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Docetaxel in combination with 5-fluorouracil in patients with metastatic breast cancer previously treated with anthracycline-based chemotherapy: a phase I, dose-finding study

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Abstract

This phase I study evaluated the maximum tolerated dose, dose-limiting toxicity and recommended dose of docetaxel in combination with 5-fluorouracil (5-FU) in patients with metastatic breast cancer previously treated with anthracycline-based chemotherapy. 32 patients received docetaxel at 60, 75, 85 or 100 mg/m^2 by 1-h intravenous (i.v.) infusion, followed, after a 1-h interval, by 5-FU at 250, 350, 500 or 750 mg/m^2/day by continuous infusion over 5 days every 3 weeks. Dose-limiting stomatitis defined the maximum tolerated dose at a docetaxel dose of 100 mg/m^2 with 5-FU 750 mg/m^2/day. None of 5 patients treated at the previous dose level (docetaxel 85 mg/m^2 with 5-FU 750 mg/m^2/day) had a dose-limiting toxicity in the first cycle, and this was, therefore, considered the recommended dose. The combination was generally well tolerated. Grade 4 neutropenia was common (29 patients; 91%), but no patient experienced febrile neutropenia of duration >3 days requiring i.v. antibiotics. An objective response was achieved by 18 patients overall (56%), and in 4 out of 5 patients treated with the determined recommended dose. No pharmacokinetic interaction between docetaxel and 5-fluorouracil was apparent. The activity of docetaxel 85 mg/m^2 with 5-fluorouracil 750 mg/m^2/day will be explored more extensively in phase II studies of patients with metastatic breast cancer previously treated with anthracycline-based chemotherapy.

Keywords: Anthracycline; Docetaxel; 5-Fluorouracil; Pharmacokinetics; Metastatic breast cancer

1. Introduction

Docetaxel (Taxotere^{TM}), a semi-synthetic taxane prepared from a non-cytotoxic precursor extracted from the needles of the European yew tree *Taxus baccata*, is one of the most active chemotherapeutic agents against metastatic breast cancer. After anthracyclines, taxanes are currently the most widely administered agents for metastatic breast cancer. As a single agent, docetaxel has demonstrated advantages over three combination regimens: mitomycin-C with vinblastine [1], methotrexate with 5-fluorouracil (5-FU) [2] and 5-FU with vinorelbine [3] in patients previously treated with anthracycline-based chemotherapy. Notably, in the comparison with mitomycin-C/vinblastine, docetaxel was associated with a significantly improved tumour response and time to progression and survival [1]. Combination regimens of docetaxel with other chemotherapeutic agents, including anthracyclines, cisplatin, cyclophosphamide, 5-FU and vinorelbine, are currently being explored with the aims of improving objective tumour response rates and prolonging survival [4–6].

5-FU is an antimetabolite which has demonstrated significant antitumour activity both as a single agent and as a component of FAC (5-FU, doxorubicin, cyclophosphamide), the most active combination regimen currently used for metastatic breast cancer [7]. 5-FU is a good candidate to evaluate in combination with docetaxel, since both agents are effective against metastatic breast cancer, but they have different mechanisms of action and tolerability profiles. Neutropenia is the principal toxicity of docetaxel, whereas mucositis (stomatitis) and diarrhoea are frequent with 5-FU [8]. In

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a tumour-bearing mouse model, therapeutic synergy was observed between docetaxel and 5-FU, and 70% of the highest non-toxic dose of each agent could be administered in combination without additional toxicity [9].

With the increasing use of anthracycline-based chemotherapy as adjuvant therapy, as well as for first-line chemotherapy against metastatic breast cancer, patients are frequently exposed to high cumulative doses of anthracyclines and are therefore at risk of resistance and cardiotoxicity [10]. The combination of docetaxel with 5-FU may be particularly useful in patients previously treated with anthracycline-based chemotherapy, but naïve to these agents.

The primary objectives of this phase I study were to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT) and recommended dose for phase II studies of docetaxel in combination with 5-FU in patients with metastatic breast cancer previously treated with anthracycline-based chemotherapy. Secondary objectives were to characterise the safety and pharmacokinetic profile of the combination, and to obtain preliminary evidence of its antitumour activity.

2. Patients and methods

2.1. Study design and patients

This was a phase I, open-label, dose-finding study conducted between May 1995 and May 1997. The study was undertaken in accordance with the Declaration of Helsinki, in compliance with local regulations, and with the approval of an independent Ethics Committee. All participants gave written informed consent.

