

SCIENTIFIC LETTER

Evaluation of long term cardiotoxicity after epirubicin containing adjuvant chemotherapy and locoregional radiotherapy for breast cancer using various detection techniques

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Breast cancer patients who present with only locoregional lymphatic metastases have good life expectancy after treatment with surgery and adjuvant anthracycline-containing chemotherapy. Anthracyclines, however, can induce cardiomyopathy, and this may become clinically manifest as chronic heart failure many years after exposure.¹ As the occurrence of this side effect is dependent on the cumulative dose given, breast cancer patients with a favourable prognosis are treated with rather low doses of anthracyclines in order to prevent severe cardiac damage.

METHODS

We investigated 56 breast cancer patients in a cross sectional design, to determine whether a low cumulative dose of the anthracycline compound epirubicin causes chronic cardiac damage.

The patients were two or more years after treatment with adjuvant chemotherapy, consisting of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC). The chemotherapy had been given after mastectomy or after breast conserving treatment, and was followed by locoregional radiotherapy (40 to 50 Gy). Thirty patients had been treated with five cycles of FEC (total cumulative dose of epirubicin, 450 mg/m²). Twenty six patients had received four cycles of FEC (total cumulative dose of epirubicin, 360 mg/m²), followed by high dose combination chemotherapy consisting of cyclophosphamide, thiotepa, and carboplatin with haematopoietic stem cell rescue. Their median age at the time of cardiac evaluation was 49 years (range 27 to 58), and the median time after chemotherapy was 37 months (range 24 to 79).

Cardiac evaluation included the following:

- a history and physical examination focusing on signs and symptoms related to cardiac failure
- radionuclide ventriculography for assessment of the left ventricular ejection fraction (LVEF) (normal value > 0.50)
- echocardiography to determine diastolic function by the ratio of early peak flow velocity to atrial peak flow velocity (E/A ratio; normal value > 1), and the early peak flow deceleration time (DT; normal < 220 ms)²
- 24 hour Holter monitoring for heart rate variability analysis as a measure of autonomic function, calculating the following time domain parameters: mean of all normal to normal RR intervals (mean NN, ms), standard deviation of all NN intervals in 24 hours (SDNN, ms), standard deviation of the average NN intervals calculated over five minute segments (SDANN, ms), the average of the five minute standard deviation of the NN interval calculated over 24 hours (SDNN index, ms), and the root mean square successive difference of RR intervals (rMSSD, ms).³

Heart rate variability in the patients was compared with heart rate variability in a control group consisting of 56 healthy age matched women. Mean values in the two groups were compared using a two tailed Student *t* test. Pearson's correlation coefficient was used to test correlations between variables. Data are expressed as mean (SD).

RESULTS

Before the start of chemotherapy none of the patients had cardiac disease or cardiac complaints. At the time of cardiac evaluation, 17 (30%) were experiencing exertional dyspnoea (New York Heart Association (NYHA) class II). None of the evaluated patients had NYHA class III or IV symptoms or apparent clinical signs of congestive heart failure on physical examination. The mean LVEF (determined in 54 patients) was 0.57 (range 0.39 to 0.73). A decreased LVEF value (< 0.50) was observed in six patients (11%).

Successful echocardiography in 53 patients showed a mean E/A ratio of 1.1 (range 0.7 to 2.5), and a mean DT of 170 (range 90 to 352) ms. The E/A ratio was < 1 in 20 of the patients (38%). Compared with the age matched healthy women, the patients had a higher mean heart rate (83 (7) v 76 (8) beats/min; *p* < 0.0001) and all heart rate variability indices reflecting short term vagal mediated fluctuations were reduced, including the SDNN index (48 (14) v 59 (16) ms, *p* = 0.001) and the rMSSD (25 (11) v 36 (16) ms; *p* < 0.0001). The SDNN and SDANN, which are more related to sympathetic activity, did not differ from the control group.

