Cancer Chemother Pharmacol (1989) 23: 101–104

Cancer Chemotherapy and Pharmacology

Prospective evaluation of chronic cardiotoxicity due to high-dose epirubicin or combination chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil

H. Havsteen[1], I. Brynjolf[2], T. Svahn[1], P. Dombernowsky[1], J. Godtfredsen[3], and O. Munck[2]

[1] Department of Oncology, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark
[2] Department of Clinical Physiology and Nuclear Medicine, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark
[3] Department of Cardiology, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark

Summary. In a prospective study the left ventricular ejection fraction (LVEF), right ventricular ejection fraction (RVEF), systolic blood pressure, ECG, and heart rate were recorded at rest and during submaximal work to compare the cardiotoxic effect of epirubicin with a combination chemotherapy without known cardiotoxicity. A total of 14 females with advanced breast cancer were treated with epirubicin at a median cumulative dose of 827 mg/m^2 (range, 550–1244). These patients had previously received cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or cyclophosphamide alone as adjuvant treatment, or CMF for advanced disease. The control group consisted of 11 females with advanced breast cancer given CMF only. The systolic blood pressure at rest as well as during submaximal work was significantly lower ($P < 0.05$) after treatment in the epirubicin group than in the CMF controls. With regard to LVEF, the median value of 54% at rest was significantly lower after treatment in the epirubicin group than in the controls (59%). There was a significant fall in LVEF at rest and during exercise in the epirubicin group, whereas no such changes were found in the CMF controls after treatment. The RVEF was unaffected. In the epirubicin-treated group one patient developed fatal congestive heart failure, and in the remaining 13 patients treatment was discontinued due to progression of the cancer and not to cardiotoxicity. Thus, the cardiotoxicity of epirubicin changed the clinical outcome in only 1 of 14 patients with advanced breast cancer.

Introduction

Anthracyclines are some of the most valuable cytostatic agents for the treatment of malignant tumors [3]. Unfortunately, the cardiotoxicity of doxorubicin, the most widely used anthracycline, reduces its usefulness. In patients with breast cancer, the doxorubicin analogue epirubicin has recently shown antineoplastic efficacy comparable to that of doxorubicin, but with a lower frequency of congestive heart failure (CHF) at identical cumulative mg doses [11].

Measurement of the left ventricular ejection fraction (LVEF) is frequently used to demonstrate CHF due to anthracyclines, and though its predictive value seems disputable, it is probably the most reliable noninvasive method for predicting CHF [1, 13, 19].

To evaluate the cardiac response of epirubicin treatment, we therefore carried out a prospective study of ejection fraction during rest and exercise in patients with advanced breast cancer treated with epirubicin and a control group given combination chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF).

Material and methods

The study included 25 female patients with advanced breast cancer who could undergo an exercise test; 11 were treated with CMF and 14 with epirubicin. Of the 14 patients, 8 received 60 mg/m^2 epirubicin alone and 6 received 45 mg/m^2 with the addition of 3 mg/m^2 vindesine on days 1 and 8 every 4 weeks. The CMF regimen consisted of 400 mg/m^2 cyclophosphamide, 40 mg/m^2 methotrexate, and 500 mg/m^2 5-fluorouracil i.v. on days 1 and 8 every 4 weeks.

The CMF treatment was given to previously untreated patients, whereas epirubicin was given to those who had previously received CMF or cyclophosphamide as adjuvant treatment (four patients) or for advanced disease (ten patients). The treatment with CMF alone or CMF followed by epirubicin was not randomized, as our standard treatment in the study period for advanced disease was CMF followed by epirubicin. The median treatment duration was 6 months (range, 3–13) in the CMF group and 9 months (range, 6–12) in the epirubicin group (no significant difference). The median age was 56 years (range, 46–64) in the CMF group and 53 years (range, 34–66) in the epirubicin group. The median cumulative dose of epirubicin was 827 mg/m^2 (range, 550–1244). Three patients treated with epirubicin had received photon irradiation to the scar area 8–11 years earlier. No patient had clinical or electrocardiographic signs of ischemic heart disease.

In the epirubicin group, treatment was discontinued due to progressive disease in all patients except one in whom the discontinuation was due to a marked fall in LVEF at rest. In the CMF group, treatment was stopped due to progressive disease in seven patients, severe subjective side effects in one, and complete remission in three.

