Cancer Chemother Pharmacol (2004) 54: 546–552
DOI 10.1007/s00280-004-0830-1

ORIGINAL ARTICLE

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Docetaxel and high-dose epirubicin as neoadjuvant chemotherapy in locally advanced breast cancer

Received: 10 December 2003 / Accepted: 29 March 2004 / Published online: 17 August 2004

Abstract *Purpose*: Epirubicin and docetaxel are two of the most active drugs against breast carcinoma. As the achievement of a pathological complete response (pCR) is important for survival of patients with locally advanced disease, we used both drugs as neoadjuvant chemotherapy. *Patients and methods*: Women with locally advanced or inflammatory breast cancer received epirubicin 120 mg/m^2 followed by docetaxel 75 mg/m^2, both on day 1, every 21 days for four cycles. Lenograstim was administered for 10 days in all cycles. *Results*: Of 51 patients included, 50 received a total of 188 cycles, with a median of 4 per patient. The median age was 47 years, tumour stage was IIIA in 14 patients and IIIB in 36. Oestrogen receptors were positive in 65% of tumours. There were 10 clinical complete responses (20%) and 29 partial responses (58%). Surgery consisted of mastectomy in 40 patients and tumorectomy in 6. After surgery, 9 pCR were recorded (18%). One patient progressed and died soon after the end of chemotherapy. After a median follow-up of 22 months, the median disease-free survival was 33.7 months. Grade 3/4 neutropenia was observed in 32% of patients, anaemia in 6%, and thrombocytopenia in 4%. Five patients had febrile neutropenia. There were no toxic deaths or grade 4 nonhaematological toxicities. *Conclusions*: Docetaxel plus high-dose epirubicin showed promising activity in patients with locally advanced and inflammatory breast cancer, at the cost of moderate toxicity.

Keywords Locally advanced breast cancer · Epirubicin · High-dose · Docetaxel · Neoadjuvant

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Introduction

Locally advanced breast cancer accounts for approximately 15% of newly diagnosed breast tumours. The term "locally advanced" refers to large primary tumours—T3 or T4—or tumours with extensive axillary involvement—N2 or N3. Neoadjuvant chemotherapy has a well-established role in the initial therapy or locally advanced breast cancer, achieving good local control and allowing conservative surgical procedures [21, 23, 35]. Although a survival advantage for this strategy has not been demonstrated, clinical trials have correlated the pathological response to chemotherapy with patient outcome [4, 9].

The rate of pathological complete responses (pCR) obtained with neoadjuvant chemotherapy is around 10% in trials with standard-dose anthracyclines [9, 16]. Theoretically, if a pCR reflects the chemosensitivity of the tumour, patients who have a pCR should have the highest disease-free survival, which has been demonstrated in several trials [4, 9, 20]. In these trials, patients having a major response had less risk of relapse and death due to tumour dissemination.

Two strategies have been used in an attempt to improve the results of neoadjuvant chemotherapy: the use of higher doses of classic anthracycline-based chemotherapy and the incorporation of new drugs such as taxanes. Anthracyclines and taxanes are the most active drugs against breast carcinoma, with response rates of over 30% in advanced disease [18, 26]. The combination of anthracyclines and taxanes is very active as first-line

chemotherapy for metastatic breast cancer, with 50–70% of patients obtaining an objective response [11, 14]. Higher responses up to 87% have been reported with increased doses of epirubicin and docetaxel plus G-CSF support [25]. Some investigators have used these combinations in the neoadjuvant setting, with promising results at standard doses [15, 28]. However, efficacy should not be obtained at any cost: toxicity remains a major concern in women with curable disease, particularly in the long term [12, 31, 36].

Considering the importance of a pCR and the activity of the combination epirubicin–docetaxel, we performed a multicentre phase II trial using high doses of epirubicin and a standard dose of docetaxel. Our goal was to increase the rate of complete responses, trying to minimize toxicity.

