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Cardioprotective Effect of Upfront Use of ACEI in Breast Cancer Patients Undergoing Treatment Using Global Longitudinal Strain to Evaluate Left Ventricular Dysfunction

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Abstract:

Introduction: The frequency of breast cancer is rising; it has become evident that chemotherapy regimens exhibit cardiotoxic effects. The myocardial injury caused by chemotherapy agents varies in severity, frequently quantified as decreases in LVEF.

Aim of the study: Assessment of the efficacy of Speckle Tracking echocardiography for the early identification of left ventricular failure in breast cancer cases receiving chemotherapy and assessing the efficacy of ACEI upfront cardioprotective effect on patients under chemotherapy or chemotherapy and radiotherapy.

Subjects and Methods: The study included 200 female breast cancer patients receiving chemotherapy. The patients were randomized to 2 groups, one of them received upfront therapy of ACE inhibitors in association with chemotherapy dose while the other did not Speckle tracking echocardiography was performed as part of the echocardiographic examination for both groups, performed at 0, 3, 6, 9, 12 months follow up after the first cycle of treatment in same week. ACE (Ramipril 1.25 mg) was administered to trace the effectiveness of ACE in myocardial protection of patients under chemotherapy or chemotherapy and radiotherapy.

Results: We found that GLS can detect subclinical left ventricular dysfunction earlier than left ventricular ejection fraction measurement in women undergoing chemotherapy. The chemotherapy-induced LV dysfunction is potentially reversible with the use of ACEI, which results in improved clinical outcomes.

Conclusions: GLS has shown potential in detecting early cardiac injury associated with chemotherapy. ACEI demonstrated cardioprotective effects in patients undergoing chemotherapy for breast cancer.

Keywords: Breast Cancer; GLS; speckle tracking echocardiography.

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1. Introduction

Breast cancer is the most prevalent malignancy among females. Approximately 2.3 million new breast cancer cases are detected worldwide annually. Breast cancer can be categorized into molecular subtypes depending on mRNA gene expression levels, providing insights into novel therapeutic methods and stratifications of cases that influence the breast cancer cases management [1]. Invasive breast cancer affects 1 in 8 women in the United States (12.4%) during their lifetime [2].

The two basic principles for therapy are to decrease the probability of local recurrence and the probability of metastatic spread. Local control of cancer is achieved through operations, whether or not it is accompanied by radiotherapy. If there is a potential for metastatic relapse, systemic treatment is recommended, which may include chemotherapy, hormonal treatment, a combination of these medications or specific treatment. In the case of locally progressive illness, systemic treatment is utilized as a palliative treatment, with operation playing a minimal or absent role [3].

Chemotherapy is the systemic therapy utilized for the treatment of breast tumors. Modern regimens for breast cancer include anthracyclines (epirubicin or doxorubicin) and newer agents, including taxanes.

In clinical applications, certain chemotherapy medications used for the management of breast cancer may induce cardiac disorders. Cardiotoxicity can result in breast cancer cases as a consequence of these chemotherapy medications, depending on the side effects of each. To avoid serious adverse effects in these patients, rehydration to prevent dehydration and the application of antidotes were commonly used in the clinic. However, recent literature has revealed that the cardiotoxic effects of dose-dense anthracyclines were not as severe as expected [4].

Speckle-tracking echocardiography has recently developed as an innovative method for the objective & quantitative assessment of global and regional cardiac function.

Speckles are natural acoustic reflections that are unique to each segment

of the myocardium. When tracked from frame to frame, we get speckle tracking, so we can get a quantitative assessment of the motion of this segment and the global function of the chamber, which can be expressed by 2D or 3D imaging. As the speckle pattern is relatively stable

From one frame to the next, speckle-tracking technology offers the ability to identify and track the same speckle throughout the cardiac cycle [5].

Global longitudinal strain is now recognized as an early marker of cardiotoxicity and is a more sensitive and reproducible measure of the left ventricular systolic function than left ventricular ejection fraction [6].

ACEI may decrease apoptosis of cardiac cells and aldosterone-induced cardiac fibrosis, systolic ventricular wall stress, reduce the pro-development impact of angiotensin II on myocytes, progress cardiac output, attenuate afterload and elevate ventricular geometry.

2. Subjects & Methods

2.1. *Subjects*

200 subjects have been enrolled in the research, with three withdrawals

Inclusion criteria

- Female.
- Breast cancer.
- Scheduled for chemotherapy and/ or radiotherapy.

Exclusion criteria

- Male.
- Diabetes.
- Hypertension.
- Ischemic heart disease.
- Cardiomyopathic patient.

