ORIGINAL ARTICLE

LEFT VENTRICULAR SYSTOLIC DYSFUNCTION PREDICTED BY EARLY TROPONIN I RELEASE AFTER ANTHRACYCLINE BASED CHEMOTHERAPY IN BREAST CANCER PATIENTS

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Background: Anthracyclines are one of the most effective chemotherapeutic agents in management of Breast cancer, however Anthracycline induced cardiotoxicity remains a matter of special concern. Detection of early toxicity by use of biomarkers like Troponins has been the focus of interest in recent years. We measured Troponin I levels after chemotherapy with anthracyclines and correlated it with ECG, Echocardiography and clinical findings. **Methods:** Patients with early Breast cancer eligible for chemotherapy were included in the study. All patients underwent clinical evaluation, Left Ventricular Ejection Fraction (LVEF) measurement by echocardiography at baseline and every 03 monthly for first year. Serum samples for TNI were obtained immediately after chemotherapy and after 24 hrs. **Results:** A total of 82 patients (all females) were included in the study. Median age was 47 (range 30–64) years. Anthracycline mediated cardiotoxicity occurred in 6 patients (7%) and was more frequent in patients with TNI elevation (p<0.001). Five patients (83%) recovered from cardiotoxicity. At multivariate analysis, TNI elevation was the only independent predictor of cardiotoxicity (95% CI 0.0007879–0.2821) and of lack of LVEF recovery (95% CI 0.002484 to 1.680). **Conclusion:** Measurements of Trop I levels after Anthracyclines can be useful in detecting early cardiotoxicity and tailoring further therapy.

Keywords: Anthracyclines; Cardiotoxicity; Breast cancer; Troponin I; Left ventricular dysfunction

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INTRODUCTION

Anthracyclines alone or in combination with other chemotherapeutic agents are one of the most active drugs in the management of breast cancer. In the adjuvant setting clinical trials have shown survival advantage after the use of anthracyclines.[1] However cardiotoxicity remains a matter of special concern in these patients who otherwise have potentially curative cancer.[2,3]

Anthracycline induced cardiotoxicity can present in acute, sub-acute and late phases. Acute cardiotoxicity is a relatively uncommon event and is usually self-limiting.[4] In adults, chronic anthracycline related cardiotoxicity typically presents within one year after termination of chemotherapy. The peak time for the appearance of symptoms of heart failure is about three months after the last dose of chemotherapy.[5,6] Symptomatic heart failure can occur even more than a decade after the last anthracycline dose.

In adults, late toxicity is of great concern in clinical situations where anthracyclines are used as part of a curative regimen. Patients with Her-2 positive Breast cancer appear to preferentially benefit from anthracyclines. As these patients are likely to be treated with Trastuzumab which has additional cardiotoxicity,[7–9] it is very important to identify early cardiotoxicity to avoid further cardiac damage which may be irreversible in a significant subset of patients exposed to Trastuzumab. Detection of early cardiotoxicity after anthracyclines can be beneficial as early treatment with ACE Inhibitors may prevent delayed cardiotoxicity.[10]

Measurement of serum troponins is useful to confirm the diagnosis of acute myocardial injury. Several studies suggest that elevations in troponin T and I may be an early marker of acute myocardial injury in patients receiving cardiotoxic therapy.[11–15] Elevations in serum troponin T in children were associated with the severity of myocardial damage from doxorubicin and predicted subsequent subclinical and clinical cardiac morbidity and mortality.[16]

Thus, early identification of patients for anthracycline related cardiac toxicity through the use of biomarkers such as troponin I holds promise for identification of patients who might benefit from preventive strategies like ACE inhibitors and planning further treatment.

MATERIAL AND METHODS

A total of 82 new patients with Breast cancer receiving neoadjuvant or adjuvant anthracycline based chemotherapy were included in the study

from Sep 2011 to Sep 2012. The study was conducted at Shaukat Khanum Memorial Cancer Hospital over a period of 12 months. The diagnosis of Breast Cancer was established by trucut biopsy or lumpectomy.

All consecutive patients fulfilling above criteria were included in study after taking informed consent. Patients with evidence of coronary artery disease, valvular heart disease, pre-treatment left ventricular dysfunction (LVEF ≤50%), acute or chronic renal insufficiency, deranged LFTs, previous exposure to anthracyclines and severe hypertension (systolic ≥180 mmHg or diastolic ≥110 mmHg) were excluded from the study.

