Docetaxel for Metastatic Breast Cancer: Two Consecutive Phase II Trials

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Abstract. *Background: Docetaxel is the most active agent for metastatic breast cancer, but the optimal treatment regimen as a single agent has yet to be defined. Patients and Methods: Two consecutive monocentric phase II trials of docetaxel in metastatic breast cancer were carried out. In Trial I, 36 patients received docetaxel 35 mg/m^2 weekly for 6 weeks every 8 weeks and in Trial II, 29 patients received docetaxel 100 mg/m^2 day 1 every 21 days. Results: Patient characteristics were comparable. However, patients with liver involvement comprised 25% of cases in Trial I and 55% in Trial II. The overall response rate on an intention-to-treat basis was 19% vs. 45% in Trial I and II respectively; time to progression was 3.8 vs. 7.5 months respectively, and overall median survival was comparable in each trial. Conclusion: Docetaxel given at 100 mg/m^2 every three weeks appears to be a safe, effective regimen that can be applied in common clinical practice for the treatment of metastatic breast cancer.*

Doxorubicin, introduced in the early 1970's, has long been considered the single most active drug in metastatic breast cancer. However, the activity of docetaxel in patients with anthracycline-resistant disease has been documented since 1995 (1). A phase III trial comparing the efficacy and toxicity of docetaxel *versus* doxorubicin in metastatic breast cancer patients receiving no prior anthracyclines demonstrated that the overall response rate was significantly superior with docetaxel (47.8% *versus* 33.3%). With the exception of neutropenia, which was comparable in the two groups, the drugs showed different toxicity profiles (2).

Data concerning efficacy of docetaxel administered weekly *versus* every 3 weeks is controversial, with response rates favouring the weekly schedule (3), every three weeks (4), or reporting no difference between the two regimens (5). The weekly regimen has been associated with a better tolerability profile (6).

Two consecutive phase II single agent docetaxel trials in metastatic breast cancer are reported. In Trial, I patients were treated with weekly docetaxel and in Trial II, docetaxel was administered every 3 weeks. All patients were seen at the same oncology center and eligibility criteria of the two trials were superimposable. The objectives of both trials were to evaluate response, time to progression and toxicity.

Patients and Methods

From June 2000 to June 2004, 65 women with histologically confirmed metastatic breast cancer and measurable disease entered two consecutive phase II trials. All patients were followed at the same oncology center. Both studies had Ethical Committee approval and informed written consent was obtained from all patients.

Eligibility critieria were identical in the two consecutive phase II trials. Women aged 18-80 years were eligibile for enrollment. In patients without organ disfunction, increased age alone did not preclude eligibility. Patients were eligible even if they had received prior adjuvant treatment with or without anthracyclines or prior palliative chemotherapy. However, no patient receiving prior taxanes was eligible. Patients with metastatic central nervous system (CNS) disease were excluded from the study. Patients were also excluded for inadequate bone marrow, kidney or liver function as evidenced by laboratory values outside the prescribed limits as follows: granulocyte count <2,000/μl; platelet count <100,000/μl; hemoglobin level <9.0 g/dl; creatinine >2.5 mg/dl; total bilirubin >2.0 mg/dl; liver transaminases more than 3 times normal and ECOG performance status >2. Patient characteristics are given in Table I.

Docetaxel was administered according to one of the two different schedules: docetaxel 35 mg/m^2 in a 30 minute *i.v.* infusion weekly for 6 weeks every 8 weeks (Trial I) or 100 mg/m^2 in a one hour *i.v.* infusion day 1 every 3 weeks (Trial II). Patients continued treatment until they experienced either progressive disease or severe toxicity. No dose reduction was carried out, but treatment was delayed to allow for marrow recovery.

Premedication in Trial I consisted of oral prednisone 50 mg (since convenient oral doses of dexamethasone are not available in Italy, the equivalent steroid dose was used) the evening before,

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Table I. *Patient characteristics.*

	Trial I	Trial II
Total number of patients	36	29
Estrogen receptor status		
Positive	17	23
Negative	16	6
Unknown	3	0
ECOG performance status		
0	27	21
1	9	8
Adjuvant therapy		
(All doxorubicin-containing)	24	15
Metastatic disease		
Bone	25	15
Liver	9	16
Lung	7	6
Soft tissue	17	13
Breast	1	4
Other	6	4

dexamethasone 8 mg *i.v.* 30 minutes prior to treatment and oral prednisone 50 mg morning and evening on day 2. In Trial II, premedication was oral prednisone 50 mg in the morning and evening prior to infusion, dexamethasone 8 mg *i.v.* 1 h prior to treatment and oral prednisone 50 mg the evening of day 1 and then morning and evening of day 2. Patients received palliative radiotherapy and full supportive care, including analgesics, antibiotics, erythropoietin and/or blood transfusions and granulocyte colony-stimulating factors as required.

