Chemotherapy-induced cardiotoxicity: Preliminary report from a tertiary cancer centre in India

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ABSTRACT

Cancer has emerged as a major public health issue in India owing to significant epidemiological and demographic transition. As per literature, the overall ten-year survival rate for cancer is at 50% across the 20 most common malignancies. However, the ten-year survival rate is even more high, i.e. approximately 80% or higher for breast, melanoma, lymphoma, and uterine cancers. Contrary to the improved long-term cancer survival rates there has been an increase in adverse cardiac effects of cancer treatment. A retrospective analysis of patients admitted at HCG Manavata Cancer Centre, Nashik was conducted. The study was conducted at a single center comprising of 115 participants. Anthracyline chemotherapy has remained a mainstay treatment approach for cancer patients. Cardiotoxic side-effects of anthracyline chemotherapy regimens often limits their dosing. Although anthracylines have been associated with improved cancer outcomes, there remains an increased risk of cardiovascular morbidity and mortality. Doxorubicin-induced cardio toxicity was 5.45% while trastuzumab cardio toxicity was 5.26% (Table 4). The estimated cardio toxicity rate for our two-year follow-up was 4.08% for all specified chemotherapy regimens. The early detection of cardio toxicity by appropriate follow-up and monitoring is essential. Evaluation of patients using LVEF as a key parameter would help prevent irreversible cardio toxic events. Our preliminary report may act as a base for researchers and academicians to conduct and review ongoing chemotherapy regimens.
Introduction
Cancer has emerged as a major public health issue in India owing to significant epidemiological and demographic transition. The prevalence of cancer in India is estimated to be 97 per 100,000 individuals with a higher prevalence rate in urban regions [1]. Elderly people have the highest cancer prevalence followed by females in reproductive age groups. As per the World Health Organization (WHO), the cancer mortality rate in India is 79 per 100,000 deaths [1]. Cancer accounts for over 6 percent of total deaths in India. The rate of cancer mortality is projected to increase in the next decade by over 900,000 deaths [1].

In a lifetime, cancer affects more than one in three people. Cancer along with cardiovascular disease are the two leading causes of death in developed countries [2]. As per literature, the overall ten-year survival rate for cancer is at 50% across the 20 most common malignancies. However, the ten-year survival rate is even more high, i.e. approximately 80% or higher for breast, melanoma, lymphoma, and uterine cancers [2]. These mortality trends reflect a significant improvement in overall cancer survival rates. Contrary to the improved long-term cancer survival rates there has been an increase in adverse cardiac effects of cancer treatment. There has been a shift in cancer treatment from cancer survival to cancer survivorship [2].

Anthracyclines have remained the primary treatment for majority of solid tumours and hematological malignancies. Anthracyclines have remained an important treatment component for adult malignancies such as lymphoma, breast cancer, and sarcoma since their introduction in the 1960’s [3]. Advancement in cancer treatment has led to increased long-term cancer survivors. However, the clinical use of anthracyclines have been associated with cardiac toxic effects which is based on the cumulative dose. Anthracycline-induced cardiac toxicity may ultimately lead to irreversible or severe forms of cardiomyopathy [4]. Due to severe long-term effects, there has been an increased need among oncologists, cardiologist, and hemato-oncologist. Although anthracyclines have saved lives, it is logical to understand, prevent, and mitigate cardiac toxic effects [4]. There is a need to develop a balance between anticancer treatment benefit and potential cardiac side effects.

Anthracycline-associated cardiac toxicity is categorized as acute onset (within seven days of treatment), early onset, and or late onset (occurrence after one year) [5]. As per current evidence, acute-onset toxicity is uncommon and occurs in less than one percent of patients. It is namely dose-independent and referred as pericarditis-myocarditis syndrome. Late-onset toxicity is common which is dose-dependent and accounts for progressive endomyocardial damage. Dose-dependent cardiac toxicity occurs decades after first exposure and namely characterized by dilated cardiomyopathy [5]. Although anthracyclines have been attributed to improved rates of overall survival and disease-free state, there is a need to treat patients judiciously. Subclinical reduction in overall left ventricular ejection fraction (LVEF) should be monitored [5].

