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The cardiotoxicity effect of different chemotherapeutic regimens in Iraqi patients with breast cancer: A follow up study

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ABSTRACT

Introduction: Breast cancer is the first in ranking among cancers in Iraq. Anthracyclines, cyclophosphamide and taxane are the most active chemotherapeutic regimens used. Anthracyclines induced cardiotoxicity through free radical formation while there is no full understanding about that of cyclophosphamide, but it thought that it may cause direct cardiac muscle damage. While, taxane induced cardiotoxicity through coronary vasoconstriction and oxidative stress. Thus; it is very important to study changes in the cardiac biomarkers as they were the most reliable and sensitive markers associated with cardiotoxicity.

Aim: This research was designed to carry out investigations on the cardiotoxicity effects of these chemotherapeutic drugs in Iraqi patients with breast cancer.

Materials and methods: This research was performed at the Department of Biochemistry, Medicine College, Baghdad University and at the Oncology Department of the Teaching Hospital, Baghdad - Iraq, during the period from May 2018 to October 2018. It was carried out on 56 women with undisturbed menstrual cycle (25–45 years), These women were divided into 3 groups: GI was of 29 women with primary breast cancer without starting any kind of chemotherapy, GII: the same 29 women of GI after finishing 4 cycles of anthracyclines (course 1) and GIII: which involved another 27 women after finishing both course 1 and course 2 (4 cycles of taxanes). Investigations included serum measurements of high sensitive cardiac troponin (hs-cTn), NT-pro-brain natriuretic peptide (NT-ProBNP), and high sensitive- C reactive protein (hs-CRP) by using ELISA technique. The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 23, when the P-values were less than 0.05, it was considered as significant.

Results: The mean (±SEM) value of the serum hs-CRP levels was decreased significantly in GIII in comparison to both GI ($p = 0.004$) and GII ($p = 0.049$) while there was no significant difference between GI and GII. Also, there was no significant difference in the mean (±SEM) value of the serum hs-cTn and the serum NT-PROBNP levels between all groups. The results also showed that there was a significant negative correlation between BMI values and serum NT-proBNP levels in GI ($r = -0.435$, $p = 0.018$), GII ($r = -0.438$, $p = 0.018$), and GIII ($r = -0.384$, $p = 0.048$). In GI, there was also a significant positive correlation between BMI and serum hs-CRP levels ($r = 0.395$, $p = 0.034$). Also, there was a significant positive correlation between serum hs-cTn levels and NT-proBNP levels in GI ($r = 0.416$, $p = 0.025$) and GII ($r = 0.467$, $p = 0.011$). Moreover, there was a significant negative correlation between the serum hs-cTn levels and serum hs- CRP concentrations ($r = -0.397$, $p = 0.040$) in GIII.

Conclusion: This study had concluded insignificant changes of cardiac biochemical markers during the chemotherapeutic treatment and that chemotherapy-induced cardiotoxicity is negligible.

1. Introduction

Breast cancer is the most common cause of deaths among women around the world [1]. In Iraq, breast cancer accounts for about one-third of the registered female cancers [2]. Most patients were treated with chemotherapeutic regimens at some time during the course of their illness depending on the tumor type, stage and the relative fitness of the patients [3]. Anthracyclines (Doxorubicin) are one of the standard

