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Clinical report

Monotherapy with docetaxel in second- or third-line treatment of anthracycline-resistant metastatic breast cancer

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Nineteen breast cancer patients pretreated with one or two anthracycline-containing regimens for visceral metastases received i.v. docetaxel 100 mg/m^2 on day 1, q 21d. Docetaxel was administered as second-line therapy in 11 patients, whereas eight patients received docetaxel in a third-line setting. In the second-line setting, complete response (CR) was achieved in two (18%), partial response (PR) in four (36%) and stable disease (SD) in three (27%) patients resulting in a response rate (RR) of 54%. In the third-line setting three (38%) patients experienced PR (RR 38%) and two (25%) SD. In the second-line setting, median time to progression was 6.5 $\pm$ 3.9 months (range 2.1–15.8) versus 4.7 $\pm$ 5.5 months (range 0.6–15.9) in the third-line setting. Median overall survival was 9.6 $\pm$ 8.0 months (range 2.7–25.8) versus 11.2 $\pm$ 6.1 months (range 4.8–18.7). Overall, no patient experienced treatment-limiting toxicities. We conclude that docetaxel induced responses in 48% of anthracycline-resistant patients enrolled into the present study. The safety profile of docetaxel was manageable and tolerable. Docetaxel represented efficacious treatment in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. [© 2000 Lippincott Williams & Wilkins.]

Key words: Chemotherapy, docetaxel, metastatic breast cancer.

Introduction

Metastatic breast cancer (MBC) represents an incurable disease in an overwhelming percentage of patients[1] despite advances in endocrine treatment[2] and the introduction of new cytotoxic drugs[3] used in mono- and in polychemotherapy regimens as well as in early high-dose[4] and ultra-high-dose trials combined with stem cell support.[5–7] Recently, the understanding of the molecular basis of breast cancer has increased considerably and resulted in emerging drug therapies with new classes of anticancer agents directed against well-defined molecular targets[8,9] which have proved to exert significant efficacy in combination with cytotoxic treatment.[10–12]

Beside anthracyclines, significant advances in the treatment of MBC have come from the introduction of taxanes including paclitaxel[13] and docetaxel.[14] These compounds have been shown to exert significant antineoplastic efficacy when used as single agents in first-line[15] as well as second-line therapy[16] of MBC including anthracycline-resistant disease,[17,18] thus representing an important improvement in the therapeutic armentarium. Efficacy of taxanes is attributable to their pharmacologic properties of binding to tubulin, promoting assembly of microtubules and inhibiting their depolymerization.[19] Taxane-associated toxicity includes hyperergic reactions, neuropathy, myelotoxicity, alopecia, nail disorders, fluid retention, diarrhea and stomatitis.[13,15,18]

Despite the broad spectrum of cytotoxic drugs used for treatment of MBC, the generation of therapy-resistant tumor cell clones followed by uncontrolled expansion of MBC resulting in the patients' death still occurs. Therefore, drug efficacy has to be weighted against toxicity and improvement of progression-free survival (PFS) and/or overall survival (OAS). In addition, selection and sequence of drugs used for second- or third-line treatment balancing prolongation of PFS or OAS against treatment-associated toxicity has been inadequately addressed until now. In the present trial efficacy of docetaxel as second- and third-line cytotoxic therapies for MBC patients pretreated with

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one or two anthracycline-containing regimens for visceral metastases was analyzed in terms of response rate (RR), PFS, OAS and qualitative as well as quantitative toxicity.

