

Evaluation of the Preventive Effects of Carvedilol on Trastuzumab-Induced Cardiotoxicity in Early-Stage and Locally Advanced HER2-Positive Breast Cancer Patients

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Received: 23, May, 2020

Accepted: 10, Sep, 2020

ABSTRACT

Background: Trastuzumab is an efficient monoclonal antibody used in the treatment of Her2-positive breast cancer. Despite its prominent effect on Her2-positive patients' disease-free Survival. Trastuzumab-induced cardiotoxicity is still one of the main challenges. Angiotensin-converting enzyme inhibitors (ACE inhibitors) are one of the most potent agents used in heart failure, which also showed confirmed cardioprotective effects against anthracycline and doxorubicin. We aimed to assess the cardioprotective effects of Carvedilol in a randomized clinical trial study.

Materials and Methods: sixty non-metastatic Her-2 positive patients (30 cases; 30 controls) were entered into the study via a simple randomization method. Carvedilol was administered for the patients with the starting dose of 3.125 mg twice a day and started 7 days before trastuzumab administration. The dose has been increased in a three-week period to reach 12.5 mg twice a day and continued until the end of therapy. All the patients underwent an echocardiography after receiving Adriamycin and Cyclophosphamide in order to measure basal Ejection Fraction (EF) and Pulmonary Artery Pressure (PAP). Each patient underwent a follow-up echocardiography in 3,6,9 and 12 months after initiation of the treatment. Finally, all the patients went through the last episode of echocardiography 1 month after the end of treatment. All the Measured PAP and EF has been recorded and analyzed

Results: EF and PAP changes for both groups had no significant changes during the course of treatment with Trastuzumab (p-value = 0.628 and p-value = 0.723, respectively). Seven patients in the intervention group and 2 patients in the control group presented with EF decrease. Also, 8 patients in the intervention and 9 patients in the control groups showed PAP increase.

Conclusion: According to our results, in patients with HER2-positive breast cancer treated with trastuzumab, Carvedilol showed no significant protective effect on trastuzumab-induced cardiotoxicity.

Keywords: Trastuzumab-induced cardiotoxicity; Carvedilol; Human epidermal growth factor receptor-2 (HER-2); Ejection fraction; Pulmonary artery pressure

INTRODUCTION

Breast cancer is one of the most common cancers worldwide which owns different subtypes with different prognostic issues^{1,2}. Breast cancers with overexpressed epidermal growth factor receptor-2 or Human Epidermal Growth Factor Receptor-2 (HER2) are among the types with poor prognosis at least until the introduction of Trastuzumab^{2,3}. HER2-positive cases which accounts for about 20-25% of breast cancers, are usually presented with more invasive nature, metastasis rate and lower response to therapy^{4,5}. In more details, HER2 overexpression is a result of amplification in *Her2/neu* oncogene in the breast cancer cells⁶.

Trastuzumab is a monoclonal Antibody with spatial resemblance to epidermal growth factor which acts by binding to the extracellular domain of HER2 receptor and block the activation of its downstream molecules⁷⁻¹⁰. According to many clinical trials conducted, this agent is an efficient adjuvant and neoadjuvant therapy in HER2- positive patients with significant decrease in mortality rate and metastasis^{11,12}. In 2001, Slamon et al. in their phase III trial dedicated the cardiotoxicity of trastuzumab which was not previously reported by early small trials. In this study, the frequency of cardiotoxicity in the presence of trastuzumab and chemotherapy regimen was 27% while this was only reported in 8% of the patients who underwent chemotherapy regimen alone. The mechanism of trastuzumab-induced cardiotoxicity is not still well established; However, according to previous studies, it may be the result of attenuation of HER2 signaling in cardiac muscles resulting in sarcomere disruption, impaired proliferation and survival of cardiomyocytes^{13,14}. All of these may lead to gradual dose-independent decrease in cardiac ejection fraction (EF). Although many patients generally well-tolerated trastuzumab and present no cardiotoxicity in the time of treatment, this problem is still one of the most challenging issues about it. Trastuzumab-induced cardiotoxicity (TIC) occurs in about 10-12% of the patients and is often presented with asymptomatic decline in Left ventricle EF¹⁵⁻¹⁸.

