The Cardiac Dysfunction of Anthracycline based Chemotherapy in Patients with Breast Cancer

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ABSTRACT

Introduction: Cancer outcomes continue to improve due to earlier detection and newer targeted therapies, with anthracycline chemotherapy playing a major role in the modern era of cancer treatment. Anthracyclines are listed among the World Health Organization (WHO) model list of essential medicines. Study aimed to evaluate the incidence of the subclinical cardiac dysfunction associated with Anthracyclines based regimen in patients with breast cancer at a tertiary care center.

Material and Methods: 110 patients with breast cancer patients receiving Anthracycline-based chemo regimen were enrolled in the study. All enrolled patients with breast cancer underwent baseline cardiac assessment and periodic monitoring of cardiac function by noninvasive diagnostic tools

Results: The incidence of Anthracycline-induced cardiac abnormalities in this study was 38.1%. The incidence of subclinical cardiac dysfunction was more than overt cardiac dysfunction. The overt cardiac abnormality was observed in 13.6% and subclinical cardiac dysfunction was observed in 24.5% of our patients.

Conclusion: Early identification of patients with subclinical cardiac dysfunction aids in early intervention and prevention of further deterioration of cardiac dysfunction.

Keywords: Breast Cancer, Anthracycline, Chemotherapy, Cardiotoxicity

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women worldwide and ranks second as the cause of cancer mortality after lung cancer. Breast cancer is the major public health problem for women throughout the world.[1] India is facing a cancer epidemic. By 2020 two thirds of the cancer cases in the world will be in poor countries, with the fifth rank in India. By 2020 breast cancer is set to exceed cervical cancer as the most cancer among all women in India. Since the 2008 GLOBOCAN estimates the incidence of breast cancer has grown by >20% and related mortality has increased by 14%.[2] Survivorship is the process of living with, through and beyond cancer. Although upward trend in breast cancer incidence could be due to better diagnosis and screening, survival in breast cancer improved substantially over the years as a result of multimodality treatment and systemic chemotherapy. Survival rate has increased by the availability of chemotherapy especially with Anthracyclines.[3] In SEER Database, breast cancer statics EBC survival rate is 89%, 10-year rate is 83% and 15-year rate is 78%.[4] Since 1989 the number of women who died of breast cancer has steadily decreased with systemic chemotherapy. The systemic armamentarium presently includes Anthracyclines and Taxanes. In Anthracyclines is a potent antitumor antibiotic and gold standard of therapy in all stages of breast cancer. The use of Anthracyclines based regimen is indicated in the high-risk node negative and hormone receptor negative settings lead to improved treatment results compared to CMF regimen. Anthracyclines based regimen more effective in terms of relapse free and disease-free survival and overall survival than CMF regimen.[5] The successful use of Anthracyclines is however restricted by the risk of developing cardiac toxicity.[6] Anthracyclines cause potential short and long term side effects related cumulative dose and known to cause acute and chronic cardiotoxicity. Fear of treatment side effect is common after diagnosis but it may help to know that preventing and controlling side effect is a major focus.[7] During and after treatment care about the side effects is an important part of survivorship in patients with breast cancer. American Society of Clinical Oncology's recommendation for breast cancer follow up care included cardiac monitoring during and after systemic chemotherapy also survivorship care plans.[8]

Study aimed to evaluate the incidence of the subclinical cardiac dysfunction associated with Anthracyclines based regimen in patients with breast cancer at a tertiary care center.

MATERIAL AND METHODS

A prospective study was conducted in the department of medical oncology at Madras Medical College. One hundred and ten (110) breast cancer patients receiving Anthracycline-based chemo regimen were enrolled in the study. All patients were informed with written consent prior to participation. All selected patients underwent a detailed examination. Demographic characteristic of the patients was entered. Baseline cardiac function was performed in all enrolled breast cancer patients.

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Inclusion criteria

- Age > 20 years < 65 years
- Performance status 0-2
- female gender
- Invasive breast cancer with both Neoadjuvant and adjuvant Anthracycline.
- Chemotherapy-naive metastatic breast cancer
- Normal renal function and liver function
- No previous chemotherapy
- No previous RT
- No previous cardiac problem.

