Section: Cardiology

Original Research Article

A STUDY ON EARLY DETECTION OF CARDIOTOXICITY IN PATIENTS ON ANTHRACYCLINE CHEMOTHERAPY WITH MYOCARDIAL STRAIN IMAGING BY ECHOCARDIOGRAPHY

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Abstract

Background: Cardiotoxicity is a recognised adverse effect of various cytotoxic medications, particularly anthracyclines, that can result in enduring health complications. **Aim:** This study aimed to detect cardiotoxicity in patients receiving anthracycline chemotherapy using myocardial strain imaging with echocardiography. **Material and Methods:** This prospective observational study included 74 adult patients who received anthracycline-based chemotherapy in the Department of Cardiology, Govt Mohan Kumaramangalam Medical College, between May 2021 and April 2022. A patient's history includes age, sex, diagnosis including the stage of the disease, previous medical and concomitant medical history, height, weight, previous treatments, including radiation therapy to the mediastinum, and performance status. Assessments were performed using echocardiography with strain calculated using GE software. **Results:** Out of 74 patients, most were females, 56 (75.7%), and 18 were male (24.3%). Thirty patients (40.5%) were aged 51–60, and 18 were aged 61–70. The percentage values of CA breast, CA stomach, lymphoma, and osteosarcoma patients were 59.5%, 29.7%, 8.1%, and 2.7%, respectively. Forty-two patients (56.8%) and 52 (43.2 %) received Doxorubicin and Epirubicin, respectively. The p-values for the distribution of the study population based on echocardiography EF and longitudinal strain were p= 0.070 and p< 0.0001, respectively. **Conclusion:** This study underscores the use of myocardial strain imaging to detect early cardiotoxicity in anthracycline-treated patients. The longitudinal strain exhibited significant alterations, suggesting its efficacy in precluding left ventricular dysfunction.

INTRODUCTION

Cardiotoxicity can manifest during the administration of various cytotoxic medications, often serving as a critical factor in determining the maximum tolerable dosage for cancer therapy and consequently impacting the tumour response. It encompasses a spectrum of cardiac manifestations, ranging from minor fluctuations in blood pressure and arrhythmias to the development of cardiomyopathy.[1] Literature suggested diverse mechanisms underlying chemotherapy-induced cardiotoxicity, such as cellular injury triggered by generating reactive oxygen species and initiating immune responses involving antigen-presenting cells within the heart.[2]

Anthracyclines, such as doxorubicin and epirubicin, exhibit strong cytotoxic properties; however, their clinical application is frequently constrained by the occurrence of cardiotoxic adverse effects.[3] Cardiotoxicity resulting from anthracyclines can be categorised into three distinct types: acute cardiotoxicity, early-onset chronic progressive cardiotoxicity, and late-onset chronic progressive cardiotoxicity.

1. Acute Cardiotoxicity: It typically occurs shortly following anthracycline chemotherapy. (i.e. immediately following anthracycline infusion in approximately 1% of patients). It often manifests

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as transient changes in cardiac function, such as arrhythmias or changes in blood pressure.[4]

2. Early onset Chronic Progressive Cardiotoxicity: It refers to the development of cardiac dysfunction within the first year of anthracycline therapy. The incidence of the early onset chronic progressive form is approximately 1.6% to 2.1%, and this occurs when the patient is on therapy or within one year after the treatment.
3. Late-onset chronic Progressive Cardiotoxicity: It occurs months to years after the completion of anthracycline treatment. This form of cardiotoxicity is often insidious in onset and may present with symptoms such as heart failure, myocardial damage, or arrhythmias. The incidence is approximately 1.6% to 23% of patients and occurs one year after completion of chemotherapy.[5] Both early- and late-onset cardiotoxicity clinically presents as dilated cardiomyopathy.

There are various risk factors associated with anthracycline-induced cardiotoxicity, such as female gender, pre-existing cardiovascular conditions, pediatric and elderly populations, Intravenous bolus administration, high single doses, and combined use with other cardiotoxic agents such as combined use with other cardiotoxic agents like cyclophosphamide, trastuzumab and paclitaxel.[6]

The cumulative dose of anthracycline plays a crucial role in determining the occurrence of clinical cardiotoxic effects. Research findings indicate that a cumulative dose of approximately 550 mg/m2 of doxorubicin is associated with an incidence of heart failure of approximately 26%. However, it is noteworthy that the incidence of heart failure appears lower when using alternative anthracyclines, such as epirubicin or idarubicin. This suggests that while the cumulative dose remains a significant factor, the specific anthracycline agent utilised can influence the likelihood and severity of cardiotoxicity.[7] Understanding these dosage thresholds and variations among anthracyclines is essential for optimising treatment strategies and minimising the risk of cardiac complications in cancer patients undergoing chemotherapy.

