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Original Article

An Assessment of Cardiac Dysfunction in Cancer Patient Receiving Chemotherapy: A Hospital-Based Non-Invasive Study

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ABSTRACT

Objectives: To assess cardiac dysfunction in cancer patients receiving anthracycline based chemotherapy and to detect cardiac dysfunction in the initial stage.

Materials and Methods: An open labelled prospective single site study of assessment of cardiac dysfunction in patient receiving chemotherapy.

Results: Post chemotherapy, more number of patients had evidence of cardiac dysfunction on the basis of history and physical examination but statistically significant association was found only in fatigability, pallor, oedema and rales. Among the users or Doxorubicin and Epirubucin based chemotherapy, cardiac dysfunction was observed in 19.56% (n = 9) and 4.3% (n = 2) respectively. Among those on Doxorubicin, in the cumulative dose range of 510-600 mg, two patients (20%) had clinical cardiac dysfunction and one patient (10%) had subclinical cardiac dysfunction.

Conclusion: Cardiac dysfunction is one of the dreaded complications of chemotherapy agent anthracycline. It adds to the co morbidity of cancer. Small increase in the risk of common and serious adverse health events, such as cardiac disease, has important public health implications. Effective steps have taken at proper time; can prevent the onset or exacerbation of these complications.

Keywords: Chemotherapy, Cardiomyopathy, 2D echocardiography, Doxorubicin, Cardiac dysfunction

INTRODUCTION

Recent advances in cancer management have improved long-term survival. Increased longevity has been accompanied by a rise in the frequency of age-related cardiovascular (CV) disease and treatment-related cardiotoxicity. Chemotherapy-related left ventricular dysfunctions have historically been considered resistant to conventional therapy and carry a poorer prognosis than other cardiomyopathies. More recent data suggest that selected forms of chemotherapy-related cardiomyopathy are reversible to some degree but response is dependent on early detection and prompt intervention. This challenges us to develop more sophisticated risk stratification and monitoring strategies that include symptom detection, and non-invasive imaging. This paradigm also suggests that a multidisciplinary team of cardiologists and oncologists may provide more comprehensive care to this complex patient population.

Modern advancements in cancer treatment over the past few decades in cancer have resulted in improved survival in cancer patients. As a result, the effect of cancer therapy on other organ systems such as the heart is more likely to become clinically relevant and lead to cardiotoxicity. In early 1970, anthracycline was shown to exhibit cumulative dose-related cardiac dysfunction.[1] Later on, von Hoff *et al*.[1] found that cardiac function in more than 2000 anthracycline-treated patients demonstrated the relative safety of low cumulative dosages and dramatically increased incidence of congestive heart failure (CHF) at higher cumulative dosages. Consequently, the use of newer chemotherapy drugs and combination leads to improvement in patient survival from cancer but simultaneously resulted in a sharp rise in the incidence of heart failure in cancer patients. Recently, many cancer patients have a risk of developing heart disease and heart failure higher than the risk of cancer recurrence.[2] The American College of Cardiology or American Heart Association guidelines define patients receiving chemotherapy as stage "A" heart failure.[3] Chemotherapy can result in left ventricular dysfunction or diastolic dysfunction ranging from mild to severe reversible or irreversible life-threatening heart failure.

The CV toxicity of cancer chemotherapeutic agents is dysrhythmias, cardiomyopathic CHF, pericardial disease, and peripheral vascular disease. Chemotherapy-related cardiac dysfunction of greatest concern for cardiologists and oncologists is those directly involving myocardium. Cardiac toxicity associated with chemotherapy can range from asymptomatic subclinical abnormality, including electrocardiographic changes and temporary left ventricular ejection fraction (LVEF) decline to life-threatening congestive cardiac failure. Cardiac dysfunction if detected early can be prevented by early initiation of treatment.

Aims and objectives

The aims of this study are as follows:
1. To assess cardiac dysfunction in cancer patients receiving anthracycline-based chemotherapy
2. To detect cardiac dysfunction in the initial stage.

MATERIALS AND METHODS

Study design

1. This was an open-labelled prospective single-site study of assessment of cardiac dysfunction in the patient receiving chemotherapy
2. Cardiac dysfunction was assessed by analysis of clinical profile (Cardiac risk factors, symptomatology, and physical examination), electrocardiogram (ECG), chest X-ray PA view, and 2D echocardiography (ECHO) pre- and post-chemotherapy
3. This study was conducted from August 2010 to October 2012.

Study population

Fifty patients aged 12–70 years with confirmed histopathological diagnosis of malignancy and being planned for chemotherapy treatment were considered for enrolment in this study.

