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Cardiotoxicity of Doxorubicin –A Prospective Study

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Abstract
Therapeutic strategy in malignancy involves use of various chemotherapeutic agents, radiation and surgery, either alone or in combination. Doxorubicin (Adriamycin) is a powerful drug in the fight against cancer. Cardiotoxicity is a major adverse effect of doxorubicin. Aim of the present study is to evaluate the profile of subacute and chronic cardiac toxicity of doxorubicin used for chemotherapy of various malignant neoplastic disorders. 100 consecutive patients referred to Cardiology Department for evaluation prior to chemotherapy with doxorubicin were enrolled in the study. Baseline and follow-up echocardiographic evaluation was carried out by two dimensional, M mode and Doppler assessment using standard transthoracic views. ECG was carefully examined for any arrhythmias, ST-T changes, conduction defects or other abnormalities. After completion of chemotherapy, patients were called for review for evaluation of cardiac status. Decline in ejection fraction after chemotherapy was observed in 39 patients, ranging up to 36% reduction compared to the baseline value. >10% decline in ejection fraction was observed in 19 patients and >15% reduction in 11 patients. The mean ejection fraction before chemotherapy was 73.95% and the mean value after treatment was 70.15%. The difference between these two was statistically significant (p=0.00039). Effect of adriamycin-based chemotherapy on Tei index was assessed. The mean value of Tei index showed no significant difference before and after treatment (0.45 vs. 0.48, p=NS). Electrocardiographic abnormalities like Brugada pattern (3% cases) and QTc prolongation (3% cases) were observed following administration of doxorubicin.
Keywords: *Cardiotoxicity, Anthracycline, Echocardiography, Ejection fraction.*

Introduction

There has been a steady improvement in the survival rate of cancer patients over the past three decades. This has resulted from the use of novel chemotherapeutic agents, advances in radiation therapy and surgical techniques. Adverse effects related to therapeutic agents cause concern for the patient as well as the treating physician which require early recognition and prompt management.

Streptomyces peucetius is a bacterium species in the genus Streptomyces from which the powerful chemotherapeutic agent doxorubicin (adriamycin) was initially isolated. Doxorubicin is a widely

used drug alone or in combination with other agents for the treatment of several malignant neoplastic disease including breast and esophageal carcinomas, sarcomas, lymphomas and leukemias. The use of anthracycline semiquinone doxorubicin is limited by the risk of delayed development of congestive heart failure, which was first reported by Lefrak et al.[(1)] in 1973. Patients with heart failure and New York Heart Association (NYHA) functional class III–IV were observed to have high mortality which exceeds 50% within 2 years. This has necessitated regular monitoring of cardiac function by echocardiography in anthracycline treated patients for early diagnosis and management of this potentially fatal complication.

Early detection of cardiotoxicity has predominantly relied upon serial cardiac imaging to identify a reduction in left ventricular (LV) function without signs or symptoms of heart failure. Serial measurement of the left ventricular ejection fraction by echocardiography is a relatively less expensive and sensitive noninvasive tool for the diagnosis and follow-up of doxorubicin-induced cardiomyopathy. International oncological guidelines define cardiotoxicity as an absolute reduction in left ventricular ejection fraction (LVEF) ≥5% in symptomatic patients (or ≥10% in asymptomatic patients) from baseline to an LVEF <55%.

Endomyocardial biopsy is another diagnostic test with high specificity in doxorubicin-induced cardiomyopathy, but with the disadvantage that it is invasive and not widely available.

Aim of the Study

To study the profile of subacute and chronic cardiac toxicity of doxorubicin used for chemotherapy of various malignant neoplastic disorders, during follow up for a mean period of six months. The study focus on the following aspects of doxorubicin-based chemotherapy:

1. Effect of doxorubicin therapy on the left ventricular systolic function.
2. Effect of the treatment on left ventricular diastolic function.
3. Change in Myocardial performance index (Tei index) following treatment with doxorubicin.

Material and Methods

One hundred consecutive patients referred to Cardiology Department for evaluation prior to chemotherapy with doxorubicin were enrolled in the study.

