Cardiac Health of Breast Cancer patients taken Anthracycline – Cyclophosphamide in Combination

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Abstract-

Background: Anthracycline-induced cardiotoxicity is a lethal yet prevalent complication of anthracycline based chemotherapy. Anthracycline treatment in certain circumstances, contribute to long-term cardiotoxicity. However very few studies authenticate the short-term use of this regimen is associated with cardiotoxic effects.

Aims: To determine occurrence of cardiotoxicity among breast cancer patients used anthracycline cyclophosphamide combination for short period of time (four cycles) as well as to evaluate the association of echocardiographic parameters of patients maintained on short course of anthracycline cyclophosphamide regimen with different factors including age, body mass index, cancer stage and dosing regimen.

Type of study: A cross- sectional prospective observational research.

Clinical setting: Clinical setting

Methodology: Formal consent was taken from (N=102) female cancer patients of age group 25 – 75 years of age visiting cancer hospital for the treatment of newly diagnosed breast cancer. All the data was recorded and analyzed using SPSS 20.0. All the subjective data recorded as frequency and percentages whereas objective data represented as mean $\pm$ S. E. M. All of the association was also analyzed using Pearson Chi-Square test, P value less than or equal to 0.05 was taken as significant. All cardiac parameters measured through echocardiogram were recorded before and after chemotherapy among patients receiving different doses. The change in echocardiographic parameters were recorded as mean ±S.E.M. The comparison of age, BMI, cancer stage and dose regimen with respect to change in cardiac parameters was analyzed by using One way ANOVA, P value ≤ 0.05 was taken as significant.

Results: Most of the overweight and obese patients received moderate to high dose. All the results of echocardiographic parameters including ejection fraction, early and late ventricular filling velocity, left ventricular end systolic diameter, left ventricular end-diastolic diameter, estimated pulmonary arterial pressure, left atrium thickness and fractional shortening before and after chemotherapy were found to lie in the normal ranges as defined in standard literature. Results strongly suggest that anthracycline cyclophosphamide combination therapy given for four cycles posed no cardiotoxic effects on tested breast cancer patients.

Conclusion: We have concluded that short-term anthracycline cyclophosphamide chemotherapy in the duration of three months is safe and the reason for this safety that found to be cardiotoxic in previous studies might be due to safe prescribing practices after taking medical, social and cardiovascular disease history of patients.

Key Words – *Anthracycline, Breast Cancer, Cardiac Parameters, Cyclophosphamide, Cardiotoxicity*

I. INTRODUCTION

Globally, cancer incidence and mortality are increasing and it is important reason for death. The World Health Organization (WHO) estimates that more than 18 million new patients of cancer are identified each year (1). With a population of almost 220 million people, Pakistan is likely to see 170,000 to 200,000 new instances of cancer are diagnosed annually (2). Among the most prevalent malignancies that endanger the health of women is breast cancer. In the world, over 1.5 million women receive a breast cancer diagnosis each year, and 500,000 people pass away as a result. Surgery, cytotoxic chemotherapy, radiation therapy and molecularly targeted endocrine therapy are frequent treatment choices for different types of breast cancer (3).

The treatment aims for patients who have breast cancer in stages I through III is to cure the disease. The treatment includes surgery to remove the breast tumor, medications and perhaps radiation therapy for the breast. The aim of treatment for women who have stage IV breast cancer that has spread to a far-off area of the body is to keep the cancer under control for as long as possible. The mainstay of stage IV breast cancer treatment is medication (4). Doxorubicin plus cyclophosphamide is one of the most widely used (neo) adjuvant

chemotherapy regimens for patients with breast cancer, also known as AC chemotherapy (5). Whether it's doxorubicin or cyclophosphamide, these drugs have the ability to produce too many reactive oxygen species (ROS), which can eventually wear out the antioxidant defense system and result in cardiomyocyte mortality. This occurrence is thought to be the main mechanism for cardiotoxicity caused by doxorubicin and cyclophosphamide (6). The primary cause of treatment-related morbidity and mortality among cancer survivors is cardiovascular adverse effects (7).

