Case Report

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Chemotherapy induced cardio toxicity with doxorubicin and cyclophosphamide in breast cancer patient - a case report

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Abstract

Breast cancer is the most commonly occurring neoplasm in women, which can be curable as well as can reduce the recurrence of cancer, with the help of various multidisciplinary approaches and thereby decrease the morbidity as well as mortality. Chemotherapy is a well-defined therapeutic approach for breast cancer, but cardiotoxicity is the most potential side-effect associated with chemotherapeutic drugs. Doxorubicin, along with cyclophosphamide, produces serious cardiotoxicity due to potential drug interaction. It is a case of a 63-year-old female patient post-menopausal with k/c/o type 2 diabetic Mellitus on medication. Clinically and radiologically, she was diagnosed with carcinoma left breast (IMC grade III, TNBC, CT2N0Mx). She underwent breast-conserving surgery (BCS) or lumpectomy without reconstruction. The HPE report suggestive of infiltrating mammary carcinoma NST grade 3. She was currently on adjuvant chemotherapy IInd cycle. Post chemotherapy, she was admitted with complaints of chest discomfort and chest pain. Screening ECHO showed grade I diastolic dysfunction and also the cardiac enzymes and cardiac marker troponins I was found to be elevated. She had undergone CAG for risk stratification. She was thought to have chemotherapy-induced cardiotoxicity associated with atypical chest pain and was advised medical follow up. Doxorubicin and cyclophosphamide-induced cardiac dysfunction and associated adverse events can be prevented or minimized with dose modification, use of cardioprotective drugs, identifying patient-related risk factors and regular cardiac monitoring of the patient receiving chemotherapy with doxorubicin and cyclophosphamide in breast cancer treatment.

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INTRODUCTION

Breast cancer is one of the most common tumours among women worldwide. Breast cancer can be effectively curable as well as can limit the disease recurrence with the help of multidisciplinary approaches like surgery, chemotherapy, radiation therapy and breast reconstruction. Chemotherapy is a highly effective therapeutic approach for several solid tumours (Gillespie *et al.*, 2012). Potential cardiovascular complications and cardiotoxicity are the significant side effects associated with

chemotherapeutic agents, which may increase the morbidity and mortality among cancer patients (Du and Goodwin, 2001). The anthracycline class of cytotoxic antibiotics uses are limited due to their cardiotoxic effect, especially doxorubicin and epirubicin. Other chemotherapeutic agents like 5-fluorouracil, mitomycin, trastuzumab, paclitaxel, ifosfamide, and cyclophosphamide are also cause irreversible myocardial damage (Dow *et al.*, 1993). Anthracycline induced cardiotoxicity ranges from subclinical cardiomyopathy to congestive heart failure and even to cardiac death. Chemotherapeutic agents like cyclophosphamide produce cardiotoxicity due to potential drug interaction in combination with anthracyline. The recommended dosage range of doxorubicin in combination therapy is 45-60 mg/m^2 every three weeks. Chemotherapy-induced cardiotoxicity is seen in two forms (Gillespie *et al.*, 2012) acute or subacute cardiotoxicity, which can occur at any time after induction of chemotherapy or up to 2 weeks after termination of chemotherapy usually accompanied by abnormalities in ventricular repolarization, ECG changes, acute coronary syndrome, acute heart failure and pericarditis or myocarditis-like syndrome. (Du and Goodwin, 2001) Chronic toxicity can occur up to 1 year or after one year of termination of chemotherapy with the clinical finding of asymptomatic left ventricular dysfunction, which leads to cardiac damage and cardiac death (Pai and Nahata, 2000; Singal and Iliskovic, 1998). We here report a case of cardiotoxicity after few days of chemotherapy with doxorubicin and cyclophosphamide.

Case Presentation

It is the case of a 63-year-old post-menopausal female patient with k/c/o type 2 diabetic Mellitus on medication. During her routine comprehensive health check-up found to have a mass in the left breast. She was asymptomatic and referred to the gynaecological oncology department for further evaluation and management. A mammogram was done on 28/06/2019, which showed healthy right mammographic study with no suspicious lesions on tomosynthesis. But the left breast lesion with features highly suspicious of malignancy as described needs further evaluation with ultrasound followed by ultrasound-guided biopsy and FNAC of axillary lymph node, BI-RADS 5 (Breast Imaging-Reporting and Data System). On USG correlation, unifocal left breast mass with suspicious features, BI-RADS 5 lesion measuring 3.4× 3.0 cm overlying sin retraction noted. Both axillae show lymph nodes with a diffuse cortical thickness of 0.4 cm and having reactive features, but the left axilla shows a round lymph node of 1.5 cm. She underwent Immunohistochemistry evaluation, which showed ER-negative, PR- weak positive in 5% of cells, Her2- negative, Ki67- 30%.

