Original article

Outcome of anthracycline-related cardiomyopathy – experience of a cardiooncology clinic at a tertiary referral cancer centre

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ABSTRACT

Introduction: The most common form of cardiotoxicity in cancer treatment is anthracycline-related cardiomyopathy.

Objective: To study the factors affecting response to heart failure (HF) therapy in patients with anthracycline-related cardiomyopathy (ARC).

Methods: Patients with ARC were included in the study. ARC was defined as left ventricular ejection fraction (LVEF) < 50% in patients who had received anthracycline based chemotherapy. 2Decho was done at baseline and every 3 months after starting anti-heart failure treatment. The primary endpoint of the study was response to anti-heart failure treatment. The patients were considered as responders when LVEF increased at least 10 absolute points. The secondary endpoint was overall survival.

Results: 177 patients with ARC were included in the study. The median cumulative dose of doxorubicin was 275 mg/m^2. Median clinical follow up duration was 19 months (range 3–73 months). 55% were responders. 25 cumulative doxorubicin dose of more than 200 mg/m^2 increased the likelihood of non-response (p = 0.008), by a factor of 3.07 (95% CI: 1.34–7.05). 25 patients expired. There was a significant difference in overall survival among responders as compared to non-responders (p value: 0.002, log rank test).

Conclusions: In patients with ARC cumulative doxorubicin dose of more than 200 mg/m^2 increased the likelihood of non-response to anti-heart failure treatment. Responders have a better overall survival compared to non-responders in patients with ARC.

Key words: anthracyclines, left ventricular dysfunction, chemotherapy

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INTRODUCTION

Advances in cancer management have substantially improved the life expectancy in the past 2 decades [1]. Cancer therapy induced cardiotoxicity is responsible for considerable morbidity and mortality. Cardiotoxicity can cause interruption of oncologic treatment and reduction of therapeutic options. It can reduce the quality of life and survival [2]. Cancer treatment-related cardiotoxicity is the leading cause of treatment-associated mortality in survivors of pediatric and adolescent cancers, after recurrence and second or subsequent malignancies [3]. Cardiotoxicity is one of the most common post-treatment issues among five- to ten--year male survivors of adult cancer and second most common issue among female survivors of adult cancer [4]. More than one-half of all patients exposed to anthracyclines show some degree of cardiac dysfunction 10 to 20 years after chemotherapy, and 5% of them develop overt HF [5].

A wide range of chemotherapy agents have been associated with cardiotoxicity [6]. The most frequent cardiotoxicity is asymptomatic or symptomatic left ventricular dysfunction frequently occurring after administration of chemotherapy including anthracyclines [7]. Other cardiotoxic effects include hypertension [8], thromboembolic disease [9], pericardial disease [10], arrhythmias [11] and myocardial ischemia [12]. Radiation therapy can also lead to coronary artery disease and fibrotic changes of the valves, pericardium and myocardium [13]. Anthracyclines are most commonly used chemotherapeutic agent in the treatment of many solid tumors and hematologic malignancies [14] and are prime example of chemotherapy-induced nonreversible cardiotoxicity (type I agents) [15].

The commonest causes of heart failure in India are rheumatic heart disease, ischemic heart disease and hypertensive heart disease. There is no epidemiological data from India on chemotherapy-related cardiac dysfunction and data on their long term outcomes are limited.

OBJECTIVE

To study the clinical profile of patients diagnosed with anthracycline-related cardiomyopathy (ARC) and factors affecting their response to heart failure (HF) therapy.

MATERIAL AND METHODS

This is an analysis of prospectively collected data of patients with ARC registered in the cardiooncology clinic at a tertiary cancer centre in Mumbai, India.

PATIENTS

Patients registered at the cardiooncology clinic in the period 2010–2015 were included. Patients who were found to have LV dysfunction due to other causes (e.g. coronary artery disease, septic cardiomyopathy) were excluded.

ARC was diagnosed by 2Decho as left ventricular ejection fraction (LVEF) < 50% in patients who had received anthracycline-based chemotherapy. ARC was graded as per NCI CTCAE (V- 3.0) criteria. All patients were given anti-heart failure treatment.

DATA COLLECTION

Demographic details, co-morbidities (hypertension, ischemic heart disease, diabetes), cancer diagnosis and treatment details including dose of drugs, serial LVEF on 2Decho, date of diagnosis of ARC, were recorded. Treatment given for ARC (ACE-inhibitors, β-blockers, aldosterone antagonist, diuretic, digoxin) and response to treatment was recorded. Daunorubicin dose was converted to doxorubicin isotoxic equivalents by multiplying by factor of 0.833 and epirubicin dose was converted to doxorubicin isotoxic equivalents by multiplying by factor of 0.67. The onset of ARC was classified as acute if it occurred within 1 week after last dose of cardiotoxic chemotherapy, early chronic progressive if it occurred within a 1 year and late chronic progressive if it occurred after 1 year after last dose of cardiotoxic chemotherapy.

