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ORIGINAL ARTICLE

Cardiac Biomarker for Acute Cardiac Toxicity in Breast cancer Patient Receiving Anthracycline or Trastuzumab in King Abdulaziz University Hospital, Observation Study

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ABSTRACT

Aim: To determine if using cardiac biomarker will predict cardiotoxicity in patients with breast cancer receiving cardiotoxic anti-cancer therapy. Chemotherapy, biological therapy and immunotherapy are associated with this type of toxicity. In our study we focused on the use of anthracycline and trastuzumab.

Methods: We conducted an observational study in which we followed patients who received cardiotoxic medication and assessed cardiac biomarker before therapy, 48-72 hours after and before next cycle. A mixed effect linear regression model was used with patient as a random intercept to model the clinical endpoints before and after the chemotherapy while controlling important demographics

Results: 30 patients with early breast cancer who are receiving treatment at King Abdulaziz University Hospital were eligible. Two patients developed drop in left ventricular ejection fraction. No patient developed symptoms of congestive heart failure. There was no correlation between the elevation in cardiac markers and the decrease in the ejection fraction.

Conclusion: In a small observational study on breast cancer patients at KAUH, there was no correlation between cardiac markers changes and reduction in the left ventricular ejection fraction. A larger cohort will be of benefit to prove if there is a significant correlation.

Key Words: Breast cancer, Anthracycline, Trastuzumab, Cardiac biomarker

INTRODUCTION

Anti-cancer agents are used in treating patients with cancer diagnosis. It includes cytotoxic chemotherapy, biological agents, hormonal therapy and immunotherapies. These agents are associated with multiple toxicities that have been reported in the literature, which is secondary to the agents or their metabolites. The toxicity profile of each agent has been reported in the literature with different ranges[1]. The shared decision of anti-cancer therapy focuses on the benefits and possible complications of these agents. The treating physician usually discuss the common side effects with each individual patient based on their diagnosis and the medical comorbidities, which, might affect the decision of selecting anti-cancer therapies[2].

Cardiac toxicity is known toxicity of anti-cancer agents affecting cancer patients. In a retrospective study, 6.6 % of patients with breast or hematological cancer who received chemotherapy went on to develop heart failure[3]. Cardiac toxicity has been reported with cytotoxic, biological therapy and immunotherapy. These complications include and not limited to myocardial necrosis leading to dilated cardiomyopathy, arrhythmias, vasospasm, or vessel occlusion leading to myocardial infarction, and pericardial disease. The mechanism of cardiac toxicity is well described in the literature[4]. Type 1 chemotherapy related cardiac dysfunction where it is associated with the myocyte destruction and a clinical presentation of a heart failure. This is usually the complication that is encountered in patients receiving anthracycline. Type 2 is associated with a myocyte dysfunction and there will be a loss of contractility of the myocardial cells with drop in the left ventricular function[5]. This complication is detected mainly by drop in the left ventricular ejection which is in majority of cases are reversible and rarely cause heart failure[6].

Chemotherapeutic agents that are associated with cardiac toxicity include anthracycline, cyclophosphamide, taxane and fluorouracil. Biological agents are associated with cardiac toxicity include trastuzumab, imatinib, sunitinib and sorafenib[7]. More recently, association has been reported between the use of immunotherapy and the development of cardiomyopathy. The incidence of cardiotoxicity varies with the type of the treatment. Doxorubicin is associated with cardiotoxicity in 3–26 % of treated patients, trastuzumab in 2–28 % and sunitinib in 2.7–11 %[8].

Anthracycline induces cardiac toxicity through different mechanisms including tissue apoptosis, oxidative stress, and interaction with TOPO2 enzyme[9]. The risk factors for this toxicity include older age more than 65, female gender, pre-existing cardiovascular disorder with ejection fraction less than 50, hypertension, smoking, hyperlipidemia, obesity, diabetes, and high accumulative dose of the anthracycline. There is no standardized definition about cardio toxicity with anthracycline. However, any patient who is presenting with ejection fraction problems or clinical heart failure after anthracycline use, it has to be taking in consideration as a possible etiology in the absence of other underlying risk factors for ischemic heart disease. Retrospective analyses in adults suggest that the incidence of congestive heart failure in patient exposed to doxorubicin was 1.7% at a cumulative dose of 300 mg/m^2, 4.7% at 400 mg/m^2, 15.7% at 500 mg/m^2, and 48% at 650 mg/m[10].

