Anti-Cancer Drugs 2002, **13,** pp. 827–832

Clinical report

A phase II study of dose-dense docetaxel and mitoxantrone in the treatment of patients with high-risk metastatic breast cancer

Ellen König,[1] Christian Kurbacher,[1] Martin Schwonzen,[2] Martina Breidenbach[1] and Peter Mallmann[1]

[1]Department of Gynecology and Obstetrics, University of Cologne, 50924 Cologne, Germany. [2]Department of Internal Medicine II, St Walburga-Hospital, 59870 Meschede, Germany.

Doxetaxel (DCT) and mitoxantrone (MX) are highly active and potentially synergistic agents in the treatment of metastatic breast cancer (MBC). This pilot study evaluates the combination of dose-dense DCT and MX in patients with MBC to determine the efficacy and toxicity of this therapy. Thirty-six patients (56.1 ±1.7 years) were studied. The patients received DCT (35 mg/m^2 q1w) and MX (6 mg/m^2 q2w) for 6 weeks of an 8-week interval. Patients with tumor response or stable disease (SD) continued the treatment for a maximum of two additional periods. Hematologic and non-hematologic parameters were determined using the WHO common toxicity score. During this study 14 patients (40%) experienced partial response, 14 (40%) SD. In 20% of the cases the disease progressed on therapy. The treatment with DCT and MX was well tolerated. Seventeen patients (47%) experienced grade 3 leukopenia. Other hematologic and non-hematologic side effects did not exceed grade 2. One patient died during therapy because of a pulmonary embolism, which was unlikely related to active agents. Dose-dense DCT and MX combines both clinical activity and convenience for the patient. Therefore, we conclude that this regimen is a promising therapy in MBC, which warrants confirmation by large-scale clinical trials. [© 2002 Lippincott Williams & Wilkins.]

Key words: Docetaxel, metastatic breast cancer, mitoxantrone, palliative chemotherapy.

Introduction

Metastatic breast cancer (MBC) is presently incurable with current chemotherapy and patients usually have a median survival time of approximately 2 years after first documentation of metastases.[1] Among many cytotoxic agents that have shown activity in advanced breast cancer, taxanes and anthracyclines represent the two most active groups of antineoplastic drugs.[2]

The taxanes paclitaxel (PCT) and docetaxel (DCT) are an exciting new class of cytotoxic agents. Both substances act to promote microtubule stabilization. DCT is a second-generation taxoid compound, which is obtained by hemisynthesis, using a precursor extracted from the needles of the European yew, *Taxus baccata*. DCT is twice as potent as PCT in promoting polymerization of tubulin.[3] The results of phase II clinical trials have shown that DCT is highly active in MBC, including patients with visceral metastases or resistance to previous chemotherapy.[4] Given as a single agent, DCT produced objective response rates between 45 and 60% with an acceptable toxicity profile.[5] At doses of 60 and 75 mg/m^2 every 3–4 weeks, response rates achieved with second-line DCT therapy were 33 and 46%.[6,7] Trudeau reported results of phase II trials with DCT as first-line therapy which demonstrated an overall response rates for liver and lung metastasis of 60 and 26%, respectively.[8] Ravdin *et al.*[9] showed an 55% response rate of DCT in anthracycline-resistant breast cancer patients. In addition, DCT has a radiation sensitizing effect,[10] like PCT.

The main dose-limiting side effect of both taxanes is myelosuppression, resulting in a significant incidence of severe, but short-lasting neutropenia. PCT and DCT are associated with acute hypersensitivity reactions like pruritus, flushing, rash and drug-induced fever, usually occurring within minutes of administration. Without steroid premedication, acute hypersensitivity reactions can be seen in up to 25% of patients.[11,12] However, without premedication, both the incidence and severity of acute hypersensitivity

Correspondence to C Kurbacher, Department of Gynecology and Obstetrics, University of Cologne, Kerpener Straße 34, 50931 Cologne, Germany.
Tel: (+49) 221 478 4909; Fax: (+49) 221 478 3411;
E-mail: Christian.Kurbacher@medizin.uni-koeln.de

reactions appear to be higher in patients treated with PCT. A typical side effect of DCT is fluid retention, which can effectively be prevented by administration of steroids.[13] Mild to moderate, dose-dependent, reversible neuropathy has also been reported with DCT, but less frequently as compared to PCT.[14] No cardiac toxicity has been observed with DCT. As with PCT, alopecia is seen in the majority of patients.