Patients received intravenous chemotherapy containing anthracyclines according to standard international protocols. Exact dose and regimen of anthracycline based chemotherapy for each patient was recorded. The study protocol was approved by scientific review committee and institutional review board.

Primary endpoint of the study was defined as absolute decrease in LVEF of ≤10 percent from baseline or decrease in LVEF below the normal limit of 50%.

Secondary endpoints of the study were clinical heart failure, exertional dyspnoea, orthopnoea, S3 gallop, acute coronary syndrome, acute pulmonary oedema and life threatening arrhythmias.

All patients underwent Left Ventricular Ejection Function measurement by echocardiography at baseline, every 3 monthly for the first year. In case of cardiotoxicity, further anthracycline therapy was withheld and LVEF was measured monthly during first 3 months of therapy and then as per protocol. In patients lost to follow up, the last evaluation was considered the final measurement. ECG was recorded after each cycle of chemotherapy.

Serum samples for TNI were taken immediately after each cycle of chemotherapy and after 24 hrs. The blood samples were centrifuged within 60 min and plasma stored immediately at -30 °C. Troponin I concentration was measured by immune enzymatic fluorescent assay (Stratus II, Dade International Inc., Miami, Florida). Troponin I levels were recorded and correlated with Echo findings.

SPSS version 19 was used for data analysis. Continuous variables were expressed as mean±standard deviation (SD). The Student's *t*-test (unpaired samples) was used to compare differences in mean values. A *p*-value of less than 0.05 was considered significant. Categorical variables (hypertension etc.) were analysed using the chi-square test.

RESULTS

Eighty-two patients (all females) completed the protocol (median age 47 years). The patients were followed for 06 months after the completion of their chemotherapy regimen. Patients' characteristics are described in table-1. Twenty-eight patients (34.14%) had hypertension which was well controlled on medication. Their anti-hypertensive drugs were continued during the study.

In the whole population, the median treatment time with anthracycline was 3 months. Anthracycline induced drop in left ventricular ejection fraction occurred in six patients (7%) with drop in LVEF below the normal limit of 50% or absolute decrease in LVEF of ≥10 units from baseline.

However, cumulative cardiotoxicity in the study group was 12%. One patient developed symptoms of CCF requiring treatment. One patient had acute coronary event and 2 patients had arrhythmias requiring treatment. Anthracycline induced cardiotoxicity was usually detected in first six months after the end of Anthracycline based chemotherapy. In case of significant drop in left ventricular ejection fraction, further treatment with anthracycline based chemotherapy was withheld and patients were treated with ACE inhibitors, beta blockers and aspirin.

Table-2 summarizes the clinical characteristics of patients with and without anthracycline induced cardiotoxicity. Cardiotoxicity occurred more frequently in patients with a lower baseline LVEF and with persistently elevated TNI after treatment.

TNI levels were elevated in 18 patients (33%). In the remaining 64 patients, TNI levels remained normal during the course of therapy. The elevated TNI level was observed in most cases, soon after the first chemotherapy cycle. Most patients showed only a transient TNI rise that normalized in subsequent cycles. At multivariate analysis, adjusted for major confounders, TNI elevation was the strongest independent predictor of cardiotoxicity (95% CI 0.003546 to 0.2535; $p < .001$).

Overall 10 cardiac events occurred in the study with 9 events in patients with elevated TNI levels and only 1 event in patients with normal TNI levels. There were no cardiac deaths in the study.

Table-1: Patients characteristics at baseline

Patient characteristics	No. of patients 82 (%)
Age Median, range	47 (30–64)
Age ≤50 years ≥50 years	32 (39) 50 (61)
Site of tumor Left Right	54 (66) 28 (34)
Menopausal status Pre- Post-	25 (30) 57 (70)
Type of surgery Conservative Mastectomy	48 (58) 34 (42)
Family History of Coronary Artery Disease	18 (22)
Hypertension	28 (34)
Hormonal Status ER: PR: HER2-NEU	60 (73) 58 (70) 26 (31)
Chemotherapy Regime AC FAC FEC	58 (70) 14 (17) 10 (13)

Table-2: Adverse cardiac events in the study population and in patients with normal TNI (N) or elevated TNI (TNI+)

Events	Total n= 82 No	TNI + n= 18 No	TNI (N) n= 64 No
LVEF reduction	6	6	0
Congestive cardiac failure	1	1	0
ACS	1	1	0
Acute pulmonary edema	0	0	0
Cardiac death	0	0	0
Arrhythmias	2	1	1
Total events	10	9	1

