Pergamon

European Journal of Cancer, Vol. 35, No. 8, pp. 1194–1201, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(99)00122-7

Original Paper

Docetaxel Compared with Sequential Methotrexate and 5-Fluorouracil in Patients with Advanced Breast Cancer after Anthracycline Failure: a Randomised Phase III Study with Crossover on Progression by the Scandinavian Breast Group

J. Sjöström,[1] C. Blomqvist,[1] H. Mouridsen,[2] A. Pluzanska,[3] S. Ottosson-Lönn,[4] N.-O. Bengtsson,[5] B. Østenstad,[8] I. Mjaaland,[9] M. Palm-Sjövall,[6] E. Wist,[10] V. Valvere,[11] H. Anderson[6] and J. Bergh[7]

[1]Department of Oncology, Helsinki University Central Hospital, Haartmaninkatu 4, FIN-00290 Helsinki, Finland; [2]University Hospital, Rigshospitalet, Copenhagen, Denmark; [3]Oncology Department of the Medical University, Lodz, Poland; [4]Sahlgrenska Sjukhuset, Göteborg; [5]University Hospital, Umeå; [6]University Hospital, Lund; [7]University Hospital, Uppsala, Sweden; [8]Ullevål Hospital, Oslo; [9]Rogaland Central Hospital, Stavanger; [10]University Hospital of Tromsoe, Norway; and [11]Estonian Cancer Centre, Estonia

The aim of this study was to compare the efficacy and tolerability of docetaxel to methotrexate and 5-fluorouracil in advanced breast cancer after anthracycline failure. A randomised multicentre trial was conducted in 283 patients with advanced breast cancer who had failed previous anthracycline treatment. Docetaxel at a dose of 100 mg/m^2 every 3 weeks ($n = 143$) was compared with sequential methotrexate and 5-fluorouracil (MF; $n = 139$) given at day 1 and 8 every 3 weeks at dosages of 200 mg/m^2 and 600 mg/m^2, respectively. After progression, crossover to the alternative treatment group was recommended. There was a significantly higher overall response rate in the docetaxel 42% (CR 8% + PR 34%) than in the MF arm 21% (CR 3% + PR 18%) ($P < 0.001$). The median time to progression (TTP) was 6.3 months in the docetaxel arm and 3.0 months in the MF arm ($P < 0.001$). Docetaxel also had a significantly higher response rate of 27% following crossover compared with MF (12%). Significantly more side-effects (leucopenia, infections, neuropathy, oedema, asthenia, skin, nail changes, alopecia) were seen in the docetaxel than in the MF group. However, grade 3 and 4 side-effects were infrequent with both drugs, with the exception of fatigue, alopecia and infections. Median overall survival (OS) including crossover phase was 10.4 months in the docetaxel and 11.1 months in the MF arm ($P = 0.79$). Based on the response rate and the primary endpoint of TTP, docetaxel is superior to sequential methotrexate and 5-fluorouracil in advanced breast cancer after anthracycline failure.

Key words: breast cancer, chemotherapy, docetaxel, anthracycline failure, methotrexate, 5-fluorouracil
Eur J Cancer, Vol. 35, No. 8, pp. 1194–1201, 1999

INTRODUCTION

PRESENTLY THERE is no consensus on the choice of chemotherapy in advanced breast cancer after anthracycline containing regimens have failed. Historically, response rates with a variety of regimens have been low and no regimen has been shown to be superior to any other [1]. Phase II studies have shown that single agent docetaxel is highly effective in metastatic breast cancer [2] and retains efficacy also in anthracycline-resistant breast cancer, with response rates ranging from 29 to 54% [3]. Therefore, we wanted to study whether the results of conventional chemotherapy after anthracycline failure could be improved. This phase III multicentre trial

Correspondence to J. Sjöström.
Received 18 Dec. 1998; revised 9 Apr. 1999; accepted 5 May 1999.

compared docetaxel at 100 mg/m^2 as a 1 h infusion day 1 every 3 weeks with sequential methotrexate 200 mg/m^2 and 5-fluorouracil (5-FU) 600 mg/m^2 days 1 and 8 every 3 weeks (MF). The choice of sequential MF as the comparison treatment was based on a retrospective analysis of breast cancer patients previously participating in a clinical trial with FEC (5-FU, epirubicin, cyclophosphamide) polychemotherapy as first line therapy at the Department of Oncology, Helsinki University. In that retrospective analysis sequential methotrexate and 5-FU demonstrated the best and consistent response of 28% [4]. A further advantage with the MF regimen was the favourable toxicity profile [5] and the previously documented anti-tumoral activity in second line therapy of advanced breast cancer [4, 6–12].

PATIENTS AND METHODS

Study design

This was an open label, randomised phase III study comparing docetaxel with methotrexate and 5-FU after failure of anthracycline treatment in advanced breast cancer. Crossover to the alternative treatment group after relapse was recommended. The primary endpoint was time to progression (TTP). Secondary endpoints were response rates and toxicities associated with the treatments. An additional objective was to evaluate whether the order of administration of the two alternative salvage therapies (docetaxel followed by MF or MF followed by docetaxel) had an impact on overall survival. Quality of life analysis studies were done in the majority of patients. The results of that part of the study will be published separately.