Patients with known heart disease or pre-existing LV dysfunction were excluded from the study.

All patients were subjected to baseline evaluation including detailed clinical history and examination of cardiovascular system, resting 12 lead ECG, chest X ray and baseline Echocardiography specifically looking for the various systolic as well as diastolic LV function parameters.

Echocardiographic Evaluation

Baseline and follow-up echocardiographic evaluation was carried out using Philips Envisor Color Doppler Echocardiography machine. Two dimensional, M mode and Doppler evaluation were done using standard transthoracic views. Ejection fraction was calculated by cubed method by M-mode measurements taken in the parasternal long axis view at the level of the tip of the anterior mitral leaflet.

Other Doppler parameters including mitral and pulmonary vein flow velocities were recorded. Pulmonary vein flow velocity was obtained from the right superior pulmonary vein by placing the cursor 1cm from its opening into the left atrium.

Tei index was calculated from the mitral inflow and left ventricular outflow tract signals obtained by placing the Doppler cursor between the anterior mitral leaflet and LVOT on the apical 5 chamber view.

Chemotherapy Regime

Carcinoma breast was the chief underlying malignancy, constituting 60% of the total number of cases. Other major neoplastic disorders were lymphoma, myeloma and sarcoma.

Adriamycin was given intravenously at a dose of 60-80mg/m^2 body surface area over 20 minutes. The dose was repeated at 3 weekly intervals to a maximum of 6 cycles.

Follow-up

After completion of chemotherapy, patients were called for review for evaluation of cardiac status.

The mean duration of follow up was 7.8 months.15 patients expired during the follow up period whereas 20 patients were lost for follow up. Remaining 65 patients were reassessed by history, physical examination, elecrocardiography and echocardiographic evaluation.

ECG was carefully examined for any arrhythmias, ST-T changes, conduction defects or other abnormalities.

Repeat Echocardiographic evaluation after completion of chemotherapy included assessment of LV systolic and diastolic function parameters as well as calculation of Tei index.

Statistical Methods

Quantitative Variables were expressed as mean and standard deviation. Qualitative variables were expressed as frequency and percentage. Pre and post-test comparison of quantitative variables was analysed by paired t test. A p-value <0.05 were considered statistically significant. Data analysis were performed using SPSS ver 11.0.

Results

This was a prospective study in which 100 patients were initially included. Mean follow up period was 7.8 months. During this period 15 patients succumbed to their illness whereas 25 patients were lost for follow-up. Data of the remaining 65 patients is available for analysis.

Patients were of the age ranging from 15-76 years. Maximum numbers of patients were in the 5th and 6th decade. 76% of the total patients initially included were females.

The underlying malignancy was carcinoma breast in 60% of cases, lymphoma in 15%, multiple myeloma in 7%, sarcomas in 6% and other neoplasms in 12%.

Echocardiographic findings

The left ventricular dimensions during diastole (LVIDD) and systole (LVIDS) showed no significant difference before and after chemotherapy. Mean LVIDD before and after treatment remained same (43mm). Similarly, the mean LVIDS before treatment was 27mm and after treatment was 28mm (*p=NS).*

Effect of chemotherapy on LV diastolic function parameters like mitral E/A ratio, isovolumic relaxation time (IVRT) and mitral E-deceleration time were also assessed. Before treatment 46% patients had mitral E/A reversal whereas 65% patients showed E/A reversal following chemotherapy. The mean mitral E/A ratio before treatment was 1.03 *vs.* 0.94 after treatment, the difference was statistically significant (*p=0.03).*

Mitral E deceleration time showed no significant difference before and after treatment. Mean value before treatment was 195.92msec *vs.* 197.75msec after therapy, the difference was not statistically significant (*p=NS).*

Isovolumic relaxation time (IVRT) showed significant increase following chemotherapy with adriamycin. Mean IVRT before treatment was 76.38msec *vs.* 85 msec after therapy (*p=0.0007).*

Effect of adriamycin-based chemotherapy on Tei index was assessed. The mean value of Tei index showed no significant difference before and after treatment (0.45 *vs.* 0.48, *p=NS*).

