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A PROSPECTIVE STUDY TO EVALUATE CARDIAC FUNCTIONS IN POST-MASTECTOMY LEFT-SIDED BREAST CANCER PATIENTS RECEIVING DOXORUBICIN BASED CHEMOTHERAPY AND CHEST WALL IRRADIATION

Oncology

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ABSTRACT

This prospective single institution study was carried out with 55 patients to evaluate the cardiac functions in left sided post mastectomy breast cancer patients who received Doxorubicin based chemotherapy with chest wall irradiation. Our study reported only 18% cardiotoxicity in contrast to about 30% in similar studies. There was a decline in the left ventricular ejection fraction after chemotherapy. Radiation did not affect left ventricular function much. The right ventricular systolic dysfunction observed in our study, as depicted by the value of TAPSE decreased after chemotherapy and then after radiation. Neither age nor the use of Taxanes following Doxorubicin administration factored much. The mean cumulative dose of Doxorubicin was confined to 360 mg/m2. Radiation induced cardiac dysfunction was mainly confined to the changes in the dimensions of the ventricles and left atrium volume. Decreased cardiotoxicity observed was probably due to short follow up of 6 months.

KEYWORDS

Doxorubicin, Radiotherapy, Cardiotoxicity, Left sided breast cancer

Breast cancer is the most common cancer in women, accounting for 25.1% of all cancers. Breast cancer incidence in developed countries is higher, while relative mortality is greatest in less developed countries[1].Cancer of breast has ranked number one cancer among Indian females with age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women.[2]

Patients presenting with breast cancer require multi-disciplinary approach incorporating diagnostic imaging,histopathological assessment, molecular-basedstudies, surgery, chemotherapy and radiation, and, if indicated, biologic and hormonal therapies. Adjuvant chemotherapy prevents the recurrence of breast cancer by eradicating occult, micro-metastatic deposits of tumour. Radiotherapy (RT) reduces the risk of local relapse and increase overall survival in carcinoma breastand isoffered to nearly all patients after conservative surgery and to selected patients after mastectomy[3]. Doxorubicin based chemotherapy and radiotherapy is an integral part in the primary treatment of breast cancer and majority of the women are offered either one or both the modalities.[4] Doxorubicin is a cardio-toxic agent that produces cardiac events ranging from arrhythmias, ischemic changes, pericarditis to cardiac failure. Left sided chest wall irradiation leads to added risk of cardiac toxicity. Doxorubicin and radiation have been implicated in causing potentially irreversible cardiac dysfunction. The successful treatment of breast cancer has improved survival but the long-term toxicities of treatment protocols take a paramount importance.[5] Subclinical cardiac changes can occur during the early phase of treatment and it can progress to chronic cardiac toxicity.

AIMS AND OBJECTIVES

The present study aims to look for the cardiotoxicities profile after use of doxorubicin and chest wall irradiation in patients of left sided breast cancer after modified radical mastectomy. Specific objectives were to assess the spectrum of changes in cardiac functions.

MATERIALAND METHODS

This prospective observational study was carried out at Radiotherapy Department of Burdwan Medical College & Hospital from January 2019 to July 2020. All left sided post mastectomy histologically proven female carcinoma of breast cases with Karnofsky status ≥ 70 planned for adjuvant Doxorubicin based Chemotherapy & Chest wall irradiation were included. Patients with cardiac or lung disease, bone marrow, liver or renal impairment were excluded.

After clinical and histological evaluation, ethical committee clearance and written informed consent doxorubicin containing chemotherapy regime were administered followed by external beam radiotherapy using Gamma rays from Telecobalt machine by 2D technique. Supraclavicular fields and axillary fields were included as per the nodal status. Baseline Chest X-Ray, ECG and 2D Echocardiography were done and were repeated at the end of chemotherapy/before starting radiation and 6 months after the end of radiation. Valvular function, pulmonary hypertension and pericardium for effusion and pericarditis were assessed. The parameters assessed in the echocardiography were - Left atrium diameter and volume, Right ventricle end diastolic volume, Tricuspid annular plane systolic excursion (TAPSE), Left ventricular internal diameter end diastole (LVIDD), Left ventricle end diastolic volume (LVEDD) and Left ventricle ejection fraction (LVEF).

Statistical Analysis

Statistical analysis was done using SPSS version 20. For categorical variables, Chi Square and Fisher Exact tests were used, while for continuous variables, the mean and SD were compared using Independent samples 't' test with 95% CI. All tests were 2-tailed and p value less than 0.05 was taken as significant.