Further evaluation of US-guided left breast biopsy suggestive of infiltrating mammary carcinoma grade III, MBR score (3+3+2=8), and mild peritumoral lymphocytic infiltrate. Clinically and radiologically she was diagnosed as having carcinoma left breast (IMC grade III, TNBC, CT2N0Mx) and was decided to go ahead for breast-conserving surgery (BCS) or lumpectomy without reconstruction. After all pre-operative evaluation and informed consent of the patient, she underwent Wide Local Excision + Sentinel LSG +Sentinel LN Biopsy (left breast) on 12/7/2019. After stabilizing the vitals, she was discharged.

The HPE report suggestive of infiltrating mammary carcinoma NST grade 3 with medullary like features pT2 N0M0. She was currently on MDTB (multidisciplinary tumour boards) adjutant chemotherapy IInd cycle with inj. Palonosetron 0.25 mg + inj. Dexona 12 mg, inj Adriamycin 96 mg, inj. Cyclophosphamide 960 mg last done on 12/08/2019 + radiation therapy+ hormone therapy. Later on 25/08/2019, she was admitted with complaints of chest discomfort and chest pain. Serial ECG did not show any changes. Screening ECHO showed no RWMA with good LV systolic function, grade I diastolic dysfunction, no MS/MR, no AS/AR, trivial TR, no PAH, good RV function. Further evaluation with TMT showed stressed up to 6mts on 'brucc' protocol and attained MPHR of 160 bpm with a workload of 7 METs. IMP – test negative for ischemia. Cardiac enzymes (CK MB -46.23 ng/ml, creatine kinase (CK)- 480.0 U/L) and cardiac marker Trop T (1. 16 ng/ml) were found to be elevated. She was treated as ACS NSTEMI with inj. Fondaparinux, antiplatelets, statins and other supportive medications. Inj. Magnex was initiated because of elevated counts and was continued for four days. Because of this, she was planned for CAG as risk stratification. Medical oncology consultation was taken for clearance for the procedure, and she cleared for the same. After PAC evaluation, she was taken for CAG on 27/08/2019, which revealed mild CAD, type 1 LAD and large LCx vessel, mild non-flow-limiting disease, sinus rhythm, no CHF. She tolerated the procedure well. Postoperatively she was shifted to CCU for observation. She was diagnosed to have chemotherapy-induced cardiotoxicity associated with atypical chest pain and was advised medical follow-up. She was discharged in a hemodynamically stable state. On 4/9/2019, she was started with chemotherapy using inj. Dexona 20 mg IV in 100 ml NS + inj. Ondansetron 8 mg, Inj paclitaxel 280 mg in 1 bottle NS through codan set

over 3 hrs and Tab. megestrol 40 mg for two weeks. Post-chemotherapy cardiac function and counts are normal—patient well-tolerated chemotherapy.

DISCUSSION

Cardiotoxicity is a dose-limiting and potential complication associated with breast cancer treatment using anthracycline-based chemotherapy and cyclophosphamide, which lead to devastating cardiac events. Studies suggest that patients who had pre-existing cardiac disease and received chemotherapy were more likely to experience cardiac disease subsequently (Du and Goodwin, 2001). Our patient had no history of previous cardiac disease. Doxorubicin based chemotherapy had a higher risk of cardiotoxicity may be more pronounced in the elderly population with an age of more than 65 years old (Swain *et al.*, 2003). Under the certain clinical condition, cyclophosphamide causes acute cardiac dysfunction, severe cardiotoxicity and cardiac death due to overdose of cyclophosphamide, in combination with cardiotoxic agents like doxorubicin or previous treatment with anthracyclines. Research suggests that patients on treatment with doxorubicin along with cyclophosphamide experienced toxicity immediately after treatment (Perez *et al.*, 2004).

