Original Research Article

A study of assessing cardiotoxicity by MUGA technique in patients treated for carcinoma breast

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Abstract

Introduction: Adriamycin is one of the commonly used chemotherapeutic drugs in breast cancer which induce cardiotoxicity ranges from benign arrhythmias to potentially lethal cardiomyopathy. **Aim:** To study on assessing adriamycin induced early cardiotoxicity in breast cancer with MUGA scan by estimating LVEF.

Materials and methods: In this prospective study with a subject of 30 female patients, histologically confirmed breast cancer stage-I –III without any co-morbidities and higher risk factors (as per protocol) with baseline LVEF >50% estimated with TC-99M MUGA scan and 2D Echo received 4 cycles of AC ± RT ± Paclitoxal ± HT. Chemotherapy given based on BSA with dosage of A=60 mg/m^2, C = 600 mg/m$^{2;}$ EBRT = 5040 Gy/5000 gy to chest wall and p=175 mg/m^2.

Results: Out of 30 patients, 4 patients received320 mg; 14 patients received 360 mg; 4 patients received 380 mg; 5 patients received 400 mg; 1 patient received 340 mg; 1 patient received 450 mg and 1 patient received 600 mg. In all the patients there is a decline in LVEF from baseline to 1st MUGA scan and Baseline to 2nd MUGA scan. From baseline - 2nd MUGA scan out of 30 patient, 3 patients had protocol defined decline LVEF i.e. <50% at doses of 380 mg, 400mg and 600 mg respectively i.e. 3 patients developed protocol defined subclinical cardiotoxicity. 2D Echo was also done in all patients at 3rd MUGA scan. In 2D Echo even though there is a decline in LVEF, no patient developed protocol defined subclinical cardiotoxicity. Mean and standard deviation (SD) was

51.97±2.72 for MUGA-3 based on null lypothesis, p value is scored as = 0.9 which is insignificant for adriamycin cardiotoxicity.

Conclusions: Out weighing the benefits and risks at lower cumulative doses, adriamycin is still considered as treatment of choice. Specific cardiac monitoring guidelines should be formed to evaluate adriamycin cardiotoxicity.

Key words

Cardiotoxicity, MUGA technique, Carcinoma of breast.

Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in female worldwide, accounting for 23% (1.38 million) of the total new cancer cases and 14% (458400) of the cancer deaths in 2008 [1]. Breast cancer is the commonest cancer in urban areas in India and accounts for 28% to 33% of all cancers in women and the overall survival is <60% presently, compared to the western countries, which has improved from 75% to 89% [1]. Breast cancer management is multimodality management including surgery, radiation & chemotherapy. Surgery and Radiotherapy are local treatment given to reduce the risk of recurrence in the breast/chest wall and regional nodes by sterilizing the local microscopic disease. Cytotoxic chemotherapy and hormonal therapy are systemic treatments which reduces the disseminated micro metastasis, thus, reducing systemic recurrences and overall mortality for breast cancer.

Since late 1980s significant advances have been made in all modalities of treatment with the advent of more successful new therapies of cancer that have raised survival rates, consents about their long term effects have now become paramount, especially toxicities related to chemotherapies such as cardiac toxicity. Breast cancer is one of the major cancer responsive to all major classes of cytotoxic drugs; alkylating agents, antimetabolites, mitoticinhibitors and the antitumor antibiotics (anthracyclins) [2] Anthracyclines are cytotoxic agents. This includes doxorubicin (adriamycin), donourubicin, epirubicin, idarubicin and mitoxantrone.

Out of all the drugs, adriamycin produces a 52% objective response rate in previously untreated patients and 28% in patients who have had prior chemotherapy and is the commonest used drug in breast cancer. But doxorubicin has undesirable side effects such as almost universal alopecia, marked controversies if the drug infiltrates the skin and cardiac toxicity. Irreversible cardiac damage is a major dose limiting toxicity, restricting life time cumulative dose (450 mg/m^2) [3]. Adriamycin induced cardiotoxicity ranges from benign arrhythmias to potentially lethal cardiomyopathy. Therefore, periodic assessment of the cardiac function is necessary at an early stage to avoid permanent cardiac damage.