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regimens for breast cancer patients [4]. These are antitumor antibiotics derived from Streptomyces bacteria that inhibit the synthesis of DNA and RNA by interfering with their base pair strands and preventing the rapidly growing and replication of cancer cells [3]. Cyclophosphamide is an alkylating agent which alkylates the nitrogen number 7 residue of the guanine and cross-link nucleobases in DNA double-helix strands leading to apoptotic cell death [3]. Taxanes are usually used as an adjuvant treatment for breast cancer patients with the non-Taxanes therapies [5]. Their mechanism of action is by disruption of the microtubule function [3]. The most common side effects of chemotherapy were the cardiovascular diseases [6]. The mechanism of cardiotoxicity depends on the type and intensity of the chemotherapeutic regimen. Most of the chemotherapeutic drugs produce many cardiovascular diseases such as heart failure, hypertension and thromboembolism. Anthracyclines are the most common chemotherapeutic drug producing cardiovascular effects especially heart failure. However, cardiotoxicity might also been associated with cyclophosphamide and taxanes [7]. Anthracyclines induced toxicity through several mechanisms including; free radical formation, apoptosis, ATP transcriptional changes and down-regulation of ATP-ase calcium of the sarcoplasmic reticulum with defects in respiration of the mitochondrial deoxyribonucleic acid [8]. The mechanism of cyclophosphamide cardiotoxicity is not precisely known, but it thought that it may cause direct damage to the endothelium with outpouring of toxic metabolites that resulted in damage to the cardiomyocytes [9]. The mechanism of taxanes cardiotoxicity is strictly related to its antitumoral activity. In fact, the antimitotic effect is due to its ability to stabilize the microtubules. This effect would be a decrease of the spontaneous contraction frequency with a greater susceptibility to arrhythmia. It has also been suggested that taxanes cardiotoxicity is due to coronary vasoconstriction [10], increased arterial stiffness and oxidative stress [11].

For the early detection of cardiotoxicity, cardiac biomarkers measurement could be a specific tool for the prediction of ventricular dysfunction and for the diagnosis of myocardial injury [12]. Previous studies reported the use of cardiac troponins and natriuretic peptides as potent biomarkers for the study of cardiotoxicity [13]. In addition; C-reactive protein (CRP) an active biomarker in the immune system was also used for the detection of cardiovascular diseases [14]. The aim of the present research was to predict the cardiotoxicity effects induced by the used chemotherapeutic regimens in Iraqi women with breast cancer along both course 1 and course 2 of their regimens as investigated by changes of the serum cardiac biochemical markers along with the chemotherapeutic effect on inflammation associated cancer.

2. Materials and Methods

The current research was run out at the Department of Biochemistry, Medicine College, Baghdad University and at the Oncology Department of the Teaching Hospital, Baghdad – Iraq, during the period from May 2018 to October 2018. It included 56 women (power of the study = 0.985), (CI = 95%) who were diagnosed by an oncology group to have had breast cancer of intermediate grade ductal carcinoma and the stage was 1–3, their age range (25–45 years). These women were classified into; group I (GI); twenty nine women who had been diagnosed as having breast cancer, before starting the chemotherapeutic regimen, group II (GII): the same 29 women of GI after finishing 4 cycles of Anthracyclines (Doxorubicin 60 mg/m^2 and Cyclophosphamide 600 mg/m^2 chemotherapy), and group III (GIII): which involved another 27 women after finishing both courses of chemotherapy; mentioned course 1 and course 2; 4 cycles Taxanes (Docetaxel) 100 mg/m^2. All metastasized tumors were excluded. Complete case history was taken from each woman, Patients diagnosed with breast cancer by Fine Needle Aspiration (FNA) and true cut biopsy by histopathology after partial or total mastectomy with axillary clearance. Also, investigations were done for patients before starting treatment such as breast ultrasound, abdominal ultrasound, computed tomography (C.T. Scan), mammography for unilateral or bilateral breast, chest X Ray and routine blood test (complete blood count, renal function test and liver function test). Exclusion criteria included pregnant women, chronic diseases (diabetes mellitus, hypertension), alcoholics, smokers, and women used anti-inflammatory drugs.

Verbal consent was taken from all the women participants. Ethical approval was received from the ethical review board (ERB) of the Biochemistry Department, Medicine College, Baghdad University, Iraq. The IEC registration number was 1088. Body Mass Index (BMI) of each involved woman was obtained by the measurement of weight in relation to height and using the following formula:

BMI = (Weight in kilograms/height in meters^2). The instruments used to measure BMI were an analogue weight scale for estimating the weight and a tape measure for the height.

Five milliliters of blood sample were collected by venipuncture of the peripheral vein from each included woman, transferred into plain tube, allowed to clot at room temperature for 30 min, then centrifugation of samples were carried out at (2000 x g) for 10 min, the serum obtained was stored at −20 C° in aliquots till the day of analysis, hemolysed samples were discarded.

