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Original Paper

Docetaxel: Response in Patients who Have Received at Least Two Prior Chemotherapy Regimes for Metastatic Breast Cancer

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It is unusual to obtain responses after two different sequential regimens in patients with metastatic breast cancer. In this retrospective analysis, data were examined on 22 patients who had already received two or three different regimens for metastatic breast cancer before being treated with 100 mg/m^2 docetaxel (or 75 mg/m^2 if clinically warranted). 13 patients received three or more courses and 21 patients were assessable for response. 5 of 21 assessable patients (24%) responded for 3–11 months and a further 6 (29%) stabilised. Toxicity (WHO grade 3 and/or 4), principally neutropenia, stomatitis and fluid retention, occurred in 10 patients. We conclude that docetaxel is an active agent in heavily pretreated patients with metastatic breast cancer, but care should be taken to minimise side-effects in this group of patients. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

BREAST CANCER is a major health problem worldwide and is the most common malignant disease of women in the Western world. In spite of increased adjuvant treatment and falling mortality rates, the incidence of breast cancer is increasing, so that it is estimated that 1 in 12 women will develop the disease in their lifetime and a large proportion of these will die from metastatic disease, despite cytotoxic chemotherapy [1].

Treatment of metastatic breast cancer with single agent or combination chemotherapy is generally disappointing. In spite of the number of drugs available achieving good response rates, they often have little impact on survival [1]. With any agent or combination, the main aim should be that of palliation, treating to control symptoms, improve quality of life and hopefully prolong survival.

Docetaxel is a semisynthetic taxoid derived from an inactive precursor obtained from the needles of the European yew tree *Taxus baccata*. It acts to promote tubulin assembly in microtubules, thus inhibiting their depolymerisation. This results in stable, non-functional microtubule bundles, disrupting mitosis and hence cell division. Preclinical studies suggested a wide spectrum of activity in animal tumour models [2], and in phase I trials responses were seen in patients with metastatic breast cancer previously refractory to other agents. The recommended dose following phase I trials was 100 mg/m^2 as an infusion over an hour every 3 weeks (for a review see [3]).

Several phase II studies have been published using docetaxel in metastatic and locally advanced breast cancer, showing an overall response rate between 54 and 68% when used as a first line single agent for metastatic disease [4–6]. This is comparable with response rates seen with doxorubicin, which has been thought of as the most effective single agent in metastatic breast cancer. Other phase II trials used docetaxel in a variety of patient groups with metastatic breast cancer, not only as first line therapy but also in patients who had had one or two previous chemotherapy regimes for metastatic disease in addition to adjuvant treatment. As a second line agent, an overall response rate of 58% was seen [7]. Even in anthracycline resistance, docetaxel has shown an overall response rate of 57% [8] and 53% [9]. None of the studies looked at the very heavily pretreated group separately

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and, although these patients were certainly included in some studies, it is unclear what the response rate is in these patients. We therefore decided to undertake a retrospective study in our own institution of those patients treated with docetaxel as a third or fourth line agent for metastatic breast cancer looking specifically at its efficacy and tolerability, since responses are rarely observed after two prior chemotherapy regimes using conventional cytotoxics [10].

PATIENTS AND METHODS

Between September 1995 and December 1996 inclusive, 22 patients with locally advanced or metastatic breast cancer were treated with docetaxel chemotherapy at Charing Cross Hospital. All had received two or more chemotherapy regimes for locally advanced or metastatic disease in addition to adjuvant therapy (tamoxifen or chemotherapy), prior to treatment with docetaxel. Details of the patients are shown in Table 1.

According to hospital protocol, patients were given 100 mg/m^2 docetaxel as a starting dose. This was modified to 75 mg/m^2 for abnormal liver function (transaminases in excess of twice the upper limit of normal) or poor performance status (WHO 3). It was administered as an intravenous infusion over an hour every 3 weeks with dexamethasone 16 mg orally daily for 1 day prior to and 4 days after docetaxel. Dose reductions to 75 mg/m^2 and 55 mg/m^2 were undertaken for a variety of reasons, including febrile neutropenia, neutrophil count < 0.5 for at least 5 days, severe fluid retention, cutaneous reactions and peripheral neuropathy (see Toxicity).