Abbreviations: TNI, troponin I; TNI+, elevated TNI; TNI (N) normal TNI; LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome $p < .001$ v elevated troponin I (by Fisher's exact test)

Table-3 Statistical analysis of adverse cardiac events

Total No n-82	TNI Normal n-64	TNI Elevated n-18	*p*-value	Odds Ratio +95% Confidence Interval
LV EF Reduced	0	6 (7.31%)	*p<0.0001	0.015 95% CI " 0.00079 to 0.28"
LV EF Normal	64 (78%)	12 (14.63)		
Congestive Cardiac failure	0	1 (1.22%)	0.17	0.065 95% CI "0.0025 to 1.7"
Normal Cardiac Function	64 (78%)	17 (20.73%)		
ACS	0	1 (1.22%)	0.17	0.065 95% CI "0.0025 to 1.7"
Without ACS	64 (78%)	17 (20.73%)		
Arrythmia	1 (1.22%)	1 (1.22%)	0.39	0.27 95% CI "0.016 to 4.5"
Normal Rythm	63 (76.82%)	17 (20.73%)		
Total Cardiac Events	1 (1.22%)	9 (10.97%)	*p<0.0001	0.030 95% CI "0.0036 to 0.25"
No Cardiac Event	63 (76.82%)	9 (10.97%)		

Abbreviations: TNI, troponin I; TNI+, elevated TNI; TNI (N) normal TNI; LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome

DISCUSSION

Anthracyclines act by inhibition of DNA and RNA synthesis by intercalation between DNA base pairs by inhibition of topoisomerase II. Myocytes damage has been attributed to the production of toxic oxygen free radicals which cause lipid peroxidation of membranes, leading to irreversible damage and myocytes replacement by fibrous tissue.[17]

One of the strongest predictor for the development of chronic anthracycline mediated cardiotoxicity is the cumulative dose. However, concomitant administration of other cardiotoxic agents, prior chest irradiation, age at the time of exposure and pre-existing cardiovascular diseases are also well-recognized risk factors.[18] Longer duration of survival is also a risk factor for cardiac toxicity.[19] Paediatric studies indicate a continuous deterioration of cardiac function for up to 30 years after treatment. The incidence of congestive heart failure after anthracycline based chemotherapy in breast cancer patients ranges between 3% and 48% according to the cumulative dose of the drug.[20]

Anthracycline-associated cardiac events may occur more frequently and at lower doses if patients are treated with combined chemotherapeutic agents or radiotherapy.[21,22] Cumulative percentages of patients developing doxorubicin related cardiac dysfunction vary from 5% at a cumulative conventional doxorubicin dose of 400 mg/m2, 26% at a dose of 550 mg/m2, and 48% at a dose of 700 mg/m2.

Current diagnosis of anthracycline induced cardiotoxicity is based on physical examination and LVEF measurements.[23] Echocardiographic examination is useful for monitoring patients with asymptomatic cardiac dysfunction but does not provide any predictive information. It is now well known that TNI elevation, soon after high dose chemotherapy (mainly based on anthracycline-containing regimens), is a strong predictor of LVEF reduction and poor cardiac outcome, particularly in patients showing persistently elevated TNI levels.

The exact mechanism for TNI elevation after chemotherapy remains unknown, but it is possible that subclinical myocardial injury may play a role. This possibility is supported by the observation that the percentage of patients with elevated TNI progressively increases in parallel with the increasing number of the cycles performed, confirming the relationship between the doses of anthracyclines and cardiotoxicity risk.

A major finding of our study is that in patients treated with anthracyclines, TNI evaluation provided an important opportunity to identify patients more prone to develop cardiotoxicity. Anthracycline induced cardiotoxicity occurred in 50% of patients with elevated TNI levels and in only 1.5% of patients with normal TNI

levels. In total 10 cardiac events were noted in the study group with nine events occurring in patients with elevated TNI levels and only one in normal TNI patients. No patient had a drop in LVEF in normal TNI subpopulation.

There were no cardiac deaths in our patients. This may be explained by prompt withdrawal of anthracyclines and starting treatment with a combination of enalapril and metoprolol. Most of our patients 5/6 (83%) recovered completely from cardiotoxicity.

Our study has some limitations as well. First, our study population was confined to a single cancer centre. Secondly, the follow up duration was short as delayed cardiotoxicity secondary to anthracyclines has been documented as well. In conclusion, treatment of breast cancer with anthracyclines may be complicated by development of asymptomatic and symptomatic cardiotoxicity. Cardiac dysfunction is reversible in most of cases with prompt withdrawal of offending agent.