A physical examination, chest X-ray, rest and exercise determinations of the left ventricular ejection fraction (LVEF), right ventricular ejection fraction (RVEF), work

Offprint requests to: P. Dombernowsky, Department of Oncology, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark

load, blood pressure, and heart rate, together with an ECG, were carried out before chemotherapy was begun. Evaluations were repeated at cumulative doses of epirubicin of 350 mg/m^2 and every 100 mg/m^2 thereafter. In the CMF group, similar evaluations were done every 6 months during therapy. The examinations of all patients were repeated after chemotherapy was terminated.

The ejection fraction measurements were all done 2–3 weeks after the last course of chemotherapy to avoid possible acute cardiotoxic effects. The baseline measurements and those done 2–3 weeks after the chemotherapy had been given were compared for evaluation of the cardiotoxic effect.

Informed consent was obtained from all patients, and the study was designed and conducted in compliance with the Helsinki Declaration II and approved by the Local Scientific Ethical Committee.

RVEF and LVEF. The RVEF and LVEF were measured before and during exercise in the left anterior oblique position. The RVEF was calculated as follows from a first-pass isotopic washout curve after a bolus injection of the patient's red blood cells labelled in vitro with approximately 370 mBq of ^{99m}Tc-methylenediphosphonate:

$$EF = \frac{EDC - ESC}{EDC} \times 100,$$

where EDC represents the end-diastolic counts and ESC, the end-systolic counts. Another bolus injection of 370 mBq was given for the exercise measurement.

For LVEF measurements, a multiple ECG-gated equilibrium cardiac blood-pool scan was carried out and the ejection fractions were calculated according to the formula above, with all counts corrected for background activity. The methods have previously been described in detail [6, 7]. In the latter paper [7] we showed that the right anterior oblique, anteroposterior, and left anterior oblique projection gave similar results for the RVEF.

In our laboratory the standard deviation of the difference between two determinations of LVEF during rest is 3.2% (EF units) when three determinations are made by two different observers. This means that a decrease or increase of 10% is significant with 99% probability [10a].

Statistical methods. The initial measurements in the epirubicin group were compared with those in the CMF group, and the measurements obtained at the maximal cumulative dose of epirubicin were compared with those obtained after treatment with CMF using the Mann-Whitney rank-sum test for unpaired data.

The measurements obtained after treatment with CMF were compared with the initial ones in the same patients. The corresponding measurements in the epirubicin group at the maximal cumulated dose were compared with the initial values in the same patients using the Pratt matched-pair signed-rank test for paired observations. The chi-square test with Yates correction was used to test the significance between two proportions. All tests were two-sided and a significance level of 5% was chosen.

Results

Table 1 shows patient characteristics such as age, performance status, extent of disease, cardiac disease (hypertension, angina, other heart disease, and drugs affecting cardiac function), and ECG in the epirubicin and CMF groups before and after treatment. There was no difference between these characteristics before and after treatment. It should be stressed that the proportion of patients in the two groups with performance status 2 after treatment, 7/14 vs 3/11, was not significantly different ($X^2 = 0.17$).

Table 2 and Fig. 1 show the hemodynamic response to submaximal exercise before and after treatment in the two groups. There were no significant differences in the work load, duration of submaximal exercise, and heart rate at rest and during exercise before and after treatment between the epirubicin and CMF groups. As to the systolic blood pressure at rest and during exercise, the median value was significantly lower ($P < 0.05$) after treatment in the epirubicin group than in the CMF controls.

Ejection fraction

There was no difference in the RVEF within and between the two treatment groups either before or after treatment. On the other hand, the median value of 54% for LVEF at rest was significantly lower after treatment in the epirubicin group than in the controls (59%). The fall in LVEF at rest from 59% to 54% after treatment in the epirubicin group was also significant ($P < 0.05$). Likewise, there was a significant fall in LVEF from 68% to 62% during exercise after treatment in the epirubicin group ($P < 0.05$), whereas no significant changes between pre- and posttreatment values were observed in the CMF controls.

