Multidisciplinary Cancer Investigation Original Article

April 2019, Volume 3, Issue 3

The Effect of N-Acetylcysteine Administration to Prevent Anthracycline-Induced Cardiotoxicity in Breast Cancer Patients

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DOI: 10.30699/acadpub.mci.3.3.16

Submitted: 8 May 2019
Revised: 11 June 2019
Accepted: 20 June 2019
e-Published: 1 July 2019

Keywords:
Anthracyclines
N-Acetylcysteine
Cardiotoxicity
Breast Cancer

Abstract

Introduction: Anthracyclines are one of the classes of chemotherapy drugs that are widely used to treat many types of cancers including breast cancer. Taking this class of medications has a significant relationship with cardiac dysfunction. N-acetylcysteine has antioxidant properties and may be effective in preventing cardiac dysfunctions. In this study, we investigated the effect of N-acetylcysteine in preventing cardiotoxicity in breast cancer patients receiving anthracycline.

Methods: A total of 60 breast cancer patients who underwent chemotherapy with anthracyclines were enrolled in the present case-control study and divided into two groups. The case group received 600 mg of N-acetylcysteine per day adjacent to chemotherapy; while the control group did not receive this medication. One month after the last chemotherapy session, troponin I was measured as a predictor of cardiotoxicity.

Results: Troponin I was positive in one patient in the case group compared with 3 patients in the control group without any significant difference among groups (P> 0.05) However, the respective mean±SD level of troponin I was 0.120±0.039 and 0.192±0.063 in the case and control groups with a statistically significant difference among groups (P <0.001).

Conclusions: Administration of 600 mg N-acetylcysteine per day during the anthracycline-based chemotherapy protocol in breast cancer patients may reduce the mean troponin I levels which can be a prediction of reduced anthracyclines cardiotoxicity.

INTRODUCTION

Breast cancer is the most common cancer among women worldwide; affecting more than two million people annually [1]. There are several common treatment methods for metastatic breast cancer (MBC) including chemotherapy, surgery, radiation therapy, hormone replacement, and immunotherapy. Chemotherapy is the first treatment choice for these patients [2]. Among various chemotherapy drugs, anthracyclines are the most commonly anticancer agents for the treatment of advanced breast cancer

patients [2].

Anthracyclines are antibiotics that are derived from Streptomyces peucetius [3]. This group of drugs has been approved for the treatment of many types of cancers including breast, ovarian, thyroid, gastric, and rectal malignancies. One of the most serious side effects of anthracyclines is cardiotoxicity. Apparently, Top2b enzyme is involved in the initiation of cardiotoxicity processes [4]. It seems that obesity may be associated with a higher risk of developing cardiotoxicity in breast cancer patients who have taken the anthracyclines regimen [5].

The four major anthracyclines that are used for cancer treatment are doxorubicin, daunorubicin, epirubicin, and idarubicin [6]. Among the various types of anthracyclines, doxorubicin is the most commonly administered drug [7].

N-acetylcysteine is an important drug that is used to treat acetaminophen overdose [8]. N-acetylcysteine administration can improve diastolic abnormality in hypertrophic cardiomyopathy (HCM) by elevating SERCA2 expression [9].

So, with regard to cardiotoxic effects of anthracyclines, the present study was designed to evaluate the cardioprotective effects of N-acetylcysteine administration in anthracycline receiving patients.

PATIENTS AND METHODS

Study Subjects

The current study was performed as a case-control study. Sixty breast adenocarcinoma patients were referred to Imam Reza hospital during a period of one year from May 2016 to May 2017 to receive chemotherapy treatment and were involved in the study. The patients were randomly divided into two groups. The first group (n=30) received N-acetylcysteine treatment (case or intervention group) while undergoing the chemotherapy and the second group (n=30) did not receive this medication. All patients underwent echocardiography, electrocardiography (ECG), and measurement of troponin I level before starting the treatment. Patients with the following conditions were excluded from the study: 1) history of ischemic heart disease (IHD) and/or chronic kidney disease, 2) echocardiography results with ejection fraction (EF) being less than 50% 3) Angiotensin-converting enzyme (ACE) inhibitor and beta blocker drug users, 4) Human epidermal growth factor receptor 2 (HER2) positive patients (due to the cardiotoxic effects of Trastuzumab), 5) patients with abnormal ECG pattern, 6) Patients with high levels of troponin I.

The study was approved by the local ethical committee and informed consent was obtained from all patients who participated in the study.

Treatment

All patients received the same chemotherapy regimen containing Adriamycin (60 mg/m^2) and Cyclophosphamide (600 mg/m^2) every two weeks for four cycles. For all patients, we performed ECG and echocardiography. Troponin I level was also measured for patients before initiation of treatment; using the ichorma™ analyzing system. Patients in the case group received oral N-acetylcysteine 600 mg daily for 2 months until the end of the fourth cycle of chemotherapy treatment. Patients in the control group received the same chemotherapy regimen without receiving N-acetylcysteine. Troponin I level was re-evaluated one month after the end of the last chemotherapy cycle in both groups. Troponin I levels above 0.3 ng/ml were considered positive.