Patients and methods

Eligibility criteria

Women had histologically or cytologically confirmed breast cancer stage IIIA or IIIB, age >18 years, good performance status (ECOG scale 0–2), normal left ventricular ejection fraction, and normal blood cell counts and biochemistry. Patients with infiltrating ductal and lobular carcinomas and inflammatory tumours were eligible. Baseline laboratory values included: neutrophils $\geq 2\times10^9$/l, platelets $\geq 100\times10^9$/l, haemoglobin ≥10 g/dl, normal bilirubin, transaminases up to 2.5 times the upper normal limit, alkaline phosphatase up to five times the upper normal limit, creatinine up to 2 mg/dl. Patients with bilateral tumours, previous therapies with taxanes, anthracyclines, as well as previous grade 2 or more neuropathy, cardiomyopathy or serious uncontrolled illness were not eligible. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Treatment plan

Epirubicin 120 mg/m^2 (30-min i.v. infusion) followed 1 h later by docetaxel 75 mg/m^2 (1-h i.v. infusion) were administered on day 1 and repeated every 21 days. Lenograstim 150 μg/m^2 per day was administered subcutaneously from days 3 to 12. Oral dexamethasone 8 mg was administered the evening before and on the evening of the day of chemotherapy. Antiemetics were administered according to local protocols. Four cycles of chemotherapy were planned prior to surgery.

Complete blood cell counts were performed at the beginning of every cycle. Treatment was delayed if any of the following occurred by day 1 of a cycle: neutrophils $<1.5\times10^9$/l, platelets $<100\times10^9$/l, grade 2 or more mucositis, bilirubin elevation, or transaminases/alkaline phosphatase more than five times the upper normal limit. Patients were withdrawn from the study if they had not recovered from these toxicities 2 weeks later, or if there was grade 3 neurotoxicity or any other grade 4 toxicity. Doses were reduced by 20% in the cases of febrile neutropenia, transaminases/alkaline phosphatase 2.5 to 5 times the upper normal limit, grade 2 cutaneous toxicity or any other grade 3 toxicity. Hypersensitivity reactions to docetaxel were treated with corticosteroids.

Patients were scheduled to undergo surgery within 4 weeks after the last chemotherapy cycle, or earlier in the case of progression. The goal of surgery was to obtain free margins of at least 1 cm. Axillary lymph node dissection was performed in all cases.

Efficacy measures

The primary endpoint of the study was the rate of complete responses, both clinical and pathological. Secondary objectives were disease-free survival and overall survival. Tumour size and nodal status were estimated before the start of chemotherapy and before surgery by palpation. The pathological response was defined as complete in the absence of tumour in both the primary and all resected lymph nodes, or partial otherwise. Partial pathological responses were not further categorized. Secondary end-points were toxicity, time to progression, and time to treatment failure. Disease-free survival was the time elapsed from entry to progression or death attributed to the tumour. Efficacy measures would include all patients receiving at least one course of chemotherapy. Data were monitored, collected and analysed by an independent organization (Biométrica, Madrid–Barcelona).

Statistical analysis

Sample size was calculated using the Simon method. Considering a minimum response rate of 60% of clinical responses, at least 45 eligible patients had to be included. Eligible patients had to receive at least one course of chemotherapy. The study would be stopped if there were fewer than 7 responses in the first 11 patients. Responses would be provided as percentages with a confidence interval (CI). The Kaplan–Meier method was used for disease-free survival and overall survival. CI were 95%.

Results

From March to December 2001, 51 patients were included in 12 participating centres. One patient was excluded because she withdrew informed consent. Thus 50 patients received at least one cycle of chemotherapy and were evaluable for response and toxicity. Table 1

Table 1 Clinical features of the 50 patients

Age (years)	
Median	47
Range	26–82
ECOG performance status	
0	41 (82%)
1	9 (18%)
Menopausal status	
Premenopausal	30 (60%)
Post/perimenopausal	20 (40%)
Oestrogen receptor	
Positive	33 (65%)
Negative	13 (25%)
Not determined	4 (8%)
Progesterone receptor	
Positive	20 (40%)
Negative	26 (51%)
Not determined	4 (8%)
Clinical stage	
IIIA	14 (28%)
IIIB	36 (72%)
Histology	
Ductal	39 (78%)
Inflammatory	9 (18%)
Lobular	2 (4%)

displays baseline characteristics. The median age was 47 years. The median tumour size was 6.8 cm (range 1–23 cm). Tumour stage was IIIA in 14 patients and IIIB in 36 (AJCC 5th ed 1997). Oestrogen receptor status was positive in 65% of patients.