Table 1. Characteristics of 25 patients with advanced breast cancer before and after treatment with epirubicin or CMF

		No. of patients	Age (median and range)	Performance status (no. of patients)		Extent of disease (no. of patients)		Cardiac disease (no. of patients)	abnormal ECG (no. of patients)
				1	2	local	dissiminated		
Epirubicin	before treatment	14	53 years (34–66)	9	5	4	10	1	0
	after treatment	14	–	7	7	4	10	1	1
CMF	before treatment	11	56 years (46–64)	9	2	6	5	1	0
	after treatment	11	–	8	3	6	5	1	1

Table 2. Hemodynamic response to submaximal exercise before and during treatment with epirubicin or CMF in advanced breast cancer (median and range)

		Work load		Heart rate (beats/min)		Systolic blood pressure mm Hg		Right ventricular ejection fraction (%)		Left ventricular ejection fraction (%)	
		KPM	Min	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
Epirubicin ($N=14$) 53 years (34–66)	before treatment	288 (150–450)	7 (3–9)	88 (54–95)	128 (104–145)	128 (105–160)	160 (130–210)	38 (28–58)	53 (36–71)	59[c] (40–68)	68[d] (50–75)
	after treatment	208 (150–450)	7 (4–15)	79 (55–100)	125 (100–150)	123[a] (110–130)	150[a] (120–210)	44 (33–52)	52 (37–61)	54[b,c] (37–67)	62[d] (47–72)
CMF ($N=11$) 56 years (46–64)	before treatment	300 (175–450)	6 (4–9)	78 (70–118)	120 (110–150)	135 (110–160)	175 (140–180)	40 (32–51)	59 (35–78)	63 (43–72)	64 (53–82)
	after treatment	300 (150–450)	6 (4–10)	80 (62–105)	128 (114–150)	130[a] (120–150)	185[a] (130–210)	42 (34–62)	55 (44–71)	59[b] (45–75)	67 (52–83)

[a] $P<0.05$; significance of difference between median values of systolic blood pressure at rest and during exercise in the epirubicin and CMF groups after treatment
[b] $P<0.05$; significance of difference between median values of LVEF at rest in the epirubicin and CMF groups after treatment
[c] $P<0.05$; significance of difference between paired data of LVEF at rest before and after treatment in the epirubicin group
[d] $P<0.05$; significance of difference between paired data of LVEF during exercise before and after treatment in the epirubicin group

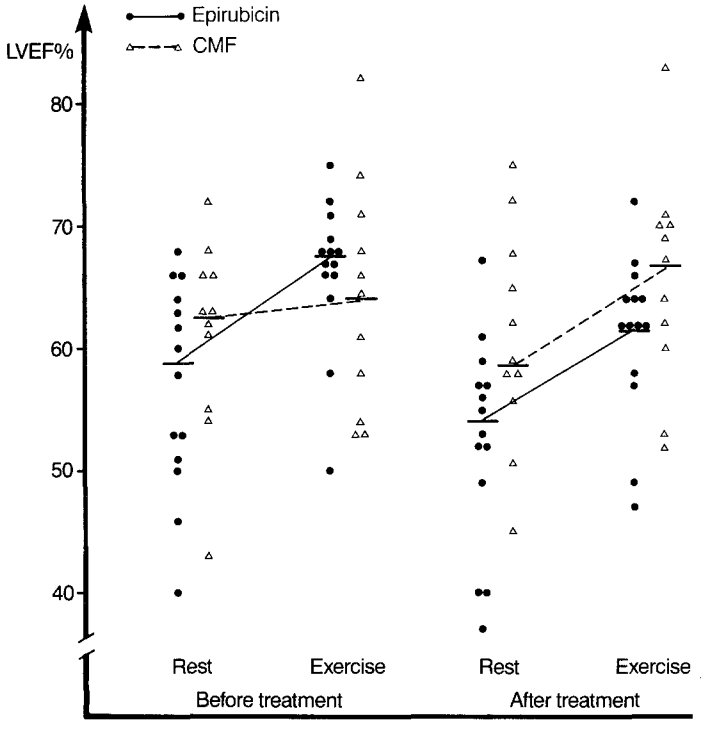

Fig. 1. Left ventricular ejection fraction (*LVEF*) from rest to exercise before and after treatment with epirubicin (●) and CMF (△). LVEF at rest was significantly decreased ($P<0.05$) after epirubicin treatment and was also significantly lower than in the CMF-treated controls. LVEF during exercise was significantly decreased after epirubicin compared with CMF. The median values are indicated by –

One female patient (52 years old) in the epirubicin group (but none in the CMF group) developed clinically overt CHF; she suffered from chronic obstructive pulmonary disease but, apart from a low RVEF, all initial measurements were normal. Her LVEF was 53% before treatment and remained normal until a cumulative dose of 797 mg/m^2 was reached. Her LVEF during rest was then only 37%; consequently, the epirubicin treatment was stopped. At this time the patient had no signs of clinical CHF. However, 4 months later she developed cardiomegaly and pulmonary congestion and died of CHF 6 months after the last dose of epirubicin.