Statistical Analysis

The results were statistically analyzed by SPSS software (Version 16, USA); using the Independent-Samples T Test to evaluate the association between categorical variables. Probabilities less than 0.05 ($P<0.05$) were considered as significant.

RESULTS

Sixty Iranian women with breast cancer were enrolled in the present study. Data have been analyzed based on detailed information taken from questionnaires, clinical exams, and laboratory tests. The characteristics of case and control groups are shown in Table 1. There was no significant difference between the two groups ($P>0.05$). After the end of the fourth cycle of chemotherapy, troponin I was positive in one of the patients in the case group and three in the control group with no significant difference. However, the mean±SD level of troponin I in the case and control groups were 0.120 ± 0.039 ng/ml and 0.192 ± 0.063 ng/ml respectively which was found to be statistically significant ($P<0.001$).

At the end of chemotherapy, patients were examined

Table 1: Characteristics of Case and Control Groups

	Case	Control	P value
Age, y, mean ± SD	51.66±16.88	51.98±15.35	>0.05
Diabetic Patients, No.	7	8	>0.05
Positive Troponin I Patients, No.	1	3	>0.05
Troponin I level , mean ± SD	0.120±0.039	0.192±0.063	<0.001[a]
Diabetic Patients With Positive Troponin I, No.	0	2	>0.05

[a] The difference is significant.

for signs and symptoms of heart failure. One of the patients in the case group and two patients in the control group had lower limb edema. Among the sixty patients in this study, 15 patients had one type of diabetes (seven patients in the case group and eight patients in the control group). Troponin I was positive in only two patients in the control group and none of the participants in the case group. The respective mean±SD troponin I level was 0.164±0.078 and 0.147±0.047 in diabetic and non-diabetic patients with no significant difference among groups (P>0.05).

DISCUSSION

In the present study, the effect of N-acetylcysteine administration on breast cancer patients receiving Anthracycline-based chemotherapy regimen was investigated. Anthracyclines are one of the most important chemotherapy drugs that are widely used in the treatment of various cancers including gastric cancer, breast cancer, and leukemia [10].

Cardiotoxicity is the most life-threatening side effect of these drugs. Prevention of anthracycline-induced cardiomyopathy can improve the quality of life and reduce the mortality of cancer patients. The production of free oxygen radicals is the main reason for anthracycline-induced cardiomyopathy. Some new cardioprotective drugs have been developed that have been found to be effective [11]. Dexrazoxane is one of the most effective cardioprotective drugs which is an iron chelator that has undergone clinical trials. In addition, Carvedilol is an antioxidant and lipid-lowering drug that can play a role in reducing the risk of anthracycline-induced cardiomyopathy [12]. One former study showed that administration of Enalapril in patients with increased troponin I level after chemotherapy can improve the function of the ventricle [13].

Another drug which was previously studied is N-acetylcysteine which is a mucolytic drug that is used as an antidote in acetaminophen poisoning. Another effect of this drug is the reduction of diastolic dysfunction and hypertrophy in HCM patients [9]. The effect of N-acetylcysteine on the reduction of doxorubicin-induced cardiomyopathy has been also reported in rats [14].

There are few clinical trials on N-acetylcysteine effects in Anthracyclines receiving patients. Randomized control trials (RCTs); using eight cardioprotective agents in cancerous patients were analyzed in a Cochrane review by van Dale et al., [15] the results of which showed that dexrazoxane has favorable effects on chemotherapy-induced heart failure. However, only one study was addressed in this review; focusing on N-acetylcysteine the results of which revealed no significant difference among intervention and control groups. In another study, Jo et al., [11] investigated the N-acetylcysteine effect on heart failure in 103 Anthracycline receiving patients by evaluating the left ventricular ejection fraction (LVEF) rather than troponin I level and found no significant difference between intervention and control groups.

In the present study, we evaluated the antioxidant effect of N-acetylcysteine in patients with breast cancer who received Adriamycin. Since, there was a correlation between elevated troponin I levels and chemotherapy-induced cardiomyopathy, troponin I can be used as a strong predictive factor for cardiotoxicity. Breast cancer patients who were selected for the study could be divided into groups without significant differences in terms of different characteristics. Despite the previous studies, we found out that N-acetylcysteine can reduce the troponin I level. In this regard, Goyal et al., have shown the cardioprotective effect of N-acetylcysteine amide on murine models receiving chemotherapy; while N-acetylcysteine was not evaluated in their study [16].

Our results show that since troponin I level may be lowered by the administration of N-acetylcysteine in breast cancer patients, it can reduce the risk of

anthracycline-induced cardiomyopathy. However, with regard to previous reports, further randomized studies with larger size are recommended to have a better understanding of the cardioprotective role of N-acetylcysteine.

ACKNOWLEDGEMENTS

The authors would like to express their thanks to all the patients participated in the study as well as the personnel of oncology department of Imam Reza hospital for their cooperation with the study.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

ETHICS APPROVAL

The study was approved by the local ethical committee and informed consent was obtained from all patients who participated in the study.

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