Anti-Cancer Drugs 2002, **13,** pp. 791–795

Clinical report

Neo-adjuvant therapy with dose-dense docetaxel plus short-term filgrastim rescue for locally advanced breast cancer

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Neo-adjuvant, dose-dense docetaxel, 100 mg/m^2 every 2 weeks $\times$ 4 cycles, was administered to 12 patients with locally advance breast cancer (LABC) (10 stage IIIa and three stage IIIb). Eligibility requirements included a PS 0–2, normal hepatic and renal function, and radiologic absence of metastatic disease. Filgrastim [granulocyte colony stimulating factor (G-CSF)] was started 1 day after chemotherapy and was given for 6 days. Complete blood counts were determined weekly. Surgery was planned upon recovery from the last dose of docetaxel and followed by 4 cycles of adjuvant doxorubicin plus cyclophosphamide (AC) and radiotherapy. Patients with ER$^+$ status received tamoxifen. The median age was 45 (range 34–73) and pre-treatment pathology revealed poorly differentiated infiltrating duct carcinoma in 11 and infiltrating lobular cancer in one, with positive ER/PR status in five. Twelve patients were treated, and all are evaluable for response and toxicity. Nine patients had a major clinical tumor response with five PR and four pathologic complete responses (pCR rate of 33%). Three patients (of whom two with stage IIIb) had progressive disease and went on to receive neo-adjuvant therapy with AC. There was one instance of grade 3 hematologic toxicity (neutropenic fever in one G-CSF non-compliant patient). There were two instances of grade 3 extra-hematologic toxicity: one patient had severe pain and one had treatment-related fatigue. After a median follow-up of 20 months (range 7–49 months) all patients are alive and eight of nine responders remain progression-free. Despite the small size of our study, we believe that dose-dense neo-adjuvant docetaxel is well tolerated and its activity warrants confirmation in a larger number of patients. [© 2002 Lippincott Williams & Wilkins.]

Key words: Breast cancer, docetaxel, neo-adjuvant chemotherapy.

Supported in part by the Evelyn Sharp Foundation and an unrestricted grant from Aventis.

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Introduction

One of the primary objectives of neo-adjuvant chemotherapy in patients with locally advanced breast cancer is to down-stage the primary tumor and allow breast conservation procedures.[1] Although breast-conserving surgery, as opposed to mastectomy, appears to be safe and acceptable for local control in certain patients, and may improve the quality of life, it is still controversial whether preoperative chemotherapy impacts on overall survival when compared with the same chemotherapy given in an adjuvant setting.[2] It is becoming increasing clear that the overall survival is improved for the fraction of women whose tumors show a pathologic complete response (pCR).[1,3] The ability to measure tumor response to neo-adjuvant chemotherapy, however, allows us to determine sensitivity or resistance to the drug(s) regimen, leaving open the possibility that patients with primary resistance may be candidates, after surgery, for subsequent treatment with non-cross-resistant adjuvant chemotherapy.

Docetaxel is a taxoid compound which promotes microtubule assembly, but inhibits subsequent tubule depolymerization, thereby blocking cells in the M phase. It is a semi-synthetic derivative of a precursor extracted from the needles of the European yew tree. Following demonstration of activity in preclinical systems, the drug has been extensively used for the treatment of many solid tumors in man. In phase II studies of docetaxel in advanced breast cancer, response rates of 47–60% have been reported in chemotherapy-naive patients with response rates of approximately 30% in previously treated patients.[4,5]

Of interest, response rates in excess of 50% were observed in patients with secondary anthracycline resistance, allowing the concept of sequential or simultaneous drug therapy for the treatment of resistant disease.[6,7] Evidence for a risk:benefit ratio favoring docetaxel is provided by several phase III trials in which docetaxel was compared with doxorubicin in metastatic breast cancer; docetaxel was more active than doxorubicin, achieving a significantly higher response (47.8 versus 33.3%; $p=0.008$) and in a shorter time (median 12 versus 23 weeks; $p=0.007$).[8] In combination with doxorubicin[9,10] or other cytotoxics,[7,11–14] similarly favorable response rates are achieved.

Retrospective and prospective studies of increased drug dosage in the adjuvant treatment of breast and ovarian carcinomas suggested that increasing the dose intensity (the ratio between the total drug dose administered throughout the treatment and the duration of treatment, or dose per unit of time) could improve the outcome of treatment.[15,16] The concept of 'dose-density' tests the hypothesis that, if hematologic toxicity can be prevented by hematopoietic support therapy, escalated doses of chemotherapeutic agents may de administered at shorter intervals, thus potentially limiting rapid tumor regrowth in the inter-treatment interval based on Gompertzian kinetics and the Norton–Simon hypothesis.[17] The setting of neo-adjuvant chemotherapy, therefore, more directly provides an arena that allows exploring the direct anti-tumor effects of drugs. As an initial step toward evaluating the efficacy of dose-dense drug delivery, we undertook an evaluation of the feasibility and activity of dose-dense docetaxel, followed by short-term granulocyte macrophage colony stimulating factor (G-CSF) in patients with locally advanced breast cancer.

