GEORGIAN BIOMEDICAL NEWS

VOLUME 2 ISSUE 3. JUL- SEP 2024

Comprehensive Cardiac Monitoring in Female Breast Cancer Patients Undergoing Chemotherapy: Importance of Right Ventricular Global Longitudinal Strain Assessment

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DOI: 10.52340/GBMN.2024.01.01.81

ABSTRACT

Background: Breast cancer is the most frequently diagnosed malignancy globally, characterized by high survival rates but emerging concerns regarding non-cancer-related mortality. A notable issue in this population is cancer therapy-related cardiovascular toxicity (CTR-CVT). This study aimed to evaluate CTR-CVT in breast cancer patients with low cardiovascular risk undergoing chemotherapy, utilizing standard 2D echocardiography, speckle tracking echocardiography (STE), and NT-proBNP measurements.

Methods: Forty-four female breast cancer patients with no prior cardiovascular disease or chemotherapy history scheduled to commence chemotherapy were recruited. Standard 2D echocardiography and STE were employed to assess both ventricles' global longitudinal strain (GLS).

Results: Although conventional echocardiographic parameters such as left ventricular ejection fraction (LVEF) and tricuspid annular plane systolic excursion (TAPSE) remained stable, a significant reduction in both left and right ventricular global longitudinal strain (GLS) was observed. Specifically, left ventricular GLS (LV-GLS) decreased from -20.2 ± 4.2 to -17.9 ± 5.2 (t-test = -3.35, df = 32, p = 0.002), while right ventricular free wall longitudinal strain (RV-FWLS) decreased from -23.2 ± 4.1 to -20.1 ± 4.2 (t-test = -2.98, df = 32, p = 0.001). Both RV-FWLS and LV-GLS decreased concurrently in 60% of patients. Isolated reductions in RV-FWLS were seen in 18% of patients, and isolated LV-GLS reductions were noted in 12%. NT-proBNP levels increased from 125.9 ± 124.4 pg/mL to 176.4 ± 166.8 pg/mL (t-test = -2.35, df = 32, p = 0.025; delta NT-proBNP = 50.5). Even in cases where NT-proBNP levels were stable, RV-FWLS exhibited a significant decline of over 15%.

Conclusions: The results highlight the significance of assessing RV-FWLS, which demonstrated a notable decline alongside LV-GLS. This underscores the necessity for a comprehensive approach to cardiac function evaluation during chemotherapy.

Keywords: Breast cancer; cardiotoxicity; cardiovascular risk factors; chemotherapy; global longitudinal strain.

BACKGROUND

Breast cancer is currently the most frequently diagnosed malignancy globally.[1] The 5-year survival rate for breast cancer (BC) is notably high, reaching up to 80%. While cancer-specific mortality rates are progressively declining, there is an alarming trend in the increasing proportion of deaths due to non-cancer causes among women with BC. This trend highlights the critical need for comprehensive care beyond cancer treatment.[2-4] Breast cancer patients are at an elevated risk of cardiovascular mortality compared to the general population during the follow-up period post-diagnosis.[5,6] Moreover, many breast cancer treatments are associated with cardiotoxic effects, emphasizing the necessity for vigilant cardiovascular monitoring and surveillance.

A proactive approach to cardiovascular (CV) risk assessment and monitoring is crucial to mitigate the adverse impact of cardiotoxicity on treatment outcomes and overall patient well-being. The frequency and nature of cardiovascular monitoring should be individualized based on factors such as the type of drug, treatment settings, combination therapies, and, critically, the patient's risk of cardiotoxicity. This risk profile should be dynamically reassessed over time.[7] However, there is a lack of evidence regarding follow-up protocols for patients with low cardiovascular risk. Therefore, the primary objective of our study was to promptly identify chemotherapy-induced cardiovascular toxicity (CTR-CVT) in breast cancer patients with low cardiovascular risk undergoing chemotherapy. We utilized a comprehensive analysis that included conventional echocardiographic parameters, global longitudinal strain, and cardiac peptide NT-proBNP to achieve this. Additionally, we aimed to evaluate the predictive value of right ventricular free wall longitudinal strain (RV-FWLS) in detecting early signs of cardiotoxicity in this low cardiovascular-risk population.