Patient population

To enter the trial, the patients were required to have histologically proven primary breast cancer that had progressed during or after first line anthracycline treatment for advanced disease or relapsed within 12 months after discontinuation of adjuvant anthracycline therapy. The patients were required to be $\geq$18 and $<$70 years old, with a performance score $\leq$2 and with normal values of WBC ($\geq 3\times10^9$/l), platelets ($\geq 100\times10^9$/l), serum bilirubin level, and serum creatinine. Patients were ineligible if they had more than one previous chemotherapy regimen for advanced disease (multiple endocrine treatments and radiotherapy were allowed), prior treatment with taxanes, any concurrent serious medical illness, clinical signs of cerebral or leptomeningeal metastases or a history of other malignancy except contralateral breast cancer, basal carcinoma of the skin or *in situ* cervical cancer. Only patients with measurable or nonmeasurable evaluable lesions were eligible. Oral and written informed consent was mandatory. The study was approved by the ethical committees of all the participating centres.

Examinations

A blood cell count (haemoglobin, leucocytes, neutrophils, platelets), serum biochemistry (AST, ALT, alkaline phosphatase, bilirubin, creatinine, calcium, sodium, potassium), ECG and staging investigations, which included chest X-ray, bone scintigraphy or X-ray of pelvis and spine and ultrasound or computer tomography (CT) of the liver, were performed within 3 weeks of the inclusion.

Serum biochemistry was repeated once during every course of treatment. Haematological nadir values were recorded after each cycle on day 8. If the nadir leucocyte count was $<1.0\times10^9$/l, the haematological investigations were repeated 3 days later. Lesions were assessed every third course, at treatment discontinuation and every 3 months during follow-up until progression. Response evaluation was performed according to WHO recommendations with modifications suggested by the EORTC [13].

In measurable lesions, complete response was defined as complete disappearance of all evidence of disease lasting for $\geq$28 days and partial response as 50% or greater reduction of tumour lasting for $\geq$28 days, without appearance of new lesions. No change was defined as less than 50% regression, but not more than 25% increase in tumour for at least 9 weeks and progressive disease as more than 25% increase in tumour area or the appearance of new lesions. For lytic bone lesions, complete response was defined as complete disappearance of all lesions on X-rays, partial response as decrease in the size of lytic lesions and progressive disease as an increase in the size of existent lesions or appearance of new lesions. For malignant effusions only three response categories were defined, complete response (disappearance of effusion), no change (persistent effusion) and progressive disease (new effusion). Partial (PR) and complete responses (CR) were confirmed within 4–6 weeks after first identification of objective response.

All adverse reactions were collected on the case report forms during the study every 3 weeks on every visit. The toxicity was graded according to the WHO criteria. Febrile neutropenia requiring intravenous (i.v.) antibiotics was recorded as WHO grade 3 infection. No bacteriological documentation of infection was required. Oedema and fluid retention were graded 1–3 according to a scale developed by Rhône-Poulenc Rorer for previous studies on docetaxel: grade 1 fluid retention was defined as asymptomatic effusion or transient oedema, grade 2 as effusion with dyspnoea or distention or oedema not resolving during the night rest and grade 3 as rest dyspnoea, tamponade, pronounced distention, oedema with significant impairment or anasarca. Toxicity and symptoms were recorded regardless of their relationship to treatment.

Treatment programme

Docetaxel was given at a dose of 100 mg/m^2 as a 1-h infusion. There was a 5-day oral premedication with dexamethasone or betamethasone 8 mg twice daily starting 12 h before treatment. Methotrexate (200 mg/m^2) was given as a short infusion ($\leq$15′) and 5-fluorouracil (600 mg/m^2) as a bolus injection ($<$5′) 1 h after methotrexate administration on days 1 and 8 every 3 weeks. Urinary alkalinisation was started immediately after methotrexate by administration of 400 ml isotonic $NaHCO_3$ as a 1 h infusion, and continued as oral therapy with $NaHCO_3$ 2 to 3 grams three times daily for 2 days from day 2. Oral leucovorin (calcium folinate) 15 mg four times daily for 2 days was started 24 h after methotrexate administration. Patients with pleural effusion or ascites were given 2 extra days of leucovorin rescue. No routine prophylactic antiemetic drugs (except from the corticosteroids in the docetaxel group) or prophylactic colony stimulation factors were given in either treatment group.

