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CLINICAL TRIAL REPORT

Dose-finding study of weekly docetaxel, epirubicin and capecitabine, as first-line treatment in advanced breast cancer

S. H. Waters · A. Gillibrand · H. Berry · S. Kumar · G. Velikova · D. J. Dodwell · Timothy J. Perren

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Abstract
Background Combinations of anthracycline, taxane and fluoropyrimidine are highly active in advanced breast cancer (ABC). In a phase II study of epirubicin 50 mg/m^2, docetaxel 75 mg/m^2, and infusional 5-FU 200 mg/m^2/day, we found dose-limiting neutropenia and frequent central venous catheter complications. An alternative approach has been tested using weekly fractionation of docetaxel, and oral capecitabine.
Methods Initially, six women with ABC were treated with epirubicin 60 mg/m^2 day 1, docetaxel 25 mg/m^2 days 1,8,15, and capecitabine 1,000 mg/m^2 twice daily days 1–14, every 21 days. Six further patients received the above with capecitabine escalated to 1,500 mg/m^2
Results Four DLTs occurred in six patients at the second dose level (febrile neutropenia in 2). There were frequent dose delays/reductions, and fatigue, nausea/vomiting, and diarrhoea were common. Overall, six of ten assessable patients achieved a partial response.
Conclusions An active regimen, but significant haematological toxicity precluded dose further escalation.

Keywords Anthracyclines · Antineoplastic combined chemotherapy protocols · Breast neoplasms · Capecitabine · Taxoids

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S. H. Waters · A. Gillibrand · H. Berry · S. Kumar · G. Velikova · D. J. Dodwell · T. J. Perren (✉)
St James's Institute of Oncology, Beckett Street, Leeds LS9 7TF, UK
e-mail: t.j.perren@leeds.ac.uk

Introduction

Combination chemotherapy for advanced breast cancer continues to attract attention because of the ability to achieve higher response rates than with single agent cytotoxics. The greatest benefits may be in untreated patients with advanced metastatic disease or aggressive local disease in the neoadjuvant setting. One particularly active regimen in advanced breast cancer is the ECF regimen of epirubicin 50 mg/m^2, cisplatin 60 mg/m^2 and infusional 5-FU 200 mg/m^2/day. In phase II studies, response rates of 84 and 98% have been reported in the metastatic/locally advanced and large, but operable carcinoma settings, respectively. This regimen was subsequently modified by escalation of the dose of epirubicin to 60 mg/m^2 and used in a randomised phase III clinical trial of primary chemotherapy in patients with large, but operable breast cancer [1].

We have previously reported a phase II study where the taxane docetaxel (T) was substituted for cisplatin, hoping to improve the patient experience by removing the necessity for inpatient treatment [2]. In 51 patients with recurrent or metastatic breast cancer, the ETF regime had a response rate of 73%. Unfortunately, there was a high rate of febrile neutropenia (39% of patients) encountered at the first dose level, and frequent central venous catheter complications.

In parallel initiatives, other groups were investigating the use of weekly rather than three weekly schedules of docetaxel, and found it to be associated with a more favourable toxicity profile, including reduction in the incidence of severe neutropenia and infections [3–5]. Preclinical studies had also provided a rationale for weekly fractionation of taxanes in terms of avoiding interval re-growth of cancer cells, and exploiting potential anti-angiogenic and anti-apoptotic effects [6].

In addition, the introduction of the tumour activated oral fluoropyrimidine capecitabine, allowed construction of a

regimen that would not only obviate the need for central venous catheters, but might exploit the pre-clinical synergy noted between taxoids and capecitabine [7, 8]. We postulated, therefore, that altering the ETF regimen by scheduling the docetaxel weekly, and replacing the infusional 5-FU with capecitabine; could avoid the difficulties encountered and provide potential benefits.

Patients and methods

Study objectives and design

The study was planned as a dose-finding matrix phase I study with objectives: to determine the toxicity profile; maximum tolerated doses; and efficacy, of the EDC regimen. Epirubicin was given at a fixed dose of 60 mg/m^2 every 21 days, while doses of docetaxel and capecitabine were escalated as shown in Table 1.

Planned endpoints for the phase 1 study were NCI-CTC toxicity following each cycle of treatment; response and response duration where measurable; and overall survival.

The study was curtailed in the phase I stage, after patients had been entered at two dose levels.

Data collection and analysis

The study was approved by the local research ethics committee and carried out within the Leeds Cancer Centre where the data were collected and analysed. Statistical analysis was performed using SPSS (for Windows version 12.0.1), with survival calculated from date of study entry to date of death from any cause, or last known contact; and progression-free survival from date of study entry to first occurrence of documented evidence of progression of disease, change in treatment, or death. Chemotherapy relative dose intensity is the dose delivered in initiated cycles, expressed as a percentage of the planned patient cohort dose (i.e. the dose before any intrapatient dose escalation).