Trastuzumab is a biological agent that is commonly used in treating patients with breast cancer who demonstrate HER2 over-expression. Different studies showed that patients who received trastuzumab had a higher chance of congestive heart failure (2.5% versus 0.5% in patients who did not receive trastuzumab). The risk factors include age above 50 and the concurrent use of anthracycline[11].

Cardiac biomarker can be released in myocardial injury. The use of biomarkers in detecting cardiac toxicity has been reported previously where multiple trials shows a conflicting data. Some of the trials showed significant correlation between the release of cardiac biomarkers and the cardiac toxicity while other trials did not show that correlation[12].

This study aimed to determine if using cardiac biomarker will predict cardiotoxicity in patients with breast cancer receiving cardiotoxic anti-cancer therapy. Chemotherapy, biological therapy and immunotherapy are associated with this type of toxicity. In our study we focused on the use of anthracycline and trastuzumab

METHODS AND MATERIALS

This observational study was conducted among patients with breast cancer who are receiving chemotherapy in the daycare at King Abdulaziz University Hospital during 2019-2020.

Patient was legible to be included in the study if they are diagnosed with early a breast cancer and they are receiving a cardiotoxic medication including anthracycline or trastuzumab. Patients must have a normal ejection fraction at the baseline. Normal cardiac function was defined by having left ventricular

ejection fraction of 50% or more. Patient must be able to give consent and agree to the protocol. The basic characteristics of each patient including age, stage, estrogen and progesterone receptor and Her 2 expression were collected.

The study protocols mandate that patient has a baseline cardiac marker to be done within 48 hours before the infusion of the chemotherapy then a second set of cardiac markers to be collected between 48 and 72 hours after chemotherapy infusion. We also collected a third set of the cardiac enzyme before subsequent cycle to make sure whether the patient had late and persistent elevation of cardiac markers. Only one encounter is allowed per patient. Collected cardiac enzyme included Troponin and Creatinine Kinase (CK-MB). Ejection fraction as a baseline has been documented to be normal to include in our cohort.

The patients who were included in the study were followed for any symptoms of congestive heart failure upon presentation for the subsequent cycle and a follow up of their ejection fraction for the next year has been done to detect late cardiac toxicity.

The definition of cardiac toxicity included the following criteria: 1) significant drop in the ejection fraction for more than 15 points, 2) drop in the ejection fraction for more than 10 points with a value below 50 or, 3) Symptoms of clinical congestive heart failure

Statistical analysis was performed using mixed effect linear regression with patient as a random intercept to model the clinical endpoints before and after the chemotherapy while controlling important demographics.

RESULTS

We identified 62 patients who are eligible to be included in our observational study for which 34 patients consent to be enrolled. Two patients were excluded because they did not provide the blood test at the second sample and additional 2 patients did not show up for the third sample for cardiac markers and were excluded. The final number for patients to be analyzed was total of 30 patients who completed the study protocol.

From these 30 patients, the median age is (49.5). 18 patients received trastuzumab and the remaining 12 patients received Anthracycline. 25 patients tested positive for estrogen and 14 patients were positive for progesterone. 18 patients overexpressed Her 2. The median Ejection fraction is 55 (range 52-65) **(Table1)**

Table1: Patient characteristics.

Age Median (range)	49.5 (38-61)
Stage	
Stage 1(%)	11 (37%)
Stage 2(%)	10 (33%)
Stage 3(%)	9 (30%)
Receptor status	
ER and/or positive	18 (60%)
HER2 overexpression	18 (60%)
Chemotherapy	
Anthracycline	12 (40%)
Trastuzumab	18 (60%)
Ejection Fraction (Median)	55

Two patients had decline in the ejection fraction which is consistent with the definition of the significant drop in the ejection fraction as per the study protocol. Both patients did not have any symptoms of congestive heart failure. Both patients recovered their ejection fraction later on and they resumed the treatment with trastuzumab as per guidelines.