Study plan

Patients older than 18 with newly diagnosed, previously untreated locally advanced breast cancer stages IIIa and IIIb were evaluated for eligibility; criteria for study entry required biopsy-proven adenocarcinoma of the breast, exclusion of metastatic disease with a negative bone scan and negative computerized tomography of the brain, chest, abdomen and pelvis; physical and sonographic bidimensional measurements of the primary tumor. Other eligibility criteria included a WHO performance status of 0–1. Patients were excluded for elevated transaminases or bilirubin. Patients were informed of the experimental nature of the study, risks and relative benefits. Signed informed consent was obtained from each patient in conformity with institutional guidelines.

Mechanisms of the study

Patients were started on docetaxel 100 mg/m^2 i.v. over 1 h; all patients were premedicated with dexamethasone 8 mg twice daily for 3 days starting the day before each treatment. Hematopoietic rescue with G-CSF, 5 μg/kg for 6 days, was started the day after each treatment. Patients returned for complete blood counts (CBC) on days 8 of therapy. Chemistries and electrolytes were monitored every 2 weeks or more often as clinically indicated. Dose modifications were planned for patients with a neutrophil count $<1500/\mu$l on the day of subsequent treatments. After the fourth course of docetaxel, patients had repeated tumor measurement evaluation by sonographic criteria before surgical resection at an interval no greater than 4 weeks after completion of chemotherapy. The choice of lumpectomy or modified radical mastectomy was left to the discretion of the surgeon and of the patient.

Following surgery, patients received four cycles of adjuvant doxorubicin plus cyclophosphamide (AC), at 3-weekly intervals, followed by involved field radiation therapy (RT) and, for patients with estrogen/progesterone-positive disease, initiation of hormonal therapy with tamoxifen. Patients were followed every 3 months for the first year and every 6 months thereafter.

Criteria for evaluation

Complete response was defined as the disappearance of disease as assessed on the surgical specimen (pathological complete response); partial response was defined, clinically, as the decrease by 50% or greater of the products of the largest perpendicular diameters of lesions measured by physical examination and radiologically, before treatment and immediately before surgery. Stable disease was a response measuring less than a partial response without the appearance of new lesions. Progressive disease was defined as the increase of the products of the largest perpendicular diameters of one lesion or by the appearance of new areas of involvement. Progression-free survival and overall survival were measured from the first day of treatment with

Table 1. Patient characteristics

Age	TNM stage	ER/PR status	Her2-neu status	Tumor measurements		Pathologic diagnosis
				PE	US	
70	3A	1+/3+	negative	7 × 6	4 × 3	IPD ductal carcinoma
55	3A	3+/1+	negative	11 × 11	7 × 6	IPD ductal carcinoma, micropapillary
44	3A	3+/1+	negative	7 × 7	7.3 × 4.6	IPD ductal carcinoma, micropapillary
44	3A	3+/−	negative	7 × 6	3.7 ln 2	IPD ductal carcinoma
38	3A	1+/2+	negative	6 × 7	3.8 × 3.2	infiltrating lobular cancer
57	3A	−/−	negative	6 × 6.5	2.5	IPD ductal carcinoma
44	3B	−/−	negative	NM	1.8 ln 1.9	IPD ductal carcinoma with lymph invasion
34	3A	−/−	negative	11 × 11	4 × 6	IPD ductal carcinoma with lymph invasion
43	3B	−/−	3+	NM	ND	IPD ductal carcinoma
41	3A	−/−	negative	5 × 6	7 × 6	IPD ductal carcinoma
42	3A	−/−	negative	10 × 10	3.3 × 2.7	IPD ductal carcinoma
54	3B	−/3+	negative	NM	1.5 × 1.5	IPD ductal carcinoma, anaplastic

PE, physical examination; US, sonography; IPD, infiltrating, poorly differentiated; ND, not done; NM, not measurable.

docetaxel to the documentation of progressive disease or death from any cause. Data were analyzed as of 15 April 2002.

Results

Twelve women with a median age of 44 (range 34–70) were registered to the study; their characteristics are shown on Table 1. The ER/PR receptor status was positive in six; Her2-neu protein was detected in one patient. Three patients had inflammatory breast cancer; as indicated in Table 1, measurement obtained by sonography differed somewhat from those measured by physical examination or by other imaging techniques (data not shown). Pathologically, the diagnosis established on core biopsies was of infiltrating duct carcinoma in 11 patients (two each with micropapillary features or lymphatic invasion; one anaplastic) and one patient had infiltrating lobular carcinoma.

Hematologic and extra-hematologic toxicities are shown in Table 2 There was only one instance of grade 3 hematologic toxicity (a patient who developed fever with a neutrophil count of 920/μl 2 weeks after the last dose of docetaxel); no toxicity was seen for platelets. Grade 1 and 2 decline of hemoglobin levels, seen in nine and two patients, respectively, did not require transfusional intervention. Forty-seven of the 48 planned treatments were administered without time delays; one patient, who developed lower extremities edema and was treated with steroids, received 3 cycles of docetaxel because of exacerbation of type II diabetes.