The primary objective of both studies was to evaluate response rates according to World Health Organization (WHO) criteria (7). Response was evaluated, according to the intention to treat, after two courses of treament, by physical examination and/or conventional X-ray and in patients in whom it was appropriate by diagnositic scans, CT, MRI, PET and bone scans. Time to progression was considered as the time from the first day of treatment to documentation of disease progression or death. Toxicity was evaluated weekly in both trials according to NCI-CTC version 1.0 criteria (8).

Results

Thirty-six patients entered Trial I and 29 patients Trial II. As Table I shows, patient characteristics were comparable. There were, however, more patients with liver involvement in Trial II (55%) than in Trial I (25%). Table II demonstrates the prior palliative treatment received. In the majority of cases, docetaxel was given as first-line palliative treatment to 53% and 62% of patients in Trial I and II, respectively.

The overall response rate (complete and partial response) to weekly docetaxel was 19% of patients compared to 45% of those treated with docetaxel every 3 weeks ($p<0.002$), as reported in Table III. In addition, the only complete response observed was in Trial II.

Table II. *Prior palliative chemotherapy in patients receiving docetaxel.*

Prior treatment	Trial I (n=36) No. patients (%)	Trial II (n=29) No. patients (%)
No prior palliative chemotherapy	19 (53%)	18 (62%)
Second-line	14 (39%)	8 (28%)
Third-line	2 (5%)	2 (7%)
Fourth-line	1 (3%)	1 (3%)

Table III. *Response to docetaxel according to treatment schedule and intent to treat.*

Response	Trial I (n=36) No. patients (%)	Trial II (n=29) No. patients (%)
Complete	0	1 (3%)
Partial	7 (19%)	12 (42%)
Stable disease	9 (25%)	9 (31%)
Progression	19 (53%)	5 (17%)
Not evaluable	1 (3%)	2 (7%)
Overall response (Complete + partial)	7 (19%)	13 (45%)

Table IV. *Grade 3-4 toxicity.*

	Trial I (n=36) No. patients (%)		Trial II (n=29) No. patients (%)	
Toxicity	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	3	0	4	6
Febrile neutropenia		0		3
Constipation	1	0	4	0
Asthenia/fatigue	0	0	1	0
Emesis	0	0	2	0
Diarrhoea	0	0	2	0
Nail changes	1	0	1	0
Neurotoxicity	1	0	2	0
Hypersensitivity	1	0	2	0

Time to progression was also significantly longer when docetaxel was given every 3 weeks (3.8 *versus* 7.5 months; $p=0.001$). The overall median survival was comparable in the two groups: 12.6 months in Trial I and 15.7 months in Trial II. As shown in Table IV, the overall tolerability profile was better with weekly docetaxel. Myelosuppression was substantially less with the weekly schedule. In Trial I, only 3 cases had grade 3 neutropenia (8%) and no grade 4 neutropenia occured. With docetaxel every 3 weeks, grade 3 and grade 4 neutropenia was observed in 4 (14%) and 6 cases (21%), respectively. No febrile neutropenia occurred.

Discussion

The two trials presented were consecutive phase II trials designed to assess tolerability and activity of weekly and 3-weekly docetaxel in metastatic breast cancer patients as they occur in common clinical practice. A total of 65 patients entered the trials. These patients were all treated and followed up at the same oncology center. With weekly docetaxel 35 mg/m^2, the overall response rate, time to progression and median overall survival were significantly worse than with 3-weekly docetaxel 100 mg/m^2. Even if the toxicity profile was more favourable with weekly docetaxel, the difference in toxicity between the two regimens was not substantially different. These results contrast with prior randomised Phase II trials comparing weekly and 3-weekly docetaxel which concluded that the regimens are equally effective (3, 9). Results in the literature with 3-weekly docetaxel in metastatic breast cancer patients receiving the drug as either first-line or further lines of palliative treatment report response rates that vary from 30% to 48% (2, 10). Weekly docetaxel gave overall response rates that range from 33% to 50%. The weekly and 3-weekly schedule are associated with comparable time to progression and overall median survival (11). Results from the present two consecutive phase II trials shows that overall response, time to progression and overall survival are within the ranges reported in the literature, both with weekly and 3-weekly docetaxel. Although neutropenia was less frequent with the weekly schedule, response and time to progression were significantly improved with 3-weekly docetaxel.

Weekly docetaxel could be recommended for use in patients at particular risk of myelotoxicity. In metastatic breast cancer patients encountered in common clinical practice, docetaxel 100 mg/m^2 every 3 weeks was safe and more effective than a weekly regimen, suggesting that this 3-weekly schedule should be the preferred schedule.

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