Gold standard for monitoring adriamycin cardiotoxicity is cardiac biopsy but limited availability and technical complexity it is not so commonly practiced [4, 5]. A change in left ventricular ejection fraction determined by 2 D Echo and TC-99 MUGA (Multiple Gated Acquisition Scan) is a very good indicator of developing cardiomyopathy [6]. TC-99 scanning is highly reproducible and probably more sensitive than Echo at detecting early change in LVEF [7]. Adriamycin is one of the commonly used chemotherapeutic drugs in breast cancer at our institution and as we have the facility of TC-99M MUGA Scan. Our objective is to study on assessing adriamycin induced early cardiotoxicity in breast cancer with MUGA scan by estimating LVEF.

Materials and methods

It was a prospective study enrolled 30 patients registered in MNJIO and RCC with confirmed diagnosis of breast cancer up to stage – III. Study

period from September 2009 to September 2011. Institutional ethical clearance is obtained and informed consent was taken from the patients in study.

Inclusion criteria

Age younger than 70 years, Patients with newly diagnosed breast cancer up to stage-III, Histologically proven breast cancer, ECOG PS 0: 1, 2, No history of other malignancies, No history of previous evidence of treatment with chemotherapy and radiotherapy to chest, adequate function of major organs, adequate cardiac function with LVEF > 50% with MUGA Scan, no co-morbid illness related to heart, kidney and liver, scheduled to receive at least 4 cycles of doxorubicin based on BSA.

Exclusion criteria

Age greater than 70 years, ECOG PS 3 or more, Co morbid conditions relating to CVS such as HTN, arrhythmias and other cardiac diseases , Baseline LVEF < 50%, co-morbid illness relating to lung, liver, kidneys, inadequate marrow function tests, renal function tests, LFTS, non complaint patients, pregnancy and earlier mediastinal irradiation.

Pre-treatment evaluation

Initial clinical evaluation consists of careful history and physical examination and all basic investigations like Hematological were doe. In Radiological investigations Chest X-ray, Ultrasound abdomen, pelvis and Mammogram. Under cardiac investigations fitness for doxorubicin chemotherapy and 2D Echo are done. Radionuclide investigations include TC-99m MUGA (Multiple Gated Acquisition Scan) $\pm$ Bone scan.

Protocol Design

Diagnosed breast cancer patients Stage I –III fit for Adriamycin/ Cyclophosphamide chemotherapy. Base line 2D Echo & MUGA Scan → After 4 cycles of AC i.e. 8-12 weeks of first dose of chemotherapy: second MUGA → During first followup (i.e. after surgery $\pm$ RT to breast /chest wall; $\pm$ paclitaxol i.e. after 8 months after last dose of chemotherapy): Third MUGA

Protocol defined subclinical cardiotoxicity is defined as absolute fall in LVEF to a final value less than 50%. Maximum follow-up is 12 months and minimum follow-up is 2 months.

All patients received 4-6 cycles of standard doses of AC, calculated based on body surface area.
Adriamycin – 60 mg / m^2
Cyclophosphamide – 600 mg /m^2

Node positive patients received 4 cycles of paclitaxol after AC, according to BSA with a dosage of 175 mg/m^2. Marrow and renal function tests were performed before each cycle of Chemotherapy. All the patients received RT to breast /chest wall on respective sides (as indicated) to a dose of 5040/5000 Gy with Medial Tangential (MT), Lateral Tangential (LT) and Supraclavicular and axilla (Direct anterior) fields on Linac with 6 Mv photons.

Procedure

A modified invivo method is used for labeling RBC in which 1 ml of stannous pyrophosphate is injected into the patient → 20-30 minutes, 15-30 milli Curi of technetium 99 M eluted from the technetium generator is injected into the patient through a peripheral vein. → After 20 minutes, ECG gated static image is acquired and planar acquisition was done by using a large field of view gamma camera (Infinia vc Hawkey 4) equipped with low energy, high resolution collimator.

