Concurrent External Radiotherapy And Doxorubicin Based Chemotherapy In Breast Cancer Patients Any Cardiac Side Effects?

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Abstract: Doxorubicin, has for long been a major component in the combination chemotherapy for Breast Cancer. At a cumulative dose of 400 and 600mg/m^2 cardiomyopathies and electrocardiographic changes have been reported which may be worsen in patients who receive external beam radiation treatment to the left chest wall. This study aimed at examining presence of cardiac sequalae that may result from concurrent use of Doxorubicin based chemotherapy and external beam radiotherapy to the chest wall in our breast cancer population. Sixty-five (65) patients with cancer of the breast on combination therapy who received 50mg/m^{2}of Doxorubicin in four divided three weekly doses and had 50Gy of external beam radiation in 25 daily fractions over 5 weeks were evaluated. The patients also had 5-florouracil 1000mg/m^2 and Cyclophosphamide 1000mg/m^2 as part of the combination chemotherapy. All patients had ECG and Echocardiography before commencement of treatment and at three and nine months post treatment. Only 55 were found evaluable at the end of the study with mean age of 48 years. Eleven patients had history of hypertension while none had any previous history of heart diseases. The pre and post-treatment ECG and Echocardiography were similar (p>005). The participants were also symptom free during the follow up period. Though this study suggests a safe combination of Doxorubicin-base chemotherapy and chest wall radiation within the period of evaluation, this may however, not exclude the possibility of long term complications.
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1. Introduction

Doxorubicin is anthracycline, cytotoxic agent used in combination with Cyclophosphamide and 5fluorouracil as first line chemotherapy in breast cancer management worldwide.

Doxorubicin has among other side effects, cardiac toxicity[1, 2], which necessitates monitoring of cardiac functions by ECG and echocardiograph before commencement of Doxorubicin based chemotherapy regimen. At a cumulative dose of 400mg – 600mg/m^2, cardiac side effects such as congestive heart failure, cardiomyopathies associated with reduction of QRS voltage, and reduction of the left ventricular ejection fraction have been reported[3,4,5], hence the need for regular follow up.

A potential increase in risk of cardiotoxicity is envisaged when Doxorubicin is used concomitantly or prior to External Radiotherapy to the mediastinal pericardial area when delivering radiotherapy to the chest wall of breast cancer patients.[7, 8]

Concurrent use of Radiotherapy and Chemotherapy is preferred because delay in commencement of radiotherapy has been shown to decrease local control of breast cancer.[9]

There is an inclination towards chemo-radiotherapy because chemotherapy potentiates the effects of irradiation, on this combination reduces total length of time for treatment, but may increase risks of cardiac toxicity.

This study aims to define the risks of cardiac toxicity in patients on combination therapy.

2. Materials and Method

Sity five new consecutive patients with confirmed diagnosis of breast cancer attending Radiotherapy clinic of University College Hospital, Ibadan, Nigeria were recruited. Treatment involved 4 courses of combination chemotherapy with Doxorubicin 50mg/m2, 5 Flourouracil, 1000mg/m2, Cyclophosphomide 1000mg/m2 given intravenously on day 1 and repeated every 21 days. External Radiotherapy commenced 3 days later with 50 Gy in 25 fractions delivered to the chest wall by tangential fields. Cobalt-60 Teletherapy machine of 1.25 MeV energy was used. Each patient was simulated prior to commencemet of radiotherapy. All patients were reviewed weekly to monitor any side effects.

All the patients had full blood count, serum urea and electrolyte, ECG and Echocardiography prior to commencement of treatment. The Echocardiography was repeated at the 3rd and 9th month after completion of treatment.

The echocardiography studies defined pre and post left ventricular ejection fraction, left ventricular end-

diastolic volume, (LVED) left ventricular (LVED) end-systolic volume, left ventricular internal Diameter (LVID) (diastolic), left ventricular Internal Diameter(Systolic) and Ejection fraction (Teicholz/Pombo method).

The objective of the study was explained to the patients and informed consent form was signed by them. Ethical clearance was obtained from the Joint University of Ibadan/University College Hospital, Ibadan ethical review committee.

Short interview with a set of questionnaires was conducted to obtain demographic data and medical history. The second part of the questionnaire consisting of data on investigation results was completed by the attending doctor.

Exclusion Criteria: Patients who have had any previous form of cytotoxic chemotherapy were excluded. Patients were withdrawn from the study when chemotherapy could not be tolerated. Patients with other co-morbid illness e.g. diabetes, were also excluded. Data Analysis Package: The data collected was analyzed using SPSS statistical soft ware.

3. Results

A total of 65 subjects were recruited but only 55 were evaluable. The reasons were deviation from study protocol and inadequate parameters for study in their Echocardiogram reports .The age group ranged from 24- 72 years while the age group 50-59 (32.7) were in majority. 37 subjects (67.2%) had parity of 4 and above. Eleven of the subjects had history of hypertension; none had history of heart disease. 48 (87.2%) of them were sedentary workers. All participants had their Full blood Count and Serum Electrolytes and Urea within normal limits. The six parameters mentioned above in the Echo-cardiograph pre and post treatment were compared.

Table 1

T-Test

Group

	TREA	N	Mea	Std.	Std. Mea
EF	Pre	55	71.011	10.9355	1.4745
	Post	55	71.338	10.5758	1.4260
LVDiD	Pre	55	4.312	.7451	.1004
	Post	55	4.309	.7542	.1017
LVDiS	Pre	55	2.798	.5183	.0699
	Post	55	2.777	.6011	.0810

The result in table 1 did not show any significant difference in the Pre and Post Echocardiographs.