The first patient was a 44-year-old female patient diagnosed with stage III breast cancer, estrogen, and progesterone receptor Her 2 overexpression positive. She received four cycles of AC followed by 4 cycles of docetaxel trastuzumab concurrently and as maintenance. The ejection fraction dropped from 53 down to 41. Patient did not have any symptoms of congestive heart failure. Trastuzumab cycle eight was delayed and repeat echocardiogram showed an increase to 52% without any evidence of left ventricular dysfunction. She resumed the treatment with trastuzumab continued for a total of 17 cycles without any further drop in the ejection fraction. The patient had an underlying hypertension and was using irbesartan. She continued the treatment of hypertension throughout her course of treatment of breast cancer. The second patient is a 50-year-old female patient with stage I breast cancer; estrogen, progesterone, and Her-2 overexpression positive. The patient received four cycles of TC concurrently with trastuzumab. The patient had echocardiogram showing a reduction of her ejection fraction from 55% down to 42%. The patient had to delay her cycle and repeated echocardiogram 4 weeks showed still a low reading of 48%. The patient was evaluated by the cardiology team and repeat echocardiogram showed improvement of her ejection fraction to 55%. The patient did not have any symptoms of congestive heart failure. There was no clear evidence of left ventricular dysfunction. The patient did not start any treatment regarding her drop in ejection fraction. After discussion with the patient, we decided to start trastuzumab again and the patient completed total of 17 cycles without further reduction in ejection fraction. One patient had an elevation in Troponin on the sample collected 56 hours after chemotherapy. She denied any symptoms of chest pain. The patient was sent to emergency to be evaluated by the emergency team. She had an ECG which was completely normal and a repeat set of cardiac enzymes in four hours seems were normal. Quality check has been made to the sample that showed elevated reporting and repeat reading from the same sample showed a normal level of reporting suggesting the laboratory error on reporting that elevated troponin reading.

Statistical analysis showed the following:

CK-MMB

Univariate analysis: There was statistically significant association between age and the level of MMB, each one unit increase in age decreases the MMB by (.0013 ± 0.00052, P = 0.0144) While there was no statistically significant difference on MMB level between the used chemotherapy drugs or stage of breast cancer or presence of ER or presence of HER (p values = 0.807, 0.0613, 0.739, 0.824; respectively),

There was a statistically significant difference between before and after the chemotherapy administration (mean difference = -0.037, 95% CI -0.014 to -0.06; P = 0.0018)

Multivariate analysis: The multivariate analysis showed the same effect for chemotherapy on MMB levels (mean difference = -0.037, 95% CI -0.014 to -0.06; P = 0.0018) when age held constant, while age effect was attenuated and became not statistically significant P = 0.251. We performed mixed effect linear regression with patient as a random intercept to model the clinical endpoints before and after the chemotherapy while controlling important demographics. (**Table 2**)

Table 2: Statistical analysis of CK-MMB

linear mixed model			
Covariates	Estimate (SE)	T value	P Value
Fixed effects*			
Intercept	0.55 (0.043)	12.691	<.001
Chemotherapy cycle (after)	0.037 (0.011)	3.275	0.0018
Age	-0.001 (0.0.0008)	-1.159	0.251
Random effect			
Patient (intercept)	Variance, 0.0018	SD, 0.043	

CTNI

Univariate analysis: There was no statistically significant association between age and the level of CTNI; P = 0.339.

Moreover, there was no statistically significant difference on CTNI level between the used chemotherapy drugs or stage of breast cancer or presence of ER or presence of HER (p values =

0.286, 0.745, 0.763, 0.424; respectively), nor before and after the chemotherapy; p = 0.321

ECHO

Univariate analysis: There was no statistically significant association between age and the ECHO (EF readings); P = 0.617. Moreover, there was no statistically significant difference on CTNI level between the used chemotherapy drugs or stage of breast cancer or presence of ER or presence of HER2 (p values = 0.49, 0.280, 0.224, 0.424; respectively), nor before and after the chemotherapy; p = 0.321

There was a statistically significant difference between before and after the chemotherapy administration (mean difference = -2.33, 95%CI -3.98 to -0.69, P= 0.007).