A total of 188 cycles were given, with a median of 4 per patient. Of the 50 patients, 42 completed the four scheduled courses, 1 declined further therapy after the first course (lost to follow-up), 2 received only two courses due to toxicity, and 5 received only three courses for the same reason. Table 2 shows the reasons for not receiving the four scheduled courses. The tumour remained stable in two patients and increased in size in another two after two courses of epirubicin–docetaxel; these four patients received two cycles of another anthracycline-based chemotherapy and were then operated upon. Surgery consisted of mastectomy in 40 patients (80%) and tumorectomy in 6 (12%). Two patients refused surgery after achieving a clinical response (one complete and one partial): they completed six courses of the same chemotherapy and then received radiation therapy. Another patient with a clinical complete response in the breast developed liver and brain metastases, and died 20 days after receiving the fourth cycle of chemotherapy; she was considered to have a progression. As indicated above, one patient was lost to follow-up, and we do not know whether she had an operation. Table 3 summarizes the results. According to local standard protocols, 47 patients received radiotherapy.

Table 2 Causes of early termination of chemotherapy

	No. of patients
Patient's decision (with good clinical response)	2
Febrile neutropenia and local progression	1
Grade 3 neutropenia, grade 2 fatigue, local progression	1
Febrile neutropenia	1
Grade 3 fatigue	1
Allergic reaction to docetaxel, grade 2	1
Cutaneous toxicity, grade 2	1

There were 10 clinical complete responses (20%) and 29 partial responses (58%), for an overall response rate of 78% (CI 67–89%). Disease remained stable in eight patients (16%) and showed local progression in two (4%). One patient was lost after the first course of chemotherapy, so that the response was unknown. After surgery, 9 pCR were recorded (18%, CI 7–32%; Table 3). Among the 42 patients who received four cycles of chemotherapy, there were 9 pCR (21%). Response was not related to hormonal receptor status (Mann–Whitney test).

Grade 3/4 neutropenia appeared in 16 patients (32%) and 40 courses (21%), anaemia in 3 patients (6%) and 4 courses (2%), and thrombocytopenia in 2 patients (4%) and 2 courses (1%). Five patients (10%) suffered febrile neutropenia. There were no toxic deaths or grade 4 nonhaematological side effects. The most common grade 1/2 side effects were alopecia, fatigue, nausea/vomiting, diarrhoea and stomatitis. The doses of both drugs were

Table 3 Summary of results

Number of cycles	
One	1 (lost to follow-up)
Two	2
Three	5
Four	42
Type of surgery	
Mastectomy	40
Tumorectomy	6
Rejected by patient	2
Nonindicated	1 (early systemic progression)
Nonapplicable	1 (lost to follow-up after one course)
Clinical response	
Complete	10 (20%)
Partial	29 (58%)
Stable	8 (16%)
Progression	2 (4%)
Non-evaluable	1 (lost to follow-up after one course)
Pathological response	
Complete	9 (18%)
Partial	26 (52%)
Stable	7 (14%)
Non-evaluable[a]	8 (16%)

[a]One patient was lost after the first cycle, one patient had disseminated disease and was not operated upon, two patients did not want to be operated upon, two of the patients who had stable clinical disease and the two patients with clinical progressive disease received an alternative chemotherapy and were then operated upon

Table 4 Haematological and nonhaematological toxicity (per patient)

Toxicity	Grades 1/2	Grades 3/4
Haematological		
Neutropenia	7 (14%)	16 (32%)
Anaemia	41 (82%)	3 (6%)
Thrombocytopenia	13 (26%)	2 (4%)
Febrile neutropenia		5 (10%)
Nonhaematological[a]		
Alopecia	40 (80%)	–
Nails	2 (4%)	–
Nausea/vomiting	19 (38%)	1 (2%)
Fatigue	28 (56%)	3 (6%)
Neuropathy	3 (6%)	2 (4%)
Myalgia	3 (6%)	–
Dizziness	1 (2%)	1 (2%)
Headache	1 (2%)	1 (2%)
Skin allergic reaction	2 (4%)	–
Peripheral oedema	1 (2%)	–
Diarrhoea	17 (34%)	1 (2%)
Stomatitis	19 (38%)	3 (6%)

[a]Other grade 1 side effects in one patient each: insomnia, gastric pain, hypotension, cough, hypothermia. No grade 4 nonhaematological side effects were recorded

reduced in six courses (3%) and six patients (12%). Dose delay occurred in 21 courses (11%) and 17 patients (34%). Table 4 displays the side effects.

The median follow-up was 22 months (range 20–29 months). At the time of this report, nine patients had relapsed after surgery and five of them (10%) had died due to disease progression. The median disease-free survival was 33.7 months (95% CI 33–34 months; Fig. 1). Median overall survival had not been reached.

