Docetaxel with epirubicin—investigations on cardiac safety

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The aim was to evaluate clinical and subclinical cardiac toxicity of epirubicin–docetaxel (ET) combination. Breast cancer patients were given epirubicin (75 mg/m^2 for 15 min), followed 1 h later by a 1-h infusion of docetaxel (75 mg/m^2) q3w as first-line treatment. Cardiac function was monitored using a 24-h ambulatory electrocardiogram (ECG), left ventricular ejection fraction (LVEF), physical examination and chest radiography. The median LVEF did not decrease during the course of the treatment: median LVEF was 64% prior to treatment and 68% after cycle 8. The 24-h ECG did not reveal any significant changes in heart rate variability. The number of extrasystoles or cardiac arrhythmia did not increase with the ET treatment. No patient experienced congestive heart failure during treatment or the mean follow-up of 34 months. We conclude that first-line ET caused no major cardiac changes during 6 months of treatment (8 cycles) or during follow-up. Twenty-four-hour ECG, combined with echocardiography to measure LVEF, was a feasible method for the close monitoring of the cardiac effects during chemotherapy. *Anti-Cancer Drugs* 14:73–77 © 2003 Lippincott Williams & Wilkins.

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Introduction

Chemotherapy has a central role in the management of metastatic breast cancer (MBC). The anthracyclines (doxorubicin, epirubicin) and the taxanes (docetaxel, paclitaxel) are widely considered to be amongst the most effective agents for patients with MBC and there is much interest in taxane–anthracycline combinations [1].

Doxorubicin–paclitaxel regimens have yielded response rates ranging from 52 to 80% [2–4]. However, studies have shown that the cardiotoxic effects of doxorubicin are aggravated by paclitaxel: paclitaxel in combination with doxorubicin has caused clinically significant cardiotoxicity in 6–20% of patients [2,5,6] and a decrease in the left ventricular ejection fraction (LVEF) in 20–50% of patients [2,7]. Paclitaxel influences anthracycline pharmacokinetics [5,8]. Recent studies imply that cardiotoxicity of paclitaxel–anthracycline combinations may be related to the cumulative anthracycline dose [9].

A decrease in LVEF is a clear indicator of cardiotoxicity [10]. Recent studies have suggested that a decrease in heart rate variability (HRV) may precede a decrease in the LVEF, as one of the first signs of cardiotoxicity [11]. Interestingly, in a study of 14 women, paclitaxel has been shown to impair HRV [12].

Substituting docetaxel for paclitaxel greatly reduces cardiotoxicity, whilst still achieving high response rates [13]. Pharmacokinetic studies have shown docetaxel not to interfere with anthracyclines [14,15]. Docetaxel–doxorubicin (AT) is accepted as an efficacious and tolerable first-line treatment for patients with MBC. A recent phase III multicenter study demonstrated that AT was more effective and less toxic than doxorubicin–cyclophosphamide (AC) [13]. The overall response rate achieved with AT was significantly better than that achieved with AC (60 versus 47%; $p = 0.012$) and clinical cardiotoxicity remained low: of 213 patients in the AT arm, one patient died from cardiac failure and 3% experienced congestive heart failure (CHF). Furthermore, studies have shown that unlike paclitaxel, docetaxel does not decrease HRV. In a study of nine women with MBC, HRV did not change after single-agent docetaxel treatment [16].

Epirubicin shares the same spectrum of antitumor activity as doxorubicin, but can be used in higher cumulative dose before causing cardiotoxicity [17]. This study was designed to further investigate the cardiac safety of epirubicin–docetaxel (ET) combination since replacing doxorubicin with epirubicin may further reduce cardiotoxicity. The primary aim was to determine the cardiac effects of 8 cycles of ET during and after treatment, and during the minimum 12-month

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follow-up. The endpoints were: (i) development of cardiac arrhythmia or impairment of HRV, (ii) decrease in LVEF and (iii) development of CHF. The feasibility of echocardiography and 24-h ambulatory ECG as a method to detect and monitor subclinical cardiac changes during chemotherapy in breast cancer was assessed.

Methods

Patients and treatment

A total of 34 women with histologically confirmed MBC were enrolled into this phase II study from June 1998 to March 2000. The number of patients was statistically estimated as appropriate for a phase II study. Eligibility criteria included: written informed consent, age 18–75 years, a ECOG performance status ≤ 2, white blood cell count $>3000/mm^3$, platelet count $\geq 130\,000/mm^3$ and liver function <3 times the normal value. Previous adjuvant treatment with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) or CEF (cyclophosphamide, epirubicin, 5-fluorouracil) was allowed. Prior hormonal therapy or radiotherapy was permitted. A history of angina pectoris, cardiac disease or hypertension was allowed if the patient was stable with medication and had a normal LVEF ($>50\%$ by echocardiography). Exclusion criteria included: clinical and radiological evidence of brain metastases, and active infection. The study was conducted according to the ethical standards described in the Helsinki Declaration. The Ethical Committee of Turku University Hospital had given approval for the protocol.