2.2. *Study design*

Randomize controlled study in which the patients were randomized into two groups:

Group A: One hundred cases that had upfront treatment of ACE inhibitors in association with chemotherapy dose prescribed by the oncology department. Dose in the prespecified range can be adjusted according to clinical and laboratory markers and patient tolerability.

Group B (Control Group): One hundred patients who received chemotherapy as

prescribed by the oncology department without ACE inhibitors.

2.3. *Methods*

Both groups had close follow-up involving clinical and echocardiographic examination after each treatment cycle or more often as per patient clinical status. Laboratory workup was ordered as deemed necessary and according to the attending physician's judgment.

A least three cardiac cycles must be developed for each loop during speckle tracking. This provides that a minimum of one complete cardiac cycle (the middle one) is consistently accessible for analysis, with no truncation.

LV GLS was recommended to have reference limits of normality of -20% for men and -20.3% for women, while LV FWLS was recommended to have reference limits of -22.5% for men and -23.3% for women [7].

The ASE/EACVl consensus document defines 15% worsening in GLS as clinically significant, which is probably a sign of subclinical left ventricular dysfunction.

Comparison between GLS and EF in early detection of myocardial dysfunction following chemotherapy and/or radiotherapy has been performed using the Philips EPIQ machine

2.4. *Statistical Methods*

The Statistical Package of Social Science (SPSS) software version 22 has been utilized for conducting data analysis in Windows 7 (SPSS Inc., Chicago, IL, the United States of America). Data has been coded and collected to help data manipulation, and it was double-entered into Microsoft Access. Standard deviations are utilized for measuring the dispersion of quantitative parametric data, while arithmetic means are utilized for measuring central tendency. Qualitative data is represented by numbers and percentages in a simple descriptive analysis. The One-Sample Shapiro-Wilks test and Kolmogorov-Smirnov test were utilized to assess the normality of the quantitative data in each research group. Subsequently, inferential statistical tests have been performed. For quantitative parametric data, the Kruskal-Wallis test has been utilized for comparing over 2 independent groups. In an independent t-test or analysis of variance

(ANOVA) to test the association between quantitative non-parametric variables. The *P*-value below 0.05 has been deemed statistically significant

3. Results

The mean age among the Study group was 43.78 years, and the mean age of the control group was 53.27 years. As illustrated in **Tables 1 and 2**, the study group shows an initial mean ejection fraction was 63.17% while after 12 months, the mean EF was 62.57%. In the control group, the initial mean ejection fraction was 66.31% while after 12 months, the mean ejection fraction was 62.95%.

Table 1: Description of initial mean ejection fraction at first presentation and after 12 months in the control group.

	Mean ± SD	SE	95% CI		Min.	Max.	Coefficient of variation	Median	Inter Quartile Range
			Lower Bound	Upper Bound					
EF%, Initial Scheme	66.3 ±3.88	0.39	65.53	67.09	58	76	5.85%	66	4.5
EF%, After 3 months	60.5 ±4.39	0.45	59.61	61.38	48	71	7.25%	60	7
EF%, After 6 months	61.52 ±4.5	0.46	60.61	62.42	50	75	7.31%	61	5.5
EF%, After 12 months	62.95 ±4.6	0.47	62.02	63.88	52	72	7.36%	63	7.5

Table 2: Description of initial mean ejection fraction at first presentation and after 12 months in the study group.

	Mean ± SD	SE	95% CI		Min.	Max.	Coefficient of variation	Median	Inter Quartile Range
			Lower Bound	Upper Bound					
EF%, Initial Scheme	63.17 ±2.53	0.25	62.67	63.67	59	69	4.01%	63	4
EF%, After 3 months	62.7 ±2.33	0.23	62.24	63.16	59	68	3.72%	63	4.5
EF%, After 6 months	62.37 ±2.19	0.22	61.94	62.8	58	68	3.51%	62	3
EF%, After 9 months	62.65 ±2.39	0.24	62.18	63.12	59	69	3.82%	63	3
EF%, After 12 months	62.57 ±2.12	0.21	62.15	62.99	58	69	3.39%	63	3

As illustrated in **Tables 3 and 4**, there is a change in the mean GLS with time between the two groups. In the control group, the initial mean GLS was -20.78%

and after 12 months mean GLS was -13.62 %. The study group's initial mean GLS was -20.78 % while after 12 months mean GLS was -19.11%.

Table 3: Description of mean GLS at first presentation and after 12 months in the control group.