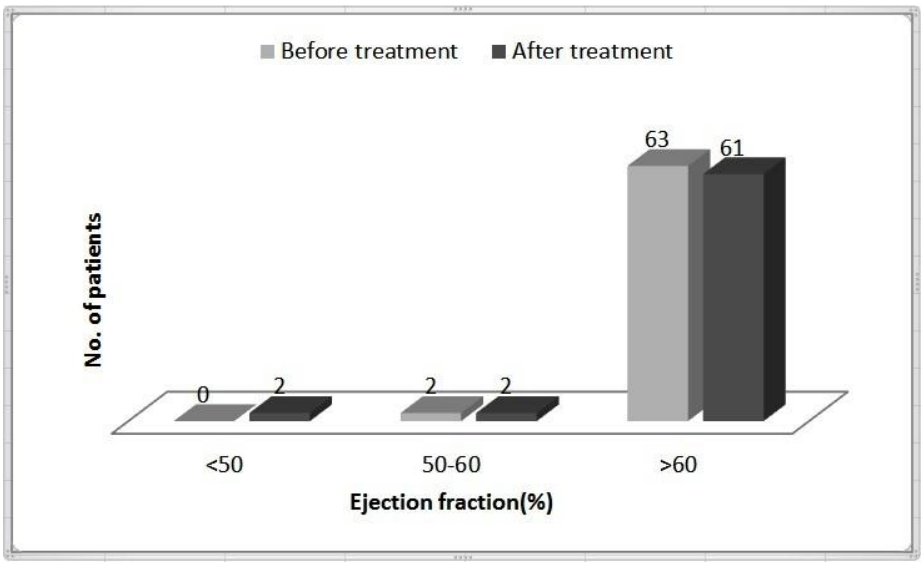
Table 1: Tei index before and after treatment

	Before	After	Diff	t value	*p*
Mean	0.45	0.48	0.023	-1.24	**NS**
SD	0.11	0.12	0.15		

Influence of chemotherapy with adriamycin on LV systolic function was evaluated by Echocrdiography. All the patients had normal ejection fraction before starting chemotherapy (Range 55-88%). Decline in ejection fraction after chemotherapy was observed in 39 patients, ranging up to 36% reduction compared to the baseline value. International oncological

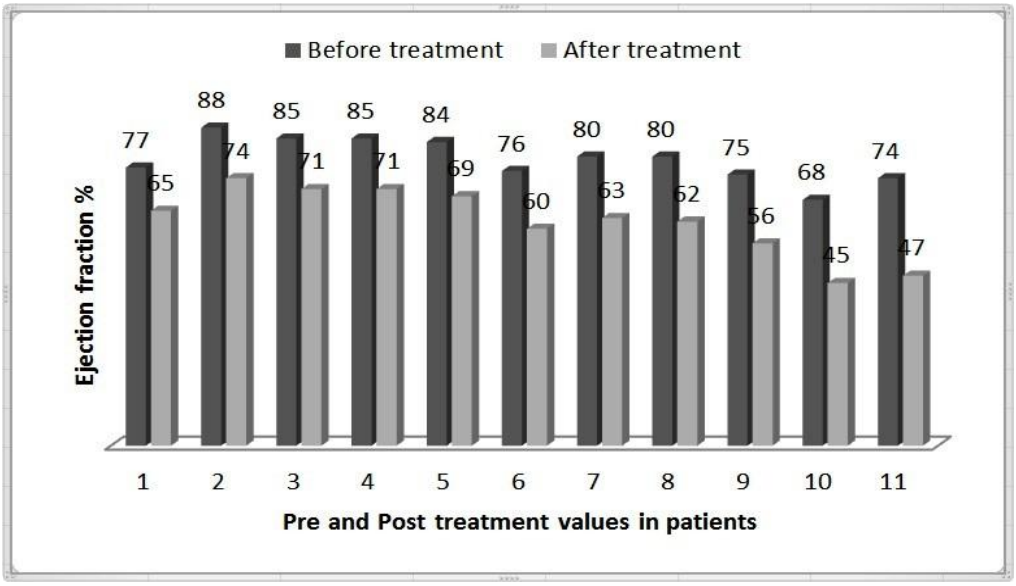
guidelines define cardiotoxicity as an absolute decrease in left ventricular ejection fraction (LVEF) >10 percent associated with a decline below its normal limit of 50%. >10% decline in ejection fraction was observed in 19 patients and >15% reduction in 11 patients. However, reduction in ejection fraction to an absolute value below 50% was observed in only 2 patients, with post-treatment values 45% and 47% (corresponding pre-treatment values being 68 and 74% respectively, relative reduction in EF being 34 and 36%).

