EARLY ASYMPTOMATIC DECLINE IN LEFT VENTRICULAR EJECTION FRACTION IN ADULT CANCER PATIENTS RECEIVING DOXORUBICIN

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ABSTRACT

Objective: To determine the frequency of doxorubicin induced early asymptomatic decline in left ventricular ejection fraction by serial echocardiography and to identify risk factors associated with cardiotoxicity.

Study Design: Quasi-experimental study.

Place and Duration of study: Oncology Department, Combined Military Hospital, Rawalpindi from January 2012 to December 2012.

Patients and Methods: Patients who were started on doxorubicin-based chemotherapy during the study period and had completed at least 300 mg/m^2 cumulative dose were included in this study. Electrocardiography, chest X-ray and echocardiography were done at baseline and one to three months after completion of chemotherapy. All patients were evaluated for the presence of the following risk factors: pre-existing coronary artery disease, diabetes mellitus, hypertension, chest wall irradiation and a cumulative dose exceeding 400 mg/m^2. Asymptomatic cardiac dysfunction was defined as ejection fraction (EF) fall greater than 10% on follow-up echocardiography with minimum or no symptoms.

Results: Significant change was observed in ejection fraction after completion of chemotherapy. Out of 54 patients, 27.8% showed 5%, 13% showed 10% decline, 16.7% had 15% decline, one (1.9%) patient had 20% decline in EF after completion of chemotherapy while 40.7% had no change in ejection fraction.

Conclusion: Thirty one percent of the patients developed ≥ 10% decline, in left ventricular ejection fraction with the use of doxorubicin in the cumulative dose range of 300-400 mg/m^2. Pre-existing coronary artery disease, hypertension and a cumulative dose exceeding 400 mg/m^2 are identifiable risk factors in this study. This entails regular monitoring for cardiac dysfunction by echocardiography during doxorubicin treatment.

Keywords: Cardiotoxicity, Doxorubicin, Echocardiographic monitoring

INTRODUCTION

Doxorubicin is one of the most potent anti-neoplastic agents in the treatment of various types of malignancies. However, its therapeutic value is limited by cumulative dose related cardiotoxicity[1]. The exact mechanism of anthracycline related cardiomyopathy is poorly understood, a commonly accepted theory involves myocardial damage caused by mitochondrial injury and free radical formation[2]. Anthracycline induced cardiotoxicity can be acute/subacute or chronic. Acute or subacute cardiotoxicity may present as electrocardio - graphic abnormalities, arrhythmias, heart block, ventricular dysfunction, an increase in plasma brain natriuretic peptide or a pericarditis-myocarditis syndrome while chronic toxicity is typically manifested as clinical heart failure[3].

A number of risk factors for the development of anthracycline cardiotoxicity have been identified. These include cumulative dose, age at the time of drug exposure, concomitant administration of other cardiotoxic chemotherapeutic agents, concurrent or prior chest irradiation, and preexisting cardiovascular disease[4].

Treatment with doxorubicin may necessitate lifelong cardiac monitoring. Clinical parameters and electrocardiographic changes are not sensitive and specific in detecting cardiotoxicity. Endomyocardial biopsy, for detecting anthracycline-induced cardiotoxicity is an invasive procedure that cannot be employed

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routinely. Echocardiography and radionuclide imaging remain good noninvasive techniques to study effects on cardiac function. Though radionuclide studies have been reported to be more sensitive in detecting systolic and diastolic dysfunction, they expose patients to ionizing radiation and are not widely available. Echocardiography is more easily available, is not dependent on the availability of radioisotopes and is less costly. Measurement of resting global left ventricular function using either first pass or equilibrium multigated blood pool imaging (MUGA scan) is an established technique for monitoring anthracycline cardiotoxicity. However, it is used less often than echocardiography. Despite problems with variability of measurements, echocardiography is generally preferred over radionuclide techniques for monitoring left ventricular ejection fraction (LVEF) during and after potentially cardiotoxic chemotherapy due to above mentioned reasons[5]. Noninvasive monitoring of cardiac function during anthracycline therapy is endorsed by the American Heart Association/American College of Cardiology (AHA/ACC). The use of echocardiography at baseline and for re-evaluation examinations to monitor patients exposed to anthracyclines was given a class-I recommendation by a task force of the ACC and the AHA[6].

