## Original Research Article

# Retrospective study of chemotherapy induced cardiotoxicity from a tertiary cancer centre in South India

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**ABSTRACT**

**Background:** Ever increasing therapeutic modalities in treatment of various malignancies has resulted in an enormous number of cancer survivors. Cancer survivors face various issues in their long term health due to the cancer and/or its treatment. Late effects including organ damage, functional disability and risk of second malignancy continue to be elucidated. One of the most debilitating and serious toxicity is cardiotoxicity due to chemotherapy.
**Methods:** This study was a retrospective analysis of all patients who developed chemotherapy induced cardiotoxicity between January 2013 to December 2015.
**Results:** A total of 16 patients developed cardiotoxicity. 13 patients had doxorubicin induced toxicity. Cardiotoxicity was noted to occur at low cumulative doses. 2 patients had complete recovery of left ventricular ejection fraction (LVEF) on follow up. 1 patient had progressive worsening of LVEF. 1 patient died due to cardiotoxicity. On detection of cardiotoxicity, most of the patients received cardiac remodeling drugs - angiotensin converting enzyme inhibitors (mostly enalapril), other drugs used were carvedilol and diuretics.
**Conclusions:** In Indian patients, cardiotoxicity can occur at very low cumulative doses of doxorubicin and in young patients too. Most of the patients did not have any underlying comorbid illnesses. We wish to highlight the need to diligently repeat cardiac screening investigations at frequent intervals to detect asymptomatic cardiotoxicity.

**Keywords:** Adriamycin, Cardiotoxicity, Cardiac monitoring, Echocardiography

## INTRODUCTION

There have been remarkable and rapid improvements in early detection and treatment of various solid and hematological malignancies. Cancer patients are now treated with complex combinations of diverse and ever increasing variety of chemotherapeutic drugs, and ionizing radiation and surgeries. This has led to "cancer" now becoming a chronic disease, on the lines of diabetes or hypertension. Patients are increasingly living for many years after diagnosis of cancer. It is now estimated that there are approximately 13.6 million adult cancer survivors in USA.[1] It has been recognized that chemotherapeutic agents can affect multiple systems like cardiac, respiratory, neurologic, endocrine and use of radiation may increase the damage. The risk of a cardiovascular event is increased due to the presence of asymptomatic anthracycline induced cardiovascular damage and coexisting comorbid illnesses and unhealthy lifestyle risk factors in cancer survivors. 65% of the adult patients diagnosed with cancer will now survive for more than 5 years.[2] In the long term, the risk of death from cardiovascular diseases exceeds that due to disease recurrence.[3] In pediatric cancer survivors, death due to cardiotoxicity is the third leading cause of death.[4] Male adult cancer survivors rate cardiac related issues as the

most common treated related toxicity concern while female cancer survivors rate it as the third most troublesome issue after arthritis and osteoporosis.[5]

National Cancer Institute defines cardiotoxicity as "toxicity that affects the heart". Cardiotoxicity from chemotherapeutic drugs includes cardiomyopathy, heart failure, coronary artery disease, cardiac arrhythmias and conduction abnormalities. Definition of cardiotoxicity has significant practical implications on the way patients are managed, but there is no universally accepted definition of cardiotoxicity. Definitions of cardiotoxicity differ in their thresholds of left ventricular ejection fraction values. Alexander et al gave the first formal definition of chemotherapy toxicity.[6] Cardiac evaluation and review committee defined chemotherapy-induced cardiotoxicity as one or more of the following: 1) reduction of left ventricular ejection fraction (LVEF), either global or specific in the interventricular septum; 2) symptoms or signs associated with heart failure (HF), 3) reduction in LVEF from baseline of at least 5% to <55% in the presence of signs or symptoms of HF, or a reduction in LVEF 10% to <55% without signs or symptoms of HF. This definition is based on review of patients on trastuzumab in various trials.[7]

