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A phase I dose-escalating study of docetaxel plus folinic acid and 5-fluorouracil in anthracycline-pretreated patients with metastatic breast cancer

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ABSTRACT

Background: Since the need for nonanthracycline-containing chemotherapy regimens increases with the increased use of anthracyclines in earlier stages of breast cancer, we investigated the feasibility of the combination of docetaxel and 5-fluorouracil (5-FU) with folinic acid (FA). Patients and methods: Anthracycline-pretreated patients with metastatic breast cancer were eligible. Docetaxel was administered as a one-hour infusion every three weeks on day 1, FA 500 mg/m² (fixed dose) as a two-hour infusion on days 1 and 15 and 5-FU as a 24-hour infusion on days 1 and 15. The dose levels tested were (docetaxel/5FU in mg/m²): 60 /1800, 75/1800, 85/1800, 100/1800, and 100/2100. Results: Altogether 28 patients were accrued and treated in this multicentre open-label study. Dose-limiting toxicities (DLTs) were not observed at dose level 1, and in two patients in each of the higher dose levels. DLTs observed were grade III/IV infection (n=4), febrile neutropenia (n=2), diarrhoea (n=1) and erythema (n=1). Partial responses were observed in 10 out of 24 evaluable patients (42%, 95% confidence interval 22.1 to 63.4%). Dose escalation beyond the highest dose level (100/2100) was deemed inappropriate, because these dose levels correspond to recommended dose levels for each drug as a single agent. Conclusion: Combination of docetaxel (100 mg/m², one-hour infusion q3 weeks on day 1), FA (500 mg/m², two-hour infusion on days 1 and 15) and 5-FU (2100 mg/m², 24-hour infusion on days 1 and 15) is a feasible regimen with encouraging activity in anthracycline-pretreated patients.

INTRODUCTION

Breast cancer is the most common malignancy in women contributing to approximately 25% of malignant tumours and 20% of cancer deaths in female patients.[1] Women with metastatic breast cancer (MBC) have a median survival of between two and three years after documentation of metastasis.[2] Many cytotoxic agents have shown activity in MBC. The most active and most commonly used agents are cyclophosphamide, 5-fluorouracil (5-FU), doxorubicin, methotrexate and more recently the taxanes paclitaxel and docetaxel. Response rates (RR) for single agents in MBC vary between 20 to 70% with anthracyclines and taxanes being the most active single agents.

Among the newly introduced taxanes, differences exist between docetaxel and paclitaxel. Recently a head-to-head comparison of docetaxel and paclitaxel in MBC was presented. Docetaxel appeared more effective with higher RR (32 *vs* 25%), longer median time to progression (3.8 *vs* 5.7 months) and longer median survival (15.4 *vs* 12.7 months), but also the toxicity differed for the two drugs, with more pronounced myelosuppression for docetaxel as compared with paclitaxel.[3] Data on the use of docetaxel as a single agent indicate high RR ranging from 40 to 68%, even when used in second-line treatment (40 to 58%).[4-7] RR in a number of phase III studies indicate that docetaxel 100 mg/m², given every three weeks as second-line treatment for MBC, is superior to either the combination regimen of mitomycin/vinblastine (12 mg/m² iv every six weeks plus vinblastine 6 mg/m² iv every three weeks) or to adriamycin

75 mg/m² given every three weeks.[4,5] Superior RR were also confirmed in patients with a poor prognosis, such as metastasis in more than three organs or predominantly visceral metastases.[4-6] Considering combination chemotherapy, anthracycline and alkylating agent-based regimens are routinely used as first-line and sometimes second-line treatment for MBC. In the first line these combinations achieve approximately a 50 to 70% RR with a median duration of 8 to 16 months.[2,8-10] However, because anthracycline-based chemotherapy in the adjuvant setting is replacing the cyclophosphamide/methotrexate/5-fluorouracil (CMF)-type regimens, patients with MBC are increasingly being exposed to high cumulative doses of anthracyclines and therefore at risk of developing anthracycline resistance and cardiotoxicity. This has prompted the search for effective nonanthracycline-containing combination regimens in metastatic disease.