RESULTS

Table No 1: Patient Profile

Age	No of Patients	%
31-40	11	20%
41-50	26	47.27%
51-60	07	12.71%
61-70	11	20%
Karnofsky Performance Score		
90 or more	29	52.72%
80	18	32.72%
70	8	14.54%
Staging AJCC		
IIA	1	1.81%
IIB	21	38.18%
IIIA	26	47.27%
IIIB	7	12.72%
Chemotherapy Regime		
AC*4 then Taxane*4	35	63.63%
FAC*6	20	36.36%
Radiotherapy Schedule		
45 Gray/20#/4 weeks	54	98.18%
40 Gray /15#/3 weeks	01	03.63%

All patients underwent Doxorubicin based chemotherapy 35 patients received Doxorubicin + Cyclophosphamide (AC) 4 cycles followed by 4 cycles of Taxane and 20 patients received 6 cycles of FAC regime (5 FU + Doxorubicin + Cyclophosphamide). Chemotherapy was followed by adjuvant External Beam Radiotherapy in Telecobalt Machine.

The incidence of subclinical cardiac dysfunction was 18% (10 of the 55 patients) after chemotherapy.

The Left ventricular ejection volume, the tricuspid annular plane systolic excursion (TAPSE), Left ventricular internal diameter end diastole (LVIDD)and Left Ventricular End Diastolic Diameter (LVEDD) all showed statistically significant deterioration both post Chemotherapy and post Radiotherapy.

Table 2: Echocardiographic Features

	Baseline	Post Chemotherapy	p value1	Post Radiation	p value2	p value3
Subclinical Findings						
Concentric LVH	2					
Grade I LVDD		6				
Grade II LVDD		4		1		
Dilated left atrium				1		
LVEF	66.29 ± SD 3.58	64.03 ± SD 3.57	0.000*	64.8 ± SD 3.15	0.000*	0.013*
Left Ventricular End Diastolic Diameter (**LVEDD**)	41.65 ± SD 2.28	41.96 ± SD 2.19	0.033*	42.05 ± SD 2.47	0.036*	0.024*
Left Atrial diameter	30.87 ± SD 2.03	30.72 ± SD 2.19	0.242	30.94 ± SD 2.47	0.584	0.009*
Left Atrium Volume	33.36 ± SD	33.45 ± SD 3.80	0.461	33.63 ± SD 3.76	0.358	0.501
Right Ventricular End Diastolic Volume (**RVEDV**)	136.12 ± SD 3.93	136.54 ± SD 4.17	0.057	137.26 ± SD 4.28	0.001*	0.008*
Tricuspid annular plane systolic excursion (**TAPSE**)	21.29 ± SD 1.49	20.67 ± SD 1.22	0.001*	20.30 ± SD 1.30	0.000*	0.032*
Left ventricular internal diameter end diastole (**LVIDD**)	45.16 ± SD 2.38	45.65 ± SD 2.37	0.002*	46.16 ± SD 2.58	0.000*	0.005*

P-value< 0.05: * Significance; 2: p-value of baseline and RT; 3: p-value of post CT and RT

DISCUSSION

Carcinoma of breast is primarily managed by surgery followed by adjuvant chemotherapy, radiotherapy, directed therapy and hormonal therapy depending on histopathological and immunohistochemistry report.The present study evaluated the changes in the cardiac status during the course of the study till its end point, i.e. 6 months after the completion of radiation by taking serial echocardiographs at the baseline or beginning of the chemotherapy, after the completion of the chemotherapy regime and lastly at the interval of six months from the completion of the radiation therapy.

Doxorubicin induced heart disease includes Supraventricular or ventricular arrhythmias, Abnormal ventricular repolarisation, QT changes in ECG, Acute coronary syndrome, Pericarditis-myocarditis. Late complications include Congestive cardiac failure and severe cardiomyopathy.Radiation induced cardiac ailments include Radiation-induced atherosclerosis, Pericardial disease, Pan carditis, Cardiomyopathy, Valvular disease, Conduction disturbances – RBBB and Atrioventricular nodal block.

Incidence of cardiac dysfunction rises steeply if cumulative dose of doxorubicin exceeds 550 mg/m^2. The present study encountered cardiac dysfunction, though asymptomatic, at lower cumulative dose range, viz., 300 to 400 mg/m^2, by serial echocardiographic measurements.