American society of Echocardiography has defined Chemotherapy Related Cardiac Dysfunction (CTRCD) as a fall of LVEF by more than 10 percentage points to less than 53%. The frequency of cardiac assessment and the modality of cardiovascular imaging is also not clearly put forth in various guidelines. Various imaging modalities (echocardiography, radionuclide imaging, cardiac magnetic resonance imaging) have been used in trials to detect cardiac dysfunction.[8] It is well known that LVEF determination by 2D Echocardiogram has interobserver variations and has poor correlation to LVEF determination by cardiac MR (CMR). CMR has the advantage of true 3D volumetric coverage. Measurement of LVEF and volumes by CMR are highly accurate and reproducible. LVEF measurements show good correlation between CMR and 3D (3 dimensional) echocardiography). LVEF values by 2D echocardiography are higher by upto 5%.[8,9] Systemic biomarkers that can predict and/or track cardiotoxicity are needed. Cardiac Troponin T and Brain natriuretic peptide levels have been studied in this respect.[10]

Ewer and Lippman et al classified cardiotoxicity into 2 types- Type 1 which is irreversible and due to myocyte injury, and Type 2 which is reversible with cessation of drug and not associated with ultrastructural abnormalities. Anthracyclines are supposed to cause Type 1 cardiotoxicity whereas trastuzumab is usually cited as example for Type 2 cardiotoxicity.[8] Type 1 injury is mediated by Topoisomerase II$\beta$, leading to mitochondrial damage and reactive $O^2$ radical formation. However, newer understanding of cardiotoxicity reveals that the mechanisms are not so simplistic. Also, patients usually receive both anthracyclines and trastuzumab

during their treatment. Type 2 injury is not dose dependant, does not cause cardiomyocyte apoptosis and is usually reversible. Type 2 cardiotoxicity is usually caused by Trastuzumab.

Cardiotoxicity has been extensively studied with the use of anthracyclines. Anthracyclines are potent drugs used in variety of cancers- breast, sarcomas, lymphomas, pediatric malignancies to name a few. Within a few years of their induction into clinical use, cardiotoxicity was noted.[11] Risk factors for anthracycline-induced cardiac toxicity include cumulative dose (especially greater than 550 mg/m$^2$), hypertension, pre-existing cardiac disease, advancing age, and prior mediastinal irradiation.[12] Anthracyclines have been known to cause cardiomyopathy, heart failure and electrocardiogram (ECG) changes. Acute or subacute cardiotoxicity with anthracyclines is rare and usually transient. It may be manifested as non-specific ST-T changes, pericarditis-myocarditis syndrome and mild reversible asymptomatic ventricular dysfunction.[12,13] Late onset cardiotoxicity is cumulative, dose related and leads to cardiomyopathy and congestive heart failure.

## METHODS

The study was a retrospective analysis of chemotherapy induced cardiotoxicity in patients treated between January 2013 to December 2015. History of diabetes mellitus, hypertension, mediastinal or chest wall irradiation, pre-existing cardiac disease, smoking, alcohol consumption and ECOG performance status of all patients were noted. As a policy, at our institution, a standard set of cardiovascular assessments are done for all patients scheduled to receive anthracycline or cardiotoxic drug containing regimens. All the patients undergo a baseline 2D echo cardiogram, electrocardiogram (ECG) and a chest x-ray. Echocardiogram and ECG are repeated in all patients at 200mg/m$^2$ – 240 mg/m$^2$ of adriamycin cumulative dose. Echo, ECG was repeated in pts who developed symptoms & signs due to cardiac dysfunction. Patients who developed cardiac dysfunction had their cardiologist consultation and repeat 2D echocardiogram every 3 month for first year.

Cardiotoxicity was defined as 1) reduction of LVEF, either global or specific in the interventricular septum; 2) symptoms or signs associated with heart failure (HF); 3) reduction in LVEF from baseline $\leq$ to 5% to <55% in the presence of signs or symptoms of HF, or a reduction in LVEF $\geq$10% to <55% without signs or symptoms of HF. All patients included in the study had left ventricular ejection fraction (LVEF) $\geq$60% at baseline. Patients with history of coronary artery disease, who had regional wall-motion abnormalities at baseline echocardiography or had an acute coronary syndrome within 1 year of cancer diagnosis were not administered anthracycline and hence excluded from the study. Patients undergoing treatment for acute lymphoblastic leukemia were excluded. Patients

developing cardiotoxicity completed their remaining treatment either with the drug withdrawn from the regimen or there was a complete change of regimen.