Study site

The study was conducted at a tertiary care hospital with permission from the Institutional Ethics Committee and after obtaining informed consent from the patient.

Inclusion criteria

The following criteria were included in the study:
1. Age >12 years of either sex.
2. Patients requiring 3–6 cycles of chemotherapy in diagnosed cases of various solid tumours and haematological malignancies with potential cardiotoxicity.

Exclusion criteria

The following criteria were excluded from the study:
1. Age <12 years and more than 70 years
2. Those unwilling
3. Coexisting cardiac disease or cardiac dysfunction pre-chemotherapy (Echo-based)
4. Requiring concomitant thoracic radiation therapy.

Methodology

After their enrolment in the study, all the persons were evaluated for:
1. General information and history of any risk factor for CV disease such as smoking, tobacco use, hypertension, diabetes mellitus, previous history of cardiac event or stroke, previous history of cardiac investigations or surgery, and family history
2. History of symptoms suggestive of cardiac disease(palpitation, dyspnoea on exertion, angina on exertion (AOE), fatiguability, and features suggestive of heart failure) were noted pre- and post-chemotherapy
3. Histories of other comorbidities were noted
4. A thorough general and systemic examination was carried out
5. Venous blood samples were taken for staging and management purposes (Complete blood count, serum electrolytes, liver enzymes, lactate dehydrogenase, serum albumin, lipid profile, fasting/postprandial blood sugars, urea, and creatinine)

6. Other investigations included electrocardiograph and chest X-ray postero-anterior view
7. Echocardiography was done pre- and post-chemotherapy to look for any chamber dilation, left ventricular ejection fraction, valvular lesion, left ventricular hypertrophy, and regional wall motion abnormality.

Instrument features: 2D echocardiography with colour Doppler, continuous wave Doppler with the transesophageal facility, and having a transducer of 2.5 MHz with video cassette recorder, printer, and ECG gating facilities of Hewlett Packard make.

Various modes used in Echocardiography are the following:

a. M Mode ECHO
b. Two-dimensional ECHO
c. Doppler ECHO
   i. Pulse wave
   ii. Continuous Doppler
d. Colour Doppler.

8. Other relevant investigations such as stress thallium and coronary angiography were carried out for management purposes when indicated.

Diagnostic criteria

Diagnosis of CHF or clinical cardiac dysfunction requires the simultaneous presence of at least two major criteria or one major criterion in conjunction with two minor criteria.[4] Major criteria: Paroxysmal nocturnal dyspnoea, neck vein distention, rales, radiographic cardiomegaly (increasing heart size on chest radiography), acute pulmonary oedema, S3 gallop, increased central venous pressure (>16 cm H_2O at right atrium), hepatojugular reflux and weight loss >4.5 kg in 5 days in response to treatment. Minor criteria: Bilateral ankle oedema, nocturnal cough, dyspnoea on ordinary exertion, hepatomegaly, pleural effusion, decrease in vital capacity by one-third from maximum recorded and tachycardia (heart rate >120 beats/min.) cardiac dysfunction:[5] Definitive or probable cardiac death, heart failure with New York Heart Association (NYHA) class symptoms and subclinical cardiac dysfunction (NYHA class I) with the decline in LVEF of 10% or more from baseline to a level of 50% or less.

Quantitative data

a) Student's *t*-test (unpaired) was used as a test of significance.

Qualitative data

a. Pearson's Chi-square test and McNemar test are applied to test the relationship between categorised independent and dependent variables
b. If the expected number in the cell was below 5 in a table, Fisher's exact test (Exact Two-sided) was used

Note

a) $P < 0.05$ is considered statistically significant.

