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Association between Left Ventricular Global Longitudinal Strain and Six Minute Walk Test Before and After Chemotherapy with Anthracycline in Breast Cancer Patients

Theresia W. Siagian*[1], Andre P. Ketaren[1], Kamal B Siregar[2], Harris Hasan[1], Abdullah A. Siregar[1], Andika Sitepu[1]

[1]Department of Cardiology and Vascular Medicine, University of Sumatera Utara, Adam Malik Hospital, Medan, Indonesia
[2]Departement of Oncology, University of Sumatera Utara, Adam Malik Hospital, Medan, Indonesia

Abstract : Background: Anthracycline-induced cardiotoxicity is associated with a poor prognosis. We can use Global longitudinal strain (GLS) to detect subclinical left ventricular dysfunction in chemotherapy patient. The distance of 6-minute walk test (6MWT) has been used as a prognostic factor in cancer patients.This study aimed to prove whether there is a correlation between left ventricular dysfunction before there are clinical signs of heart failure and decreased functional capacity of 6MWT in breast cancer patients.
Methods: This is a cohort prospective study of 35breast cancer patients who have chemotherapy with anthracycline regimen. The patients were evaluated before the initiation of anthracycline therapy, after 3 cycles and 6 cycles. Patients underwent standard echocardiography and 6MWT at the first visit. After 3 cycle patient underwent echocardiography and after 6 cycle patient underwent echocardiography and 6MWT.
Results: The mean age was 45.83 ± 6.96 years. There was a significant difference in percentage reduction of GLS after chemotherapy 3 cycles and 6 cycles (10.49 ± 4.94 vs. 20.717 ± 9.616, p = 0.001). GLS is correlated with a decrease in total distance 6MWT after 6 cycles (R^2 = -0.084) and the correlation of percentage reduction of GLS and distance of 6MWT has p = 0.028 and R^2 = -0.112.
Conclusion: There is a correlation between the percentage reduction of GLS and distance of 6MWT in breast cancer patients with anthracycline chemotherapy for 6 cycles (R^2 = -0.112).
Keyword: GLS, 6MWT, anthracycline, chemotherapy, breast cancer.

Introduction

Breast cancer is the most common cancer in women other than skin cancer. The incidence of breast cancer worldwide in 2012 reached 43.1 million people with a mortality rate of 12.9 million.[1] The development in the treatment of breast cancer patients has led to the number of cancer patients who survived more than before the last two decades. The 5-year survival rate in breast cancer patients reaches 90 %. One of the therapies that developed rapidly in the treatment of breast cancer is chemotherapy. The side effects of chemotherapy on

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the cardiovascular system are known as cardiotoxicity. Breast cancer patients who fall in heart failure have a mortality rate of 60% within 2 years.[2]Research Jensen *et al* found a decrease in ejection fraction by 25% in 59% of breast cancer patients where 20% of patients had heart failure in a period of 3 years.[3]Anthracycline therapy is well known for its adverse cardiac effects. Anthracycline-induced cardiotoxicity(AIC) is associated with a poor prognosis. A classic heart failure treatment can potentially reverse cardiac dysfunction at the early stage of cardiac toxicity, timely detection of AIC is crucial.[4-6]

Transthoracic echocardiography is recommended for monitoring the left ventricular function in patients receiving anthracyclines. In routine practice, left ventricular systolic function is assessed primarily by the left ventricular ejection fraction (LVEF), measured by two-dimensional echocardiography imaging. However, LVEF depends on operator experience and is not sufficiently sensitive to detect subclinical myocardial dysfunction.[7,8] To overcome these limitations, two-dimensional speckle-tracking imaging has been proposed. This technique allows for a study of global and regional myocardial deformation, especially the longitudinal component, which appears to be the most sensitive. A recent expert consensus paper strongly recommends GLS assessment for the detection of subclinical left ventricular dysfunction due to anthracycline therapy.[9]

Physical activity is becoming increasingly important for cancer patients during treatment and rehabilitation. Among the many types of tests available, a 6-minute walk test (6MWT) is acceptable to assess functional exercise capacity because it is cheap, easy to perform, and is generally considered submaximal.[10,11]In the last 2 decades, 6MWT has been increasingly used in cancer research for outcome evaluation. The distance of 6MWT has been used as a prognostic factor for survival rates in lung cancer patients and is associated with other health aspects of breast cancer.[12,13]A study conducted by Krishnasamy *et al* found that there was a correlation between the decrease in GLS and decreased functional capacity assessed by the shortening of 6MWT distance.[14]

This study aimed to prove whether there is an association between left ventricular dysfunction in the early stages before there are clinical signs of heart failure examined by using GLS and decreased functional capacity of 6MWT in breast cancer patients receiving anthracycline chemotherapy.