## RESULTS

The case records of patients who developed cardiotoxicity between January 2013 to December 2015 were reviewed. 16 patients developed cardiotoxicity, out of which 12 patients had doxorubicin and 1 had fatal liposomal doxorubicin induced cardiotoxicity.

Totally 1329 doses of doxorubicin were administered in this time period. Commonest dose at which doxorubicin was administered was 50-60 mg/m$^2$. Only 1 patient had hypertension as a risk factor. No other underlying risk

factors like cardiac disease, history of chest wall irradiation, smoking, alcohol consumption were noted among the patients.

**Table 1: Underlying diagnosis in patients with cardiotoxicity.**

| Diagnosis | No of patients |
|---|---|
| Breast carcinoma | 3 |
| Lung carcinoma | 1 |
| Ewing's Sarcoma | 3 |
| Osteosarcoma | 2 |
| Non Hodgkin Lymphoma | 4 |
| Hodgkin Lymphoma | 1 |
| Wilms tumor | 1 |
| Ovarian cancer | 1 |

**Table 2: Type of drug and the cumulative dosage at cardiotoxicity.**

| Drug | Age of patient (years) | Dose (mg/m$^2$) | Diagnosis | Status at last follow up |
|---|---|---|---|---|
| ADR | 56 | 100 | HL | Persisting low LVEF, disease in remission |
| ADR | 38 | 400 | NHL | LVEF 45% 2 year post treatment after 2 year, worsened to 25%, progressive disease on treatment |
| ADR | 54 | 150 | NHL | LVEF normalized, disease in remission |
| ADR | 20 | 200 | NHL | Disease in remission |
| ADR | 19 | 180 | Met osteosarcoma | Persistent cardiac dysfunction, died due to progressive disease |
| Cisplatin | 55 | 100 | Ca lung (on concurrent chemoradiation) | Persistent cardiac dysfunction, progressive disease |
| Actinomycin D | 3 | 135 µg/kg | Wilms tumor | Cardiac function normalized, completed SIOP protocol, pt died of disease relapse |
| Liposomal doxorubicin | 65 | 90 | Ovarian cancer | Died of cardiac failure |
| ADR | 16 | 60 | Mediastinal Ewing's sarcoma | Died of progressive disease |
| ADR, Trastuzumab | 51 | ADR (240), T (38 mg/kg) | Breast cancer | Persistent LVEF 40% disease in remission |
| ADR | 20 | 250 | osteosarcoma | Persistent cardiac dysfunction, died due to progressive disease |
| ADR | 12 | 200 | Metastatic Ewing's sarcoma | Died due to progressive disease |
| ADR | 62 | 300 | NHL | Persistent LVEF 40%, relapsed disease,in remission on 3rd line chemotherapy |
| ADR | 20 | 240 | Non metastatic Ewing's sarcoma | LFU |
| ADR | 43 | 240 | Breast cancer | Persistent LVEF 45%, disease in remission |
| ADR | 65 | 240 | Breast cancer | Persistent LVEF 45%, disease in remission |

ADR – adriamycin  T- trastuzumab LFU – lost to follow up; LVEF- left ventricular ejection fraction

ECG details were unavailable for 4 patients, 2 patients had sinus tachycardia, 1 had left bundle branch block

(LBBB) and 1 had left ventricular hypertrophy. Baseline LVEF was >55% in all the patients. The underlying

diagnosis of patients is mentioned in Table 1. Cumulative dose of drug at which cardiotoxicity was detected, age of patients and status at last follow up are shown in Table 2. Only 5/15 patients had symptoms of cardiotoxicity in the form of breathlessness, chest pain, fatigue, giddiness. Rest of the 10 patients had subclinical cardiac dysfunction.

