Assessment of Carvedilol Therapy in Prevention of Heart Failure in HER2 Positive Breast Cancer Patients Receiving Trastuzumab

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Abstract- Breast cancer is the most common cancer among the female population, and its prevalence is increasing worldwide. Trastuzumab (Herceptin) therapy improves prognosis in HER2 positive patients, but Heart Failure (HF) is one of its known complications. In this study, we aimed to assess the potential benefits of prophylactic carvedilol therapy in patients receiving Herceptin. Sixty five patients with HER2 positive breast cancer were enrolled in the study. All of the patients received Herceptin. Twenty seven patients also received carvedilol 6.25 mg twice daily, and 38 patients had usual care. Echocardiography was performed at baseline, and after three months in both groups and changes in cardiac function, parameters were compared between two groups. After 3 months, LA volume index (P=0.012), TAPSE (P=0.009), Tei index (P=0.015) and Lateral Longitudinal Strain (P=0.024) were significantly better in patients receiving carvedilol. Carvedilol can be effective in the prevention of systolic and diastolic dysfunction following Herceptin therapy.

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Introduction

Breast cancer is the most common malignancy and the second leading cause of death from malignancy in Western countries (1,2). In approximately 15-25% of patients with breast cancer, Human Epidermal Growth Factor receptor 2 or HER2 gene is overexpressed which is associated with poor prognosis (3,4). This receptor is a transmembrane tyrosine kinase growth factor receptor family member and plays a role in normal cell growth and cell differentiation. Overexpression of this gene in breast cancer is associated with increases recurrence and mortality rates (5). Trastuzumab or Herceptin is a humanized monoclonal antibody which blocks the HER2 receptor and results in improving the prognosis. It reduces the rate of recurrence and deaths by 50% in 3 years of follow up (6,7).

Herceptin is well tolerated in most patients, without significant side effects, but cardiotoxicity may occur, ranging from asymptomatic left ventricular dysfunction to symptomatic heart failure (8). The prevalence of cardiac dysfunction is increased with concomitant use of anthracyclines and reaches up to 18% (9). Cardiac injury is not dose dependent, and in most cases, it is reversible within 2 to 4 months of discontinuing the drug (10). However, the reversibility of Herceptin cardiotoxicity is questioned recently (11). Furthermore, discontinuing Herceptin therapy would have a negative effect on cancer prognosis (12).

HER2 which is also known as erbB2 acts as a receptor for neuregulins, which have a role in cardiac development and trabeculation in animal models (3). Neuregulins also are released from coronary artery endothelium during oxidative stress, and by activating e-

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NOS and protein kinase B, take part in reducing free oxygen species (13). Thus, blocking the HER2 receptor may result in endothelial dysfunction which may have a role in Herceptin cardiotoxicity (13).

Carvedilol is a nonselective β blocker which also has α1 blocker effects. Based on blocking the β1 receptor, it can modulate activating of the neurohormonal system by decreasing cardiac sympathetic tone and releasing renin from the kidney. Thus, this drug can prevent cardiac remodeling (14). On the other hand, carvedilol has α1-blocker effects that can inhibit coronary artery vasoconstriction and may help to balance NO-dependent endothelial dysfunction (15,16). In recent studies, positive and beneficial cardioprotective effects of carvedilol has been suggested (17-19).

Based on the benefits of carvedilol mentioned earlier and the negative effects of Herceptin cardiotoxicity on cardiac function and baseline cancer, the preventive role of carvedilol on Herceptin cardiac dysfunction was assessed in this study with detailed echocardiographic parameters.

Materials and Methods

The study was a double-blind, randomized clinical trial with a control group that was performed in Imam Khomeini hospital during 2015-2017. The study population were patients with HER2-positive breast cancer treated with Herceptin as adjuvant therapy or as a treatment for metastatic cancer. Patients were referred from oncologist specialists.

The inclusion criteria were every HER2 positive breast cancer patients who were a candidate for receiving Herceptin therapy. Patients did not receive concomitant anthracycline therapy.

The exclusion criteria were as follows: history of heart failure in the past or Left Ventricular Ejection Fraction (LVEF) of less than 50% in previous echocardiography, history of high dose anthracycline therapy, clinical symptoms consistent with heart failure, existence of absolute or relative contraindications for use of beta-blockers, history of atherosclerotic coronary artery disease, severe valvular or congenital heart disease, and current consumption of beta blockers before initiation of study or previous use of cardiotoxic drugs.

Patients were randomly assigned to carvedilol and control groups. Randomization was done by permuted block method; that is, patients were divided into 4 member groups, and from each group, 2 patients were randomly assigned to carvedilol group, and the other 2 were assigned to control group.