The US FDA-approved labeling for doxorubicin indicates that in adults, a 10 percent decline in LVEF below the lower limit of normal, or an absolute LVEF 45 percent, or a 20 percent decline in LVEF at any level is indicative of deterioration of cardiac function. In children, they endorse the use of an absolute decrease in fractional shortening by ≥10 percent from baseline, or to <29 percent, or an absolute decrease in LVEF by ≥10 percent from baseline or to <55 percent as an indications to discontinue anthracycline[7].

This study was conducted as a preliminary investigation to evaluate the frequency of doxorubicin induced early asymptomatic decline in left ventricular ejection fraction by serial echocardiography and to identify risk factors associated with cardiotoxicity.

PATIENTS AND METHODS

This quasi-experimental study was conducted at Oncology Department, Combined Military Hospital Rawalpindi from 1st January 2012 to 31st December 2012. This study was approved by the ethics committee of the institute. All newly diagnosed adult cancer patients who received doxorubicin for the first time and who gave informed consent were enrolled in the study. All those patients were included in the study that had left ventricular ejection fraction (LVEF) greater than or equal to 50% at baseline. Patients having congestive cardiac failure or valvular heart diseases were excluded from the study.

A detailed history including history of hypertension or coronary artery disease, diabetes mellitus and mediastinal or chest wall irradiation was taken. Physical examination of cardiovascular system was done at baseline and at each follow-up to rule out valvular heart disease and congestive cardiac failure. Blood complete picture, 12-lead ECG, chest X-ray and echocardiography were done at baseline, and within one to three months after completion of chemotherapy. During echocardiography ejection fraction (EF) was calculated by M-mode and modified Simpson's formula. In order to reduce inter-observer variability, echocardiography was performed by the same physician for each patient at different time points. Intra-observer variability was reduced by taking the mean of three readings during each echocardiography. Subclinical cardiac dysfunction was defined as fall of ejection fraction >10% during follow-up echocardiography. The risk factors studied were presence of preexisting coronary artery disease, hypertension, diabetes mellitus, chest wall or mediastinal irradiation and cumulative dose >400 mg/m^2.

Statistical package for social sciences (SPSS) version 18 was used for statistical analysis. Descriptive statistics were used to describe the results. Paired sample t-test was applied for the

comparison of pre and post EF. Role of various risk factors was analyzed by using chi-square test. A *p*-value <0.05 was considered as significant.

Table-1: Baseline characteristics of adult cancer patients receiving doxorubicin (n = 54).

	Mean (SD)	Range
Age in years	47.74(14.6)	22-80
No of cycles of chemotherapy received	6.96(1.0)	6-8
Cumulative dose of Doxorubicin (in mg/m^2)	348.15(50.4)	300-400
Baseline LVEF* (%)	61.67(3.4)	55-65

*LVEF: Left ventricular ejection fraction

Table-2: Association of change in ejection fraction (EF) with different risk factors in patients receiving doxorubicin.

Risk Factor	Change in EF		*p*-value
	≥ 10% (n = 17)	< 10% (n = 15)	
CAD	6 (35%)	3 (20%)	0.013
DM	2 (12%)	6 (40%)	0.669
HTN	6 (35%)	2 (13%)	0.004
Radiation	2 (12%)	3 (20%)	0.667
Cumulative dose ≥ 400	12 (71%)	14 (93%)	0.025

CAD: coronary artery disease, DM: diabetes mellitus, HTN: hypertension

RESULTS

Sixty patients were enrolled in the study during the study period who received at least 300 mg/m^2 of Doxorubicin for their cancer treatment. Six patients were excluded as they did not receive full course of chemotherapy due to progression of disease or severe side effects or they were lost to follow up. Fifty four patients, 21 (38.9%) female and 33 (61.1%) male, were included in the study. Twenty eight (51.8%) patients received 300 mg/m^2 of doxorubicin, while 26 (48.1%) patients received 400 mg/m^2 or more cumulative dose of doxorubicin. The baseline characteristics of 54 patients are shown in Table-1.

