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The Value of Troponin Measurement in Assessment of Anthracycline Induced Cardiotoxicity in Breast Cancer Patients

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ABSTRACT

Purpose: Anthracyclines are the most frequent cause of treatment induced cardiotoxicity affecting about 7-15% of patients receiving more than 450-500 mg/m^2, cumulative dose **[16]**. The aim of the present study is to determine the efficacy of a new biochemical marker, cardiac troponin (cTnI), in the diagnosis of acute cardiac myocyte injury by anthracycline contaning chemotherapy and to compare its value versus the standard echoparameters.

Material and Methods: The study included 31 premenopausal breast cancer patients presented to NEMROCK during the period September 98 to June 99. Only 26 patients completed the full course of chemoradiotherapy protocol (6 cycles of FAC and concomitant radical RT) with serial serum monitoring of Troponin-1 performed 24 hrs after each cycle. In addition to serial serum CK-MB and echocardiogram on cycles 2,4 and 6.

Results: Analysis of variance with repeated measures revealed high statistical significance between the baseline serum troponin I and subsequent measures after each cycle. Serial values of CK-MB concentrations revealed no statistical significant change from the base line measurement. Also, there was statistical significance between the baseline fractional shortening and those values after the second, fourth and sixth cycle of treatment. Multivariate analysis of various risk factors related to cardiotoxicity revealed statistically significant difference between the mean dose of irradiation delivered to the heart volume and serum troponin I after the 2nd cycle (p =0.02) and this may be explained by the combined effect of chemoradiation. Also, there was a high statistically significant relationship between the adriamycin dose and the serum troponin I level after the 5th cycle of chemotherapy due to the cumulative effect of anthracyclines (p =0.0004).

Conclusion: The use of serial serum monitoring of cardiac troponin I as an early sensitive detector of acute myocyte injury could be of value following anthracycline base chemotherapy.

***Key words**: Cardiac troponin I - Anthracyline - Cardiotoxicity - Breast cancer.*

INTRODUCTION

Anthracylines are common antitumor agents that are widely used to treat patients with a variety of neoplastic diseases. However, acute and severe dose related chronic cardiomyopathy are a major limitation to optimal use of anthracycline antibiotics **[15]**.

Retrospective studies of doxorubicin-induced cardiotoxicity indicated that the incidence of clinical congestive heart failure in patients who received more than 450 mg/m^2 cumulative dose was 7-15%. Cancer patients with clinically important heart disease are thus generally not eligible for anthracycline therapy **[16]**.

Anthracyclines are among the most commonly used chemotherapeutic agents used in the management of breast cancer patients. They lower the risk of recurrence in pre and post menopausal node positive women and substantially improve the event-free survival and time to progression among such group of patients **[8]**.

The aim of the present study is to assess the validity and efficacy of serum troponin I and serum enzyme creatine kinase CK-MB versus the standard echocardiography for early diagnosis of acute dose related cardiomyopathy induced by anthracyclines in breast cancer patients treated by adjuvant anthracycline regimen (FAC), as well as to assess any additional cardiotoxic effect with the use of concomittant postoperative irradiation.

MATERIAL AND METHODS

This study included thirty one premenopausal breast cancer patients who presented to NEMROCK during the period September 98 to June 99 (inclusive) with pathologically proven breast carcinoma planned

to receive adjuvant 6 cycles of anthracyclines containing chemotherapy (FAC regimen). However, only 26 patients were evaluable and continued their treatment course.

All patients were subjected to pretreatment full history, physical examination and cardiac assessment using baseline ECG and echocardiography with determination of ejection fraction to exclude patients with any cardiac abnormalities. Also, measurement of baseline serum cardiac enzyme CK-MB and serum troponin I concentration were among the laboratory investigations included.

All patients received FAC regimen [4]: Fluorouracil 500 mg/m^2 adriamycin 50 mg/m^2 and endoxan 500 mg/m^2. It was given intravenously as bolus injection at 3 weeks interval for 6 cycles guided by the hematological recovery. Blood samples were taken 24 hours after administration of chemotherapy to assess the serum troponin I and DK-MB concentrations using a microassay procedure intended for the quantitation of antibodies to troponin and CK-MB [3]. This technique is thus based on microparticle enzyme immunoassay (MEIA) technology. Echocardiography was done at two cycles interval for serial monitoring of the LVED, LVES, fractional shortening and LVEF. Radiation therapy was given concomitantly with chemotherapy treatment for patients candidate for irradiation to a dose level of 50GY/25 treatments/5 weeks, mainly on cobalt 60 machines.

The study data were tabulated and statistically analyzed using the arithmetic mean, standard deviation, analysis of variance with repeated measures and Fisher's exact test.