The treatment was repeated every 3 weeks (next cycle started on day 22) providing the WBC count was $\geq 3.0\times10^9$/l and platelets $\geq 100\times10^9$/l. Otherwise the treatment was postponed by 1 week. If more than 1 week's delay was necessary, the doses were reduced by 10% and the treatment was given

when levels of WBC $\geq 3.0\times10^9$/l and platelets $\geq 50\times10^9$/l were reached. Treatment was discontinued if more than 3 weeks delay was necessary. The doses of the next course were reduced by 10% if there was grade 4 leucopenia (WBC count $<1.0\times10^9$/l) for more than 3 days and by 20% if the patient had experienced febrile leucopenia (WBC count $<1.0\times10^9$/l) or grade 4 thrombocytopenia (platelets $<25\times10^9$/l). Doses were not re-escalated. At the beginning of the study all patients were started at full doses of the two regimens, whilst after a protocol amendment on 10 October 1995 patients with impaired liver function (AST (aspartate amino transferase) and/or ALT (alanine amino transferase) $>1.5\times$upper normal limit associated with alkaline phosphatase $>2.5\times$upper normal limit) were treated with docetaxel at a reduced dose (75 mg/m^2) because the incidence of febrile neutropenia has been shown to be significantly higher among these patients than among patients with normal liver function [14]. The treatment was recommended to be continued until objective signs of disease progression or until intolerable toxicity developed. Responding and stable patients were to receive at least six treatment cycles and could continue treatment indefinitely unless toxicity necessitated prior interruption of treatment. If further chemotherapy was considered after disease progression, salvage therapy with the alternative treatment group (crossover) was recommended (MF for patients treated with docetaxel and docetaxel for patients treated with MF). Toxicity and efficacy data was collected only up to discontinuation of the initial treatment except for crossover response and overall survival.

Statistical analysis

The sample size was calculated to allow the detection of a 50% difference in the time to progression (TTP) with a power of 80% at the significance level of 0.05. Differences in TTP and overall survival (OS) were tested by means of the log-rank test, and treatment response (CR, PR, NC, PD) was evaluated with the chi-square test for trends with CR classified as 4, PR as 3, NC as 2 and PD as 1. Univariate and multivariate analyses were performed with Cox multivariate regression to compensate the treatment comparisons for potential influence of imbalanced prognostic factors on TTP. All tests were two-sided and performed primarily in the intention-to-treat population.

All the efficacy analyses were done according to the intention-to-treat (ITT) principle. The ITT population was defined as all randomised patients except one, who in retrospect had no breast cancer recurrence. The analyses of response, TTP (measured from the date of randomisation until tumour progression or death or last follow-up visit) and OS were done both on the ITT population and evaluable patients. Eligible patients were those fulfilling all the inclusion criteria. In the OS analysis of evaluable patients were included all the eligible patients. In the TTP analysis of evaluable patients were included all the eligible patients who received at least one course of treatment. Furthermore in the analysis of response rate in the evaluable population was included every eligible patient receiving at least one cycle of treatment and having the reference lesions recorded at baseline and at least on one study assessment.

Separate TTP subgroup analyses were performed in the protocol on the patients with primary anthracycline resistance (in patients with recurrence during anthracycline adjuvant treatment or with PD as best response on first line anthracycline treatment for recurrence); visceral metastases (metastases in internal organs i.e. lung, pleura, liver, etc.); liver metastases; soft-tissue metastases (metastases in skin, lymph nodes, contralateral breast or subcutaneous tissue); bone metastases; with metastases documented only at one organ site or at three or more organ sites.

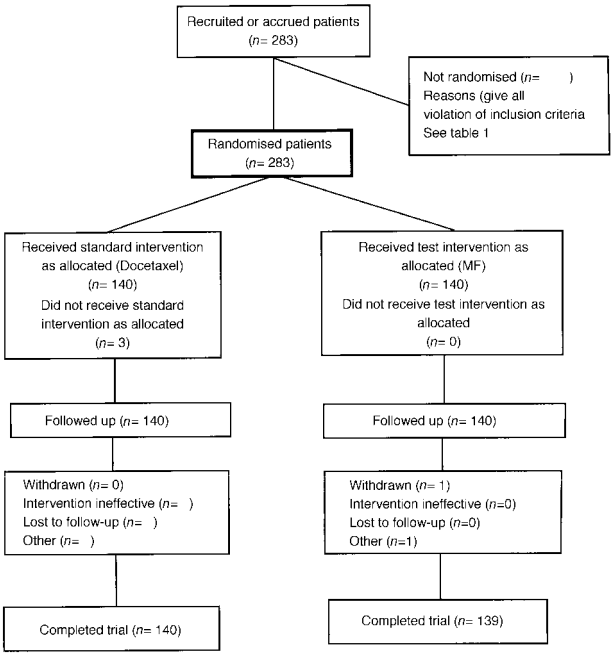

Figure 1. Flow chart of the progress of patients through the trial (adapted from Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996, 276, 637–639).