Since taxanes and anthracyclines are among the most effective agents against breast cancer displaying different mechanism of action, their combination is a logical step in developing new active chemotherapy regimens to improve the therapeutic results in this disease. Recent phase II studies have shown that DCT and PCT can be effectively combined with anthracyclines, increasing the response rate up to 90%. However, the combination of PCT and doxorubicin is complicated by a relatively high risk of cardiotoxicity.[15–17] In a phase I study with the combination of PCT and doxorubicin, 50% of the patients showed a reduced left ventricular ejection fraction and 20% of them developed congestive heart failure.[18] In contrast, DCT is rarely associated with cardiotoxicity.[19] Unlike PCT, DCT does not appear to increase the cardiotoxic effect of both doxorubicin and epirubicin.[20–23]

The response rate of epirubicin and doxorubicin as first-line regimen of breast cancer ranges from 25 to 62%.[24] Mitoxantrone (MX) is an anthracendione inducing an objective response rate of 13–51% in patients with MBC.[20,25] The toxicity profile of MX is significantly better than that of other anthracycline-based regimens, especially in terms of alopecia, nausea, vomiting and cardiotoxicity.[26,27]

Kouroussis *et al.*[5] conducted a dose-escalation study of DCT in combination with MX as first-line treatment in patients with MBC and found a response rate of 78% when chemotherapy was administered every third week. The median duration of response was 12.5 months. No cardiac toxicity could be shown. Grade 2 and 3 neurosensory toxicity occurred in 17% of the patients.

Taxanes can be effectively given on a weekly schedule without increasing toxicity. Since DCT might be considered the more active taxane in MBC, we initiated a phase II study in order to evaluate the efficacy and toxicity of the combination of dose-dense weekly DCT and biweekly MX in patients with MBC.

Materials and methods

A total of 36 patients with advanced MBC were included in this phase II study, which was performed in two centers. Inclusion criteria were as follows: age 18–78 years; WHO performance status (PS) of 0–2; measurable disease; life expectancy of at least 3 months; adequate hematologic parameters; adequate hepatic (serum bilirubin <1.5 mg/dl), renal (serum creatinine <1.5 mg/dl) and cardiac function.

Table 1. Treatment plan

	Day							
	1	8	15	22	29	36	43	50
DCT 35 mg/m^2	×	×	×	×	×	×		
MX 6 mg/m^2	×		×		×			

During the treatment period, patients received DCT at 35 mg/m^2 i.v. over 1 h once a week and MTX at 6 mg/m^2 i.v. as bolus injection every second week, starting with the administration of both substances in the first week (Table 1).

Chemotherapy was administered over 6 weeks of an 8-week period followed by a rest of 2 weeks.

As premedication dexamethasone 8–16 mg i.v. and ondansetron 8 mg i.v. were given prior to DCT and MX.

In order to assess the efficacy of this treatment a re-evaluation of the metastatic status was performed during the 2 weeks of the recovery period. Tumor response was assessed according to the WHO criteria. Patients with a regression or a steady disease continued the chemotherapy for a maximum of two more intervals. Then the treatment plan lasted for a maximum of 24 weeks (18 weeks of therapy and 6 weeks of recovery). Patients with progressive disease were switched to another chemotherapy regimen.

Hematologic and non-hematologic parameters were determined before each administration of chemotherapy to measure the toxicity of this treatment according to the WHO criteria. If necessary, patients received granulocyte colony stimulation factor. Therapy was continued in the presence of a leukocyte count $>1500/\mu$l, platelet count $>75\,000/\mu$l, hemoglobin count >8.0 mg/dl and no grade 3 or 4 non-hematological toxicity.

Results

Characteristics of the patients

Thirty-six patients with advanced MBC were enrolled. The mean age was 56.1 ± 1.6 years. Twenty-seven patients had two or more involved organs. The median number of metastatic sites was 2 (range 1–5).

Twenty-nine (81%) had visceral metastasis. Eighteen patients (50%) had not received prior chemotherapy. Thirty-three percent (n=12) of the patients had previous adjuvant chemotherapy. Ten patients (28%) were pretreated with anthracyclines. Seventy-eight percent (n=28) of the patients got this treatment as first-line therapy, 22% (n=8) as second-line chemotherapy.

