

Screening of Myocardial Cardiotoxicity Induced by Anticancer Chemotherapy and the Importance of Global Longitudinal Strain

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Abstract

Introduction: The improvement of survival in patients with cancer and the expansion of therapeutic options have led to the emergence of a new profile of cardiotoxicity, specifically associated with antimitotic agents. Our study aimed to assess the incidence of chemotherapy-induced myocardial toxicity in patients with cancer. **Patients and Methods:** We conducted a looking-forward longitudinal cohort study including all patients admitted to the Cardiology departments of Aristide le Dantec Hospital and Dalal Jamm National Hospital Centre for pre-chemotherapy check-up. The included patients did not undergo any pre-existing cardiopathy. **Results:** Over a period of two years ranging from January 2019 to December 2021, a total of 37 patients were included in the study. Notably, there was a female predominance (92%) with an average age of 49.7 years \pm 13.69. Breast cancer accounted for 70% of the neoplasms. Laboratory findings revealed moderate anemia in 19 patients (51%). At inclusion, the left ventricle (LV) was of normal size (LV

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diastole at 44.46 ± 4.97 mm). The systolic function of the left ventricle was normal in all patients, with an average ejection fraction (EF) of $63.1\% \pm 5.80$ and a mean global longitudinal strain (GLS) of $-20.4\% \pm 2.58$. The most commonly used agents were anthracyclines. During follow-up, 3 patients (8.1%) developed clinical symptoms of left heart failure, and LV dysfunction on echocardiography was observed in 5 (13.5%) patients, with a significant decrease in EF < 50%. Overall, we observed a significant decline in mean global longitudinal strain and average EF at 3 months ($p < 0.000$) and 6 months ($p < 0.000$). Among 14 patients (8 at 3 months, 6 at 6 months), a decrease in delta strain $\geq 15\%$ was noted, and 5 of them (13.5%) developed LV dysfunction during subsequent follow-up. **Conclusion:** The incidence of cardiac toxicity is not negligible, hence the importance of early screening. Strain imaging is an essential tool that should be performed as part of the assessment before chemotherapy and re-evaluated during treatment.

Keywords

Cancer, Chemotherapy, Global Longitudinal Strain, Cardiotoxicity

1. Introduction

Cancer is currently one of the most frequent causes of morbidity and mortality, with over ten million new cases reported worldwide each year and more than half of these deaths occur in developing countries [1].

In Senegal, cancer is a significant public health issue, and the number of patients with cancer continues to rise. According to the International Agency for Research on Cancer (IARC), the annual number of women diagnosed with breast cancer in sub-Saharan Africa is expected to nearly double by 2040 due to aging and population growth [2].

This can be attributed to the rising incidence of the disease. Additionally, advancements in cancer therapy over the past two decades have significantly improved the prognosis of patients with cancer. Chemotherapy for cancer has rapidly evolved, with increasing emphasis on combinations of antimetabolic agents, leading to promising results over time [3].

However, the progress in therapeutic options over recent decades is not without consequences. It has given rise to new profiles of toxicity, some of which can be severe and may occur throughout the course of cancer treatment and even in the long term [4].

Among these, cardiovascular events secondary to treatment represent one of the most concerning complications.

The incidence of chemotherapy-induced myocardial toxicity varies and depends on several parameters, including the type of drug used, cumulative dose, and cardiovascular risk factors of the patient. The risk of heart failure induced by doxorubicin increases with the cumulative dose of anthracycline: 3% to 5% with

400 mg/m², 7% to 26% with 550 mg/m², and 18% to 48% with 700 mg/m² [5].

Numerous studies have demonstrated the utility of strain imaging in evaluating myocardial cardiotoxicity induced by chemotherapy. Some research teams have proposed combining biomarkers with echocardiography, particularly the analysis of longitudinal myocardial deformation, to detect and stratify patients at risk of cardiotoxicity [5]. Even at low doses of anthracycline (150 mg/m²), an altered strain has been identified as a predictor of future left ventricular systolic dysfunction, occurring within months or up to a year [6].

Therefore, assessing myocardial deformations provides an excellent means of predicting left ventricular systolic impairment, and it should be studied early and progressively to prevent irreversible cardiac dysfunction [7]. According to the European Society of Cardiology (ESC) recommendations [8], cardiotoxicity is defined by a decrease in left ventricular ejection fraction (LVEF) of 10% or more compared to baseline, with an LVEF < 50%, or a decrease in delta strain greater than 15%, associated with elevated troponin levels. The delta strain represents the variation in strain at a given time (T) compared to its initial value [8].

