Original Research Paper Medical Science

Prediction of Cardiotoxicity in Carcinoma Breast Patients Treated with Anthracyclines and Taxanes Based on 2D Echocardiography and Biomarkers

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ABSTRACT

Aim

The aim is to assess the incidence of cardiotoxicity after chemotherapy with anthracyclines and taxanes in carcinoma breast patients based on 2D echocardiographic assessment of systolic, diastolic function, and elevation in high sensitive troponin I prior to initiation and post chemotherapy.

Methods

It was a prospective observational single-center study, which enrolled female patients with locally advanced or metastatic breast cancer, who had been treated with anthracyclines and taxanes. All patients underwent cardiac evaluation, which included history and physical examination, baseline electrocardiogram, echocardiography, and troponin I estimation prior to initiation of therapy and at 3, 6 and 12 months after first dose of chemotherapeutic agent.

Results

A total of 50 female patients (mean - 48.7 years) with carcinoma breast were recruited for the present study. It was observed that 6 % of cases had fall in EF, 34% patients had change in diastolic dysfunction and 26 % patients had elevated troponin I levels at one year follow-up post chemotherapy. It was observed that troponin I had a positive predictive value of 23.08 % and negative predictive value of 100 %, while diastolic dysfunction had a positive predictive value of 17.65 % and negative predictive value of 100 %. EF levels significantly decreased from pre-chemotherapy (63.78%) to 12 months follow-up (59.7%). There was significant elevation in troponin I levels from pre-chemotherapy (14.32 pg/mL) to 12 months follow-up (25.1 pg/mL). The occurrence of grade I and II diastolic dysfunction was significantly higher in hypertensive patients ((p<0.05) as compared to normotensives and diabetics (p<0.05) as compared to non-diabetics. But contrastingly, troponin levels were found to be significantly elevated only in hypertensive patients (p<0.05) and there was no statistical significance between diabetics and non-diabetics.

Conclusion

Anthracyclines and taxanes induced cardiotoxicity can be predicted at an early stage using biomarkers like troponin and assessment of diastolic function. Regular cardiac function monitoring is necessary in patients on chemotherapy who are known hypertensives and diabetics.

KEYWORDS Chemotherapy, carcinoma, cardiotoxicity, 2D echocardiography, troponin, biomarker

Introduction

Breast cancer accounts for one of the most commonly encountered neoplasia among the women throughout the world, accounting for around 1.6% death every year (Florescu et al., 2013). With constant research and dedicated efforts, new chemotherapeutic agents have been recognized. These agents effectively combat against various kinds of malignancies and have increased the life expectancy of the breast cancer patients as well (Siegel et al., 2012). It is said 'nothing comes without paying a price', likewise cardiotoxicity due to this chemotherapeutic agents have become a matter of extreme concern for the cancer survivors. Anthracyline derivatives have demonstrated dose depending cardiotoxicity which varies widely from subclinical myocardial dysfunction to irreversible heart failure or even death (Mercuro et al., 2007). The incidence of cardiotoxicity for doxorubicin, one of the widely used anthracycline derivative is found from 4% to >36% in patient receiving 500–550 mg/m^2(Bovelli et al., 2010). Taxanes, such as paclitaxel and docetaxel are other potential neoplastic agents which alone or with anthracyclines are responsible for cardiotoxicity. They produce repercussion cardiotoxic effects like cardiac heart failure, rhythm and conduction disturbances, and ischemia (Yeh et al., 2004). There is a need for early and prompt diagnosis of patients, who are at risk for progressive heart failure and can benefit from therapeutic modalities. Doppler echocardiography is one of the standard diagnostic tool which measure parameters such as left ventricular ejection fraction (LVEF) and left ventricular

fractional shortening (LVFS). However, this allows late diagnosis of cardiac dysfunction so we also considered measurement of diastolic dysfunction. Troponin evaluation, which can predict subclinical and clinical cardiac morbidity and mortality was also evaluated (Bovelli et al., 2010). Thus, the main aim of our study is to assess the incidence of cardiotoxicity after chemotherapy with anthracyclines and taxanes in carcinoma breast patients based on 2D echocardiography and elevation in high sensitive (hs) troponin I levels.

