

Cardiac troponin T for early detection of cardiotoxicity in breast cancer patients treated with epirubicin

Research Article

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Abstract: The aim of the study was to investigate the role of cTnT for the prediction of long term cardiac dysfunction after epirubicin-containing adjuvant chemotherapy for breast cancer. The study group comprised of 45 patients (all female; mean age 48 ± 8 years), treated with epirubicin-containing adjuvant chemotherapy for stage 2 and stage 3 breast cancer. Patients received either 4 cycles of cyclophosphamide plus epirubicin (90 mg/m^2) ($n=23$; stage 2 breast cancer) or 6 cycles of cyclophosphamide plus epirubicin (75 mg/m^2) plus fluorouracil ($n=18$; stage 3 breast cancer). Venous blood samples were drawn, before and 72 hours after, every cycle of chemotherapy for the measurement of cTnT. Cardiac assessment was carried out at baseline and 1 year after chemotherapy by clinical evaluation, electrocardiography, radio-nuclide ventriculography (RNV) and transthoracic echocardiography. All patients remained free of clinical heart failure during the study period. In 26 patients (63%), cTnT was elevated after chemotherapy. Mean left ventricular ejection fraction, assessed by RNV at baseline and one year after chemotherapy, were $61 \pm 8\%$ and $56 \pm 7\%$ ($p < 0.0001$). The sensitivity and specificity of cTnT for the detection of left ventricular systolic dysfunction at one year were 69% and 39% respectively. Echocardiographic examinations at baseline and one year after chemotherapy revealed a significant decrease in E/A ratio from 1.15 ± 0.3 to 0.9 ± 0.2 in cTnT positive patients, suggesting diastolic dysfunction. In conclusion, elevated serum cTnT levels after epirubicin-containing adjuvant chemotherapy for stage 2 and stage 3 breast cancer, predict future cardiac dysfunction with moderate sensitivity and poor specificity.

Keywords: Breast cancer • Chemotherapy • Epirubicin • Cardiotoxicity • cTnT

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1. Introduction

Anthracycline-induced cardiotoxicity is a potential obstacle for the management of cancer patients [1]. As it may take years for cardiac dysfunction to be clinically evident, an early biomarker is needed to predict cardiac toxicity after anthracycline exposure [1-4]. Cardiac troponin T (cTnT) and troponin I (cTnI) assays have a very high myocardial tissue sensitivity, reflecting even microscopic zones of myocardial necrosis [5].

Elevation of cTnT and cTnI levels were previously reported to predict subsequent cardiac dysfunction in patients treated with various anthracycline-containing chemotherapy regimens [6,7]. Epirubicin is the stereoisomer of doxorubicin with potentially less side effects [8,9]. We investigated the role of cTnT for predicting long term systolic and diastolic dysfunction after epirubicin-containing adjuvant chemotherapy for breast cancer.

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2. Material and Methods

2.1. Study population

The study group comprised of 45 patients (all female; mean age 48 ± 8 years), treated with epirubicin-containing adjuvant chemotherapy for stage 2 and stage 3 breast cancer. Patients received either 4 cycles of cyclophosphamide plus epirubicin (90 mg/m^2) ($n=23$; stage 2 breast cancer) or 6 cycles of cyclophosphamide plus epirubicin (75 mg/m^2) plus fluorouracil ($n=18$; stage 3 breast cancer). All of the patients had undergone either modified radical mastectomy or breast-saving surgery before enrollment. Patients with metastasis, ischemic or valvular heart disease, any type of cardiomyopathy, heart failure, baseline left ventricular ejection fraction (LVEF) less than 50%, and uncontrolled hypertension were excluded from the study. Two patients were dropped out due to new onset metastasis within one year, and two additional patients were lost during follow up. The remaining 41 patients completed the follow up at one year.

The study protocol was approved by the local ethics committee, and all of the patients and the control subjects gave written informed consent.

2.2. Cardiac assessment

Cardiac assessment was done at baseline and 1 year after chemotherapy by clinical evaluation, electrocardiography (ECG), transthoracic echocardiography and radionuclide ventriculography (RNV). Left ventricular ejection fraction (LVEF) was determined by RNV using the left anterior oblique projection at baseline and 1 year after chemotherapy. Significant systolic dysfunction due to chemotherapy was defined as a final LVEF $<50\%$, or an absolute drop of more than 10% in LVEF at one year. Left ventricular diastolic function was assessed by transthoracic echocardiography (GE Vingmed System 5; Horten-Norway). Among diastolic function parameters; early transmitral flow velocity to atrial flow velocity (E/A) ratio, isovolumic relaxation time (IVRT) and deceleration time of early transmitral flow velocity (DT) were measured from apical four-chamber view.

2.3. cTnT and CPK-MB measurements

Venous blood samples were drawn before (T0) and 72 hours (T1) after every cycle of chemotherapy. The samples were centrifuged at 11000 rpm for 2 minutes and serum was stored at -20°C until the end of the study. Serum cTnT was measured by electrochemiluminescence immunoassay (Elecsys 2010; Roche Diagnostics, Indianapolis, IN) and a value of $> 0.01 \text{ ng/ml}$ was considered elevated. CK-MB was

Table 1. Sensitivity and specificity of cTnT for the detection of systolic dysfunction at 1 year.

