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ORIGINAL ARTICLE

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Docetaxel monotherapy in heavily pretreated metastatic breast cancer: a multicenter, community-based feasibility trial

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Abstract *Purpose*: To evaluate the efficacy and safety of docetaxel in heavily pretreated and anthracycline-resistant patients with metastatic breast cancer in an outpatient setting. *Patients and methods*: Between February 1996 and June 1998, 98 consecutive patients who had progressed during or relapsed following prior anthracycline-containing chemotherapy were enrolled into the trial. Docetaxel was administered at a dose of 100 mg/m^2 by intravenous infusion every 3 weeks. The administration of colony-stimulating factors was at the discretion of the attending physician. Premedication with dexamethasone was mandatory for all patients. *Results*: Of the 98 patients, 93 were evaluable for toxicity and response. Patients had received two palliative regimens (median, range 1–5) prior to docetaxel treatment. The most frequent toxicity observed was leukopenia grade III and IV (WHO grading system) which occurred in 47% of patients (grade IV only in 14%). Except for alopecia grade III (64% of patients), nonhematologic side effects grade III-IV were rare (1–7% of patients) and included nausea, stomatitis, diarrhea, peripheral neuropathy, fluid retention and pulmonary toxicities. There were no treatment-related deaths. Objective responses occurred in 40% of patients (CR 6%, PR 34%), and stable disease in 38% of patients. The median duration of response was 5.3 months (range 0.7–18.1 months) while the median survival was 15 months (range 2–36 months). *Conclusion*: Docetaxel is a highly active agent in patients with anthracycline-resistant metastatic breast cancer, even in heavily pretreated patients, with moderate toxicity.

Key words Metastatic breast cancer · Docetaxel · Anthracycline

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Introduction

In the pre-taxane era, doxorubicin-containing regimens were considered standard of care in metastatic breast cancer patients [5, 18, 34]. While leading to objective response in a substantial number of patients, these regimens have not dramatically altered the prognosis of these patients in terms of overall survival. Until recently,

there was no promising third-line treatment for patients who became refractory to alkylating agents and doxorubicin. During the last few years, however, several promising cytotoxic agents with pronounced antitumor activity in metastatic breast cancer have appeared [19]. Of these agents, the taxanes docetaxel and paclitaxel have been evaluated most extensively for efficacy in breast cancer.

Docetaxel is a semisynthetic taxoid derived from the needles of the European yew *Taxus brevifolia*. This agent inhibits tubulin depolymerization and enhances the formation of microtubule bundle aggregates disrupting mitosis, thus causing cell death [28]. In vitro, docetaxel has been found to be more potent than paclitaxel in promoting abnormal microtubule stabilization [8, 12, 20, 28]. In phase I and II studies, responses have been observed even in heavily pretreated patients with metastatic breast cancer [25, 27], while the first-line use of docetaxel in metastatic breast cancer has produced an overall response rate of up to 73% [15]. In addition, Aapro [1] has reported an objective response rate of 48% with docetaxel as compared to 33% with doxorubicin ($P = 0.008$), demonstrating the superiority of docetaxel over an anthracycline in terms of response rate.

We now report the results of a phase II clinical trial of single-agent docetaxel administered to patients with metastatic breast cancer who had progressed under or relapsed following prior anthracycline-based regimens.

Patients and methods

Patients

Between February 1996 and June 1998, 98 patients were enrolled into the trial. Eligibility criteria included: histologically proven metastatic breast cancer; at least one prior chemotherapy, with one of the prior regimens required to have included an anthracycline with subsequent demonstration of refractoriness of the disease defined as progression during therapy or relapse within 3 months of the last anthracycline administration; a Karnofsky performance status ≥60%, an estimated life expectancy of ≥12 weeks, adequate hematologic function (hemoglobin >10 g/dl, white blood cell count $\geq 3.5 \times 10^{-3}$ g/l, granulocyte count $\geq 2.0 \times 10^{-3}$ g/l and platelet count $\geq 100 \times 10^{-3}$ g/l), adequate hepatic function (serum transaminases less than twice the upper limit of normal, total serum bilirubin level ≤1.5 mg/dl, alkaline phosphatase <200 mg/dl) and renal function (serum creatinine ≤2.0 mg/dl); and written informed consent.