It is reported that increased risk of cardiotoxicity and hemorrhagic cystitis when doxorubicin is given with cyclophosphamide. Risk of cardiotoxicity induced by anthracycline is mainly related to the cumulative dose of drug administration, infusion rate or can completely independent of dose, advanced age, sex (mainly female population are more vulnerable to cardiotoxicity), prior mediastinal radiation, pre-existing heart disease and hypertension (Bhanumathi *et al.*, 1992; von Hoff *et al.*, 1979). The chemotherapy-induced cardiac events may include mild blood pressure change, thrombosis, ECG changes, arrhythmias, myocarditis, pericarditis, myocardial infarction, cardiomyopathy, cardiac failure (left ventricular failure) and congestive heart failure.

Post cardiac monitoring is required to reduce cardiotoxicity after chemotherapy. Regular screening must be done for evidence of cardiomyopathy and related cardiac dysfunction induced by chemotherapy which can be diagnosed by chest x-rays, ECG, and also LV (left ventricular) EF (ejection fraction), fractional shortening and 2- dimensional, M-mode and colour Doppler echocardiographic examination which is used to assess left ventricular systolic function (Schwartz *et al.*, 1987). The mechanism of doxorubicin-induced cardiotoxicity due to necrosis and apoptosis of cardiac myocytes followed by myocardial fibrosis, co-administration of cyclophosphamide aggravate the toxicity due to potential drug interaction with doxorubicin and results in endothelial dysfunction, and coronary artery vasospasm leads to LV dysfunction and pericarditis. The elevated troponin (I and T) after chemotherapy is related to increased risk for developing cardiotoxicity. Biomarkers like B – type natriuretic peptide and cardiac troponins are used for monitoring myocardial damage in patients receiving breast cancer chemotherapy. Elevated troponin I $\geq$0.5 ng/ml 12-72 hours after chemotherapy is a potent indicator of poor cardiac outcome and left ventricular dysfunction during post-chemotherapy (Cardinale *et al.*, 2004).

Recent studies showed early carvedilol, enalapril(angiotensin-converting enzyme) administration and also the anti-oxidant like probucol and vitamin E, gave protection against chemotherapy-induced toxicity and prevented adverse effects (Cardinale *et al.*, 2006). But it is established based on a limited number of clinical trials. Dexrazoxane is the only US food, and drug administration(FDA) approved cardio-protective drug reduces the risk of chemotherapy-induced cardiotoxicity and associated cardiac adverse event in patients with breast cancer undergoing anthracycline chemotherapy with or without cyclophosphamide and underlying heart disease. Also, cancer response, overall survival and progression-free survival were not affected by dexrazoxane (Macedo *et al.*, 2019). Dexrazoxane readily penetrates through the cell membrane and acts as an intracellular chelating agent and produces cardioprotection by chelation of intracellular iron which may decrease the anthracycline-induced free radical formation and reduce the chance for CHF and associated cardiac events (Swain *et al.*, 2003).

Studies suggest that dexrazoxane is administered as slow intravenous injection or rapid infusion not more than 30 minutes before doxorubicin administration, and the recommended dose is ten times more than that of scheduled doxorubicin dose. Liposomal formulation of anthracyclines shows less cardiotoxicity with improved index and spectrum of activity of doxorubicin in therapeutic use. Research showed doxorubicin when administered as a prolonged, continuous intravenous infusion over more than 48-96 hour found to be less cardiotoxic and per day dose greater than 50 mg/m^2 appears to be a two-fold increased risk for toxicity (Legha, 1982). The patient should be evaluated before starting chemotherapy for assessing cardiovascular risk for the prevention of cardiotoxicity.

CONCLUSIONS

Cardiotoxicity is the most common adverse effect associated with anthracycline-based chemotherapy in combination with cyclophosphamide will aggravate the cardiotoxic effects which may adversely affect the clinical outcome of treatment, quality of life and patient survival. To prevent or to minimize the cardiotoxicity associated with breast cancer chemotherapy, clinicians should consider the risk factors before chemotherapy, which include dose modification, rate of administration, advanced age, gender and underlying heart disease. It is essential to monitor the cardiac functions of the patient during and following post-chemotherapy with doxorubicin and cyclophosphamide, or cardioprotective drugs can be administered before doxorubicin and cyclophosphamide chemotherapy. It is mandatory to develop more specific strategies for the prevention, diagnosis and treatment of chemotherapy-induced potential cardiotoxicity as well as effective management of cardiovascular complications.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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