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# Docetaxel Alternating with Epirubicin and Cyclophosphamide: a Feasibility Study in Breast Cancer Patients

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**Docetaxel is one of the most active drugs used in the treatment of breast cancer. However, its major side-effect, myelosuppression, hampers full-dose combination chemotherapy. We have, therefore, developed an alternating schedule of docetaxel with epirubicin and cyclophosphamide, together with granulocyte colony-stimulating factor, to ameliorate neutropenia. We studied the feasibility of such a strategy, decreasing the treatment interval from 21 days to 14 days, thus further increasing the dose intensity. As expected, myelosuppression was common, complicated by neutropenic fever, which did not exceed preset criteria. Other side-effects were also as expected: alopecia, malaise, nausea and vomiting. After two alternating courses of chemotherapy, a partial response was documented in 15 of 17 patients. We conclude that this alternating schedule is very active against breast cancer and warrants further phase II studies. © 1997 Elsevier Science Ltd.**

**Key words: docetaxel, alternating chemotherapy, epirubicin, cyclophosphamide, lenograstim, feasibility study**

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## INTRODUCTION

CONVENTIONAL CHEMOTHERAPY for metastatic or recurrent breast cancer no longer amenable to surgical and/or radiation treatment usually provides no more than a partial and transient response. Approximately half of the patients will achieve a partial remission and only 10% a complete remission [1,2]. On theoretical grounds, a higher dose intensity of conventional combination chemotherapy may improve response rates, and indeed several clinical studies have shown this to be the case [3–6]. Whether survival can be improved by dose intensification has yet to be demonstrated. In the past, the dose-limiting toxicity of high-dose chemotherapy was myelosuppression, resulting in severe leucopenia and concomitant infectious complications. However, the duration and severity of these side-effects can be decreased to acceptable levels by the use of haematopoietic growth factors, such as granulocyte colony-stimulating factor (rHuG-CSF [lenograstim]).

Several studies have been performed in recent years to investigate the feasibility of high-dose anthracyclines and cyclophosphamide, two highly active drugs currently available for the treatment of breast cancer [7,8]. In one pilot study, epirubicin administered at a high dose of 120 mg/m$^2$ i.v. push and cyclophosphamide 830 mg/m$^2$ i.v. push every 2 weeks proved to be highly efficacious, with acceptable toxicity [8]. However, mucositis and leucopenia limited further dose escalation or more frequent drug administration.

The currently available taxoids, paclitaxel and docetaxel, form a new class of anticancer agents that are highly active against breast cancer. Reported response rates for single-agent chemotherapy with docetaxel vary between 57% [9,10] and 68% [11,12]. Early phase II studies with docetaxel found tumour responses in patients previously treated with doxorubicin [12,13].

Bone marrow suppression has been the single most important side-effect of docetaxel. Hypersensitivity and skin reactions can be managed by prophylactic comedication with corticosteroids, $H_1$- and $H_2$-receptor blocking agents [14]. Docetaxel-induced oedema and pleural effusion may also be observed after prolonged administration [15], but prophylactic comedication with corticosteroids has reduced the frequency and severity of these reactions [16]. High, cumulative doses of taxoids may also be associated with neurotoxicity although a lower severity and incidence have been reported with docetaxel [11,12,14].

The aim of the present study was to examine the feasibility of an intensified first-line chemotherapy regimen using cycles of docetaxel and a combination of epirubicin and cyclophosphamide with rHuG-CSF support, and decreasing the interval between courses, in advanced breast cancer patients. Phase II and III studies of high-dose intensive treatment

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versus standard chemotherapy are planned, using the experience gained from this study.

## PATIENTS AND METHODS

*Patient population*

Only patients over 18 years of age with World Health Organization (WHO) performance status $\leq 2$ were enrolled in this study. Patients were eligible if they had advanced metastatic breast cancer disease not amenable to treatment strategies other than chemotherapy. Adequate haematological, renal and hepatic functions were required and a complete initial work-up, including bone X-rays, bone and CT scans (to reveal assessable or measurable disease), was performed before the start of treatment. Patients were excluded if they had undergone previous chemotherapy for metastatic disease. Informed, signed consent was obtained from each patient prior to the start of treatment.

*Study design*

The study was non-randomised and single centre. Up to three courses of treatment were given (see treatment schedule below) with the interval between schedules being 21 days in one group of patients and 14 days in the other. At one stage in the study, epirubicin was replaced by doxorubicin because of a lack of availability of the former.

*Treatment schedule*

Each course (cycle) of the chemotherapy regimen consisted of A alternating with B and C:

**A**—docetaxel 100 mg/m$^2$ i.v. given as a 1-hour infusion
**B**—epirubicin 120 mg/m$^2$ i.v. push (or doxorubicin 75 mg/m$^2$) and cyclophosphamide 830 mg/m$^2$ i.v. (in 5–15 min) administered before 1300 hours
**C**—lenograstim 150 μg/m$^2$/day s.c. on days 2–10 after A and B or until the white blood cell (WBC) count rose above $5\times10^9$/l

The dose of docetaxel was based on a body surface area of 2.2 mg/m$^2$ maximally.