DATA ANALYSIS

The primary endpoint of the study was response to anti-heart failure treatment. Patients were considered responders if LVEF increased by at least 10 absolute points and non-responders if LVEF increased fewer than 10 absolute points or deteriorated after starting anti-failure treatment. Patients were considered complete responders if LVEF increased to 50% post anti-heart failure treatment, partial responders if LVEF increased at least 10 absolute points but less than 50%. Follow up period was included from date of diagnosis of ARC till August 2016. Patients without follow up echocardiography at 3 months were excluded from analysis. Secondary endpoint was overall survival.

Statistical analysis was done using PASW software package (version 18). Categorical data are presented as absolute values and percentages and compared using the chi-square test or the Fisher exact test, as appropriate. Continuous variables are presented as mean or median. Univariate logistic regression analyses were performed to evaluate the association between a predictor variable and response (partial or complete) to anti-heart failure

treatment. Candidate variables were age, cardiovascular risk factors (hypertension, diabetes mellitus), cumulative anthracycline dose, time to development of LV dysfunction after last dose of cardiotoxic chemotherapy, mediastinal radiotherapy, chemotherapy regimen (anthracycline with or without trastuzumab), grade of LV dysfunction. The association was expressed as odds ratio and its 95% confidence interval (CI). Survival was described with the Kaplan-Meier method, and differences between patients with and without response (partial or complete) were tested with the log-rank test.

RESULTS

247 patients were referred to the cardiooncology clinic for LV dysfunction in the period 2010–2015. 185 of these patients were diagnosed to have anthracycline-related cardiomyopathy. 8/185 patients were excluded as there was no follow up. Data of 177 patients could be analysed.

Median age at diagnosis of cardiotoxicity was 45 years (range 1–78 years). Females were predominant (79.1%). The clinical characteristics are summarised in table 1. Breast cancer was the commonest cancer followed by bone tumors (primitive neuroectodermal tumour, osteogenic sarcoma). Median cumulative dose of doxorubicin was 275 mg/m^2 (range 16–600 mg/m^2).

The onset of ARC was acute in four patients (2.3%), early chronic progressive in 109 (61.6%) and late chronic progressive in 64 (36.2%). LV dysfunction was detected at a median period of 5 months (range 1 day – 20 years) after receiving the last dose of chemotherapy. 64.4% patients were detected in the first year after last dose of cardiotoxic chemotherapy. Most patients had grade 2 ARC (tab. 2). Mean left ventricular ejection fraction (LVEF) at diagnosis of ARC was 31% (range 10–45). 107/177 (60%) in our study group were asymptomatic and were detected to have ARC either during routine monitoring or during pretreatment evaluation for relapse. 70/177 patients (39.5%) presented with symptoms and or signs of cardiac failure. 20 (11.3%) patients required inpatient management. Of these 9 (5.1%) required intensive care unit management. Details of anti-heart failure treatment was given in table 3. Median clinical follow up duration was 19 months (range 3–73 months). Median echocardiography follow up duration was 14 months (range 3–73 months). 17 patients expired due to progressive disease, 7 due to left ventricular failure and in 1 patient the cause could not be ascertained.

TABLE 2.
Grades of anthracycline-related cardiomyopathy (ARC) (as per CTCAE V 3.0).

Grade of cardiomyopathy	N (%)
Grade 2 (LVEF 40–50%)	76 (42.9%)
Grade 3 (LVEF 20–39%)	66 (37.3%)
Grade 4 (LVEF < 20%)	28 (15.8%)
Grade 5 (death due to LVF)	7 (4%)

TABLE 1.
Clinical characteristics of 177 patients with anthracycline-related cardiomyopathy (ARC).

Characteristic	N (%)	Characteristic	N (%)
Sex		**Chemotherapeutic drugs**	
Males	37 (20.9%)	Doxorubicin/epirubicin	123 (69.5%)
Females	140 (79.1%)	Doxorubicin/epirubicin + paclitaxel	27 (15.3%)
Age in years		Doxorubicin/epirubicin + paclitaxel + trastuzumab	14 (7.9%)
≤ 20	30 (16.9%)	Doxorubicin/epirubicin + trastuzumab	1 (0.6%)
21–40	48 (27.1%)	Doxorubicin/epirubicin + mitoxantrone	5 (2.8%)
41–60	75 (42.4%)	Doxorubicin/epirubicin + trastuzumab +mitoxantrone	1 (0.6%)
> 60	24 (13.6%)	Daunorubicin	6 (3.4%)
Cancer diagnosis*		**Cumulative dose (doxorubicin equivalent)**	
Breast	114 (64.4%)		
PNET/Ewings	21 (11.9%)	≤ 200 mg/m^2	42 (23.7%)
OGS	13 (7.3%)	> 200–300 mg/m^2	100 (56.49%)
Soft tissue sarcoma	7 (4.2%)	> 300 mg/m^2	35 (19.8%)
NHL	11 (6.2%)		
ALL	5 (2.8%)		
Hodgkin's disease	2 (1.1%)		

*Others – 1 each of wilms tumor, neuroblastoma, nasopharyngeal cancer and ovarian cancer.