Table 1. *Patient disposition and treatment discontinuation*

	Docetaxel	MF
Patient disposition		
Randomised	143	140
ITT population	143	139
Treated	140	140
Eligible	136	131
Eligible and evaluable for OS	136	131
Eligible and evaluable for TTP	134	131
Eligible and evaluable for RR	130	127
Crossed over to alternative treatment	48	74
Reason for treatment discontinuation $n=268$ (treatment ongoing $n=14$)		
Complete response	4	2
Progressive disease	69	112
Toxicity	30	4
Grade 3–4*	9	4
Death	8	5
Toxic death	3	1
Progressive disease	5	4
Patient refusal	12	3
Protocol violation	2	1
Lost to follow-up	0	1
Other	10	5

*Oedema was graded at a scale of 1–3. MF, methotrexate and 5-fluorouracil; ITT, intention to treat; OS, overall survival; TTP, time to progression; RR, response rate.

The toxicity analysis was performed on all the patients receiving at least one course of treatment ($n = 279$) and tested with chi-square test for trends. The only data collected or analysed in the crossover phase was response to treatment and survival.

RESULTS

Randomisation and eligibility

A total of 283 patients with metastatic breast cancer were randomised into this study between December 1994 and October 1997 from 22 centres in Scandinavia, Estonia and Poland. The participating institutions and principal investigators are listed in the acknowledgment. 143 patients were allocated to the docetaxel and 140 patients to the MF arm (Figure 1; Table 1). One patient in the MF arm was later found to have no recurrence and was excluded from all the efficacy analyses. Another 15 patients did not meet all the eligibility criteria, 7 (5%) in the docetaxel arm and 8 (6%) in the MF arm. Of these, 12 had received more than one chemotherapy regimen for metastatic breast cancer, 1 patient had

Table 2. Patient and tumour characteristics (n=282)

Characteristic	Docetaxel ($n = 143$) (%)	MF ($n = 139$) (%)
Age		
Median (range)	50 (27–69) years	51 (26–69) years
Menopausal status		
Premenopausal	18 (13)	11 (8)
Postmenopausal	122 (85)	127 (91)
Unknown	3 (2)	1 (1)
Performance status, WHO		
0	45 (32)	38 (27)
1	81 (57)	79 (57)
2	17 (12)	22 (16)
Axillary lymph node metastases at primary diagnosis		
N0	35 (25)	42 (30)
N1–3	92 (64)	88 (63)
NX	16 (11)	9 (7)
Hormone receptor status at primary diagnosis		
ER+	50 (35)	43 (31)
ER–	57 (40)	61 (44)
Unknown	36 (25)	35 (25)
Disease free interval (DFI)		
Median (range)	1.56 (0–22.8) years	1.41 (0–10.2) years
Previous chemotherapy		
Adjuvant	70 (49)	62 (45)
Advanced disease	120 (84)	121 (87)
5-FU in the regimen	99 (69)	96 (69)
MF in the regimen	44 (31)	46 (32)
Anthracycline-containing chemotherapy		
Adjuvant only	24 (17)	17 (12)
Advanced disease only	117 (82)	119 (86)
Both	2 (1)	2 (1)
None	0 (0)	1 (1)
Anthracycline resistance		
Primary	50 (35)	51 (37)
Other	93 (65)	88 (63)
Previous hormonal therapy		
Adjuvant	43 (30)	40 (29)
Advanced disease	61 (43)	50 (36)
Previous radiotherapy for recurrence	56 (39)	52 (37)
Organs involved at time of metastases		
Visceral	105 (73)	96 (69)
Liver	73 (51)	57 (41)
Bone	66 (46)	54 (39)
Soft tissue	69 (48)	70 (50)
Number of organs involved		
= 1	50 (35)	53 (38)
= 2	57 (40)	46 (33)
≥ 3	36 (25)	40 (29)
Tumour lesions (% of pts)		
Measurable disease	124 (87)	131 (94)
Evaluable disease only	19 (13)	8 (6)

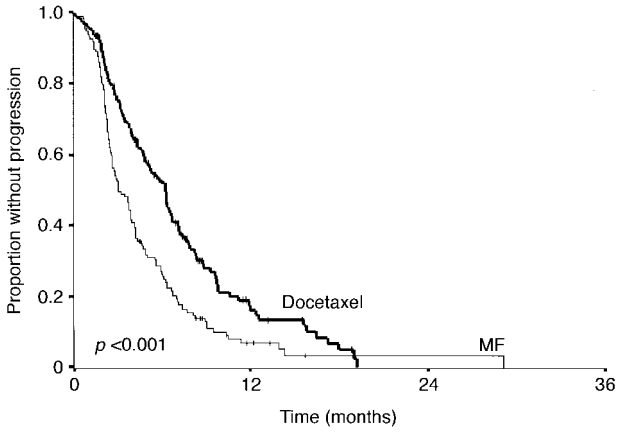

Figure 2. Time to progression (TTP) with docetaxel versus methotrexate and 5-fluorouracil (MF) $n = 282$, $P < 0.001$.

never received previous anthracycline, 1 patient had a leucocyte count which was too low, and in 1 patient the serum creatinine value at inclusion was missing. Furthermore 3 patients, who never received any treatment due to rapidly deteriorating performance status, were excluded from the analysis of TTP and response in the evaluable patient subset. A further 8 patients (4 in both arms) in whom the reference lesions were recorded only at baseline were excluded from the analysis of response rate in evaluable patients. The major efficacy analyses followed the intention-to-treat principle and included all the randomised patients except the 1 without metastases. The magnitude of the difference in the efficacy analyses of evaluable patients was virtually identical to the ITT analyses.

