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Clinical report

Epirubicin/docetaxel regimen in progressive breast cancer—a phase II study

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The purpose of this investigation was to evaluate the efficacy and toxicity of 6 months' treatment with the combination of epirubicin and docetaxel in metastatic breast cancer. Thirty-eight women (mean age 51 years, range 35–72) with metastatic breast cancer were treated with a regimen of epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 every 3 weeks, given 4 times if progression was seen upon evaluation after 4 courses or 8 times in responding/stable patients. The patients received 285 cycles of combination treatment and two treatments with docetaxel or epirubicin alone. When neutropenia with fever was observed, further cycles were given with dose reduction. The median cumulative docetaxel dose was 462 mg/m^2 (range 199–600) and that of epirubicin 476 mg/m^2 (range 199–740). The overall response rate was 54% (95% CI 37–71), with a median duration of response of 14.8 months (95% CI 8.8–27.8). Median time to progression was 12 months, median survival 26 months. Neutropenia below 0.5 $\times$ 10^9/l occurred following 113 (39%) of the total of 285 cycles given; 21 patients (55%) were hospitalized for febrile neutropenia. We conclude that dose tailoring is required in treatment with an epirubicin and docetaxel regimen to avoid grade 3/4 adverse effects in a significant number of patients treated for metastatic breast cancer. [© 2002 Lippincott Williams & Wilkins.]

Key words: Breast cancer, docetaxel, epirubicin, response.

Introduction

Anthracyclines and taxanes are among the most effective modes of chemotherapy currently available for the treatment of progressive breast cancer. These two chemotherapy groups differ in their mechanism of action. The anthracyclines induce DNA damage via inhibition of topoisomerase II enzyme. Epirubicin has an efficacy similar to that of doxorubicin as first-line treatment for breast cancer; however, its toxicity profile, especially in terms of cardiotoxicity, is more favorable.[1] The taxanes induce cytotoxicity by binding to tubulin. Docetaxel is a potent promoter of tubule polymerization. It inhibits microtubule depolarization. Docetaxel has proved superior in efficacy to the anthracyclines[2,3] and it has exceeded the activity of mitomycin plus vinblastine.[4]

Excessive toxicity and adverse effects requiring hospitalization should be avoided or at least minimized during palliative chemotherapy. Drug doses are commonly adjusted using body surface area, which however, standardizes poorly for the interpatient variation in pharmacokinetics of many cytotoxic drugs.[5] Two extensive prospective studies have shown that an increase in dose in chemotherapy resulted in a significant increase in general overall toxicity, and an increased incidence of severe infections and septic episodes without survival benefit in breast cancer.[6,7] The patient should be able to maintain normal activities during the course of palliative chemotherapy; excessive toxicity or hospitalization due to adverse effects should be avoided.

The intracellular biologic activity of taxanes, including docetaxel, is related to their concentration and the duration of exposure.[2] In clinical practice balancing issues on toxicity and efficacy is important in the non-curable stage of disease. This study was designed to investigate prospectively an epirubicin–docetaxel combination, with respect to individual tolerance to the regimen in a phase II study.

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Patients and methods

Patients

A total of 38 patients were enrolled from June 1998 to March 2000. Eligible patients were women aged 18–75 years with histologically confirmed metastatic breast cancer, with measurable and/or evaluable disease. Earlier chemotherapy with adjuvant CMF or CEF (cyclophoshamide 600 mg/m^2, methotrexate 40 mg/m^2 or epirubicin 60 mg/m^2, 5-fluorouracil 600 mg/m^2 q3 weeks i.v. $\times$ 6–9) and prior hormonal therapy or radiotherapy were permitted if the total cumulative dose of epirubicin was <400 mg/m^2. Eligibility requirements included the presence of progressive measurable or evaluable disease, a performance status $\leqslant 2$, a white blood cell count >3000/mm^3, a platelet count of $\geqslant 130\,000$/mm^3 and liver functions <3 times the normal value.

Patients with clinical and/or radiological evidence of brain metastases were excluded, as were those with evidence of active infection. A history of angina pectoris, cardiac disease or hypertension was not a reason for exclusion if the patient was stable on medication and LVEF was normal (above 50% by echocardiography). The study was conducted according to the ethical standards described in the Helsinki Declaration. The Ethical Committees of Turku University Hospital and Satakunta Central Hospital had given approval for the protocol, and written informed consent was obtained from all patients. Two centers recruited 38 patients to a phase II study. All 38 patients were assessable for toxicity and 37 (97%) were assessable for response.