The chemotherapeutic regimens were used according to different diagnoses. Patients of carcenoma (CA) breast (18.5%) either received 6 cycles of TAC (Docetaxel, Doxorubicin, Cyclophosphamide) or FAC (5-Fluorouracil, Doxorubicin, Cyclophospha-mide) regimen chemotherapy, all patients of Hodgkin Lymphoma (22.2%) received six cycles of ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine) while patients of Non Hodgkin Lymphoma (NHL) (59.3%) received 6 to 8 cycles of CHOP chemotherapy (Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone).

Average baseline EF was 61.67% (SD = 3.365) which decreased significantly to an average EF of 55.93% (SD = 6.873) ($p < 0.001$).Twenty two out of 54 (40.7%) patients had no change in ejection fraction after completion of chemotherapy. Fifteen (27.8%) showed insignificant change i.e. <10% decline in EF. Seventeen out of fifty four (31.5%) patients developed ≥ 10% decline in EF after chemotherapy. (Figure)

All (100%) patients received intravenous boluses of doxorubicin over 30 minutes. Association of various risk factors with the development of fall in ejection fraction was also studied. In our study diabetes mellitus and chest wall radiation did not prove to be the risk factors for a fall in EF, while previous coronary artery disease, hypertension and cumulative dose ≥ 400 mg/m^2 proved to be the risk factor for decline in EF in patients receiving doxorubicin containing chemotherapy. (Table-2)

DISCUSSION

Cardiotoxicity is a well-established side effect of doxorubicin and other anthracycline

anti-cancer drugs. Its incidence increases with the increasing cumulative dose of this drug. However, very few studies have evaluated subclinical decline in cardiac function in relatively lower cumulative dose range. This study was aimed to find the frequency of asymptomatic cardiac dysfunction with the use of lower dose range of doxorubicin.

Our study shows that asymptomatic and symptomatic cardiac dysfunction can be detected at lower cumulative doses of doxorubicin by serial echocardiographic measurements. The frequency of significant decline in ejection fraction i.e ≥ 10% was 31.5% (17 out of 54 patients). Other studies that have evaluated the decline in cardiac function recorded the values up to 50%. Shaikh et al[8] in their study found that fifteen (14%) children developed cardiac dysfunction within a month and 28 (25%) children within a year after use of doxorubicin in cumulative dose < 300 mg/m^2. Mohta et al[9] observed in pediatric patients that 30% of the patients had significant cardiac dysfunction on echocardiographic evaluation at a mean cumulative dose of 365 mg/m^2. The lesser decline of ejection fraction in our study could be explained by the prospective design of our study. Most of the studies looking at the decline in ejection fraction are retrospective in nature. In our study all the patients were evaluated before entry into the study by echocardiography and cardiology consultation was taken before starting doxorubicin. Other possible factors could be measurement method employed. Some of the studies have used the tei index for measuring cardiac function. In our study we made more frequent measurements of cardiac function. Earlier interventions in the form of institution of beta blockers and ACE/ARB blockers might have explained the difference.