Patient characteristics

There were no significant differences between the docetaxel and MF groups with respect to the patient characteristics (Table 2). Only 14% of the patients were included after adjuvant anthracycline treatment only. 36% of the patients had primary resistance to anthracyclines (recurrence during anthracycline adjuvant treatment or PD as best response on first line anthracycline treatment). 69% of the patients in both arms had received 5-fluorouracil (5-FU) containing adjuvant or first line chemotherapy whilst 31% in the docetaxel and 33% in the MF arm had received MF containing adjuvant or first line chemotherapy (16% in the docetaxel arm and 17% in the MF arm had received both 5-FU and MF containing chemotherapy previously).

Median follow-up of the 99 patients alive at the time of analysis was 11 months (range 4–36).

Treatment compliance

The total number of courses administered was 1645, 887 in the docetaxel and 758 in the MF arm. The median number of courses per patient was 6 (range 1–20) in the docetaxel and 4 (range 1–19) in the MF arm. The median relative given dose per course (given dose per course/planned dose per course) was 99% in both groups with ranges of 54–106% and 44–111% in the docetaxel and MF groups, respectively. The median relative dose-intensity (given dose per time/planned dose per time) was 95% (range 40–103%) in the docetaxel and 94% (range 41–103%) in the MF group. 8 patients in the docetaxel group received a starting dose of 75 mg/m^2 because of elevated liver enzymes at baseline.

Time to progression

The median TTP was 6.3 months (range 2 days–19 months) in the patients treated with docetaxel and 3.0 months (range 6 days–29 months) in the MF arm ($P < 0.001$) (Figure 2). The significance level was the same in the evaluable patient population ($n = 265$). In all the efficacy subgroup analyses (listed in the statistics section), the median TTP was significantly longer in the docetaxel group and the difference was largest in the subgroup of patients with metastases at only one organ site (7.2 versus 2.9 months; $P < 0.0001$). In univariate analysis of prognostic factors (shown in Table 2), only WHO performance status less than 2, the presence of bone metastases, ER positivity and docetaxel treatment predicted a longer TTP (Table 3). In the multivariate analysis of these prognostic factors, WHO performance status of 2 predicted a shorter TTP, whilst oestrogen receptor positivity and docetaxel treatment predicted a longer TTP.

Tumour response

The overall response rate (CR + PR) in the intention to treat population was 42% in the docetaxel and 21% in the MF arm ($P < 0.001$) (Table 4). If the 14 cases non-evaluable for treatment response were excluded, the corresponding response rates were 46 and 22%, respectively. In 15 patients (8 in the docetaxel group and 7 in the MF group) PR or CR response was not confirmed within 4–6 weeks as stated in the protocol.

Table 3. Univariate and multivariate analyses of the correlation of patient and tumour prognostic factors on TTP

		Univariate		Multivariate analysis	
Factor	*n*	Relative risk (95% CI)	*P* value	Relative risk (95% CI)	*P* value
Treatment group	282				
MF versus docetaxel		1.72 (1.32–2.23)	<0.001	1.60 (1.17–2.17)	0.003
Peformance status	282				
1 versus 0		1.03 (0.77–1.39)	0.80	1.10 (0.78–1.57)	0.58
2 versus 0		1.90 (1.26–2.83)	0.002	1.73 (1.08–2.77)	0.022
Bone metastases	281				
Yes versus no		0.68 (0.52–0.88)	0.004	0.75 (0.54–1.03)	0.08
ER	211				
Positive versus negative		0.69 (0.50–0.93)	0.02	0.73 (0.53–1.01)	0.06

TTP, time to progression; CI, confidence interval; MF, methotrexate and 5-fluorouracil; ER, oestrogen receptor.

Table 4. Response to treatment

Response	Docetaxel $n=143$ n (%)	MF $n=139$ n (%)
Complete response	12 (8)	4 (3)
Partial response	49 (34)	25 (18)
No change	47 (33)	43 (31)
Progression	26 (18)	62 (45)
Non-evaluable	9 (6)	5 (4)

$P=0.0001$, chi-square test for trends. MF, methotrexate and 5-fluorouracil.

Excluding these responses, the response rates were 37% in the docetaxel group and 16% in the MF group ($P=0.0001$).