RESULTS

A total of 50 patients were enrolled in the study, who received 3–6 therapeutic cycles each. Among these 50, two patients were lost to follow-up and two patients received radiation therapy. Hence, these were excluded from the study. In these patients, the analysis of cardiac dysfunction was done pre- and post-chemotherapy. The remaining 46 patients constituted 25 with breast cancer, 16 non-Hodgkin's Lymphoma, four Hodgkin's lymphoma, and one patient with stomach cancer. Cardiac risk factors such as hypertension, type II diabetes mellitus, obesity, dyslipidaemia, and smoking were present in 17 patients before the start of chemotherapy. Few patients among these had more than one risk factor. About 26% of the population was obese. About 73% of patients with cardiac dysfunction had one or more cardiac risk factors. There was statistically no significant association observed in breathlessness on exertion (BOE) when compared pre-chemotherapy versus post-chemotherapy with $P = 0.332$. The symptom of AOE was compared pre- and post-chemotherapy and the association was statistically non-significant with $P = 0.50$. The symptom of palpitation was compared pre- and post-chemotherapy and the association was statistically non-significant with $P = 1.000$. Fatigability was noted in a significant number ($n = 8$) of patients pre-chemotherapy as well as ($n = 13$) post-chemotherapy and the association was statistically significant with $P = 0.021$. The cardinal symptoms of CV system involvement, namely, BOE, AOE, fatigability, and palpitation were studied in pre- and post-chemotherapy. Although the number of patients having symptoms increased post-chemotherapy, the difference was statistically significant only in the case of fatigability. Post-chemotherapy, more number of patients had evidence of cardiac dysfunction on the basis of history and physical examination but a statistically significant association was found only in fatigability, pallor, oedema, and rales and a total number of patients having clinical heart failure were 10% ($n = 5$) of the study population. The most common ECG changes observed post-chemotherapy were ST-T changes in four patients out of a total of six patients having ECG alteration. These four patients further underwent stress thallium and coronary angiography revealing no abnormality. Cardiac arrhythmia was present in two patients in the form of atrial fibrillation (AF) with controlled ventricular rate and sinus bradycardia. However, a statistically significant association for ECG alterations was not established. Chest X-ray changes were assessed for cardiomegaly. There was a statistically non-significant association between pre- and post-chemotherapy on chest X-rays in terms of cardiomegaly. Post-chemotherapy cardiac dysfunction in terms of decrease in EF more than

10% was observed in 24% (n = 11) of patients; out of these, 11% (n = 5) were clinical and 13% (n = 6) were subclinical. Symptomatic cardiac dysfunction occurred in 11% (n = 5) patients; out of these, 6.5% (n = 3) patients were in the TAC chemotherapy receiving group and 4.3% (n = 2) in the CHOP chemotherapy receiving group and all were receiving doxorubicin dose range from 300 to 540 mg. The distribution of patients receiving doxorubicin and epirubicin-based chemotherapy was 73.91% (n = 34) and 23.91% (n = 11), respectively. Out of this, cardiac dysfunction was observed in 19.56% (n = 9) and 4.3% (n = 2), respectively. The comparison of diastolic dysfunction between two chemotherapy agents was statistically not significant as per Fisher's exact test (P = 0.701). Doxorubicin was given in the cumulative dose of 270–375 mg for 16 patients, 450–480 mg for eight patients, and a cumulative dose of 510–600 mg for ten patients. Among these, in 270–375 mg cumulative dose, 1 patient (6.2%) had clinical cardiac dysfunction while 3 patients (18.7%) had subclinical cardiac dysfunction. In the cumulative dose of 450–480 mg, 2 patients (25%) had clinical cardiac dysfunction. In the cumulative dose range of 510–600 mg, 2 patients (20%) had clinical cardiac dysfunction and 1 patient (10%) had subclinical cardiac dysfunction.

DISCUSSION

Cardiac dysfunction is one of the dreaded complications of the chemotherapy agent anthracycline. It adds to the comorbidity of cancer. The small increase in the risk of common and serious adverse health events, such as cardiac disease, has important public health implications. Effective steps taken at the proper time; can prevent the onset or exacerbation of these complications. This study was carried out to detect cardiac dysfunction in patients receiving chemotherapy. In this study, 46 patients receiving chemotherapy for breast cancer, non-Hodgkin's Lymphoma, Hodgkin's Lymphoma, and stomach cancer were studied. They received anthracycline-based chemotherapy which included doxorubicin and epirubicin. Different risk factors were studied such as hypertension, type 2 diabetes mellitus, obesity, dyslipidaemia, and smoking. About 73% of patients with cardiac dysfunction had one or more cardiac risk factors. Similar risk factors were studied by Ryberg *et al.*[6] and Piccirillo *et al.*[7] which showed a significantly increased risk of cardiac dysfunction in the presence of these risk factors. Patients were 16–70 years of age with a mean age of 36 years and 51 years, respectively, for males and females. The mean age of the total study population was 46.27 ± 14.71 years. Mean age in Khattry *et al.*[8] was 44 years. There was no statistically significant association of cardiac symptoms such as BOE, AOE, and palpitation pre- and post-chemotherapy. However, there was an increase in the number of symptoms in the post-chemotherapy group. The increase in fatigability in the post-chemotherapy group was statistically significant. This may be due to side effects of chemotherapy agents or associated malignancy. In this study, ECG showed ST and T wave changes in 8.6% (n = 4) patients. On further evaluation, coronary angiography in two patients and stress thallium in two patients were done. There was no evidence of coronary artery disease. Cardiac arrhythmia such as AF and sinus tachycardia was present in 4.3% (n = 2) patients. Similar non-specific ST and T wave changes had been described by Galderisi *et al.*[9] 5-Fluorouracil has been associated with ECG signs of myocardial ischemia and less frequently with arrhythmias as studied by Hrovatin *et al.*[10] In Shan *et al.*[11] the study, chronic anthracycline cardiotoxicity manifests often as life-threatening arrhythmias. There was no significant association of cardiomegaly on chest X-rays in pre- and post-chemotherapy received patients. No other significant X-ray changes were present. This observation was consistent with the study by Khattry *et al.*[8]