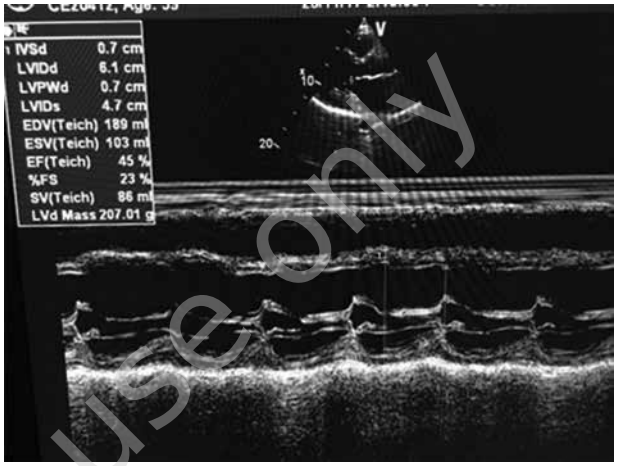
TABLE 3.
Treatment given for anthracycline-related cardiomyopathy (ARC).

Drugs	N (%)
ACE inhibitors ± diuretics	124 (70.1%)
Beta-blockers ± diuretics	3 (1.7%)
Angiotensin receptor blocker ± diuretics	1 (0.6%)
Digoxin	20 (11.3%)
ACE inhibitors + digoxin ± diuretics	17 (9.6%)
ACE inhibitors + β-blockers ± diuretics	7 (4%)
ACE inhibitors +β-blockers +digoxin ± diuretics	5 (2.8%)

* Does not include the details of ionotropes.

Response could be assessed in 159 patients. 26.4% (42/159) patients were complete responders, 32.7% (52/159) patients were partial responders and 40.9% (65/159) patients were non-responders. Mean post treatment LVEF in responders (partial or complete) was 48% (range 15–60%) and in non-responders it was 30% (range 10–45%). Univariate analysis of predictor variables on response (partial or complete) to anti-heart failure treatment was done (tab. 4). Cumulative doxorubicin dose of more than 200 mg/m^2 increased the likelihood of nonresponse (p = 0.008), by a factor of 3.07 (95% CI: 1.34–7.05). Median survival was not reached. The overall mean survival was significantly better in responders (partial or complete) as compared to non-responders (fig. 1).

FIGURE 1.
59-year-old female, developed anthracycline induced cardiomyopathy 4 years after anthracycline-based chemotherapy for breast cancer.



The cardiac chambers are dilated. The LVEF was 15–20% at diagnosis and has improved to 45–50% with anti-heart failure treatment. M-Mode and PLAX view.

DISCUSSION

Anthracyclines are well-known to cause dose-dependent cardiotoxicity [1]. A study by Van Hoff et al. found that with cumulative doxorubicin doses of less than 400 mg/m^2 body surface area, the congestive heart failure (CHF) incidence was 0.14% and it in-

TABLE 4.
Univariate analysis of predictor variables on response to anti-heart failure treatment.

	Responder (partial or complete)	Non-responder	P value
Age < 60 (134)	**79 (59%)**	**55 (41.%)**	0.55
≥ 60 (25)	**15 (60%)**	**10 (40%)**	
Mediastinal/L breast radiation yes (46)	**26 (56.5%)**	**20 (43.5%)**	0.53
no (113)	**68 (60.2%)**	**45 (39.8%)**	
Dose of doxorubicin			
≤ 200 mg/m^2 (39)	30 (76.9%)	9 (23.1%)	0.01
> 200 mg/m^2 (119)	63 (52.9%)	56 (47.1%)	
grade of LV dysfunction			
LVEF < 40% (115)	71 (61.7%)	44 (38.3%)	0.28
LVEF ≥ 40% (44)	23 (52.3%)	21 (47.7%)	
Time to development of LV dysfunction			
≤ 6 mths (85)	53 (62.4%)	32 (37.6%)	0.23
> 6 mths (74)	41 (55.4%)	33 (44.6%)	
HT yes (27)	**18 (66.7%)**	**9 (33.3%)**	0.256
no (132)	**76 (57.6%)**	**56 (42.4%)**	
DM yes (28)	**17 (60.7%)**	**11 (39.3%)**	0.51
no (131)	**77 (58.8%)**	**54 (41.2%)**	
Regimen			
anthracyclines without herceptin (84)	83 (58%)	60 (42%)	0.29
anthracyclines with herceptin (16)	11 (68.8%)	5 (31.2%)	

creased to 7% and 18% at doses of 550 mg/m^2 and 700 mg/m^2 respectively [16]. In a retrospective analysis of three trials, Swain et al. confirmed that cardiac events became more frequent with increased cumulative doses of doxorubicin [17]. In our study 23.86% patients had developed ARC at lower cumulative doses of 200 mg/m^2 or less. Factors other than cumulative dose of anthracyclines, such as sequential and concomitant use of adjuvant therapies, genetic predisposition are known to contribute to the risk of ARC [18, 19].