In Africa, and particularly in Senegal, there is a scarcity of studies investigating the impact of anticancer therapy on the cardiovascular system. Therefore, our primary objective was to evaluate the incidence of chemotherapy-induced myocardial toxicity in patients with cancer followed in our departments.

2. Materials and Methods

Our study was conducted at the Cardiology and Oncology departments of the Aristide Le Dantec University Hospital (CHU-HALD) in Dakar and the Dalal Jamm National Hospital Centre in Guediawaye. These two hospitals are level 3 healthcare facilities, comprising services in oncology, medicine, surgery, biology, medical imaging, and cardiology. The majority of patients with cancer in Senegal receive care in these two healthcare settings.

This was a looking-forward comparative longitudinal cohort study, conducted from January 1, 2019, to July 31, 2022. The study received approval from the relevant administrative authorities and informed consent was obtained from the patients. We included patients with diagnosed and staged cancer who had never received prior chemotherapy and/or thoracic radiotherapy, were at WHO stage 1 or 2, and were evaluated by the cardiology service before chemotherapy. These patients underwent an electrocardiogram and Doppler echocardiography and consented to participate in the study.

Patients with renal insufficiency (glomerular filtration rate < 40 mL/min/1.73 m²), liver failure, or heart failure, as well as those with hemoglobin levels < 8.5 g/dL and platelet counts < 140,000/mm³, were not included. Additionally, patients with major psychiatric or neurological disorders, uncontrolled infections, or advanced metastases were not included.

Patients were excluded based on the following criteria: inability to be followed

up due to family, social, and/or geographical reasons, inability to undergo adequate echocardiographic measurements due to echogenicity issues, and those who presented with altered left ventricular systolic function at the initial evaluation.

We examined epidemiological and clinical data, including the presence of cardiovascular risk factors (CVRFs) such as high blood pressure, diabetes, and known dyslipidemia; we also assessed the presence of symptoms or a cardio-pulmonary syndrome, including dyspnea, chest pain, palpitations, heart failure, pulmonary condensation syndrome, and pleural effusion. We evaluated the overall condition using the WHO performance index and studied the clinical localization of the cancer and the presence or absence of metastases.

Paraclinical data included laboratory results and echocardiography (cavity size, indexed left ventricular mass, left ventricular systolic function: LVEF by Simpson Biplane, global longitudinal strain (GLS), and left ventricular diastolic function). The echocardiographic standards used for this study were based on the American Society of Echocardiography (ASE) 2015 recommendations [9]. For this work, we utilized the Vivid E9 echocardiography machine from General Electric. Images were recorded by the same operator, and two other independent operators performed the proofreading.

Regarding therapeutic aspects, we examined chemotherapy data, including protocols used, cumulative doses, and whether or not radiotherapy was administered.

For the follow-up, we re-evaluated patients at 3 months and 6 months.

Clinical outcome criteria included the onset of cardio-pulmonary symptoms and/or a decrease in global longitudinal strain (GLS) based on the calculation of delta strain ($\text{Delta strain} = 100 - (\text{GLS at a given time} \times 100 / \text{baseline GLS})$) > 15%, associated with a left ventricular dysfunction (LVEF by Simpson Biplane) where LVEF < 50%.

All collected data were entered and analyzed using SPSS 17.0 software. For quantitative variables, we calculated means with their standard deviations, while qualitative variables were expressed as percentages. Continuous variables were compared using ANOVA, and ordinal variables were analyzed using the Chi-square test or Fisher's exact test. The difference was statistically significant if the p-value < 0.05.

3. Results

During the study period, a total of 37 patients met the inclusion criteria, after excluding 40 patients (3 due to geographical barriers, 13 who died during the study, 8 lost to follow-up, 10 unable to complete echocardiographic follow-up due to financial constraints related to chemotherapy costs, and 6 with poor echogenicity for accurate echocardiographic parameter estimation).

The average age was 49.7 ± 13.69 years. 92% of the patients were female, accounting for a sex ratio of 0.09. More than half of our patients had a moderate

socioeconomic status (51%).

