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ORIGINAL ARTICLE

Effects of four cycles of anthracycline based chemotherapy on cardiac ejection fraction in breast cancer patients.

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ABSTRACT…. Objective: To assess the impact of four cycles of anthracycline chemotherapy on left ventricle ejection fraction in breast cancer patients. **Study Design:** Analytical Observational, Cohort study. **Setting:** Department of Oncology, Jinnah Postgraduate Medical Center, Karachi, Pakistan. **Period:** July 2023 to August 2024. **Methods:** A total of 56 patients with histologically confirmed BC cases of any age group were analyzed. A sample size of 56 was determined using OPENEPI, with a 95% confidence interval and 80% power. Data were collected through a predefined proforma, covering demographic information, breast cancer details, echocardiography findings (specifically left ventricular ejection fraction [LVEF]), and doxorubicin side effects. Treatment involved use of doxorubicin with LVEF measured at baseline and after four cycles of drug. **Results:** In a total of 56 patients, the mean age was 47.07±11.69 years. The baseline LVEF was 62.86±2.77%, which decreased to 60.50±5.32% after four treatment cycles. Comorbid conditions like hypertension, and a combination of hypertension and diabetes were noted in 32.1%, and 10.7% patients, respectively. All four drug cycles were administered to 92.9% of patients, with 14.3% requiring treatment discontinuation due to adverse events. **Conclusion:** Patients with elevated baseline LVEF levels tend to sustain higher LVEF levels after undergoing chemotherapy. These results emphasize the significance of vigilant LVEF monitoring in breast cancer patients treated with anthracycline chemotherapy, to enhance the management of potential cardiotoxicity.

Key words: Anthracycline, Breast Cancer, Cardiotoxicity, Chemotherapy, Doxorubicin.

INTRODUCTION

Breast cancer (BC) is the most common type of cancer among women, comprising over 30% of all cancers. Almost 2.1 million cases of BC are diagnosed annually, while mortality is reported among nearly half a million cases worldwide.[1] Among patients aged 65 and above, cardiovascular complications are the primary cause contributing to mortality in BC cases, leading to the 24% mortality in this age group, and accounting for 12.5% across all age groups.[2,3]

Cardiotoxic drugs such as trastuzumab and anthracyclines increase the risk in chemotherapy treatments.[3] Radiation may also impact the heart directly, especially in the case of breast cancer from the left side. The existence of other cardiovascular risk factors like obesity and a sedentary lifestyle may also add to this risk among breast cancer patients.[1-4] Anthracycline-containing regimens continue to be the mainstay of chemotherapy for breast cancer despite their well-documented cardiac toxicity profile due to their substantial impact on reducing breast cancer recurrence.[5]

In a clinical study, a group of seventy-eight breast cancer patients who had not previously received anthracycline therapy were examined before and immediately after undergoing 4-6 cycles of anthracycline chemotherapy. A study indicated that the global systolic strain was significantly reduced both immediately after treatment, and six months later (from -19.0 ± 2.3% to -17.5±2.3% [p<0.001] and -18.2±2.2% (p=0.01) respectively) among BC patients who underwent 4-6 cycles of anthracycline chemotherapy.[6] However, there was no clinically significant change in the average

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left ventricular ejection fraction (LVEF) at any of the four-time points measured (58±2%, 56±3%, 55±2%, and 57±2%, respectively).[6] Safaei et al[7] examining 49 BC patients including 21 healthy females with breast cancer revealed that following chemotherapy, 19.0% patients (3 symptomatic and 1 asymptomatic) displayed signs of doxorubicin cardiotoxicity in post-chemotherapy cardiovascular magnetic resonance (CMR) scans. Compared to baseline measurements, significant differences were observed in biventricular ejection fraction, left ventricular end-systolic volume index, and all 3D global strain values after chemotherapy ($p<0.05$). More than half of the participants also experienced a notable change in all right ventricular global strain values. One patient (4.76%) exhibited diffuse myocardial edema in post-chemotherapy CMR scans, 14.3% showed signs of myocardial fibrosis. The study subjects were clinically monitored for a period ranging from four to ten months. There were 38.1% patients who reported symptoms such as dyspnea on exertion and fatigue during follow-up appointments. However, none of the CMR markers were found to be associated with the development of these symptoms.[7] The main objective of the research was to evaluate the influence of four cycles of anthracycline chemotherapy on LVEF in individuals diagnosed with BC.