A cine image is acquired into the system, where LVEF is calculated by outlining the LEFT ventricle manually and automatically.

After completion of treatment first follow up was at 2 months. Here a TC-99M MUGA scan and 2D Echo were done along with local examination and systemic examination. Patients with normal LVEF were kept on follow up for every 12 weeks for 2 years followed by 3-6 months for 3rd years and every 6-12 months next 2 years, then

annually. With annual 2D Echo (or) MUGA Scan. Patients with subclinical cardiotoxicity i.e. drop in LVEF < 50% from baseline were advised close cardiac monitoring.

Results

The demographic characteristics of the study population were as Age from 20 to 69 years. Average dose of adriamycin was 250-400 mg/m^2 with protocol defined cardiotoxicity of LVEF < 50%. Among 30 patients all were females with histopathologically diagnosed breast cancer and all the patients received adriamycin and cyclosphosphamide calculated based on BSA with dosages of A=60 mg/m^2 , C=600 mg/$m^{2.}$ Out of 30 patients, 4 patients received320 mg; 14 patients received 360 mg; 4 patients received 380 mg; 5 patients received 400 mg; 1 patient received 340 mg; 1 patient received 450 mg and 1 patient received 600 mg.

In all the patients there was a decline in LVEF from baseline to 1st MUGA scan and Baseline to 2nd MUGA scan.From baseline-2nd MUGA scan out of 30 patient, 3 patients had protocol defined decline in LVEF i.e. <50% at doses of 380mg, 400 mg and 600 mg respectively i.e. 3 patients developed protocol defined subclinical cardiotoxicity. 2D Echo was also done in all patients at 3rd MUGA scan. In 2D Echo eventhough there was a decline in LVEF, no patient developed protocol defined subclinical cardiotoxicity. Age group of 30-39 women were more affected with breast cancer (**Table – 1**).

Table - 1: Age distribution in study.

Age group in years	No. of patients
20-29	2
30-39	14
40-49	10
50-59	2
60-69	2

On average LVEF estimated at base line was 61.6% and after 4-6 cycles it was 60.3% and i st follow up it was 50.6% (**Figure – 1**). Right side of breast is mostly affected in study (**Figure – 2**). Out of 30 patients, 3 patients had asymptomatic decline in % LVEF. i.e. <50% in the final LVEF (MUGA3), Mean and standard deviation (SD) were calculated for MUGA-3 based on null lypothesis, taking average weight = 50 (i.e. LVEF = 50) as per **Table – 2**.

Mean = 51.97

SD = 2.72 with for the given sample n=30

Z_{obs} value was calculated to get p value using $Z_{obs}=x-\mu/\sigma/\sqrt{}$ n = (51.97-50) / 2.77 /√30=3.88

Using the Z-score table, p value is scored as = 0.9

Table - 2: Decline in LVEF.

Total No. of Patents	Decline < 50%	> 50%
30	3	27

Since this value is higher than the value of significance (0.05), the null hypothesis is significant and the observation below the hypothesis (i.e. VEF <50% can be ignored) as per **Table - 3**.

Discussion

In breast cancer adriamycin based adjuvant chemotherapy is a very popular method of management, because of its efficacy [1]. Large metaanalysis of early clinical trials in breast cancer established in superiority of adriamycin based adjuvant treatment over traditional CMF regimen with an absolute 4% improvement in overall survival at 10 years.

But the long term toxicity of adriamycin is cardiac toxicity which limits the dose. In late 1970s, a retrospective analysis by Van Hoff, et al. identified the total cumulative dose as a major risk factor for doxorubicin related CHF. The estimated cumulative percentage of patients who developed CHF are 3% at 400 mg/m^2, 7% at 550 mg/m^2 and 18% at 700mg/m^2. On the basis of this study, a maximum cumulative dose tolerance dose of 450-500 mg/m^2 is often recommended.