Response

A total of 382 cycles were administered. The median number of administered cycles was 12 (range 2–24), referring to two chemotherapy blocks. Thirty-five patients were assessable for tumor response. The overall response rate was 40%, assessed by physical examination, X-ray, computed tomography or ultrasound investigation. No complete responses (CR) occurred in this study population. Partial responses (PR) were seen in 14 patients (40%). Fourteen patients had a stable disease (SD) on therapy (40%). Disease progression (PD) during chemotherapy occurred in seven patients (20%) (Table 2).

Three patients discontinued the treatment after 2–4 weeks because of rapidly progressing disease.

Remissions were seen at all kinds of metastatic sites. Six of the 14 patients with PR had received prior therapy with anthracyclines, 13 of the 29 patients (45%) with visceral metastasis showed a PR and eight patients (28%) a SD. Five of the patients with PR received this chemotherapy as second-line therapy.

The median time to progression was 3 months (range 0–23 months). The median duration of response was 7 months, with intervals from 1 to 23 months. At present three of those patients (6, 8 and 10 months after treatment) show no sign of progression.

Toxicity

Leukopenia was observed in 27 patients (75%). Four patients. (11%) developed grade 1 and six patients (17%) grade 2 leukopenia. Seventeen patients (47%) experienced leukopenia grade 3. However, no patient was hospitalized due to leukopenic fever.

Table 2. Response of the therapy [patients n=35 (%)]

CR	PR	SD	PD
0	14	14	7
0	40	40	20

Table 3. Hematological toxicity of the treatment

Hematological toxicity		Grade			
		1	2	3	4
Leukopenia	n	4	6	17	0
	%	11	17	47	0
Anemia	n	17	7	0	0
	%	47	19	0	0
Thrombocytopenia	n	6	1	0	0
	%	17	3	0	0

No grade 4 leukopenia was observed. In order to administer the chemotherapy in a timely manner, patients with grade 3 leukopenia received granulocyte colony stimulating factor. Anemia was seen in 24 of the patients (67%) including grade 1 and grade 2 toxicity. Seven patients (20%) showed a mild thrombocytopenia of grade 1 or 2 (Table 3).

Non-hematological toxicity was mild to moderate. Nevertheless two patients discontinued the treatment because of pronounced mucositis and esophagitis. Reversible grade 1 and 2 alopecia was observed in 23 of the patients (64%). Twenty-five of the patients (69%) reported mild to moderate nausea and vomiting. Two cases of moderate dysuria and relapsing urinary tract infection, two cases of moderate neuropathy, and one case of dyspnea occurred. No cardiac failure was observed.

One patient died suddenly during therapy. She was 69 years of age, and had advanced MBC with liver metastases and bone involvement. Four years (47 month) before, death nodal-positive breast cancer was diagnosed and she received an adjuvant chemotherapy (CMF) and tamoxifen after surgery and radiation. Thirty-one months later advanced bone metastases were found, and she was put on letrozol daily and pamidronate monthly. After 3 months MBC progressed with liver metastasis and chemotherapy of DCT and MX was started. No concomitant diseases were present; ECG and a transthoracic echocardiogram showed no pathologic results while starting therapy. The duration of therapy was 5 weeks without complaints. At this time the patient showed no hematological toxicity; she has not received granulocyte colony stimulating factor. The counts of thrombocytes were normal and the kreatinine values were slightly increased. Other laboratory parameters were normal. Eight days after the fifth application of chemotherapy the patient died by sudden death with a few minutes history of dyspnea reported by her husband. The family physician found her in the bathroom without consciousness, breathing and circulation. He supposed pulmonary embolism and decided not to start

cardiopulmonary resuscitation. The toxicity profiles of DCT and MX do not include thromboses or pulmonary embolism. From this perspective, a causal relationship between the serious adverse event and the chemotherapy was considered unlikely.

Discussion

Recent phase II studies with DCT and/or MX in patients with breast cancer showed promising results concerning efficacy and safety of the treatment regimen.