ECGs were normal throughout the study except in a patient with hypertension and hyperlipidemia, who developed mild ischemia during exercise at a cumulative dose of 1100 mg/m^2 epirubicin.

Discussion

The long-term administration of doxorubicin is limited by cumulative, dose-dependent, chronic cardiotoxicity. In retrospective studies, the incidence of CHF has been estimated to be approximately 3%–4% after a cumulative dose of 450 mg/m^2 and 6%–10% after 550 mg/m^2 [12, 14, 18]. The incidence rises steeply after higher cumulative doses. In a recent study, CHF occurred in 14% of the patients who received 430–600 mg/m^2 doxorubicin on a 3-week schedule [9].

Epirubicin is an anthracycline analogue with antitumor activity similar to that of doxorubicin, but with reduced cardiotoxicity in animal models [8, 10, 17]. In clinical prospective randomized trials its antitumor activity has been found to be identical to that of doxorubicin in breast cancer and soft tissue sarcoma [4, 11, 15].

The evaluation and prediction of anthracycline cardiotoxicity still remain a problem, and it would be of great value to have a simple method for demonstrating subclinical cardiotoxicity. Endomyocardial biopsy has been used for this purpose but is not widely accessible [2]. Chest X-ray, electrocardiography, and systolic time intervals have not been able to predict cardiotoxicity [1]. Measurements of LVEF by radionuclide angiocardiography give a reliable estimation of the heart function; Alexander et al. [1] have found that the LVEF at rest can predict CHF, al-

though other authors consider the sensitivity to be too low [13, 19]. The addition of exercise LVEF is said to increase the sensitivity but lower the specificity [13].

In this study, a moderate but significant decrease in LVEF was found in patients with advanced breast cancer undergoing epirubicin treatment compared with CMF-treated patients (Table 2, footnote *b*). The analysis of paired data showed a fall in LVEF at rest (Table 2, footnote *c*) and during exercise (Table 2, footnote *d*) in the epirubicin groups.

The range of LVEF before treatment was 40%–72%. However, the LVEF at rest also varied much as previously found among 22 healthy controls, where the range was 46%–68% [6]. Furthermore, after treatment the systolic blood pressure at rest and during exercise was significantly lower with epirubicin than with CMF (Table 2, footnote *a*). The RVEF did not change after either treatment. Our results suggest that the cardiotoxic effect was due to the epirubicin treatment and not to progression of the malignant disease as such (Table 1), although the two treatment groups were not truly equivalent with regard to previous chemotherapy.

In human studies, it has been shown that high-dose cyclophosphamide (240 mg/kg over a 4-day period) has cardiotoxic properties [16], but this observation has not been confirmed by others with the normally used dose of cyclophosphamide [5]. Furthermore, the combination of 5-fluorouracil, methotrexate, and vindesine has not been shown to be cardiotoxic, and in the present study treatment with CMF did not result in significant changes in the ejection fractions during rest or exercise.

Jain et al. [11] treated 24 patients with advanced breast cancer with 85 mg/m^2 epirubicin every 3 weeks. Four of these patients developed clinical CHF at total doses of 1035, 1105, 1162, and 1234 mg/m^2. In the present study, where the median dose of epirubicin was 827 mg/m^2, only one patient developed CHF at a cumulative dose of 797 mg/m^2.

In contrast to CMF, epirubicin is cardiotoxic at a high total dose. Of 14 patients, 1 developed fatal CHF several months after discontinuation of the treatment. In the remaining patients, the epirubicin treatment was discontinued due to progression of the cancer and not to cardiotoxicity. Thus, despite the decrease in LVEF in the epirubicin group as a whole, the cardiotoxicity of epirubicin changed the clinical outcome in only one patient.