Treatment schedule

The schedule combination was epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 administered every 3 weeks. Epirubicin was given as a 15-min i.v. infusion, followed by a pause for 1 h, where after docetaxel was administered as a 1-h infusion on day 1. The treatment was preceded by prednisolone 40 mg given orally the previous night and continued b.i.d. on days 1–3 (3 day schedule). Prophylactic antiemetic was given according to routine practice (5-HT blocker prior to chemotherapy infusion). Mid-cycle counts were taken on day 10/11. The aim was to give 8 cycles for responding/stable patients. The study schedule was based on earlier experience with these drugs, aiming at a dose level applicable without growth factor support, and data from studies with doxorubicin and docetaxel.[8,9] The starting dose of 75 mg/m^2 of epirubicin and docetaxel was reduced by 25% (both drugs) in cases of hospitalization due to febrile neutropenia requiring antibiotics. The dose was further tailored by reducing both drugs if necessary in order to avoid febrile neutropenia requiring hospitalization. No limitations were given concerning the use of granulocyte growth factors. Prior to each cycle, measurements of toxicity (WHO) were made, the aim being to establish a dose level allowing outpatient treatment without inter-cycle hospitalization.

Monitoring, study parameters and statistical analysis

Patient evaluation at baseline was based on physical examination, bone scan, computed tomography/ultrasound of metastatic and/or suspected organs, chest radiograph, ECG, 24-h Holter monitoring, and detection of LVEF by echocardiography. Subsequent evaluation comprised physical examination and re-imaging of disease areas, ECG recording and echocardiography, and 24-h Holter by cycle 4 and 8. When clinically indicated, the investigations were repeated during follow-up.

Response was defined according to WHO criteria[10] after cycle 3 and at close of treatment. Patients were reviewed every 3 months, with radiological evaluation of disease status when symptoms occurred or at 6-month intervals until relapse. Complete response (CR) and partial response (PR) were re-evaluated after 4 weeks at the end of the treatment. The duration of response was calculated from the first demonstration of response to documented disease progression. In cases of bone lesions, osteolytic lesions were considered evaluable. If bone lesions became more sclerotic, uptake in skeletal scintigrams decreased and alkaline phosphates normalized, the response was defined as PR.

Monitoring of source data was performed at research sites. At closing date of the study, 30 September 2001, all patients had been followed up for a minimum of 12 months. The date of recurrence or death was used to calculate the time from the first chemotherapy to progression and overall survival time. Both these times and duration of response were estimated as functions of time by the non-parametric Kaplan–Meier method.

Results

Patient and disease characteristics

Patient and disease characteristics are summarized in Table 1. The basic criterion was histologically confirmed adenocarcinoma of the breast with progressive metastatic disease. The median age was 51 years (range 35–72 years), with seven patients (18%) aged over 60 years. Twenty-five (70%) had received prior adjuvant chemotherapy and seven had received antiestrogen hormonal treatment. Twenty-nine (76%) had received postoperative radiotherapy. One of the patients had initially local recurrence (surgically removed) and mediastinal lymphadenopathy considered being due to cancer. No response to treatment was observed in lymph nodes of this patient; biopsy in mediastinoscopy after 4 cycles showed sarcoidosis, rendering this patient non-evaluable for response.

Response and survival

Objective responses (CR/PR) were observed in 20/37 patients, giving an overall response rate of 54% (95% CI 37–71) including five patients who evidenced complete response (14%; 95% CI 5–29). Four patients had early progression. Median time to progression was 12 months and median survival 26 months.

Table 1. Patient characteristics

	N	%
Age (years)		
median	51	
range	35–72	
ECOG PS		
median	1	
range	0–2	
Prior treatment		
adjuvant chemotherapy	25	66
antiestrogens	6	13
Prior XRT to chest wall	29	76
Prior XRT to left chest wall	18	47
Hypertension	6	16
Cardiovascular disease	1	3
No. of organs involved		
1	17	45
2	12	32
$\geqslant 3$	9	24
Disease sites involved		
bone	21	55
liver	12	32
lung	19	50

PS: performance status; XRT: radiotherapy.

Site of treatment failure

After a minimum follow-up of 12 months, 32 patients (84%) had relapsed, primarily 21 (55%) at the original disease sites, seven (18%) at new sites and five (14%) in the CNS.

Treatment duration

Thirty-eight (patients (100%) completed at least 3 cycles of treatment, 36 completed at least 6 cycles and 33 (87%) the maximum of 8 cycles. The patients received 285 cycles of combination treatment and 2 cycles with docetaxel (because of unclear cardiac situation) or epirubicin (temporary elevation of liver enzymes) alone were given. The median cumulative dose of docetaxel was 462 mg/m^2 (range 199–600) and that of epirubicin was 476 mg/m^2 (range 199–740). The reason for discontinuation for the five patients who received less than 8 cycles of combination was progressive disease (four patients) and missing diagnosis (one patient).