Patient selection

Eligible patients were aged 18–70 with a histological diagnosis of breast cancer and locally advanced or metastatic disease. Patients with large, but operable primary tumours without evidence of distant metastases were excluded. No patient had received previous chemotherapy for metastatic disease, and no patient had received previous taxanes. Adjuvant anthracycline containing chemotherapy was permitted if completed at least 18 months prior to study entry, and if not exceeding a cumulative dose of 300 mg/m^2 of doxorubicin, or 400 mg/m^2 of epirubicin. All patients had World Health Organization performance status 2 or better with projected life expectancy of at least 12 weeks. Adequate bone marrow, hepatic and renal function were required along with adequate cardiac function as defined by left ventricular ejection fraction of >50%. During the dose escalation phase of this study patients were not required to have measurable disease. Patients who were pregnant or breast feeding were excluded. Written informed consent was required before study entry.

Dose escalation

Dose-limiting toxicity (DLT) was defined as any of the following occurring during the first two cycles of chemotherapy: grade 3 or greater non-haematological toxicity (excluding alopecia); grade 4 neutropenia; grade 3 thrombocytopenia; or any event leading to >20% reduction in a planned dose of any drug or interruption to planned doses of capecitabine of more than 7 days. Three patients were planned to be treated at each dose level. If one of the three experienced a DLT, three further patients were to be recruited at that dose level. In the event, that no additional patients experienced DLT, the dose would be escalated to the next dose level. Otherwise, the maximum tolerated dose would be declared.

Treatment protocol

Epirubicin was administered as a slow intravenous bolus on day 1 of each 21-day treatment cycle, immediately prior to docetaxel. Docetaxel was administered as a 1 h intravenous infusion and given on days 1, 8 and 15 of cycles 1, 3 and 5, and on days 1 and 8 only of cycles 2, 4 and 6. Dexamethasone prophylaxis was administered in a dose of 8 mg orally 12 h pre-, 8 mg IV 1 h pre-, and 8 mg orally 12 h post-docetaxel. Capecitabine was administered orally twice

Table 1 Chemotherapy dose levels

	Dose level 1 (mg/m^2)	Dose level 2 (mg/m^2)	Dose level 3 (mg/m^2)	Dose level 4 (mg/m^2)	Dose level 5 (mg/m^2)
Epirubicin	60	60	60	60	60
Docetaxel (weekly)[a]	25	25	30	30	35
Capecitabine (daily)	1,000	1,500	1,500	2,000	2,000

[a] Days 1 and 8 only in cycles 2, 4, 6

daily in divided doses, on days 1–14 of each treatment cycle; it was taken within 30 min of food ingestion and swallowed with water. All patients received prophylactic anti-emetics and non-steroidal anti-inflammatory drugs for arthralgia or myalgia related to docetaxel, if required.

Each patient was planned to receive six cycles of treatment. At the discretion of the investigator, patients experiencing no significant toxicity during the first two cycles were eligible for dose escalation by a single dose level for the remainder of their treatment. Treatment was initially delayed 1 week in case of low neutrophil or platelet counts (Supplementary Table 1), and doses were reduced for prolonged haematological or grade 3/4 non-haematological toxicity.

Before the first dose of treatment all patients had the following: physical examination including neurological examination; measurement of height, weight and performance status; measurement of full blood count, electrolytes, liver function and bone biochemistry; calculation of glomerular flow rate according to the Cockcroft and Gault formula [9]; assessment of left ventricular ejection fraction by echocardiogram or MUGA (multiple uptake gated acquisition) scan; assessment of measurable and evaluable disease by chest X-ray and cross-sectional imaging.

Throughout the treatment programme, all patients had full blood counts measured weekly. Physical examination, further biochemistry and NCI-CTC toxicities were measured every 3 weeks. Assessment and imaging of measurable and evaluable disease were performed every three cycles. Response was assessed according to RECIST criteria [10].

Results

Patient characteristics

Twelve patients were registered between April 2002 and February 2005: six were treated at dose level 1 (DL1) and 6 at DL2. The majority of patients had symptomatic metastatic disease and were chemotherapy naïve, as shown in Table 2.