Anthracyclines treat various conditions of cancer of breast, stomach, uterus, ovaries, bladder and lung (8). Various possible short and long-term adverse effects associated with anthracycline include bone marrow suppression, vomiting, myocardial infarction , developmental anomaly of the spinal cord, and high numbers of abnormal blood cells (9). Anthracyclines can cause cardiotoxicity, lower left ventricular ejection fraction, and eventually lead to heart failure (10). The irreversible development of nonischemic dilated cardiomyopathy is a side effect of anthracyclines (doxorubicin and daunorubicin), and this effect increases with use time and dose (On *total amount of a drug* 450 mg/m2, a 5-8% incidence is found) (11). Doxorubicin (DOX), a specific anthracycline, preferentially concentrate in mitochondria of cardiomyocytes, possessing a major effect on both the shape and activity of these organelles (12).

Once echocardiographic or clinical evidence of worldwide cardiac dysfunction becomes apparent, a finding of heart damage is generally obtained very delayed during the illness's natural course. Fractional shortening (FS) and ejection fraction are the most common methods of left ventricular (LV) performance used in surveillance (13).

The primary indicator of systolic function of left ventricle is the left ventricular ejection fraction (LVEF). LVEF is defined as portion of chamber volume expelled in systole in relative to the volume of the blood in the ventricle at the end of diastole (14) .

An investigation of the cardiotoxic effects of current anthracycline dosage on left ventricular ejection fraction was done by Prajith Jeyaprakash et al. Pre and post anthracycline-based therapy, the LVEF was assessed using magnetic resonance imaging or echocardiography, with a 6-month follow-up LVEF evaluation. 62.6 percent was the weighted mean baseline LVEF for all trials. Whether the doxorubicin equivalent anthracycline dose was administered continuously (P=0.29) or in accordance with known cardiotoxicity cutoffs (250 mg/m2, P=0.21; 360 mg/m2, P=0.40; and 400 mg/m2, P=0.66), there was no significant difference in the LVEF (15).

Fengfeng Cai et.al reviewed in this study that anthracyclines are among the most important drugs for the breast cancer management. It is important to consider the risk elements for cardiotoxicity while using these medications. Measurements of cardiac function should be done with precision and the total amount of dosage should be kept to a minimum. The prevention of chronic cardiotoxicity is challenging, however extended infusion regimes for the delivery of anthracyclines have a lower risk and novel doxorubicin liposomal formulations deal low cardiac toxicity than conventional doxorubicin (16).

II. METHODOLGY

A cross- sectional prospective observational research comprising patients (n=102) visiting cancer Centre in Karachi treating with anthracycline regimens. The data was collected from medical records and the duration of data collection was based on the completion of four cycles of anthracycline taken by patients. Formal consent was taken from (N=102) female cancer patients of age group 25 – 75 years of age visiting cancer hospital for the treatment of newly diagnosed breast cancer. All the data was recorded and analyzed using SPSS 20.0. All the subjective data recorded as frequency and percentages whereas objective data represented as mean $\pm$ S. E. M. All of the association was also analyzed using Pearson Chi-Square test, P value less than or equal to 0.05 was taken as significant. All cardiac parameters measured through echocardiogram were recorded before and after chemotherapy among patients receiving different doses. The change in echocardiographic parameters were recorded as mean ±S.E.M. The comparison of age, BMI, cancer stage and dose regimen with respect to change in cardiac parameters was analyzed by using One way ANOVA, P value $\leq$ 0.05 was taken as significant.

Cancer patients were selected by convenient sampling method using inclusion and exclusion criteria as mentioned below.

Inclusion Criteria

- Diagnosed breast cancer patients in oncology unit.
- Patients prescribed combination of anthracycline and cyclophosphamide chemotherapy (AC).
- Breast cancer patients agreed to take part in research.

Exclusion Criteria

- Patients maintained on non-anthracycline based chemotherapy
- Children less than 16 years.
- Breast cancer patients who were not taking anthracycline for the first time.
- Patients who were on radiation before anthracycline therapy
- Patients expired during study.

III. RESULTS

1. Demographic data and BMI of tested breast cancer patients

Table 1 showed that among 102 tested patients, highest number of patients were found in age group 36-45 years 36 (35.3 %) followed by 46-55 year 31 (30.4%), 25-35 years 20 (19.6 %), 56-65 years 13 (12.7%) and 66-75 years 2 (2.0%) respectively. Table 1 showed marital status of tested patients, majority of patients were married 98 (96.1%) while unmarried were 4 (3.9%). Table 1 showed occupational status, that majority of patients were house wives 98 (96.1%) and employed were 4 (3.9%). Table 1 showed educational status, that majority of patients were illiterate 35 (34.3%), followed by primary 16 (15.7 %), intermediate 16 (15.7 %), matric 11 (10.8%), graduate 10 (9.8%), secondary 9 (8.8 %) and postgraduate 5 (4.9%) respectively. Table 1 showed the BMI category of tested patients, it was found that highest number of patients was in obese category 40 (39.2%) followed by overweight 38 (37.3%), normal weight 22 (21.6%) and underweight 2 (2.0%) respectively.

