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Research Article

GLOBAL LONGITUDINAL STRAIN AS A PREDICTOR OF CARDIOTOXICITY IN BREAST CANCER PATIENTS RECEIVING ANTHRACYCLINE AND/OR TRASTUZUMAB TREATMENT IN A TERTIARY CARE CENTRE IN EASTERN INDIA

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ABSTRACT

Objectives: The objective of the study was to find out whether global longitudinal strain (GLS) poses as a novel marker of left ventricular (LV) systolic function and it was to be seen whether GLS could predict cardiotoxicity earlier than Ejection fraction (EF).

Methods: Fifty-two patients set to receive anthracycline and/or trastuzumab-based chemotherapy for breast carcinoma were selected – clinical parameters and baseline echocardiography (EF, E/e,' LV S,' Tricuspid annular plane systolic excursion, Pulmonary artery systolic pressure and GLS) were measured and followed up at 3 months and 6 months. The echocardiography profiles of patients with and without cardiotoxicity were compared.

Results: Incidence of cardiotoxicity is found 11.5%. On 3rd month, the mean LV GLS, as well as its difference regarding the baseline value, were significantly higher in the group with cardiotoxicity in comparison to those without cardiotoxicity. On 6th month, there was a significant drop in the EF and LV GLS, E/e', and LV s' in the patients with cardiotoxicity. LV GLS on the 3rd month remained an independent predictor of cardiotoxicity, maintaining a statistically significant association in multivariate models.

Conclusion: GLS is indeed a more sensitive marker of LV systolic functions than EF. It predicted cardiotoxicity earlier than EF and accurately. This study also provided a cutoff value for LV GLS at 3 months in predicting who would develop cardiotoxicity at 6 months, so that the chemotherapy regimen could be modified in such patients.

Keywords: Cardiotoxicity, Chemotherapy, Breast carcinoma.

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INTRODUCTION

Trastuzumab is a humanized monoclonal antibody made to target human epidermal growth factor 2 receptors which are highly expressed in different of tumors, including 25–30% of invasive breast carcinomas [1]. Anthracyclines, trastuzumab, and some tyrosine kinase inhibitors have depressive effects on heart function. Hence many cancer survivors are at definite risk for the development of morbidity related to heart from their cancer treatment. Echocardiographic myocardial strain imaging enables identification of subclinical left ventricular (LV) systolic dysfunction before it is clinically evident as heart failure symptoms or a reduction in LV ejection fraction (LVEF). Early identification of depressed ventricular function enables change in the chemotherapy protocol, either by increasing the interval between doses or reducing the total cumulative dose. Newer cancer drugs have positively affected the life of cancer survivor, resulting in more than 12 million survivors but also with some side effects, such as cardiotoxicity causing mortality related to cardiac issues [2-4]. Chemotherapy-induced cardiotoxicity is defined as "a decrease of LVEF by 5% or more to <55% in the presence of symptoms of HF or an asymptomatic decrease in LVEF by 10% or more to <55%" [5]. Detection of people with high risk for having cardiotoxicity before toxicity will come to surface would be the goal to reduce death. Global longitudinal strain (GLS) is a newer technique suited to diagnose alteration in cardiac contractile function early [6]. However, there is no cutoff point of GLS to detect toxicity. The American Society of Echocardiography and the European Association of Cardiovascular Imaging have agreed that deformity changes precede ventricular dysfunction. A drop >15% in GLS, immediately after or during anthracycline treatment, is the most useful criteria to suspect cardiotoxicity, while a reduction <8% might exclude its diagnosis [6]. However, there is a grey zone between those values.

METHODS

Patients with age ≥18 years, diagnosis of breast cancer, with neither previous antineoplastic treatment nor radiotherapy, normal LVEF (according to the last recommendations of the ASE and the European Association of Cardiovascular Imaging (>54%, by use of the Simpson's method), on the first Doppler echocardiogram before treatment and antineoplastic treatment planning with anthracyclines and/or trastuzumab were enrolled [7]. Echocardiography was done with Philips Ultrasound system with model EPIQ 7. Patients with inappropriate acoustic window, presence of cardiac arrhythmias and/or non-sinus rhythms, use of beta-blockers and/or angiotensin-converting-enzyme inhibitors and/or angiotensin receptor blockers, moderate or severe heart valve disease were excluded from the study. The patients underwent echocardiography at baseline, before initiating the anthracycline, and then every 3 months, during a 6 month follow-up. Two protocols were used:

1. FEC (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2) in 3 cycles, every 21 days, followed by docetaxel 100 mg/m^2 in other 3 cycles, every 21 days.
2. Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 in 4 cycles, every 21 days, followed by docetaxel 100 mg/m^2 every 21 days, for 4 cycles, for both adjuvant and neoadjuvant treatments.