The study population consisted of women (median age 58 years; range: 38–73 years; haemoglobin 100 g/l) with metastatic breast cancer previously treated with, though not necessarily resistant to, anthracycline-based chemotherapy Patients had to have measurable or evaluable progressive disease; local ipsilateral recurrence after conservative breast surgery or contralateral breast cancer was not sufficient. Histological proof of breast carcinoma at first diagnosis was required for all patients, and at study entry histological or cytological proof of metastasis was desirable, but not required, for those with a single metastatic lesion. Other inclusion criteria were WHO performance status $\leqslant 2$, normal haematological values (neutrophils $\geqslant 2\times10^9$/l, platelets $\geqslant 100\times10^9$/l, haemoglobin $\geqslant 100$ g/l); normal liver function tests (total bilirubin below upper limit of institutional normal range (N), alanine and aspartate transferases $\leqslant 2$N); and normal renal function (creatinine $\leqslant 140$ μmol/l, and if borderline values, creatinine clearance $\geqslant 1$ ml/s).

Patients had to have received at least one anthracycline-containing regimen, either as neoadjuvant or adjuvant treatment or for metastatic disease. Only one line of chemotherapy was permitted for metastatic disease. Patients could have received prior 5-FU, provided it was administered only in intravenous (i.v.) bolus, but not prior docetaxel or paclitaxel. Up to two lines of prior hormonal therapy were permitted as adjuvant therapy or for metastatic disease. Radiation therapy could have been given at sites other than those used to assess response provided at least 4 weeks had elapsed since the last session. Patients had to have fully recovered from the toxic effects of previous antitumour therapy except for alopecia.

Further exclusion criteria included: a history of malignancy other than non-melanoma skin cancer and excised *in situ* cervical carcinoma; known clinical brain or leptomeningeal involvement; symptomatic peripheral neuropathy of grade $\geqslant 2$; uncontrolled infection; and other serious illnesses and medical conditions.

2.2. Treatment plan

Nine escalating dose levels of docetaxel and 5-FU were planned. Docetaxel was to be administered at 60, 75, 85 or 100 mg/m^2 as a 1-h i.v. infusion, followed, after a 1-h interval, by 5-FU at 250, 350, 500, 750 or 1000 mg/m^2/day by continuous infusion over 5 days. Treatment was repeated every 3 weeks until progression, unacceptable toxicity or patient refusal occurred; patients with no symptomatic improvement after four cycles were also withdrawn. Thereafter, further treatment, if any, was at the discretion of the investigator.

To avoid docetaxel-related hypersensitivity reactions and oedema, all patients received prophylactic premedication: oral methylprednisolone (64 mg) was given 1 day and 3 h before and 1 day after the first docetaxel infusion, and oral diosmine (500 mg) was given twice daily from the first infusion.

Dose levels were assigned at recruitment, and no intrapatient dose escalation was allowed. At least 3 patients were assigned to each dose level, with a 1-week interval between entry of the first patient and the next 2 patients. Before escalating to the next dose level, the 3 patients had to have received at least one cycle and been observed for acute toxicity for at least 2 weeks. If 1 out of the 3 patients at the same dose level developed DLT, 3 more patients were entered at the dose level. The MTD was defined as the dose level at which at least two consecutive of the first 3 patients or at least 3 of the first 6 patients entered developed DLT during the first cycle. Once the MTD was determined, 2 further patients were treated at the previous dose level, to confirm its status as the recommended dose, i.e. the highest safe dose of the two drugs when used in combination.

Toxicity was graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC). DLT

included: grade 4 neutropenia (neutrophil count $<0.5\times10^9$/l) for longer than 7 days; febrile neutropenia (grade 4 neutropenia with grade $\geqslant 2$ fever) for longer than 3 days and requiring i.v. antibiotics; non-recovery of the neutrophil count (to $\geqslant 1.5\times10^9$/l) or platelet count (to $\geqslant 100\times10^9$/l) on day 21 of each cycle; grade 4 thrombocytopenia; grade 4 nausea/vomiting; grade 2 neurotoxicity; and any grade 3/4 toxicity, excluding alopecia and anaemia.