Patients and methods

Patients

The present trial for second- and third-line cytotoxic treatment of MBC with docetaxel was initiated in June 1995 and conducted according to the Declaration of Helsinki after having been approved by the Ethical Committee of the Medical Faculty and the University Hospital. Patient characteristics are shown in Table 1. Overall, 19 female patients with a median age of 52.5 ± 8.3 (range 29–63) years suffering from histologically verified metastatic breast cancer were included. Locations of metastatic disease included liver (13 patients), lung (12 patients) and lymph nodes (five patients). In six patients, visceral metastases occurred simultaneously with skeletal metastases. Other metastatic sites were skin (three patients), spleen (two patients), kidney (one patient), peritoneum (one patient), pleura (one patient) and mediastinum (one patient), respectively. All patients were pretreated with at least one and a maximum of two anthracycline-containing chemotherapeutic regimens for MBC, thus necessitating the compassionate use of rescue medication. Preceding therapeutic regimens for MBC (excluding adjuvant treatment for early disease) are summarized in Table 2.

Docetaxel was administered in the second-line setting for metastatic disease in 11 patients and in the third-line setting in eight patients, respectively. All patients were evaluable for efficacy and toxicity of the present therapeutic protocol.

Table 1. Patient characteristics

No. of patients	$n = 19$
Age	52.5 ± 8.3 (29–63) years
Locations of metastatic disease (no. of patients)	
liver	13
lung	12
lymph nodes	5
bone	6
skin	3
pleura	1
other	spleen (2), kidney (1), peritoneum (1), mediastinum (1)

Table 2. Preceding chemotherapy for metastatic disease[a]

	Second-line arm	Third-line arm
Anthracyclines	11	8
Taxanes	0	0
Gemcitabine	0	6
Other	0	1

[a]No. of patients.

Inclusion criteria

Inclusion criteria consisted of histologically confirmed breast cancer, bidimensionally measurable visceral metastases verified by CT or MRI scan, tumor progression after at least one and a maximum of two anthracycline-containing chemotherapeutic regimens, performance status WHO 0–1 (Karnofsky index $\geqslant 60$), age 19–79 years, creatinine clearance $\geqslant 30$ml/min, life expectancy > 12 weeks and a signed patient consent to participate in the study. An interval of at least 4 weeks was required between last dose of chemotherapy and start of docetaxel treatment.

Exclusion criteria

Exclusion criteria consisted of more than two various cytotoxic regimens for MBC, bone metastases as the only manifestation of the disease, inadequate hematologic function (as defined by white blood cells $< 3.0 \times 10^9$/l, granulocytes $< 1.5 \times 10^9$/l, platelets $< 100 \times 10^9$/l), the staging procedure being carried out more than 2 weeks before onset of chemotherapy, second malignancy with the exception of *in situ* cervical cancer or adequately treated basal cell or squamous cell carcinoma of the skin, history of atrial or ventricular arrhythmias and/or history of congestive heart failure (even if medically controlled), history of clinical and electrocardiographically documented myocardial infarction and pre-existing motor or sensory neurotoxicity $>$ grade 1 according to WHO criteria (consistant with moderate or severe paresthesia and/or objective weakness with or without functional impairment). Finally, active infection or any other serious underlying medical condition which would impair the ability of the patient to receive cytotoxic treatment, altered mental status that would prohibit the understanding and giving of informed consent, pregnancy and breast feeding, severe hepatic dysfunction (bilirubin $\geqslant 1.5\times$ upper limits of normal or transaminases $\geqslant 3.0\times$ upper limits of normal), and creatinine clearance < 30 ml/min.

Cytotoxic therapy

Dose and schedule. Docetaxel (100 mg/m^2 body surface) was given by 1 h continuous infusion on day 1 of a 21 day cycle.

Supportive therapy. Antianaphylactic drug therapy administered concomitantly with docetaxel consisted of 8 mg dexamethasone twice daily orally for 3 days beginning 1 day prior to chemotherapy. Standard antiemetic medication consisted of 5-HT$_3$ antagonists.

Evaluation of patients. Baseline evaluation included chest X-ray or CT scan, ultrasound or CT/MRI scan of the abdomen, bone scan and cardiac ultrasound as well as a complete blood cell count and blood chemistry. Prior to treatment, patients were staged according to the TNM classification for breast cancer. Tumor measurement (baseline and response evaluation; see Inclusion criteria) was carried with CT or MRI scan. Identical methods were used for evaluation at baseline and for further tumor assessment performed at every alternate cycle of cytotoxic treatment. Hematologic and non-hematologic toxicities according to WHO criteria were assessed weekly.