EF= Ejection Fraction

LVDiD =Left ventricular Internal diameter in Diastole.

LVDiS=Left ventricular Internal diameter in systole.

Table2

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower	95% Confidence Interval of the Difference Upper
EJEFRAC	Equal variances assumed	.035	.852	-.159	108	.874	-.3264	2.05132	-4.39243	3.73970
	Equal variances not assumed			-.159	107.879	.874	-.3264	2.05132	-4.39248	3.73975
LVDIAD	Equal variances assumed	.025	.874	.022	108	.983	.0031	.14296	-.28028	.28646
	Equal variances not assumed			.022	107.984	.983	.0031	.14296	-.28028	.28646
LVDIAS	Equal variances assumed	1.494	.224	.190	108	.849	.0204	.10703	-.19179	.23252
	Equal variances not assumed			.190	105.713	.849	.0204	.10703	-.19185	.23257

Findings In this Table also did not show any differences in the parameters Pre and Post Treatment.

LVDIAD=Left ventricular end diastolic volume.

LVDIAS=Left ventricular end systolic volume.

Table 3

Pearson Correlation Coefficients

Prob > |r| under H0: Rho=0

Number of Observations

	EJEFRAC1	LVEDV1	LVESV1	LVEF1	LVDIAD1	LVDIAS1
EJEFRAC2	0.10980	-0.08350	0.11246	0.04214	0.19211	-0.07468
	0.4431	0.6609	0.5541	0.8250	0.1640	0.5915
LVEDV2	-0.01771	0.48872	0.34859	-0.09889	0.10177	0.11621
	0.9274	0.0053	0.0546	0.5966	0.5859	0.5336
LVESV2	0.01221	0.74924	0.51813	0.17608	0.14644	0.38839
	0.9499	<.0001	0.0028	0.3434	0.4318	0.0308
LVEF2	0.04769	0.02123	-0.03405	-0.15244	-0.04396	-0.04771
	0.8060	0.9098	0.8557	0.4130	0.8143	0.7988
LVDIAD2	-0.00904	0.16288	0.23420	-0.23884	0.85206	0.30172
	0.9498	0.3813	0.2048	0.1957	<.0001	0.0252
LVDIAS2	-0.12791	0.11094	0.42290	-0.50817	0.19288	0.54761
	0.3711	0.5524	0.0178	0.0035	0.1583	<.0001

Correlations were significantly present between Pre treatment Left ventricular end diastolic volume LVEDV1 and Post treatment Left ventricular end systolic volume LVESV P : 0.001. Same was noticed for Pre treatment Left ventricular internal Diameter Diastolic (LVDIAD1)and post treatment

Left ventricular internal diameter diastolic LVDIAD2 p: .0001, this was also true for internal diameter systolic pre and post treatment with p: .0001

Table 4

Age Group	Number	%
20-29	1	1.8
30-39	12	21.8
4049	16	29.0
50-59	18	32.7
60-69	6	10.9
70-79	2	3.6
Total	55	100

4. **Discussion**

Chemo-radiotherapy is a regimen of cancer treatment being used for most Head and Neck and gynaecological malignancies, it is also now being used in Breast cancer cases, the idea is to take advantage of the synergistic effect of the cytotoxic chemotherapy and radiotherapy. This prospective study has shown that there is little or no harmful effect on the heart when Doxorubicin based cytotoxic chemotherapy is combined with radiotherapy of the chest wall of breast cancer patients. The differences noticed in the parameters of the echocardiograph of the 55 patients studied pre and post treatment were not statistically significant as shown in the Tables 1 and 2. No serious side effects were observed during the 9 month post treatment follow -up.

As shown in Table 3, correlations were significantly present between Pre treatment Left ventricular end diastolic volume LVEDV1 and Post treatment Left ventricular end systolic volume LVESV P : 0.001. Same was noticed for Pre treatment Left ventricular internal Diameter Diastolic (LVDIAD1) and post treatment Left ventricular internal diameter diastolic LVDIAD2 p: .0001, this was also true for internal diameter systolic pre and post treatment with p: .0001. These observations did not translate to any observable clinical signs among the study group

Clement IP et al in their study of cardiac dysfunction following initiation of Doxorubicin therapy reported that LV systolic and diastolic function were not related to doxorubicin dose, however the decrease in LV ejection fraction with Doxorubicin were more notable in patients who received concurrent mediastinal irradiation with Doxorubicin.

In our study there was no notable difference in LV ejection fraction pre and post current irradiation and Doxorubicin.

Minow R.A et al reported cardiomyopathy to be of increase in uncontrolled hypertensive patients exposed to Doxorubicin even at lower doses.

It was also observed that congestive Heart failure was more likely to be fatal if it developed shortly after the last dose of Doxorubicin. There were 11 patients with controlled hypertension among the patients studied, non had any adverse reaction expect for a patient whose last course of Doxorubicin had to be delayed because of dizziness and easy fatigability she however admitted to having these symptoms periodically even before the commencement of treatment. In conclusion our results on a general note did not reveal any adverse cardiac side effects as seen on the outcome of the echocardiographs within the study period of 9 months, however in view of the limited number of patients involved in this study it might be difficult to conclude on the safety of this regimen of treatment. A larger and longer study will be required to ascertain the long term safety of the regimen.

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