Patients were given epirubicin (75 mg/m^2 15-min i.v. infusion) followed 1 h later by docetaxel (75 mg/ m^2, 1-h infusion) every 3 weeks. The doses given were based on earlier studies that have demonstrated the levels applicable without growth factor support [18–20]. Midcycle counts were taken on day 10–11. The aim was to give 8 cycles to responding/stable patients. The starting dose of 75 mg/m^2 for both epirubicin and docetaxel was reduced by 25% if the patient was hospitalized due to febrile neutropenia, required antibiotics or developed prolonged neutropenia.

Premedication of prednisolone (40 mg) was given orally the night before treatment and continued b.i.d. on days 1–3. A prophylactic anti-emetic was given according to routine practice (5-HT blocker prior to chemotherapy infusion).

Cardiac monitoring, study parameters and statistical analysis

Cardiac function was evaluated at baseline with physical examination; chest radiograph; ECG; detection of LVEF by bidimensional echocardiography (standardized interpretation by excluding inter-investigator variability using methods of complete reproducibility: Acuson Sequoia or Toshiba Powervision equipment); and 24-h ambulatory ECG monitoring.

The 24-h monitoring was started the day before the first cycle and continued throughout the treatment day. The 24-h ambulatory ECG was recorded during normal activity with the patients' normal sleep–wake rhythm. The ambulatory ECGs were recorded either with a Marquette 8500 (General Electric Company, Marquette, MI) on C-cassette tapes or with a Marquette SEER MC solid-state recorder (General Electric Company) on MC memory cards. The duration of the recordings was 24–36 h. The two-channel recordings were analyzed with a MARS 8000 Arrhythmia Review Station (Marquette Electronics, Milwaukee, WI). The QRS complex classifications were manually reviewed and relabeled where needed. The recordings were checked for incorrectly measured R–R intervals and corrected as required. The ST segment was measured under visual control at 0.06 s after the J point. The final report contained average, minimum and maximum heart rates for the whole recording as well as hourly rates, and the count of ventricular and supraventricular premature beats, couplets and runs.

HRV was assessed in frequency and time domain. Spectral analysis was used to quantify the periodic components of HRV. Spectral power of HRV was calculated with fast Fourier transformation algorithm. Power spectra was quantified in three frequency bands: very-low-frequency power (VLF) from 0.0033 to 0.04 Hz, low-frequency (LF) power from 0.04 to 0.15 Hz and high-frequency power (HF) from 0.15 to 0.40 Hz. VLF variability is associated with sympathetic vasomotor regulation. LF variability relates to baroreflex activity, and is modulated by both sympathetic and parasympathetic control. HF variability is vagally mediated and reflects respiratory sinus arrhythmia.

Mean R–R interval, standard deviation of R–R intervals (SDNN) and root mean square of successive differences in R–R intervals (RMSSD) were calculated to assess HRV in the time domain. SDNN is used to assess overall variability in heart rate, whereas RMSSD reflects beat-to-beat variability

The assessment of CHF was performed according to the New York Heart Association clinical criteria [21]. The diagnostic criteria for CHF were new onset of dyspnea, presence of peripheral edema, cardiac enlargement or pulmonary congestion on chest radiograph, or pulmonary rales at auscultation.

The response to treatment was defined according to the WHO criteria [22]. In the case of bone lesions, osteolytic lesions were considered evaluable. If bone lesions became

more sclerotic, but partial response was found in other lesions, the response was defined as partial response.

Statistical analysis

Analysis of variance for repeated measurements was performed using the BMDP statistical package (2V) to study changes in the heart rate, the number of extrasystoles and HRV. Log transformations were performed for non-Gaussian data. The data are shown as mean (SD). Ninety-five percent confidence interval levels were computed for response and for LVEF deviations.

