Research Article

Effect of Carvedilol on Echocardiographic Ejection Fraction, Brain Natriuretic Peptide and C - Reactive Protein in Trastuzumab Treated Females with Breast Cancer

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ABSTRACT

Trastuzumab therapy represents the standard of care for HER2 positive breast cancer patients, which is highly complicated by cardiotoxicity. The aim of the study was to elucidate the possible effects of carvedilol on echocardiographic ejection fraction, serum brain natriuretic peptide and serum C- reactive protein in trastuzumab treated females with HER2 positive breast cancer. A total of 26 females with HER2 positive breast cancer were included in this study. The patients were randomized into two groups, 13 patients in each group. Group I included patients were treated with trastuzumab therapy for 8 cycles with 21 day apart. Group II included patients were received trastuzumab therapy with carvedilol 3.125 mg, orally, twice daily dose for 8 cycles. Echocardiography was used to measure ejection fraction at zero time, 4th and 8th cycles in both groups. Serum brain natriuretic peptide and C- reactive protein were measured at zero time, 2nd, 4th, 6th and 8th cycles in both groups. Treatment with trastuzumab therapy caused significant decrement in echocardiographic ejection fraction at only 8th cycle in comparison to baseline readings ($P < 0.05$). Combined trastuzumab plus carvedilol caused significant increase in echocardiographic ejection fraction compared with that of trastuzumab therapy group ($P < 0.05$). Regarding serum brain natriuretic peptide and C- reactive protein, trastuzumab therapy caused significant increment in both these markers in comparison to baseline readings ($P < 0.05$). Combined trastuzumab plus carvedilol caused significant decrement in serum brain natriuretic peptide and C- reactive protein compared with that of trastuzumab therapy group ($P < 0.05$). Carvedilol causes significant increment in echocardiographic ejection fraction and significant decrease in serum brain natriuretic peptide and C- reactive protein in trastuzumab treated patients.

Keywords: Carvedilol, Trastuzumab, Cardiotoxicity, Ejection fraction, BNP, C-RP

INTRODUCTION

Breast cancer is a malignant tumor that begins in the cells of the breast. It is the most often diagnosed cancer and among females it represents the second leading cause of cancer death[1]. Breast cancer cells may have many different types of receptors, one of the most important receptor being: human epidermal growth factor receptor (HER2), a member of the epidermal growth factor receptor (EGFR) family that includes HER1, HER2, HER3, and HER4. 25-30% of breast cancers are over expressing the HER2 receptor[2]. Trastuzumab is a humanized monoclonal antibody directed against the HER2 protein[3]. Since 2006 concurrent treatment with trastuzumab is truly the standard of care for females with early HER2 positive breast cancer[4]. Trastuzumab binds to HER2 receptor with high affinity and blocks the effects of neuregulin-1 (NRG-1). In general, NRG-1 binds to and activates HER4 receptor, which is then primed for binding to HER2 receptor. Binding of NRG-1 to HER2 receptor initiates cell survival pathways, which maintain cardiac function and inhibit apoptosis. This binding initiates a change in mitochondrial respiration, leading to decrease the production of ROS and increase cell survival. Furthermore, NRG-1 signaling is able to reveal cardioprotective properties through the activation of FAKs (focal adhesion kinases). FAK is important in maintaining the function and structure of sarcomeres[5]. Additionally, the increased stress on the cardiomyocyte results in the upregulation of circulating angiotensin II (ANG II). ANG II upregulation has two detrimental effects on the cardiomyocyte. First, ANG II is a potent inhibitor of NRG. The second detrimental effect on the cardiomyocyte is that ANG II leads to the activation of NADPH oxidase[6], which produces ROS. TIC is reported to be reversible and is not dose-related. However, some cases have resulted in thrombosis and stroke, disabling HF, and/or death[7]. Early detection of patients at risk for cardiotoxicity represents a fundamental goal for oncologists and cardiologists, by allowing for the definition of personalized interventions or antineoplastic therapeutic strategies. Most of the approaches frequently used in clinical practice such as echocardiography denoted low predictive power and low diagnostic sensitivity in detecting subclinical myocardial damage. The use of some other techniques, like endomyocardial biopsy, is uncooperative in clinical practice due to the invasiveness of the techniques. Therefore, there is growing expectation for newer, cost effective and non-invasive diagnostic tools for the early recognition of patients liable to developing drug induced