Table 1 : Frequency of demographic data and BMI of tested patients

Variables	Category	Frequency (%)
Age (Years)	25-35	20 (19.6%)
	36-45	36 (35.3%)
	46-55	31 (30.4%)
	56-65	13 (12.7%)
	66-75	2 (2.0%)
	Total	102 (100.0%)
Marital status	Married	98 (96.1%)
	Unmarried	4 (3.9%)
	Total	102 (100%)
Occupational status	Employed	4 (3.9%)
	House Wife	98 (96.1%)
	Total	102 (100%)
Educational status	Illiterate	35 (34.3%)
	Primary	16 (15.7%)
	Secondary	9 (8.8%)
	Matric	11 (10.8%)
	Intermediate	16 (15.7%)
	Graduate	10 (9.8%)
	Postgraduate	5 (4.9%)
	Total	102 (100%)
BMI (kg/m^2)	Underweight	2 (2.0%)
	Normal weight	22 (21.6%)
	Overweight	38 (37.3%)
	Obese	40 (39.2%)
	Total	102 (100.0%)

Values are expressed in frequency & percentage

BMI=Body Mass Index

2. Cumulative dose categories of anthracycline and cyclophosphamide in tested patients

Table 2 showed distribution of cumulative dose of anthracycline and cyclophosphamide among 102 treated breast cancer patients. Doses are divided into three categories that is low dose, moderate dose and high dose. It was found that highest number of patients received moderate dose 73 (71.6 %) followed by low dose 16 (15.7%) and high dose 13 (12.7 %) respectively.

Table 2 : Cumulative dose of anthracycline and cyclophosphamide

Chemotherapy treatment	Dose category	Frequency (%)
Anthracycline and cyclophosphamide	Low dose	16 (15.7%)
	Moderate dose	73 (71.6%)
	High dose	13 (12.7%)

3. Patient medical and social history of tested breast cancer patients

Table 3 showed that among 102 tested breast cancer patients, cardiac symptoms were not found in majority of patients 100 (98.0%) while 2 (2.0%) patients had cardiac symptoms.

Among them, majority of patients were not found hypertensive 75 (73.5%) against 27 (26.5%) hypertensive patients. Majority of patients were not diabetic 86 (84.3%) while 16 (15.7%) were diabetic. Tobacco smoking was not noted in majority of patients 96 (94.1%) against 6 (5.9%) smoker patients. There is no family history cardiovascular disease (CVS) in majority of patients 76 (74.5%) while 26 (25.5%) patients were found to have CVS disease.

Table 3 : Patient medical and social history of tested breast cancer patients

Descriptive		Frequency (%)
Presence of cardiac symptoms	Yes	2 (2.0%)
	No	100 (98.0%)
	Total	102 (100.0%)
Hypertension	Yes	27 (26.5%)
	No	75 (73.5%)
	Total	102 (100.0%)
Diabetes	Yes	16 (15.7%)
	No	86 (84.3%)
	Total	102 (100.0%)
Tobacco smoking	Yes	6 (5.9%)
	No	96 (94.1%)
	Total	102 (100.0%)
Family History Of CAD	Yes	26 (25.5%)
	No	76 (74.5%)
	Total	102 (100.0%)

4. Association between body mass index and dose categories of anthracycline cyclophosphamide in study group

Table 4 showed that there is strong association between BMI and dose of anthracycline and cyclophosphamide received by breast cancer patients. Out of 102 patients, underweight patients (n=2) received low dose 2 (100.0%). Among normal weight patients (n=22), the highest number of patients received low dose 12 (54.5%) followed by moderate dose 10 (45.5 %) respectively. Among overweight patients (n= 38), the highest number of patients received moderate dose 34 (89.5%) followed by low dose 2 (5.3%) and high dose 2 (5.3%) respectively. Out of 102 patients 40 patients were belong to obese category among them 29 (72.5%) received moderate dose followed by high dose 11 (27.5%) respectively.