Cumulative dose of doxorubicin is the single most important determinant of cardiac toxicity. Lefrak et al.[6] in their study found that incidence of congestive cardiac failure rose to unacceptably high levels when cumulative dose of drug exceeded 550 mg/^{m2}.Von Hoff et al[7] found that cumulative probability of developing drug-induced heart failure was 0.03 at 400 mg/m^2, 0.07 at 550 mg/m^2 and 0.18 at 700 mg/m^2.

Radiation injury to the myocardium is primarily caused by damage to the microvasculature, leading to inflammatory and thrombotic changes, capillary loss, focal ischemia, and interstitial fibrosis; these can cause congestive heart failure. In a study by Skyttä et al[8] it was reported that RT did not cause any immediate significant changes in LV systolic or diastolic function except for minor diastolic function. However according to Wethal T et al[9] and Darby SC et al[10] changes may be observed over time and clinically significant cardiac adverse events may emerge during long-term follow-up.

Subclinical cardiac impairment occurred in 18% of our study population. Dresdale et al.[11] reportedsubclinical cardiac dysfunctionin 21% of patients.In the present study the most significant echocardiography finding at the end of chemotherapy was the fall in the mean value left ventricle ejection fraction (LVEF) by 2.26%p value of 0.000, which was statistically significant. This was comparable to the findings of Vinin NV et al[12] who reported a fall of 3.34 in the mean value from the baseline of 66.79 % SD ± 3.73 to 63.45 % SD ± 3.54. A total of 45 patients showed fall in the ejection fraction, though of very minimal value, that translate to 81%. The mean value of ejection fraction after the radiation did not fall but increased from 64.03 SD ± 3.73 after the chemotherapy to 64.80 SD ± 3.15 with p value of 0.013 which was significant. This is in conformity with the finding of Lo Q et al[13], who detected subclinical cardiac dysfunction by 2-D strain imaging in LV after left-sided breast cancer RT, but LVEF remained unchanged.In our study, it was observed that there was a slight but statistically significant fall in the mean value of TAPSE after the chemotherapy and further fall after RTwhich was also statistically significant. The fall from the baseline value observed mean value after RT was approximately 1 mm similar to reported by Skyttä et al[14] who reported 1.4 mm fall after RT. In the present study there were 3 cases who reported more than 4 mm fall in mean TAPSE value. Measurement of RV function is a sensitive indicator of radiation-induced myocardial injury and an attractive tool for the follow-up of patients after RT.

Rui Zhao et al.[15] reported significant increase in the RVEDV after 6 cycles of Doxorubicin based chemotherapy, among 36.4% (24 of 74) of the patients. In our study, mean value of RVEDV increaseis not statistically significant (p=0.057), however the number of patients who shows increased in RVEDV was 12.72% (7 of 55) of the patients. Inpost RT phase the mean value increased to 137.26 SD ± 4.28 which was significant (p=0.008) similar to other studies.

Marijana Tadic et al.[16] reported greater diameter and higher volume among patients undergoing chemotherapy and radiation. Left atrium diameter and volume, in our study do not show any significant pattern of change. The baseline mean for left atrium diameter was 30.87 SD± 2.03, the mean value after the chemotherapy was 30.72 SD± 1.91 which was statistically insignificant. The mean value after the RT was 30.94 SD± 2.00 which was statistically significant in comparison with the post chemotherapy mean value (p = 0.009). The changes in the mean left atrium volume were minimal and statistically insignificant.

Anthracyclines administration results in increased internal diameter of the left ventricle in diastole, LVIDD. Narayan HK, et al[17] also reported increment in the LVIDD among children receiving doxorubicin for various cancers. At the baseline, the mean LVIDD was 45.16 SD± 2.38 with slight increment in the post chemotherapy period value to 45.65 SD± 2.37 with p value of 0.002. There was further increment in the post

RT period with mean value of 46.16 SD± 2.58 (p = 0.005). In our study the mean value of LVEDD was increased from baseline to post chemotherapy and after the radiation. This is in conformity with the findings of Hyun Ju Yoon et al[18] and Skyttä et al[14].