RESULTS

Initially, this study included 31 patients. However, only 26 patients were evaluable as they completed the full course of post-operative adjuvant chemotherapy and radiation therapy treatment. The mean age of patients was 41.4 years (range 29-50 years). As regards the histopathology, 24 patients had invasive duct carcinoma, one patient had invasive lobular carcinoma and the last had mixed papillary and tubular carcinoma. Grade II tumors was encountered in 24 patients and grade III tumors in the remaining two patients (Table 1).

Baseline conventional 12 leads and resting ECG was done and it was normal in all patients. A-mode echocardiography was done for the assessment of systolic function and the overall contractility. The mean baseline left ventricular ejection fraction was 64.6% while the mean fractional shortening was 36.1% (Table 2).

Serial serum troponin I and serum CK-MB concentrations were detected 24 hours after each cycle of chemotherapy, with the mean values of serum troponin I concentrations being shown in (Table 3). Analysis of variance with repeated measures revealed statistically significant difference between the baseline serum troponin I level and subsequent measures after each cycle (Table 5). Serial values of serum CK-MB concentrations revealed no statistically significant difference between the baseline and the subsequent measurements (p >0.05), as all recorded concentrations were within normal range (0-10ng/ml) so that serum troponin I was much more sensitive than serum CK-MB in detecting acute myocardial injury.

M-mode echocardiography was done at two cycles interval to assess LVEF, fractional shortening and the overall contractility. The results were statistically significant between the base line fractional shortening and those after the second, fourth and sixth cycles of chemotherapy (Table 2). Comparing the effect of radiotherapy to either right or left chest wall revealed no relevant statistically significant difference in echo-parameters after the 6th cycle.

Correlation between the ejection fraction after the 6th cycle of chemotherapy and other possible risk factors related to cardiotoxicity including hypertension, the mean irradiation dose delivered to the heart from the internal mammary field, the tangential field, and the primary side (Rt. or Lt.) revealed statistically significant impact only for the hypertension present before treatment (p =0.05) (Table 3).

Multivariate analysis of various risk factors related to cardiotoxicity including adriamycin dose, the mean dose of irradiation delivered to the heart volume involved in the field of irradiation and the volume of the heart involved in the field of irradiation, was performed. The dependent factors were the serum troponin I level after the 2nd cycle, after the 5th cycle and the LVEF after the 6th cycle. The results revealed a statistically significant relation between the mean dose of irradiation delivered to the heart and the serum troponin level after the 2nd cycle and this may be explained by the combined effect of irradiation and chemotherapy in the induction of cardiac myocyte injury (p =0.02). As well, there existed a statistical significance between the mean dose of adriamycin given and the serum troponin I after the 5th cycle of chemotherapy (p =0.0004)

which could be attributed to the cumulative effect of doxorubicin which became evident later at the fifth cycle (Table 4).

To study the possible difference in radiation dose delivered to the heart and its impact on the induction of cardiotoxicity as an additional factor together with adriamycin, dose volume histograms were done for twenty patients (10 had right-sided disease and 10 left-sided disease). The effect of irradiation was analysed to know the contribution of irradiation from IMC and tangential fields on the volume of the heart involved in the field of irradiation in right and left-sided diseases. The results revealed that the mean dose of irradiation delivered from the IMC in cases of left-sided disease to the heart was 17 gy and 11 gy in right sided diseased patients while the mean dose of irradiation delivered from the tangential fields in case of left sided disease to the heart was 1.2 gy and 0.57 gy in right sided diseased patients. This denotes that the main contribution of irradiation to the heart is from the IMC field whether in case of right or left-sided disease, but the contribution is more on the left side, however, the effect of tangential fields on the heart is negligible. The mean dose of irradiation to the IMC was calculated using the dose value hsitogram computer system.

Table (1): Patients' characteristics (26 patients receiving chemoradiation)

Character	No.	Percent
Age (yrs):		
Mean	41.4±8.6	
Range	29-50y	
Menstrual status:		
Premenopausal	23	88.5%
Perimenopausal	3	11.5%
Histopathology:		
Invasive duct carcinoma	24	92.3%
Invasive lobular carcinoma	1	3.8%
Mixed tubular and papillary	1	3.8%
Tumor grade:		
Grade II	24	92.3%
Grade III	2	7.6%
Adriamcyin dose mg/cycle	50 mg/m^2	
Mean	85.5±10.4 mg	

Table (2): Effect of adriamcyin containing chemotherapy on echoparamaters in 26 patients receiving chemoradiation.