METHODS

This analytical observational cohort study was conducted at the department of Oncology, Jinnah Postgraduate Medical Center, Karachi, Pakistan from July 2023 to August 2024. The inclusion criteria were histologically confirmed BC cases of any age group. However, patients with non-confirmed breast cancer, those who declined participation, or those diagnosed with benign lesions or metastatic cancer were excluded. Patients who had previously undergone anthracycline-based chemotherapy were excluded from the study. To determine the sample size, the online tool OPENEPI was utilized. Using the mean LVEF values before chemotherapy (60.15±7.90) and after (54.60±6.85)[7], it was determined that a sample size of 56 was appropriate, assuming a confidence interval of 95% and a power of 80%. The sampling strategy employed was a non-probability consecutive sampling technique. The research commenced after securing clearance from the institutional review board (letter number: F.2.81/2022-GENL/343/JPMC, dated: 30-12-2022). Informed and written consents obtained from all study participants.

The collected data encompassed four main sections: demographic information (age, parity, gravidity, menopausal status, marital status, etc.), clinical parameters pertinent to breast cancer (tumor type, stage, and grade), echocardiography findings focusing on LVEF, and a record of all side effects observed from the doxorubicin chemotherapy. All patients underwent a treatment regimen that involved the administration of doxorubicin (60 mg/m2; cumulative dose of 350–450 mg/m^2) for 4 consecutive cycles every 2 weeks. Their health was closely monitored for any cardiovascular symptoms and potential side effects linked to the treatment. Echocardiographic assessment was performed using a commercial ultrasound instrument (Philips EPIQ 7), with the images being digitally preserved. LVEF was calculated employing the Simpson rule. This echocardiographic evaluation was conducted both before and after chemotherapy by an expert cardiologist, who was blind to the patients' medical backgrounds. The definition of cardiotoxicity based on LVEF was characterized as a decline exceeding 10% to a terminal value of less than 55% in asymptomatic patients or a decrease of at least 5% to a terminal value of less than 55% in symptomatic individuals. All the data were collected on specifically designed proforma. Data analysis was performed using IBM-SPSS Statistics, version 26.0. Quantitaitve data were expressed as mean and standard deviation, whereas, frequency and percentages were reported for qualitative data. LVEF was compared using independent of paired sample t-test. Pearson's correlation was applied for correlation analysis. $P<0.05$ was considered significant.

RESULTS

In a total of 56 patients, the mean age was 47.07±11.69 years. The variability in duration of administering four cycles of drug spans 13.38±8.39 weeks. Hypertension was the most

common comorbidity, reported in 18 (32.1%) patients. Residential status was urban among 36 (64.3%) patients. There were 50 (89.3%) patients who were asymptomatic at the time of enrollment. The mean baseline LVEF was 62.86±2.77%. Clinical characteristics revealed that the cancer mostly developed on the left side in 32 (57.1%), right side in 19 (33.9%) and bilateral in 5 (8.9%) patients. All four cycles of drug were administered in 52 (92.9%) patients. Table-I is showing demographical and clinical characteristics of patients.

Characteristics		Frequency (%) / Mean±SD
Gender	Male	2 (3.6%)
	Female	54 (96.4%)
Age in years (mean±SD)		47.07±11.69
Comorbid	Diabetes mellitus	4 (7.1%)
	Hypertension	18 (32.1%)
	Hypertension + Diabetes mellitus	6 (10.7%)
Residential status	Urban	36 (64.3%)
	Rural	20 (35.7%)
Ethnicity	Afghani	2 (3.6%)
	Balochi	9 (16.1%)
	Hindi	3 (5.4%)
	Punjabi	7 (12.5%)
	Pushtoon	6 (10.7%)
	Sindhi	11 (19.6%)
	Urdu	18 (32.1%)
Family History of Breast cancer		15 (26.8%)
Breast cancer side	Right	19 (33.9%)
	Left	32 (57.1%)
	Bilateral	5 (8.9%)
Symptoms	Asymptomatic	50 (89.3%)
	Asymptomatic , Dyspnea	1 (1.8%)
	Dyspnea	1 (1.8%)
	Dyspnea, Fatigue	1 (1.8%)
	Dyspnea, Chest pain, peripheral Edema, Fatigue	2 (3.6%)
	Dyspnea, peripheral Edema, Fatigue	1 (1.8%)
Number of Drug Cycle	1	1 (1.8%)
	2	1 (1.8%)
	3	2 (3.6%)
	4	52 (92.9%)
Stages of Cancer	2	18 (32.1%)
	3	27 (48.2%)
	4	11 (19.6%)
Grades of Cancer	1	2 (3.6%)
	2	23 (41.1%)
	3	31 (55.4%)
Adverse Event		52 (92.9%)
Adverse events requiring discontinuation of therapy		8 (14.3%)

Table-I. Demographical and clinical characteristics of patients (N=56)