Methods

It was a prospective observational single-center study, which enrolled female patients with locally advanced or metastatic breast cancer, who had been treated with anthracyclines (doxorubicin), taxanes (paclitaxel), as per the selected regimen. The study was conducted at Osmania General Hospital and Medical College, Hyderabad, India from January 2014 to December 2015. The study is approved by the Institutional Ethics Committee and was conducted according to the principles of Declaration of Helsinki. The written informed consent was also obtained from all the enrolled patients in their local language. All patients underwent cardiac evaluation, which included history and physical examination, baseline electrocardiogram, echocardiography, and troponin I estimation prior to initiation of therapy and at 3, 6 and 12 months after first dose of chemotherapeutic agent.

Inclusion criteria

1. Patients were included if:
2. Females > 18 years of age
3. Diagnosed to have carcinoma breast by histopathology
4. Patients who were initiated on chemotherapy regimens containing adriamycin and taxanes, irrespective of prior radiotherapy and surgery for carcinoma breast.
5. LVEF > 55% prior to initiation of chemotherapy

Exclusion criteria

1. Patients were excluded if:
2. Males with breast cancer.
3. Patients with extensive metastasis.
4. Prior history of CAD, cardiomyopathy
5. LV EF < 55% prior to initiation of chemotherapy

Evaluation

2D echocardiography - 2D echocardiographic assessment of LVEF was done by Simpson's biplane method. The Simpson's method assumes the LV cavity to be a stack of disks of equal height and the LV volume is calculated by summating the volumes of all the disks. In practice, this is accomplished by manually tracing the LV endocardial border in the apical four- and two-chamber views, both at end-diastole and at end-systole, and the built-in software available on the echocardiography equipment automatically provides LV volumes and ejection fraction.

The recently published American Society of Echocardiography guidelines have provided age, gender and ethnicity specific normal values of LV volumes and EF based on data extracted from six large contemporary databases. According to this data, the normal LVEF using the biplane Simpson's methods is 63 ± 5%, which means that LVEF in the range of 53–73% should be classified as normal (Lang et al., 2015).

Diastolic function – It was assessed based on E, A, E/A ratio, E/e', IVRT, DT using tissue Doppler imaging using Philips IE33 echocardiographic machine.

Grades of diastolic dysfunction:

Grade 1: Impaired relaxation—mismatch between energy requirement and supply—ventricle does not relax fully, LA contribution augmented.

Grade 2: Pseudonormal appearance: In addition to Grade I, LA pressure rises, causing pseudonormalization of flow pattern.

Grade 3 and 4: Restrictive pattern—the ventricle is so stiff and noncompliant, even

Troponin I was determined using a research-phase highly sensitive assay based on LOCI technology and run on a Dimension Vista 1500 System (Siemens Healthcare Diagnostics, Deerfield, IL). This high sensitive troponin I (hsTnI) assay has a range of 0.5 to 20,000 pg/mL and a 10% coefficient of variation of 3 pg/mL. All values of troponin I >30 pg/mL were considered elevated.

Statistical analysis

All the data was analyzed using SPSS software version 17.0. Appropriate statistical tests were used to determine incidence of cardiotoxicity after chemotherapy. Comparisons were done using chi-square test and one-way anova. Descriptive results are expressed as mean and SD of various parameters in different groups. Probability value (***p*** value) was used to determine the level of significance ***p*** value < 0.05 was considered as significant, ***p*** value < 0.01 was considered as highly significant.

Results

A total of 50 female patients with carcinoma breast were recruited for the present study. Monitoring of cardiovascular function was done before, during, and after completion of chemotherapy based on biomarkers and 2D echocardiography**.**

The mean age in the study population was 48.7 years, 32 % of cases were in the age group of 31 – 40 years followed by 30 % of cases who were in the age group of 41 – 50 years **(table 1).** It was observed that 6 % of cases had fall in EF and 34% patients had change in diastolic dysfunction at one year follow up post chemotherapy **(table 2 and 3).**