Echo parameter	Baseline Mean±SD	2nd cycle Mean±SD	4th cycle Mean±SD	6th cycle Mean±SD	*p*-value
LVED (cm)	4.8±0.5	4.64±0.5	4.74±0.6	5±0.8	0.15
LVES (cm)	3.1±0.3	3.04±0.4	3.05±0.6	3.3±0.8	0.07
LVEF (%)	646±5.2	62.8±6.2	62.1±6.7	60.2±8.6	0.06
LVFS (%)	36.1±4.5	32.8±5.6	33±5.7	32.5±6.6	0.01*

* Correlation between baseline LVFS% and subsequent values after 2nd, 4th and 6th cycles of chemotherapy was significant at *p* value = 0.01.

Table (3): Correlation between the left ventircular ejection fraction after 6 cycles of adriamycin containing chemotherapy and other risk factors in 26 evaluable patients receiving chemoradiation.

Risk factor	EF < 60%		EF ‡ 60%		Total	*p*-value
	No. of patients	%	No. of patients	%		
Hypertension	4	80%	1	20%	5	
Normal B.P.	7	32%	14	68%	21	0.05
Mean irradiation dose delivered to the heart volume from (IMC+Tangential fields)						
3<10Gy	4	40%	6	60%	10	
10-<15Gy	2	28.5%	4	71%	6	
>15Gy	5	50%	5	50%	10	0.81
Primary tumor site						
Right side	8	53%	6	47%	14	
Left side	3	25%	9	75%	12	0.32

Table (4): Multivariate analysis of the various risk factors related to cardiotoxicity in 26 evaluable patients receiving chemo-radiation.

Dependent factor	Independent parameters: *p*-value Regression coefficient (Rc)		
	Adriamycin dose	Mean dose of irradiation given to the heart volume	Volume of irradiation
Troponin after second cycle of chemotherapy	0.35 -8.666	0.02 -0.0245	0.39 -2.0903
Troponin after fifth cycle of chemotherapy	0.0004 -0.00421	0.06 0.019	0.01 6.98
Ejection fraction after sixth cycle of chemo-therapy	0.36 -0.04056	0.5 -0.348074	0.9 0.84

Table (5): Baseline serum troponin I level and after each cycle of adriamycin-containing chemotherapy in 26 evaluable patients receiving chemo-radiation.

S-Troponin I	Mean (ng/ml) SD
Baseline	0.020±0.12
After 1st cycle	0.062±0.26
After 2nd cycle	0.470±023
After 3rd cycle	0.500±0.89
After 4th cycle	0.560±0.25
After 5th cycle	0.630±0.36
After 6th cycle	0.690±0.20

* Correlation between baseline serum troponin I level and subsequent level after each cycle of chemotherapy was statistically significant at *p* value =0.004 (ANOVA with repeated measures).

DISCUSSION

Anthracyclines are the most frequent cause of treatment induced cardiotoxicity [4] and seven to fifteen percent of patients receiving more than 450 mg/m^2 cumulative dose of doxorubicin are affected [16]. The present study was designed to determine the benefit of a new biochemical marker cTnI in early diagnosis of acute cardiac myocyte injury induced by anthracycline containing chemotherapy [2].

This study included thirty-one premenopausal breast cancer patients. Only twenty six patients completed their treatment course and hence were evaluable for data analysis.

The M mode echocardiography parameters revealed the mean LVED was 4.8 cm, LVES was 3.1 cm, while the mean for ejection fraction was 64.6% and the mean of fraction shortening was 36.1%. The resting ECG revealed no abnormality.

The mean serum troponin I level was 0.02 ng/ml, the normal level is <0.04 ng/ml while the serum CK-MB concentration was within normal range. In this study, serum tropionin I concentrations were prospectively measured 24 hours after administration of doxorubicin containing chemotherapy for 6 cycles. The mean serum troponin I level was 0.062 ng/ml after the first cycle and 0.63 ng/ml after 5th cycle and 0.69 after 6th cycle with statistically significant difference (p =0.004) indicative of cardiac damage at the myocyte level. For serum CK-MB concentrations, there was no statistical significance throughout the study. Mair [9] reported that creatine kinase CK-MV and lactate dehydrogenase isoenzyme I were not heart specific. By contrast, cTnI and cTnT were usually not detectable in patients without myocardial damage, which is a prerequisite for high diagnostic performance because cTnT could be reexpressed similar to CK-MB and LDH in chronically damaged human skeletal muscle while cTnI could not be expressed in skeletal muscle during fetal development, so an increase in cTnI has been reported only after myocardial damage [2].