References

1. Alexander J, Dainiak N, Berger HJ, Goldman L, Johnstone D, Reduto L, Duffy T, Schwartz P, Gottschalk A, Zaret BL (1979) Serial assessment of doxorubicine cardiotoxicity with quantitative radionucleide angiocardiography. N Engl J Med 300: 278–283
2. Billingham ME, Mason JW, Bristow MR, Daniels JR (1978) Anthracycline cardiomyopathy monitored by morphologic changes. Cancer Treat Rep 62: 865–872
3. Blum RH, Carter SK (1974) Adriamycin. A new anticancer drug with significant clinical activity. Ann Intern Med 80: 249–259
4. Brambilla C, Rossi A, Bonfante V, Ferrari L, Villani F, Crippa F, Bonadonna G (1986) Phase II study of doxorubicin versus epirubicin in advanced breast cancer. Cancer Treat Rep 70: 261–266
5. Bristow MR, Mason JW, Billingham ME, Daniels JR (1978) Doxorubicin cardiomyopathy: evaluation by phonocardiography, endomyocardial biopsy and cardiac catherization. Ann Intern Med 88: 168–175
6. Brynjolf I, Kelbæk H, Munck O, Godtfredsen J, Larsen S, Eriksen U (1984) Right and left ventricular ejection fraction and left ventricular volume changes at rest and during exercise in normal subjects. Eur Heart J 5: 756–761
7. Brynjolf I, Gjørup T, Vestergaard B, Jensen AM, Munck O (1985) Right ventricular ejection fraction determined in three projections. Nucl Med Commun 6: 281–286
8. Casazza AM (1979) Experimental evaluation of anthracycline analogs. Cancer Treat Rep 63: 835–844
9. Dresdale A, Bonow RO, Wesley R, Palmeri ST, Barr L, Mathison D, D'angelo T, Rosenberg SA (1983) Prospective evaluation of doxorubicin-induced cardiomyopathy resulting from postsurgical adjuvant treatment of patients with soft tissue sarcomas. Cancer 52: 51–60
10. Giuliani FC, Spreafico F, Casazza AM (1983) Preclinical studies on new anthracyclines: antitumor, toxicologic and pharmacologic properties. In: Anthracyclines and cancer-therapy. Excerpta Medica, Amsterdam, p 192
10. aGjørup T, Kelbæk H, Vestergaard B, Fogh J, Munck O, Mørup Jensen A (1989) Reproducibility in the analysis of multigated radionuclide studies of left ventricular ejection fraction. Investigative Radiology (in press)
11. Jain KK, Casper ES, Geller NL, Hakes TB, Kaufmann RJ, Currie V, Schwartz W, Cassidy C, Petroni GR, Young CW, Wittes RE (1985) A prospective randomized comparison of epirubicin and doxorubicin in patients with advanced breast cancer. J Clin Oncol 3: 818–826
12. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA (1973) A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer 32: 302–314
13. McKillop JH, Bristow MR, Goris ML, Billingham ME, Bockemuehl K (1983) Sensitivity and specificity of radionuclide ejection fractions in doxorubicin cardiotoxicity. Am Heart J 106: 1048–1056
14. Minow RA, Benjamin RS, Gottlieb JA (1975) Adriamycin (NSC-123127) cardiomyopathy: an overview with determination of risk factors. Cancer Chemother Rep 6: 195–201
15. Mouridsen HT, Somers R, Santoro A, Mulder JH, Bramwell V, Van Oosterom AT, Sylvester R, Thomas D, Pinedo HM (1984) Doxorubicin vs epirubicin in advanced soft tissue sarcomas. An EORTC randomized phase II study. In: Bonadonna G (ed) Advances in anthracycline chemotherapy: epirubicin. Masson Italia Editori, Milano, p 95
16. O'Connell TX, Berenbaum MC (1974) Cardiac and pulmonary effects of high doses of cyclophosphamide and isophosphamide. Cancer Res 34: 1586–1591
17. Soldani G, Del Tacca M, Giovannini L, Bertelli A (1981) The effects of antiadrenergic and antihistaminic drugs on ECG alterations induced by anthracyclines in rats. Drugs Exp Clin Res 7: 31–36
18. Von Hoff DD, Layard MW, Basa P, Davis HL, Von Hoff AL, Rozencweig M, Muggia FM (1979) Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 91: 710–717
19. Wheeler RH, Ensminger WD, Thrall JH, Anderson JL (1982) High-dose doxorubicin: an exploration of the dose-response curve in human neoplasia. Cancer Treat Rep 66: 493–498

Received November 2, 1987/Accepted May 17, 1988