Pulse, blood pressure, electrocardiogram, echocardiography parameters -EF (calculated by use of the Simpson's method, E and A wave, tissue Doppler of septal and lateral mitral annulus, E/E' ratio, S

wave of the left ventricle, Tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (PASP). Three apical views (long axis, four chambers, and two chambers) and three left ventricle short axis view (basal, mid, apical) were acquired during three consecutive cardiac cycles in the left lateral position in breath-hold position. Care taken to confirm that the basal short axis must contain tip of mitral valve and middle level contains papillary muscle. Apical short axis should not contain a papillary muscle that was ensured. Gain and compression were adjusted to avoid dropout of LV border. Depth and sector angle adjusted manually to include LV and sector size is minimized to achieve a higher frame rate. To determine the cardiac events, LV inflow and outflow verification recorded. After selecting one cardiac cycle endocardial border traced by automatic function algorithm. Inaccurate segmental tracking was overridden by operator. GLS is the mean of sum total of peak strain of 18 LV segments [8]. The images were analyzed in the same device (Philips EPIQ 7 ultrasound system) and the same working station.

RESULTS

Out of 61 patients, 52 were included in this study. Six patients were excluded because of their high BMI and three patients due to poor acoustic window to the LV GLS acquisition and EF calculation. Mean age of the population was 52.47±6.66 years. About 9% of patients received adjuvant radiotherapy, and 45.1% did not. About 52.9% of patients have undergone surgery before chemotherapy. About 68.6% of patients had ductal carcinoma, and 31.45% had lobular carcinoma as diagnosis. Baseline EF was 62%. Incidence of cardiotoxicity was 11.5% in this study. Despite the lack of a statistically significant association, the mean age of the patients with cardiotoxicity was higher than that without it. In addition, 83% of those patients underwent radiotherapy, which is clinically relevant. All patients had been treated with anthracyclines. Two out of six patients (40%) who developed cardiotoxicity received trastuzumab. Mean heart rate was 78/min in patients with cardiotoxicity and 70/min in ones without cardiotoxicity which was statistically significant. Mean systolic blood pressure and mean diastolic blood pressure were 118 and 77, respectively, in the cardiotoxicity group and 125 and 83, respectively, in the non-cardiotoxicity group. In the cardiotoxicity group, 68.9% had ductal carcinoma and 31% had lobular carcinoma. In the cardiotoxicity group, 66% and in the non-cardiotoxicity group, 51% had surgery before computed tomography. The means of the echocardiographic variables of the patients with and without cardiotoxicity are shown in Table 1. On the 3rd month, the mean LV GLS, as well as its difference regarding the baseline value, were significantly higher in the group with cardiotoxicity. On the 6th month, there was a significant drop in the EF and LV GLS, in addition to changes in the S wave of the left ventricle and E/E.' However, TAPSE and PASP measures did not change during follow-up. Table 2 shows EF and GLS values in patients with cardiotoxicity. To assess the association of each echocardiographic variable with cardiotoxicity, Cox regression analysis was performed. The variables with p≤0.05 on Cox regression univariate analysis went to multivariate analysis of independent predictors of cardiotoxicity: EF (Simpson's method), LV GLS on the 3rd month, and diastolic function. Only LV GLS on the 3rd month remained an independent predictor of cardiotoxicity, maintaining a statistically significant association in multivariate models.

Table 1: Echocardiographic characteristics of patients

Variables	Cardiotoxicity		p-value
	Yes (%)	No (%)	
Baseline Echo			
EF 1	62.83±1.602	62.44±3.408	0.786
TAPSE	19.70±2.087	20.26±2.483	0.602
PASP	19.17±2.483	19.67±2.992	0.698
GLS 1	−19.13±0.752	−20.30±1.925	0.109
E/E'1	8.48±1.780	7.61±1.839	0.401
LV S' 1	8.26±1.317	8.34±0.753	0.835
Echo 3 months			
EF 2	60.00±4.336	62.16±3.219	0.145
TAPSE 2	19.91±1.957	20.72±2.789	0.501
PASP 2	19.00±1.897	19.62±2.741	0.594
GLS 2	−13.42±1.670	−17.49±7.976	0.033*
E/E' 2	08.55±2.294	7.80±1.770	0.741
LV S' 2	8.20±1.738	8.41±0.767	0.226
% difference in EF 3 months	4.50±1.2	1.46±1.94	0.216
% difference in GLS3 months	16.73±11.22	13.85±39.59	0.035*
Echo 6 months			
EF 3	49.40±2.966	62.18±3.339	0.001*
TAPSE 3	19.68±2.167	20.87±2.816	0.365
GLS 3	−12.88±1.303	−17.02±7.856	0.049*
PASP 3	18.58±1.97	19.42±2.741	0.594
E/E' 3	9.96±4.481	7.79±1.576	0.045*
LV S' 3	7.10±1.785	8.36±0.731	0.003*
% difference in GLS 6 months	34.40±32.46	2.63±2.44	0.006*
% difference in EF 6 months	41.39±29.58	18.18±41.65	0.194

EF: Ejection fraction, TAPSE: Tricuspid annular plane systolic excursion, PASP: Pulmonary artery systolic pressure, GLS: Global longitudinal strain, LVS': Left ventricular S wave, LV E/E': Ratio of left ventricular E and E' wave; suffix number denotes duration in month

Table 2: Description of the cases with cardiotoxicity

Cases	EF			GLS		
	Baseline	3 months	6 months	Baseline	3 months	6 months
1	62	62	52	−18.3	−16.9	−12.7
2	64	61	45	−18.9	−15.5	−14.5
3	64	63	52	−18.5	−14.2	−11.2
4	60	60	48	−18.7	−13.4	−12.2
5	63	63	53	−17.1	−14.7	−12.0
6	64	64	50	−17.3	−17.0	−13.8

EF: Ejection fraction, GLS: Global longitudinal strain

DISCUSSION

The results of the present study showed that the LV GLS was an excellent predictor of cardiotoxicity in this population, with high efficacy for its early diagnosis.