5-FU has been available since the 1950s[11] and still holds a position within the treatment of breast cancer. As a single agent it has only modest activity and much research has been focused on identifying agents that might modulate its cytotoxic effects.[12] In the clinical setting, 5-FU is most often incorporated as part of a combination regimen. Docetaxel in combination with 5-FU has been evaluated in nude mice against subcutaneously implanted advanced colon adenocarcinoma[13] and mammary adenocarcinoma MA 13/C.[14] Interestingly, in a mouse model of colon adenocarcinoma, a combination of docetaxel/5-FU was the most synergistic of all combinations tested, and no additional toxicity was observed when approximately 70% of the full dose of each agent was administered. Because of the promising synergistic activity in preclinical models of breast cancer, the combination docetaxel and 5-FU was studied in patients with MBC. We reasoned that in taxane-naive, anthracycline-pretreated patients with MBC, combining docetaxel with an intensified protracted infusion of FA/5-FU might further improve efficacy and prove useful as an alternative nonanthracycline-containing second-line treatment. Therefore, the primary objectives of this dose-finding study were to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and recommended dose for phase II studies of the combination of docetaxel and FA/5-FU, with the latter being administered by protracted infusions on day 1 and 15, in anthracycline-pretreated, taxane-naive patients with MBC. Secondary objectives were to characterise the safety and to obtain preliminary evidence of the antitumour activity.

PATIENTS AND METHODS

Patient selection

In a period of two years, 28 patients with histologically confirmed breast cancer at first diagnosis were enrolled by four hospitals. Histological or cytological proof of metastasis was not required. Main inclusion criteria were: ≥1 chemotherapeutic regimen with anthracyclines for either an adjuvant setting or metastatic disease, ≤1 previous chemotherapy for metastatic disease and not suitable for endocrine therapy (prior 5-FU-containing chemotherapy was allowed provided it had been administered only as an iv bolus); measurable and/or evaluable disease; adequate haematopoietic reserve (white blood cells ≥3 x 10^9/l and thrombocytes ≥100 x 10^9/l); adequate liver function with bilirubin ≤ the upper-normal limit (UNL), ALAT and ASAT ≤2.5 the UNL, alkaline phosphatase ≤5 x UNL unless bone metastases were present in the absence of any liver disorder. Prior radiotherapy should have concluded at least four weeks before entering the study. Written informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committees.

Study design and treatment

To define the MTD of combined docetaxel, FA and 5-FU, the initial approach was to add escalating doses of docetaxel to a fixed dose of FA and 5-FU. In a later stage, the dose of 5-FU was escalated. Patients were treated on an outpatient basis with cycles every three weeks. Docetaxel was administered as a one-hour infusion every three weeks on day 1, FA 500 mg/m² as a two-hour infusion on days 1 and 15 and 5-FU as a 24-hour infusion on days 1 and 15. Efficacy for docetaxel at a dose of 60 mg/m² as a single agent has been observed. For 5-FU a wide range of routes and schedules of administration are available, and the starting dose of 1800 mg/m² is well within the acceptable range. With this information, the following dose levels were defined (docetaxel/5-FU in mg/m²): 60 /1800, 75/1800, 85/1800, 100/1800, and 100/2100. To enable the 24-hour infusion, all patients received an intravenous port system and portable pump. At least three patients were treated before a subsequent dose level was started. For toxicity evaluation, patients were required to receive at least two cycles of chemotherapy. Observed toxicity during these two complete cycles guided the final decision on the MTD. Doses were not escalated in individual patients. If DLT occurred in one of the three patients, an additional three patients were included at the same level. The MTD was reached if DLT was seen in two of the first three patients or in three out of six patients in one dose level.