Dose modifications were planned for toxicity. For DLT, with the exception of grade 3 neuropathy, for which patients were withdrawn, treatment was discontinued until recovery to grade 1 and restarted at the subsequent cycle. The restarting dose was at the dose level below and/or modified as appropriate to the toxicity. If mild hypersensitivity occurred despite prophylactic premedication, the rate of docetaxel infusion could be reduced until recovery of symptoms then resumed at the initial planned rate. No dose reduction was planned for oedema, but the patient could be withdrawn from the study at the discretion of the investigator. No prophylactic antiemetic treatment was allowed at the first cycle. Prophylactic antiemetic treatment with metoclopramide was allowed from the second cycle, and granisetron or ondansetron could be given interventionally for nausea and vomiting.

2.3. Patient evaluations

Evaluations at baseline, during the study (every two courses), and at the end of treatment included a medical history, data on toxicity and physical examination every course, an electrocardiogram, radiology examinations (X-rays, abdominal and other computed tomography (CT) scans, and ultrasounds for all measurable and evaluable disease), haematological and biochemical assessments every week, and other investigations as clinically indicated. Patients were monitored regularly for toxicity, and were asked to report clinical adverse events to the investigator. Haematological assessments were made twice weekly, or every 2 days until recovery in patients with grade 4 neutropenia or febrile neutropenia. Irrespective of the reason for discontinuation, patients were observed for toxicity during the first month after the last drug treatment.

The pharmacokinetics of docetaxel and 5-FU were evaluated during the first cycle of chemotherapy. Blood samples for docetaxel analysis were collected before infusion (time 0), at 30 min after the start and 5 min before the end of docetaxel infusion, and at 15 and 45 min and 2, 5, 24, 48, 72, 96 and 120 h post docetaxel infusion. Blood samples for 5-FU analysis were collected at time 0 and at 1, 4, 23, 47, 71, 95 and 119 h after the start of 5-FU infusion. Plasma docetaxel and 5-FU levels were measured by high-performance liquid chromatography (HPLC), as previously described [11,12]. The limits of quantification were 10 ng/ml for docetaxel and 6.25 ng/ml for 5-FU. Docetaxel pharmacokinetic parameters were determined using a Bayesian approach with the concentration–time data from each patient, and a previously defined population model [13,14]. A three-compartment structural model with first-order elimination was used. For 5-FU, pharmacokinetic parameters were calculated using a non-compartmental analysis with a Siphar® program (SIMED, Créteil, France). Docetaxel data were compared with those from studies examining single-agent docetaxel administered as an hourly infusion at doses from 75 to 100 mg/m^2 [15]. 5-FU parameters were compared with those previously reported for the single agent in continuous infusion for 5 days at doses from 300 to 2250 mg/m^2/day [16,17]. To be evaluable for tumour response, patients had to have received at least two cycles of treatment, unless disease progression occurred earlier. Tumour response data were reviewed by an independent radiologist. The duration of a partial response dated from the start of treatment until the first documentation of progression; the duration of a complete response was from the time it was first documented. Patients receiving further antitumour therapy before progression were censored at the start date of the new treatment. The time to progression was estimated from the start of treatment to progression. The time to progression was censored at the date of the start of the new antitumour therapy in case of objective response or stable disease at the date of patient discontinuation. After patient discontinuation from the study treatment, tumour measurements were performed every 3 months for those not treated with any further therapy with an objective response or stable disease until relapse or progression occurred.

3. Results

32 patients with metastatic breast cancer previously treated with anthracycline-based chemotherapy were enrolled into the study. The median age was 58 years (range: 38–73) and all patients had a WHO performance status of zero or one (Table 1). 19 patients (59%) had two or more involved organs and the most frequent disease site was bone (19 patients; 59%). All patients had received one previous chemotherapy regimen; previous chemotherapy was commonly administered as neoadjuvant or adjuvant treatment (17 patients; 53%) or for metastatic breast cancer (15 patients; 47%).

In total, 245 cycles of chemotherapy were administered during the study. The median number of cycles per patient was seven (range: 2–18). The median relative dose intensity was 0.98 (range: 0.75–1.01) for docetaxel and 0.99 (range: 0.62–1.04) for 5-FU.