Investigations included serum measurements of high sensitive cardiac troponin (hs-cTn), high sensitive C-reactive protein (hs-crp) and human N-terminal pro-brain natriuretic peptide (NT-ProBNP) by using the enzyme linked immunosorbent assay sandwich (ELISA) technique [15]. Kit materials used for measurements of the studied biochemical parameters were provided from Germany. The Statistical Package for Social Sciences (SPSS) version 23 was used for the statistics. ANOVA and Student's t-tests were used to test for the statistical significance. Linear regression was utilized to test for the correlations between the different parameters. When the P-value was less than 0.05 it was considered as significant.

3. Results

No significant differences in the mean (±SEM) values of age between group I (38.79 ± 0.91 years) and group III (39.59 ± 0.95 years) and in the mean (±SEM) values of BMI between group I (30.04 ± 0.94 kg/m^2) and group III (31.78 ± 1.24 kg/m^2) participants as observed in [Table 1].

The mean (±SEM) values of serum hs-CRP concentrations was significantly decreased in GIII (3.77 ± 0.50 μg/ml) compared to each of GI (7.23 ± 0.95 μg/ml) and GII (5.72 ± 0.88 μg/ml), but no significant difference between GI and GII was observed. The mean (±SEM) values of serum hs-cTn levels was increased with the progression of the chemotherapeutic treatment; (GI: 11.14 ± 0.40 ng/L, GII: 11.60 ± 0.49 ng/L, and GIII: 11.86 ± 0.78 ng/L), but did not reach a significant level. Also, the mean (±SEM) values of serum NT-ProBNP did not significantly differ among the studied groups of women; GI, GII, and GIII (430.24 ± 20.74 ng/ml, 404.99 ± 21.14 ng/ml, and 425.80 ± 24.68 ng/ml, respectively) [Table 2].

The results also revealed that there was a significant negative correlation between BMI values and serum NT-proBNP levels in GI ($r = -0.435$, $p = 0.018$), GII ($r = -0.438$, $p = 0.018$), and GIII ($r = -0.384$, $p = 0.048$). In GI, there was also a significant positive correlation between BMI and serum hs-CRP levels ($r = 0.395$, $p = 0.034$). Also, there was a significant positive correlation between serum hs-cTn levels and NT-proBNP levels in GI ($r = 0.416$, $p = 0.025$) and GII ($r = 0.467$, $p = 0.011$). Moreover, there was a significant negative correlation between the serum hs-cTn levels and serum hs- CRP concentrations ($r = -0.397$, $p = 0.040$) in GIII.

Table 1
Mean (±SEM) values of age and body mass index (BMI) of Group I and Group III participants.

Parameter	Group I (n = 29)	Group III (n = 27)	p-value
Age (years)	38.79 ± 0.91	39.59 ± 0.95	0.546
BMI (kg/m^2)	30.04 ± 0.94	31.78 ± 1.24	0.245

The t-test revealed no significant difference in both age and BMI between the two groups. $P < 0.05$ was considered significant.

Table 2
The mean (±SEM) values of the serum hs-CRP, Hs-CTn, NT-PROBNP between Group I, Group II and Group III participants.

Parameter	GI (n = 29)	GII (n = 29)	GIII (n = 27)	p-values
hs- CRP (μg/ml)	7.23 ± 0.95^{NS}	5.72 ± 0.88	3.77 ± 0.50•	GI&GII = 0.189 GI&GIII = 0.004 GII&GIII = 0.049
Hs-cTn ^{NS} (ng/L)	11.14 ± 0.40	11.60 ± 0.49	11.86 ± 0.78	GI&GII = 0.565 GI&GIII = 0.384 GII&GIII = 0.759
NT-ProBNP ^{NS} (ng/L)	430.24 ± 20.74	404.99 ± 21.14	425.80 ± 24.68	GI&GII = 0.417 GI&GIII = 0.889 GII&GIII = 0.511

ANOVA and t-test revealed; • significant decrease in hs-CRP in GIII in comparsion to both GI [P = 0.004] and GIII [P = 0.049], NS; non-significant differences.

4. Discussion

The number of women involved in this study was relatively low [29] because these women had primary breast cancer with early stages [stages 1 and 2] and most of cases that we encountered were in advanced stages [stages 4 and 3] as well as the difficulties to complete the follow-up study course of the chemotherapeutic treatment [3 months].