Safety

Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria (NCI-CTC).[15] DLT was defined as follows: (1) a white blood cell count (WBC) ≤1 x 10^9/l or absolute neutrophil count (ANC) ≤0.5 x 10^9/l for more than seven days, (2) febrile neutropenia, defined as WBC

≤1 x 10^9/l or ANC ≤0.5 x 10^9/l and fever defined as either three oral temperature elevations above 38 °C during a 24-hour period or a single oral temperature above 38.5 °C, (3) severe infections requiring hospitalisation, i.e. pneumonia, sepsis, septic shock, in combination with WBC ≤1.9 x 10^9/l or ANC ≤0.9 x 10^9/l, (4) platelets ≤25 x 10^9/l, and (5) any grade III or IV nonhaematological toxicity. In case of grade ≥3 toxicity, treatment was discontinued until recovery to grade ≤1 and subsequent cycles were reduced to one dose level below and/or according to the specific toxicity. Prophylactic antiemetic treatment was allowed. Patients were treated until progression or unacceptable toxicity or patient's refusal or stable disease without symptomatic improvement after four cycles, whichever occurred first.

Table 1
Patient characteristics

Number enrolled	28
Number assessable	
for toxicity	28
for tumour response	24
Age in years	51 (34-72)
WHO performance status	
0	7
1	16
2	5
Prior chemotherapy	
• Adjuvant CMF	6
• 5-FU injections	28
• Chemotherapy for advanced disease	22

Study treatment
Premedication with dexamethasone was given to all patients to prevent the onset of hypersensitivity reactions and reduce the incidence and severity of fluid retention. Dexamethasone 8 mg (oral) was given twice a day on days -1 to 4 (day 1 is the day of docetaxel administration). Docetaxel was administered before FA with an interval of one hour between the end of the one-hour infusion of docetaxel and the start of the two-hour infusion of FA. The FA administration was immediately followed by the 24-hour 5-FU infusion.

Study assessments
Pretreatment evaluation included a complete history and physical examination, complete blood count, biochemistry assessment, urinalysis, chest X-ray and computerised tomography of chest or abdomen as required to evaluate measurable lesions. During treatment, physical examination, WHO performance status, full blood count, blood chemistry and toxicity assessment were obtained weekly or more frequently if clinically indicated. Tumour assessment was performed after every 3rd cycle of therapy. Standard WHO response criteria were used.

Statistical analysis
The analysis of this phase I study is primarily descriptive. Values are presented as median with ranges unless stated otherwise.

RESULTS

Patient population
Twenty-eight patients were enrolled in the study. The patient characteristics are summarised in *table 1*. All patients had received anthracycline-containing chemotherapy, mostly as epirubicin. Twenty-two patients received chemotherapy for metastatic disease.

Drug delivery
Twenty-eight patients received a total of 144 cycles of treatment (median 6, range 2 to 13), 17 received six or more treatment cycles. A total of five dose levels were tested. At the first dose level three patients were tested, at the third dose level seven patients because of logistics and at the other dose levels six patients were tested. All patients were evaluable for toxicity. Chemotherapy on day 1 was postponed by one week in 3/144 cycles because of haematological toxicity grade III/IV. In one patient on level 5 the dose of docetaxel was reduced for the next three cycles after the occurrence of febrile neutropenia. The dose of 5-FU on day 15 was omitted in the last cycle in four patients because of haematological toxicity grade III, because of progression in five patients and because of refusal in three patients; the dose of 5-FU on day 15 was omitted in any cycle in three patients because of haematological toxicity grade III.

Safety: haematological and gastrointestinal toxicity
Table 2 shows any grade III or IV haematological and gastrointestinal toxicity during treatment. Grade III or IV neutropenia occurred on day 1 and 14 of treatment during 10/144 cycles (grade III 8, grade IV 2). After a one-week delay, the WBC counts rose to levels above 3.0 g/l. In two patients treatment was stopped because of a DLT. At the different dose levels 1 to 5, the nadirs for platelets/WBC (g/l) were 136/1.1, 71/0.8, 20/0.4, 45/0.2 and 54/0.7, respectively. No grade III/IV mucositis or hand-foot syndrome or grade III/IV oedema or neurotoxicity was observed.