*Prophylactic measures*

Prophylactic medication was mandatory to prevent hypersensitivity reactions and other side-effects of docetaxel. The corticosteroid dexamethasone (8 mg per os) was recommended, to be given 13 hours, 7 hours and 1 hour before the docetaxel infusion. The corticosteroid was to be given at the same dose twice daily and continued for 96 hours (4 days; total 7 doses) starting from the evening of the day of infusion.

*Dose modifications*

Dose modifications were made based on nadir values of WBC counts and platelet counts. If WBC counts were $<3.0\times10^9$/l and ANC $<2\times10^9$/l and/or platelets $<75\times10^9$/l, treatment was postponed for 1 week until the WBC count was $>3.0\times10^9$/l and/or platelets $>75\times10^9$/l. If, after a delay of 2 weeks, WBC and platelets counts were still below the threshold of $3.0\times10^9$/l (ANC $\leq2\times10^9$/l) and/or $75\times10^9$/l, respectively, patients were withdrawn from the study. A dose reduction of 25% could be made following a febrile neutropenic episode.

Concomitant radiotherapy on painful metastases was allowed. However, lesions used as response parameters could not be irradiated as this would invalidate the study results.

*Evaluation of response*

Patients were treated for two courses of chemotherapy (i.e. A+B+A+B). A response to treatment (made according to WHO criteria) was then assessed using parameters selected before treatment was started. An additional treatment course (A+B) could be given if a response was documented after the first two courses of chemotherapy.

The feasibility of this treatment approach was accepted if the duration of any neutropenic episode did not exceed grade IV for more than 7 days in 3 out of 5 patients, each evaluated after two courses of chemotherapy, or if no more than three febrile neutropenic episodes were seen in 3 out of 5 patients, for each treatment schedule.

If any other side-effects exceeded grade III (particularly skin reactions or stomatitis) in more than 3 of 5 patients during the 3-week interval therapy, a primary end-point would have been reached. The exceptions to this were nausea, vomiting and hair loss.

## RESULTS

Seventeen patients were treated according to the protocol. The first 13 patients were treated with epirubicin; the next 4 patients were treated with doxorubicin at a dose of 75 mg/m$^2$. The median age of the patients was 45 years (range 34–54). The predominant sites of disease were liver (7 patients), bone (9 patients), soft tissue/skin (11 patients) and lung (6 patients).

As expected, the main toxicity was myelosuppression. Details of nadir values for WBC counts and ANC after the first course of treatment are given in Table 1.

No cumulative haemotological toxicity was seen in subsequent treatment courses. Recovery was always complete by day 14. Neutropenic febrile episodes were seen in 2 patients treated with the 21-day interval, and in 2 patients in the 14-day interval group. Neutropenic fever was evident in 2 of the 4 patients treated with 75 mg/m$^2$ of doxorubicin. Hospitalization was necessitated three times during the studies. Other side-effects observed in the study included fatigue and asthenia, although no patient stopped treatment because of toxicity during this preliminary evaluation. In contrast, no evidence of neuropathy or severe fluid retention was found in any patient. Alopecia was seen in all patients, whilst nausea and vomiting, particularly in relation to the administration of cyclophosphamide and (epi)doxorubicin, never exceeded grade III after premedication.

Partial responses were seen and documented in 14 of the 17 patients evaluable for response. One patient achieved a complete remission; 2 patients had progressive disease. The overall response rate was 88%.

*Table* 1. *Nadir values after first course of treatment*

| Nadir | Interval 3 weeks | | Interval 2 weeks | | Doxorubicin | |
|---|---|---|---|---|---|---|
| | A | B | A | B | A | B |
| WBC ($10^9$/l) | 7.0 | 0.9 | 2.9 | 0.7 | 10.7 | 0.4 |
| (range) | 3.5–14.6 | 0.3–1.3 | 1.0–8.2 | 0.5–1.1 | 9.2–18.7 | 0.3–4.8 |
| ANC ($10^9$/l) | 3.4 | 0.28 | 1.6 | 0.11 | 7.0 | 1.2 |
| (range) | 1.7–9.3 | 0.01–0.63 | 0.07–7.6 | 0.03–0.3 | 1.5–16.1 | 0.08–3.7 |

ANC, absolute neutrophil count; WBC, white blood cell.

## DISCUSSION

New agents that are highly active against breast cancer, such as vinorelbine, paclitaxel, docetaxel and editrexate, can now be studied in combination chemotherapy against breast cancer. However, because docetaxel, given at a standard dose of 100 mg/m$^2$ every 3 weeks, results in significant myelosuppression, combining it with other myelosuppresive drugs is not an attractive treatment option. Lowering the dose of doxetaxel may negatively affect treatment outcome [17].

An alternating schedule using the most active drugs currently available—docetaxel, epirubicin, doxorubicin and cyclophosphamide—given in high frequency and escalated doses and facilitated by supportive administration of lenograstim, has the promise of achieving better results than those obtained by administration of a single compound.

A preliminary analysis of the results of a study using such a strategy supports the feasibility of this treatment approach. The major adverse events encountered in this study were as expected. The incidence of neutropenic fever, however frequent, did not exceed the end-points defined before the study. We believe that the feasibility of using this combination has been demonstrated. Further studies in a larger number of patients using a strict phase II protocol seems warranted, because so many patients achieved a response. Such studies are under way.


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