cardiotoxicity[8]. Uses of easily measurable biomarkers in blood, like brain natriuretic peptides (BNP) and C-reactive protein (C-RP), have been assessed in animal models and in clinical studies. Many studies have linked HF diagnosis and worse outcome with higher levels of these circulating markers[9,10]. Carvedilol is a nonselective β-blocker drug with additional vasodilating, antiinflammatory and antioxidative properties. Carvedilol is used in the management of hypertension and angina pectoris, and was the first drug among β-blockers to be approved in the management of CHF in adults[11]**.** Accumulating evidences have revealed that carvedilol protects against chemotherapy-induced cardiotoxicity through its antioxidant properties[12]. The goal of this study is to assess the value of the use of carvedilol in prevention of trastuzumab induced cardiotoxicity in female patients receiving trastuzumab for breast cancer that over expressed HER2 receptor.

PATIENTS AND METHODS

Patients

The study sample included women who attended the oncology unit in Al-Sadar medical city in Al-Najaf Al-Ashraf Governorate from 1st of April 2013 to the 25thof July 2014 with established new diagnosis of HER2 positive breast cancer. Exclusion criteria were patients with past-medical history of heart disease, renal failure, diabetes mellitus or thyroid diseases. Twenty six patients were enrolled in this study and divided randomly into 2 groups, 13 patients per group. In group I patients were treated with trastuzumab regimen for 8 cycles with 21 days interval. In group II patients were treated with trastuzumab regimen plus carvedilol 3.125 mg administered orally twice daily for 8 cycles with 21 days interval. Each patient was informed about treatment.

The study protocol was approved by ethical committees of Al-Nahrain College of medicine. Carvedilol was manufactured by TAD Pharma GmbH, Germany. Batch NO. N73094.

Echocardiography (ECHO)

Each individual included in the study (both patients groups), underwent echocardiography, at zero time, 4th and 8th cycles.

Study was performed by a protocol specified by using Kretz technique type and model 530D with 2-4 MHZ transducer made in Australia in 1996 for determining LVEF.

LVEF represents the percent ratio of the difference between end diastolic and end systolic volumes to the end diastolic volume[13].

Collection of Blood Samples

Five ml of blood was collected at zero time and at 2nd, 4th, 6th and 8th cycles for evaluation of trastuzumab-induced cardiotoxicity based on changes of the serum BNP and C-RP biomarkers. Each blood sample was centrifuged at 2500 rpm for 15 minutes, and then serum was collected and frozen at - 80 until measurement.

Measurement of BNP

Using commercially available human BNP ELISA kit (catalog number CSB-E07970h) from Cusabio Biotech Co., LTD.

Measurement of C-RP

Using commercially available human C-RP ELISA kit (catalog number CSB-E07921h) from Cusabio Biotech Co., LTD.

Statistical Analysis

Statistical analyses were performed using SPSS 16.0 for windows Inc. Data of quantitative variables were expressed as mean ± SEM. Differences in each variable through treatment cycles in the same group were compared using paired-sample Student's t-test. Unpaired-sample Student's t-test was used for the comparisons between the two groups variable. In all tests, P<0.05 was considered to be statistically significant.

RESULTS

Anthropometry

There was no significant difference in anthropometric data of the two patients groups included in this study as shown in Table 1.