Tolerability

280 patients were evaluable for non-haematological safety analysis (3 patients never received treatment in the docetaxel group). 269 patients were evaluable for haematological toxicity analysis since data of haematological nadir-values were missing in 11 patients. Haematological toxicity is reported as both maximal toxicity per patient and maximal toxicity per course and non-haematological toxicity only as maximal toxicity per patient. There were more cases of leucopenia, infections, oedema, peripheral neuropathy, asthenia, nail changes, skin toxicity, stomatitis, alopecia, allergy and diarrhoea in the docetaxel arm (Tables 5 and 6). One patient in the docetaxel group had a mild anaphylactic reaction during the second docetaxel infusion despite premedication. Conjunctivitis was the only side-effect that occurred significantly more often in the MF arm. All the causes of deaths during study treatment were evaluated by an external reviewer. There were 3 treatment related deaths in the docetaxel arm (2 febrile leucopenias and 1 generalised infected erythroderma) and 1 in the MF arm (febrile leucopenia) (Table 1). In the patient classified as dying from generalised skin toxicity docetaxel treatment was continued despite skin and nail toxicity, fluid retention, mucositis and febrile neutropenia occurring at her fourth course. After her fifth course she developed a generalised ulcerating skin reaction, mucositis, extreme fatigue, massive oedema (15 kg gain of weight in 19 days) and leucopenic fever.

Reasons for treatment discontinuation

At the time of analysis 14 patients were still on treatment with the first trial medication. The reasons for treatment discontinuation in the other 269 patients are reported in Table 1. Treatment discontinuation due to toxicity was more

Table 5. Non-haematological adverse events

	Percent of evaluable patients ($n=280$)							
	Grade 1		Grade 2		Grade 3		Grade 4	
	Docetaxel	MF	Docetaxel	MF	Docetaxel	MF	Docetaxel	MF
Nausea	23	24	23	22	6	10	0	1
Stomatitis*	28	31	26	9	6	4	3	1
Diarrhoea†	17	16	34	20	10	9	0	1
Conjunctivitis‡	5	12	7	14	0	1	0	0
Infection*	16	18	23	13	23‖	6‖	3	0
Fluid retention*	22	16	37	9	3	2	ND	ND
Peripheral neuropathy*	24	6	19	0	5	1	0	0
Asthenia*	5	3	23	6	12	2	0	0
Skin toxicity*	25	12	11	5	1	0	1	0
Alopecia*	4	21	17	11	71	16	3	1
Nail toxicity*	13	2	15	0	5	0	0	0
Local phlebitis	10	11	4	6	1	0	0	0
Allergy§	14	4	0	1	1	0	1	0

*$P<0.001$, worse in the docetaxel arm. †$P<0.05$, worse in the docetaxel arm. ‡$P<0.01$, worse in the MF arm. §$P<0.01$, worse in the docetaxel arm. ‖Includes febrile neutropenia. ND, not defined; MF, methotrexate and 5-fluorouracil.

Table 6. Haematological adverse events

	Grade 1		Grade 2		Grade 3		Grade 4	
	Docetaxel	MF	Docetaxel	MF	Docetaxel	MF	Docetaxel	MF
	Per cent of evaluable patients ($n=269$)							
Leucopenia*	5	21	14	25	35	13	42	3
Thrombocytopenia	7	3	0	4	2	2	1	4
Anaemia	38	24	11	18	2	2	0	0
	Per cent of courses ($n=1474$)							
Leucopenia	8	19	18	13	44	4	15	1
Thrombocytopenia	1.4	1.8	0.4	1.5	0.3	0.4	0.1	0.6
Anaemia	19	18	3	5	0.4	0.3	0	0

*$P<0.0005$, worse in the docetaxel arm. MF, methotrexate and 5-fluorouracil.

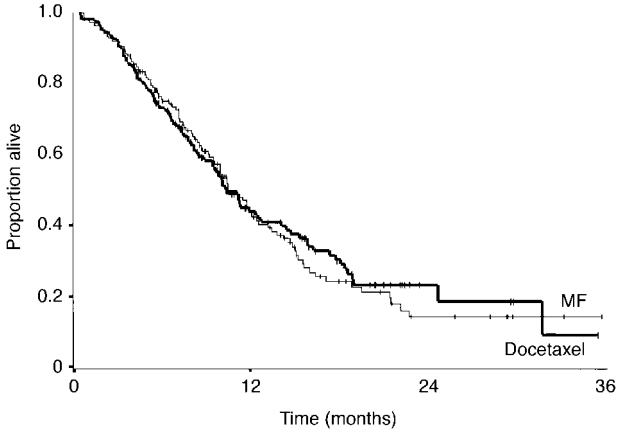

Figure 3. Overall survival (OS) with docetaxel versus methotrexate and 5-fluorouracil (MF) $n = 282$, $P = 0.79$.

common in the docetaxel arm (30 pts) mainly due to cumulative toxicities, i.e. oedema (14 pts), peripheral neuropathy (7 pts) or both (6 pts). Of the 34 patients who discontinued treatment due to toxicity, 22 of 30 (73%) in the docetaxel arm and 2 of 4 (50%) in the MF arm had received 6 or more cycles of treatment.