Dose-limiting toxicity
At level 1, no DLT events were seen (*table 3*). At level 2 (n=6) one serious infection related to the continuous infusion system and one case of diarrhoea NCI-CTC grade IV occurred. At level 3 (n=7) there was one serious infection due to staphylococcal pneumonia and one patient with leucopenic fever/febrile neutropenia. At level 4 (n=6)

Table 2
Haematological toxicity per dose level*

DOSE LEVEL	DOCETAXEL/5-FLUOROURACIL (MG/M²)	NO. OF PTS/ CYCLES	NEUTROPENIA		IDEM ON DAY TREATMENT		PLATELETS	
			III	IV	III	IV	I	II
1	60/1800	3/16	1/4	0/0	0/0	0/0	0/0	0/0
2	75/1800	6/22	4/5	1/1	0/0	0/0	0/0	0/0
3	85/1800	7/42	6/18	5/14	1/2	0/0	4/10	1/1
4	100/1800	6/36	3/6	1/3	1/1	1/1	0/0	1/2
5	100/2100	6/28	4/12	2/3	1/5	1/1	0/0	1/1
Total		28/144	18/45	9/21	3/8	2/2	4/10	3/4

** Worst NCI-CTC grade during entire treatment, per patient/total number of cycles per involved patients.*

Table 3
Gastrointestinal toxicity per dose level*

DOSE LEVEL	DOCETAXEL/5-FLUOROURACIL (MG/M²)	NO. OF PTS/ CYCLES	NAUSEA		VOMITING	
			III	IV	III	IV
1	60/1800	3/16	2/2	2/2	2/4	1/1
2	75/1800	6/22	2/2	1/1	2/2	1/1
3	85/1800	7/42	2/2	1/2	1/1	3/4
4	100/1800	6/36	1/1	1/4	1/5	0/0
5	100/2100	6/28	0/0	0/0	0/0	0/0
Total		28/144	7/7	5/9	5/12	5/6

** Worst NCI-CTC grade during entire treatment, per patient/total number of cycles per involved patients.*

there was one case of febrile neutropenia grade IV and one of staphylococcal sepsis. At level 5 (n=6) one serious infection related to the continuous infusion system and one erythema grade III/IV (possibly allergic) were observed. Because the maximum dose levels as applied for the single agents were reached at dose level 5, further dose escalation was not carried out, although formally the MTD was not reached. A third infusion with 5-FU/FA per cycle on day 8 was not considered feasible, as the nadir for docetaxel is on day 7 and the mean duration is seven days.[16]

Efficacy

Twenty-four patients were evaluable for response (*table 4*). Four were not evaluable. There were no complete responses. There were ten partial responses leading to an overall RR of 42% (95% confidence interval 22.1 to 63.%).

Table 4
Dose-limiting toxicities (DLT) per dose level

DOSE LEVEL	DOCETAXEL/5-FLUOROURACIL (MG/M²)	NO. OF PTS/ CYCLES	NO DLT	GRADE III/IV INFECTION	DIARRHOEA	FEBRILE NEUTROPENIA	ERYTHEMA
1	60/1800	3/16	3				
2	75/1800	6/22	4	1	1		
3	85/1800	7/42	5	1		1	
4	100/1800	6/36	4	1		1	
5	100/2100	6/28	4	1			1

Table 5
Dose reductions and relative dose intensity per dose level

DOSE LEVEL	DOCETAXEL/5-FLUOROURACIL (MG/M²)	CYCLES WITH DOSE REDUCTIONS /TOTAL CYCLES	NUMBER OF PATIENTS INVOLVED
1	60/1800	0/16	0/3
2	75/1800	0/22	0/6
3	85/1800	0/42	0/7
4	100/1800	0/36	0/6
5	100/2100	3/28	1/6
Total		3/144	1/28