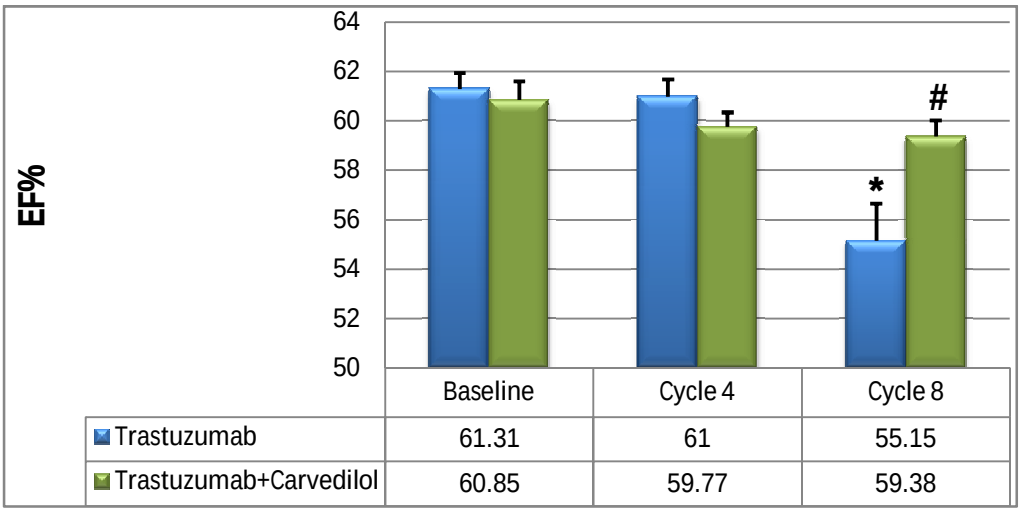
Table 1: Anthropometric data for all included patients in this study.

Anthropometric data	Mean ± SEM (Group I)	Mean ± SEM (Group II)
Age (year)	38.38 ± 2.27	41.07 ± 2.08
Weight (kg)	71.61 ±1.87	67.61 ± 1.48
Height (cm)	158.84 ±2.35	161.92 ± 1.35
Body Surface Area (m^2)	1.73 ± 0.03	1.71 ± 0.019
Body Mass Index (kg/m^2)	28.02 ± 0.85	25.87 ± 0 .67

Effect of Different Treatment Regimen on Echocardiographic Ejection Fraction (%)

In comparison with baseline levels, there was a significant reduction in echocardiographic ejection fraction (%) at only the 8 cycle in trastuzumab regimen (p< 0.05) as shown in Figure 1.

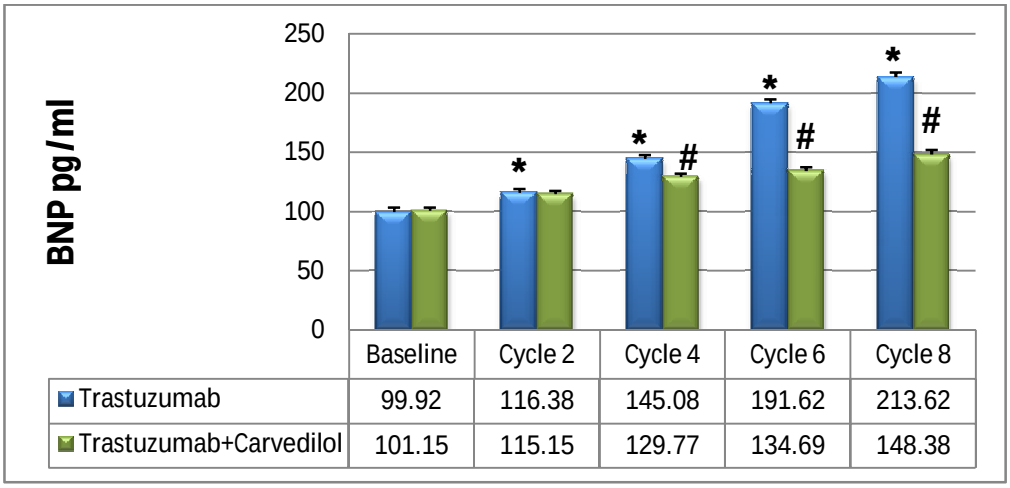
In comparison between treatment groups, there was no significant difference (P > 0.05) in echocardiographic ejection fraction (%) at base line and after 4 cycles of treatment as shown in Figure 1. At 8 cycles of treatment echocardiographic ejection fraction (%) of group II was significantly (P < 0.05) higher than that of group I as shown in Figure 1.