Table 4 : Association between body mass index and combination of anthracycline and cyclophosphamide

Body mass index	Dose categories of anthracycline and cyclophosphamide				P-Value
	Low dose	Moderate dose	High dose	Total	
Underweight	2 (100%)	0 (0%)	0 (0%)	2 (100%)	0.0001
Normal Weight	12 (54.5%)	10 (45.5%)	0 (0%)	22 (100%)	
Over Weight	2 (5.3%)	34 (89.5%)	2 (5.3%)	38 (100%)	
Obese	0 (0%)	29 (72.5%)	11 (27.5%)	40 (100%)	

Applied Fisher's Exact Test

5. Comparison of age groups with respect to change in cardiac parameters after chemotherapy

Table 5 showed the comparison of age groups with change in cardiac parameters before and after anthracycline and cyclophosphamide therapy. It was found that there is non-significant change observed in ejection fraction, early and late ventricular filling velocity, left ventricular end systolic diameter, left ventricular end diastolic diameter, estimated pulmonary arterial pressure, left atrium and fractional shortening.

Table 5: Comparison of age groups with change in cardiac parameters

Cardiac parameters	Age groups	n	Mean± S.E.M	F	Sig
Change in ejection fraction (%)	25-35	20	1.10±1.250	.431	.786
	36-45	36	.83 ± .879		
	46-55	30	2.26 ± .089		
	56-65	13	1.08 ± .970		
	66-75	2	4.00 ± .000		
	Total	101	1.40 ± .531		
Change in early and late ventricular filling velocity (E/A)	25-35	19	.073 ±.101	1.015	.404
	36-45	32	-.112±.063		
	46-55	25	.003 ± .074		
	56-65	13	-.127 ±.091		
	66-75	2	-.155 ±.055		
	Total	91	-.045±.039		
Change in left ventricular end systolic diameter(mm)	25-35	20	-.51 ±.792	2.135	.083
	36-45	35	1.30 ± .662		
	46-55	30	-.35 ± .850		
	56-65	13	-.75 ± .728		
	66-75	1	8.0 0±.		
	Total	99	.23 ±.407		
Change in left ventricular end diastolic diameter (mm)	25-35	20	-.23 ±.971	1.200	.316
	36-45	35	1.53 ±.811		
	46-55	30	-.58 ±.931		
	56-65	13	-.59 ±1.063		
	66-75	1	4.00 ±.		
	Total	99	.28 ±.474		
Change in estimated pulmonary arterial pressure (mmHg)	25-35	19	3.53±1.973	2.415	.065
	36-45	31	1.87 ±1.130		

	46-55	24	2.13± 1.467		
	56-65	13	1.15± 2.130		
	66-75	2	17.50 ±.500		
	Total	89	2.54 ±.794		
Change in left atrium (mm)	25-35	20	.55 ±.909	.632	.641
	36-45	35	-.06 ±.549		
	46-55	30	.58 ±.841		
	56-65	13	1.85 ±.750		
	66-75	1	-1.00 ±.		
	Total	99	.50 ±.382		
Change in fractional shortening (%)	25-35	20	1.14 ±1.746	1.610	.178
	36-45	35	-.89 ±1.064		
	46-55	30	-.33 ±1.443		
	56-65	13	.87 ±.839		
	66-75	1	-15.53 ±.		
	Total	99	-.23 ±.698		

All the values are expressed in mean ± S.E.M

6. Comparison of BMI groups with respect to change in cardiac parameters after chemotherapy

Table 6 showed the comparison of BMI groups with change in cardiac parameters before and after anthracycline and cyclophosphamide therapy. It was found that there is non-significant change observed in ejection fraction, early and late ventricular filling velocity, left ventricular end systolic diameter, left ventricular end diastolic diameter, estimated pulmonary arterial pressure, left atrium and fractional shortening.

Table 6: Comparison of BMI groups with change in cardiac parameters

Cardiac parameters	**BMI groups**	**n**	**Mean±S.E.M**	**F**	**Sig**
Change in ejection fraction (%)	Underweight	2	.5 ±1.500	1.098	.354
	Normal weight	22	-.05 ±1.194		
	Overweight	37	1.18 ±.875		
	Obese	40	2.45 ±.827		
	Total	101	1.40 ±.531		
Change in early and late ventricular filling velocity (E/A)	Underweight	2	-.335 ±.1350	1.031	.383
	Normal weight	21	-.087 ±.0924		
	Overweight	33	.033 ±.0695		
	Obese	35	-.076 ±.0551		
	Total	91	-.045 ±.0395		
Change in left ventricular end systolic diameter(mm)	Underweight	2	-4.50 ±2.500	1.428	.240
	Normal weight	21	1.27 ±1.148		
	Overweight	36	.0 8 ±.512		
	Obese	40	.07 ±.640		
	Total	99	.23±.407		
Change in left ventricular end diastolic diameter (mm)	Underweight	2	-4.50±.500	.850	.470
	Normal weight	21	.60 ±.976		
	Overweight	36	.68 ±.851		
	Obese	40	.00 ±.719		
	Total	99	.28 ±.474		
Change in estimated pulmonary arterial pressure (mmHg)	Underweight	2	.50 ±4.500	1.463	.230
	Normal weight	19	2.89 ±2.174		
	Overweight	31	.48 ±1.135		
	Obese	37	4.19 ±1.175		
	Total	89	2.54 ±.794		
Change in left atrium (mm)	Underweight	2	-.50 ±1.500	.104	.958