Informed consent was obtained from all patients before enrolling them in the study. A questionnaire was filled by patients containing demographic data, history of DM, hypertension, dyslipidemia, renal failure, cigarette smoking, and family history of heart failure. Baseline echocardiography (GE, Vivid 7) was performed in all patients. LVEF was determined by eyeball and simpson's method (20,21). End systolic and end diastolic diameters and volumes of left ventricle (LV), also parameters of right ventricle (RV) like RV diameter, tricuspid annular plane systolic excursion (TAPSE) , RV (TDI) tissue doppler imaging (S') were measured (22). LV diastolic function (E` and E/E` ratio), Tei index (23), septal and lateral S wave by TDI, septal and lateral strain and strain rate by Doppler method were measured and calculated (24-26).

Before administration of Herceptin, Carvedilol at a dose of 6.25 mg twice daily was initiated in the case group. Herceptin was given with a loading dose of 8 mg/kg in 90 minutes and then 6 mg/kg every 3 weeks in both groups. After 3 months of treatment with Herceptin, all patients were undergone follow up echocardiography. Patients were advised to come earlier for a visit, in case of exertional dyspnea or lower extremity edema. If the patients were symptomatic and echocardiography showed evidence of heart failure (LVEF <50% or a decrease in EF over 10%) patient`s follow-up was stopped, Herceptin was discontinued, and the patient was referred for heart failure therapy. Otherwise, follow up was continued for 3 months. Carvedilol was continued for 3 months to the time of follow up echocardiography.

The study was performed without a placebo. The cardiologist who interpret the echocardiographic data and the person who analyzed data were blind to carvedilol and control group. The analysis was done via SPSS 22. Independent *t*-test was used for comparing between two groups and paired. *t*-test was used for comparing baseline and follow up data in each group.

Results

Sixty five patients were enrolled in the analysis phase. 27 patients were in the carvedilol group, and 38 patients were in the control group. The mean age was 46.5-years-old, and the mean BMI and mean BSA were 24.5, and 1.7, respectively. There were no significant differences in these parameters between the two groups.

No patient had a history of DM, hypertension, renal failure, or smoking. Two patients had a history of dyslipidemia (one patient in each group), and one patient

had a family history of heart failure. Thus, heart failure risk factors were not prevalent in this study in order to assess their correlation to cardiac dysfunction.

There was no significant difference in echocardiographic parameters between carvedilol and control group at baseline. Table 1 shows the baseline echocardiographic parameters in two groups.

Table 1. Baseline echocardiographic parameters in carvedilol and control groups in HER2 positive breast cancer patients receiving Herceptin

Parameter	Carvedilol (SD)	Control (SD)	*P*
LV end systolic diameter	3.1 (0.46)	3.2 (0.5)	0.2
LV end diastolic diameter	4.6 (0.43)	4.58 (0.49)	0.86
LV end systolic volume index	21 (3.8)	20.5 (4.1)	0.57
LV end diastolic volume index	48.9 (8.4)	47.1 (6.2)	0.33
LA volume index	33 (8.3)	32.9 (9.7)	0.82
LVEF (eye ball)	54.6 (1.9)	54.8 (1.8)	0.52
LVEF (Sympson)	56.3 (3.7)	56.9 (3.6)	0.61
TAPSE	24 (3.5)	26 (3.2)	0.02
RV S	11.6 (0.99)	11.9 (0.82)	0.25
RV diameter	2.47 (0.3)	2.48 (0.2)	0.9
E/E`	10.3 (2.7)	10.1 (2.2)	0.81
E`	8.6 (1.6)	8 (1.6)	0.12
Tei index	0.47 (0.05)	0.48 (0.04)	0.2
Septal S	4.98 (1.1)	4.96 (1.3)	0.94
Lateral S	4.8 (1.4)	5.1 (1.9)	0.41
Septal strain	-20.1 (8.8)	-20.2 (6)	0.94
Lateral strain	-20 (9.8)	-20.9 (8.7)	0.7
Septal strain rate	-1.1 (0.5)	-1.2 (0.6)	0.09
Lateral strain rate	-1.1 (0.67)	-1.1 (0.65)	0.34

In the first step, changes in echocardiographic parameters at 3 months were compared with baseline in each group separately. In the carvedilol group, LV end-diastolic diameter was reduced significantly from 4.6 cm to 4.4 cm (*P*=0.004). Left atrial volume index (LAVI) was also reduced significantly from 32.9 cc to 27.9 cc (*P*=0.01). There was no significant change in other parameters. Table 2 shows changes at 3 months in echocardiographic parameters in the carvedilol group.