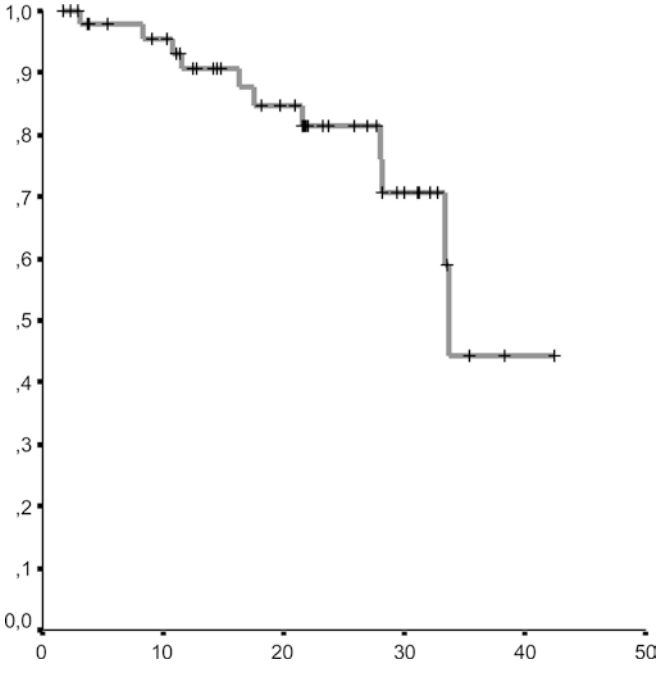

Fig. 1 Disease-free survival. The median was 33.7 months

Discussion

In the present study, 18% of patients with locally advanced breast cancer achieved a pCR with neoadjuvant epirubicin and docetaxel. Until 1996, in several studies percentages lower than 10% had been found with the use of standard-dose anthracycline-containing regimens [9, 16]. By that time, investigators already recognized that the achievement of a pCR increased relapse-free survival. Neoadjuvant chemotherapy can allow conservative procedures and give information about response to chemotherapy, but it does not offer a survival advantage as compared with adjuvant therapy [16, 23, 27]. However, patients achieving complete responses have less risk of relapse, as demonstrated by NSABP-B18 in 1998 [9]. In that trial, women were randomised to receive either preoperative or postoperative anthracycline chemotherapy. The rate of disease-free survival was 85% in patients with a pCR and 68% in those with a partial response. Further efforts to improve efficacy have included the use of higher doses of anthracyclines and the addition of taxanes.

High-dose anthracycline regimens are feasible, as demonstrated by an EORTC phase I study [3]. In a phase II study, doxorubicin 20 mg/m^2 per day for 3 days was used along with vinorelbine, cyclophosphamide and 5-fluorouracil: the pCR rate was 22% but at the cost of considerable haematological toxicity [5]. A British trial used four courses of cyclophosphamide, doxorubicin, vincristine and prednisolone, after which, patients with a clinical response were randomized to receive four courses of the same chemotherapy or docetaxel 100 mg/m^2 [30]. The pCR rates were better for the docetaxel arm: 34 vs 16%. Two patients (3.6%) in the docetaxel arm died due to the side effects of chemotherapy, even though fewer episodes of leucopenia were recorded in this arm. In another study, docetaxel 100 mg/m^2 achieved a pCR in 19% of patients, but with high haematological toxicity [1]. Whether such increases in the rate of pCR may translate into a survival advantage remains uncertain, because no formal comparison has been made between adjuvant chemotherapy and neoadjuvant regimens containing a taxane of high-dose anthracyclines. In an American trial, doxorubicin 90 mg/m^2 was used for four cycles [4]. Although patients also received adjuvant cyclophosphamide, methotrexate and 5-fluorouracil (CMF) (which might have been a confounding factor), the Cox analysis indicated that a major response to doxorubicin was the strongest predictive factor for long-term survival.

Another American trial from the MD Anderson Cancer Center combined doxorubicin and docetaxel, both at 60 mg/m^2, followed by adjuvant CMF [33]. Included were 70 patients, and the rate of pCR was 10%, with considerable haematological toxicity. In summary, there is an obvious need to improve the rate of pCR in the neoadjuvant setting, but toxicity remains a concern.