	Baseline	Cycle 4	Cycle 8
Trastuzumab	61.31	61	55.15
Trastuzumab+Carvedilol	60.85	59.77	59.38

* P<0.05 compare to baseline values of the same treatment group.
# P<0.05 compare to group I

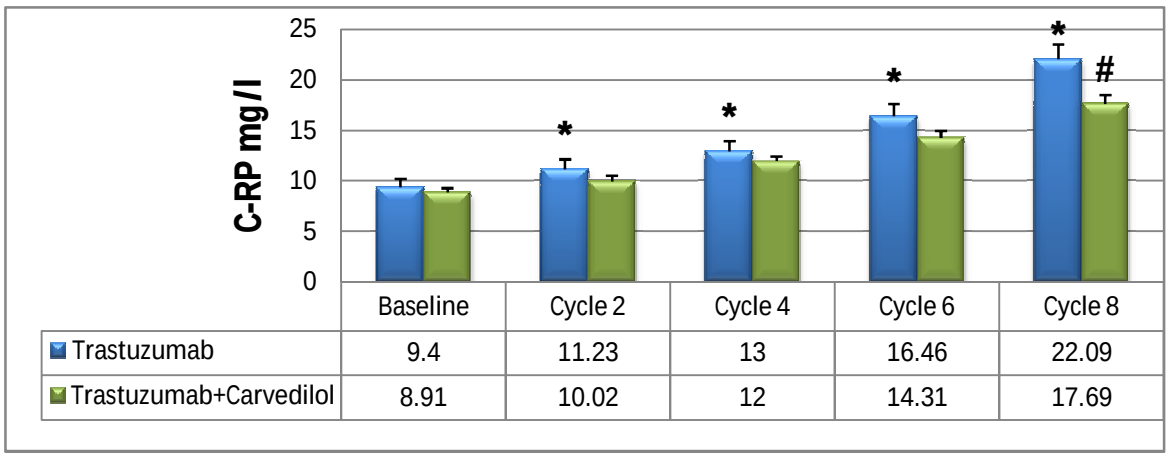
Figure 1: Mean ± SEM values of echocardiographic ejection fraction (%)at baseline and after 4 and 8 cycles in both groups (trastuzumab based regimen, n=13 and trastuzumab plus carvedilol, n=13).



	Baseline	Cycle 2	Cycle 4	Cycle 6	Cycle 8
Trastuzumab	99.92	116.38	145.08	191.62	213.62
Trastuzumab+Carvedilol	101.15	115.15	129.77	134.69	148.38

* P<0.05 compare to baseline values of the same treatment group.
# P<0.05 compare to group I

Figure 2: Mean ± SEM values of serum brain natriuretic peptide (BNP) at baseline and after 4 and 8 cycles in both groups (trastuzumab based regimen, n=13 and trastuzumab plus carvedilol, n=13).



	Baseline	Cycle 2	Cycle 4	Cycle 6	Cycle 8
Trastuzumab	9.4	11.23	13	16.46	22.09
Trastuzumab+Carvedilol	8.91	10.02	12	14.31	17.69

* P<0.05 compare to baseline values of the same treatment group.
# P<0.05 compare to group I

Figure 3: Mean± SEM values of serum C- reactive protein (C-RP) at baseline and after 4 and 8 cycles in both groups (trastuzumab based regimen, n=13 and trastuzumab plus carvedilol, n=13).

Effect of Different Treatment Regimens on Serum BNP Level

In comparison with baseline levels, there was significant increment in serum BNP level (pg/ml) after 2, 4, 6 and 8 cycles in trastuzumab regimen group ($p< 0.05$) as shown in Figure 2. In comparison between treatment groups, there was no significant difference ($P > 0.05$) in serum BNP level at base line and after2 cycles of treatment as shown in Figure 2. After 4, 6, 8 cycles of treatment, serum BNP level of group II was significantly ($P < 0.05$) lower than that of group I as shown in Figure 2.

Effect of Different Treatment Regimens on Serum C-RP Level

In comparison with baseline level, there was significant increment in serum C-RP level (mg/l) after 2, 4, 6 and 8 cycles in trastuzumab regimen group ($p< 0.05$) as shown in Figure 3. In comparison between treatment groups, there was no significant difference ($P > 0.05$) in serum C-RP level at base line and after 2, 4 and 6 cycles of treatment as shown in Figure 3. After 8 cycles of treatment, serum C-RP level of group II was significantly ($P < 0.05$) lower than that of group I as shown in Figure 3.