SUMMARY AND CONCLUSION

There is increased risk of cardiotoxicity in left sided breast cancer patients receiving Doxorubicin based chemotherapy along with chest wall irradiation. Our study showed impaired cardiac function in 18% cases as compared to about 30% in worldwide studies. It may be due to our short follow up of the patients (six months after radiation completion).As observed from the present study it is quite safe for breast cancer patients to receive Doxorubicin based chemotherapy with cumulative dose of less than 400 mg/m2 along with left sided chest wall irradiation. A study with larger sample size and longer duration of follow up in term of several years is required for more definitive conclusions.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359–86.
2. Gupta A, Shridhar K, Dhillon PK. A review of breast cancer awareness among women in India: cancer literate or awareness deficit. Eur J Cancer 2015; 51: 2058–66.
3. Letizia Deantonio, Giuseppina Gambaro, Debora Beldi.Hypofraetionated radiotherapy after conservative surgery for breast cancer: analysis of acute and late toxicity.Deantonio et al.radiation oncology 2010,5:112
4. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. NEngl J Med 1998;339: 900-905.
5. Mansoorulhaq Lone, RefutArah Banoo, Mohammad Ashraf, Nazir Ahmad Khan, KhurshidAslam, Zahoor Ahmad Wafai. Assessment of cardiovascular functions in survivors of breast cancer patients treated with chemo-radiation. International Journal of Contemporary Medical Research 2017;4(7):1504-1509.
6. Lefrak EA, Pitha J, Rosenheim S, et al: A clinico-pathologic analysis of Adriamycin cardiotoxicity. Cancer 32:302-314, 1973
7. Von Hoff Ann Intern Med 18:475478, 1974DD, Layard M, Basa P, et al: Analysis of risk factors for development of Adriamycin-induced congestive heart failure. Proc Am Asso Can Res and ASCO 19:215, 1978
8. Skyttä, T., Tuohinen, S., Boman, E. et al. Troponin T-release associates with cardiac radiation doses during adjuvant left-sided breast cancer radiotherapy. Radiat Oncol 10, 141 (2015). https://doi.org/10.1186/s13014-015-0436-2
9. Wethal T, Lund MB, Edvardsen, et al. Valvular dysfunction and left ventricular changes in Hodgkin's lymphoma survivors. A longitudinal study. Br J Cancer. 2009;101 (4):575-581. doi:10.1038/sj.bjc.6605191
10. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368:987–98.
11. Dresdale, A. R. et al. Prospective randomized study of the role of N-acetyl cysteine in reversing doxorubicin-induced cardiomyopathy. Am. J. Clin. Oncol. 5, 657–663 (1982)
12. Vinin NV, Prem SS, Pillai A, Reddy KS, Halanaik D, et al. (2015) Early Cardiac Changes Due to Doxorubicin Based Chemotherapy and Radiotherapy in Early and Locally Advanced Carcinoma Breast Patients: An Observational Study. J Nucl Med RadiatTher S7: S7-004. doi:10.4172/2155-9619.1000S7-004
13. Lo Q, Hee L, Batumalai V, Allman C, MacDonald P, Delaney GP, et al. Subclinical cardiac dysfunction detected by strain imaging during breast irradiation with persistent changes 6 weeks after treatment. Int J RadiatOncol Biol Phys. 2015;92:268–76.
14. Tanja Skyttä, Suvi Tuohinen, Tina Luukkaala, Vesa Virtanen, Pekka Raatikainen & Pirkko-Liisa Kellokumpu-Lehtinen (2019) Adjuvant radiotherapy induces cardiac changes among patients with early breast cancer: a three-year follow-up study, Acta Omcologia 58:9, 1250-1258, DOI: 10.1080/0284286X.2019.1630751
15. Rhui Zhao, Fang Shu, Chujie Zhang, Feiyang Song, Yuchen Xu, Ye Guo, Kai Xuei, Jinyi Lin, Xiahang Shu, David H His, Leilei Cheng. Early detection and prediction of anthracycline-induced right ventricular cardiotoxicity by 3-diamensional echocardiography. JACC: Cardiac Oncology Vol 2, Issue1, March 20120, pages 13-22
16. Marijana Tadic, Martin Genger, Cesare Cuspidi, Evgeny Belyavskiy, Athanasios Frydas, Aleksander Dordevic, Daniel A. Maorris, Jakob Volkl, Abdul Shokor Parwani, Burkert Pieske and Sabine Habfeld. Phasic left atrium function in cancer patients before initiation of anti-cancer therapy. J Clin Med. 2019 April; 8(4): 421
17. Narayan Hk, Wei W, Feng Z, et al. Cardiac mechanics and dysfunction with anthracyclines in the community: results from the PREDICT study. Open Heart2017; 4:e000524. doi:10. 1136/openhrt-2016-000524
18. Yoon HJ, Kim KH, Kim JY, et al. Chemotherapy-Induced Left Ventricular Dysfunction in Patients with Breast Cancer. J Breast Cancer. 2016;19(4):402-409. doi:10.4048/jbc .2016.19.4.4