Early detection of fall in cardiac function has important clinical implications. According to ACC administration of ACE inhibitors/ARB blockers and beta blockers should be done for class 1 heart failure. Whether start of early intervention affects the long term complications of cardiac function in chemotherapy induced myocardial damage is not known. Nevertheless, studies have shown that beta blockers and

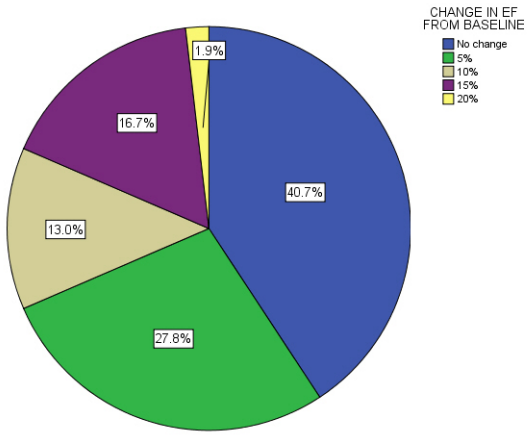

Figure-: Change in ejection fraction (EF) from baseline in patients receiving doxorubicin (n = 54).

ACE/ARB blockers have a salutary outcome on cardiac remodeling[10].

This study was unique as it was prospective in design and it used echocardiography for measurement of ejection fraction which is widely available. Most of the studies that we found were retrospective in nature and dependent on patient's records. Our study was limited by its sample size and perhaps cardiac function should have been evaluated by MUGA scan as well. Earlier studies have shown that MUGA scan is more reliable than echocardiography. Clearly future studies should focus on the frequency of cardiac evaluations and address the issue of most cost effective method of cardiac function assessment. A longer follow up of the patients in which early decline in cardiac function is recorded is also warranted. Paucity of literature about the long term complications of doxorubicin is perhaps explained by the physicians' belief that it is reversible and perhaps the treating physicians focus more on the immediate morbidity and mortality of cancer. With the increasing number of patients surviving after cancer therapy there is an emergent need for future studies in this direction.

An important aspect of our study was to identify various risk factors which can be linked to cardiac dysfunction with the use of doxorubicin. An interesting finding of our study was statistically significant relationship between increasing cumulative dose of doxorubicin and cardiotoxicity as 71% patients with significant decline in LVEF had received doxorubicin dose of 400 mg/m^2. This result is similar to the results of other studies. Lefrak et al[11] in their study found that incidence of congestive cardiac failure rose to unacceptably high levels when cumulative dose of drug exceeded 550 mg/m^2, viz., from 4% at 500-550 mg/m^2 to 18% at 551-600 mg/m^2 and to 36% at a dose of 601 mg/m^2 or more. In another study of 3941 patients incidence of symptomatic heart failure was 0.14% in those who received doxorubicin in dose <400 mg/m^2 and 18% in the dose > 700 mg/m^2.[12] Based upon these observations it has been generally recommended that cumulative dose of doxorubicin should be limited to < 550 mg/m^2.

The present study found statistically significant association of history of coronary artery disease and hypertension with cardiac dysfunction. Out of 17 patients with significant decline in LVEF after receiving doxorubicin based chemotherapy, 35% patients had previous history of coronary artery disease and 35% patients had hypertension. The results are similar to those in the studies by Von Hoff et al[13] and Hershman DL et al[14] who found that patients with preexisting cardiac disease and hypertension had increased probability of developing cardiac dysfunction due to doxorubicin.

Studies have shown that anthracycline-associated cardiac damage may become clinically more evident in patients who have already received cardiac injury from radiotherapy[15]. Interestingly chest wall radiation and diabetes mellitus could not be identified as a risk factor for doxorubicin induced cardiotoxicity in our study population. This could be due to small sample size of our study.

CONCLUSION

Treatment with doxorubicin chemother-apy is associated with a high degree of clinical and sub-clinical cardiotoxicity. The development of functional cardiotoxicity can be predicted by changes in ejection fraction between echocardiographic studies performed as pre-treatment and after use of anthracyclines. Previous history of coronary artery disease, hypertension and dose exceeding 400 mg/m^2 has been identified as risk factors for development of cardiac dysfunction with the use of doxorubicin. This entails regular monitoring for cardiac dysfunction by echocardiography during and after completion of treatment.

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