In our study, we combined both strategies: the use of high-doses of epirubicin and the addition of docetaxel. An 18% rate of pCR seems superior to what has been reported in classical studies of neoadjuvant therapy and is quite similar to that seen in the recent studies mentioned above [1, 3, 30]. We cannot say if this improvement resulted from the incorporation of docetaxel or from the use of epirubicin at high doses. However, an Italian trial with standard-dose epirubicin plus docetaxel found a pCR rate of only 13%, which suggests that the dose of epirubicin played an important role in achieving the good results that we observed [22]. Likewise, in a recent trial with doxorubicin 50 mg/m^2 plus docetaxel 75 mg/m^2, a 13% rate of pCR was found [13].

Conservative surgical procedures were performed in only 20% of our patients, even when the clinical overall response was 79%. This might reflect the fact that some surgeons do not rely much on the effects of neoadjuvant chemotherapy. Almost all patients achieving a clinical complete response turned out to have a pCR, which indicates that, in cases of chemosensitive disease, four courses of this scheme are enough to get an appropriate response. In the trial from the MD Anderson Cancer Center mentioned above, most patients also underwent a modified mastectomy, although 63% had been downstaged with neoadjuvant doxorubicin–docetaxel [33].

The follow-up in our study was short, because overall survival was not one of the primary objectives. So we were unable to assess the long-term effect of our scheme. The median time of disease-free survival was 33.7 months. The reports of most studies of neoadjuvant chemotherapy do not provide information on disease-free survival or overall survival [1, 22, 33]. Cance et al. used doxorubicin alone followed by adjuvant CMF and reported a median time to distant failure of 33 months; although not strictly comparable to our trial, the survival results appear to be similar [4].

Toxicity was moderate in our study. Grade 4 side effects were only related to haematological parameters (one-third of patients had grade 3/4 neutropenia). Grade 3 nonhaematological side effects were uncommon and no toxic deaths were registered. These data provide evidence that out scheme can be safely used in a clinical setting outside clinical trials. However, five patients (10%) had an episode of febrile neutropenia, two patients experienced grade 3 neuropathy and three had grade 3 fatigue. In the aforementioned British trial, toxicity was much greater, probably because therapy was more prolonged [30]. Limiting neoadjuvant chemotherapy to four courses could also limit the appearance of side effects, but even so toxicity is not negligible. Although toxicity in our trial compares favourably with that seen with other schemes, attention should be paid especially to the haematological side effects.

Increasing the doses of cytotoxic drugs could improve the results. However, the dose of epirubicin cannot be increased beyond the one we used. With regard to docetaxel, there is some experience in metastatic disease, especially with weekly schedules [19, 24], but it is not known if it would work in the neoadjuvant setting. Also, recent reports indicate that the addition of gemcitabine to the combination epirubicin–taxane enhances the number of pCR, but at the cost of unacceptable toxicity [17, 29].

Another strategy to improve the efficacy of neoadjuvant chemotherapy could be the use of dose density, which has demonstrated its efficacy in the adjuvant setting [6]. Dose density is also being tested in one arm of the Canadian MA-21 trial of adjuvant chemotherapy [32]. Some studies of neoadjuvant chemotherapy with anthracyclines have shown an increase in the response rate without any difference in survival [2, 7, 10], but this modality still deserves additional experiences with the addition of taxanes. In this regard, promising preliminary results of a phase I/II Austrian trial with weekly epirubicin and docetaxel at doses of 30 and 35 mg/m^2/week, respectively, have been reported [34]. However, this trial included both neoadjuvant and palliative treatments. Docetaxel alone 40 mg/m^2 per week for 6 weeks every 8 weeks achieved a 16% of pCR in a Spanish study [8]. However, 77% percent of patients experienced fatigue. As a continuation of our trial, we have initiated another phase II study with the administration of epirubicin and docetaxel every 2 weeks, in the hope that increasing dose-density might improve results but without unacceptable toxicity.

In conclusion, neoadjuvant chemotherapy with docetaxel and high-dose epirubicin achieved an 18% rate of pCR in patients with locally advanced breast cancer. Toxicity was moderate. Considering the importance of major responses in this setting, future trials should explore the possibility of increasing the rate of pCR while not producing unacceptable toxicity.

Acknowledgements We are indebted to Dr Beatriz Gil-Alberdi for her assistance in preparing the manuscript. The authors acknowledge the work of Biométrica in doing the monitoring and the statistical analysis of the study and Aventis Pharma for the general coordination of the project.

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