Table 6
Response rates

DOSE LEVEL	DOCETAXEL/5-FLUOROURACIL (MG/M²)	NO. OF PATIENTS	NE	PR	SD	PD
1	60 /1800	3	0	1	2	0
2	75 /1800	6	1	2	1	2
3	85 /1800	7	0	3	2	2
4	100 /1800	6	0	4	2	0
5	100 / 2100	6	3	0	3	0
Total		28	4/28	10/24	10/24	4/24

DISCUSSION

Our study demonstrates that the combination of docetaxel, FA and 5-FU continuous infusion is effective and feasible at doses 100/500/2100 mg/m². The predominant dose-limiting toxicities were febrile neutropenia, grade III or IV infection, diarrhoea and erythema grade III/IV. In two patients the grade III/IV infection was related to the intravenous port system. Our study is thus in line with other phase I studies which show that concomitant administration is feasible and effective. Haematological toxicity was the predominant DLT in our as well as in other reported phase I studies. This haematological toxicity, however, did not lead to toxic deaths in any of these studies and thus appears to be manageable.[17-19] In one study 5-FU was given as bolus injections for three to five days with longer intervals of three to four weeks or as continuous infusions for five days every three to four weeks.[17,19] Further dose escalation beyond docetaxel 60 mg/m² was not feasible in these studies. The fact that in our study we were able to reach a dose of docetaxel 100 mg/m² is probably due to increased tolerability of prolonged infusions of 5-FU as compared with bolus injections, and to spreading the 5-FU infusions over two days in a three-week cycle. Meanwhile, phase II trials have demonstrated the efficacy of 5-FU/FA by bolus injection in patients pretreated with anthracyclines.[20] Experimental and clinical data indicate a far higher activity of 5-FU if it is given as a protracted infusion, and especially at higher dose intensity.[21-26] Although response rate was not the primary endpoint of the study, the observed antitumour activity of 42% of patients treated with this combination is in accordance with response rates observed in phase II studies in which docetaxel was combined with protracted 5-FU infusions.[20] The schedule presented in our study thus provides an alternative schedule of protracted infusions.

The oral fluoropyrimidine capecitabine has recently become available. Capecitabine was designed to generate 5-FU preferentially in tumour tissue, thus giving a more targeted approach. In a randomised phase III study in anthracycline-pretreated patients with MBC, combination of capecitabine and docetaxel led to improved RR (42 *vs* 30%, p=0.006), time to progression (6.1 *vs* 4.2 months, p=0.0001) and overall survival (14.5 *vs* 11.5 months, p=0.0126) when compared with docetaxel monotherapy.[27] These improvements in efficacy came at the cost of a somewhat higher toxicity, as expressed as a higher incidence of hand-foot syndrome and gastrointestinal side effects. When comparing the feasibility of capecitabine and the continuous 5-FU infusions described in this study, it is obvious that oral administration increases feasibility and patient comfort and precludes problems related to continuous infusion regimens observed in two patients in our study. With intermittent continuous 5-FU infusion we observed no hand-foot syndrome, which occurs in up to 25% of patients treated with capecitabine, and no mucositis. Formally the MTD was not reached in our study, but at dose level 5 the maximum dose levels were reached as applied for single agents and further dose escalation was not considered appropriate.

In conclusion the combination of docetaxel (100 mg/m², one-hour infusion q3 weeks on day 1), FA (500 mg/m², two-hour infusion on days 1 and 15) and 5-FU (2100 mg/m², 24-hour infusion on days 1 and 15) is a feasible regimen with encouraging activity in anthracycline-pretreated patients. A disadvantage of this regimen is the need for an indwelling central venous catheter with the associated increased risks of infection and thrombosis, and extra costs. Currently available oral formulations such as capecitabine have overcome these practical hurdles and have proven to prolong survival when given in combination with docetaxel.[27] For patients unable to receive anthracyclines, the encouraging activity of docetaxel combined with 5-FU/FA provides a valuable alternative.

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