Profile of morbidity of the population

The population had a low morbidity profile. The incidence of the risk factors that could be related to cardiotoxicity was very low, and no statistically significant association could be demonstrated except mean baseline hazard ratios (HR). That profile differs from that of other studies, which had cases of smoking, previous use of chemotherapy, and radiotherapy, in addition to a higher frequency of systemic arterial hypertension and diabetes mellitus [9,10]. The low morbidity profile can be associated with the lower incidence of cardiotoxicity observed in this population.

Incidence of cardiotoxicity

This study found a cardiotoxicity incidence of 11.5%, lower than that reported by other studies. The definition of cardiotoxicity is not uniform in different studies, complicating evaluation of the actual occurrence of event. The cardiotoxicity incidence in a systematic review published in 2014 ranged from 13% to 32% [10]. Studies published by Sawaya *et al.* and Baratta *et al.* have found an incidence of 20%, using the same definition as of the trastuzumab committee [11,12]. In study by Baratta *et al.*, if the cardiotoxicity incidence calculated only on patients with breast cancer, a 12% rate was found, similar to that of this population [12].

Marker of cardiotoxicity: 2D strain

Like all previous studies with this objective, results of our study confirm LV GLS as an excellent independent predictor of cardiotoxicity, which can

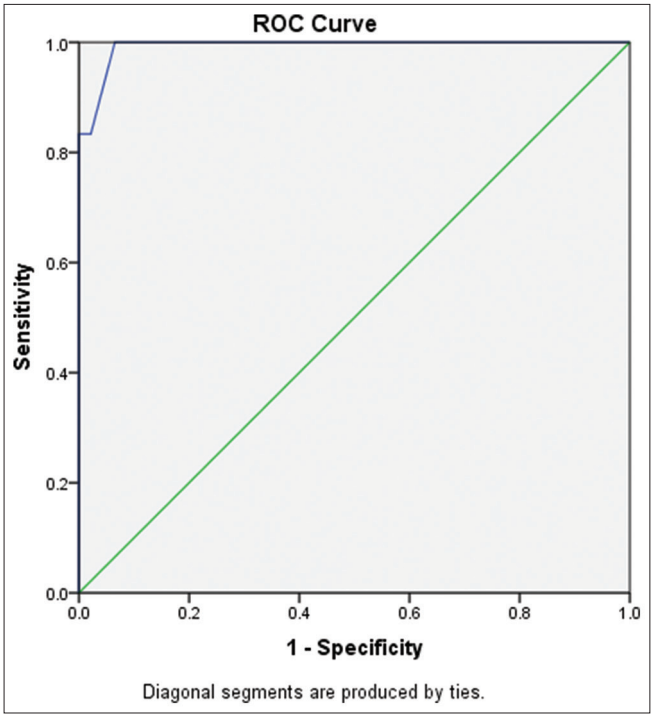

Chart 1: Global longitudinal strain as a predictor of cardiotoxicity at 3 months

be assessed by use of the data from Cox regression (p=0.004, HR=2.77; 95% confidence interval: 1.39–5.54). Among the six patients who developed cardiotoxicity, only one did not have a significantly raised GLS value at 3 months. In the rest five patients LV GLS change occurred from the 3rd month onward, while EF (Simpson's method) changed significantly only on the 6th month. In this study, it is found that for the absolute value of GLS (at 3 months) −17.5 the sensitivity of diagnosing cardiotoxicity is 100% and specificity is 93%, that for −16.5, the sensitivity of is 83% and specificity is 97%, while that for −15.5, the sensitivity of diagnosing cardiotoxicity is 83% and specificity is 100%. We chose −15.5 as the cutoff LV GLS value for defining cardiotoxicity (Chart 1).

CONCLUSION

The results derived from the study show that GLS is indeed a more sensitive marker of LV systolic functions than EF. It predicted cardiotoxicity earlier than EF and accurately. This study also provided a cutoff value for LV GLS (−15.5) at 3 months in predicting who would develop cardiotoxicity at 6 months, so that the chemotherapy regimen could be changed in those groups of patients to prevent further deterioration of cardiac contractility and its consequences.

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AUTHOR'S CONTRIBUTION

Equal contributions from all authors for data collection, statistics, and manuscript writing

CONFLICTS OF INTEREST

There were no conflicts of interest.

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ETHICAL CLEARANCE

Obtained from Institutional Ethical Committee.

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