	Normal weight	21	.40 ±.515		
	Overweight	37	.38 ±.672		
	Obese	39	.72 ±.683		
	Total	99	.50 ±.382		
Change in fractional shortening (%)	Underweight	2	3.62 ±5.329	1.120	.345
	Normal weight	21	-2.37 ±2.044		
	Overweight	36	.76 ±.759		
	Obese	40	-.19 ±1.141		
	Total	99	-.23 ±.698		

All the values are expressed in mean ± S.E.M

7. Comparison of cancer stage groups with respect to change in cardiac parameters after chemotherapy

Table 7 showed the comparison of cancer stage groups with change in cardiac parameters before and after anthracycline and cyclophosphamide therapy. It was found that there is non-significant change observed in ejection fraction, early and late ventricular filling velocity, left ventricular end systolic diameter, left ventricular end diastolic diameter, estimated pulmonary arterial pressure, left atrium and fractional shortening.

Table 7: Comparison of cancer stage groups with change in cardiac parameters

Cardiac parameters	Cancer stage	n	Mean±S.E.M	F	Sig
Change in ejection fraction (%)	stage not known	40	1.07 ±.831	.168	.954
	stage I	2	-.50 ±1.500		
	stage II	11	2.09 ±1.331		
	stage III	43	1.56 ±.914		
	stage IV	5	2.00 ±1.414		
	Total	101	1.40 ±.531		
Change in early and late ventricular filling velocity (E/A)	stage not known	35	-.137 ±.0584	2.583	.061
	stage I	2	.260 ±.7400		
	stage II	10	.252 ±.1397		
	stage III	39	-.051 ±.0547		
	stage IV	5	-.058 ±.0490		
	Total	91	-.045 ±.0395		
Change in left ventricular end systolic diameter(mm)	stage not known	38	.16 ±.666	.375	.826
	stage I	2	-2.50 ±3.500		
	stage II	11	1.17 ±1.735		
	stage III	43	.16 ±.566		
	stage IV	5	.40 ±1.030		
	Total	99	.23 ±.407		
Change in left ventricular end diastolic diameter (mm)	stage not known	38	.32 ±.777	.952	.438
	stage I	2	-3.50 ±3.500		
	stage II	11	1.86 ±1.421		
	stage III	43	-.20 ±.723		
	stage IV	5	2.20 ±1.594		
	Total	99	.28 ±.474		
Change in estimated pulmonary arterial pressure (mmHg)	stage not known	36	2.44 ±1.143	.321	.863
	stage I	2	3.50 ±1.500		
	stage II	9	.00 ±1.443		
	stage III	37	3.14 ±1.496		
	stage IV	5	3.00 ±2.000		
	Total	89	2.54 ±.794		
Change in left atrium (mm)	stage not known	38	.13 ±.619	.269	.897
	stage I	2	.50 ±.500		
	stage II	11	.35 ±.746		

	stage III	43	.93 ±.661		
	stage IV	5	-.20 ±.663		
	Total	99	.50 ±.382		
Change in fractional shortening (%)	stage not known	38	.02 ±1.184	.238	.916
	stage I	2	.71 ±3.095		
	stage II	11	-.13 ±2.554		
	stage III	43	-.80 ±1.030		
	stage IV	5	2.20 ±1.724		
	Total	99	-.23 ±.698		

All the values are expressed in mean ± S.E.M

8. Comparison of dose regimen groups with respect to change in cardiac parameters after chemotherapy

Table 8 showed comparison of dose regimen groups with change in cardiac parameters before and after anthracycline and cyclophosphamide therapy. It was found that there is non-significant change observed in ejection fraction, early and late ventricular filling velocity, left ventricular end systolic diameter, left ventricular end diastolic diameter, estimated pulmonary arterial pressure, left atrium and fractional shortening.