Of the 5 symptomatic patients 1 developed symptoms after 4th cycle of chemo (for cumulative adriamycin dose of 240 mg/m$^2$), 1 after first cycle (cumulative adriamycin dose of 60 mg/m$^2$); 1 after 2 cycles (Cumulative adriamycin dose of 100 mg/m$^2$); 1 during chemoradiation (CTRT) with cisplatin at 100 mg/m$^2$ cumulative dose; 1 with actinomycin 135mcg cumulative dose.

For the rest of the patients (i.e., 10) who were asymptomatic, cardiotoxicity was diagnosed when the evaluation was carried out after the completion of treatment or as and when the cumulative doses exceeded (for adriamycin 240 mg/m$^2$ as practiced at our institute), or as per the recommendation for a particular drug (e.g. like for trastuzumab every 3 months).
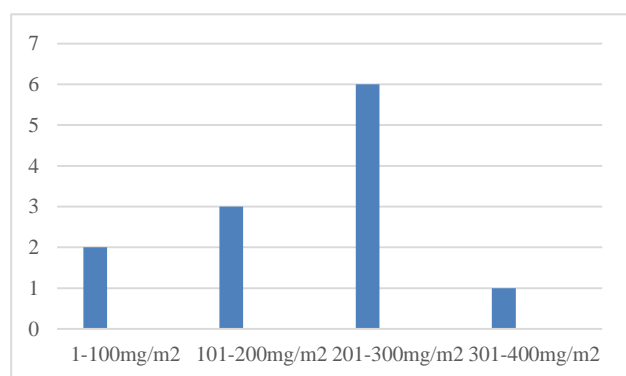


**Figure 1: Cumulative dose distribution among anthracycline induced cardiotoxicity patients.**

Mean drop in ejection fraction noted was 44.5% for all the patients included and 42.7% for anthracycline cardiotoxicity. Mean dose at which anthracycline cardiotoxicity developed was 216mg/m$^2$. Cumulative doses of anthracycline were 1) up to 100mg/m$^2$ for 2pts 2) 101-200mg/m$^2$ for 3 patients 3) 201-300mg/m$^2$ for 6 patients 4) 301-400mg/m$^2$ for1 patients respectively (Figure 1).

A 3 year old child with wilm's tumor being treated with Actinomycin D developed acute cardiac toxicity which recovered completely with cardiac medications ( digoxin, diuretics) and the child was continued on the SIOP protocol. One patient with carcinoma breast who developed cardiotoxicity, underwent coronary angiogram which was normal, that patient received planned taxane and is in remission and on follow up. 65 year old lady with ovarian cancer on second line liposomal doxorubicin developed cardiotoxicity and died due to heart failure. LVEF normalized in 2 patients. 1 patient who received

400 mg/m$^2$ of adriamycin (8 CHOP cycles), developed cardiac toxicity 2 year later. This patient had progressive worsening of cardiac LVEF from 40% to 25% in last follow up. Pt is on cardiac medications. In remaining patients, LVEF has remained stable at 40-45%, on serial 3 monthly echocardiograms. Most of the patients received angiotensin converting enzyme inhibitors (ACE inhibitors: enalapril or ramipril). 14 patients got enalapril 2.5 mg OD as their ACE inhibitor, 4 patients received ACE inhibitors with a beta blocker (carvedilol / metoprolol), 3 patients received diuretics.

## DISCUSSION

In a retrospective analysis of over 4000 patients receiving doxorubicin performed by Von Hoff and colleagues, 2.2% of the patients developed clinical signs and symptoms of congestive heart failure.[14] However the study was based on only clinician-identified signs and symptoms of congestive heart failure, asymptomatic decreases in left ventricular function were not identified. Thus the incidence of subclinical left ventricular dysfunction may have been higher than those reported. This study demonstrated that one of the greatest determinants of cardiac dysfunction is the cumulative dose of doxorubicin, with a sharp increase occurring at a cumulative dose of 550 mg/m$^2$.