	Systolic dysfunction ($n=13$)	Normal systolic function ($n=28$)
cTnT (+) ($n=26$)	9	17
cTnT (-) ($n=15$)	4	11

Sensitivity: $9/13 = 69\%$

Specificity: $11/28 = 39\%$

Positive predictive value: $9/26 = 35\%$

Negative predictive value: $11/15 = 73\%$

cTnT (+): Patients with elevated cardiac troponin T ($> 0.01 \text{ ng/ml}$)

cTnT (-): Patients with normal cardiac troponin T ($< 0.01 \text{ ng/ml}$)

measured for the assessment of possible major cardiac damage using immunologic ultraviolet assay (Roche/Hitachi 917; Roche Diagnostics, Indianapolis, IN) and a value of $> 24 \text{ U/l}$ was considered elevated.

2.4. Statistical analysis

All statistical analyses were performed using SPSS software version 11.5 (SPSS, Inc., Chicago, Illinois). Data were presented as mean $\pm$ standard deviation. Comparisons between groups were done using the chi-square test for categorical variables and ANOVA for continuous variables. A value of $p < 0.05$ was considered statistically significant.

3. Results

All patients remained free of clinical heart failure during the study period. Serum cTnT levels were within normal range at the baseline evaluation as well as before each cycle of chemotherapy. In 26 patients (63%), cTnT was elevated ($> 0.01 \text{ ng/ml}$) at least after one cycle of chemotherapy. Serum CK-MB levels remained within the normal range after each cycle of chemotherapy. Mean LVEF assessed by RNV at baseline and one year after chemotherapy were $61 \pm 8\%$ and $56 \pm 7\%$ ($p < 0.0001$). Systolic dysfunction defined as a final LVEF $<50\%$, or an absolute drop of more than 10% in LVEF at one year developed in 13 of the 41 patients (31.7%). The sensitivity and specificity of cTnT for the detection of left ventricular systolic dysfunction at one year were 69% and 39% respectively. The corresponding negative and positive predictive values were 73%, and 35% (Table 1).

Echocardiographic examinations at baseline and one year after chemotherapy revealed a significant decrease in E/A ratio from 1.15 ± 0.3 to 0.9 ± 0.2 in cTnT positive patients ($p < 0.005$). Final IVRT and DT were both similar when compared to baseline values in these patients.

4. Discussion

Treatment with anthracycline-containing chemotherapy is associated with significant reductions in the rates of recurrence and death among patients with breast cancer [10-11]. Because of the relatively younger mean age at diagnosis and higher survival rates after chemotherapy, patients with breast cancer need to be followed up for the long term consequences of treatment [12-13]. Although anthracycline-induced cardiac toxicity can be documented by endomyocardial biopsy, the invasive nature of the procedure limits the usefulness of this technique [14]. RNV and echocardiography are the main instruments for the detection of cardiac toxicity. Whereas highly accurate quantification of the decline in systolic function can be carried out by RNV, echocardiography offers advantages when anthracycline-induced diastolic dysfunction is also in question [15,16].

As expected, our study reveals that epirubicin-containing adjuvant chemotherapy may result in cardiac toxicity one year after the completion of therapy. Increased levels of cTnT along with significant reductions in LVEF and E/A ratio suggest a deterioration of both systolic and diastolic functions. In line with our results, anthracycline-containing chemotherapy has been previously demonstrated to cause subclinical diastolic dysfunction before systolic dysfunction becomes evident [17,18].

Four of our patients with elevated cTnT levels had normal cardiac function at one year. One year follow-up is a relatively short period to reveal the long-term cardiotoxicity of anthracyclines which may develop years after the completion of the chemotherapy, and

these four patients with elevated cTnT levels may be prone to develop cardiac dysfunction years after the completion of the chemotherapy [1,2].

Several clinical studies have reported increased levels of cardiac troponins after anthracycline-containing chemotherapy regimens. Measurement of these molecules for the prediction of future cardiac toxicity is associated with widely varying sensitivity and specificity [6,7,19-21]. These variations are possibly due to inhomogeneous characteristics of the studies. The present study indicates a moderate sensitivity (69%) and poor specificity (39%) of cTnT for the prediction of epirubicin induced systolic dysfunction detected by RNV at one-year follow-up. In asymptomatic patients, measurement of cTnT can help ruling out cardiac toxicity as the negative predictive value of a normal test result is 73%. We have also found that elevated levels of serum cTnT may predict a significant reduction in E/A ratio one year after chemotherapy, suggesting a possible diastolic dysfunction superimposed on systolic dysfunction. Formation of free radicals and superoxides resulting in systolic, as well as diastolic dysfunction is the most common hypothesis regarding the pathogenesis of cardiac toxicity, although the mechanism is not completely understood.

In conclusion, elevated serum cTnT levels after epirubicin-containing adjuvant chemotherapy for stage 2 and stage 3 breast cancer predict future systolic dysfunction documented by RNV with moderate sensitivity and poor specificity. Echocardiographic examinations reveal a possible diastolic dysfunction superimposed on systolic dysfunction among cTnT positive patients.

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