METHODS

In this observational cohort study, we enrolled 38 female patients aged 18 years and older, with 76% of participants being under 60 years of age. All subjects were newly diagnosed with breast cancer and were scheduled to undergo chemotherapy. Key inclusion criteria included the absence of prior cardiovascular disease and no previous chemotherapy

treatment. After excluding five patients due to poor image quality and refusal to attend follow-up visits, 33 participants were assessed at the second visit. The study adhered to the principles of the Declaration of Helsinki and received approval from the Tbilisi State Medical University Biomedical Research Ethics Committee (Approval Number N3-2021/87, March 23, 2021). Written informed consent was obtained from all participants prior to their involvement in the study.

Demographic data and medical histories of the participants were collected, as detailed in Table 1. Sixty percent of participants received anthracyclines (doxorubicin 60 mg/m² combined with cyclophosphamide 600 mg/m² or epirubicin 100 mg/m² with cyclophosphamide 600 mg/m²) administered intravenously in 21-day cycles, while 40% received HER2-targeted therapy.

TABLE 1. Demographic Data of Study Population

Variables	
Age, years, mean±SD	49.8±12.9
Weight, kg, mean±SD	79.1±20.0
Height, cm, mean±SD	162.1±6.50
BMI, kg/m², mean±SD	28.5±6.80
No alcohol consumption, %	100
No smoking history, %	100
Diabetes mellitus, n, %	1(3)
Hypertension, n, %	5(15)
Systolic blood pressure, mmHg	121.9±18.5
Diastolic blood pressure, mmHg	79.1±10.6
Heart rate, bpm, mean±SD	77.7±12.4
Creatinine, µmol/L, mean±SD	75.9±11.1
GFR, mL/min/1.73 m², mean±SD	91.2±17.5

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; SD, standard deviation.

Diagnostic assessments included standard 2D echocardiography using a Vivid E9 ultrasound machine (GE Healthcare, Horten, Norway) with an M5S transducer (1.7-3.3 MHz). Measurements followed American Society of Echocardiography (ASE) guidelines. They assessed left ventricular ejection fraction (LVEF), left ventricular dimensions, and right ventricular function at baseline (T0) and after three months (T1), which corresponded to the fourth cycle of anthracycline and targeted therapy.

Echocardiographic images were captured at an average frame rate of 70-90 frames per second and stored digitally across three cardiac cycles. LVEF was calculated using the biplane Simpson's method from apical 4- and 2-chamber views, with three consecutive heart cycles recorded per view. Septal and posterior wall thicknesses, left ventricular (LV), aorta, and left atrial diameters were also measured according to ASE standards. Right ventricular function was assessed using the RV-focused apical 4-chamber view. Tricuspid annular plane systolic excursion (TAPSE) was measured as the vertical displacement of the tricuspid annulus from end-diastole to end-systole using M-mode, and the tissue Doppler-derived tricuspid lateral annular systolic velocity (S wave) was obtained by aligning the Doppler cursor with the basal segment and the tricuspid annulus. Speckle tracking echocardiography (STE) was performed according to ASE guidelines. All patients remained in sinus rhythm throughout the study. Peak-systolic strain in the left ventricle was calculated automatically from the mean of six traced segments in each apical 2D view (two-, three-, and four-chamber), with left ventricular global longitudinal strain (LV GLS) computed by averaging the peak-systolic strain across these views. Right ventricular free wall strain (RVFWS) was calculated using the standard RV-focused apical 4-chamber view.

A relative reduction in LVEF of 10% or a decrease to below 53%, combined with a change in global longitudinal strain (GLS) greater than 15% from baseline, was considered indicative of chemotherapy-induced cardiovascular toxicity (CTR-CVT).

Tracking quality was visually assessed, and segments that did not initially track correctly were manually adjusted. Segments that still could not be tracked correctly after adjustment were excluded from the analysis. Poor-quality images that made speckle-tracking analysis infeasible in two or more consecutive segments were also excluded.

Electrocardiograms (ECGs) were performed at baseline and at the follow-up visit to monitor rhythm changes, with ECG characteristics presented in Table 2.

TABLE 2. ECG characteristics

Waves, intervals	Baseline, ms mean±SD	Follow-up, ms mean±SD
P	112±9.9	112.1±9.6
PR	158.2±23.2	155.9±20.0
QRS	81.9±24.1	74.9±14.9
QT	367.0±40.5	365.0±39.9
QT_c	410.8±37.8	409.5±34.6

Abbreviations: QT_c, corrected QT interval.