	Mean ± SD	SE	95% CI		Min.	Max.	Coefficient of variation	Median	Inter Quartile Range
			Lower Bound	Upper Bound					
GLS%, Initial Scheme	-21.7 ±1.8	0.18	-22.06	-21.34	-26	-18	8.31%	-22	3
GLS%, After 3 months	-20.7 ±1.78	0.18	-20.43	-19.71	-24	-16	8.84%	-20	2
GLS%, After 6 months	-15.41 ±1.04	0.11	-15.62	-15.2	-17.5	-14	6.73%	-15	1.5
GLS%, After 12 months	-13.62 ±0.87	0.09	-13.8	-13.45	-19	-13	6.38%	-14	1

Table 4: Description of mean GLS at first presentation and after 12 months in the study group.

	Mean ± SD	SE	95% CI		Min.	Max.	Coefficient of variation	Median	Inter Quartile Range
			Lower Bound	Upper Bound					
GLS%, Initial Scheme	-20.78 ±1.26	0.13	-21.03	-20.53	-23.5	-18.2	6.08%	-21	2
GLS%, After 3 months	-15.68 ±2.66	0.27	-16.21	-15.15	-22	-12.5	16.96%	-15	3
GLS%, After 6 months	-16.43 ±2.09	0.21	-16.84	-16.01	-22	-14	12.7%	-16	2
GLS%, After 9 months	-17.6 ±1.7	0.17	-17.49	-17.26	-22	-15	9.67%	-17	2
GLS%, After 12 months	-19.11 ±1.75	0.18	-19.46	-18.76	-22	-15	9.18%	-19	1

As illustrated in **Figures 1 and 2**, the mean change in EF among the study group was -1.27%, and the mean change in GLS within the study group was -20.94%.

General Linear Model (GLM) repeated measure ANOVA

Descriptive Statistics

	N	Mean	SD	Mean EF% relative to Initial
EF % Initial Scheme	100	63.17	2.53	
EF % After 3 months	100	62.70	2.33	-0.74%
EF % After 6 months	100	62.37	2.19	-1.27%
EF % After 12 months	100	62.57	2.12	-0.95%

Pairwise Comparisons Bonferroni method

		Mean Difference	SE	P Value	95% Confidence Interval for Difference		
					Lower Bound	Upper Bound	
EF % Initial Scheme	EF % After 3 months	0.47	.150	0.01369	0.066	0.874	P < 0.05 S
EF % Initial Scheme	EF % After 6 months	0.80	.195	0.00050	0.275	1.325	P < 0.001 HS
EF % Initial Scheme	EF % After 12 months	0.60	.198	0.01912	0.066	1.134	P < 0.05 S
EF % After 3 months	EF % After 6 months	0.33	.136	0.10410	-0.037	0.697	P > 0.05 NS
EF % After 3 months	EF % After 12 months	0.13	.164	1.00000	-0.312	0.572	P > 0.05 NS
EF % After 6 months	EF % After 12 months	-0.20	.151	1.00000	-0.607	0.207	P > 0.05 NS

Figure 1: Description of changes in EF% with time within the study group throughout chemotherapy cycles.

General Linear Model (GLM) repeated measure ANOVA

Descriptive Statistics

	N	Mean	SD	Mean GLS relative to Initial
GLS Initial Scheme	100	-20.78	1.26	
GLS After 3 months	100	-15.68	2.66	-24.53%
GLS After 6 months	100	-16.43	2.09	-20.94%
GLS After 12 months	100	-19.11	1.75	-8.02%

Pairwise Comparisons Bonferroni method

		Mean Difference	SE	P Value	95% Confidence Interval for Difference		
					Lower Bound	Upper Bound	
GLS Initial Scheme	GLS After 3 months	-5.10	.304	0.00000	-5.915	-4.279	P < 0.001 HS
GLS Initial Scheme	GLS % After 6 months	-4.35	.251	0.00000	-5.027	-3.673	P < 0.001 HS
GLS Initial Scheme	GLS After 12 months	-1.67	.190	0.00000	-2.180	-1.154	P < 0.001 HS
GLS After 3 months	GLS % After 6 months	0.75	.138	0.00000	0.375	1.119	P < 0.001 HS
GLS After 3 months	GLS After 12 months	3.43	.259	0.00000	2.732	4.128	P < 0.001 HS
GLS % After 6 months	GLS After 12 months	2.68	.190	0.00000	2.171	3.195	P < 0.001 HS

Figure 2: Description of changes in GLS% with time within the study group throughout chemotherapy cycles.

4. Discussion

This study included 200 female breast cancer patients from August 2021 to August 2022 receiving chemotherapy or chemotherapy and radiotherapy at the oncology department, Faculty of Medicine, Fayoum University. The research received approval from the ethical committee of the Faculty of Medicine at Fayoum University.

Patients have been divided into two equal groups; the first took ACEI while the other did not. Both groups had close follow-up involving clinical and echocardiographic examinations after each treatment cycle or more often as per patient clinical status. Laboratory workup was ordered as deemed necessary and according to the attending physician's judgment.