Adverse Event	Frequency n (%)
Cardiovascular	6(10.7%)
Gastrointestinal	5(8.9%)
Renal Insufficiency	2(3.6%)
Hepatotoxicity	2(3.6%)
Infusion-related reaction	3(5.4%)
Allergic Reaction	2(3.6%)
Weakness	53(94.6%)
Hair Loss	53(94.6%)
Mouth Sores	38(67.9%)
Difficulty in Sleeping	36(64.3%)
Shortness of Breath	11(19.6%)
Flu like symptoms	4(7.1%)
Fever	6(10.7%)
Fatigue	44(78.6%)
Nausea	49(87.5%)
Vomiting	51(91.1%)
Poor Appetite	30(53.6%)
Skin Rash	1(1.8%)
Low Blood Counts	8(14.3%)

Table-II. Frequency of adverse events

Post-treatment (after 4-cycles), the mean LVEF was 60.50±5.32%. Table-III is showing comparison of outcomes at 4th cycle in patients with mean LVEF (%). At the "Baseline LVEF" showing no statistically significant result (p= 0.584), and the "LVEF after 4-cycles" indicating statistically significant results (p-value 0.001) between the two groups. This suggests that the "Stable Disease" group may have adverse effects on the cardiac function following 4-cycles of drug during chemotherapy.

Variables		Outcome		P-Value
		Mean	SD	
Baseline LVEF (%)	Drug Discontinued due to unacceptable toxicity (n=5)	62.20	4.20	0.584
	Stable Disease (n=51)	62.92	2.65	
LVEF after Four Cycles (%)	Drug Discontinued due to unacceptable toxicity (n=5)	53.40	10.73	0.001
	Stable Disease (n=51)	61.20	4.05	

Table-III. Comparison of outcome at the fourth cycle in patients with mean LVEF

Independent sample t-test applied

Correlation analysis between the mean LVEF

at baseline (Mean±SD 62.86±2.77) and after four cycles (Mean±SD 60.50±5.32) indicated a statistically significant correlation (p-value 0.001). The correlation coefficient (r) between baseline LVEF and LVEF after the four cycles is 0.415 indicating a moderately positive correlation between the two variables suggesting that those who had a higher LVEF after 4-cycles were patients with a higher baseline LVEF. (Table-IV)

Correlation	Mean	SD	(r)	P-Value
Baseline LVEF (%)	62.86	2.77	0.415	0.001
LVEF after four cycles (%)	60.50	5.32		

Table-IV. Correlation between mean LVEF at baseline and after four cycles of treatment

Pearson's correlation applied

DISCUSSION

The patients who discontinued chemotherapy due to unacceptable toxicity (n=5) experienced a significant decrease in LVEF (53.40±10.73), as compared to those with stable disease (n=51) who had a higher LVEF (61.20±4.05). Consequently the study showed that there was a significant positive correlation between the baseline LVEF and LVEF after four cycles of anthracycline chemotherapy administration (r=0.415) and a highly significant p-value of 0.001. This study suggested that patients with higher baseline LVEF tended to maintain higher LVEF levels following chemotherapy. Thus the findings underscore the importance of closely monitoring LVEF in breast cancer patients undergoing anthracycline chemotherapy to better manage potential cardiotoxicity and ensure optimal patient outcomes. In line with the findings of previous research, Anthracyclines are known for their robust anti-cancer attributes, supported by substantial empirical evidence. Nevertheless, their effectiveness is compromised by the dose-related risk of cardiotoxicity.[8] Our study also corroborates the link between anthracycline-based treatments and the risk of cardiotoxicity, as observed in multiple randomized controlled trials conducted across various cancer types. Specifically, our research aligns with the observations made by Zheng et al.[9] These consistent findings collectively emphasize the association between anthracycline use and cardiotoxicity in cancer treatment.

Recent investigations have delved into alternative regimens for early-stage breast cancer, and our data also resonates with some of these inquiries. Some studies have suggested that non-anthracycline-containing regimens may achieve superior disease-free survival, potentially providing alternative treatment options for specific patient groups.[10] Researchers have shown that regimens such as docetaxel, carboplatin, and trastuzumab (TCH) may offer comparable efficacy while reducing the risk of severe congestive heart failure, further expanding treatment choices for breast cancer patients.[11-13]