Table 2: Incidence of cardiotoxicity as defined by CREC at 1 year follow-up

Ejection fraction	Frequency	Percent
Fall in EF	3	6.0
No fall in EF	47	94.0
Total	50	100.0

Table 1: Patient distribution based on age

Age group (years)	No. of patients	%
31 – 40	16	32
41 – 50	15	30
51 – 60	14	28
≥61	5	10
Total	50	100
Mean ± SD	48.7 ± 9.6	

Table 3: Incidence of change in diastolic dysfunctions at 1 year follow-up

Diastolic dysfunction	Frequency	Percent
Change in DD	17	34.0
No DD	33	66.0
Total	50	100.0

It was observed that troponin I had a positive predictive value of 23.08 % and negative predictive value of 100 %, while diastolic dysfunction had a positive predictive value of 17.65 % and negative predictive value of 100 %, indicating there is no probability of cardiac toxicity in chemotherapeutic patients with normal diastolic function and normal troponin I levels **(table 4 and 5).**

Table 4: Predictive value of troponin I

Test Parameter	Fall in EF	No Fall in EF
Troponin I elevated	3	10
Troponin I normal	0	37
Total	3	47

Statistic	Formula	Value	95% CI
Sensitivity	a / a + b	100.00%	29.24% to 100.00%
Specificity	d / c + d	78.72%	64.34% to 89.30%
Positive predictive value	a / a + c	23.08%	5.04% to 53.81%
Negative predictive value	d / b + d	100.00 %	90.51% to 100.00%

Table 5: Predictive value of diastolic dysfunction

Diastolic dysfunction	Fall in EF	No Fall in EF
Present	3	14
Absent	0	33
Total	3	47

Statistic	Formula	Value	95% CI
Sensitivity	a / a + b	100.00%	29.24% to 100.00%
Specificity	d / c + d	70.21%	55.11% to 82.66%
Positive predictive value	a / a + c	17.65%	3.80% to 43.43%
Negative predictive value	d / b + d	100.00%	89.42% to 1

EF levels significantly decreased from pre-chemotherapy to 12 months follow-up. Multiple comparisons revealed that EF levels were significantly lower at 3 months, 6 months and 12 months compared to pre chemotherapy **(table 6 and 7).**

Table 6: Ejection fraction levels before and after chemotherapy

Parameter	Prior to Chemotherapy	3 months	6 months	12 months	F value
Ejection fraction (mean ± SD)	63.78 ± 3.51	62.02 ± 2.85	60.6 ± 4.16	59.7 ± 3.96	11.76

Table 7: Multiple comparison *p* values for ejection fraction

p value	3 months	6 months	12 months
Prior to chemotherapy	0.017	<0.001	<0.001
3 months		0.054	0.002
6 months			0.230

It was observed that 26 % of cases had elevated troponin I levels at one year follow-up post chemotherapy. Multiple comparisons were done and it was observed that the mean troponin I levels were significantly higher at 6 months and 12 months compared to pre-chemotherapy levels (**table 8, 9 and 10).**

Table 8: Frequency of elevated troponin I at one year follow-up post chemotherapy

Troponin levels	Frequency	Percentage
Elevated Trop I	13	26.0
Normal Trop I	37	74.0
Total	50	100.0

Table 9: Troponin I levels before and after chemotherapy

Parameter	Prior to Chemotherapy	3 months	6 months	12 months	F value
Troponin I (mean ± SD)	14.32 ± 6.07	18.52 ± 8.54	20.8 ± 13.9	25.1 ± 17.5	6.63

Table 10: Multiple comparison *p* values for troponin I

p value	3 months	6 months	12 months
Prior to chemotherapy	0.091	0.009	<0.001
3 months		0.354	0.008
6 months			0.082

Occurrence of grade I diastolic dysfunction was significantly higher at 6 months and 12 months compared to pre-chemotherapy and at 3 months follow up. Occurrence of grade II diastolic dysfunction was significantly higher at 12 months compared to 6 months, 3months and pre chemotherapy (p <0.05) **(table 11).** There was also a significantly higher incidence of global hypokinesia at 6 months and 12 months compared to pre chemotherapy and 3 months follow up (p <0.05) **(table 12).**