DISCUSSION

The use of trastuzumab in breast cancer over expressing HER2 protein has significantly augmented response rates and improved survival in female with early-stage and metastatic disease[3]. However, the unpredictably high incidence of cardiotoxicity, up to a third of females treated with trastuzumab might develop a cardiotoxicity[14,15], has produced great concern regarding its use. Indeed, the occurrence of impaired cardiac function restricts the selection of possible oncological therapies to those considered less aggressive and as a result less effective[16]. Patients who develop heart problems when treated with trastuzumab might have to discontinue this treatment, which could affect their chances of cure.

Effect of Trastuzumab Based Regimen on Clinical and Biochemical Parameters of the Present Study

In the present study, there was no significant change in the echocardiographic ejection fraction after 4 treatment cycles in comparison to baseline values ($P> 0.05$). This finding is in accordance with that revealed by McArthur and Chia[17] but is in contrary to that of Dores[18]. Trastuzumab caused significant reduction in echocardiographic ejection fraction after 8 treatment cycles in comparison to baseline values ($P < 0.05$). This finding is in agreement with that revealed by Russo[19]. The mechanism beyond this effect is thought to block cardiomyocyte HER2 signaling. So that trastuzumab interfering with normal growth, repair, counteraction of undue sympathetic tone and survival of cardiomyocytes[20,21]. Trastuzumab results in significant increase in serum BNP level after subsequent treatment cycles compare with baseline level ($P < 0.05$). These results agree with that revealed by Feola[22] and Perik[23]. This increase in serum BNP level may be due to increase load on cardiac myocyte which may be due to gene expression of renin and promoted expression of AT1 receptor in trastuzumab treating patient. BNP was observed early after administration of trastuzumab, allowing us to identify the females at most risk after the first two cycles of therapy. This result was in agreement with revealed by Sandri[24] who suggest that BNP might be useful parameter to predict or detect trastuzumab induced cardiotoxicity. Trastuzumab caused significant increment in serum C-RP level as compared with baseline values ($P < 0.05$). These findings agree with that revealed by Onitilo[25] but disagree with that revealed by Fallah[26].

Effect of Carvedilol on Clinical and Biochemical Parameters of the Present Study

Carvedilol produced significant increment in echocardiographic ejection fraction in comparison to that of trastuzumab based regimen group ($P < 0.05$). These results are in consistency with that revealed by Hashim[12] and Elitok[27] but with doxorubicin rather than trastuzumab. These results are also in consistency with that revealed by cook[28] who found that during trastuzumab treatment fewer patients in the beta-blocker arm had evidence of ventricular dysfunction than in the arm that did not take beta-blocker.

The mechanism beyond these effect are that carvedilol is positioned to inhibit a number of pathological processes that responsible for the progression of heart failure, including: reduction of heart rate, preload and after load; inhibition of the sympathetic nervous system and the renin-angiotensin system; scavenging oxygen radicals; suppression of pathological organ remodeling[29].

Carvedilol significantly decreased serum BNP level in comparison to trastuzumab group ($P < 0.05$). This finding is in consistency with that revealed by Chang-chun[30] who found that carvedilol therapy significantly decrease plasma BNP and improve cardiac function compared with control group in patient with CHF. This decrement in serum BNP level may be due to decrease load on cardiac myocyte by direct effect on α-receptor and by indirect effect by inhibition of renin-angiotensin system. Regarding C-RP, carvedilol reduced its serum level in significant way as compared with that of trastuzumab treated group ($P < 0.05$). This finding is in consistency with that revealed by Yasunari[31] who found that carvedilol decreased C-RP levels significantly in hypertensive patient.

The reason beyond this effect is that carvedilol has been reported to have an antiinflammatory effect by inhibiting IL-10 and IL-18[32] and by inhibiting the expressions of vascularcell adhesion molecule-1 (VCAM-1), inter-cellular adhesion molecule-1 (ICAM-1), and IL-8 via NF-κB in the human endothelial cells[33].

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