Duration of therapy. In case of complete remission (CR), two additional chemotherapy cycles were administered. In case of stable disease (SD) or partial remission (PR), a total of eight cycles was given. Documented progression of disease according to WHO criteria resulted in discontinuation of the treatment protocol.

Statistical analysis

Data are presented as mean $\pm$ SD. Statistical significance was assessed using the log-rank test (PFS and OAS) or the χ^2 test (toxicity, comparison of response rates), both performed with the BMDP-PC program package using a significance level of 0.05.

Results

This analysis covers the period between June 1995 and November 1997 during which 19 female patients with anthracycline-resistant MBC were enrolled to receive docetaxel as second- and/or third-line cytotoxic treatment. This report covers a mean observation period of 24.1 $\pm$ 3.9 (range 17.4–32.8) months.

Administered dosages of docetaxel

Overall 131 treatment cycles were administered all of which could be given in the assigned dose and schedule. A mean number of 6.9 treatment cycles was administered in this cohort.

Clinical responses (Table 3)

Out of 19 patients, two (11%) achieved CR, seven (37%) PR, five (26%) experienced SD and five (26%) PD with an overall RR of 48%.

Among 11 patients who received docetaxel as second-line treatment, two (18%) patients presented with CR, four (36%) with PR, three (27%) experienced SD and two (18%) PD resulting in an overall RR of 54% for patients receiving docetaxel as second-line treatment. Among eight patients who received docetaxel as third-line treatment, three (38%) patients had PR and two (25%) SD resulting in an overall RR of 38% in this cohort of patients.

Duration of responses (Table 4)

PFS. Median PFS for all patients was 6.2 $\pm$ 4.6 (range 0.6–15.9) months. In patients receiving docetaxel as second-line treatment, median PFS was 6.5 $\pm$ 3.9 (range 2.1–15.8) months versus 4.7 $\pm$ 5.5 (range 0.6–

Table 3. Clinical responses to docetaxel as second- or third-line cytotoxic treatment

	Overall (n=19)	Second-line (n=11)	Third-line (n=8)
CR	2 (11)[a]	2 (18)	0
PR	7 (37)	4 (36)	3 (37.5)
SD	5 (26)	3 (27)	2 (25)
PD	5 (26)	2 (18)	3 (37.5)

[a]Percentages in parentheses.

Table 4. PFS and OAS in patients receiving docetaxel as second- or third-line cytotoxic treatment

	Overall (n=19)	Second-line (n=11)	Third-line (n=8)
PFS	6.2 $\pm$ 4.6 (0.6–15.9)[a]	6.5 $\pm$ 3.9 (2.1–15.8)	4.7 $\pm$ 5.5 (0.6–15.9)
OAS	9.1 $\pm$ 7.3 (2.7–25.8)	9.6 $\pm$ 8.0 (2.7–25.8)	11.2 $\pm$ 6.1 (4.8–18.7)

[a]Values are presented as median $\pm$ SD (range).

15.9) months in patients receiving docetaxel as third-line treatment. There was no statistically significant difference in PFS between these two cohorts.

OAS. Median OAS for all patients was 9.1 ± 7.3 (range 2.7–25.8) months. In the second-line setting, median OAS was 9.6 ± 8.0 (range 2.7–25.8) months versus 11.2 ± 6.1 (range 4.8–18.7) months in the third-line setting (p=NS).