Table 11 : Diastolic dysfunction before and after chemotherapy

Diastolic dysfunction	Prior to chemotherapy	3 months	6 months	12 months
No DD	31	29	25	21
Grade I	19	20	22	22
Grade II	0	1	3	7
Chi square	13			
p value	0.04			

Table 12: 2D Echo finding before and after chemotherapy

2D Echo	Prior to chemotherapy	3 months	6 months	12 months
No RMWA	46	50	48	48
No RWMA concentric LVH	4	0	0	0
Global hypokinesia	0	0	2	2
Chi square	16.16			
p value	0.013			

Diastolic dysfunction and troponin I levels were disrupted in subgroup of patients depending upon radiotherapy, diabetes, hypertension and location of breast carcinoma. The detailed results are outlined in **table 13 and 14.**

Table 13: Troponin elevation in several subgroups of patients

Characteristics	Troponin I elevated, n (%)	Troponin I normal, n (%)	p-value
Radiotherapy	4 (33.3%)	6 (13.5%)	$X^2 = 2.37$ p = 0.12
No Radiotherapy	8 (66.7%)	32 (86.5%)	
Right sided carcinoma of breast	8 (26.7%)	22 (73.3%)	$X^2 = 0.01$ p = 0.89
Left sided carcinoma of breast	5 (25.0%)	15 (75.0%)	
Diabetics	3 (30.0%)	7 (70.0%)	$X^2 = 0.10$ p = 0.75
Non-diabetic	10 (25.0%)	30 (75.0%)	
Hypertension	7 (50.0%)	7 (50.0%)	$X^2 = 5.80$ p = 0.01
No Hypertension	6 (16.7%)	30 (83.3%)	

Table 14: Diastolic dysfunction in several subgroups of patients

Demographics	No diastolic dysfunction, n (%)	Grade I, n (%)	Grade II, n (%)	p-value
Radiotherapy	2 (9.5%)	4 (19.0%)	3 (19.0%)	$X^2 = 3.9$ p = 0.14
No Radiotherapy	19 (90.5%)	18 (81.0%)	4 (57.1%)	
Right sided carcinoma of breast	13 (43.3%)	14 (46.7%)	3 (10%)	$X^2 = 1.01$ p = 0.60
Left sided carcinoma of breast	8 (40%)	8 (40%)	4 (20%)	

Diabetics	0 (0.0%)	8 (80.0%)	2 (20.0%)	$X^2 = 9.25$ p = 0.01
Non-diabetic	21 (52.5%)	14 (35.0%)	5 (12.5%)	
Hypertension	2 (14.3%)	7 (50.0%)	5 (35.7%)	$X^2 = 10.26$ p = 0.006
No Hypertension	19 (52.8%)	15 (41.7%)	2 (5.6%)	

Discussion

In our study, 50 female patients diagnosed to have carcinoma breast and planned to be kept on anthracycline and taxane based chemotherapy were followed up for 1 year. 2D echocardiography and troponin I levels were measured prior to initiation of therapy and upto 1 year at regular intervals. It was found that incidence of cardiotoxicity was 6% in our study, accounting for 3 patients who had fall in EF at 1 year follow-up that obliged with the definition of chemotherapy induced cardiotoxicity (Seidman et al., 2002). Two of them had global hypokinesia of LV, while third patient had a fall in EF > 10% from baseline value after chemotherapy.

Many studies have evidenced that LVEF is an insensitive and inaccurate tool for detecting anthracycline induced cardiotoxicity at an early stage (McKillop et al., 1983). This can be attributed to significant changes in systolic function which do not occur until a considerable amount of morphological damage has occurred. After this point, deterioration proceeds rapidly and the prognosis is poor. Thus, we also assess diastolic abnormalities and we observed a high prevalence of diastolic abnormalities, although LVEF was normal. 34 % of cases had change in diastolic dysfunction at 1 year follow-up post-chemotherapy. This suggests that diastolic impairment precedes systolic dysfunction, in agreement with previous reports (Marchandise et al., 1989; Stoddard et al., 1992). Thus, in comparison with LVEF, the assessment of diastolic function by echocardiography may show cardiotoxicity at an earlier stage.