Diagnosis and treatment

Docetaxel was given intravenously over 1 h at a dose of 100 mg/m^2, and cycles were repeated every 21 days. Treatment was administered at least for two cycles and in case of absence of primary progression until progressive disease (PD) occurred. Restaging procedures were scheduled every three cycles. A dose reduction of 25% for the next therapy course was mandatory for patients who experienced grade III or IV (WHO grading system) neutropenia, grade III or IV diarrhea despite adequate therapy, grade II neurotoxicity or any other toxicity of grade III or IV, except alopecia. Patients with grade IV hypersensitivity reactions had to be withdrawn from the study. Individually, dose reduction to 55 mg/m^2 was at the discretion of the attending physician as was primary or secondary use of granulocyte colony-stimulating factor (G-CSF, 5 μg/kg). Premedication to avoid hypersensitivity reactions consisted of 2×8 mg dexamethasone daily given orally from the day prior to therapy until days 3 to 5 after therapy. No prophylactic antiemetic treatment was scheduled. At the physician's discretion, antiemetics such as ondansetron 8 mg twice daily were prescribed as needed.

Pretreatment evaluation included a medical history, physical examination, assessment of performance status, complete blood cell count, blood chemistry, electrocardiography, chest radiography and optional chest computed tomography (CT), abdominal CT and radionuclide bone scan. Physical status, complete blood cell counts and serum chemistry were obtained before each treatment cycle. Encountered toxicities were classified according to the WHO grading system.

Response evaluation

Sites of measurable metastases were assessed every three cycles. WHO criteria were used for evaluation of response. Stable disease (SD) was defined corresponding to this definition and under the exclusion of criteria valid for complete remission (CR), partial remission (PR) or PD, respectively. The duration of survival was calculated from the beginning of this treatment.

Statistical analysis

Survival curves were calculated and plotted according to the method of Kaplan and Meier. Statistical comparisons of survival curves were performed using a *t*-test. *P*-values <0.05 were considered to be significant. Comparison of response to prior anthracycline-based treatment with docetaxel treatment was performed using the χ^2-test.

Results

Patients

Of the 98 patients, 93 were eligible for analysis of toxicity and response (Table 1), while 5 were lost to follow up. Most patients had a good performance status (Karnofsky performance status: median 90, range 60–100) despite advanced disease. The majority (77%) of women were postmenopausal at the time of diagnosis of metastatic spread. The median number of preceding palliative therapy regimens was two (range one to five). The majority of tumors were ductal carcinomas.

Treatment

The 93 patients were treated with 518 courses of docetaxel. A dose reduction was required in 151 courses (29%) (median 20% reduction, range 5–50%), while 367 courses (71%) were administered with the planned dose of 100 mg/m^2. The median dose intensity for all 518 administered courses was 100 mg/m^2 (range 50–100 mg/m^2). The median number of courses given to patients was six (range two to ten). All cycles were administered within the scheduled time frame every 21 days.

G-CSF was given to 36 patients during a median of two courses (range one to nine), in 25 patients with therapeutic and in 11 patients with prophylactic inten-

Table 1 Characteristics of the 93 eligible patients

Age (years)	
Range	29, 3–77.8
Median	57
Karnofsky index	
Range	50–100
Median	90
Menopausal status ($n=93$)	
Pre	21 (23%)
Post	72 (77%)
Metastatic locations	
Lung	27 (29%)
Liver	38 (41%)
Bone	45 (51%)
Soft tissue/lymph nodes	45 (49%)
Central nervous system	3 (3%)
Bone marrow	2 (2%)
Other	6 (6%)
Number of metastatic sites	
1	28 (30%)
2	28 (30%)
3 or more	37 (40%)
Pretreatment	
Adjuvant + neoadjuvant	48 (52%)
Anthracycline-based	18
CMF-based	27
Others	3
Palliative	93 (100%)
Anthracycline-based	93 (100%)
CMF-based	48 (52%)
Others[a]	31 (33%)
Docetaxel treatment as	
Palliative second-line therapy	35 (38%)
Palliative third-line therapy	43 (46%)
Palliative fourth-line therapy	10 (11%)
Palliative fifth-line therapy	4 (4%)
Palliative sixth-line therapy	1 (1%)

[a] Includes cisplatinum, vinca alkaloids, gemcitabine, mitomycin C

tion. Dexamethasone was administered to all patients, the most common dose being 16 mg daily over 3 to 5 days, starting 1 day prior to docetaxel.