Methods

This was a single-center, prospective cohort study. Eligibility requirements for screening were the following: patients with breast cancer, requiring anthracycline therapy, age 18-55 years and baseline LVEF> 50%. Exclusion criteria were have had chemotherapy before, patients with ischemic heart disease, valvular heart disease, patients with walking disorders, patients with karnofsky score ≤ 70, poor echo window, and patients refuse to participate in the study.

The chemotherapy protocol given is a combination of chemotherapy regimens, one of which uses the anthracycline group: Doxorubicin, or Epirubicin with 3 weeks / 21 days interval of 6 cycles as determined by the oncology team.

Echocardiography examinations were performed using a Vivid S6 imaging device (GE Medical systems) with a 3.5 MHz variable frequency transducer. The left ventricular end diastolic and end systolic volumes were measured from the apical two and four-chamber views; LVEF was calculated using Simpson's rule. GLS was computed from high frame rate (>50 frames/s) apical views (four, two, and three chambers). By tracing the endocardial borders on an end-systolic frame, myocardial speckles were automatically tracked on the subsequent frames. Adequate tracking was verified and was manually corrected if necessary. GLS was obtained as the average of regional strains. Percentage change in GLS was calculated between baseline and after 3 cycles also after 6 cycles. Other classic diastolic and systolic parameters were recorded according to current guidelines.

6MWT was used to evaluate exercise endurance. Patients performed a timed 6-minwalk of 30 m laps and total distance walked was calculated.

The patients were evaluated at three time points: before the initiation of anthracycline therapy; after 3 cycles of chemotherapy, and after 6 cycle chemotherapy. Patients underwent a clinical examination, standard echocardiography, and 6MWT at the first visit. After 3 cycle patient underwent echocardiography and after 6

cycle patient underwent echocardiography and 6MWT. All patients provided written informed consent. The study was approved by our ethics committee.

Descriptive statistics were used to represent characteristics at the entry of the study. The data were assessed for normality of distribution and transformed as appropriate. Results were expressed as frequencies and percentages for categorical variables, mean • } standard deviation (SD) for normally distributed variables and median (interquartile range) for non-normally distributed variables. The normality test of numerical variables on all subjects using Shapiro Wilk. Differences in GLS values before and after chemotherapy will be tested with the t-dependent test when the distribution is normal. The degree of association between GLS, cardiac parameter and functional capacity was assessed using Pearson's correlation for continuous normally distributed variables and Spearman's correlation for categorical and non-normally distributed variables.

Results

There are 143 new breast cancer patients from April 2017 to November 2017, where samples that meet inclusion and exclusion criteria are 35 people. Characteristics of research subjects can be seen in Table 1. From table 1 it can be seen that the number of patients with tumor location on the right is 65.7% (n = 23), left 28.6% (n = 10) and bilateral 5.7% (n = 2). For the risk factor of coronary heart disease, hypertension was found in 34.2% of study subjects (n = 12) and no diabetes or smoking was found in all subjects.