In the present study there was a significant decrease in the level of hs-CRP in GIII compared to both GI and GII since cancer and inflammation were connected to each other. Inflammation encourages the development and the progression of tumor. While tumor introduces an inflammatory medium [16]. Increased levels of serum CRP was also associated with progression of the disease of different malignancies including breast cancer [17]. Also, high level of serum hs-CRP may suggest cardiac stress because inflammation is essential in heart disease [18, 19]. Present studies have indicated that there is a positive association between cancer and hs-CRP level. Oxidative damage associated with inflammation may cause carcinogenesis by tumor-suppressor genes or DNA repair post-translational modifications [20]. Also, inflammatory cytokines may promote tumor progression by inhibiting apoptosis and by stimulating vascular permeability, angiogenesis and cell motility via intracellular enzymes and transcriptional factors [21, 22].

The present study showed that there was a non-significant differences in the serum level of hs-cTn and NT- ProBNP among the studied groups; these results may indicate that the cardiotoxicity effects of chemotherapy may occurred during courses of treatment and then after an improvement had occurred. This is in congruence with a present study stated that anthracyclines induced myocyte damage occurs only within hours after the drug administration [23]. In addition, in pediatrics; there is an increment of troponin T only for 1–3 days after doxorubicin infusion [24] and in adults the increase of troponin I occurs only within hours after high-dose chemotherapy (HDC) [25]. Concerning NT-ProBNP; Sandri et al. (2005) examined 52 patients treated with HDC for aggressive malignancies. They noticed three different behaviors of NT-proBNP concentrations: (1) there was an increase of serum NT-proBNP levels up to 72 h after the end of chemotherapy in 17 patients, (2) initial elevated NT-proBNP levels with return to baseline values after 72 h in 19 patients, and (3) no NT-proBNP rise in 16 patients. The evaluation of the left ventricular function showed that only the persistent increase of plasma NT-proBNP early after HDC was greatly associated with cardiac dysfunction [26]. Also, the non-significant change in the level of NT-ProBNP between the pretreatment and post treatment was in agreement with Sawaya et al. study (2012) [27].

In a study achieved by Dodos et al. (2008); they found that cTnT did not exceed the upper limit of the normal range in any patient and that seven patients had low levels of elevation of cTnT. Also, NT-ProBNP level did not significantly changed after anthracyclines treatment, these results were in agreement with the results of the present study [28].

The significant negative correlations between BMI and serum NT-proBNP and hs-c-Tn in the three studied groups were in agreement with that observed by Teodora ZJ et al. (2017) who observed that obese patients had significantly lower NT-proBNP and hs-cTn. They stated that there was a significant negative correlation between BMI and NT-proBNP [29]. Also, the significant positive correlation of BMI and serum hs-CRP in GI was in concordance with previous studies reported that adipose tissue is the major origin of inflammatory cytokines that stimulates the production of CRP by the liver [30, 31]. The present study revealed the role of inflammatory process associated with chemotherapy induced damage as found by the significant changes of hs-CRP and suggested that cardiotoxicity induced by chemotherapy was transient and may occurred during courses of the treatment. The significant negative correlation between NT-ProBNP and BMI in the three studied groups of BC women before and after the chemotherapeutic treatment may indicate that adipocytes play a role in the metabolism of this protein and also it may recommend comparing the levels of this biochemical parameter in women with normal BMI and obese ones. Regarding the significant positive correlation between hs-CRP and BMI in group I is attributed to the role of adipocytes in the inflammatory process and its secretion of several cytokines that induces the synthesis and releases of CRP and that the correlation was disappeared in groups 2 and 3 because of chemotherapy downregulation of inflammation processes.

5. Conclusion

This study concluded insignificant changes of cardiac biochemical markers during the chemotherapeutic treatment and that chemotherapy induced cardiotoxicity is negligible.

Declaration

Author contribution statement

Zainab Nazar Hasan Anber: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Basil Oied Mohammed Saleh: Conceived and designed the experiments.

Safana Ali Al-Rawi: Performed the experiments.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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