Crossover treatment

At the time of analysis 122 patients were evaluable for crossover response. 38 patients were still in remission on the allocated treatment, which implies that 50% of eligible patients were actually crossed over. 74 patients were crossed over to docetaxel of whom 27% responded (CR + PR) and 48 patients to MF of whom 12% responded ($P = 0.03$).

Overall survival

In this crossover designed study a similar overall survival was observed in the two arms (Figure 3). Median overall survival was 10.4 in the docetaxel and 11 months in the MF arm. The difference in survival remained non-significant even after exclusion of the 16 ineligible patients ($P = 0.86$).

DISCUSSION

The results of the present study demonstrate the superiority of docetaxel over MF in terms of time to progression and response rate. Overall survival was the same in both arms. However, we were unable to assess the impact of docetaxel alone on survival, since patients were encouraged to crossover upon progression to their originally assigned treatment. After progression the patients in the MF arm were more frequently crossed over to the alternative treatment. Moreover, the response rate of docetaxel was significantly higher than MF after crossover. Thus, any potential survival advantage due to the higher efficacy of docetaxel may have been offset by the better results of crossover treatment in the MF group. The reason why fewer patients in the docetaxel arm were crossed over could not be ascertained, since reasons for not giving crossover treatment were not recorded in the case report forms.

Our results are similar to those of a study reported by Nabholtz and colleagues comparing mitomycin C-vinblastine to docetaxel in a study with almost identical inclusion criteria [15].

In accordance with the present study, Nabholtz and colleagues observed higher response rates (30 versus 12%) and longer TTP (19 versus 11 weeks) for patients randomised to docetaxel. In that study the docetaxel group also experienced a significantly prolonged survival (11.4 versus 8.7 months). The preliminary results of another randomised study by Chan and colleagues, comparing single agent docetaxel to doxorubicin at a dose of 75 mg/m^2 after failure on alkylating agents, has also recently been published [16]. The response rate was higher in the docetaxel group (47 versus 32%).

The higher efficacy of docetaxel was achieved at the cost of a less favourable toxicity profile. A higher fraction of patients had to discontinue the treatment due to side-effects in the docetaxel arm. The better efficacy of docetaxel and the design of an unlimited number of cycles contribute to a high incidence of treatment discontinuation due to toxicity, rather than due to progression. However, only 29% of patients who discontinued due to toxicity had received less than the planned 6 cycles. The high rate of grade 3 or 4 (26% of pts) infections in the present study group might partly be due to the fact that febrile neutropenia without bacteriological documentation was included in the infection rate. The low incidence of severe nausea and vomiting in both treatment arms was notable despite no routine prophylactic antiemetic treatment except the corticosteroid premedication in the docetaxel arm. The incidence of grade 2 oedema (distention or dyspnoea) was high in the docetaxel arm (37 versus 9% in the MF arm) but the incidence of grade 3 oedema (rest dyspnoea, significant impairment) was low and similar in both treatment arms. We observed only one very mild allergic reaction to docetaxel. 2 of the 3 treatment related deaths in the docetaxel group were due to febrile leucopenia and one due to generalised skin toxicity complicated by leucopenic infection. However; some patients did receive 10–20 courses of docetaxel without any severe toxicity indicating a considerable inter-individual variability in the incidence of side-effects. There was one treatment related death due to febrile leucopenia in the MF group.

The relatively high incidence of side-effects may reflect our inclusion of patients with grossly elevated liver enzymes [14]. Although the starting dose of docetaxel in these patients was reduced by 25% at the latter part of the study, 16 patients with elevated liver enzyme values were randomised before the protocol was amended. The decision to include patients with compromised liver functions reflects our commitment to conduct the study in patients representing the common clinical setting.

Another source of increased toxicity, particularly stomatitis in the docetaxel group, may have been the 5-day corticosteroid premedication. Recent reported studies have confirmed that a 3-day regimen is equally effective in preventing toxicity, but is associated with significantly fewer complications [17].

Despite these considerations, however, it is obvious that the toxicity with docetaxel was more pronounced than with MF, and that the toxicity profile of docetaxel requires special attention by the physician in order to optimise the results of treatment with this drug in advanced breast cancer.

We conclude that single agent docetaxel at 100 mg/m^2 every 3 weeks is preferable to days 1 and 8 MF every 3 weeks in patients with metastatic breast cancer after anthracycline failure. In this setting docetaxel induced more responses, and TTP was significantly and substantially longer. We were unable to identify any subgroup of patients for whom docetaxel was not more efficacious. Toxicities were more frequent with docetaxel than with MF. Taken together with the results

of other recently reported studies, these observations suggest that single agent docetaxel should be considered as the treatment of choice in metastatic breast cancer after anthracycline failure.