In this study, five out of 46 patients (11%) who received doxorubicin were clinically diagnosed with heart failure. Minow *et al.*[12] also reported heart failure in 0.4–9% of patients who received doxorubicin. In Khattry *et al.*,[8] clinical heart failure was observed in 3% of the study population. This may be attributed to the average age in our study population being more; also, more cardiac risk factors were present in the study population. Khattry *et al.*[8] studied cardiotoxicity in low cumulative doses of doxorubicin.

The incidence of subclinical cardiac dysfunction in this study was 13% (n = 6). In our study, diagnosis of subclinical cardiac dysfunction was done on the basis of falls in LVEF more than 10% or LVEF <50% as measured by 2D echocardiography. In Khattry *et al.*[8] study, subclinical cardiac dysfunction was present in 27% of patients. Agarwala *et al.*[13] observed that 40% of children receiving doxorubicin-based chemotherapy developed subclinical cardiac dysfunction. Mohta *et al.*[14] observed that 30% of the paediatric patients had significant cardiac dysfunction on echocardiographic evaluation at a mean cumulative dose of 365 mg/m^2. Similarly, in Dresdale *et al.*,[15] out of 87 asymptomatic patients who received 430 mg/m^2 of doxorubicin 21% showed abnormal LVEF at rest by radionuclide angiogram. Subclinical cardiac dysfunction was low in our study may be due to different assessment methods, that is, we measured LVEF by echocardiography while another used radionuclide angiogram. In our study, 54% (25) of patients had breast cancer. Out of this, cardiac dysfunction was present in 20% (n = 5). Among these five patients, two got Docetaxel, doxorubicin and cyclophosphamide (TAC), one received doxorubicin and cyclophosphamide (AC), and two received 5 fluorouracil, epirubicin and cyclophosphamide (FEC) chemotherapy. In our study, the distribution of patients receiving doxorubicin

and epirubicin-based chemotherapy was 73.91% (n = 34) and 23.91% (n = 11), respectively. Out of these patients, cardiac dysfunction was observed in 26.47 (n = 9 out of 34) and 18.18 (n = 2 out of 11), respectively. The comparison of cardiac dysfunction between two chemotherapy agents was statistically not significant. There was significant cardiac dysfunction observed in different studies as discussed in a meta-analysis by Smith *et al*.[16]

In this study, we compared the cumulative dose of doxorubicin in the range of 270–375 mg, 450–480 mg, and 510–600 mg. It was observed that in the cumulative dose range of 270–375 mg, 6.2% had clinical cardiac dysfunction and 18.7% had subclinical cardiac dysfunction. In the dose range of 450–480 mg, 25% had clinical cardiac dysfunction. In the cumulative dose of 510–600 mg, 20% had clinical cardiac dysfunction and 10% had subclinical cardiac dysfunction. In the study by Khattry *et al*.,[8] 16% developed subclinical cardiac dysfunction at the cumulative dose of 300 mg and 28.8% developed clinical cardiac dysfunction at the cumulative dose of 450 mg. These findings were in concordance with our study in the mentioned cumulative dose range. Lefrak *et al*. studied cardiac dysfunction in the cumulative dose of 500–550 mg, 551–600 mg, and more than 600 mg.[17] He noted that the clinical cardiac dysfunction increased from 4% to 18% when the cumulative dose increased from 500 mg to 600 mg.

Limitation

This study is limited by the small sample size and lack of a control group of healthy individuals. This makes it difficult to estimate the influence of age and other confounding factors and to relate our findings to the general population. 2D echocardiography has the disadvantage of LVEF assessment as it is image quality dependent and subject to certain measurement variability.

CONCLUSION

Modifiable risk factors such as hypertension, type 2 diabetes mellitus, obesity, smoking, and dyslipidaemia predispose cancer patients to increased cardiac toxicity of the chemotherapeutic drugs/regimens such as anthracycline. Steps for optimal control of the risk factors and modified cancer chemotherapy regimens if possible should be adopted to prevent cardiac toxicity. Non-invasive investigations such as echocardiography should be freely used at various intervals of cancer treatment to detect early cardiac dysfunction.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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