Cumulative doses of doxorubicin of 400, 550, 700 mg/m$^2$ lead to heart failure incidence rates of 3%, 7% and 18% of patients, respectively.[15] Several studies have now shown that cardiotoxicity occurs at much lesser cumulative doxorubicin dosage. Swain et al analyzed three trials to determine rates of CHF and estimated that 5% of patients at cumulative dose of 400mg/m$^2$, 26% at 550, and 48% at 700 mg/m$^2$, which is much higher than that estimated by Von Hoff et al.[16] Speyer et al too noted 4% cardiac event incidence in the doxorubicin cumulative dose range of 275-399 mg/m$^2$.[17]

Perez et al noted 51.1% patients had < 15% decrease in LVEF and LVEF that remained at or above the radiologic lower limit of normal (LLN).[18] They also noted that 2.9% had LVEF ≤15% decrease in LVEF and LVEF that decreased to or below the LLN. Limat et al noted that 20% of patients who received CHOP chemotherapy for high grade lymphomas had a cardiac event. 14 out of 27 patients who had a cardiac event had symptomatic CHF.[19] They noted 3 deaths due to anthracycline cardiotoxicity within 1 year of therapy. They also noted cardiotoxicity at cumulative doxorubicin doses as low as 200mg/m$^2$ onwards.

In the Childhood Cancer Survivor Study, a study of 14,358 5-year survivors of childhood malignancies, use of <250 mg/m$^2$ of anthracycline was associated with a 2.4-fold higher risk of developing congestive heart failure compared to those patients who did not receive anthracyclines.[20] This risk increased to 5.2-fold with the use of >250 mg/m$^2$ of doxorubicin. Tukenova et al

studied cardiovascular mortality in 4122 childhood cancer survivors in Britain and France.[21] They found increased risk of cardiac death with radiation dose as little as 5Gy and cumulative anthracycline dose >360mg/m$^2$.

Patients in the Indian subcontinent tend to present 1-2 decades earlier compared to western population. Indian cancer patients also have higher prevalence of malnutrition at diagnosis. Chemotherapy tolerance is poorer in Indian patients, hence the general perception that anthracycline cardiotoxicity would occur at cumulative dosage ≥450 mg/m$^2$ may not be correct. There are scant Indian published studies highlighting this. Negi et al reported 2.67% incidence of asymptomatic LVEF decrease in breast cancer patients taking anthracycline based therapy.[22] Khattry et al noted subclinical cardiac dysfunction in 27% of patients and 3% patients had symptomatic CHF.[23] They also noted coronary artery disease as underlying risk factor in 20% of their patients. However, this study had only 30 patients. Surprisingly, we noted only 1 patient to have hypertension, rest of our patients did not have any documented risk factor. Mohta et al reported 29% incidence of cardiac dysfunction occurring at a mean cumulative anthracycline dose of 365mg/m$^2$ in children being treated for leukemia.[24] They mention about increased risk of cardiotoxicity in children with malnutrition. Since, ours is a retrospective study we cannot comment on the nutritional status of these patients. There is one case report of trastuzumab induced dilated cardiomyopathy in an Indian patient being treated for breast cancer.[25]

## CONCLUSION

Our study suggests that subclinical cardiac dysfunction due to doxorubicin is high. Most of patients who developed cardiotoxicity did not have any risk factor. Complete recovery of LVEF was seen in only 2 (13%). So, it is all the more imperative that we need to watch for cardiac toxicity and regularly monitor for the same, even at much lower doses. We propose that in our Indian patients we need to repeat Echocardiography at much lesser cumulative doses (200-240mg/m$^2$).