Toxicity

Encountered toxicities are detailed in Table 2. Among severe toxicities, leukopenia grade III was the most frequent and was seen in the majority of patients. Among patients with leukopenia grade IV, none suffered from febrile infection. Only two patients with leukopenia grade III had febrile infection of grade II. These two patients required short hospitalization for treatment with intravenous antibiotics. There was no neutropenia- or infection-related death. Anemia was never dose-limiting or a clinically significant side effect, as none of the patients required erythrocytes. Only one patient experienced grade III thrombopenia without bleeding complications. No grade IV thrombocytopenia was observed and no platelet transfusions were required.

No prophylactic antiemetics were given. However, nausea and vomiting was seen in 30% of the patients (grade I 13%, grade II 14%, and grade III 3%), but only 3% of the patients required intravenous antiemetics.

Table 2 Toxicities (WHO grade) in 93 evaluable patients. The numbers (%) of patients are shown

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	9 (7%)	17 (14%)	39 (33%)	16 (14%)
Infection	5 (4%)	5 (4%)	2 (2%)	0
Thrombopenia	2 (2%)	5 (4%)	1 (1%)	0
Anemia	4 (3%)	4 (3%)	0	0
Nausea	15 (13%)	16 (14%)	3 (3%)	0
Diarrhea	8 (7%)	11 (9%)	8 (7%)	0
Stomatitis	29 (25%)	13 (11%)	0	1 (1%)
PNP	18 (15%)	11 (9%)	3 (3%)	0
Skin	6 (5%)	6 (5%)	0	0
Fluid retention	10 (9%)	13 (11%)	1 (1%)	0
Alopecia	7 (6%)	6 (5%)	75 (64%)	1 (1%)
Pulmonary	1 (1%)	2 (2%)	1 (1%)	0

Diarrhea grade III was a dose-limiting side effect in eight patients. Stomatitis grade IV was seen in one patient. Peripheral neurotoxicity grade III was a side effect in three patients. Neurotoxicities were characterized by severe para- and hyperesthesias in fingers and feet as well as by weakness of lower extremities.

Fluid retention occurred in 14 patients, but none of them showed generalized edema, and all were successfully treated with diuretics given orally. Nail toxicity (grade II) was a frequent ($n=51$) treatment-related side effect. Alopecia was the most common side effect, but was irreversible in only one patient. Pulmonary side effects were seen in one patient and consisted in dyspnea on exertion. Among patients with any grade III or IV toxicities (except alopecia and nail toxicity), 27 (29%) had abnormal serum transaminases and or bilirubin levels at the beginning of treatment. There was no correlation between moderately elevated liver function parameters and subsequent toxicity.

No patient suffered from hypersensitivity reaction; furthermore, no cardiac, renal or hepatic toxicities occurred in a total of 518 courses of chemotherapy. No patient had to be withdrawn because of toxicity.

Response and survival

Response data are given for 93 eligible patients. Objective responses occurred in 38 patients (40%) with 6% of patients presenting with CR and 34% with PR. An additional 35 patients (38%) experienced SD. Primary progression during therapy occurred in a total of 20 patients (22%). These patients were taken off study, and administration of further therapy was at the discretion of the physician responsible for the patient.

The presence of skeletal metastases correlated significantly with better response ($P=0.04$) as compared to the presence of visceral metastases. The response rates in relation to metastatic site are given in Table 3.