Additionally, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were measured using a chemiluminescence immunoassay on a Snibe Maglumi 800 analyzer before cancer therapy and at the follow-up visit. NT-proBNP levels exceeding 125 pg/mL, corresponding to the 99th percentile reference limit, were considered elevated.

Statistical analyses were performed using SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation (SD). All statistical tests were two-tailed t-tests, and Pearson correlation coefficients were calculated to assess associations. A p-value of <0.05 was considered statistically significant.

ISSN (Online): 2720-8796 ISSN (Print): 2720-7994

RESULTS

The study included 33 breast cancer patients, with a mean age of 49.8 ± 12.8 years. The mean cumulative dosage of doxorubicin at follow-up was 431 mg/m² ± 38 mg, epirubicin was 665 mg/m² ± 90 mg, and HER2-targeted therapy was administered for 4-5 cycles.

According to the latest baseline cardiovascular toxicity risk stratification, 85% of our cohort was classified as low cardiovascular (CV) risk (either no risk factors or one moderate risk factor).[7] (Tab.3)

TABLE 3. Cardiovascular risk factors

Risk Factors	*N (%)*	*Risk score*
Age 65-70 years	5(15)	M2
Hypertension	5(15)	M1
Diabetes mellitus	1(0.03)	M1
Obesity (BMI >30)	10(30)	M1
Baseline NT-proBNP>125 pg/ml	6(18)	M1
No CV risk	6(18)	-

Abbreviations: M1, moderate risk 1; M2, moerate risk 2.

Echocardiographic Parameters

During follow-up visits, no significant changes were observed in left ventricular ejection fraction (LVEF) following chemotherapy. LVEF values remained stable, with measurements changing from 64.6 ± 4.3 to 65.0 ± 3.6 (t-test = 0.70, df = 32, p = 0.486), and a mean ΔLVEF of 0.4 ± 3.2. Similarly, tricuspid annular plane systolic excursion (TAPSE) showed no significant changes post-chemotherapy, transitioning from 24.8 ± 3.1 to 25.5 ± 5.5 (t-test = 0.65, df = 32, p = 0.527), with a mean ΔTAPSE of -0.7 ± 4.3.

In contrast, a notable decrease was observed in both left and right ventricular global longitudinal strain (LV-GLS, RV-FWLS) from baseline to the follow-up period. LV-GLS decreased from -20.2 ± 4.2 to -17.9 ± 5.2 (t-test = -3.35, df = 32, p = 0.002), with a mean ΔLV-GLS of -1.9 ± 3.2, representing an average percentage change of -8.2 ± 14.2%. Similarly, RV-FWLS decreased from -23.2 ± 4.1 to -20.1 ± 4.2 (t-test = -2.98, df = 32, p = 0.001), with a mean percentage change of -10.6 ± 21.6%. Refer to Table 4 (supplemental material) for detailed data.

Notably, more patients experienced changes in RV-FWLS compared to LV-GLS (21% vs. 12%, respectively). Additionally, 36% of patients displayed concurrent changes in both ventricles, highlighting the importance of evaluating both the left and right ventricles for a comprehensive assessment of cardiac function during chemotherapy.

Peptide Levels

The study revealed a significant increase in NT-proBNP levels following chemotherapy, with a shift from 125.9 ± 124.4 pg/mL to 176.4 ± 166.8 pg/mL (t-test = -2.35, df = 32, p = 0.025; delta NT-proBNP = 50.5 pg/mL) in 61% of cases. Notably, in patients where NT-proBNP levels remained stable (39%), RV-FWLS exhibited a more than 15% decrease in more patients than LV-GLS. This observation suggests that RV-FWLS may be a more sensitive indicator of cardiotoxicity in this context.

ECG Characteristics

Most patients (87.9%) exhibited normal sinus rhythm, with only a small proportion (9.1%) experiencing sinus tachycardia. All other ECG parameters were within normal ranges.