Table 8: Comparison of dose regimen groups with change in cardiac parameters

Cardiac parameters	Dose regimen of anthracycline and cyclophosphamide	n	Mean±S.E.M	F	Sig
Change in ejection fraction (%)	Low dose regimen	16	-.38±1.381	1.277	.283
	Moderate dose regimen	72	1.90±.647		
	High dose regimen	13	.85±1.055		
	Total	101	1.40±.531		
Change in early and late ventricular filling velocity (E/A)	Low dose regimen	15	-.075±.1016	.148	.862
	Moderate dose regimen	65	-.031±.0474		
	High dose regimen	11	-.084±.1057		
	Total	91	-.045±.0395		
Change in left ventricular end systolic diameter(mm)	Low dose regimen	16	1.66±1.456	1.206	.304
	Moderate dose regimen	70	-.07±.419		
	High dose regimen	13	.11±1.155		
	Total	99	.23±.407		
Change in left ventricular end diastolic diameter (mm)	Low dose regimen	16	1.29±1.034	1.002	.371
	Moderate dose regimen	70	.33±.601		
	High dose regimen	13	-1.18±.916		
	Total	99	.28±.474		
Change in estimated pulmonary arterial pressure (mmHg)	Low dose regimen	13	-.31±2.141	1.104	.336
	Moderate dose regimen	64	3.05±.928		
	High dose regimen	12	2.92±2.172		
	Total	89	2.54±.794		
Change in left atrium (mm)	Low dose regimen	16	.64±.584	1.537	.220
	Moderate dose regimen	70	.16±.477		
	High dose regimen	13	2.15±1.096		
	Total	99	.50±.382		
Change in fractional shortening (%)	Low dose regimen	16	-2.39 ±2.666	1.797	.171
	Moderate dose regimen	70	.62±.674		
	High dose regimen	13	-2.10±2.051		
	Total	99	-.23±.698		

All the values are expressed in mean ± S.E.M

IV. DISCUSSION

Breast cancer is the most prevalent type of cancer in both men and women common (17). In both developed and developing countries, the incidence of breast cancer is fairly high (18). Anthracycline with cyclophosphamide is one of the most well-liked adjuvant chemotherapy regimens, also referred to as AC chemotherapy, for patients with breast cancer (19). Cardiovascular adverse effects are the main reason for treatment-related morbidity and mortality in cancer survivors. Anthracycline are the most cardiotoxic of all the chemotherapeutic medicines, therefore this is particularly true of them (20).

Present study is the prospective study conducted in the Karachi in order to investigate the incidence of cardiotoxicity in newly diagnosed breast cancer patients receiving four cycles of anthracycline plus cyclophosphamide regimens. In past estimates it is alarmed that more prevalence of breast cancer in women aged more than 60 years in past is shifting towards younger ages and rising in post-menopausal women aged above 50 years in coming years in Pakistan (21).

Present study (Table 1) in continuation with the past estimates showed the similar pattern of incidence of breast cancer among different age groups as highest number of breast cancer patients were found in age group 36-45 years (22) Table 2 showed distribution of cumulative dose of anthracycline and cyclophosphamide and found that highest number of patients received cumulative anthracycline cyclophosphamide combination at moderate dose (23).

Present study showed patient medical and social history of tested breast cancer patients, it was found that most of the patients did not find cardiac symptoms, hypertension, diabetes, family history Of CAD and tobacco smoking (Table 3).

Previous studies indicated that higher BMI is associated with incidence of breast cancer
(24). It was evaluated that highest number of breast cancer patients were found in obese category. As the dose of chemotherapy prescribed is based on body surface area thus body mass index is suggestive of dose of chemotherapy chosen. The present study also indicated that most of the overweight and obese patients received moderate to high dose ($P = 0.0001$). Thus, it is suggested that there is a strong association between BMI and dose prescribed (Table 4).

All the results of cardiac parameters before and after combined anthracycline and cyclophosphamide chemotherapy that include ejection fraction, early and late ventricular filling velocity, left ventricular end systolic diameter, left ventricular end-diastolic diameter, estimated pulmonary arterial pressure, left atrium thickness and fractional shortening were found to lie in the normal ranges as defined in standard literature (Table 5-11). Thus, all the patients remained in the safe window with respect to cardiac toxicity either before or after anthracycline containing combined chemotherapy. The results of present study showed that prescribing practices of anthracycline is appropriate in the tested population.