Results

Patient characteristics and treatment

Patient characteristics are listed in Table 1. The median age was 55 years (range 35–72 years), with seven patients (21%) aged over 60%. The median ECOG performance status was 1 (range, 0–2). Twenty patients (59%) had received adjuvant chemotherapy with CMF and two (6%) with CEF. Three patients (9%) had received antiestrogen treatment, one patient (3%) had been treated with luteinizing hormone-releasing hormone analog and another with letrozole for metastatic disease. Twenty-two patients (65%) had received prior postoperative radiotherapy to the chest wall, 14 (41%) to the left side. Sixteen patients (48%) were treated after modified radical mastectomy to 45–49 Gy and six (18%) patients after breast-conserving surgery to 60 Gy. Twenty-eight patients (82%) had at least one cardiovascular risk factor including cardiovascular disease, chest wall radiotherapy or previous chemotherapy with anthracyclines (two patients with previous exposure to epirubicin) or cyclophosphamide. One patient had two cardiovascular risk factors, right chest wall radiotherapy and ischemic cardiovascular disease, requiring continuous medication.

Table 1 Patient characteristics

Characteristic	Patients ($n = 34$)	
	N	%
Age (years)		
mean	55	
range	35–72	
Prior treatment		
20 (CMF)		59
2 (CEF)		6
3 (2 tamoxifen; 1 goserelin)		9
Prior RTX		
to chest wall	22	65
to left chest wall	14	41
after MRM	16	47
after BCS	6	18
Hypertension/cardiovascular disease	4	12
Number of organs involved		
1	17	50
≥ 2	17	50
Disease sites		
bone	13	38
liver	11	32
lung	21	62
other	11	32

RTX = radiotherapy; MRM = modified radical mastectomy; BCS = breast-conserving surgery.

The patients received 287 cycles of chemotherapy. For all patients, the median cumulative dose of docetaxel was 462 mg/m^2 (range 208–612 mg/m^2) and that of epirubicin 476 mg/m^2 (range 214–642 mg/m^2). While median doses are relatively low due to dose reductions required as a result of neutropenic episodes, the individual doses were as high as clinically possible. Therefore cardiotoxicity was evaluated at clinically appropriate doses. The number of cycles remained close to planned, as 8 cycles were given to 32 patients (94%).

The median value for hemoglobin decreased from 125 to 115 g/l during the 6 months' treatment. One patient was given 7 cycles and monitored for cardiac investigation at the time of cycle 8, which was not given due to progressive disease.

Efficacy

Thirty-three patients were evaluable for efficacy. One patient with a local recurrence and mediastinal lymphadenopathy had a biopsy taken after cycle 4, which showed sarcoidosis and rendered the patient non-evaluable for response. The overall response was 67% (95% CI 47–80%), including five (15%) complete responses and 17 (52%) partial responses.

Cardiac safety profile

Clinically evident cardiac toxicity was not observed during the treatment or follow-up (mean 34 months at the closing date in September 2002, minimum above 25 months) in any patients. LVEF did not decrease during the course of the study. The median value for LVEF was 64% before treatment, 66% at cycle 4 and 68% at cycle 8. Table 2 shows the effect of ET on LVEF in individual patients. Four patients developed an asymptomatic decrease in LVEF of over 10% (12%; 95% CI 3.3–27%), remaining at a normal level (above 50%) after cumulative doses of epirubicin ranging from 199 to 556 mg/m^2 and docetaxel ranging from 199 to 566 mg/m^2. One patient experienced a fall below the normal level of 50% (patient no. 6; 3%). This decrease most likely resulted from acute pulmonary embolism, a condition known also to lower LVEF. Her fall in LVEF was reversible and systolic heart function normalized during follow-up. All patients with a decrease in LVEF had predisposing factors to cardiac adverse effects such as chest radiotherapy, high age, previous anthracyclines or cyclophosphamide chemotherapy. Chest radiographs for all 34 patients showed no cardiac enlargement/pulmonary congestion during or after treatment until study close.

There were no changes in HRV as measured either by spectral analysis or by time domain. Table 3 shows the results of the 24-h cardiac monitoring. All 34 patients were evaluable for cardiac safety. The treatment did not increase the number of extrasystoles. The 24-h ambulatory ECG detected tachycardia in one patient during infusion of epirubicin and docetaxel at cycle 4, but the 24-h ECG was normal by cycle 8. Another patient showed an increase in supraventricular and ventricular extrasystoles at cycle 4. This increase was clinically asymptomatic and was still present at cycle 8. In total, the incidence of detectable subclinical changes was 6%.

