Effect of valsartan on echocardiographic fraction shortening, troponin I, malondialdehyde in breast cancer females treated with trastuzumab

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Abstract

Background: Trastuzumab therapy is highly effective in HER2 positive breast cancer patients, but it is complicated by cardiotoxicity. Objective: To elucidate the possible effects of valsartan medication on echocardiographic fraction shortening, serum troponin I and serum malondialdehyde in trastuzumab treated patients with HER2 positive breast cancer. Patients and Methods: A total of twenty six female patients with HER2 positive breast cancer were enrolled in this study. The patients were randomized into two groups, thirteen patients in each group. Group I included patients who received trastuzumab medication for 8 cycles with 21 days apart. Group II included patients who treated with trastuzumab medication with valsartan 40 mg, orally, once daily dose for 8 cycles. Echocardiography was used to measure fraction shortening at zero time, 4th and 8th cycles in both groups. Serum troponin I and malondialdehyde were measured at zero time, 2nd, 4th, 6th and 8th cycles in both groups. Results: Treatment with trastuzumab medication caused a significant reduction in echocardiographic fraction shortening at an only 8th cycle in comparison to baseline level readings (P < 0.05). Combined trastuzumab plus valsartan medications caused a significant increment in echocardiographic fraction shortening in comparison with that of trastuzumab medication group (P < 0.05). Regarding serum troponin I and malondialdehyde, trastuzumab medication caused a significant increment in both these markers compared with those baseline readings (P < 0.05). Combined trastuzumab plus valsartan caused significant reduction in troponin I and malondialdehyde in comparison with that of trastuzumab medication group (P < 0.05). Conclusion: Valsartan causes significant increase in echocardiographic fraction shortening level and cause significant reduction in serum troponin I and malondialdehyde in trastuzumab treated patients.

Keywords: Valsartan, Trastuzumab, Cardiotoxicity, Fraction shortening, Troponin I, MDA.

Introduction

Breast cancer is a malignant tumor that represents the second leading cause of cancer death among females [1]. Breast cells have many types of receptors, one of the most important receptor being: human epidermal growth factor receptor (HER2). Twenty five to thirty percent of breast cancers are over expressing the HER2 protein [2]. Trastuzumab is a humanized monoclonal antibody directed against the HER2 receptor [3]. Since 2006 concurrent treatment with trastuzumab therapy is truly the standard of care for female patients with early HER2 positive breast cancer [4]. Trastuzumab binds with high affinity to HER2 protein and blocks the effects of neuregulin-1 (NRG-1). Normally, NRG-1 binds to and activates the HER4 protein, which is then primed for binding to HER2 protein. Activation of NRG-1 to HER2 protein initiates the cell survival pathways that maintain cardiac function and inhibit apoptosis. This activation initiates an alteration in mitochondrial respiration, leading to reduction in the production of ROS (reactive oxygen species) and increase cell survival. Moreover, NRG-1 signaling has
ability to reveal cardio-protective properties through the stimulation of FAKs (focal adhesion kinases). FAK is essential in maintaining the sarcomeres function and structure [5]. Furthermore, the increased stress on the cardiomyocyte leading to upregulation of circulating AGII (angiotensin II). This upregulation has two detrimental effects on the cardiomyocyte. Firstly, AGII is a potent inhibitor of NRG. Secondly, AGII leads to the activation of NADPH oxidase [6], which is responsible for production of ROS.

Trastuzumab induces cardio toxicity (TIC) is not dose-related and is reported to be reversible. However, in some cases like thrombosis, disabling HF, and/or death have been resulted [7]. Early detection of female patients at risk for cardio toxicity represents a main goal for oncologists and cardiologists, by permitting for the definition of personalized interventions or anticancer therapeutic strategies. Most approaches that frequently used in clinical practice like echocardiography denoted low diagnostic sensitivity and low predictive power in detecting subclinical cardiomyocyte damage.

The use of some other techniques, such as endo-myocardial biopsy, is uncooperative in clinical practice owing to the invasiveness of the techniques. Therefore, there is emergent expectation for newer, cost effective and non-invasive diagnostic tools for the early recognition of patients liable to developing drug induced cardio toxicity [8]. Uses of easily measurable biomarkers in blood, like serum troponin I (CTnI) and serum malondialdehyde, have been evaluated in clinical studies. Many studies have associated the severity of myocardial inflammation or cardiac ventricular wall stress caused by remodeling with higher levels of these circulating markers [9, 10].