Table 1.Clinical Characteristics of 35 patient

Variable	**Number(%) or mean±SD (n=35)**
Age (Year ± SD)	45.83 ± 6.96
Body weight (kg ± SD)	54.43 ± 8.34
Tumor Location (n, %)	
- Right	23 (65.7)
- Left	10 (28.6)
- Bilateral	2 (5.7)
Risk Factor (n, %)	
- Hypertension	12 (34.2)
- Diabetes Mellitus	0 (0)
- Smoker	0 (0)
Tumor Histopathology (n, %)	
- Invasive ductal Breast Ca	31 (88.5)
- Intraductal Breast Ca	1 (2.9)
- Invasive Lobular Breast Ca	1 (2.9)
- Pleomorphic Lobular Breast Ca	1 (2.9)
- Infiltrative Ductal	1 (2.9)
Grading (n,%)	
- 1	3 (8.6)
- 2	24 (68.8)
- 3	8 (22.9)
Chemotherapy Regimen (n, %)	
- Doxorubicin + Paclitaxel	27 (77.1)
- Doxorubicin + Brexel	4 (11.4)
- Epirubicin + Cycloposhamid+5FU	2 (5.7)
- Epirubicin + Paclitaxel	2 (5.8)
Total dose after 3 cycles (mg ± SD)	243.89 ± 81.749
Total dose after 6 cycles (mg ± SD)	487.77 ± 163.50

Table 2. Clinical and Echocardiographical characteristic of 35 patient

Variable	Baseline	After 3 cycle	P value	After 6 cycle	P value
LVEF (%)	57.60 ± 4.10	54.37 ± 3.89	0.000	50.89 ± 4.54	0.04
GLS (%)	-21.26 ± 1.75	-19.043±1.92	0.000	-16.77±2.6	0.231
Percentage reduction of GLS(%)	-	10.49 ± 4.94	-	20.717 ± 9.616	0.001
E/A	1.2 ± 0.11	0.9 ± 0.136	0.06	0.826 ± 0.14	0.455
E/e'	6.8451 ± 1.7	7.58 ± 1.594	0.000	8.35±2.04	0.063
TAPSE	23.20 ± 1.795	22.14 ± 2.08	0.000	20.89 ± 1.66	0.000
6MWT(m)	359.74 ± 57.673	-	-	349.14 ± 48.183	0.001
Hb	12.12 ±1.39	-	-	11.40 ± 0.97	0.000

Table 2 shows the comparison of echocardiography and clinical parameters at the start of the study, after chemotherapy 3 cycles and 6 cycles. There is a decrease in the ejection fraction of Simpson compared to initial value even after 3 cycles of chemotherapy ejection fraction value is still within normal limits that is> 50%. The mean value of LVEF before chemotherapy was 57.6% to 54.3% after 3 cycles of chemotherapy and decreased to 50.8% after 6 cycles of chemotherapy (p = 0.001). There was a significant difference in percentage reduction of GLS after chemotherapy 3 cycles and 6 cycles (10.49 ± 4.94 vs. 20.717 ± 9.616, P = 0.001). TAPSE and E/e' was decreased after 3 cycles of chemotherapy. Whereas after 6 cycles only TAPSE decrease even though TAPSE value still in normal limit. Decreased 6MWT distance was also found after 6 cycles compared before chemotherapy (359.74 ± 57.673 vs 349.14 ± 48.183, p = 0.001).

Table 3. Univariate association between GLS and 6MWT before and after 6 cycle chemotherapy

Variables	Baseline	P value	After 6 cycle	P value
GLS(%)	-21.263 ± 1.74	0.487	-16.77 ± 2.60	0.05
6MWT(m)	358. 74 ± 57.67		349.14 ± 48.13	

Table 4. Correlation GLS and 6MWT after 6 cycle chemotherapy

Variables	6MWT after 6 cycle chemotherapy	P value	R^2
GLS	-16.77 ± 2.60	0.05	- 0.084
Reduction of GLS	4.49 ± 3.43	0.106	0.049
Percentage reduction of GLS	20.71 ± 9.61	0.028	- 0.112

In this study, the 6MWT examination has been done before chemotherapy and after chemotherapy 6 cycles. Table 3 presented that GLS is associated with 6MWT values after chemotherapy 6 cycles even before GLS chemotherapy did not correlate with 6MWT. Table 4 presented that the value of GLS was related to the decrease of 6MWT value after 6 cycles of chemotherapy although the correlation was weak (R^2 = -0.084) while the percentage reduction of GLS and 6MWT had a correlation with p = 0.028 and R^2 = -0.112.