Discussion

This study shows that moderate dose ET (E 75 mg/m^2, T 75 mg/m^2) is not cardiotoxic in patients with MBC. The doses used were clinically effective as can be seen in the response rate and hematological toxicity. We administered 8 cycles (over 6 months) and observed a clinically significant reversible decrease in LVEF only in one patient. Cardiac effects and response results observed in our study are similar to those obtained in other recent ET studies. Sessa *et al.* studied ET in 70 patients with advanced breast cancer, and noted low cardiotoxicity and an overall response rate of 66% [23]. Viens *et al.* examined ET in 65 patients with MBC as first-line therapy, and found an overall response rate of 69.4% and low cardiotoxicity [24]. No significant cardiotoxicity was observed in that study.

LVEF is a commonly used and reliable indicator for chemotherapy-induced cardiotoxicity in clinical practice. LVEF did not decrease significantly during ET treatment in the present study. The only patient with a decrease in LVEF to abnormal values (below 50%) suffered from pulmonary embolism during the study and her LVEF returned to normal during follow-up.

Decreased HRV is an early sign of autonomic neuropathy [25], which can present a problem with the use of anthracyclines in breast cancer [26]. It has been observed that autonomic impairment and a decrease in HRV is seen in most patients after high doses of anthracycline-based chemotherapy [11]. Thus, a decrease in HRV might be used as an early indicator for cardiotoxicity and development of CHF also in patients receiving chemotherapy. Until now, a decrease in HRV has been associated with increased mortality in patients with severe heart failure [27] and myocardial infarction [28,29].

There was no significant decrease in any of the HRV parameters in this study. Therefore, first-line ET treatment can be considered safe for the heart. Earlier, we reported that single treatment with docetaxel in patients with previous anthracycline therapy does not deteriorate HRV [30].

The aim of the 24-h monitoring was to collect more detailed and specific data on possible adverse effects during the drug infusion. We observed a detectable tachycardia in one patient and an increase in extrasystolia in another patients' recording at the fourth infusion. Tachycardia was not recorded on the following recording. Thus, the ET medication is not likely to have any stressful acute effects on the heart.

Table 2 **Documented effects of ET combination in patients with a decrease in LVEF**

Patient no.	Cycle no.	LVEF decrease (%) (baseline–lowest)	Cumulative dose docetaxel/ epirubicin (mg/m^2)	Cardiac risk factors
6	7	11 (59–48)	488/488	previous thoracic wall radiotherapy; pulmonary emboli; LVEF was normalized (51%) 12 months after treatment
9	7	11 (71–60)	199/199	age
10	7	13 (85–72)	208/418	previous CEF
18	7	7 (64–57)	556/566	previous CMF and radiotherapy

Table 3 **Results of 24-h cardiac monitoring at baseline, and at cycles 4 and 8 of ET treatment**

	Baseline mean (SD)	Fourth cycle mean (SD)	Eighth cycle mean (SD)	*p* value
Heart rate (b.p.m.)	80 (10)	83(9)	84 (10)	0.01
Ventricular extrasystoles	33 (79)	95 (295)	27 (112)	0.29
Supraventricular extrasystoles	63 (165)	187 (434)	101 (136)	0.048
VLF HRV	527 (360)	468 (297)	440 (286)	0.72
LF HRV	258 (263)	219 (160)	216 (164)	0.90
HF HRV	108 (136)	90 (68)	82 (61)	0.81
SDRR (ms)	117 (29)	111 (27)	112 (26)	0.33
RMSSD (ms)	22 (9)	21 (8)	19 (7)	0.37

Comparisons are made with analysis of variance for repeated measures. Skewed data were transformed before statistical comparisons.

The ET combination does not appear to be associated with similar cardiotoxicity problems that paclitaxel–anthracycline combinations are. Doxorubicin–paclitaxel has reportedly caused clinically significant cardiotoxicity in 6–20% of patients and a decrease in the LVEF in 20–50% of patients [2,5–7,13]. A recent study has shown that paclitaxel increases the conversion of doxorubicin to the cardiotoxic doxorubicinol, which may be one of the factors related to the high incidence of CHF seen with this combination [31]. There are patients who suffer cardiotoxicity or CHF with AT [13]. No pharmacokinetic interactions of clinical significance have been observed with ET combinations [32]. Our results demonstrate that ET has a good cardiotoxic profile. Importantly, it proved safe even for patients with risk factors, such as old age, left thoracic wall irradiation, hypertonia and/or angina pectoris and previous chemotherapy.

In conclusion, first-line chemotherapy in metastatic breast cancer with ET did not cause clinical cardiac side effects in patients with breast cancer. Furthermore, no decrease in HRV as a marker of autonomic impairment and subclinical cardio toxicity was observed.

Ambulatory 24-h ECG in combination with echocardiography showed to be a feasible method to assess cardiac functioning during normal activities of the patients.

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