Cardiovascular risk factors were found in 20 patients, including high blood pressure (28%), diabetes (8%), and obesity (33%). In our study, breast cancers predominated, accounting for 70% (n = 26) of cases. We also identified cases of cervical, stomach, bladder, ovarian, and oropharyngeal cancers. Sixteen patients (43%) experienced metastasis with pulmonary involvement observed in 10 patients. The clinical characteristics of the studied patients are detailed in **Table 1**.

Table 1. Clinical characteristics of studied patients (N = 37).

Characteristics	Mean/Numbers	Percentage/standard deviation
Mean age (years)	49.7	±13.69
Low Socioeconomic level	14	38.00
Female	34	92.00
Localization of Neoplasia		
Stomach	1	3.00
Bladder	1	3.00
Ovary	1	3.00
ORL (hypopharynx, larynx)	2	5.00
Cervix	6	16.00
Breast	26	70.00
CVRF		
Diabetes	3	8.00
HBP	10	28.00
Overweight or obesity	12	33.00
Hemoglobin (g/dL)	12.1	± 1.45
GFR (mL/min/m ²)	97.6	± 24.81
LVH	8	22.00

ORL: otorhinolaryngology, CVRF: cardio-vascular risk factors, HBP: High Blood Pressure, GFR: glomerular filtration rate, LVH: left ventricle hypertrophy.

Moderate anemia was present in 19 patients (51%), with an average hemoglobin level of 12 ± 1.45 g/dL. Moderate renal impairment was found in 2 patients (5%), with estimated GFR of 41 and 55 mL/min/m².

On electrocardiography, all patients had regular sinus rhythm, with an average heart rate of 82 ± 13.5 /min. Left ventricular diastolic hypertrophy was observed in 8 patients (22%).

Anthracycline-based protocols were used in 68% (n = 25) of the patients.

3.1. Doppler Echocardiography at Baseline

The mean tele-diastolic diameter of the left ventricle (LV) was 44 ± 4.97 mm with the mean tele-systolic diameter of the LV being 28.54 ± 4.05 mm. The average ejection fraction (EF) was $63.11 \pm 5.8\%$. The mean global longitudinal

strain (GLS) was $-20.54 \pm 2.58\%$. No diastolic dysfunction was observed. The right ventricular systolic function was normal in all our patients (**Table 2**).

Table 2. Echocardiographic data and evolution of the means of parameters after chemotherapy.

Parameters	Baseline	3 months	6 months	p-value
Global Strain (%)	-20.40 ± 2.58	-18.54 ± 1.78	-14.54 ± 2.91	<0.001
LV telediastole (mm)	44.46 ± 4.97	45.50 ± 4.15	48.20 ± 3.61	NS
LV telesystole (mm)	28.54 ± 4.05	28.60 ± 3.40	33.60 ± 8.20	NS
FEVG SB (%)	63.11 ± 5.80	61.64 ± 6.36	52.00 ± 13.91	<0.001
LA Surface (cm ²)	14.16 ± 3.87	14.70 ± 2.20	14.82 ± 1.56	NS
RA Surface (cm ²)	11.29 ± 2.51	12.30 ± 1.89	12.24 ± 2.42	NS
LA Volume (ml/m ²)	23.22 ± 8.72	25.90 ± 1.89	24.85 ± 13.91	NS
Basal RV (mm)	31.33 ± 5.70	30.48 ± 4.38	33.70 ± 5.1	NS
TAPSE (mm)	22.37 ± 3.67	22.61 ± 2.95	20.70 ± 2.14	NS

NS: non-significant; LV: left ventricle; LVEF SB: Left ventricular ejection fraction by Simpson's biplane method; LA: left atrium; RA: right atrium; RV: right ventricle; TAPSE: tricuspid annular systolic excursion.

3.2. Patient Outcomes

At 3 months after chemotherapy, a significant decrease in mean GLS was noted (-18.54 ± 1.78 , $p = 0.000$), along with a reduction in the mean delta strain by $9.38 \pm 7.30\%$ compared to the initial value. Eight patients (22%) experienced a significant decrease in strain. Among them, four patients had a significant decrease in left ventricular ejection fraction (LVEF).

At 6 months after chemotherapy, a significant decrease in mean GLS was observed (-14.54 ± 2.91 , $p < 0.001$) (**Table 2**). We found a significant decrease in delta strain in 16 patients (43.2%), with 15 patients (93.7%) being treated with anthracyclines. Only one patient experienced a significant reduction in strain under a carboplatin-taxane protocol, with cumulative doses of 750 and 240 mg/m², respectively.