CONCLUSION

Monitoring of TNI levels during anthracycline based chemotherapy can potentially identify patients at risk of cardiotoxicity.

Author's disclosure of conflict of interest:
We have no potential conflict of interest.

AUTHORS' CONTRIBUTION

This study was conceived and designed by AS including acquisition of data. Analysis and interpretation of data was done by MUDS. Drafting of manuscript and Critical revision was done by NSi, SI and MUDS.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365(9472):1687–717.
2. Yeh ET, Tong AT, Lenihan DJ, Yusuf SW, Swafford J, Champion C, *et al*. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation 2004;109(25):3122–31.
3. Floyd JD, Nguyen DT, Lobins RL, Bashir Q, Doll DC, Perry MC. Cardiotoxicity of cancer therapy. J Clin Oncol 2005;23(30):7685–96.
4. Wojnowski L, Kulle B, Schirmer M, Schlüter G, Schmidt A, Rosenberger A, *et al*. NAD(P)H oxidase and multidrug resistance protein genetic polymorphisms are associated with doxorubicin-induced cardiotoxicity. Circulation 2005;112(24):3754–62.
5. Von Hoff DD, Rozencweig M, Layard M, Slavik M, Muggia FM. Daunomycin-induced cardiotoxicity in children and adults. A review of 110 cases. Am J Med 1977;62(2):200–8.
6. Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, *et al*. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979;91(5):710–7.
7. Keefe DL. Trastuzumab-associated cardiotoxicity. Cancer 2002;95(7):1592–600.
8. Esteva FJ, Valero V, Booser D, Guerra LT, Murray JL, Pusztai L, *et al*. Phase II study of weekly docetaxel and trastuzumab for patients with HER-2 overexpressing metastatic breast cancer. J Clin Oncol 2002;20(7):1800–8.
9. Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. J Clin Oncol 2004;22(2):322–9.
10. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, *et al*. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patient by angiotensin-converting enzyme inhibition. Circulation 2006;114(23):2474–81.
11. Cardinale D, Sandri MT, Martinoni A, Tricca A, Civelli M, Lamantia G, *et al*. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. J Am Coll Cardiol 2000;36(2):517–22.
12. Lipshultz SE, Rifai N, Sallan SE, Lipsitz SR, Dalton V, Sacks DB, *et al*. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. Circulation 1997;96(8):2641–8.
13. Auner HW, Tinchon C, Linkesch W, Tiran A, Quehenberger F, Link H, *et al*. Prolonged monitoring of troponin T for the detection of anthracycline cardiotoxicity in adults with hematological malignancies. Ann Hematol 2003;82(4):218–22.
14. Cardinale D, Sandri MT, Martinoni A, Borghini E, Civelli M, Lamantia G, *et al*. Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. Ann Oncol 2002;13(5):710–5.
15. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, *et al*. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation 2004;109(22):2749–54.
16. Specchia G, Buquicchio C, Pansini N, Di Serio F, Liso V, Pastore D, *et al*. Monitoring of cardiac function on the basis of serum troponin I levels in patients with acute leukemia treated with anthracyclines. J Lab Clin Med 2005;145(4):212–20.
17. Tripathy D, Seidman A, Keefe D, Hudis C, Paton V, Lieberman G. Effect of cardiac dysfunction on treatment outcomes in women receiving trastuzumab for HER2-overexpressing metastatic breast cancer. Clin Breast Cancer 2004;5(4):293–8
18. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. N Engl J Med 1998;339(13):900–5.
19. Carver JR, Shapiro CL, Ng A, Jacobs L, Schwartz C, Virgo KS, *et al*. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. J Clin Oncol 2007;25(25):3991–4008.
20. Wojtacki J, Lewicka-Nowak E, Lesniewsky-Kmak K. Anthracycline-induced cardiotoxicity:clinical course, risk factors, pathogenesis, detection and prevention-review of the literature. Med Sci Monit 2000;6(2):411–20.
21. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin. A retrospective analysis of three trials. Cancer 2003;97(11):2869–79.
22. Jones AL, Barlow M, Barrett-Lee PJ, Canney PA, Gilmour IM, Robb SD, *et al*. Management of cardiac health in trastuzumab treated patients with breast cancer: Updated United Kingdom National Cancer Research Institute recommendations for monitoring. Br J Cancer 2009;100(5):684–92.
23. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: A retrospective analysis of three trials. Cancer 2003;97(11):2869–79.

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