The cardiotoxicity of the anthracycline and cyclophosphamide regimen was best described by calculating the change in cardiac parameters by subtracting echocardiographic findings of individual patients after giving chemotherapy from echocardiographic findings of before giving chemotherapy. The beginning of early cardiotoxicity shows in a period of one year of starting cancer treatment (25). The total amount of anthracycline at 320 mg/m^2 resulted in a considerable reduction in LVEF. It demonstrated a declining trend with increasing anthracycline dose (26). A previous study found that anthracycline and cyclophosphamide regimens were given to freshly identified breast cancer patients for the first time. Measurements included ejection fraction, fractioning shortening, left ventricular end-diastolic diameter, and left ventricular end-systolic diameter. The echocardiographic results from the first dose of anthracycline and the day after it were not substantially different from one another. However, there were noticeable variations between the echocardiographic values at baseline, one day after the last anthracycline dose, and six months after the anthracycline therapy ended with a steady and continuing reduction in functional markers like EF and FS (27).

The present study in contrast with previous findings depicted the safety of chemotherapy in short term use as the comparison between age groups, BMI groups, cancer stage groups and dose regimen groups with change in cardiac parameters that include ejection fraction, early and late ventricular filling velocity, left ventricular end systolic diameter, left ventricular end-diastolic diameter, estimated pulmonary arterial pressure, left atrium thickness and fractional shortening showed no significant difference (28).

Present study strongly suggests that anthracycline cyclophosphamide combination therapy given for four cycles posed no cardiotoxic effects on tested breast cancer patients. The reason for this safety of anthracycline containing regimen that found to be cardiotoxic in previous studies might be due to safe prescribing practices after taking cardiovascular disease history, age and weight of the patients (29).

V. CONCLUSION

Present study strongly suggests that anthracycline cyclophosphamide combination therapy given for four cycles posed no cardiotoxic effects on tested breast cancer patients. Most of the previous studies authenticate the cardiotoxicity of anthracycline after six months to one year use of combined chemotherapy but the data for short term (four cycles) use of anthracycline containing combined chemotherapy is not sufficient to reach any conclusion. This study thus helps us in understanding the cardiotoxic effects of anthracycline containing chemotherapy after short term use (four cycles).

Limitation of the Study

The current investigation has contributed significantly to our knowledge about the prevalence of anthracycline induced cardiotoxicity. The limitations of our study which may affect the result's perception and predictability are.

- This study was short term three months study.
- Sample size of study was small.