Figure 1 illustrates an example of a female patient with breast cancer from the study who received a cumulative dose of 608 mg/m² of anthracyclines. Prior to chemotherapy, her GLS was -23.70% (LVEF = 73%), which decreased to -6.7% (LVEF = 29%) at 6 months of follow-up. Patients treated with anthracycline protocols had 16.5 times higher risk (OR = 16.5, CI [1.892 - 148.606]) of having a strain reduction compared to those without anthracyclines.

Regarding left ventricular ejection fraction (LVEF), there was a significant decrease in the mean to 52.00 ± 13.91 ($p < 0.001$). Eight (22%) patients experienced a significant reduction in their LVEF, among whom 5 (13.5%) had left ventricular dysfunction (LVEF < 50%) (**Figure 2**). This dysfunction was associated with congestive signs in 3 of them. In our series, the delta strain value became signifi-

cant starting from an average cumulative dose of 257.33 mg/m² ($p = 0.043$). As the cumulative dose increased, the alteration became more pronounced. **Figure 2** illustrates the different delta strain values based on the cumulative dose.

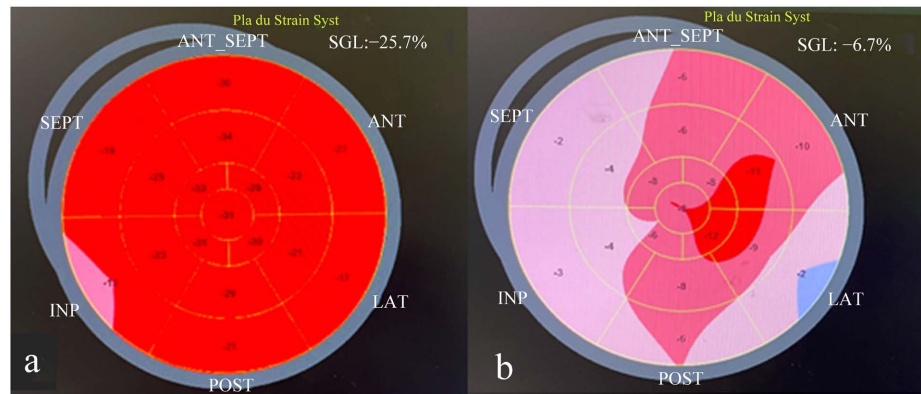


Figure 1. Blue eyes of a patient showing the values of longitudinal global strain (LGS) before (a) and after 6 months (b) of chemotherapy.

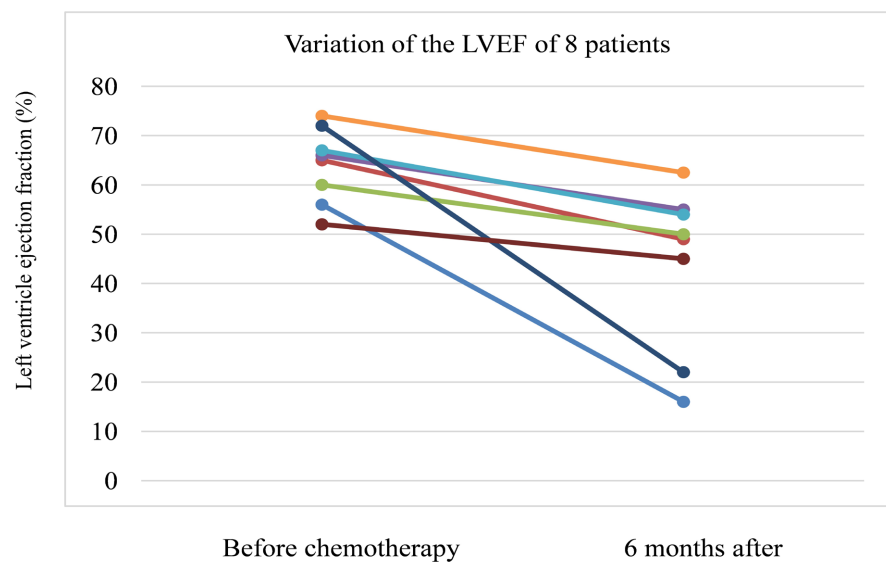


Figure 2. Evolution of left ventricular ejection fraction after chemotherapy in the 8 patients who showed a significant decrease.