In addition, researchers are actively exploring the molecular predictors of anthracycline response, such as topoisomerase II alpha gene aberrations. These markers have the potential to aid in patient selection, minimizing the risk of anthracycline-associated cardiotoxicity among specific subgroups. However, it's crucial to emphasize that further prospective studies are essential to validate these findings in a clinical context and translate them into improved patient care. Several factors might explain the observed findings in this study as documented in research conducted to identify the effects of Dexrazoxane in reduction of the occurrence and severity of anthracycline-induced cardiotoxicity.[14] Data has shown that doxorubicin and epirubicin, are well-documented to have adverse effects on the heart, leading to decreased LVEF and other cardiovascular issues.[15] The observed reductions in LVEF (mean 62.86% at baseline to mean 60.50% after four cycles) can be directly attributed to the cardiotoxic nature of these drugs. Consequently, the study has logically proved that anthracycline-induced cardiotoxicity is often dose-dependent. The longer duration of drug cycles (mean 13.38 weeks) and the cumulative dose received by patients over the four cycles may have contributed to the observed decline in LVEF. This is supported by the significant p-values ($p<0.001$) in the independent t-tests comparing LVEF before and after the four cycles. Therefore the study implies that a more personalized approach to breast cancer treatment may be beneficial, taking into account

patient-specific factors and cardio-protective strategies. Identifying molecular predictors of anthracycline response, could further enhance the individualization of therapy and reduce the risk of cardiotoxicity. Firstly, the observed decrease in LVEF following anthracycline chemotherapy highlights the importance of rigorous cardiac monitoring, regular assessment, and potential modifications of chemotherapy doses during cancer treatment. The mean LVEF at baseline of 62.86% with a standard deviation of ±2.77, while the mean LVEF after four cycles decreased to 60.50% with a standard deviation of ±5.32 underscores the need for close collaboration between oncologists and cardiologists to ensure patient safety and minimize the risk of cardiotoxicity and highlights the importance of individualized treatment especially in patients with lower baseline LVEF. The study's results suggest that tailoring treatment based on individual patient characteristics, such as age, gender, and comorbidities, may be essential to mitigate the adverse outcomes. This personalized approach could help identify patients at higher risk of experiencing a decrease in LVEF and enable healthcare providers to make informed decisions regarding treatment options.[16] In a broader context, the findings emphasize the need for ongoing research into novel methods for monitoring, preventing, and treating anthracycline-induced cardiotoxicity. The standard deviations in LVEF changes indicate varying degrees of response to therapy. Real-world clinical practice can benefit from using baseline LVEF as a screening tool to identify patients at higher risk of significant LVEF reductions during treatment. Therefore this study is particularly relevant as the use of anthracyclines in breast cancer treatment remains a cornerstone, and it is crucial to continue improving their safety profile by adapting treatment strategies and enhance patient care.

Future research can build upon this study by investigating molecular predictors of treatment response, as this research has far-reaching implications, from optimizing patient care and treatment safety to guiding future research endeavors focused on improving the efficacy and safety of breast cancer therapies.[17] This study provides valuable insights into the impact of anthracycline chemotherapy on breast cancer patients. The baseline characteristics including age, duration of drug cycle, and mean LVEF, of the 56 participants were meticulously examined, and notable findings emerged. The data were further analyzed to determine associations and outcomes. The study revealed that while anthracycline chemotherapy is a crucial component of breast cancer treatment, it carries a small increased risk of cardiotoxicity as evident with previous researches.[18] Importantly, this side effect has not deterred its use in the adjuvant setting, primarily because the clinical benefits significantly outweigh the risk. Efforts to mitigate cardiotoxicity through methods such as cardiac function monitoring, dose limitation, cardioprotectants like dexrazoxane, and innovative formulations have shown promise, offering reassurance to both patients and healthcare providers.[19]

Despite the substantial progress made in this field, anthracycline-induced cardiotoxicity remains a persistent concern for cancer survivors. This underscores the importance of continued research to identify patients at higher risk of cardiotoxicity and to develop innovative methods for monitoring, prevention, and treatment of this adverse effect.[20] As we move forward, the goal is to enhance the safety and effectiveness of breast cancer treatment, ultimately improving the quality of life and outcomes for patients.

Several limitations are worth noting in this study. The study featured a relatively low sample size, comprising 56 participants, which may limit the generalizability of the findings to a broader population. The utilization of a non-probability consecutive sampling technique means that not every individual had an equal opportunity to be included in the study, potentially introducing sampling bias. The single-center nature of the study conducted at a specific medical center may constrain the broader applicability of the findings to different settings or populations. These limitations highlight the importance of cautious interpretation and potential directions for future research.

CONCLUSION

Patients with elevated baseline LVEF levels tend to sustain higher LVEF levels after undergoing chemotherapy. These results emphasize the significance of vigilant LVEF monitoring in breast cancer patients treated with anthracycline chemotherapy, to enhance the management of potential cardiotoxicity and promote results.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Faiza Mahar	Data collection, drafting, responsible for data's integrity, approved publication.	
2	Ghulam Haider	Study protocol, Proof reading, critical revisions, approved publication.	
3	Abdul Rehman	Data synthesis, Literature review, Critical review, Approved publication.	
4	Haris Ahmed Shah	Data synthesis, Literature review, Critical review, approve publication.	
5	Sana Seher	Data synthesis, Literature review, Critical review, approved publication.