage IIIB	3
Stage IV	8
Recurrent	24
Chest wall	9
Regional LN	10
Both	5
Histology	
Invasive ductal	33
Special type	2

Results

Patients Enrolled

From February 1998 to November 2001, 45 women were enrolled in this regimen. Ten patients, who received radiation only to bone metastases with palliative intent, were excluded from the analysis. Of 35 patients analyzed, 11 had untreated advanced disease and 24 had recurrent disease (Table 1). The median patient age was 58 years, with a range of 27-82 years. Seven patients were premenopausal and 28 were postmenopausal. Pathological assessment revealed invasive ductal carcinoma in 33 patients. Other histological types, such as mucinous carcinoma or angiosarcoma, were identified in 2 patients.

Treatment Delivered

A total of 40 sites were irradiated with a total median dose of 60 Gy, ranging from 54–69 Gy. The

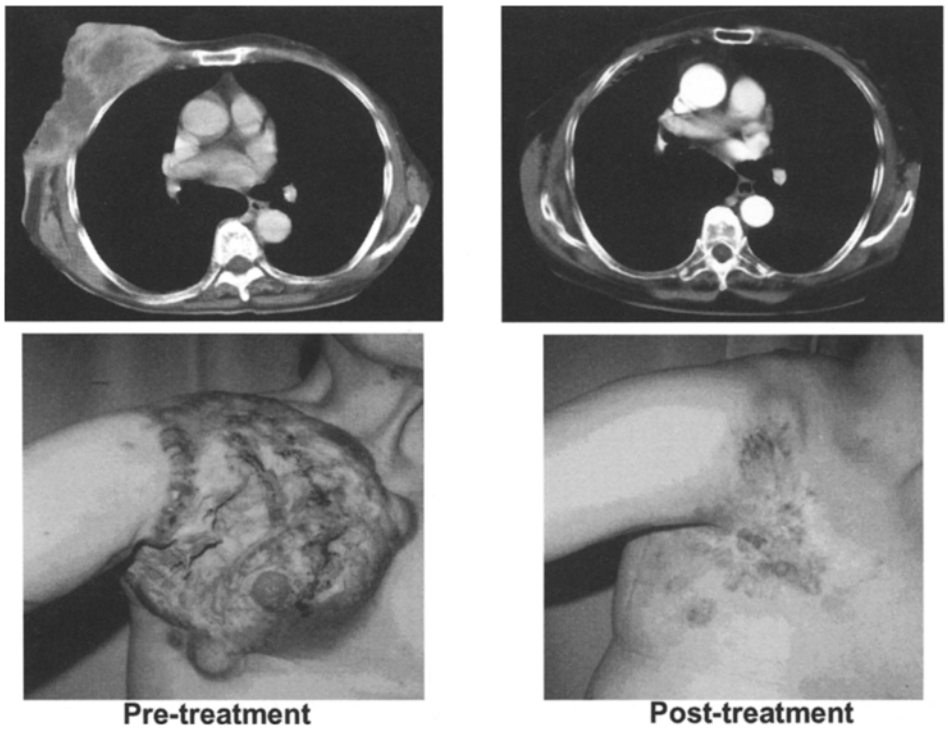

Fig 2. Pre-treatment and post-treatment CT scans from a 71-year-old woman with T4N3M1 (bone) breast cancer treated with 56 Gy breast irradiation and palliative-dose radiation to bone metastases with 4 courses of weekly docetaxel. She remains alive 2 years and 5 months post-treatment.

11 patients with advanced tumors received radiation to the primary breast and axillary region to a total median dose of 62 Gy, ranging from 56 to 69 Gy. Recurrent lesions in the chest wall ($n_S = 15$) were irradiated to a median total dose of 60 Gy, ranging from 54 to 68 Gy. (The sign "n_S" represents the number of sites from all patients in the study.) Fourteen patients with regional lymph node metastases received a median radiotherapy dose of 60 Gy, ranging from 54 to 66 Gy. Palliative dose of median 30 Gy irradiation to bone metastases were administered at 17 sites.