However, the degree of cardiotoxicity is higher when sensitive methods are used and in a recent retrospective analysis of 3 clinical trials reported risk of CHF as 5% at 400 mg/m^2, 16% at 500 g/m^2 and 26% at 550 mg/m^2 had been reported.

Table - 3: Incidence of protocol defined cardiotoxicity against cumulative dose of adriamycin.

Cumulative dose of adriamycin in mg	No. of patients who received the particular cumulative dose	No. of patient developed protocol defined cardiotoxicity
320	4	0
340	1	0
360	14	0
380	4	1
400	5	1
450	1	0
600	1	1

Figure - 1: Average percentage of LVEF estimated by TC-99M MUGA scan.

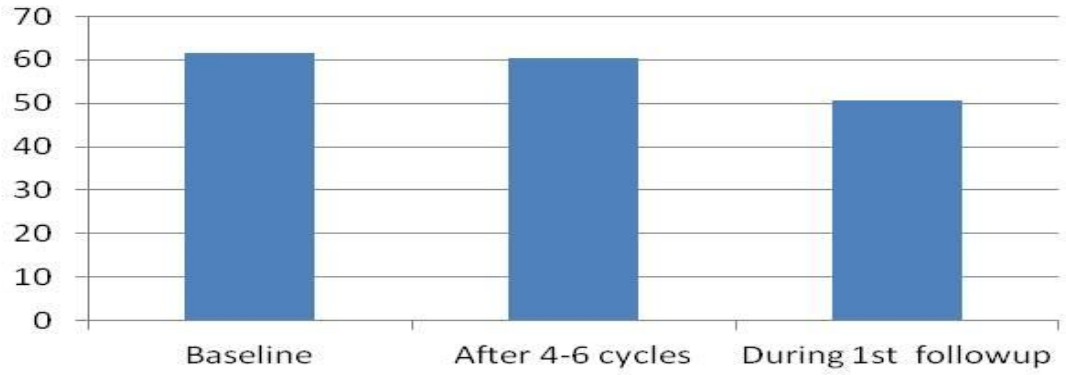
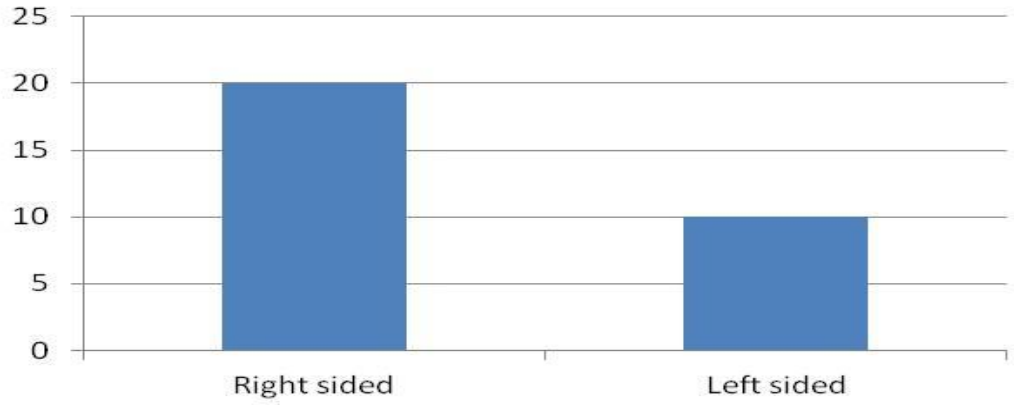


Figure - 2: Side of breast cancer.



In breast cancers, the cumulative dose of adriamycin used is low 240-300mg/m^2. Symptomatic heart failure with these cumulative doses are rare, asymptomatic cardiotoxicity with a decreased LVEF is often observed [8]. In (NCCTCG) N9831 trial, after 4 cycles of CT, 8.5% of 2992 breast cancer patients had an asymptomatic decline in LVEF. LVEF can be estimated by various methods, but the most commonly used are 2D Echo and MUGA Scan.

The two techniques cannot be compared directly; patient should always be assessed with the same technique when monitoring cardiac changes during treatment over time [9].