## REFERENCES

1. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith B. Cancer treatment and survivorship statistics. CA Cancer J Clin. 2012;62:220-41.
2. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. Cancer statistics. CA Cancer J Clin. 2006;56:106-130.
3. Carver J, Shapiro CL, Ng A, Jacobs L, Schwartz C, Virgo KS, et al. American Society of Clinical Oncology Clinical Evidence Review on the Ongoing Care of Adult Cancer Survivors: Cardiac and Pulmonary Late Effects. J Clin Oncol. 2007;25:3991-4008.
4. Armstrong GT, Liu Q, Yasui Y, Neglia JP, Leisenring W, Robison LL. Late Mortality Among 5-Year Survivors of Childhood Cancer: A Summary From the Childhood Cancer Survivor Study. J Clin Oncol. 2009;27:2328-38.
5. Schultz PN, Beck ML, Stava C, Vassilopoulou-Sellin R. Health profiles in 5836 long term cancer survivors. Int J Cancer. 2003:488-95.
6. Alexander J, Dainiak N, Berger HJ, Goldman L, Johnstone D, Reduto L et al. Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. N Engl J Med. 1979;300:278-83.
7. Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol. 2002;20:1215-21.
8. Plana JC, Galderisi M, Barac A, Ewer MS, Bonnie K, Scherrer-Crosbie M et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report fromthe American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J. 2014;1063-93.
9. Kerkhove D, Fontaine C, Droogmans S, De Greve J, Tanaka K, Van De Veire N, et al. How to monitor cardiac toxicity of chemotherapy: time is muscle. Heart. 2014;100:1208-17.
10. Chatterjee K, Zhang J,Honbo N, Karliner JS. Doxorubicin cardiomyopathy, Cardiology 2010;115:155-62.
11. Tan C, Tasaka H, Yu KP, Murphy ML, Karnofsky DA et al. Daunomycin, an antitumor antibiotic, in the treatment of neoplastic disease. Clinical evaluation with special reference to childhood leukemia. Cancer. 1967;20:333-53.
12. Floyd JD, Nguyen DT, Lobin RL, Bashir Q, Doll DC and PerryMC. of cancer therapy. J Clin Oncol. 2005;23:7685-96.
13. Yeh ETH, Tong AT, Lenihan DJ, Yusuf SW, Swafford J, Champion C et al. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis and management. Circulation. 2004;109:3122-31.
14. Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91:710-7.
15. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer. 1973;32:302-14.
16. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003;97:2869-79.

17. Speyer JL, Green MD, Zeleniuch-Jacquotte A, Wernz JC, Rey M, Sanger J, et al. ICRF-187 permits longer treatment with doxorubicin in women with breast cancer. J Clin Oncol. 1992;10:117-27.
18. Perez EA, Suman VJ, Davidson NE, Kaufman PA, Martino S, Dakhil SR, et al. Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial. J Clin Oncol. 2004:22;3700-4.
19. Limat S, Demesmay K, Voillat L, Bernard Y, Deconinck E, Brion A. Early cardiotoxicity of the CHOP regimen in aggressive-Hodgkin's lymphoma. Ann Oncol. 2003;14:277-81.
20. Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. Br Med J. 2009;339:b4606.
21. Tukenova M, Guibout C, Oberlin O, Doyon F, Mousannif A, Haddy N et al. Long-term overall and cardiovascular mortality following childhood cancer: The role of cancer treatment. J Clin Oncol. 2010;28:1308-15.
22. Negi P, Kingsley PA, Chopra S, Chaudhry NK, Mahajan MK. Detection of subclinical anthracycline induced cardiotoxicity in breast cancer survivors. CHRISMED J Health Res. 2014;1:36-9.
23. Khattry N, Malhotra P, Grover A, Sharma SC, Varma S. Doxorubicin induced cardiotoxicity in adult Indian cancer patients. Indian J Med Paediatr Oncol. 2009;9-13.
24. Mohta R, Saxena A, Jain Y, Gupta S, Thavaraj V, Narain S, Arya LS. Anthracycline associated cardiac toxicity in children with malignancies. Indian Pediatr. 2002;39:549-55.
25. Karmakar S, Dixit R, Nath A, Kumar S, Karmakar S. Dilated cardiomyopathy following trastuzumab chemotherapy. Indian J Pharmacol. 2012;44:131-3.