In comparing troponin T and troponin I, using ELISA tests in diagnosing acute myocardial infarction, Pentilla et al. [13] found that cTnI showed better earlier sensitivity than troponin T (p =0.43) and that it had the highest cardiac specificity. Also Missove [11] found that cTnI was significantly increased in anthracycline treated patients compared with both the anthracycline naive patients and the control one.

Concerning the relation between serum cardiac TnI and the severity of clinical, electrocardigraphic and quantitative angiographic features in unstable angina, Janorkar [8] found that elevated values of cTnI tend to be associated with the severity and extent of coronary lesions, clinical severity of unstable angina and marked ECG changes, with the follow-up results confirming the potential value of cTnI in predicting the course of coronary artery disease [1].

In the present study, analysis of variance with repeated measures revealed high statistically significant difference between the baseline serum troponin I and subsequent measures after each cycle. Serial values of CK-MB concentrations revealed no statistically significant difference from the baseline measurement, also M mode echocardiography was done at two cycles interval to assess the systolic parameters and the overall contractility showing statistically significant difference between base line fractional shortening and those after the 2nd, 4th and 6th cycle of treatment.

Hughes et al. [7] measured serum troponin T concentrations in 50 patients with early stage left breast conserving radiation therapy. Comparison of pretreatment and post treatment serum troponin T values revealed no changes in troponin T concentrations after 46Gy whole breast irradiation measured after the last day of treatment. They concluded that an elevated troponin T level during or shortly after left breast irradiation should not be attributed to treatment.

In a study for early detection of anthracycline induced cardiotoxicity by radionuclide angiography, Massing et al. [10] found that the left ventricular diastolic dysfunction was probably an early marker for anthracylcine cardiotoxicity, the sensitivity of which is close to that of ejection fraction in the detection of infraclinical cardiotoxicity.

In a study for assessment of early epirubicin cardiotoxicity in women with breast cancer who received mean cumulative dose of epirubicin 360 mg/m2, Walder et al [16] found that the diastolic left ventricular parameters significantly differed before and after completion of chemotherapy while ejection fraction as a systolic parameter did not significantly differ before and after treatment. So, in conclusion, the left ventricular diastolic dysfunction at mean cumulative dose of 360 mg/m2 may be an early sign of epirubicin cardiotoxicity. As regards anthracylcine cardiotoxicity, Nielsen et al. [12] found, in a study of 135 patients with breast cancer, that congestive heart failure occurred in 35% of patients receiving >1000 mg/m2 epirubicin and that LVEF is of no value in prediction of congestive heart failure (CHF).

As regards the risk factors for developing induced cardiotoxicity, Schaadt et al. [14] found that the age and left ventricular ejection fraction were among the potentials for developing cardiotoxicity. Three combined criteria, namely age >50 ys, baseline LVEF <60% and decrease in the LVEF to <50% had a positive predictive value of 70% and a negative predictive value of 98%, so we can conclude that serial monitoring of LVEF is highly indicated during treatment [4].

In our study, the mean age of the patients was 41.4y and the mean baseline LVEF was 64.6%. Using multivariate analysis of various risk factors related to cardiotoxicity including doxorubicin dose, the mean dose of irradiation delivered to the heart volume involved in the field of irradiation and the volume of heart involved, the results revealed statistical significance between the mean dose of irradiation delivered to the heart volume and serum troponin I after the 2nd cycle. This may be explained by the combined effect of irradiation and chemotherapy. Also, there was high statistical significant relation between the adriamycin dose and serum troponin I level after the 5th cycle which may be explained by the cumulative effect of chemotherapy.

In a study done at the NCI Cairo [6], it was reported that the technique of postmastectomy radiotherapy using direct photon beam for IM irradiation appeared to expose the heart to a relatively high dose of radiation. However, exposure through the tangential fields seems to be an important factor for cardiotoxicity especially when there is an overlap between the IMC field and tangential fields within the cardiac tissue. The results are similar to ours which showed that the main contribution of irradiation to the heart volume involved in the field of irradiation was from the IMC whether in right or left sided diseases with more contribution on the left side, while the contribution of tangential fields is negligible.

Follow-up of the 26 evaluable patients 6 months after ending the study with echocardiography to assess LVEF revealed that the mean LVEF was 53.5% and fraction shortening was 30.1% with statistically significant difference (p =0.002). These figures are less than those recorded at presentation and this could be attributed to the persistent cumulative effect of anthracyclines.

Therefore, as a conclusion, serial monitoring of serum cardiac troponin I (cTnI) could be of value as an early sensitive detector for anthracycline induced acute myocyte injury. Also, follow-up of patients with echocardiography to evaluate any functional abnormalities that can alter their quality of life is highly recommenced. Finally, we believe that the use of cardioprotectors or liposomal forms of anthracyclines for high risk patients is advisable.

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