Analysis of the efficacy of docetaxel versus the prior anthracycline-based treatment is shown in Table 3. The overall response rate (CR and PR) for docetaxel was 40% compared to 27% achieved with the prior anthra-

Table 3 Response to prior anthracycline treatment and to docetaxel treatment in relation to metastatic site among 93 eligible patients

	CR	PR	SD	PD
Anthracycline ($n=93$)	8 (9%)	17(18%)	23 (25%)	45 (48%)
Docetaxel				
Overall ($n=93$)	6 (6%)	32 (34%)	35 (38%)	20 (22%)
Bone metastasis ($n=22$)	2 (9%)	5 (23%)	11 (50%)	4 (18%)
Liver metastasis ($n=29$)	2 (5%)	11 (38%)	10 (34%)	6 (21%)
Lung metastasis ($n=18$)	1 (5%)	6 (33%)	7 (39%)	4 (22%)
Liver + lung metastasis ($n=9$)	1 (11%)	3 (33%)	4 (45%)	1 (11%)
Other metastatic sites ($n=15$)	0	7 (47%)	3 (20%)	5 (33%)

cycline-containing regimen. Among the 45 patients (48%) had failed previous anthracycline-based pretreatment, 16 (35%) responded to docetaxel monotherapy with 1 CR (2%) and 15 PR (33%); another 33% had SD ($P=0.0009$) (Table 4). Median overall response (OR) duration was 5.3 months (range 0.7–18.1 months), and among the CR 7.1 months (range 3.7–15.4 months). Patients with PR had a median response duration of 5.8 months (range 1.8–18.1 months), and median duration of SD was 4.8 months (range: 0.7–16.7 months).

Median progression-free survival (PFS) was 10 months for all patients. At the time of analysis, there was no statistically significant difference in PFS between patients with CR, PR and SD (not reached 20 months, 15 months, respectively). The median overall survival (OS) (Fig. 1) was 15 months (range 2–36 months), whereas among the CR median OS was not reached. Patients with PR had a significantly longer OS than patients with SD (19 months vs 15 months, $P=0.02$; Fig. 2) and than patients with PD (12 months, $P=0.01$; Fig. 3). The number of metastatic sites was not predictive of survival.

During the trial 25% of patients died (median 7 months after the first docetaxel course) from metastatic disease with no therapy-related deaths.

Discussion

In this trial, we demonstrated the efficacy and safety of outpatient docetaxel as monotherapy in patients with metastatic breast cancer refractory to anthracycline-based chemotherapy. The overall response rate (CR + PR) of eligible patients was 40% with CR occurring in 6% and PR in 34% of patients. These findings are consistent with the results of various other phase II trials which have shown response rates ranging from 23% to 58% [3, 6, 9, 16, 23, 27, 29, 30, 32, 35, 36] in anthracycline-resistant patients with metastatic breast cancer. Compared to response rates of up to 68% in early as well as recent trials [7, 10, 11, 13, 17, 24, 27, 32]

Table 4 Response to docetaxel in patients with primary progression under the prior anthracycline treatment ($n=45$, 48%)

Response	*n* (%)
CR	1 (2)
PR	15 (33)
SD	15 (33)
PD	14 (32)

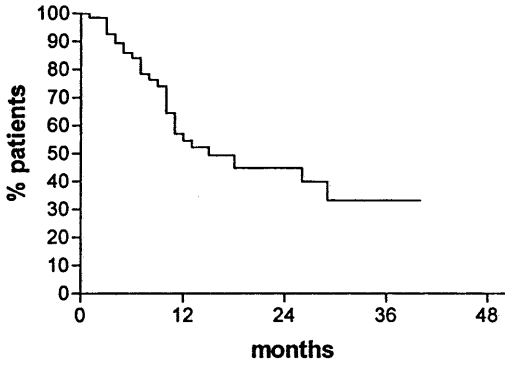

Fig. 1 Median overall survival

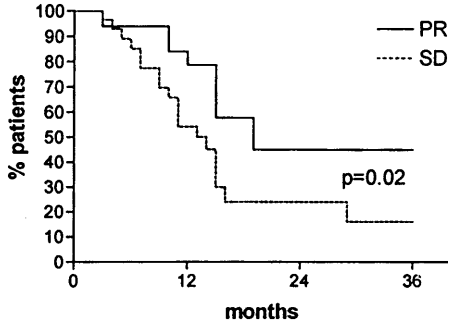

Fig. 2 Median overall survival in relation to response showing the survival of those with stable disease (—) compared with the survival of those with partial remission ([arrowhorizex])