Breast cancer cases from the oncology department Fayoum university fulfilling the inclusion criteria who had already received their first cycle were selected and underwent echocardiographic assessment and follow up of ventricular function by EF and GLS performed at 0, 3, 6, 9, 12 months follow up after the first cycle of treatment in the same week. These assessments were performed in the cardiology department, Faculty of Medicine, Fayoum University.

Comparison between GLS and EF in early detection of myocardial dysfunction following chemotherapy and/or radiotherapy has been performed using the Philips EPIQ machine

GLS is a preclinical indicator of cardiac dysfunction that has been identified (8). It is widely recognized that GLS offers independent and incremental prognostic information according to the long-term probability of cardiovascular mortality and morbidity [9].

The longitudinal myocardial fibers that are responsible for longitudinal shortening appear to be especially susceptible to a variety of cardiac conditions, such as cardiotoxicity, at a relatively early stage [10].

Administration of ACEI during chemotherapy cycles prevented further deterioration of myocardial dysfunction, even with improvement of ventricular function at the end of the cycle.

Our study revealed that GLS is an efficient early predictor of myocardial dysfunction and proved superiority to EF. Our study also revealed that administration of ACEI during cycling of chemotherapy prevents worsening of myocardial dysfunction and improves clinical outcomes.

Our study agreed with D. van der Linde et al., who monitored breast cancer cases who received chemotherapy from 2014 to 2017 over four years. The LV function has been evaluated utilizing 2D speckle tracking imaging, 3D left ventricular ejection fraction, and Simpson's method. Additionally, the myocardial strain was determined. They determined that GLS could detect subclinical left ventricular dysfunction caused by chemotherapy in breast cancer cases before 3D left ventricular ejection fraction [11].

Our result agreed with Gripp et al., who revealed that GLS was an excellent predictor of myocardial toxicity, demonstrating high efficacy in early diagnosis in 58 patients (study done from 2015 to 2016) [12].

Also, our study agreed with the meta-analysis conducted by Oilkonomou et al., who aimed to explore the prognostic value of GLS for the prediction of myocardial dysfunction induced by cancer therapy between 2011 and 2018. They concluded that GLS could be used in the detection of early subclinical ventricular dysfunction [13].

Our study also agreed with that conducted by Gripp et al [12], who included 49 breast cancer cases to study the applicability of strain in early identification of cardiotoxicity in cases treated for breast cancer. They concluded that strain could allow early identification of chemotherapy-induced cardiotoxicity.

Also, our data agreed with a meta-analysis done by Dong et al., who evaluated the protective and prophylactic effect of ACEI in 702 cases with breast cancer undergoing chemotherapy and concluded that ACEI has an important effect on decreasing the reduction of myocardial function [14]. In new clinical research that

was presented on June 11, 2019, 468 cases were randomly assigned to either the carvedilol, lisinopril, or placebo groups. The research indicated that the cardiotoxicity-free survival rate has been enhanced in both carvedilol (HR 0.49) and the lisinopril (hazard ratio 0.53) groups in comparison to the placebo group. In comparison to placebo (47%), carvedilol (31%), and lisinopril (37%), cases who received anthracyclines experienced a greater incidence of cardiac conditions. They involved data from the angiotensin converting enzyme inhibitor /ARB arm of this investigation into our meta-analysis of EF induced by chemotherapy [15].

Additional studies have verified that ACE inhibitors may diminish aldosterone-induced cardiac fibrosis as well as apoptosis of cardiac cells, enhance cardiac output, minimize the pro-growth effects of angiotensin II on myocytes, enhance ventricular geometry, and lower afterload as well as systolic ventricular wall stress [16, 17].

Furthermore, the activity of ACE was reported to be elevated in comparison to that of control groups following chemotherapy. In vivo, the administration of Ramipril following chemotherapy significantly reduced cardiac angiotensin converting enzyme activity and enhanced cardiac remodeling, death, and cardiac functioning [18]. It was further shown that ramipril may prevent fibrosis in the cardiac interstitium and inhibit collagen accumulation. These findings indicate that the advantages of angiotensin-converting enzyme inhibitors in breast tumor cases undergoing chemotherapy or chemotherapy and radiotherapy are associated with the suppression of cardiac ACE, which is essential for the progression of this cardiomyopathy.

5. Conclusion

Global longitudinal strain can detect subclinical left ventricular dysfunction earlier than left ventricular ejection fraction measurement in women undergoing chemotherapy or chemotherapy and radiotherapy. The chemotherapy or chemotherapy and radiotherapy-induced LV dysfunction is potentially reversible with the use of ACEI, which results in improved clinical outcomes and provides cardioprotective effects.

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