Trudeau *et al.*[8] administered DCT (100 mg/m^2) as first-line therapy every 3 weeks to patients with MBC and reported an overall response rate of 56%. Docetaxel as second-line therapy in advanced breast cancer led to an overall response rate of 40%.[28] It could be demonstrated in several studies that the combination of DCT with a number of other cytotoxic agents had an enhanced activity.[29] Phase I/II studies showed high response rates when DCT was combined with doxorubicin.[30]

The activity of MX against breast cancer is high and therefore the effectiveness is comparable to single administration of doxorubicin.[31,32,33]

Von Minckewitz *et al.*[34] reported an overall response rate of 37% in 32 evaluated patients (three complete and nine partial remissions) treated with a combination of DCT and MX. SD was observed in a further 56% of the patients.

In our trial, DCT and MX were administered as chemotherapy in patients with high-risk metastatic breast cancer in an outpatient setting. The patient population was characterized by a high grade of visceral metastasis. Thirty-three percent had previously been exposed to adjuvant or palliative anthracycline-based chemotherapy.

Our treatment regimen resulted in an overall response rate of 40%, but we observed no complete remission. This could be related to the high prevalence of visceral involvement, bone metastasis, relatively high tumor burden and prior chemotherapy. Despite these unfavorable patient characteristics, responses occurred at all disease sites, including a high response rate in patients with liver or visceral involvement. During the treatment 40% of the patients showed a stabilization of the disease.

In summary, the results of our study confirm the activity of DCT and MX reported in recent phase II studies.

In preliminary studies investigating the combination of anthracyclines and DCT, neutropenia and neutropenic fever were the main dose-limiting events determining severe myelosuppression as the main toxic effect of this combination.

In the present study, the combination of DCT and MX was well tolerated. The most important toxicity consisted of neutropenia, but no grade 4 leukopenia or leukopenic fever was observed. One reason for this finding is possibly the relatively mild side effects of MX compared to the toxicity profile of other anthracyclines like doxorubicin or epirubicin. A second reason could be the use of granulocyte colony stimulating factor in our trial. Other hematologic toxicities in our study were mild to moderate.

Kerbrat *et al.* reported a 16–19% decrease in left ventricular ejection fraction (LVEF) in three patients who received a combination of epirubicin and DCT.[22] Investigating the combination of doxorubicin and DCT, Dieras *et al.*[35] and Misset *et al.*[36] observed a decrease of LVEF in 10 and 2% of the patients, respectively. Other studies determined a 4% incidence of cardiac heard failure in the treatment of metastatic breast cancer with DCT and doxorubicin.[37,38]

However, our treatment regimen with DCT in combination with MX was not associated with congestive heard failure or decreased LVEF, which was probably due to the low toxicity profile of MX. This observation suggests that our schedule is safe in terms of cardiotoxicity for patients with normal baseline cardiac function. One patient died suddenly during therapy 8 days after the fifth application, probably because of a pulmonary embolism. This was judged to be unlikely related to the therapy (see Results).

However, two patients developed a severe mucositis/esophagitis and had therefore to discontinue chemotherapy, but other non-hematologic toxicity did not exceed grade 2. Because of the pretreatment with corticosteroid, fluid retention was only a minor clinical problem during our clinical trial.

Dose-dense DCT and MX combines both clinical activity and convenience for the patients. Therefore this regimen is a promising therapy in MBC.

Conclusions

In summary, dose-dense DCT (35 mg/m^2 weekly) in combination with MX (6 mg/m^2 biweekly) is a feasible and active combination for patients with MBC. In our phase II study a high-risk population with advanced MBC was recruited. Nevertheless, the overall response rate was 40%, the rate of stable

disease 40%. The regimen was associated with a remarkably tolerable toxicity profile. However, this data has to be confirmed by large-scale phase III clinical trials with a longer follow-up phase.