Within the patient group age independent correlations were found between the E/A ratio and heart rate variability indices including SDNN (*r* = 0.42; *p* = 0.003), SDANN (*r* = 0.44; *p* = 0.002), and the SDNN index (*r* = 0.33; *p* = 0.026).

A subanalysis of cardiac function data was performed between patients with exertional dyspnoea (*n* = 17 of 56; 30%) and those without exertional dyspnoea (table 1). There was no difference in age or time after chemotherapy between these two groups, and the mean LVEF was comparable. However, patients with exertional dyspnoea had a lower E/A ratio and a longer DT, indicating impaired diastolic function. Furthermore, all heart rate variability indices in these patients were reduced compared with the patients with no exertional dyspnoea. Overall, no differences were found between the two chemotherapy regimens. Left sided thoracic radiotherapy was not associated with a greater degree of cardiac damage.

COMMENT

Our data show that a low cumulative dose of epirubicin (360-450 mg/m²), which is considered safe with respect to cardiotoxicity in the short term,⁴ seems to induce chronic mild cardiac damage in a substantial proportion of the patients.

Table 1 Comparison of patients with and without exertional dyspnoea

Characteristic	With exertional dyspnoea (n=17)	Without exertional dyspnoea (n=39)	Mean difference (95% CI)	p Value
Radionuclide ventriculography				
LVEF	0.57 (0.8)	0.58 (0.7)	0.01 (-0.43 to 0.45)	NS
Echocardiography				
E/A ratio	1.0 (0.3)	1.2 (0.4)	0.2 (0.01 to 0.39)	0.005
DT (ms)	196 (52)	164 (38)	-32 (-59.45 to -4.55)	0.003
Heart rate variability				
Heart rate (beats/min)	85 (7)	82 (8)	-3 (-7.17 to 1.17)	NS
SDNN (ms)	117 (23)	144 (38)	27 (10.82 to 43.18)	0.01
SDANN (ms)	108 (23)	134 (37)	26 (10.05 to 41.95)	0.01
SDNN index (ms)	42 (10)	52 (17)	10 (2.85 to 17.15)	0.02
rMSSD (ms)	20 (8)	28 (12)	8 (2.65 to 13.35)	0.01

Data are mean (SD) or mean and 95% confidence interval (CI).

DT, deceleration time; E/A ratio, ratio of early peak flow velocity to atrial peak flow velocity; LVEF, left ventricular ejection fraction; mean NN, mean of all NN intervals (NN=normal to normal RR interval); rMSSD, root mean square of successive differences of NN intervals; SDANN, standard deviation of the average NN intervals computed over five minute segments; SDNN, standard deviation of all NN intervals; SDNN index, average of all standard deviations of NN intervals computed over five minute segments.

Abnormal systolic function was found in 11% of the patients, while abnormal diastolic function occurred in 38%. Autonomic function as measured by heart rate variability was generally impaired—in particular vagal activity—compared with the healthy age matched controls. Thirty per cent of the patients experienced exertional dyspnoea which was not present before chemotherapy, and this complaint seemed to be related to diastolic and autonomic dysfunction. The positive age independent correlation found between the heart rate variability and diastolic function suggests that the reduction in heart rate variability in these patients may be secondary to diastolic dysfunction.

CONCLUSIONS

Our findings stress the importance of careful cardiac follow up in patients treated with anthracyclines, including those treated with low cumulative doses. It is evident that normal systolic function does not exclude cardiotoxicity. As previous reported,⁵ diastolic and autonomic dysfunction may be earlier signs of chronic anthracycline induced cardiac damage. Whether the affected patients are at increased risk of severe congestive heart failure in the long term needs further follow up.

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CORRECTION

Constantinides S, Lo TSN, Been M, Shiu MF. Early experience with a helical coronary thrombectomy device in patients with acute coronary thrombosis. *Heart* 2002;**87**:455–60

The figures accompanying the captions to figs 4 and 5 were inadvertently transposed. Thus, the figure accompanying fig 4 caption (on page 457) is fig 5, and the figure accompanying fig 5 caption (on page 458) is fig 4. The error is regretted.