Table 1
Patient and disease characteristics at baseline

	Patient demographics n[a] (%)
Number of patients	32 (100)
Median age in years (range)	58 (38–73)
WHO performance status:	
0	20 (63)
1	12 (38)
Number of organs involved:	
1	13 (41)
2	15 (47)
$\geqslant 3$	4 (13)
Disease sites:	
Bone	19 (59)
Liver	9 (28)
Skin	7 (22)
Lung	6 (19)
Pleura	6 (19)
Lymph node	5 (16)
Soft tissue	2 (6)
Uterus	1 (3)
Ovary	1 (3)
Number of previous chemotherapy regimens:	
1	28 (88)
2	4 (13)
Intent of previous chemotherapy:	
Neoadjuvant and adjuvant	4 (13)
Neoadjuvant only	1 (3)
Adjuvant only	12 (38)
Metastatic breast cancer	15 (47)
Resistance to anthracyclines:	
Not resistant	27 (84)
Primary resistance	2 (6)
Secondary resistance	3 (9)

[a] Unless otherwise stated.

3.1. Toxicity

All patients were evaluable for toxicity. Overall, the combination was well tolerated at all dose levels. Reasons for treatment discontinuation are listed in Table 2.

Chemotherapy was delivered on time in 97% (237) of cycles. Of the eight chemotherapy delays, only two lasted for longer than 7 days, due to stomatitis and dysrhythmia (not related to the study drug, but related to thyroid dysfunction) with docetaxel 75 mg/m^2 and 5-FU 350 mg/m^2/day and due to infection with docetaxel 85 mg/m^2 and 5-FU 750 mg/m^2/day. There were no dose modifications in 95% of cycles (232). Dose reductions were required for docetaxel in nine cycles (4%) and 5-FU in four cycles (2%). The main reasons of a dose decrease for docetaxel were non-haematological such as stomatitis (five cycles at dose levels VI, VII and VIII) neurosensory (two cycles at dose levels I and VIII), vomiting (one cycle at dose level III) and skin toxicity (one cycle at dose level VIII).

The most frequent haematological adverse event was neutropenia. Grade 4 neutropenia occurred in 29 patients (91%) and 70% of evaluable cycles (168 of 240 evaluable). The median time to nadir of grade 4 neutropenia was 9 days (range: 5–15 days) and the median duration of grade 4 neutropenia until the recovery to at least grade 1 was 7 days (range: 2–12 days).

Although grade 4 neutropenia was frequent, no patient experienced febrile neutropenia defined as per protocol (duration >3 days and requiring i.v. antibiotics). However, 6 patients (19%) presented with a single episode of febrile neutropenia, as defined as grade 4 neutropenia with grade $\geqslant 2$ fever irrespective of the duration and the administration of i.v. antibiotics; only 1 patient required i.v. antibiotics, for fever of duration $\leqslant 3$ days (Table 3). No grade 3–4 anaemia or thrombocytopenia occurred.

The most frequent acute non-haematological toxicities considered to be possibly or probably related to treatment were stomatitis and infection; most of these adverse events were of mild or moderate severity. 13 out of 20 patients who experienced stomatitis had grade 1 episodes; only 5 patients had grade 3 episodes, at dose levels combining docetaxel 85–100 mg/m^2 with 5-FU 500–750 mg/m^2/day. Grade 3 stomatitis occurred in 2 patients at the first cycle (100/750) and in 3 patients at the second, third and sixth cycle, respectively (100/500: 1 patient; 85/750: 2 patients) (Table 4). Severe (grade 4) infection was reported in 1 case, and 13 out of 17 patients who experienced infection had only grade 1 episodes.

The most frequent chronic non-haematological toxicities considered to be possibly or probably related to treatment were alopecia, nail disorders and fluid retention. Alopecia was almost universal. Severe fluid retention and nail disorders were rare, affecting only 1 and 2 patients, respectively. In the case of the severe fluid retention, peripheral oedema became severe after the fourth cycle at the dose level of 75/250. Despite severe fluid retention, the patient received docetaxel for another four cycles. Furthermore, the low value of the albuminemia at baseline has probably increased the severity of the adverse event. Mild and moderate fluid retention were reported in 12 and 3 cases, respectively. There were two incidences of grade 3 neurotoxicity (neurosensory and neuromotor in 1 patient each).