Table 1. *Patient characteristics*

No. of patients	22
Assessable for response	21
Assessable for toxicity	22
Age (years)	
Range	34–68
Median	48
Sites of disease	
Locoregional	15
Bone	6
Lung	8
Liver	9
Other	
Choroidal	1
Adrenal	1
Cerebral	1
No. of sites involved	
1	7
2	9
> 2	6
ER status of primary	
Negative	9
Positive	4
Unknown	9
Prior therapy	
Adjuvant	
Endocrine (tamoxifen)	12
Chemotherapy (CMF)	4
Metastatic	
Endocrine agents	17
Anthracycline-containing regimen	18
Anthracenedione-containing regimen	15
Non-anthracycline-containing regimen	11
First line chemotherapy	
Anthracycline-containing	15
Non-anthracycline-containing	7
Second line chemotherapy	
Anthracycline-containing	14
Non-anthracycline-containing	8

ER, oestrogen receptor; CMF, cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2.

The patients were assessed for response and toxicity at each cycle of treatment. Assessment was by 3-weekly clinical examination and by radiological scans performed before treatment, after three cycles, and at the end of treatment or at relapse.

Criteria for response

WHO criteria were used for the definition of response and response duration [10]. A complete response (CR) was defined as the complete resolution of all detectable disease for at least 4 weeks. A partial response (PR) was defined as a reduction of 50% or more of the sum of the perpendicular diameters of all measurable lesions without progression at an alternative site for at least 4 weeks. Progressive disease (PD) was that in which measurable lesions reached 25% or greater of the sum of the perpendicular diameters, or the development of disease at a new site. Stable disease (SD) was that which fell between a PR and PD.

Response duration was defined as from the date the criteria were first met to documented date of progression.

Toxicity

Toxicity was evaluated using WHO criteria. Haematological counts were performed on the day of treatment. Mid-cycle counts were performed if clinically indicated.

RESULTS

Although all patients were evaluated for toxicity, only 21 were evaluable for response, as 1 patient stopped treatment due to a bleeding gastric ulcer after one course of docetaxel and dexamethasone and subsequently received paclitaxel. Patient characteristics are shown in Table 1.

The age range was 34–68 years. Performance status was not always documented, but the majority were 0–2. 15 patients had multisite disease, mainly locoregional disease (68%) with or without further metastatic spread. Of note, 17/22 had liver and/or lung metastases. 4 patients had locally advanced disease at initial presentation and thus prior chemotherapy had been neoadjuvant or primary medical therapy. All had received both an anthracycline-containing and a non-anthracycline-containing regimen (see Tables 1 and 2). Regimes were standardised: FEC: 5-fluorouracil 600 mg/m^2, epirubicin 50 mg/m^2 and cyclophosphamide 600 mg/m^2 given three weekly; MMM: mitomycin C 8 mg/m^2, methotrexate 30 mg/m^2 and mitozantrone 8 mg/m^2; CMF: cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2, epirubicin single agent at 75 mg/m^2 every 3 weeks. 3 patients had had prior radio-

Table 2. *Response to previous chemotherapy*

	Complete response	Partial response	Stable disease	Progressive disease
First line metastatic	0	7	8	7
Second line metastatic	0	7	4	11
Third line metastatic	0	1	1	3

Table 3. Dose of docetaxel administered

Total no. of courses	No. of patients
1	3
2	4
3	2
4–6	11
>6	2
Start dose (mg/m^2)	
100	12
75	7*
55	3†
Dose reductions (mg/m^2)	
from 100	7
from 75	4

*Due to poor performance status (3), fluid retention (1) and extensive liver metastases (3). †Extensive previous treatment for visceral and bone metastases.

therapy to a disease site, but all had assessable disease elsewhere.

Docetaxel therapy commenced at full dose (100 mg/m^2) in 12 of the 22 patients. In 7 of these 12 patients (58%) treatment was reduced to 75% and 4 (57%) of these needed further dose reduction (to 55 mg/m^2) due to toxicity (Table 3). The mean and median number of cycles administered was four.

Response

One patient achieved a CR and 4 achieved PRs, i.e. an overall response rate of 24% (Table 4). One of the patients with a PR had complete radiological resolution of her liver metastases. The majority of patients (5/6) who had disease stabilisation actually showed tumour regression, especially of locoregional disease, but did not fulfil the criteria of a PR. 3 patients had a PR or CR at initial disease sites but developed meningeal or cerebral disease during treatment after the response was documented. 10 patients had PD.

