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Antracycline Induced Early Onset Chronic Cardiotoxicity in Cancer Patients

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ABSTRACT

Objective: To assess the patients for early onset chronic cardiotoxicity who have been taking anthracyclines as part of their cancer treatment.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Oncology department, Combined Military Hospital, Rawalpindi Pakistan, from Dec 2020 to May 2021.

Methodology: One hundred patients with solid or hematological malignancies taking anthracyclines for more than three months and less than a year were included in the study. They underwent 2 dimensional echocardiography by consultant cardiac physician to look for cardiotoxicity. Cardiotoxicity was defined as left ventricular ejection fraction less than 60%. Age, gender, duration of anthracyclines use and presence of comorbid illness were correlated with presence of early onset chronic cardiotoxicity in our study participants.

Results: Out of 100 cancer patients using anthracyclines for more than three months and less than 12 months included in the study, 55(55%) were males while 45(45%) were females. Sixty-nine (69%) had ejection fraction more than 60% on echocardiography while 31(31%) had <60%. Chi-square test revealed that presence of comorbidities (type 2 DM/ Hypertension) had statistically significant association with presence of cardiotoxicity in our study (*p*-value 0.002).

Conclusion: Cardiotoxicity emerged as a significant adverse effect related to anthracycline use among patients suffering from various types of malignant conditions. Patients with preexisting medical conditions like diabetes or hypertension were more at risk of developing cardiotoxicity with these agents.

Keywords: Anthracycline, Cancer, Cardiotoxicity.

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INTRODUCTION

Cancer epidemiology has been an interesting topic for clinicians, researchers and public health experts across the globe.[1] Both developed and developing countries have shown an increase in diagnosis of this potentially lethal condition.[2] Last two decades have revolution the diagnostic and treatment strategies for various types of malignant conditions and patients have been managed in a better way.[3] Weighing the risks and benefits of newer treatment options has always been a challenge for the treating team and a multidisciplinary approach is usually beneficial in this regard.[4] Multiple treatment strategies are employed in management of solid or hematological malignancies during the course of treamtent.[5] Despite clear benefit of Anthracyclines for these patients in terms of cancer control; they have certain adverse effects which may compromise the quality of life of the patients using this medication.[6]

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Cardiotoxicity has been associated with a number of chemotherapeutic agents used for managing cancer patients including the Anthracyclines. Cardinale *et al*. showing that cardiotoxicity was a relatively common finding among patients taking anthracyclines. Patients were more prone to develop this adverse effect within one year of treatment and dependent on the dose of anthracycline used.[7] Groarke *et al*, highlighted the importance of early and repeated assessments of cardiac function in these patients.[8] Sandamali *et al*. published data based on Srilankan patients suffering from cancer and using Anthracyclines. They revealed that more than 30% of the patients included in their study developed some form of cardiotoxicity. They recommended long-term follow-up to detect early-onset chronic progressive cardiotoxicity among patients using anthracyclines for any malignant condition.[9]

A large number of patients suffering from cancer present at advanced stage in our part of the world and warrant use of anthracyclines. Like all other chemotherapeutic agents, anthracyclines have variety of adverse effects. A local study done by

Shaikh *et al*. summarized that high incidence of cardiotoxicity was observed among patients taking anthracyclines which warranted repeated assessments.[10] Ours is a biggest military oncology unit in the country with huge patients turn over. We therefore planned this study with the rationale to assess the patients for early onset chronic cardiotoxicity who have been taking anthracyclines as part of their cancer treatment.

METHODOLOGY

This comparative cross-sectional study was conducted at Oncology Unit of Combined Military Hospital, Rawalpindi Pakistan, form December 2020 to May 2021. Sample size was calculated by using the WHO sample size calculator by using population prevalence proportion of cardiotoxicity with anthracyclines as 10.2%[11] and keeping margin of error as 10%. Non-probability consecutive sampling technique was used to gather the sample.

Inclusion Criteria: Patient from 18 to 70 years of age from both genders who were taking any anthracycline for any solid or hematological malignancy for more than three months and less than one year were included in the study.

Exclusion Criteria: Patients with ischemic heart disease and taking cardio-selective drugs such as B-blockers, Ca channel blockers, anti-arrhythmic and cardiac glycosides (assessed on patient history) and those with conduction defect on ECG or those with valvular heart disease and previously diagnosed heart failure on echocardiography were excluded from the study. Hyperkalemic patients were also not included in the study. Patients with any significant cardiac history before the start of anthracyclines were excluded as well.

After taking written informed consent from all the potential participants and ethical approval (via letter no A-157/5/21) from ethical review board of hospital, patients fulfilling above mentioned inclusion and exclusion criteria were included in the study. Anthracyclines are so far considered as most effective chemotherapy medication with various modes of action including free radical formation, lipid peroxidation, direct membrane effects, and enzyme interactions. Commonly used anthracyclines in practice include Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitoxantrone and Valrubicin.[12] Two-dimensional echocardiogram was performed by consultant cardiologist on all the study participants and interpreted for cardiotoxicity. Cardiotoxicity was defined as left ventricular systolic dysfunction as <60%.[13] Comorbidities studied in our analysis were type-II diabetes mellitus and hypertension.