3.2. Maximum tolerated dose and recommended dose

DLT was reported for 2 patients with docetaxel 75 mg/m^2 and 5-FU 350 mg/m^2/day (grade 4 vomiting and grade 4 infection), but no other patient had DLT at this dose level and the dose escalation process was continued. The MTD was reached at docetaxel 100 mg/m^2 and 5-FU 750 mg/m^2: grade 3 stomatitis occurred in the first 2 of the 3 patients treated at the first cycle. Once the MTD was determined, 2 further patients were treated at the previous dose level, i.e. docetaxel 85 mg/m^2

Table 2
Reasons off treatment

Patient No.	Dose level	Cycle at end of study	Reason off treatment	Comment (including type of toxicity or cause of death)	Date of death or last contact
00001	1	4	Progressive disease		31/10/96
00002	1	9	Other: CR after nine cycles		13/08/97
00003	1	16	Consent withdrawn/refused further treatment	Many cures and she wanted to stop	
00004	2	11	Consent withdrawn/refused further treatment	She doesn't want to continue	15/06/96
00005	2	6	Progressive disease		16/12/96
00006	2	13	Progressive disease		09/01/97
00007	3	11	Progressive disease		22/05/96
00008	3	4	Progressive disease		26/05/96
00009	3	3	Adverse experience	Skin	21/06/96
00010	3	7	Adverse experience	Nail disorders	
00011	3	4	Progressive disease		26/01/97
00012	3	9	Other: no further benefit expected		12/02/97
00013	4	16	Consent withdrawn/refused further treatment	16 cycles already done	20/01/97
00014	4	8	Consent withdrawn/refused further treatment	The patient wants to stop	02/03/97
00015	4	12	Progressive disease		22/03/97
00016	4	18	Consent withdrawn/refused further treatment	18 cycles already done	
00017	5	4	Consent withdrawn/refused further treatment	The patient wants to stop any treatment	
00018	5	7	Progressive disease		
00019	5	6	Progressive disease		26/02/97
00020	6	9	Adverse experience	Pulmonary, peripheral oedema	11/05/97
00021	6	3	Progressive disease		10/09/96
00022	6	10	Consent withdrawn/refused further treatment	Wants to stop	
00023	6	12	Consent withdrawn/refused further treatment	12 cycles already done	
00024	6	8	Other: no further benefit expected		
00025	7	10	Consent withdrawn/refused further treatment	10 cycles already done	
00026	7	5	Adverse experience	Neuro-motor related to previous irradiation on lumbar column	
00027	7	6	Adverse experience	Cardiac dysrythmia, pulmonary not related to the study drug but related to thyroid dysfunction	
00028	7	4	Consent withdrawn/refused further treatment	Anxiety	
00029	7	8	Adverse experience	Peripheral oedema	
00030	8	5	Progressive disease		
00031	8	8	Adverse experience	Peripheral oedema	
00032	8	4	Other: complete response		

CR, complete response.

Table 3
Incidence of grade 4 neutropenia and febrile neutropenia, by patients

Docetaxel (mg/m^2)/ 5-fluorouracil (mg/m^2/day)		Grade 4 neutropenia		Febrile neutropenia[a]
		Incidence	Median days duration (range)	Incidence
I	60/250	3/3	4 (2–7)	1/3
II	75/250	3/3	7 (3–12)	0/3
III	75/350	6/6	7 (2–12)	1/6[b]
IV	75/500	2/4	7 (3–11)	1/4
V	85/500	3/3	7 (4–9)	1/3[c]
VI	100/500	5/5	7 (2–11)	2/5
VII	85/750	4/5	7 (3–10)	0/5
VIII	100/750	3/3	4 (2–7)	0/3
	All	29/32 (91%)	7 (2–12)	6/32 (19%)

[a] Defined as grade 4 neutropenia with grade $\geqslant 2$ fever irrespective of the duration and the administration of intravenous (i.v.) antibiotics.
[b] Patient given i.v. antibiotics, fever $\leqslant 3$ days.
[c] Patient given oral antibiotics, fever < 3 days.