Endomyocardial biopsy is considered as the gold standard for evaluating anthracycline-related cardiac toxicity [6]. However, this technique has several limitations such as quality of biopsied sample, invasive nature, and the success rate for obtaining a sample of damaged myocardium. Thus, endomyocardial biopsy is considered as an unsuitable first-line option for detecting or monitoring cardiac toxicity. Alternatively, magnetic resonance imaging (MRI) and nuclear angiography can be used for the detection of cardiac toxicity [6]. However, echocardiography can be used as a cheaper and non-radioactive technique. It is easily available and presently considered as the best choice for continued cardiac toxicity evaluation. Continuous monitoring of patients using echocardiography should remain the mainstay for evaluating cancer treatment related cardiac toxicity. Although chemotherapy agents improve

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survival rate, assessing and monitoring cardiac toxic effects should be an integral part of patient management.

Materials and Methods
A retrospective analysis of patients admitted at HCG Manavata Cancer Centre, Nashik was conducted. The study was conducted at a single center comprising of 115 participants. Patients were randomly selected with different chemotherapy regimens. Patients treated with Doxorubicin (Adriamycin), epirubicin, trastuzumab (Herceptin) and liposomal doxorubicin (Lipodox) were included in the study. All study participants were observed for 24 months.

All participant medical records were retrospectively evaluated. Participant data was collected from 01 January 2014 to 31 December 2014. Patients who received chemotherapy agents that induce cardiac toxic effects were included in the study.

All study participants were included for follow-up evaluation for two years, i.e. from 01 January 2015 to 31 December 2016. All study participants were screened for hypertension, chest pain, breathlessness, and oedema over feet during follow-up. The follow-up of all patients lasted for two years, i.e. till 31 December 2016. At the time of follow-up, patients were questioned for breathlessness, hypertension, chest pain, and oedema over feet. A detailed examination of cardiovascular system was done at baseline and at each follow up. Renal function tests, liver function tests, 12-lead ECG, chest X-ray and echocardiography was done after every four cycles of chemo and whenever indicated if patient had any symptoms.

Decrease in LVEF by 10% or symptoms related to decrease in cardiac activity (dyspnoea, lower limb oedema, pulmonary oedema) were taken in to consideration to determine cardio toxicity. A clinically significant decline in LVEF was defined as per standard criteria, i.e. a final LVEF of less than 50% or a 10% change from baseline. A non-clinically significant decline in LVEF was defined as a drop of 10% but a final LVEF of more than 50%.

Chemotherapy regimen
Doxorubicin
- For Breast patients – 50-60 mg per meter square body surface area per dose. Repeat cycle every three weeks
- For Non-Hodgkin’s Lymphoma, 50 mg per meter square body surface area per dose. Repeat cycle after three weeks
- Hodgkin’s lymphoma 25 mg per meter square area per dose, repeat cycle after two weeks

Epirubicin
- 90 mg per meter square body surface area per dose. Repeat cycle after 3 weeks.

Lipodox
- 60 mg per meter square body surface area are per dose. Repeat dose after 4 weeks.

Herceptin
- Loading dose 8mg/kg and maintenance dose 6mg/kg

Results
The study included a total of 115 patients of which 102 were females and 13 were males. A total of 93 (80%) of patients had breast cancer, 5 (4.34%) had ovarian cancer and 17 (14.78%) had lymphoma (Table 1). The mean age and average dose of each chemotherapy drug has been stated in Table 2. A total of 17 patients (14.78%) could not undergo 2D-Echocardiography due to personal and financial limitations (Table 3). The cardio toxicity of our patients was estimated by ruling out patients who had not undergone 2D-Echo. A total of 17 patients did not have their 2D-echo performed. Doxorubicin-induced cardio toxicity was 5.45% while trastuzumab cardio toxicity was 5.26% (Table 4). The estimated cardio toxicity rate for our two-year follow-up was 4.08% for all aforementioned chemotherapy regimens.
Table 1. Type of Malignancies Reported in Study Population

| Malignancy     | Breast | Ovary | Lymphoma |
|----------------|--------|-------|----------|
| Males          | 1      | 0     | 11       |
| Females        | 92     | 5     | 6        |
| Total          | 93     | 5     | 17       |