Aim

This study aimed to assess the myocardial strain, which helps in the early detection of cardiotoxicity in patients receiving anthracycline chemotherapeutic regimens.

MATERIALS AND METHODS

This prospective observational study included 74 adult patients who received anthracycline-based chemotherapy at the Department of Cardiology, Govt Mohan Kumaramangalam Medical College, between May 2021 and April 2022.

All patients were informed of the study design at enrolment, and detailed consent regarding their willingness to participate was obtained. Ethical committee approval was obtained before the study commenced.

Inclusion Criteria

Both male and female patients aged > 18 years are appropriate for anthracycline-based chemotherapy, regardless of individual diagnosis or disease stage. The study included patients who were on additional chemotherapeutic agents and those who had their echocardiograms performed.

Exclusion Criteria

Patients with a clinical history of heart failure or ejection fraction (EF) on initial examination <55%, whose initial echocardiograms were not interpretable, those with wall motion abnormalities on initial echocardiograms, and patients with strain on initial echocardiograms that could not be calculated were excluded from the study.

The treating medical oncologists identified potential patients. Written informed consent was obtained from all participants before initiating any study-specific procedure. Procedures performed as part of the subject's routine clinical management and obtained before signing the informed consent may be utilised for screening or baseline purposes, provided the procedure was performed within the timeframe specified in the protocol. A patient's history includes age, sex, diagnosis including the stage of the disease, previous medical and concomitant medical history, height, weight, previous treatments, including radiation therapy to the mediastinum, and performance status. Assessments were performed using echocardiography with strain calculated using GE software.

Statistical Analysis

Data entry was done in Microsoft Excel. Statistical analyses were performed using the SPSS version 23. Statistical significance was set at p-value < 0.05; all statistical tests were two-sided. Categorical variables are presented as numbers (percentages) and were compared using the chi-square test. Continuous variables are presented as the mean± standard deviation and were compared between groups by t-test or analysis of variance as appropriate.

RESULTS

Of the 74 patients in the present study, the majority of the study population was between the age group of 51 and 60 years, with 30 patients (40.5%). Eighteen patients (24.3%) were between 61 and 70 years old. Ten patients (13.5%) were aged 41–50 years and > 71. The remaining six patients (8.1%) were < 40. [Table 1]

The sex distribution in the study population was as follows: 56 patients (75.7%) were females, and 18 patients (24.3%) were males.

In the present study, based on carcinoma, 44 patients (59.5%) had CA breast cancer. Twenty-two

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patients (29.7%) had CA stomach, six patients (8.1%) had lymphoma, and two patients (2.7%) had osteosarcoma.

Based on the type of anthracycline used in the present study, 42 patients (56.8%) received doxorubicin, and 32 (43.2%) received epirubicin.

In our present study, the mean value of 1st Echocardiogram EF was found to be 63.82± 3.44, the mean second Echocardiogram EF was found to be 62.46± 3.51, and the mean third Echocardiogram EF was found to be 62.88± 3.82. There was a statistically significant difference between the three Echocardiogram EF values (p=0.070). [Table 2]

In the present study, the mean longitudinal strain for the first visit was -19.57±1.12 and after 3 to 6 months, was found to be -12.09±6.59. There was a statistically significant difference between the two longitudinal strains (p<0.0001). [Table 4]

Table 1: Demographic data of the study population

		Number of Patients	Percentage
Age group	<40	6	8.1%
	41-50	10	13.5%
	51-60	30	40.5%
	61-70	18	24.3%
	>71	10	13.5%
Gender	Female	56	75.7%
	Male	18	24.3%
Type of carcinoma	CA breast	44	59.5%
	CA stomach	22	29.7%
	Lymphoma	6	8.1%
	Osteosarcoma	2	2.7%
Type of Anthracycline used	Doxorubicin	42	56.8%
	Epirubicin	32	43.2%

Table 2: Distribution of the study population based on ECHO EF

ECHO OF	Mean	Std. Deviation	P value
1st	63.82	3.44	0.070
2nd	62.46	3.51	
3rd	62.88	3.82	