Table 5. Factor associated with 6MWT using univariate and multivariate

Variables	Univariate				Multivariat			
	Baseline		After 6 cycle chemotherapy		Baseline		After 6 cycle chemotherapy	
	Mean	P value (R^2)	Mean	P value(R^2)	P value	R^2 =0.057	P value	R^2= 0.143
TAPSE	23.2 ± 1.79	0.272 (-0.019)	20.89 ± 1.6	0.111 (0.016)	0.696		0.87	
LVEF	57.6 ± 4.1	0.466 (-0.03)	50.89 ± 4.5	0.193 (-0.007)	0.677		0.311	
E/A	1.2 ± 0.11	0.308 (-0.022)	0.82 ± 0.14	0.024 (0.087)	0.815		0.296	
E/e’	6.84 ± 1.79	0.251 (-0.016)	8.34 ± 2.04	0.369 (-0.27)	0.355		0.931	
Hb	12.12 ± 1.39	0.382 (-0.027)	11.4 ± 0.97	0.487 (-0.03)	0.729		0.852	
GLS	-21.26 ± 1.74	0.487 (-0.015)	-16.77 ± 2.6	0.05 (-0.084)	0.304		0.55	

From univariate analysis presented that TAPSE, LVEF, E/A, E/e', Hb, and GLS did not affect 6MWT before chemotherapy. After 6 cycles of chemotherapy, it can be seen that E/A (0.82 ± 0.14, p = 0.024) and GLS (16.77 ± 2.6, p = 0.05) may affected 6MWT. But after multivariate analysis there was no relationship between E /A (p = 0.296) and GLS (p = 0.55) after 6 cycles of chemotherapy (Table 5).

Discussion

This study was a prospective study that aimed to determine the association between GLS and UJ6M before and after anthracycline regimen in breast cancer patients.

Most subjects were excluded because of poor echo window echocardiography due to breast cancer lesions on the left and interfere with the examination, the patient did not continue chemotherapy until the 6th cycle and treated with a regimen other than the anthracycline.

Although LVEF is the most commonly used parameter for cardiotoxic monitoring due to chemotherapy, its prognostic value is controversial. The new echocardiography technique with GLS can detect subclinical left ventricular dysfunction.[15] In theory, the decrease in GLS that is thought to have a cardiotoxic effect is> 15% of baseline.[9]Sawaya*et al* and Stoodley *et al* demonstrated a decrease of GLS after chemotherapy with the anthracycline.[15,16] In this study there was a 20% decrease after the 6th cycle chemotherapy.

Khrisnasamy *et al* show an independent relationship between GLS and functional capacity using 6MWT.[14] Physical activity is becoming increasingly important for cancer patients during treatment and rehabilitation. Among the many types of tests available, a 6MWT is acceptable to assess functional exercise capacity because it is cheap, easy to perform, and is generally considered submaximal.[10,11] In the last 2 decades 6MWT has been increasingly used in cancer research for outcome evaluation. The distance OF 6MWT has been used as a prognostic factor for survival rates in lung cancer patients and is associated with other health aspects of breast cancer.[12,13] Distance of 6MWT describes the activity capability for a certain period of time submaximal. While the distance of breast cancer patients is 6-12% lower than healthy people. Therefore 6MWT can be recommended for cancer patient[10]. This study found a correlation between percentage reduction of GLS with decreasing distance 6MWT (Table 4). This is in accordance with previous research by Khrisnasamy *et al.*[14] Weak correlation of this result may be due to the many other factors that also affect this 6MWT that may not be in value in this study such as weight, height, patients who have often exercised. Another very important factor that influenced 6MWT especially in cancer patients is psychological motivation and this is not included in this research variable.

It was also found that LVEF did not affect 6MWT (Table 5). This may be due to EF value that was still within the normal range of> 50% even if the value of GLS had dropped compared to the initial value.

However, the current study had several limitations. In this study many confounding variables that can not be excluded and one of them was the psychological motivation of breast cancer patients was not included in this study so it is necessary to do the inspection of objective psychological motivation with the questionnaire to see whether this variable greatly affect 6MWT in cancer patients. For the future, further echocardiographic assessment should be made in patients after the 3rd chemotherapy and the 6th chemotherapy with anthracycline to see a decrease in GLS, LVEF, and symptoms of heart failure.

Based on the results of data analysis obtained in this study can be concluded that there was an association between the decrease in GLS and 6MWT in breast cancer patients who received chemotherapy anthracycline regimen for 6 cycles found.

Conflict of interest: None declared.

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