- Single center study

REFERENCES

1. Martins-Teixeira MB, Carvalho I. Antitumour anthracyclines: progress and perspectives. ChemMedChem. 2020;15(11):933-48.
2. Yusuf A. Cancer care in the time of COVID-19—a perspective from Pakistan. ecancermedicalscience. 2020;14.
3. Sturgeon KM, Deng L, Bluethmann SM, Zhou S, Trifiletti DM, Jiang C, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. European heart journal. 2019;40(48):3889-97.
4. Cai F, Luis MAF, Lin X, Wang M, Cai L, Cen C, et al. Anthracycline-induced cardiotoxicity in the chemotherapy treatment of breast cancer: Preventive strategies and treatment. Molecular and clinical oncology. 2019;11(1):15-23.
5. Waks AG, Winer EP. Breast cancer treatment. Jama. 2019;321(3):316-.
6. Yeo W, Lau TK, Kwok CC, Lai KT, Chan VT, Li L, et al. NEPA efficacy and tolerability during (neo) adjuvant breast cancer chemotherapy with cyclophosphamide and doxorubicin. BMJ supportive & palliative care. 2022;12(e2):e264-e70.
7. Zhang P, Zhang J, Zhao L, Li S, Li K. Quercetin attenuates the cardiotoxicity of doxorubicin–cyclophosphamide regimen and potentiates its chemotherapeutic effect against triple-negative breast cancer. Phytotherapy Research. 2022;36(1):551-61.
8. Saleh Y, Abdelkarim O, Herzallah K, Abela GS. Anthracycline-induced cardiotoxicity: mechanisms of action, incidence, risk factors, prevention, and treatment. Heart failure reviews. 2021;26(5):1159-73.
9. Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of anthracyclines. Frontiers in cardiovascular medicine. 2020;7.
10. Georgiadis N, Tsarouhas K, Rezaee R, Nepka H, Kass GE, Dorne JL, et al. What is considered cardiotoxicity of anthracyclines in animal studies Corrigendum in/10.3892/or. 2020.7717. oncology reports. 2020;44(3):798-818.
11. Das KC, Muniyappa H, Kundumani-Sridharan V, Subramani J. Thioredoxin decreases anthracycline cardiotoxicity, but sensitizes cancer cell apoptosis. Cardiovascular Toxicology. 2021;21(2):142-51.
12. Pashaei Y, Mehrabi M, Shekarchi M. A review on various analytical methods for determination of anthracyclines and their metabolites as anti–cancer chemotherapy drugs in different matrices over the last four decades. TrAC Trends in Analytical Chemistry. 2020;130:115991.
13. Bozza WP, Takeda K, Alterovitz W-L, Chou C-K, Shen R-F, Zhang B. Anthracycline-Induced Cardiotoxicity: Molecular Insights Obtained from Human-Induced Pluripotent Stem Cell–Derived Cardiomyocytes (hiPSC-CMs). The AAPS journal. 2021;23(2):1-12.
14. Lee K, Kang I, Mack WJ, Mortimer J, Sattler F, Salem G, et al. Effect of high intensity interval training on matrix Metalloproteinases in women with breast Cancer receiving Anthracycline-based chemotherapy. Scientific reports. 2020;10(1):1-7.
15. Varghese SS, Eekhoudt CR, Jassal DS. Mechanisms of anthracycline-mediated cardiotoxicity and preventative strategies in women with breast cancer. Molecular and Cellular Biochemistry. 2021;476(8):3099-109.
16. Saleh Y, Abdelkarim O, Herzallah K, Abela GS. Anthracycline-induced cardiotoxicity: mechanisms of action, incidence, risk factors, prevention, and treatment. Heart failure reviews. 2020:1-15.
17. Caparica R, Bruzzone M, Poggio F, Ceppi M, de Azambuja E, Lambertini M. Anthracycline and taxane-based chemotherapy versus docetaxel and cyclophosphamide in the adjuvant treatment of HER2-negative breast cancer patients: a systematic review and meta-analysis of randomized controlled trials. Breast cancer research and treatment. 2019;174(1):27-37.
18. Neuendorff NR, Loh KP, Mims AS, Christofyllakis K, Soo W-K, Bölükbasi B, et al. Anthracycline-related cardiotoxicity in older patients with acute myeloid leukemia: a Young SIOG review paper. Blood advances. 2020;4(4):762-75.
19. Spînu Ș, Cismaru G, Boarescu P-M, Istratoaie S, Negru AG, Lazea C, et al. ECG Markers of Cardiovascular Toxicity in Adult and Pediatric Cancer Treatment. Disease Markers. 2021;2021.
20. Murabito A, Hirsch E, Ghigo A. Mechanisms of anthracycline-induced cardiotoxicity: is mitochondrial dysfunction the answer? Frontiers in cardiovascular medicine. 2020;7:35.
21. Tantawy M, Pamittan FG, Singh S, Gong Y. Epigenetic Changes Associated With Anthracycline-Induced Cardiotoxicity. Clinical and Translational Science. 2021;14(1):36-46.
24. Shandilya M, Sharma S, Das PP, Charak S. Molecular-Level Understanding of the Anticancer Action Mechanism of Anthracyclines. Overview of Doxorubicin-Clinical Use, Resistance, Side Effects, and Palliative Care: IntechOpen; 2020.
25. Cadeddu Dessalvi C, Pepe A, Penna C, Gimelli A, Madonna R, Mele D, et al. Sex differences in anthracycline-induced cardiotoxicity: the benefits of estrogens. Heart failure reviews. 2019;24(6):915-25.
26. Russo M, Della Sala A, Tocchetti CG, Porporato PE, Ghigo A. Metabolic aspects of anthracycline cardiotoxicity. Current treatment options in oncology. 2021;22(2):1-21.
27. Kibudde S, Mondo CK, Kibirige D, Walusansa V, Orem J. Anthracycline induced cardiotoxicity in adult cancer patients: a prospective cohort study from a specialized oncology treatment centre in Uganda. African Health Sciences. 2019;19(1):1647-56.
28. Anqi Y, Yu Z, Mingjun X, Xiaoli K, Mengmeng L, Fangfang L, et al. Use of chocardiography to monitor myocardial damage during anthracycline chemotherapy. Echocardiography. 2019;36(3):495-502.
29. Liang B, Liang Y, Gu N. Pharmacological mechanisms of sodium-glucose co-transporter 2 inhibitors in heart failure with preserved ejection fraction. BMC Cardiovascular Disorders. 2022;22(1):1-15.

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