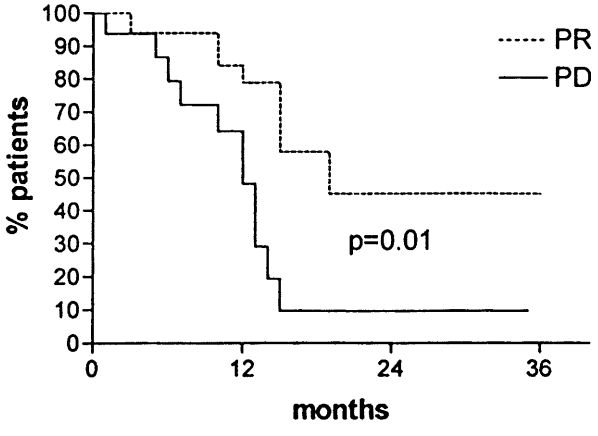

Fig. 3 Median overall survival in relation to response showing the survival of those with progressive disease ([arrowhorizex]) compared with the survival of those with partial remission (—)

with docetaxel used as first- or second-line palliative treatment, our study seems to have yielded modest results. However, reports with docetaxel monotherapy as a third-line regimen (median) in metastatic breast cancer are rare.

Despite the finding of Ten Bokkel Huinink et al. [33] of no major difference in response in relation to the number of prior chemotherapies, we explain the difference between our findings and those of studies with higher response rates by the fact that patients had received a median of two prior palliative chemotherapy regimens. However, similar to the findings of other investigators, we also demonstrated that docetaxel is one of the most active cytotoxic agents in heavily pretreated metastatic breast cancer patients with considerable efficacy even after failure of anthracycline-based treatment: 35% of the patients experienced an objective response after failure of preceding palliative anthracyclines with acceptable toxicities. Furthermore, it is of clinical interest that these results were obtained from a community-based trial and not, as is usual, from a single-center academic hospital, and that all patients received this treatment on an outpatient basis.

In patients with metastatic breast cancer, excellent response rates of 70–80% following docetaxel- and anthracycline-containing regimens have been reported [21]. The importance of these combinations has recently been demonstrated in a randomized trial in which the efficacy of docetaxel and anthracyclines was compared with that of anthracyclines and cyclophosphamide in 429 anthracycline-naive patients [22]. The docetaxel-containing regimen was found to be superior to the combination of anthracycline and cyclophosphamide (RRs of 60% and 47%, respectively). Considering that our patients had progressed under various previous therapy regimens, it did not seem reasonable to combine docetaxel with other cytotoxic agents.

Based on the excellent data on docetaxel-containing regimens, the combination of docetaxel with other chemotherapeutic agents will be of increasing interest particularly in an earlier stage of the disease. Thus, a series of neoadjuvant regimens are currently under investigations in which docetaxel and other cytotoxic agents are combined. The efficacy of docetaxel and cisplatinum [14], or epidoxorubicin [31] have been investigated in recent trials and RRs of 67% and 100%, respectively, have been found.

The toxicities observed in this trial were manageable. The most frequent toxicity was leukopenia grade III to IV which was present in 16% of the courses (grade IV only 3.5%), but only two patients required intravenous antibiotics and hospitalization. There were no treatment-related deaths. In contrast to the findings of other investigators [29] who recommended that a dose level of 75 mg/m^2 in heavily pretreated breast cancer patients should not be exceeded, we found 100 mg/m^2 docetaxel to be safe and feasible, even in a multicenter, outpatient setting. In spite of this, as has been recently reported, docetaxel must be used cautiously and some patients need strict dose adaptations [2]. We think that it was important to give the G-CSF administration to the discretion of the attending physicians because the intensity of pretreatment was different between patients. Anemia and thrombocytopenia were generally mild and did not have to be treated. This fact is remarkable in view of the cumulative toxicity to bone marrow after several chemotherapy regimens prior to current docetaxel treatment. Fluid retention which occurred in only 10% of all the 518 courses was manageable with diuretics and was never a therapy-limiting problem. This was probably due to the strict dexamethasone prophylaxis, which has also been recommended by others [4, 26].

In conclusion, docetaxel is highly active in patients with metastatic breast cancer. Even extensively pretreated and anthracycline-resistant patients may benefit from this agent. The toxicities observed were acceptable under these conditions. Further investigations should focus on early detection of anthracycline refractoriness in order to optimize and individualize therapy at an earlier stage of the disease and on combining docetaxel with other active agents.

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