Overall, the incidence of myocardial cardiotoxicity secondary to chemotherapy administration was 13.5% ($n = 5$).

4. Discussion

This study has certain limitations, notably the small sample size. The follow-up was significantly impacted by the COVID-19 pandemic, and due to lack of funding, we were unable to measure cardiac biomarkers, including NTproBNP and troponin.

The average age of the patients was 49.7 years, with a female predominance. Odunga Abuodha *et al.* found a similar average age of 47.7 years as well as a fe-

male predominance [10]. In most studies examining chemotherapy-induced cardiotoxicity in Africa, breast cancer cases are predominant [11] [12] [13].

In this relatively young population, the overall cardiovascular risk was generally low. However, 28% had high blood pressure (HBP) and 8% had diabetes. New recommendations in cardio-oncology consider HBP, diabetes, obesity, and both active and former smoking as moderate-risk factors for inducing cardiotoxicity [8].

We observed a non-significant increase in the mean diameter of the left ventricle after chemotherapy. In his study conducted on 2234 patients treated with anthracyclines, Moussavi [14] also reported that an increase in tele-diastolic left ventricular dimension was predictive of major cardiac events. For low doses of anthracyclines, there is histological remodeling involving peri-vascular and/or interstitial fibrosis, vacuolization, and early myocyte degeneration, which may explain the relationship between histology and changes in left ventricular measurements [15].

In our study, 5 patients (13.5%) developed chemotherapy-induced cardiomyopathy. Among them, 3 patients (8.1%) presented with symptomatic heart failure. These findings align with several other studies, although there is variability in the reported incidences, ranging from 2% to 34% depending on the studies [5] [16] [17]. This difference could be explained by varying cumulative doses of antimitotic agents across different studies, variable follow-up periods, and differences in the criteria used to define cardiotoxicity.

Global longitudinal strain

In our study, a significant decrease in delta strain was observed in 16 patients (43.2%). Numerous studies have highlighted the importance of strain in evaluating chemotherapy-induced cardiotoxicity. Florescu *et al.* found that 35% of their patients developed cardiotoxicity, and a reduction in strain of >11% compared to baseline predicted LVEF impairment [18]. Boyd, in a study including patients with subclinical systolic left ventricular dysfunction and preserved systolic function, also demonstrated strain alterations [19].

Among 10 patients who developed cardiomyopathy due to trastuzumab treatment after 6 months, Fallah-Rad *et al.* showed that at 3 months, these patients already had strain alterations [20]. An association between Nt-pro BNP levels > 97 pg/mg and a >15% reduction in strain would detect LVEF impairment in 100% of patients, as seen in Baratta *et al.*'s study [21].

All these studies consistently indicate that strain is an early marker for detecting cardiotoxicity, even before the onset of left ventricular dysfunction [21] [22] [23]. The majority of our patients receiving anthracyclines experienced a significant reduction in strain, and 8 (21.6%) of them also had an LVEF decrease below 50%.

There are significant interindividual variations in cardiac sensitivity to anthracyclines, with the cumulative total dose of doxorubicin responsible for cardiotoxicity ranging from 75 to 500 mg/m² [24] [25] [26].

A landmark study conducted by Bristow in 1950, based on a cohort of 3941 patients, established a cumulative anthracycline dose threshold of 400 to 500 mg/m² to avoid systolic dysfunction. Interestingly, at a cumulative dose of 400 mg/m², only 0.14% showed systolic impairment, but this proportion increased to 7% at 550 mg/m² and 18% beyond 700 mg/m². So the higher the cumulative dose, the greater the risk of heart failure [3] [26].

As studies progressed over the years, this threshold has been revised downward. Pio found 8.8% left ventricular dysfunction (LVSD) for doses between 150 and 300 mg/m² [24]. Mornos and Oikonomou discovered that even with lower average cumulative anthracycline doses than our study (240 mg/m² and 259 mg/m², respectively), patients developed systolic dysfunction [25] [26].

5. Conclusion

Oncology has seen significant progress, particularly due to chemotherapy, which has rapidly evolved in recent years, improving the prognosis and survival of patients with cancer. However, the incidence of cardiac toxicity is not negligible, highlighting the importance of early screening. Strain imaging is an essential tool that should be performed as part of the pre-chemotherapy assessment and re-evaluated during treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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