64.4% patients in our study developed ARC within first year after last dose of anthracycline chemotherapy. Regular cardiac monitoring in the first year may be beneficial. Many patients in our study group were asymptomatic. The long term outcomes of patients with asymptomatic ARC needs to be studied. The ESMO guidelines recommend that in patients with subclinical cardiotoxicity induced by type I agents, identified also by increase in cardiac troponin, treatment with ACE inhibitors (enalapril) may prevent LVEF reduction and associated cardiac events (level IIA recommendation) [20]. The 2015 European Society of Cardiology position paper on cancer treatments and cardiovascular toxicity also states that initiation of cardioprotection (i.e. neurohormonal inhibition) may be considered in patients who develop a troponin increase during treatment with high-dose anthracycline therapy [21].

Left ventricular ejection fraction (LVEF) is one of the most commonly reported measures of left ventricular (LV) systolic function. However LVEF is an insensitive measure of subclinical cardiac injury as the decline evident only once significant damage has occurred [22]. Current monitoring techniques (e.g. 2Decho, MUGA) have limited ability to detect early cardiac damage [23]. The utility of sensitive imaging modalities (i.e. single-photon emission computed tomography, magnetic resonance imaging; exercise or dobutamine stress testing) as well as novel biochemical markers (brain natriuretic peptide, troponin I) that allow more accurate detection and quantification of subclinical cardiac damage have been explored [24–26]. Cardinale et al. demonstrated that increase in troponin I was a strong predictor of LV dysfunction soon after chemotherapy among cancer patients [27]. Current studies are unable to confirm definitively the clinical usefulness of natriuretic peptides as cardiotoxicity biomarkers. There is an ongoing clinical trial to assess the role and timing of troponin and BNP testing in patients receiving anthracycline-based chemotherapy (PREDICT trial: NCT 01032278). Another clinical trial aimed to study the role of serial strain imaging in patients receiving cardiotoxic chemotherapy is ongoing (SUCCOUR trial: Strain Surveillance during Chemotherapy for improving Cardiovascular Outcomes, ACTRN12614000341628).

In our study 59.1% patients were responders (partial or complete). The overall survival was better in responders in our study. Cumulative dose of doxorubicin was the only factor that was significantly associated with response to therapy.

Several studies have shown that early treatment with ACE inhibitors together with β-blockers after anthracycline use results in normalization of EF and improves symptoms in patients who have anthracycline-induced cardiomyopathy. Cardinale et al. studied the effect of medical therapy with enalapril and carvedilol for 201 patients with decreased EF (< 45%) secondary to anthracyclines [28]. Enalapril and when possible carvedilol were started when left ventricular impairment was detected. The authors found that patients treated 1–4 months after anthracycline administration were significantly more likely to respond to medical therapy with improved EF and none of the patients treated after 6 months of anthracycline administration had complete recovery of EF. In another study from the same center, 2625 patients receiving anthracycline chemotherapy underwent echocardiography every three months during anthracycline therapy and for one year after completion of anthracycline therapy, and every six months for four additional years [29]. ACE inhibition (e.g. enalapril) and β-blocker treatment was initiated immediately after an impaired LVEF was detected in 226 patients. Eleven percent of the patients totally recovered a normal LVEF and 71 percent of the patients improved their LVEF by more than 5 percent.

Developing and understanding optimal prevention, early detection and treatment strategies for cancer therapy induced cardiotoxicity is an important aspect of cancer patients care, and may have a significant impact on the overall prognosis and survival of cancer patients.

The primary limitation of the present study is its retrospective nature. Mixed cohort with different therapeutic regimens were included. Data on change/stoppage of chemotherapy after development of LV dysfunction and the oncologic outcome was not captured.

CONCLUSION

Most patients with anthracycline-related cardiomyopathy were asymptomatic. ARC occurred even at lower cumulative doses. Most patients were detected to have LV dysfunction in the first

year after last dose of cardiotoxic chemotherapy and there was a higher frequency of non-response in patients who received doxorubicin more than 200 mg/m^2. The mean overall survival was significantly better among responders in patients with ARC.

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Aruna Alahari Dhir: concept, interpretation of data, revising article for important intellectual content, final approval;
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