Table 4
Incidence of grade 3/4 or moderate/severe non-haematological toxicity probably or possibly related to treatment, by patients

	Docetaxel (mg/m^2)/5-fluorouracil (mg/m^2/day)																	
	I 60/250		II 75/250		III 75/350		IV 75/500		V 85/500		VI 100/500		VII 85/750		VIII 100/750		All	
Number of patients	3		3		6		4		3		5		5		3		32	
Grade[a]	*3*	*4*	*3*	*4*	*3*	*4*	*3*	*4*	*3*	*4*	*3*	*4*	*3*	*4*	*3*	*4*	*3*	*4*
Acute																		
Stomatitis	–	–	–	–	–	–	–	–	–	–	1[c]	–	2[c]	–	2	–	5	–
Infection	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	1
Vomiting	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	1
Chronic																		
Neuromotor	–	–	–	–	–	–	–	–	–	–	–	–	1[d]	–	–	–	1	–
Neurosensory	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–	1	–
Grade[b]	*M*	*S*	*M*	*S*	*M*	*S*	*M*	*S*	*M*	*S*	*M*	*S*	*M*	*S*	*M*	*S*	*M*	*S*
Non-NCI-gradeable																		
Nail disorders	1	1	1	–	1	1	3	–	–	–	1	–	1	–	1	–	9	2
Asthenia	–	–	–	–	3	–	1	–	1	–	1	–	1	–	1	–	8	–
Fluid retention	–	–	–	1	1	–	–	–	–	–	1	–	1	–	–	–	3	1

DLT, dose limiting toxicity.
[a] National Cancer Institute (NCI) Common Toxicity Criteria.
[b] M, moderate, S; severe.
[c] Not a DLT as occurred in the second, third and sixth cycles.
[d] Not a DLT as did not occur in the first cycle.

with 5-FU 750 mg/m^2/day. At the first cycle, none of the 5 patients treated at this dose level experienced DLT, and this was, therefore, considered the recommended dose.

3.3. Pharmacokinetics

The pharmacokinetics of docetaxel and 5-FU were evaluated during the first cycle (Table 5). For both agents, data were concordant with studies evaluating the single agents. As expected, the area under the plasma concentration curves (0–∞ for docetaxel; 0–120 h for 5-FU) increased with dose. Total body clearance (CL) values were stable for both agents over the dose levels investigated. The kinetics of both agents were linear. For docetaxel, the mean overall CL was 22.7 l/h/m^2, compared with 20.7±6.6 l/h/m^2 ($n=609$ with normal hepatic function) in the single-agent studies [15]. The range of CL across the dose levels for 5-FU was 116–164 l/h/m^2, as compared with 110–150 l/h/m^2 in the single-agent studies [18,19].

3.4. Tumour response

Tumour response was not the focus of this study, but all patients received at least two cycles of treatment and were, therefore, evaluable for tumour response. Data were reviewed by an independent radiologist. 2 patients (6%) achieved a complete response and 16 (50%) a partial response, giving an objective response rate of 56%.

Objective responses were most common at the three highest feasible dose levels, being 77% at the docetaxel [mg/m^2]/5-FU [mg/m^2/day] 85/500 (V), 100/500 (VI) and 85/750 (VII) dose levels combined. At the recommended dose of docetaxel 85 mg/m^2 with 5-FU 750 mg/m^2/day, 4 out of 5 patients achieved an objective response (one complete response, three partial responses). Of 5 patients with primary or secondary resistance to anthracyclines, 1 had a complete response and 2 had a partial response.

At a median follow-up time of 46.3 months (cut-off date April 1999), the median time to progression was 36 weeks; data were censored in 2 patients due to surgery. The median duration of response in responding patients was 46 weeks, with 1 patient censored due to surgery. The median survival time was 16 months; 9 patients were still alive at the cut-off date.

4. Discussion

This study establishes docetaxel 85 mg/m^2 (1-h infusion) followed by 5-FU 750 mg/m^2/day (5-day continuous infusion) given every 3 weeks as the recommended dose of the combination for phase II evaluation in patients with metastatic breast cancer previously treated with anthracycline-based chemotherapy. This dose was well tolerated and preliminary tumour response data suggest that it was clinically effective.

The combination of docetaxel and 5-FU was well tolerated at all dose levels given, and the MTD (docetaxel

Table 5
Pharmacokinetics of docetaxel and 5-fluorouracil when given in combination

Docetaxel (mg/m^2)/ 5-fluorouracil (mg/m^2/day)		*n* of patients	Docetaxel		5-fluorouracil	
			AUC 0–∞ (μg h/ml)	CL (l/h/m^2)	AUC 0–120 h (mg h/l)	CL (l/h/m^2)
I	60/250	3	2.73±0.2	22.5±1.9	11.9±5.0	116±40
II	75/250	3	3.69±0.4	20.8±2.4	8.3±3.2	164±54
III	75/350	6	3.11±0.8	25.0±5.5	11.5±1.9	154±20
IV	75/500	4	3.89±0.9	20.0±4.7	18.2±4.2	144±34
V	85/500	3[a]	4.34±1.6	21.1±8.0	19.3±6.7	140±43
VI	100/500	5	4.63±1.5	22.8±5.5	19.3±3.2	133±18
VII	85/750	5	3.54±0.8	25.2±6.9	28.9±6.1	135±26
VIII	100/750	3	5.10±1.1	20.4±4.5	34.3±11.1	119±47

AUC, area under the plasma concentration–time curve; CL, total body clearance.
[a] $n=2$ for docetaxel (1 patient excluded due to chromatographic interferences).