Data was entered and analyzed by using Statistical Package for Social Sciences version 23.0. The qualitative data were presented as frequency distribution and quantitative data were presented as Mean±SD. Relationship of various variables with cardiotoxicity was analyzed by using Pearson Chi-square analysis and Binary logistic regression analysis by keeping *p*-value ≤0.05 as significant to establish correlation.

RESULTS

Of 100 cancer patients using anthracyclines for more than three months and less than 12 months included in the study, 55(55%) were male while 45(45%) were female. Mean age of the cancer patients using anthracycline included in the analysis was 43.63±8.759 years. Sixty-nine (69%) had ejection fraction more than 60% on echocardiography while 31(31%) had <60%. Table-I summarized the main demographic features of the study participants. Table-II revealed that upon application of Pearson chi-square test, presence of comorbidities (type 2 DM/ Hypertension) had statistically significant association with presence of cardiotoxicity in our study (*p*-value-0.004) while age (*p*-value-0.860), duration of anthracycline use (*p*-value-0.183) and gender (*p*-value-0.079) had no such relationship.

Table-I: Characteristics of Patients Included in the Study

Study Parameters	n(%)
Age (years) Mean+SD	43.63±8.759 years
Gender	
Male	55(55%)
Female	45(45%)
Ejection fraction	
<60%	31(31%)
>60%	69(69%)
Presence of comorbidities	
No	47(47%)
Yes	53(53%)
Duration of Anthracycline use	
3-6 months	82(82%)
6-12 months	18(18%)

DISCUSSION

Cancer management strategies have been evolving in last three decades. Various new agents have been introduced but still few older agents are considered as most effective drugs to manage the malignant conditions. Pakistan is a developing

country with limited budget for health especially oncological problems. A recent study emphasized on the patterns of various malignancies in Pakistan highlighting the huge chunk of cases presenting in advanced phase of disease requiring aggressive therapy.[14] Potent agents like anthracyclines are commonly used to treat the patients with advanced disease and cause certain adverse effects as well. We conducted this study with the objective to assess the patients for early onset chronic cardiotoxicity who have been taking anthracyclines as part of their cancer treatment.

Table-II: Pearson chi-square for Relationship of Various Factors with the Presence of Early Onset Chronic Cardiotoxicity among the Target Population

Socio-demographic factors	Ejection fraction>60%	Ejection fraction<60%	*p*-value
Age			
<40 years	41(59.4%)	19(61.3%)	0.860
>40 years	28(40.6%)	12(38.7%)	
Gender			
Female	42(60.9%)	13(41.9%)	0.079
Male	27(39.1%)	18(58.1%)	
Duration of Anthracycline use			
3-6 months	59(85.5%)	23(74.2%)	0.183
6-12 months	10(25.4%)	08(25.8%)	
Presence of comorbidities			
No	39(56.5%)	08(25.8%)	0.004
Yes	30(43.5%)	23(74.2%)	

Goel *et al*.[15] published a study to study the vulnerability of patients towards cardiotoxicity with Trastuzumab who have suffered from reduced ejection fraction in response to anthracyclines. They concluded that left nevtricular function was a common finding among patients using anthracyclines and predicted cardiotoxicity with Trastuzumab as well. Our study design was simple and we just studied the cardiotoxicity with anthracyclines and found out that it affects cardiac function in considerable number of patients.

Demissei *et al*.[16] studies patients of breast cancer using various medications and looked for an increase in cardiac biomarkers among these patients. They concluded that anthracycline was associated with increase in biomarkers both at the start of treatment and in long run. We specifically focused on anthracyclines and did not include patients who were using other medications and revealed that early onset chronic cardiotoxicity was found in more than 30% of our study participants.

Multiple strategies could be employed to prevent the cardiotoxicity found in patients using anthracyclines. Gujral *et al*.[17] used prophylactic beta-blocker or ACE inhibitor for this purpose and found out that beta blocker was effective in this regard, though efficacy was modest. We did not use any therapeutic agents in our study but found a significant relationship between presence of comorbidities and cardiotoxicity among study participants which may explain beneficial use of beta blockers in this regard.

Abu-Khalaf *et al*.[18] studies this phenomenon from another perspective and looked for the cost-effectiveness of screening patients of breast cancer using anthracyclines for presence of cardiotoxicity. They came up with the findings that screening patients for cardiotoxicity especially those with low base line left ventricular systolic function could be cost effective strategy among this high risk population. Presence of cardiotoxicity in significant number of patents in our study supported their results. Patients with comorbid illnesses like DM or HTN should be screened at priority for cardiac problems.

We could not establish with precision that cardiotoxicity was a result of underlying malignant condition or other coexisting treatment or anthracyc-lines. This becomes one of the main limitations of our study. Baseline echocardiography findings before the start of anthracyclines would have given useful information and helped us in ascertaining cardio toxic effects of this group of medications used in cancer patients.

CONCLUSION

Cardiotoxicity emerged as a significant adverse effect related to anthracycline use among patients suffering from various types of malignant conditions. Patients with preexisting medical conditions like diabetes or hypertension were more at risk of developing cardiotoxicity with these agents.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

II & RA: Data acquisition, data analysis, critical review, approval of the final version to be published.

MN & AK: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AG & RK: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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