There were 4 responses (1 CR, 3 PRs) in those patients starting at full dose, and only 1 response in the dose reduced group (a patient with liver disease rather than poor performance status).

Toxicity

All patients had some evidence of toxicity, especially grade 1 or 2 side-effects (Table 5) that are common with docetaxel, such as alopecia, skin and nail changes and mild oedema. The most serious side-effect was neutropenia, with febrile neutropenia occurring in 5 patients (all grade 3 or 4), 1 with life threatening *Listeria* pneumonia. Fluid retention occurred in 5 patients. Toxicity was, however, sufficient to be responsible for dose reductions in the majority of patients during treatment.

Table 4. Response and duration of response to docetaxel

Response	No. of patients (%)	Duration (months)
Complete response	1 (5)	7
Partial response	4 (19)	11,4,3,5
Stable disease	6 (29)	3,4,2,4,4,3
Progressive disease	10 (48)	
Non-assessable	1	

Table 5. Side-effects of docetaxel therapy

	Toxicity (using WHO criteria) (n = 22)				
	0	1	2	3	4
Alopecia	3	5	14	0	0
Nausea and vomiting	20	2	0	0	0
Haematological	12	0	5	1	4
Stomatitis/ulceration	18	2	0	1	1*
Fluid retention	17	1	3	1	0
Malaise	13	6	3	0	0
Neuropathy	21	1	0	0	0
Infection	16	0	1	3	2†

*Acute gastrointestinal bleed. †*Listeria* pneumonia.

DISCUSSION

Our study demonstrates that, in heavily pretreated patients with advanced breast cancer, docetaxel achieves an interesting response rate of 24%. This is understandably worse than the response rate observed in patients with less heavily pretreated metastatic disease, where patients generally received docetaxel at 100 mg/m^2 every 3 weeks [5–8]. Ravdin and colleagues reported a study of docetaxel in advanced anthracycline or anthracenedione resistant breast cancer in which all patients had received one or two prior chemotherapy regimes for metastatic disease in addition to adjuvant chemotherapy [8]. The response rate seen was 57%, but there was no information on how many of the patients included in the analysis had been given two rather than only one prior treatment for metastatic disease. Of note in the study, 95% of patients experienced at least one episode of grade 4 neutropenia, but the duration of docetaxel-induced neutropenia was short-lived.

A French group reported a large study to test tolerability to docetaxel in patients given between one and 12 prior chemotherapy treatments [11]. Docetaxel 30–175 mg/m^2 was used, but there were no response data. Eighty-seven per cent of the patients experienced grade 4 neutropenia, 27% had febrile neutropenia and their conclusion was good tolerability of the drug.

The majority of our patients were treated with a reduced dose of docetaxel, either at the start or during the course of treatment due to poor initial performance status or extensive liver metastases or toxicity, respectively, and this may have contributed to the reduced efficacy in our series. However, a Japanese study [12] used 60 mg/m^2 in a phase II trial and showed a response rate of 44.4% as first or second line therapy for metastatic disease, and Dieras and associates [13] reported a 50% overall response rate with 75 mg/m^2 as first line therapy. There may be a trend towards increased efficacy with increased dose, but as our study shows, it may not be easy to compare response rates from relatively chemotherapy naive patients with those from heavily pretreated patients.

Serious side-effects seen in our patients were neutropenia and infectious complications. Malaise, although of grade 1–2, was reported in nearly half the patients. Fluid retention was reported less than expected and was only mild in our study. This may have been due to the use of dexamethasone prophylaxis which also has other side-effects, e.g. restlessness, agitation, dyspepsia and sleep disturbance. In our series, 1 patient had a major gastrointestinal haemorrhage after the first course of docetaxel and a large gastric ulcer was found on endoscopy.

Our study was unable to assess quality of life and none of the studies published so far have had that information. Even the recently undertaken 'Compassionate Use' programme, which allowed free access to docetaxel for patients with metastatic breast cancer in the U.K. had no quality of life questionnaire. In treating metastatic breast cancer, even if a response is achieved, response duration is usually measured in months, so drug toxicity and quality of life become extremely important.

Further studies should, we believe, focus on the development and validation of a suitable quality of life instrument that can be used with accuracy in patients receiving taxanes. The outcome of these investigations should assist clinicians in making decisions about therapy in heavily pretreated patients with metastatic breast cancer.

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