100 mg/m^2 with 5-FU 750 mg/m^2/day) was the eighth highest out of the nine dose levels planned. The finding that mucositis (stomatitis) was the DLT defining the recommended dose is in agreement with earlier dose-finding studies evaluating this combination in patients with various advanced solid tumours [18] and recurrent/metastatic breast cancer [19]. In the recurrent/metastatic breast cancer study, the definitions of the DLTs were more conservative than those in this present study and led to a lower recommended dose of docetaxel 50 mg/m^2 with 5-FU 500 mg/m^2/day for 5 days.

The recommended dose-defining DLT of stomatitis in this study is in contrast with published combination studies of docetaxel with doxorubicin, vinorelbine, or doxorubicin/cyclophosphamide in metastatic breast cancer, where the DLT was neutropenia or febrile neutropenia [5,6,20]. Mucositis is, however, known to be associated with 5-FU treatment, and is frequently observed with other 5-FU-based combination regimens for metastatic breast cancer [21–25].

Although not the recommended dose-defining DLT, neutropenia was universal in this study, with 91% of patients experiencing grade 4 neutropenia. This was as expected, since both docetaxel and 5-FU are known to be haematotoxic [26]. However, the duration of grade 4 neutropenia was short, the incidence of febrile neutropenia was very low, and infection was dose-limiting in only 1 patient.

The pharmacokinetics of docetaxel and 5-FU did not appear to be influenced by their combination, as compared with historical data from studies of single-agent therapy. Docetaxel and 5-FU can therefore be administered together without any relevant drug interaction according to this administration schedule. In agreement with these findings, no relevant modification of the pharmacokinetics of these two compounds was observed in a study performed in patients with various advanced solid tumour types and using similar conditions of drug administration [18]. The 85 mg/m^2 dose of docetaxel determined for use in combination with 5-FU is only slightly lower than that recommended for single-agent chemotherapy (100 mg/m^2). Single-agent docetaxel has also shown activity at lower doses, with objective response rates of 52% and 44% at doses of 75 and 60 mg/m^2, respectively [4]. Although tumour response assessments were preliminary in the present study, the objective response rate (one complete response and three partial responses in 5 patients) at the recommended dose was high in this population of patients relapsing after anthracyclines. In a phase I study of docetaxel in combination with doxorubicin, the recommended dose for docetaxel was determined to be either 75 or 60 mg/m^2, and objective response rates were 90% and 66%, respectively [5,20]. In the present study, objective tumour responses were observed at all dose levels, the median duration of response was approximately 1 year (46 weeks), and approximately one-quarter of patients (9 patients) were still alive at a median follow-up time of 46.3 weeks.

Several studies have shown that single-agent docetaxel is effective against metastatic breast cancer, even in patients with anthracycline-resistant disease [1,27–29]. Although patients in this study were not required to have anthracycline resistance, all had been previously treated with at least one anthracycline-based regimen. Although data are preliminary, it is interesting to observe that of those with anthracycline resistance, 3 out of 5 patients achieved an objective tumour response.

The good tolerability and lack of pharmacokinetic interaction in this study demonstrate that docetaxel and 5-FU can be combined safely in patients with metastatic breast cancer previously treated with anthracycline-based chemotherapy. The recommended dose for further evaluation in patients with metastatic breast cancer is docetaxel 85 mg/m^2 (1-h infusion) followed by 5-FU 750 mg/m^2/day (5-day continuous infusion) given every 3 weeks. Phase II studies will further examine the efficacy of the combination, but preliminary data from this study suggest a high activity of the recommended dose in patients previously treated with anthracycline-

based chemotherapy. The combination is of particular interest for the treatment of patients with anthracycline failure. Furthermore, the use of a portable pump allows the chemotherapy to be administered on an outpatient basis.

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