Figure 1: Change in Ejection fraction after treatment



The mean ejection fraction before chemotherapy was 73.95% and the mean value after treatment was 70.15%. The difference between these two was statistically significant (p=0.00039). The mean reduction in ejection fraction is 4.68% (95% confidence interval 1.98-7.26). Even though there is decline in ejection fraction, the reduction is not clinically significant.

Figure 2: Magnitude of reduction in patients with maximal decline in Ejection fraction



The maximal decline in ejection fraction was 36.48% (from the baseline 74% to 47% on follow up post chemotherapy).

The change in the mean ejection fraction values before and after chemotherapy was statistically significant (73.95% *vs.* 70.15%, p= 0.00039).

Table 2: Mean LV Ejection fraction before and after therapy

	Mean EF	SD	Paired t value	*P*
Before treatment	73.95	6.84	3.76	0.00039
After treatment	70.15	7.41		

Electrocardiographic abnormalities after chemotherapy

ECG taken during follow up was compared with baseline ECG and fresh changes, if any were noted.

A 47 year old male patient with normal baseline ECG, who was treated for lymphoma developed Type I Brugada pattern in the ECG after chemotherapy. Another patient a 15 year old male, treated for acute leukemia on follow up developed Type II Brugada pattern in the ECG.

Follow up ECG in a 60 year old female showed prolongation of QT interval with a corrected QT of 505msec. and symmetrical T wave inversion in leads V_2-V_6.Prolongation of QT_c (470msec) with coved up ST segment and T wave inversion in V2-V6 was noted in another patient during follow up.

Discussion

Anthracyclines are effective anticancer agents, but their use is limited by dose-dependent cardiotoxicity that may lead to congestive heart failure.

Patients with cardiotoxicity may present with clinical or subclinical heart failure. Risk of early and late subclinical cardiotoxicity were evaluated in several studies[1,2]. One major predictor of development of cardiotoxicity is higher cumulative dose of the drug[3].

Only a few studies have evaluated the incidence of late anthracycline-induced clinical heart failure in long-term survivors. In a meta-analysis by Swain et al[4], a group of 630 patients who were randomized to a doxorubicin-plus placebo arm of three Phase III studies, two studies in patients with breast carcinoma and one study in patients with small cell lung carcinoma, estimated cumulative 26% of patients would experience doxorubicin-related CHF at a cumulative dose of 550 mg/m2. The study shows that doxorubicin-related CHF occurs with greater frequency and at a lower cumulative dose than previously reported.

In a retrospective analysis, cardiac failure developed at a cumulative doxorubicin dose of 400 mg/m2 in 3% patients, increasing to 7% at 550mg/m2 and to 18% at 700mg/m2[5].

In a retrospective analysis, Von Hoff et al[5] identified total cumulative dose as a major risk factor for doxorubicin-related CHF. The estimated cumulative percentage of patients who developed CHF at a cumulative doxorubicin dose of 400 mg/m2 was 3%, increasing to 7% at 550mg/m2 and to 18% at 700mg/m2.

Hequet et al[6] analyzed a group of patients who previously received doxorubicin-based chemotherapy for lymphoma. Echocardiograms were performed at least 5 years after therapy with anthracyclines. Of 141 assessable patients (median age, 54 years; median cumulative dose of doxorubicin, 300mg/m2), only one developed CHF. Criteria of subclinical cardiomyopathy were found in 39 patients.