Ten patients received biweekly docetaxel concurrently with radiotherapy. A median of 3 docetaxel courses were delivered, ranging from 1 to 8. Three courses of total 32 courses were delivered with the dose reduced for poor bone marrow function. A weekly docetaxel regimen was administered to 25 patients. The median number of courses was 5, ranging from 1 to 8. Four courses of total 127 courses were delivered with the dose reduced for poor bone marrow function. Two patients received only one course of docetaxel, one of whom had Grade 3 neutropenia and one of whom had a hypersensitivity reaction at the second administration.

Table 2. Treatment Response by Radiation Site and Schedule

States	(site)	CR	PR
All sites	(40)	68% (27/40)	28% (11/40)
Breast + Ax*	(11)	64% (7/11)	36% (4/11)
Chest wall	(15)	73% (11/15)	20% (3/15)
Regional LN**	(14)	64% (9/14)	29% (4/14)
Biweekly	(11)	64% (7/11)	27% (3/11)
Weekly	(29)	69% (20/29)	28% (8/29)

Ax, Axillary lymph nodes; LN, Lymph nodes

Response and Survival

The local response to treatment according to the irradiated tumor site and schedule is shown in Table 2. For all sites combined, $n_S = 40$, the CR rate was 68% and the PR rate was 28%. CR and PR rates were 64% and 27%, respectively, in the biweekly docetaxel group, and 69% and 28%, respectively, in the weekly docetaxel group. There were no statistically significant differences in response rates between the two groups. Fig 2

Table 3. Adverse Effects

Grade	0	1	2	3	4
Hematological Adverse Effects					
Neutropenia					
All cases	23%	31%	29%	14%	3%
Biweekly	10%	10%	50%	20%	10%
Weekly	24%	44%	20%	12%	0
Lymphocytopenia					
All cases	3%	0	46%	51%	
Biweekly	0	0	40%	60%	
Weekly	4%	0	48%	48%	
Anemia					
All cases	69%	17%	14%	0	0
Thrombopenia					
All cases	91%	6%	3%	0	0
Non hematological Adverse Effects					
Alopecia					
All cases	66%	17%	17%	0	
Biweekly	20%	30%	50%	0	
Weekly	84%	12%	4%	0	
Radiation dermatitis					
All cases	6%	63%	29%	3%	3%
Biweekly	0	70%	30%	0	0
Weekly	12%	60%	24%	4%	4%
Nausea					
All cases	80%	26%	3%	0	0
Hypersensitivity	Grade 1 : 3% (biweekly case)				
Diarrhea	Grade 1 : 3% (weekly case)				
Radiation pneumonitis	Grade 2 : 3% (biweekly case)				
Pneumonia	Grade 4 : 3% (weekly case)				
Eruption	Grade 1 : 3% (weekly case)				
Alkaline phosphatase	Grade 2 : 3% (weekly case)				

shows an advanced case in which CR was locally. The overall treatment response including the non-irradiated sites, CR, PR, SD and PD rates for all patients were 40%, 37%, 11% and 11%, respectively. CR and PR rates were 9% and 82% for advanced disease patients, 54% and 17% for recurrent patients, 20% and 70% for biweekly patients and 44% and 28% for weekly patients. A significant difference in the CR rate between advanced disease patients and recurrent patients was observed ($p = 0.014$). There was no statistically significant difference in the CR rate between biweekly and weekly patients.

Overall survival rates at 1 and 2 years after treatment were 83% and 49%, respectively. The corresponding patient survival rates, in previously untreated patients with advanced disease were 78% and 39%, and in those with recurrent disease were 84% and 54%.

Toxicity

Adverse effects are shown in Table 3. Lung toxicities developed in 2 patients. One had Grade 2 radiation pneumonitis and one had Grade 4 pneumonia. These patients had unresectable advanced primary tumor with wide chest wall invasion. Grade 3-4 neutropenia occurred in 17% (6/35) of all patients and in 30% (3/10) and 12% (3/25) of biweekly and weekly patients, respectively. Grade 4 neutropenia was observed in one patient receiving biweekly docetaxel. Grade 3 lymphocyte toxicity was observed in 51% (18/35) of all patients, and in 60% (6/10) or 48% (12/25) of patients receiving biweekly or weekly docetaxel, respectively. Hemoglobin and platelet toxicities were graded as mild or moderate. Grades 1 and 2 alopecia were observed in 17% (6/35) of all patients. The incidence of alopecia was significantly higher in biweekly patients (Grade 2, 50% vs.