Exclusion criteria

- Age >65 years
- Performance status 3-4
- Previous RT
- Previous chemotherapy
- Known cardiac problem
- Synchronous, Metachronous breast cancer

All enrolled patients with breast cancer underwent baseline cardiac assessment and periodic monitoring of cardiac function by non-invasive diagnostic tools with Electrocardiography parameters heart rate, QTc dispersion and Conventional Echocardiography, 2D, 3D echocardiography, color flow Doppler and TDI at 1st, 3rd,and 9th month during treatment. Baseline cardiac function before starting chemotherapy with Anthracycline. Cardiac monitoring during treatment and follow up at 1 month (T1) 3rd month (T2) and ninth month (T3). Baseline cardiac dimension compared with follow up during and after completion of chemotherapy in patients with breast cancer

RESULTS

In this study population age group range was 25-65 years. The mean age of the patient was 47 years. Of the 110 patients sixty-five patients were pre-menopause and forty-five patients were post-menopause. Postmenopausal patients twenty-four (58.3%) out of 45 women had cumulative dose-related cardiac dysfunction. Among 110 patients 31patients (31%) had pre-existing hypertension. Of the 110 patients 39 patients (35.4%) were diabetes and 71 patients (64.5%) patients were nondiabetes.

Among 110 patients one hundred and six patients completed the designated number of cycles of chemotherapy according to their protocol. 23 patients were treated with neoadjuvant, 78 were treated with adjuvant and 9 patients were treated with palliative chemotherapy anthracyline based schedules, with baseline cardiac monitoring and normal cardiac function define treatment. Mean age 47.2 years were studied. The most common dose of doxorubicin used was 50mg/m^2 to 60 mg/m2 per cycle of chemotherapy. The schedule of administration of doxorubicin was similar in all patients. All patients received doxorubicin by intravenous infusion over two hours. Four patients received a cumulative dose of 50-60mg/m2 were excluded as they did not receive the full course of chemotherapy due to the progression of cardiac dysfunction and had developed acute myocardial infarct after the first dose of doxorubicin. They were stopped from

LVD grading	T□(%) (No=110)	T□(%)	T□(%)
Grade 1	11.80%	15.40%	24.50%
Grade 2	2.70%	12.70%	12.70%
Grade 3	3.6	6.30%	10%

Table-1: Cumulative dose vs LVD grading

No. of cycles	No.	LVD (N)	%	Dose Mg/m2
1 cycle	4	4	3.60%	50-60
4 cycle	78	38	48.7.%	200-240
6 cycle	28	15	53.50%	>240

Table-2: Number of cycles vs cardiac dysfunction

Dose mg/m2	TEI index	No. of patients	%
50-60 mg/m2	>0.45	4(110)	3.60%
200-240mg/m2	>0.45	27(78)	38.50%
>240mg/m2	>0.45	15(28)	57.60%

Table-3: Dose vs TEI indiex

Anthracycline-based regimen and treated at the cardiology department according to guidelines. Seventy-six patients (71.6.%) received at cumulative dose 200-240mg/m^2 of doxorubicin, while twenty-eight (26.4%) patients received at cumulative dose more than 240mg/m^2 of doxorubicin. Mean cumulative dose of doxorubicin range was 200-360 mg/m^2. All enrolled patients were underwent serial electrocardiography and echocardiography monitoring. Sixty-eight patients (61.8%) had either no change or less than 5% fall in LVEF. Forty-two patients (38.1%) had shown a decline in LVEF. Among forty two patients, in follow up echocardiography, four patients (3.6%) developed AMI and symptomatic CCF with severe left ventricular dysfunction after receiving 50-60mg/m^2 dose of doxorubicin, while twenty seven patients (24.5%) developed asymptomatic cardiac dysfunction at 200-360mg/m^2 in the form of ECG abnormalities with LVEF reduction by 5% from baseline ejection fraction with normal fractional shortening FS >29% and fifteen patients(13.6%) were symptomatic cardiac dysfunction at 200-360mg/m2 cumulative dose of doxorubicin with reduction of LVEF by 10% and >10% from baseline ejection fraction and reduced fractional shortening FS <29%. Overall Subclinical cardiac dysfunction was identified in forty-two patients (38.1%) at cumulative dose 200-360mg/m2. Cardiac dysfunctions had been shown at cumulative close as low as 200 mg/m2 well below levels currently assumed to induce cardiac injury. Performance status, Receptor status, Neoadjuvant or adjuvant chemotherapy did not show any significant relation with cumulative doxorubicin dose. Tissue Doppler imaging measurement was correlated with cumulative dose-dependent toxicity. This study observation in eleven patients decreased LVEF >10% from baseline value had significant overt left ventricular dysfunction with grade 2 which was defined E/A ratio <1 and E/E' ratio> 8. Four patients showed LVEF < 55% and global hypokinesia. In the same patients TEI otherwise defined myocardial performance index (MPI) elevated >0.4

which was a marker of left ventricular diastolic dysfunction. TEI results showed forty-two patients developed mild to moderate LV dysfunction. Most LV diastolic dysfunction are grade 1 (17 of the 42 patients) grade 2 (14 of the 42patients) grade 3 (11 of the 42 patients) at cumulative doxorubicin dose of 200- 360mg/m^2. Four patients out of 42 developed acute severe LV dysfunction at dose of 50mg-60mg/m^2.