The experience with adriamycin cardiotoxicity proved that early detection and treatment of cardiotoxicity could significantly reduce the development of overt CHF and Death. In the present study, no patients developed CCF and acute cardiac failure. But out of 30 patients, 3 patients had asymptomatic decline in % LVEF. i.e. <50% in the final LVEF (MUGA3), at doses of (380 mg, 400 and 600 mg respectively) and this observation is consistent with studies that have evaluated subclinical cardiac dysfunction by Navinkhattry, et al. (doxorubicin induced cardiotoxicity in adult Indian patients on chemotherapy) [10]; similarly agarwala, et al. [11] observed that 40% of children undergoing doxorubicin-based chemotherapy developed, subclinical cardiac dysfunction at a cumulative dose of 180-200mg/m^2 which is also supported by Palmeri, et al. [12] and Dresdle, et al. [13] and Nousheen Fathima, et al. [14], who observed early cardiotoxicity with MUGA scan at 210, 380,450,550 and 615 mg/ m^2 with an incidence of 2.4, 2.9, 4.8, 16 and 31.2%.

In a study conducted by Navinkhattory, et al. [10], doxorubicin induced cardiotoxicity in adult Inclian patients on chemotherapy from June 2000-2001. EF were seen at baseline, 300 mg/m^2 and 450 mg/ m^2 cumulative doses in 30 patients, 3% patients developed CCF, while 27% of the patients developed subclinical cardiac dysfunction.

In the study of Palmeri, et al. [12], out of 48 patients that received a mean dose of doxorubicin of 338 mg/m^2 found that 63% of their patients had some fall in LVEF as measured by rest and exercise radionuclide angiography.

Dresdale, et al. [13] in 87 asymptomatic patients that received >430 mg/m^2 of doxorubicin found abnormal LVEF at rest by radionuclide angiogram in 21% patients. Mohta, et al. [15] in pediatric patients observed that 30% of the patients had significant cardiac dysfunction on 2D Echo at a mean cumulative dose of 365 mg/m^2. Agarwala, et al. [11] observed that 40% of children undergoing doxorubicin based chemotherapy developed subclinical cardiac dysfunction at a cumulative dose of 180-200 mg/mg^2. In Nosheen Fathima, et al. [14] study, 42 patients with different cancers received adriamycin (average dose =95.2 $\pm$ 6.82 mg / cycle, protocol dose 65 $\pm$ 10 mg/m^2) in each of 6 cycles and assessed LVEF with MUGA & 2D Echo for early cardiotoxicity. The incidence of subclinical cardiotoxicity was 2.4, 2.4, 4.8, 16, 31.2% at median cumulative doses of 210, 380, 450, 550, and 615 mg/m^2.

In the present study during first follow up when a MUGA scan and 2D Echo were done, there is decrease in LVEF with MUGA Scan. In this study P value calculated for MUGA-3 using null hypothesis and Z table P value is 0.9, which is higher than the value of significance 0.5. Hence, observation below i.e. LVEF <50% (EFC 50%) can be ignored. The above observation is probably due to low cumulative doses used in breast cancer compared to the 450mg/M^2. So far however long term clinical impact of these form of subclinical cardiotoxicity is not clear. But strict monitoring is necessary when the cumulative dose are high according to Batist, et al. [16], who emphasized that cardiotoxicity starts with the first dose of Adriamycin.

Conclusion

The frequency and severity of adriamycin cardiotoxicity increases in a dose dependant manner. When cumulative doses are high frequent monitoring of LVEF is necessary. The risk of life threatening CHF following current adriamycin based adjuvant chemotherapy for breast cancer is low, but the long term effect of commonly encountered sub-clinical cardiotoxicity is not yet clear. Out weighing the benefits and risks at lower cumulative doses, adriamycin is still considered as treatment of choice. Even the test like radionuclide

ventriculography are not so sensitive in detecting early changes of cardiotoxicity. Hence, more pharmacological studies should be done on biomarkers to detect early cardiac damage. Specific cardiac monitoring guidelines should be formed to evaluate adriamycin cardiotoxicity.

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