Valsartan and is a medication that selectively inhibits angiotensin in receptor (AT1). This of medications was developed following the angiotensin-converting enzyme (ACE) inhibitors, as an attempt to provide more specific actions on the renningiogens in system (RAS) [11]. Valsartan interact with the AT1 receptor thereby selectively inhibiting its physiological actions. The final step of the RAS pathway is the activation of the AT1 receptor. By blocking the effect of the AT1 receptor, Valsartan result in reduce blood pressure (BP), as well as attenuates sympathetic cut flow, improves kidney function, reductions vascular smooth muscle contraction, and also result in declining in progression of atherosclerosis lesions [11, 12]. Valsartan medication was firstly approved in Europe in 1996 in the management of hypertension in adults. Additionally, it has been shown to have cardio-protective effect, with reduction in morbidity and mortality [13, 14]. In general, these effects are comparable to those achieved with ACE inhibitors, with the further advantage of a lower incidence of unwanted effects such as dry cough and angioedema [13]. The goal of this study is to assess the value of the use of valsartan in the prevention of TIC in female patients receiving trastuzumab for breast cancer that over expressed HER2 receptor.

Patients and Methods

Patients

The study sample involved female patients who attended the oncology center in Al-Sadar medical city in Al-Najaf Al-Ashraf Governorate from April 2013 to the July 2014 with established new diagnosis breast cancer with HER2 positive. Exclusion criteria were female patients with the past-medical history of heart disease, kidney failure, and DM or thyroid diseases.

Twenty six female patients were involved in this study and divided randomly into 2 groups, 13 female patients per group. In group (I) patients were treated with trastuzumab medication for 8 cycles with 21 days interval. In group (II) patients were treated with trastuzumab medication plus valsartan40 mg administered orally twice daily for 8 cycles with 21 days interval. Each female patient was informed about treatment. The ethical committees of Al-Nahrain Faculty of medicine approved the study protocol.

Echocardiography (ECHO)

Each individual patient included in this study (both patients groups), underwent echocardiography, at zero time, and at 4th and 8th cycles. The study was achieved for determining left ventricular fraction shortening (LVFS). LVFS reveals the relative change of left ventricular internal dimension during the cardiac cycle; it is measured as the difference ratio between end diastolic and end systolic internal diameters to the end diastolic internal diameter.
To achieve the percent of fraction shortening multiply this by 100. It is the most commonly applied M-Mode derived a measure of left ventricular systolic function [15].

Collection of Blood Samples

5 cc of blood was collected at zero time and at 2nd, 4th, 6th and 8th cycles for assessment of TIC based on changes of the serum CTNI and MDA biomarkers. Each blood sample was centrifuged for 15 minutes at 2500 rpm, and then serum was collected and frozen at -70 until measurement.

Measurement of Troponin I

Using commercially available human CTNI ELISA kit (catalog number CSB-E05139h) from Cusabio Biotech Co., LTD.

Measurement of Malondialdehyde (MDA)

Statistical Analysis

Statistical analyses were performed using SPSS 17.0 for windows. Inc. Data of quantitative variables were expressed as mean ± SEM. Differences in each variable through cycles of treatment in the same group were compared using paired-sample Student’s t-test. The comparisons between the two groups variable accomplished by unpaired-sample Student’s t-test in all tests, P<0.05 was considered to be statistically significant.

Results

Anthropometry

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

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

<table>
<thead>
<tr>
<th>Anthropometric data</th>
<th>Mean± SEM (Group I)</th>
<th>Mean± SEM (Group II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>38.38± 2.27</td>
<td>41.07± 2.08</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.61±1.87</td>
<td>67.61± 1.48</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.84±2.35</td>
<td>161.92± 1.35</td>
</tr>
<tr>
<td>Body Surface Area (m²)</td>
<td>1.73±0.03</td>
<td>1.71± 0.019</td>
</tr>
<tr>
<td>Body Mass Index (kg / m²)</td>
<td>28.02± 0.85</td>
<td>25.87± 0.67</td>
</tr>
</tbody>
</table>

Effect of Different Treatment Regimen on Echocardiographic Fraction Shortening (FS %)

In comparison with baseline levels, there was a significant decrease in FS % at only the eighth cycle in trastuzumab regimen (p<0.05) as shown below in Figure 1. In comparison between treatment groups, there was no significant difference (P > 0.05) in FS % at baseline and after four cycles of treatment as shown below in Figure 1. At eighth cycle of treatment FS % of group II was significantly (P < 0.05) higher than that of group I as shown in Figure 1.

Figure 1: Mean± SEM values of echocardiographic fraction shortening (%) at baseline and after four and eight cycles in both groups (trastuzumab based regimen, n=13 and trastuzumab plus valsartan, n=13)

P<0.05 compare to baseline values of the same treatment group
# P<0.05 compare to group I
**Effect of Different Treatment Regimens on Serum Troponin I Level**

In comparison with baseline levels, there was significant increment in serum CTNI level (ng/ml) after two, four, six and eight cycles in trastuzumab regimen group ($p< 0.05$) as shown below in figure (2). In comparison between treatment groups, there was no significant difference ($P > 0.05$) in serum CTNI level (ng/ml) at baseline and after two and four cycles of treatment as shown below in figure (2). After six and eight cycles of treatment, serum CTNI level (ng/ml) of group II was significantly ($P < 0.05$) lower than that of group I as shown in figure (2).