It was observed that 26 % of cases had elevated troponin I levels at one year follow-up post chemotherapy in our study. Out of these 13 patients, only 3 had fall in ejection fraction consistent with definition of chemotherapy induced cardiotoxicity. Cardinale et al. have reported that the measurement of troponin I predicted the development of later cardiac events in patients treated with high doses of anthracyclines (D Cardinale et al., 2002). The present study confirms the value of measuring troponin in patients with breast cancer treated with anthracyclines, taxanes and clarifies its optimal timing. Although troponin was not an independent predictor of later cardiotoxicity, its measurement combined with the assessment of EF and diastolic function, increased the sensitivity .Thus, measuring both diastolic function and troponin may be of value in predicting the absence of toxicity after chemotherapy.

Cardinale et al. showed that the troponin I pattern after high dose chemotherapy allows to stratify the risk of cardiac events in cancer patients in the 3 years thereafter (Daniela Cardinale et al., 2004). Patients without troponin I elevation after chemotherapy had a good prognosis. Indeed, no significant reduction in LVEF was observed in this group, and a very low incidence of cardiac events (1%) occurred during the follow-up. In our study, it was observed that the mean troponin I levels were significantly higher at 6 months and 12 months compared to pre-chemotherapy levels. So, these patients with raised troponin levels need close cardiac monitoring and initiation of cardioprotective strategies.

Prior radiotherapy is also considered a risk factor for chemotherapy induced cardiotoxicity (Yusuf et al., 2011). Marks et al. demonstrated 27%, 29%, 38%, and 42% incidence of myocardial perfusion abnormalities in asymptomatic patients with breast cancer at 6, 12, 18, and 24 months after radiotherapy, respectively (Marks et al., 2005). Similarly, our results show that more number of radiotherapy patients had elevated troponin and diastolic dysfunction as compared to those who have not undergone radiotherapy.

Moreover, the occurrence of grade I and II diastolic dysfunction was significant higher in diabetics ($p<0.05$) as compared to non-diabetics and was also significantly higher in hypertensives ($p<0.05$) as compared to normotensives. Thus, if early onset diastolic dysfunction is taken as an indicator for later toxicity, diabetics and hypertensives have higher incidence compared to non-diabetics and normotensives who have taken chemotherapy.

As contrast to diastolic dysfunction, troponin levels were found to be significantly elevated only in hypertensive patients ($p<0.05$) and there was no statistical significance between diabetics and non-diabetics.

In our study, troponin I had a positive predictive value of 23.08 % and negative predictive value of 100 % and diastolic dysfunction had a positive predictive value of 17.65 % and negative predictive value of 100 %. From the above findings we can predict that patients with normal EF, diastolic function and within normal range of troponin I at the end of one year follow up have lesser probability of having cardiotoxicity after chemotherapy.

In nutshell, several implications can be made. A high prevalence of diastolic abnormalities were observed, although LVEF was normal. This suggests that diastolic impairment precedes systolic dysfunction, in agreement with previous reports by Stoddard et al. (Stoddard et al., 1992). Thus, in comparison with LVEF, the assessment of diastolic function by echocardiography may show cardiotoxicity at an earlier stage.

Troponin I, by revealing the presence as well as the persistence of myocardial injury after chemotherapy, is able to discriminate patients at higher risk of developing a clinically relevant cardiotoxicity from those with a good clinical outcome.

Troponin I level also stratifies cardiac risk at a very early phase, long before any impairment in heart function and symptoms develop, and when many preventive therapeutic strategies are likely to be effective. Troponin I could be used to assess as well as to monitor the safety and the effectiveness of different antineoplastic treatments. Finally, we can suppose that cardioprotective therapies that might limit or prevent the troponin I raise after chemotherapy, could improve cardiac prognosis of these patients.

Conclusion

Thus, we conclude that anthracycline and taxane induced cardiotoxicity can be predicted at an early stage using biomarkers like troponin and assessment of diastolic function apart from systolic function. Regular cardiac function monitoring is necessary in patients on chemotherapy who are known hypertensives and diabetics as incidence of troponin elevation and diastolic dysfunction is more common among them.

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