Toxicity profile (according to WHO criteria)

In the second-line arm, anemia grades 1 and 2 occurred in seven (64%), grade 3 in one (9%), leukopenia grades 1 and 2 in four (36%) and grades 3 and 4 in six (55%), and thrombocytopenia grade 4 in one (9%) patient. In addition, polyneuropathy grades 1 and 2 occurred in three (27%) and grade 3 in one (9%) patient; three (27%) patients experienced onycholysis, whereas trophic nail changes could be observed in two (18%) patients. All patients treated with docetaxel as second- or third-line therapy for metastatic breast cancer experienced grade 3 alopecia.

In the third-line setting, anemia grades 1 and 2 occurred in two (25%), and grade 3 in one (13%) patient, respectively, leukopenia grades 1 and 2 in two (25%) and grades 3 and 4 in five (63%) patients. Neurotoxicity grade 1 occurred in one (13%) patient, and one (13%) further patient experienced onycholysis and trophic nail changes.

Discussion

MBC has to be considered an incurable disease with conventional dosages of currently available cytotoxic or endocrine agents.[1–3] However, in an attempt to preserve organ function, chemotherapy continues to be the mainstay of treatment of MBC with visceral involvement. Within this context, toxicity and tolerability of treatment influencing quality of life have to be taken into account and weighed versus the likelihood of mostly transient remissions achieved by cytotoxic treatment.[20] The present analysis was based upon these assumptions. Inclusion criteria of patients consisted of histologically confirmed diagnosis of MBC with visceral involvement and progression under at least one prior anthracyline-containing chemotherapy regimen for at least 1 month. Docetaxel has been shown to exert efficacy in MBC. Thus, the EORTC–Clinical Screening Group performed two consecutive phase II studies with two dose levels (75 and 100 mg/m^2) of docetaxel as first-line treatment in patients with MBC. The response rates were 52% at a dosage of 75 mg/m^2 and 68% at a dose of 100 mg/m^2, respectively.[21,22] Furthermore, in four phase II trials including 134 anthracycline-resistant patients, treatment with single-agent docetaxel produced response rates ranging from 29 to 54% with an overall response rate of 41%, a median time to progression of 4.3 months and a median OAS of 10.6 months.[23] Finally, a prospective randomized phase III trial comparing single-agent docetaxel (100 mg/m^2/1 h infusion) with mitomycin plus vinblastine in patients with MBC who had progressed despite receiving an anthracycline-containing regimen showed a significant increase in favor of docetaxel of RR (30 versus 11.6%), time to progression (19 versus 11 weeks) and OAS (11.4 versus 8.7 months).[18]

In the present study, the results on docetaxel for MBC progressing despite anthracycline-based chemotherapy are corroborated. We report that in anthracyline-resistant disease docetaxel was able to induce an overall RR of 48%. These results support previous findings which have reported RRs ranging from 29–54% for docetaxel[18,23] in similar settings and schedules. It is worth mentioning in the current context that docetaxel was able to induce considerable RR not only in second-line (54%), but also in the prognostically very serious situation of third-line therapy with a RR of 38%. Furthermore, time to progression and duration of OAS was similar to previous trials.[18] In addition, the use of docetaxel was associated with relatively mild to moderate side effects with leukopenia representing the most common toxicity. Neither hematologic nor non-hematologic toxicities led to treatment discontinuation. The feasibility of administration of a total of 131 treatment cycles all of which were given as assigned illustrates the relatively low toxicity of the chosen dose. Frequency of neurologic effects and nail changes representing docetaxel-specific toxicities was similar to previous trials,[18] although the present study used a 3 day corticosteroid premedication.

Our data have demonstrated the advantage of early use of docetaxel for the treatment of patients with MBC in order to improve results. The efficacy of docetaxel in even late anthracycline-resistant disease not only corroborates this assumption, but also makes these drugs, i.e. anthracyclines and taxanes, attractive partners for polychemotherapy schedules administered to patients with early or advanced breast cancer within the frame of controlled clinical trials.[24] Within this context combination chemotherapy of docetaxel and doxorubicin as first-line treatment of metastatic breast cancer patients resulted in overall RRs ranging between 57 and 77%.[24]

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