![Graph of Troponin I Level](image)

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

**Figure 2:** Mean± SEM values of serum CTNI (ng/ml) at baseline and after two, four, six and eight cycles in both groups (trastuzumab based regimen, $n=13$ and trastuzumab plus valsartan, $n=13$)

**Effect of Different Treatment Regimens on Serum MDA Level:**

In comparison with baseline level, there was significant increment in serum MDA level (mg/l) after two, four, six and eight cycles in trastuzumab regimen group ($p< 0.05$) as shown below in figure (3). In comparison between different treatment groups, there was no significant difference ($P > 0.05$) in serum MDA level (mg/l) at base line of treatment as shown below in figure (3). After two, four, six and eight cycles of treatment, serum MDA level of group II was significantly ($P < 0.05$) lower than that of group I as shown in figure (3).

![Graph of Malondialdehyde Level](image)

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

**Figure (3):** Mean± SEM values of serum malondialdehyde(mg/l) at baseline and after two, four, six and eight cycles in both groups (trastuzumab based regimen, $n=13$ and trastuzumab plus valsartan, $n=13$)
Discussion

The use of trastuzumab medication in HER2 positive breast cancer has significantly improved response rates and enhanced survival in female patients with early-stage and metastatic disease[3].

However, the highly incidence of cardio toxicity, up to one third of female patients treated with trastuzumab medication might develop a cardio toxicity [17, 18] has produced great concern regarding its use. Definitely, the occurrence of cardio toxicity restricts the selection of possible oncological regimens to those considered less aggressive and as a result less effective [19]. Female patients who develop heart problems when treated with trastuzumab medication 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 FS % after four treatment cycles in comparison to baseline values (P>0.05). Trastuzumab medication caused significant reduction in FS % after eight treatment cycles in comparison to baseline values (P < 0.05). This finding supports previous animal experiments demonstrating that fraction shortening significantly declined from a mean of 32% in control groups to a mean of 23% in trastuzumab treated groups.

The proposed mechanism beyond this effect is thought to block cardiomyocyte HER2 signaling pathway. So that trastuzumab medication interfering with normal growth, repair, counteraction of undue sympathetic strength and survival of cardiomyocytes [21, 22]. Trastuzumab also produced highly significant increase in serum CTNI level (ng/ml) in comparison to the baseline readings (P < 0.01). Several studies revealed the same result after about one month and three month respectively [23, 24].

In this study the timing of detectable serum CTNI appeared to precede the maximal decline in LVFS at cycle eight, for example trastuzumab produced highly significant increment in serum CTNI level at cycle two in comparison to the baseline readings. This result was similar to that demonstrated in previous studies, where the CTNI increased soon after chemotherapy represents strong predictor of myocardial injury and poor cardio logical outcome, with the highest risk detected in patients showing a persistent (1 month) CTNI increase[25,26,17].The mechanism for CTNI elevation after chemotherapy can be indicated that subclinical cardiomyocyte damage may arise. Because the mechanism underlying TIC is considered dissimilar to that of anthracyclines, elevation of this biomarker through trastuzumab therapy further complicates our knowledge about cardio toxic effects of anticancer treatment [27, 28].

However, CTNI was detected early after treatment with trastuzumab medication, allowing us to identify the female patients at greatest hazard after the first two cycles of treatment. A possible explanation for the elevation of CTNI during trastuzumab treatment is by blocking of HER2 receptors, expressed on cardiomyocytes, which result in the loss of survival pathways that mediated by HER2.

These pathways seem to have a protective effect on cardiac function, because they generally blunt the pathways effects of stress signaling [28]. Trastuzumab caused a high significant increase in serum MDA level in comparison to baseline values (P < 0.01). This finding is in consistency with that revealed by Dirican et al. and Keith et al. [29, 30].

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

In patients with doxorubicin-induced cardio toxicity, ACE-inhibitors can improve symptoms of CHF and can avert a decline in LVEF [31]. Echocardiograph fraction shortening was highly significant increased by valsartan in comparison to trastuzumab based regimen group (P < 0.01). According to our knowledge, no previous studies agree or disagree with present result. Valsartan caused highly significant decrement in serum TRP I. This finding is in accordance with that reported by Cardinale et al., who showed that the percentage of patients who showing an increased TRP I value during follow-up and a mean TRP I value at each step was higher in control subjects than in the ACE-inhibitor group. Valsartan caused significant decrease in serum MDA levels. This finding support
the presence of antioxidant effect of valsartan when administered in experimental animal model. The antioxidant effect of valsartan attributed to block Ang II effects, which is regarded as a pro-oxidant through stimulate the generation of reactive oxygen species [32].

Conclusion

Valsartan causes significant increase in echocardiographic fraction shortening level and cause significant reduction in serum troponin I and malondialdehyde in trastuzumab treated patients.

References