1. Clemons M, Leahy M, Valle J, *et al*. Review of recent trials of chemotherapy for advanced breast cancer: studies excluding taxanes. *Eur J Cancer* 1997, **33**, 2171–2182.
2. Clemons M, Leahy M, Valle J, *et al*. Review of recent trials of chemotherapy for advanced breast cancer: the taxanes. *Eur J Cancer* 1997, **33**, 2183–2193.
3. Van Oosterom AT. Docetaxel (Taxotere) an effective agent in the management of second-line breast cancer. *Semin Oncol* 1995, **22**, 22–28.
4. Porkka K, Blomqvist C, Rissanen P, *et al*. Salvage therapies in women who fail to respond to first-line treatment with fluorouracil, epirubicin, and cyclophosphamide for advanced breast cancer. *J Clin Oncol* 1994, **12**, 1639–1647.
5. Fisher B, Redmond C, Dimitrov NV, *et al*. A randomized clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node-negative breast cancer who have estrogen-receptor-negative tumors. *N Engl J Med* 1989, **320**, 473–478.
6. Gewirtz AM, Cadman E. Preliminary report on the efficacy of sequential methotrexate and 5-fluorouracil in advanced breast cancer. *Cancer* 1981, **47**, 2552–2555.
7. Herrmann R, Manegold C, Schroeder M, *et al*. Sequential methotrexate and 5-FU in breast cancer resistant to the conventional application of these drugs. *Cancer Treat Rep* 1984, **68**, 1279–1281.
8. Kaye SB, Sangster G, Hutcheon A, *et al*. Sequential methotrexate plus 5-FU in advanced breast and colorectal cancers: a phase II study. *Cancer Treat Rep* 1984, **68**, 547–548.
9. Perrault DJ, Erlichman C, Hasselback R, *et al*. Sequenced methotrexate (MTX) and 5-fluorouracil (5FU) in refractory metastatic breast cancer: a phase II study. *Proc Am Soc Clin Oncol* 1983, **2**, 100.
10. Plotkin D, Waugh WJ. Sequential methotrexate-5-fluorouracil (MF) in advanced breast carcinoma. *Proc Am Soc Clin Oncol* 1982, **1**, 80.
11. Plotkin D, Ray M, Chien P. Sequential methotrexate-5-fluorouracil in advanced breast and colorectal cancers: a nonrandomized pilot study. *Proc Am Soc Clin Oncol* 1988, **7**, 25.
12. Tisman G, Wu SJ. Effectiveness of intermediate-dose methotrexate and high-dose 5-fluorouracil as sequential combination chemotherapy in refractory breast cancer and as primary therapy in metastatic adenocarcinoma of the colon. *Cancer Treat Rep* 1980, **64**, 829–835.
13. Miller AB, Hoogstraten B, Staquet M, *et al*. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
14. Bruno R, Hille D, Riva A, *et al*. Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. *J Clin Oncol* 1998, **16**, 137–196.
15. Nabholtz J, Thuerlimann B, Bezwoda WR, *et al*. Taxotere versus mitomycin C plus vinblastine in patients with metastatic breast cancer who have failed an anthracycline-containing regimen. *Proc Am Soc Clin Oncol* 1998, **17**, 390.
16. Chan S, Friedrichs K, Noel D, *et al*. A phase III study of Taxotere (T) versus doxorubicin (D) in patients (pts) with metastatic breast cancer (MBC) who have failed an alkylating containing regimen. *Breast Cancer Research and Treatment* 1997, **23**, 1.
17. Riva A, Fumoleau P, Roché H, *et al*. Efficacy and safety of different corticosteroid premedications in breast cancer patients treated with Taxotere®. *Proc Am Soc Clin Oncol* 1997, **16**, 188a.

Acknowledgements—The study was conceived and conducted by the Scandinavian Breast Group and supported by Rhône-Poulenc Rorer S.A. Antony, France. The following physicians entered patients onto this study: Johan Ahlgren, Örebro; Gun Anker and Per Eystein Lønning, Bergen; Gudjon Baldursson and Helgi Sigurdsson, Reykjavik, Nils-Olof Bengtsson, Umeå; Jonas Bergh and Sigrid Sjögren, Uppsala; Carl Blomqvist and Johanna Sjöström, Helsinki; Carl Gadeberg, Vejle; Jörgen Hansen, Västerås; Reino Heikkilä and Ingvil Mjaaland, Stavanger; Ragnar Hultborn, Susanne Ottosson-Lönn, Gothenburg; Anita Kupp and Vahur Valvere, Tallinn; Ebbe Lindegaard Madsen, Sønderborg; Per Malmström and Margareta Palm-Sjövall, Lund; Henning Mouridsen, Copenhagen; Dagny Pettersson Skiöld, Stockholm; Preben Philip, Næstved; Anna Pluzanska, Lodz; Terje Risberg and Erik Wist, Tromsø; Carsten Rose Odense; Martin Söderberg, Karlstad; Lena Tennvall, Malmö; and Bjørn Østenstad, Oslo. We thank Tom Wiklund, Helsinki for an external review, study nurse Hannele Sara and secretaries Maaret Helintö and Minna-Liisa Luoma. The source data verification for the study was performed by Rhône-Polenc Rorer.