Table 3: Distribution of the study population based on longitudinal strains

Longitudinal Strain	Mean	Std. Deviation	P value
1st visit	-19.57	1.12	<0.0001
3 to 6months	-12.09	6.59	

DISCUSSION

Cardiotoxicity refers to the inability of the heart to pump blood throughout the body efficiently. Anthracyclines, recognised as highly effective chemotherapeutic agents for treating osteosarcoma in children, adolescents, and adults, carry significant risks. Despite their efficacy, cardiotoxicity stands out as a significant long-term consequence, impacting the survival and quality of life of cancer survivors, including those with osteosarcoma.8

Cardiac imaging utilising echocardiography to measure global longitudinal strain and cardiac troponin levels can identify early myocardial injury before left ventricular dysfunction manifests.[9]

In our study, the majority of the study population were females (75.7%), the rest were male (24.3%), and 30 patients (40.5%) were between the age group of 51 and 60 years. This result is similar to the report by Rasheed et al. Their study reported that 12 individuals (24%) identified as male and 38 individuals (76%) identified as female and also mentioned that ages ranged from 20 to 67 years.[10]

Based on the carcinoma in our study, the majority of patients (59.5%) had carcinoma breast cancer after anthracycline-based chemotherapy. This result is similar to the report done by Jacobse et al.; They reported that in long-term breast cancer survivors treated at ages 40-50 years, there is an association between breast cancer and anthracycline-based chemotherapy.[11]

Based on the types of anthracyclines used in our study, most patients received doxorubicin (56.8%), and the remaining patients received epirubicin (43.2%). This result is similar to that reported by Ardelean et al., who concluded that the levels of cTnI in the doxorubicin group were notably higher (3.2 ng/mL, p = 0.002) than those in the epirubicin group (2.7 ng/mL). However, the two groups had no significant differences (p = 0.096 and p = 0.172, respectively).[12]

In our study, the mean values of 1st, 2nd, and 3rd echocardiography EF were 63.82± 3.44, 62.46± 3.51, and 62.88± 3.82, respectively, and the p-value was 0.070, indicating they were statistically significant. This result is similar to that reported by Cardinale et al., who reported that LVEF assessment is a key component in evaluating cardiotoxicity induced by anthracycline-based chemotherapy, and 131 (5%) patients skipped the 1 LVEF assessment; no patient skipped >1 LVEF assessment. Although the study does not provide detailed information on the correlation between echocardiographic findings and cardiac death, the utilisation of

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echocardiography in assessing LVEF suggests its relevance in monitoring cardiac function and potentially identifying cardiotoxicity, which may contribute to understanding the relationship between echocardiography and cardiotoxicity.[13]

In our study, the mean longitudinal strains for the first visit and after 3 to 6 months were -19.57±1.2 and -12.09±6.57, respectively, and there is a significant difference between these two longitudinal strains ($p< 0.0001$). This is similar to the report done by Paaladinesh et al.; They mentioned that the alterations of myocardial deformation precede significant changes in left ventricular ejection fraction (LVEF) during cancer chemotherapy and also specifically mentioned that by using tissue Doppler-based strain imaging, peak systolic longitudinal strain rate has most consistently detected early myocardial changes during therapy.[14]

Limitations: The study's limitations include a small sample size (74 patients) and single-center design, potentially limiting generalizability. Exclusion criteria, such as pre-existing heart conditions, might bias findings. The short 3 to 6-month follow-up duration may overlook long-term cardiotoxic effects. Additionally, the study primarily focuses on myocardial strain imaging, neglecting other potential markers and confounding factors like concomitant medications. While informative, these findings may not fully represent diverse patient populations or chemotherapy regimens. Addressing these limitations in future research could enhance understanding and improve early detection strategies for anthracycline-induced cardiotoxicity.

CONCLUSION

This study highlights the significance of early cardiotoxicity detection in anthracycline-treated patients using myocardial strain imaging with echocardiography. The longitudinal strain showed significant alterations, suggesting its efficacy in identifying myocardial injury before left ventricular dysfunction onset. While echocardiography-derived ejection fraction remained relatively stable, the predominance of female patients and the association between anthracycline type and cardiac troponin levels emphasise tailored monitoring approaches. Integrating myocardial strain imaging into routine assessments enables prompt cardiotoxicity management, potentially reducing long-term cardiac complications.

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