The cumulative incidence of cardiac failure and the risk factors were assessed by Kremer et al[7] in a cohort of 607 children who had been treated with anthracyclines. The cumulative incidence of A-CHF was 2.8%, after a mean follow-up time of 6.3 years and a mean cumulative dose of anthracyclines of 301 mg/m2.

Thirty-nine survivors of childhood malignancy were examined by Poutanen et al[8]. The mean time from the diagnosis was 8.6 (3.9 to 16.8) years and between cardiac evaluations was 4.1 (3.3 to 5.1) years. Left ventricular contractility was found to decrease slowly even years after cardiotoxic cancer therapy in children.

Electrocardiographic Abnormalities

Antthracycline therapy is known to be associated with electrocardiographic abnormalities. Out of the 65 patients, four showed ECG changes in the form of Brugada pattern, pathological Q waves

suggestive of MI and prolongation of QT interval as well as corrected QT interval.

Previous studies designed in adult patients have suggested that anthracyclines could cause various electrocardiographic abnormalities including T-wave inversion, ST segment elevation or depression, decreased QRS voltage, prolonged QT interval and arrhythmias including AV block, and supraventricular and ventricular arrhythmias[9]. Acute cardiotoxicity described as electrocardiographic abnormalities and arrhythmias occurs in 11-41% of patients treated during or after the administration of doxorubicin[1,10]. The acute cardiac toxicities such as electrocardiographic abnormalities and arrhythmias after doxorubicin infusion are associated with the release of vasoactive substances[11]. Doxorubicin-associated arrhythmia can also occur many years after the completion of the therapy. This effect usually correlates with chronic impairment of left ventricular function.

Doxorubicin has not so far been implicated as a causative agent of brugada ECG pattern. Two out of the 65 patients in the present study showed Brugada pattern in the ECG following chemotherapy with adriamycin. One patient had Type I Brugada pattern while the second patient had Type II Brugada pattern. Both patients did not have any symptoms attributable to the ECG abnormality nor did they fulfill other criteria required for diagnosis of Brugada syndrome. However considering the low prevalence of Brugada syndrome in the general population, the above observation showing 3.1% incidence of Brugada ECG pattern following adriamycin based chemotherapy is statistically significant.

Prolongation of the QT interval was another observation found in patients receiving adriamycin. Two out of the 65 patients in the study group showed QT prolongation after chemotherapy. One patient had a corrected QT interval (QT_c) of 505 msec while the other patient had a QT_c of 470 msec.

Acute cardiotoxicity described as electrocardiographic abnormalities and arrhythmias occurs in 11-41% of patients treated during or after the administration of doxorubicin[12]. Although these are usually non-specific electrocardiographic repolarization abnormalities, there can be serious rhythm disturbances that are associated with mortality in rare instances.

Conclusion

This is a prospective study of 65 consecutive patients treated with adriamycin for the treatment of various malignant neoplastic disorders including carcinoma breast, lymphoma, multiple myeloma and sarcomas and followed up for mean period of 7.8 months. Decline in ejection fraction to an absolute value below 50% with >10% relative reduction compared to the baseline value was observed in only 2 patients. The mean ejection fraction before chemotherapy was 73.95% and the mean value after treatment was 70.15%. The difference between these two was statistically significant (p=0.00039). Adriamycin was found to have variable influence on different diastolic function parameters. There was significant fall in Mitral E/A ratio. Mitral E/A reversal were observed in 46% patients before starting chemotherapy and in 65% cases after treatment. The mean reduction was 0.088 which is statistically significant (p=0.03).There was significant increase in Isovolumic Relaxation Time (IVRT), the mean difference being 8.62 which is statistically significant (p=0.0007). Mitral E-Deceleration time showed no significant change following treatment. No significant change in Tei index (mean value 0.45 *vs.* 0.48 before and after treatment respectively, p=NS). Electrocardiographic abnormalities like Brugada pattern (3% cases) and QTc prolongation (3% cases) were observed following administration of doxorubicin.

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