DISCUSSION

Current guidelines emphasize the importance of assessing initial cardiovascular (CV) risk factors before initiating cancer treatment. However, establishing a practical approach for every clinical scenario remains challenging.[7-11] Cardiovascular monitoring frequency should be tailored based on various factors, including the type of drug administered, treatment settings, combination therapies, and the patient's risk of cardiotoxicity.[7] Despite being classified as low-risk, breast cancer patients are still at a higher risk of experiencing cardiovascular events compared to those without breast cancer. Therefore, the primary objective of our study was to closely monitor breast cancer patients classified as having low cardiovascular risk and to detect early alterations in cardiac structure and function indicative of cardiotoxicity. Specifically, we aimed to evaluate the role of the right ventricular global longitudinal strain (RV-FWLS) in predicting cardiotoxicity.[12]

Our study found a significant decline in global longitudinal strain in both ventricles, indicating potential cardiotoxicity, with more pronounced changes in RV-FWLS compared to left ventricular global longitudinal strain (LV-GLS). This discrepancy may be due to the thinner right ventricle wall, making RV-FWLS alterations a more subtle early indicator of cardiotoxicity. This is consistent with findings by Keramida et al., who identified a cut-off value of 14.8% for RV-GLS changes as a predictor of cardiotoxicity in breast cancer patients undergoing trastuzumab therapy.[13] The correlation with NT-proBNP levels further highlighted the significance of RV-FWLS. In patients with stable NT-proBNP levels, significant decreases in RV-FWLS (>15%) were observed, unlike LV-GLS. This suggests that RV-FWLS changes may precede alterations in NT-proBNP levels, supporting its potential as an early marker of cardiotoxicity.

Recent research increasingly supports the predictive value of RV-GLS in assessing cardiotoxicity. Boczar et al. demonstrated a notable decrease in RV-free wall longitudinal strain in breast cancer patients treated with anthracyclines, consistent with Laufer-Perl et al.'s findings of reduced RV strain following anthracycline therapy.[14,15] Similarly, Plank et al. investigated the impact of doxorubicin on RV strain in lymphoma patients, revealing subclinical RV dysfunction without significant changes in LVEF after six months of follow-up.[16]

Using a 15% decline in RV-FWLS as a benchmark for cardiotoxicity, our findings suggest that RV-FWLS may serve as a more nuanced indicator of cardiac toxicity. This underscores

ISSN (Online): 2720-8796 ISSN (Print): 2720-7994

the importance of incorporating multiple cardiac markers and imaging modalities to assess cardiotoxicity comprehensively.

The findings of our study may prompt a re-evaluation of current surveillance protocols for breast cancer patients. This raises several questions: Should we rely solely on initial risk stratification, or is there a need for enhanced vigilance for cardiovascular diseases in breast cancer patients, considering their elevated risk compared to individuals without breast cancer? Is the current cardiac marker alone sufficient for effective surveillance of these patients? Additionally, could RV-FWLS serve as a crucial predictor of subclinical cardiotoxicity? Addressing these questions through further research is essential to refine surveillance protocols for this patient population.

Study Limitations

Several limitations of our study should be acknowledged. The primary limitation is the small sample size, which may affect the generalizability of the findings. Additionally, the relatively short follow-up may only partially capture long-term cardiotoxic effects. More significant, longitudinal studies are needed to better assess early detection of cardiotoxicity and the potential role of RV-FWLS as a predictive marker.

CONCLUSIONS

In conclusion, our study underscores the importance of vigilant monitoring of low cardiovascular-risk breast cancer patients. It highlights the potential role of RV-FWLS in the early detection of chemotherapy-induced cardiovascular toxicity (CTR-CVT). The significance of our study lies in its contribution to enhancing the understanding of cardiovascular health management in breast cancer patients undergoing chemotherapy. By emphasizing the need for tailored cardiovascular monitoring based on individual risk profiles, our study advocates for a proactive approach to mitigating the impact of cardiotoxicity on treatment outcomes and overall patient well-being.

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ACKNOWLEDGEMENTS

We extend our deepest gratitude to Dr Lika Gachechiladze and Dr. Elene Gogua, oncologists from the Clinical Oncology Institution, for their invaluable assistance in providing patients for this study. We also thank Tamar Gaprindashvili and Mata Gujabize for their professional help and support throughout the project. Special thanks to David T. for his expert statistical analyses, which were crucial to the success of this research. This work was supported by the Tbilisi State Medical University Grant for Young Investigators and the Shota Rustaveli National Science Foundation of Georgia under Ph.D. Educational Programs Funding, Grant No. PHDF-22-323.

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ISSN (Online): 2720-8796 ISSN (Print): 2720-7994

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Georgian Biomedical News
ISSN (Online): 2720-8796 ISSN (Print): 2720-7994