Table 2. Baseline and 3rd month of follow up echocardiographic parameters in carvedilol group in HER2 positive breast cancer patients receiving Herceptin

Parameter	Baseline (SD)	3rd month (SD)	*P*
LV end systolic diameter	3.1 (0.46)	3.08 (0.42)	0.34
LV end diastolic diameter	4.6 (0.43)	4.46 (0.43)	0.004
LV end systolic volume index	21 (3.8)	20.1 (4.3)	0.28
LV end diastolic volume index	48.9 (8.4)	47.1 (6.5)	0.18
LA volume index	33 (8.3)	27.9 (8.4)	0.01
LVEF (eye ball)	54.6 (1.9)	53.7 (4.9)	0.25
LVEF (Sympson)	56.3 (3.7)	56.2 (6.6)	0.93
TAPSE	24 (3.5)	24.7 (3.1)	0.21
RV S	11.6 (0.99)	11 (1.2)	0.2
RV diameter	2.47 (0.3)	2.5 (0.26)	0.5
E/E`	10.3 (2.7)	10 (4.1)	0.71
E`	8.6 (1.6)	8.66 (1.8)	0.89
Tei index	0.47 (0.05)	0.46 (0.06)	0.42
Septal S	4.98 (1.1)	5 (1.2)	0.74
Lateral S	4.8 (1.4)	4.7 (1.4)	0.58
Septal strain	-20.1 (8.8)	-18.1 (9.7)	0.28
Lateral strain	-20 (9.8)	-20.7 (10.2)	0.7
Septal strain rate	-1.1 (0.5)	-1.3 (0.49)	0.96
Lateral strain rate	-1.1 (0.67)	-1.3 (0.63)	0.37

In the control group, at 3 months, there was a significant reduction in LVEF by eyeball (*P*=0.02) and

Sympson (*P*=0.01) method, TAPSE (*P*=0.011), septal S (*P*=0.03), and septal (*P*=0.001) and lateral strain (*P*=0.003). Also, there was a significant increase in Tei index (*P*=0.009). There were no other significant changes. Table 3 shows changes at 3 months in echocardiographic parameters in the control group.

Table 3. Baseline and 3rd month of follow up echocardiographic parameters in control group in HER2 positive breast cancer patients receiving Herceptin

Parameter	Baseline (SD)	3rd month (SD)	*P*
LV end systolic diameter	3.2 (0.5)	3.07 (0.49)	0.1
LV end diastolic diameter	4.58 (0.49)	4.47 (0.41)	0.14
LV end systolic volume index	20.5 (4.1)	20.8 (3.2)	0.68
LV end diastolic volume index	47.1 (6.2)	46.3 (4.9)	0.53
LA volume index	32.9 (9.7)	33.4 (9.3)	0.42
LVEF (eye ball)	54.8 (1.8)	53.2 (4)	0.02
LVEF (Sympson)	56.9 (3.6)	54.5 (5.2)	0.01
TAPSE	26 (3.2)	24.7 (3.2)	0.01
RV S	11.9 (0.82)	12 (1.3)	0.9
RV diameter	2.48 (0.2)	2.55 (0.25)	0.11
E/E`	10.1 (2.2)	10.4 (2.5)	0.33
E`	8 (1.6)	7.8 (1.3)	0.45
Tei index	0.48 (0.04)	0.51 (0.06)	0.009
Septal S	4.96 (1.3)	4.7 (1.2)	0.03
Lateral S	5.1 (1.9)	4.8 (1.8)	0.07
Septal strain	-20.2 (6)	-16.3 (9.7)	0.001
Lateral strain	-20.9 (8.7)	-16.4 (10.2)	0.003
Septal strain rate	-1.2 (0.6)	-1.1 (0.49)	0.58
Lateral strain rate	-1.1 (0.65)	-1.1 (0.63)	0.9

In the second step, changes in echocardiographic parameters at 3 months from baseline were compared between the two groups. LAVI was decreased in the carvedilol group but increased in the control group, and this difference was significant (*P*=0.012). TAPSE was reduced in the control group but was increased in the carvedilol group (*P*=0.009). Tei index was reduced in the carvedilol group and was increased in the control group (*P*=0.015). Changes in lateral strain were significantly different between the two groups (*P*=0.024). Table 4 shows the changes in echocardiographic parameters in 2 groups.