Table 2 Patient characteristics

	Dose level 1 ($n = 6$)	Dose level 2 ($n = 6$)
Age		
Median	53.5	52.5
Range	33–65	41–60
Stage		
Locally advanced only	1	2
Metastatic	5	4
Performance status		
0	3	5
1	3	1
Symptomatic	4	5
Sites of disease		
Breast	3	5
Axilla	2	4
Chest wall	1	0
Bone	4	2
Lung	1	2
Mediastinum	0	2
Liver	1	2
Para-aortic nodes	1	2
HR status		
ER+/PR+	3	4
ER+/PR−	1	0
ER−/PR−	2	2
HER-2 status		
Positive	0	1[a]
Negative	6	5
Prior chemotherapy		
Non-antrhacycline	0	1
Anthracycline	1[b]	1
Prior radiotherapy		
Adjuvant	0	1
Consolidation	0	2
Palliative	0	1
Prior hormones		
Adjuvant tamoxifen	2	2
Metastatic tamoxifen	1	1
Metastatic fulvestrant	1	0

[a] Recorded after trial entry

[b] For pregnancy-associated inflammatory cancer, bone metastases present at diagnosis

Dose level 1 delivery

Six patients were treated with a total of 28 cycles of chemotherapy (median 5, range 3–6).

Two patients received all six cycles and four were withdrawn early. Reasons for withdrawal were progression of disease in three patients (2 at cycle 3, and 1 at cycle 5); requirement for laparotomy for diverticular abscess in one patient during cycle five (see below).

No cycles of chemotherapy were delayed.

Four patients had dose escalation from cycle 3 onwards: two of these completed six cycles of treatment, one required subsequent dose reduction, and one stopped treatment after cycle 3.

Table 3 Worst haematological toxicity

	Number of cycles affected (%)		Number of patients affected (%)	
	DL1 28 cycles total	DL2 32 cycles total	DL1 $n = 6$	DL2 $n = 6$
Grade 3 neutropenia	5 (18)	14 (43)	4 (67)	2 (33)
Grade 4 neutropenia	0	7 (22)	0	4 (67)
Febrile (G4) neutropenia	0	2 (6)	0	2 (33)

The two remaining patients each had dose reductions on two occasions (cycles 2 and 3).

The relative dose intensity of epirubicin was 96%; of docetaxel 95%; and of capecitabine 107%.

Dose level 1 toxicity

All six patients were fully evaluable for dose-limiting toxicities (DLT) during cycles 1 and 2.

Amongst the first cohort of three patients treated at dose level 1, DLT was reached during the second treatment cycle in the third patient entered. She developed grade 3 non-neutropenic infection, and went on to develop further grade 3 non-neutropenic infection and diarrhoea in both cycles 3 and 4. This complication was later discovered to be due to a diverticular abscess that was diagnosed by imaging and confirmed by subsequent laparotomy. Three further patients were, therefore, entered into dose level 1. Overall, during the cycles used to evaluate DLT, the most severe haematological toxicity was non-febrile grade 3 neutropenia which occurred in 1 cycle (of 12).

Amongst all 28 cycles received by the six patients treated at dose level 1, grade 3 neutropenia occurred in five cycles, affecting four patients. No febrile grade 3 neutropenia was seen and no grade 4 neutropenia. Grade 3 anaemia affected one patient. No grades 3/4 thrombocytopenia was seen (Table 3).

Non-haematological toxicity was mild though common, with 64% of cycles associated with grades 1 or 2 fatigue and 54% with grades 1 or 2 nausea (detailed in Supplementary Table 2).

Dose level 2 delivery

Six patients received a total of 32 cycles of chemotherapy at dose level 2.

Five patients received all six cycles. One patient withdrew after cycle 2 because of grade 3 diarrhoea requiring prolonged hospitalisation.

Nine cycles were delayed, and only one patient completed all six cycles without delay.

One patient had a dose escalation in cycle 3; however, she required dose de-escalation from cycle 4. Four further patients had dose reductions on 1 occasion in either cycle 3 or 4. The relative dose intensity of epirubicin was 97%; of docetaxel 102%; and of capecitabine 85%.

Dose level 2 toxicity

All six patients were fully evaluable for DLT during cycles 1 and 2.

Amongst the first cohort of three patients treated at dose level 2, DLT was reached during the first treatment cycle in the first patient entered, with febrile grade 4 neutropenia and grade 3 diarrhoea. Three further were, therefore, entered at dose level 2. There were three further DLTs: one patient experienced grade 4 neutropenia in cycle 1; one patient had grade 3 non-neutropenic infection (of uncertain aetiology) in cycle 2; and one patient had grade 3 diarrhoea and grade 3 transaminitis in cycle 1 (possibly related to oral antibiotic therapy with amoxicillin and clarithromycin for a respiratory tract infection). Non-febrile grade 3 neutropenia also occurred in five cycles (3 patients).