DISCUSSION

Anthracycline is the key component of the chemotherapy regimen in breast cancer. The anthracycline-based regimen is the standard of care and first line management in both Neoadjuvant and adjuvant chemotherapy in all stages of breast cancer irrespective of age and sex. However despite their impact on survival outcomes, Anthracycline-induced cardiac toxicity is a major clinical problem.

The incidence of sinus tachycardia, sinus bradycardia and QTc dispersion was 30% (n=42), 7.6% and 9.5% (n=42) respectively. In our study the incidence of clinically diagnosed cumulative dose doxorubicin-induced symptomatic cardiotoxicity was 13.6% and incidence of congestive heart failure with acute myocardial infarct was 3.6% and was in general agreement with the range 0.4 to 9% reported by others. Though the incidence of congestive heart failure was low, the incidence of subclinical cardiac dysfunction was high 38% (no 42 of the 110 patients).

This observation was consistent with studies that have evaluated subclinical cardiac dysfunction. Palmeri et al in their group of 48 patients received a mean dose of doxorubicin at 338mg/m^2 found that 63% of their patients had subclinical cardiac dysfunction with a fall in LVEF.[9] Similarly Agarwala et al observed that 40% of children undergoing doxorubicin-based chemotherapy developed subclinical cardiac dysfunction at a cumulative dose of 180 – 200 mg/m2. The cumulative dose of doxorubicin was the single most important determinant of cardiac toxicity.[10] In our study at cumulative dose 200- 360mg/m^2 of doxorubicin forty two percent developed subclinical cardiac dysfunction. Among 42 patients twenty-seven patients (24.5%) had an asymptomatic cardiac dysfunction at cumulative dose of 200-360mg/m^2. This study result was consistent increased incidence of left ventricular diastolic dysfunction grade I to grade III events at a cumulative dose 200-360mg/m^2 Similar inference was drawn by Dresdale et al and showed that 87 asymptomatic patients who received >430mg/m2 of doxorubicin found abnormal LVEF in 21%.[11]

Our study results showed fifteen patients 13.6% had signs of cardiac failure after cumulative dose of doxorubicin dose range 200-360mg/m^2. Vonhoff et al found that drug-induced cardiac failure was high (0.03) at cumulative dose more than 400mg/m^2.[12] In our study 31 patients had hypertension. All 31 patients had LVEF >60% at baseline with normal LV function in echocardiography. Twenty-one (67.7%) out of 31 patients with doxorubicin-induced cardiac dysfunction compared to normotension in which twenty-eight (40.5%) out of 79 patients developed cardiac dysfunction.

Similarly with pre-existing diabetic patients twenty four (61.5%) out of 39 developed left ventricle dysfunction grade 1 to grade 3 at cumulative dose 200mg- 360mg/m^2. Both HT and DM had an increased probability of developing cardiac dysfunction due to cumulative dose doxorubicin in patients with breast cancer. The similar inference was drawn by Minow et al and Vonhoff et al.[12,13] This present study found statistically significant association of concomitant use of cyclophosphamide and doxorubicin with cardiac dysfunction (regression coefficient = 11.28). This result was similar to those studies by Minow et al and Vonhoff et al, it was now standard practice to use lower cumulative dose ceiling in patients exposed to both cyclophosphamide and doxorubicin.[12,13] The high incidence of subclinical cardiac dysfunction in our patients reinforces the need for strict monitoring on doxorubicin during treatment.

CONCLUSION

The incidence of co-existing conditions, such as diabetes, hypertension and obesity was more in patients with subclinical cardiac dysfunction. All patients with subclinical cardiac dysfunction at an early stage were identified by non-invasive methods like ECG and ECHO. Early identification of such patients with subclinical cardiac dysfunction aids in early intervention and prevention of further deterioration of cardiac dysfunction. Vigilant screening for treatment-related left ventricular overt cardiac dysfunction. Accurate monitoring of cardiac function before, during and after Anthracycline treatment.

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