Table 4. Echocardiographic parameters` changes at 3rd month comparing to baseline in carvedilol and control groups in HER2 positive breast cancer patients receiving Herceptin

Parameter	Carvedilol (SD)	Control (SD)	*P*
LV end systolic diameter	0.03 (0.21)	-0.1 (0.47)	0.09
LV end diastolic diameter	-0.14 (0.24)	-0.12 (0.5)	0.8
LV end systolic volume index	-0.97 (4.5)	0.3 (4.6)	0.27
LV end diastolic volume index	-1.8 (6.9)	-0.8 (7.8)	0.58
LA volume index	-5 (9.4)	0.33 (5.7)	0.012
LVEF (eye ball)	-0.9 (4.1)	-1.6 (4)	0.52
LVEF (Sympson)	-0.11 (6.7)	-2.3 (5.3)	0.14
TAPSE	0.7 (2.9)	-1.4 (3.1)	0.009
RV S	0.29 (1.1)	0.02 (1.5)	0.44
RV diameter	0.04 (0.31)	0.067 (0.25)	0.7
E/E`	-0.25 (3.4)	0.3 (2)	0.41
E`	0.03 (0.13)	-0.13 (0.23)	0.6
Tei index	-0.006 (0.04)	0.027 (0.06)	0.015
Septal S	0.04 (0.69)	-0.23 (0.63)	0.1
Lateral S	-0.09 (0.89)	-0.3 (0.99)	0.38
Septal strain	1.9 (9.2)	3.9 (6.9)	0.32
Lateral strain	-0.6 (8.9)	4.5 (8.9)	0.024
Septal strain rate	-0.04 (0.48)	0.003 (0.49)	0.7
Lateral strain rate	-0.1 (0.59)	0.009 (0.51)	0.41

Discussion

Although it is said that Herceptin cardiotoxicity is reversible and it can be resolved within 2-4 months after discontinuing therapy (27), some evidence are against this fact. Telli *et al.,* (28) reported evidence of LV dysfunction in 71% of patients in more than 6 months of follow up. Cardinale *et al*., (29) showed that about 40% of trastuzumab cardiomyopathy did not improve in follow up. Thus, this chance of irreversibility of Herceptin cardiotoxicity which would elevate the risk of future cardiac events, and risk of cancer progression because of discontinuing Herceptin therapy, makes preventive strategies for drug toxicity of value.

In baseline measures of our study, 56 of patients had Tei index between 0.4 and 0.59, 26 patients had septal strain larger than -19, and 26 patients had abnormal lateral strain. 39 patients had septal strain rate larger than -1.5 and 41 patients had abnormal lateral strain rate. Thus, in a large number of patients, structural abnormalities were initiated before reduction of global LVEF and maybe if these parameters are set for detecting cardiotoxicity of the drug, the prevalence of cardiac dysfunction may become more than what was reported previously. However, the value of detecting such changes in preventive or therapeutic strategies is unknown.

In addition, although there was no significant difference in echocardiographic parameters between the two groups at baseline, the course of variation was different at 3 months in two groups. In the carvedilol group, LAVI was significantly reduced at 3 months, compared to baseline but it had no significant change in the control group. The change in LAVI between two groups was also significantly different. Thus, it seems that carvedilol is effective in reducing LA volume, which reflects LA pressure over time and this pressure can be determined by diastolic function. It can be concluded that carvedilol may have a beneficial effect on diastolic function.

In the control group, reduction in TAPSE, Tei index, and the lateral strain were significant at 3 months. The changes in these three parameters also differ significantly between the two groups. TAPSE is reflecting right ventricular systolic motion. Tei index reflects both LV systolic and diastolic function, and the lateral strain shows LV systolic function. Thus, it can be concluded that carvedilol may have a positive preventive effect on LV and RV systolic function.

In a recent work, cardiomyopathy (diastolic dysfunction and reduction of EF) and also rise of troponin was seen in patients with breast cancer , who received Trastuzumab (30).

Seicean *et al.,* (27) showed the benefits of beta blockers in the prevention of heart failure in Herceptin therapy. However, in that study clinical signs of heart failure were the goal and echocardiographic parameters were not assessed. Kalam and Marwick (31) reported the usefulness of beta blocker pretreatment before anthracycline and Herceptin in the prevention of reducing LVEF in echocardiography. In this study, changes in LVEF between groups was not significant despite other echocardiographic evidence of beta blocker`s usefulness. One reason may be the short follow up time which was only 3 months in this study (in Seicean, for instance, patients were followed for 3 years). Longer follows up time may show a significant difference in LVEF between the two groups.

Negishi *et al*., (32) used a global longitudinal strain to show the preventive benefit of beta blocker in Herceptin therapy. In this study, we used the Doppler strain technique, but the result was similar in lateral strain.

In conclusion, carvedilol may have beneficial effects in the prevention of cardiac dysfunction in patients receiving Herceptin but a larger study with a longer follow up period is recommended to determine this hypothesis more accurately.

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