References

1. Flamm Honig S. Treatment of metastatic disease. In: Harris JR, Lippman ME, Morrow M, *et al.*, eds. *Breast diseases*. Philadelphia, PA: Lippincott 1996: 669–73.
2. Alexopoulos A, Kouroussis C, Malamos N, *et al.* Docetaxel in combination with mitoxantrone and granulocyte colony-stimulating factor as front-line chemotherapy in metastatic breast cancer: a multicenter phase II study. *Ann Oncol* 2001; **12**: 793–8.
3. Awada A, Piccart M. New agents in development for cancer therapy. *Consultant Series* 1997; **18**: 11–34.
4. Stemmler HJ, Gutschow K, Sommer H, *et al.* Weekly docetaxel (Taxotere) in patients with metastatic breast cancer. *Ann Oncol* 2001; **12**: 1393–8.
5. Kouroussis C, Kakolyris S, Souglakos J, *et al.* Dose escalation study of docetaxel in combination with mitoxantrone as first line treatment in patients with metastatic breast cancer. *J. Clin Oncol* 1999; **17**: 862–9.
6. Taguchi T, Adachi I, Enomoto K, *et al.* Docetaxel (RP 56976) in advanced or recurrent breast cancer: early and late phase II clinical studies in Japan. *Proc Am Soc Clin Oncol* 1994; **13**: 87.
7. Fumoleau P, Chevallier B, Dieras V, *et al*. Evaluation of two doses of docetaxel (Taxotere) as first line chemotherapy in advanced breast cancer: Report of the EORTC Clinical screening group (EORTC-CSG). Presented at *2nd Eur Congr on Senology*, Vienna, Austria 1994.
8. Trudeau ME. Docetaxel (Taxotere): an overview of first line monotherapy. *Semin Oncol* 1995; **22**(suppl 13): 17–21.
9. Ravdin P, Valero V, Burris H, *et al.* Phase II trial of Docetaxel in advanced anthracycline resistant or anthracenedione-resistant breast cancer. *J Clin Oncol* 1995; **13**: 2879–85.
10. Choy H, Rodrigues F, Wilkox B, *et al*. Radiation sensitizing effects of Taxotere (RP 56976). *Proc Am Ass Cancer Res* 1992; abstr 2991.
11. Wanders J, van Oosterom AT, Gore M, *et al.* Taxotere toxicity protective effects of premedication. *Eur J Cancer* 1993; **29A**(suppl 6): S206 (abstr 1148).
12. Schrijvers D, Wanders J, Dirix L, *et al.* Coping with toxicities of docetaxel (Taxotere). *Ann Oncol* 1993; **4**: 610–1.
13. Piccart MJ, Klijn J, Mauriac L, *et al.* Weekly docetaxel with or without prophylactic steroids as 2nd line treatment for metastatic breast cancer (BrCa): a randomized trial of the EORTC BC Study Group. *Ann Oncol* 1994; **5**(suppl 8): 27 (abstr O131).
14. New P. Neurotoxicity of Taxotere. *Proc Am Ass Cancer Res* 1993; **34**: 233 (abstr 1393).
15. Gianni L, Munzone E, Capri G, *et al.* Paclitaxel by 3-hours infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose finding and sequence-finding study. *J Clin Oncol* 1995; **13**: 2688–99.
16. Berg SL Cowan KH, Balis FM, *et al.* Pharmakokinetics of taxol and doxorubicin administered alone and in combination by continuous 72-hour infusion. *J Natl Cancer Inst* 1994; **86**: 143–5.
17. Seidmann AD, Hudis C, Crown JPA, *et al.* Phase II evaluation of Taxotere (PR 56976, NSC 628503) as initial chemotherapy for metastatic breast cancer. *Proc Am Soc Clin Oncol* 1993; **12**: 63 (abstr 52).
18. Gehl J, Boesgaard M, Paaske T, *et al.* Combined doxorubicin and paclitaxel in advanced breast cancer: effective and cardiotoxic. *Ann Oncol* 1996; **7**: 687–93.
19. Verweij J, Clavel M, Chevallier B. Paclitaxel (Taxol) and doxetaxel (Taxotere): not simply two of a kind. *Ann Oncol* 1994; **5**: 495–505.
20. Dieras V, Bartiesr S, Beuzeboc P, *et al.* Phase II study of docetaxel in combination with doxorubicin as 1st line chemotherapy of metastatic breast cancer. *Breast Cancer Res Treat* 1998; **50**: 262 (abstr).
21. Itoh K, Fugii H, Minami H, *et al.* Phase I and pharmacologic study of docetaxel combined with doxorubicin for advanced breast cancer. *Proc Am Soc Clin Oncol* 1997; **16**: 174a (abstr 610).
22. Kerbrat P, Viens P, Roche H, *et al.* Docetaxel in combination with epirubicin as first line chemotherapy of metastatic brest cancer: Final results. *Proc Am Soc Clin Oncol* 1998; **17**: 151a (abstr 579).
23. Raab G, Borquez D, Harstrick A, *et al.* Phase I study of docetaxel in combination with epirubicin as first line chemotherapy in metastatic breast cancer. *Proc Am Soc Oncol* 1998; **18**: 168a (abstr 644).
24. Launchbury AP, Habboubi N. Epirubicin and doxorubicin: a comparison of their characteristics, therapeutic activity and toxicity. *Cancer Treat Rev* 1993; **19**: 197–228.
25. Dieras V. Docetaxel in combination with doxorubicin: a phase I dose-finding study. *Oncol* 1997; **11**(suppl 6): 17–20.
26. Smyth JF, Cornbleet MA, Stuart-Harris RC, *et al.* Mitoxantrone as first line chemotherapy for advanced breast cancer: results of a European Collaborative Study. *Semin Oncol* 1984; **11**(suppl 1): 15–8.
27. Cowan JD, Neidhardt J, McClure S, *et al.* Randomized trial of doxorubicin, bisantrene, and mitoxantrone in advanced breast cancer: a Southwest Oncology Group study. *J Natl Cancer Inst* 1991; **83**: 1077–84.
28. Neidhart JA, Gochnour D, Roach R, *et al.* A comparison of mitoxantrone and doxorubicin in breast cancer. *J Clin Oncol* 1986; **4**: 672–7.
29. Van Oosterom AT. Docetaxel (Taxotere): an effective agent in the management of second-line breast cancer. *Semin Oncol* 1995; **22**(suppl 13): 22–8.
30. Bissery MC, Vrignaud P, Lavelle F. Preclinical profile of docetaxel (Taxotere): efficacy as a single agent and in combination. *Semin Oncol* 1995; **22**: 3–16.
31. Bourgeois H, Gruia G, Dieras V, *et al.* Docetaxel (D) in combination with doxorubicin (Dx) as 1st-line CT of metastatic breast cancer (MBC): a phase I dose finding study. *Proc Am Soc Clin Oncol* 1996; **15**: 148 (abstr 259).