Toxicity

Hematological toxicity is presented in Table 2 and non-hematological toxicity in Table 3. The median hemoglobin value decreased from 125 to 115 during the 6 months' treatment. Five patients required blood transfusions (2 units of red cells/patient). Significant neutropenia was observed in 80% of patients (Table 2). The neutrophil nadir was below 0.5×10^9/l after 114 of the cycles (39%). Forty-two percent of antibiotics were required after cycle 1, 18% after cycle 2, 13% after cycle 3, 5% after cycle 4, 6% after the cycle 5, 5% after cycle 6, 9% after cycle 7 and 2% after cycle 8 of chemotherapy. Granulocyte growth factor was prescribed for 27 patients (71%) over 427 days to prevent/curtail neutropenic infections.

Other clinically more significant adverse effects included alopecia (97%), fatigue (13%), stomatitis (56%), diarrhea (58%), neurosensory (45%) and skin/nail (34%) changes, and fluid retention above 3 kg (34%) (Table 3). One patient had a reversible fall in LVEF below the normal level of 50%. This patient had pulmonary embolism during treatment, a condition also known to lower LVEF. The mean performance status evaluated with WHO index was 0.92 prior to cycle 1, 0.86 prior to cycle 2 and 0.91 prior to cycle 8.

Table 2. Number (%) of patients experiencing major hematological toxicity

Toxicity	*N* (%)
Neutropenia ($< 0.5 \times 10^9$/l)	30 (79%)
Leukopenia ($< 1.0 \times 10^9$/l)	23 (61%)
Thrombocytopenia (< 100) 4 (11%)	
Anemia (< 100 g/l)	13 (34%), 5 required blood transfusions
Patients requiring antibiotics	33 (87%)
No. of infection cycles	73/298 (25%)

Table 3. Number (%) of patients experiencing major non-hematological toxicity

	Grade 1/2	Grade 3/4
Alopecia	1 (3%)	37 (97%)
Fluid retention $\geqslant 3$ kg	13 (34%)	–
Weight loss $\geqslant 3$ kg	7 (18%)	–
Nausea/vomiting	35 (92%)	3 (8%)
Neurosensory	16 (42%)	1 (3%)
Neuromotor	19 (50%)	4 (10%)
Fatigue	17 (45%)	3 (8%)
Diarrhea	21 (55%)	1 (3%)
Mucositis/stomatitis	20 (53%)	1 (3%)
Skin/nail	13 (34%)	–

Discussion

Taxanes and anthracyclines are currently among the most effective chemotherapeutic agents available in the treatment of advanced breast cancer. Thus, the logical approach has been to combine drugs of these two groups. In such combinations, synergistic toxicity is probable. Recently, epirubicin 75 mg/m^2 combined with docetaxel 80 mg/m^2 has been recommended for further studies.[12] The study dose level was selected on the basis of earlier reports.[8,9] We were interested to develop a regimen for an outpatient approach. Therefore, when neutropenic infections occurred, this was an indication to reduce doses in following cycles; this was found necessary in more cases than initially estimated. The response rate seen in this study is comparable to anthracyclines/paclitaxel combinations.[13–15] Comparing the results of the current study to an alternating and sequential approach with docetaxel and FEC (5-fluorouracil, epirubicin and cyclophosphamide), our response rate was lower and non-hematological toxicity significantly higher.[16] Avoidance of excessive toxicity is among the aims in palliative chemotherapy of metastatic cancer and less toxic approaches should therefore be preferred in standard practice when different schedules show comparable response rates.

The epirubicin–docetaxel combination showed no excess in cardiac toxicity. However, the incidence of other adverse events, especially diarrhea, stomatitis and neurosensory toxicity, was high. Moderate to severe neutropenia was common. In view of the incidence of neutropenic fever requiring treatment, either a lowering of initial dose levels to 50 mg/m^2 or the use of prophylactic colony stimulating factors could be considered. Since no data so far have proved the benefit of higher dose levels in palliative chemotherapy for metastatic breast cancer, the less aggressive approach may well be recommended. Estimation of clinical benefit, including quality of life and costs of treating adverse effects, additionally to response rate improves the evaluation of applicability of a given schedule, while obtaining stable disease may prove to be almost equally beneficial as objective response for these patients treated for incurable disease.[17]

Corticosteroid premedication should ameliorate docetaxel-induced toxicity. Since a 3-day premedication regimen had been reported to be as effective as a 5-day regimen,[18] we used that, also to avoid severe steroid-related side effects. The length of premedication should perhaps be longer in combination treatment, as our adverse effect rate was high. A common comment from patients was that it took 3 months to recover physically after the study treatment.

A report with a high incidence of CNS failure after epirubicin–docetaxel treatment in breast cancer has recently been published.[19] Among patients in the present study, even long-standing responses have been observed and so far the rate of CNS metastases has been 10%, a figure within the range of 10–15% usually reported.[20]

In conclusion, the findings here showed that a combination of epirubicin and docetaxel is effective and safe, but requires individual dose adjustment to avoid hospitalization due to neutropenic infection and/or use of growth factors to maintain a feasible dose level in individual patients. The response was not significantly jeopardized by the dose

modification and no excess of CNS relapses has been observed.

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