Multivariate analysis for Echocardiography or Troponin was not significant.

DISCUSSION

Cancer is a growing challenge worldwide. There have been multiple types of anti-cancer therapy that can be used in treating cancer patients including chemotherapy, biological therapy, and immunotherapy. Anti-cancer therapy has been associated with multiple toxicities including myelosuppression, nephrotoxicity, secondarily malignancy and cardiac toxicity. Cardiac toxicity has been associated with certain medications and has been reported with the different ranges in the literature[4,13].

Anthracycline and trastuzumab have a well-documented known risk of cardiac toxicity. The accumulative dose of anthracycline correlates with cardiac toxicity. Anthracycline-induced cardiac toxicity usually irreversible and patient develop persistent drop in the left ventricular ejection fraction[13,14]. It is very important to discuss this possible complication with patients before starting the chemotherapy and of higher priority in patient who has cardiac problem in the past, elderly age than 65 and the concurrent use of other cardiotoxic medication. Trastuzumab has been associated with cardiac toxicity which is usually reversible. The use of trastuzumab and cardiac toxicity has been well reported in different clinical trials. Multiple anti HER 2 overexpression therapy has a different incidence of cardiac toxicity[15,16]. Majority of these cases are reversible, and patients will have improvement in left ventricular ejection fraction after stopping the medication. In patients who developed drop in the left ventricular ejection fraction with trastuzumab, it has been recommended that we restart the medication back again once the ejection fraction improved and the patient does not have any symptoms of congestive heart failure. Discussion with the patient about the benefit versus risk ratio is very important in such case.

In our observational study, we found two patients out of thirty who developed drop in the ejection traction. None of these patients developed permanent cardiac toxicity and none of these patients developed any symptoms to suggest a congestive heart failure. One patient had slightly elevated troponin which was not associated with any ischemic finding on the ECG or further increase in the markers after that. We could not find any correlation about changes in the cardiac functions in correlation with the cardiac biomarkers. The number of patients were very small, however there is no patients who had true elevation in the cardiac biomarkers even patient who had drop in their ejection fraction. In univariate analysis, the level of CK-MMB was statically significant. However, these finding is not clinically significant. Both troponin and echocardiography were not significant.

As we mentioned earlier, cardiac biomarkers have been tested in the past with multiple clinical trials and has a conflicting data where some trials suggested correlation between the increase in the cardiac enzymes and the development of cardiac toxicity while other trials did not support that the use of such medications including anthracycline or trastuzumab is very important in reducing the risk of cancer recurrence and also improving patient overall survival in breast cancer patient. It is highly recommended to involve patient in the risk and benefit discussion regarding the use of these medications especially, they are essential part of breast cancer protocols. Patients with multiple risk factors or had a history previously of ischemic heart disease may benefit to be evaluated by the cardiology team to have a further assessment before starting such medication with known cardiac toxicity effect.

The development of cardio-oncology is an emerging specialty focusing on prevention and management of cardiovascular diseases in cancer patients by evaluating patients with risk factors to develop cardiac toxicity[17,18]. Patients with cardiac toxicity secondary to chemotherapy should be evaluated in such specialized services to ensure compliance to published guidelines to reduce patient risk and enhance faster recovery. Cardiac health is important survivorship topic to be followed in patient who received cardiotoxic therapy especially in young or high-risk population.

CONCLUSION

The use of cardiac markers to detect cardiac toxicity in patients receiving anti-cancer therapies that associated with the cardiac toxicity is still experimental. We could not find any correlation as the number of patients was small. However, if a larger cohort to be included, it might show some correlation.

As part of practice, we recommend the use of the international guidelines that was validating in the clinical trial to follow on patients who received cardiotoxic anti-cancer therapy.

Limitation: The study was limited because the number of patients was relatively small. Increasing the number might improve the correlation between the cardiac markers and the risk of cardiac toxicity in patients receiving such treatments.

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