32. Von Hoff DD, Clark GM, Weiss GR, *et al.* Use of *in vitro* dose response effects to select antineoplastics for high-dose or regional administration regimens. *J Clin Oncol* 1986; **4**: 1827–34.
33. Henderson IC, Allegra JC, Woodcock T, *et al.* Randomized clinical trial comparing mitoxantrone with doxorubicin in previously treated patients with metastatic breast cancer. *J Clin Oncol* 1986; **4**: 1827–34.
34. Bennet JM, Muss HB, Doroshow JH, *et al.* A randomized multicenter trial comparing mitoxantrone, cyclophosphamide and fluorouracil with doxorubicin, cyclophosphamide and fluorouracil in the therapy of metastatic breast cancer. *J Clin Oncol* 1988; **6**: 1611–20.
35. Von Minckwitz G, Costa SD, Loibl S, Caminada M-C, Kaufmann M. Kombination von Docetaxel und Mitoxantron zur Terapie des metastasierten Mammakarzinoms—eine Phase I–II Studie. *Tumordiagn Ther* 1998; **19**: 52–5.
36. Misset JL, Dieras V, Bozec *et al*. Long term follow up of the phase I/II study of docetaxel and doxorubicin as 1st line chemotherapy of metastatic breast cancer. *Proc Am Soc Clin Oncol* 1998; **17**: 160a (abstr 613).
37. Nabholtz JM, Mackey JR, Smylie M, *et al.* Final results of a phase II study of docetaxel, doxorubicin and cyclophosphamide (TAC) as 1st line chemotherapy in metastatic breast cancer patients. *Breast Cancer Res Treat* 1998; **50**: 27 (abstr).
38. Sparano JA, Ju P, Scheafer PL, *et al.* Phase II trial of doxorubicin and docetaxel plus granulocyte-colony stimulating factor in metastatic breast cancer: An Eastern Cooperative Oncology Group Study (E1196). *Breast Cancer Res Treat* 1998; **50**: 27 (abstr).

(Received 3 June 2002; accepted 18 June 2002)