Amongst the 32 cycles of chemotherapy received by the six patients treated at dose level 2, grade 3 neutropenia occurred in 14 cycles and affected five patients. None of these episodes were associated with fever. Grade 4 neutropenia occurred in seven cycles and affected four patients; two of these episodes were associated with fever. There was no other grade 3/4 haematological toxicity (Table 3).

Non-haematological toxicity was again mild though common, with 38% of cycles associated with grades 1 or 2 fatigue and 25% with grades 1 or 2 nausea, and 13% with grade 3 nausea (Supplementary Table 2).

Outcome data

Ten patients (5 at each dose level) had measurable disease and have been evaluated for response according to RECIST criteria. Partial response was seen in 6/10 patients (95% confidence interval 26–88%): 1 at DL1; 5 at DL2 (Supplementary Table 3). Median time to progression was 56 weeks (95% CI, 0–122 weeks); and median survival 83 weeks (33–133).

Discussion

The debate about the merits of combination versus sequential single agent treatment for metastatic breast cancer remains active, with a large phase III study showing superior survival with capecitabine–docetaxel compared with docetaxel alone [11]. Interestingly, two phase III trials comparing this combination with sequential treatment have reported opposing preliminary findings [12, 13].

In a small group of patients, we have shown clear antitumour activity, but limiting myelosuppression with the EDC combination. Two-thirds of those treated experienced grade 4 neutropenia, and one-third, febrile neutropenia. In retrospect, the occurrence of grade 4 neutropenia during regular monitoring would be expected, and a less conservative definition of DLT would now seem appropriate. In addition, the doses of docetaxel and capecitabine achieved were significantly lower than their active single agent doses: higher doses might have been reached, had a lower starting dose of epirubicin been selected, or arrived at by dose de-escalation. Nevertheless, the frequency of non-haematological toxicity was worse than with ETF, and unlikely to be acceptable for a palliative treatment. Skin toxicity and diarrhoea were probably limited by the doses of capecitabine achieved.

A number of other studies of these three agents have been performed with differing schedules. Pagani et al. report treatment of 62 patients with varying combinations of anthracycline, docetaxel and fluoropyrimidines, including eight patients with TEX: epirubicin 40 mg/m^2 and docetaxel 35 mg/m^2 day 1 and 8 of a 21-day cycle, with capecitabine 1,650 mg/m^2/day days 1–14 [14]. There were five DLTs including one toxic death, with frequent GI tract toxicity. Dose delays were necessary in four patients, and no dose escalation was performed. In contrast, Venturini et al. have investigated three weekly docetaxel 75 mg/m^2, along with epirubicin 75 mg/m^2 and capecitabine 2,000 mg/m^2/day days 1–14, for their TEX regimen. In phase II, they showed activity comparable with the reference ECF studies, with modest fatigue, nausea and neutropenia (16% febrile) [15]. An interim report from their phase III study comparing TEX to TE, suggests toxicity is similar in both arms with overall less febrile neutropenia (3.5%), although occasional severe diarrhoea (1.5% grade 3/4) [16]. In addition, the Austrian Breast and Colorectal Cancer Study Group have piloted TEX plus pegfilgrastim, as preoperative chemotherapy in patients with large but operable disease only [17]. In 11 patients, six cycles were well tolerated with no grade 4 toxicity or grades 3/4 neutropenia.

Taken together, the evidence suggests that in combination with epirubicin and capecitabine, weekly fractionation of docetaxel increases toxicity: a conclusion at odds with our prior expectation, and with published outcomes of docetaxel–capecitabine combination studies. We note that shortening of the docetaxel treatment in every even cycle (days 1 and 8 only) had no clear impact on haematological toxicity. When used as a single agent, significantly less neutropenia was seen with weekly than 3-weekly schedules of docetaxel, in both the large TAX327 trial in advanced prostate cancer [18], and a recent meta-analysis of palliative treatment of non-small cell lung cancer [19]. However, neither has shown any significant differences in non-haematological toxicity. An alternative approach that may have merit is the replacement of docetaxel with paclitaxel. Here, weekly fractionation has significant theoretical advantages supported by clinical data, including one study of paclitaxel–capecitabine [20].

Despite the encouraging outcome data we have observed, we conclude that the combination of weekly docetaxel, epirubicin and capecitabine in advanced breast cancer, is unlikely to benefit from further evaluation due to dose-limiting neutropenia and frequent mild toxicity, at relatively low doses of individual agents.

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Conflict of interest statement D. Dodwell and T. Perren have received honoraria for advisory work and speaking engagements from Aventis and F. Hoffmann-La Roche, and S.Waters has received training funded by F. Hoffmann-La Roche.

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