Grade 2 edema was seen only in one patient, who was treated with steroids as recommended and who did not receive the last course of docetaxel because of steroid-induced diabetes exacerbation. Two patients had grade 2 neuromuscular toxicity; other systemic symptoms, such as fatigue, were grade 3 in one patient. The occurrence of bony pain, of grade 3 in one patient, and grade 2 and 1 in four and three patients, respectively, was seen concomitant to filgrastim administration and judged to be unrelated to the study drug. Grade 2 dyspnea on exertion, without pulmonary or cardiovascular findings, was experienced by two patients. Ocular toxicity, consisting of excessive tearing, was of grade 2 in two patients. Typical dystrophic nail changes associated with docetaxel therapy were seen in five patients.

Table 2. Clinical toxicities

	Toxicity grade				
	0	1	2	3	4
Neutrophils	11	–	–	1	–
Hemoglobin	1	9	2	–	–
Platelets	12	–	–	–	–
Edema	11	–	1	–	–
Fatigue	6	4	1	1	–
Onycholysis	6	3	2	–	–
Pain	4	3	4	1	–
Neurologic	4	5	3	–	–
Mucositis	9	3	–	–	–
Dyspnea on exertion	9	1	2	–	–
Ocular	9	1	2	–	–

Response to treatment and response duration are summarized in Table 3. There were nine responses; of these, five were partial and four were complete pathologic remissions (pCRs). Three patients did not have surgery after docetaxel: two patients with progressive disease and one with inflammatory breast cancer, with stable disease,

Table 3. Response and overall survival

Study patient	Stage	Axillary lymph nodes (pathology)	Pathologic response	Response duration (months)
1	3A	0/7	PR	49 +
2	3A	12/26	PR	49 +
3	3A	0/19	PR	47 +
4	3A	10 /18	PR	31 +
5	3A	0/15	pCR	27 +
6	3A	1/23	PR	23
7	3B	0/5	pCR	15 +
8	3A	0/20	pCR	11 +
9	3A	0/6	pCR	10 +
10	3A	no surgery	PD	5
11	3B	no surgery	SD	4
12	3B	no surgery	PD	3

received AC neo-adjuvantly, and only one responded. In addition, patient #7, who had an inflammatory breast cancer, with no measurable disease after 4 cycles of docetaxel and negative skin biopsies, also received neo-adjuvant AC and chest wall RT before proceeding to surgery. All patients remain alive at an average of 26 months (range 7–49); response is continuing for all but one of the responding patients, who progressed after 34 months.

Discussion

Although large trials have shown that neo-adjuvant chemotherapy does not improve the overall survival of patients with locally advanced breast cancer,[1,2] the greatest survival advantage is seen in those who experience pCRs.[3,18–20] Since only a minority of patients enjoy such responses, more effective neo-adjuvant therapies are needed.

While use of anthracycline-based neo-adjuvant chemotherapy in the treatment of locally advanced breast cancer is established,[21] further research in its treatment is necessary to define optimal methods of local therapy and the role of other active agents such as docetaxel. Based on its activity when used alone or in combination with other agents in metastatic breast cancer and because of its lack of cross-resistance with anthracyclines, a recent study has evaluated the incorporation of docetaxel in pre-operative chemotherapy.[22] In this neo-adjuvant randomized study, four cycles of docetaxel, 100 mg/m^2 were administered to patients who had received (and responded to) 4 cycles of a regimen of doxorubicin, cyclophosphamide, vincristine and prednisone. These patients were compared to a cohort randomized to 4 additional cycles of initial therapy, for a total of 8 cycles. Treatment cycles were administered every 21 days and the total duration of planned treatment was 24 weeks. The clinical CR were higher for the docetaxel-containing treatment (94 versus 66%, respectively, $p=0.001$) and so was the rate of pCR (34 versus 16%, $p=0.04$). The outcome for the proportion of patients (approximately one-third of the total patient population) who had not responded after the first 4 cycles of chemotherapy and who were subsequently also treated with docetaxel, was substantially lower, with a pCR in less than 2% of patients. The superior outcome for patients treated with docetaxel did not change when data were analyzed by intent to treat.

In conclusion, our study was a small, feasibility study which aimed to evaluate the activity of neo-adjuvant dose-dense docetaxel with filgrastim support for patients with stage III breast cancer. Therapy was administered over 8 weeks and was well tolerated. We found a response rate of 75% and a complete pathologic remission rate of 33%. Despite the very small sample size, the data suggest that achievement of pre-operative tumor reduction may be achieved safely and rapidly. Since pCRs are correlated with longer progression-free and overall survival, we believe that exploration of this concept in a large patient population is feasible.

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(Received 7 May 2002; accepted 11 June 2002)