Table 2. Chemotherapy Drugs, Mean Age, and Average Dose in Study Population

| Name of Medication | Doxorubicin | Epirubicin | Trastuzumab | Liposomal Doxorubicin |
|--------------------|-------------|------------|-------------|----------------------|
| No. of Patients    | 68 (M= 13; F= 55) | 23 (M= 0; F= 23) | 19 (M= 0; F= 19) | 05 (M= 0; F= 5) |
| Mean age           | 49.22 years | 49.60 years | 47.52 years | 46.8 years |
| Average Dose*      | 321.11mg (Min- 70mg; Max- 552mg) | 418.52mg (Min-210mg; Max- 720mg) | 2630.33mg (Min-408mg; Max- 7499mg) | 249mg (Min- 130mg; Max- 360mg) |

* per meter square body surface area per dose

Table 3. 2D- Echocardiography Status of Study Population

| Name of Medication | 2 D Echocardiography performed | 2 D Echocardiography not performed | Total patients |
|--------------------|---------------------------------|-----------------------------------|----------------|
| Doxorubicin        | 55                              | 13                                | 68             |
| Epirubicin         | 20                              | 3                                 | 23             |
| Trastuzumab        | 19                              | 0                                 | 19             |
| Liposomal Doxorubicin | 4                              | 1                                 | 5              |
| TOTAL              | 98                              | 17                                | 115            |

Table 4. Cardiac Toxicity Status in Study Population

| Name of Medication | No. of patients with cardiac toxicity | Percentage |
|--------------------|--------------------------------------|------------|
| Doxorubicin        | 3 out of 55                          | 5.45%      |
| Epirubicin         | None                                 | 0          |
| Trastuzumab        | 1 out of 19                          | 5.26%      |
| Liposomal Doxorubicin | None                             | 0          |
| Total              | 4 out of 98                          | 4.08%      |

Discussion

Anthracyline chemotherapy has remained a mainstay treatment approach for cancer patients. Cardiotoxic side-effects of anthracyline chemotherapy regimens often limits their dosing. Although anthracylines have been associated with improved cancer outcomes, there remains an increased risk of cardiovascular morbidity.
and mortality [7]. Trastuzumab and anthracylines are well-known cardio-toxins. The rates of asymptomatic and symptomatic changes in LVEF differ among different patient populations [8]. This current retrospective study aimed at assessing the real-world implications and outcomes of trastuzumab and anthracycline use. This is one of the few studies that examines the different risk factors, specifically decline in LVEF in a general cancer cohort. Cardio toxicity increases with an increase in total cumulative dose of trastuzumab or anthracylines [9]. We report a cardio toxicity rate of 5.45% due to doxorubicin. The average dose of doxorubicin was 321.11mg (Min- 70mg; Max-552mg). There was no epirubicin and liposomal doxorubicin induced cardio toxicity. Trastuzumab-induced cardio toxicity was 5.26% (with cumulative average dose 2630.33mg). Patients who had symptoms of heart failure were treated with beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and diuretics. Follow-up of patients with reported heart failure symptoms was conducted. All patients with a decline in LVEF and symptoms of heart failure were discontinued from ongoing chemotherapy.

Limitations
Our study was a representation of cancer patients in a tertiary cancer centre based in a tier-2 city in India. The main limitation of the study was a small sample size. The patients representing each chemotherapy drug class were not consistent in order to provide a comparative cardio toxicity outcome. A larger cohort of patients is required to showcase cardio toxicity post-chemotherapy. The study did not include biomarkers essential for assessment of cardio toxicity in cancer patients receiving cardio toxicity [10,11].

Conclusion
This is one of the very few retrospective studies conducted in India to highlight chemotherapy induced cardio toxicity. The early detection of cardio toxicity by appropriate follow-up and monitoring is essential. Evaluation of patients using LVEF as a key parameter would help prevent irreversible cardio toxic events. Identification of cardiac issues also helps in discontinuation of chemotherapy regimen. Disseminating knowledge on cardio toxic events in cancer patients is highly recommended to ensure higher standards of treatment and quality of care. Our preliminary report may act as a base for researchers and academicians to conduct and review ongoing chemotherapy regimens.

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Conflict of Interest
None

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