4%). Grade 3-4 radiation dermatitis was observed in 6% (2/35) and Grade 2 in 29% (9/35) of patients. Nausea was mild in most patients.

Discussion

Docetaxel is an antimicrotubule agent that has demonstrated substantial activity against breast cancer[13-15]. The concurrent use of chemotherapy and radiation treatment is increasing for the management of advanced and recurrent breast cancers, based on the desire to incorporate a taxane in systemic management and the possible additive or synergistic benefits of concurrent taxane/radiation treatment[10, 16, 17]. Paclitaxel has been used successfully in Phase I and II settings with various dosing schedules[18, 19]. Only a few studies have been published on radiation with concurrent docetaxel in breast cancer[16].

Indeed, the docetaxel/radiotherapy combination has shown remarkable synergistic cytotoxic activity *in vitro*. Tumor reoxygenation and repopulation as a result of taxane exposure may also be important in radiation enhancement. It could be suggested, therefore, that taxanes enhance radiosensitivity in at least two ways. First, they cause cell cycle synchronization at the G2/M radiosensitive phase, known to be the most radiosensitive phase of the cell cycle, and second, taxanes activate a number of genes. However, it appears that the effects of taxanes are mainly p53-independent and involve phosphorylation of the Bcl-2 gene protein. This protein allows cells to escape apoptosis, and subsequent reoxygenation of surviving tumor cells[3, 19]. Although paclitaxel and docetaxel both result in microtubule stabilization, docetaxel has been shown to be more potent in promoting tubulin polymerization[1].

Many modalities have been used in the treatment of advanced or recurrent breast cancer, but it is still difficult to achieve long time survival with good quality of life. For inoperable disease, radiotherapy with chemotherapy has been able to provide good local control. In our series, a 68% local CR rate was observed even though many patients in this study had advanced disease. The patients with unresectable advanced primary tumor rarely achieved CR in our previous experience. The few differences in response rates were observed based on tumor site or docetaxel administration schedule. The small difference noted may be caused by tumor heterogeneity, such as tumor size, or disease extension. Most of the advanced patients had systemic disease. Koukourakis *et al.* reported improved tumor control with additional docetaxel following a course of docetaxel and radiotherapy[20]. One such patient with an advanced primary tumor and lung metastases after completion of radiotherapy and continuous docetaxel, achieved a CR in our series. Patients with multiple bone metastases had improved pain after treatment, although the responses were PR to SD.

Pulmonary toxicity was observed in 5.7% of the patients. The case of pneumonia may have been in association with radiation pneumonitis. It was suggested that this patient showed evidence of *Pneumocystis carini* infection by CT scan, but protozoan was not proved. The pneumonia may also have been associated with lymphocytopenia caused by lymphocyte accumulation in the irradiated area, despite the administration of radiation by electron beam to a large volume of lung. Severe neutropenia occurred in 17% of all patients, and was more frequent in the biweekly group, 30% vs. 12% for the weekly group. Weekly docetaxel administration may thus be safer in this regard. Severe lymphocyte toxicity was observed in 51% of all cases, 60% in the biweekly and 48% in the weekly administration groups. Mason *et al.* reported that docetaxel possesses immunomodulative properties[21]. Their results showed that docetaxel stimulates immune cells to infiltrate the tumor, thereby possibly contributing to lymphocytopenia. In addition, hemoglobin and platelet toxicities were minimal in the current study. Grade 2 alopecia occurred more frequently with biweekly than weekly administration, indicating that the weekly schedule may better preserve quality of life. Severe radiation dermatitis occurred in 6% of patients. Skin toxicities are a problem when using radiation with docetaxel[22].

Conclusion

Based on these data, the combination of docetaxel with radiotherapy is an active regimen in patients with inoperable advanced or recurrent breast cancer when the irradiated pulmonary volume is carefully observed. Although this study had a limited number of patients, the results serve as a springboard for future prospective studies. We determined the recommended dose of docetaxel with concomitant radiotherpy to be 20 mg/m^2 weekly for a Phase II study. Further studies are

also required to assess the effects of concurrent treatment on local tumor control and longer overall outcome.

Acknowledgment

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