As Angiotensin Converting Enzyme (ACE) inhibitors and beta blockers were among the most effective medications in reduced-EF heart failure and showed

effective protection against doxorubicin-induced cardiotoxicity¹⁹, many studies evaluated their effect on trastuzumab-induced cardiotoxicity. According to MANTIORE double-blinded randomized clinical trial, perindopril and bisoprolol had a significant protective effect on Left Ventricle EF (LVEF) decrease with p-value < 0.001²⁰.

Guglin et al. performed a comprehensive study in 2019 on 468 HER2-positive breast cancer patients in order to evaluate the protecting effect of carvedilol and Lisinopril in patients receiving only trastuzumab or trastuzumab plus anthracycline. Neither carvedilol nor Lisinopril showed meaningful protecting effect on trastuzumab-induced cardiotoxicity in the patients who only received trastuzumab, while in the patients who received both trastuzumab and anthracycline, Lisinopril and Carvedilol had a significant protective effect²¹. These results were discordant with the result of CECCY trial which stated no significant protective effect of carvedilol on anthracycline-induced cardiotoxicity²². In this study, we aimed to assess the protective effect of carvedilol in the non-metastatic HER2-positive breast cancer patients.

MATERIALS AND METHODS

This study has been designated as a randomized clinical trial to evaluate the effect of carvedilol in patients with early and locally advanced HER2-positive breast cancer who were under Trastuzumab regimen. Patients and the intervention administrator were not blinded. However the main outcome assessor (echo-man) was kept unaware of patients groups. This project was approved by ethics committee of Tehran University of Medical Sciences and privacy of the patients has been completely preserved during the research.

Details of randomization, sampling, binding and other issues were described in the registered protocol in IRCTID: IRCT20190628044046N1.

Inclusion and Exclusion criteria

This study has been conducted on the patients with recently diagnosed HER2-positive breast cancer in the stages I to IIIA who signed the consent letter and has been candidate for trastuzumab therapy. Of note, patients with the following criteria were

excluded from the research: 1-previous history of cardiomyopathy, uncontrolled hypertension and cardiac structural disorders; 2-Left ventricular EF < 50% or history of proved heart failure; 3-contraindication for beta blocker consumption such as symptomatic bradycardia, Asthma and cardiac conduction disorders; 4-patients already taking beta blockers; 5-history of myocardial infarction; 6-patients who had the history of chest radiotherapy; 7-previous cancer chemotherapy; 8-patients with Glomerular Filtration Rate (GFR) < 30 ml/min/1.73m² and 9-patients who did not sign the consent letter.

Sampling

According to the sample size calculation, 60 patients (30 cases; 30 controls) with mentioned inclusion criteria referred to Sina hospital since 2017 until 2019 were entered to the study via simple randomization method.

Chemotherapy regimen

All the patients received AC-TH treatment protocol consisting Adriamycin and Cyclophosphamide, followed by Paclitaxel and Trastuzumab 2mg/kg weekly for a period of 12 weeks as neoadjuvant therapy. next, Trastuzumab with dose of 6mg/kg was administered every three weeks for a period of one year as adjuvant therapy.

Echocardiographic studies

All the patients underwent an echocardiography after receiving Adriamycin and Cyclophosphamide in order to rule out the anthracycline-induced cardiotoxicity. EF and Pulmonary Artery Pressure (PAP) has been measured and recorded as basal EF and basal PAP. Each patient underwent a follow-up echocardiography in 3,6,9 and 12 months after initiation of the treatment. Finally, all the patients went through the last episode of echocardiography 1 month after the end of treatment.

All the Echocardiographic studies have been conducted by an echocardiography fellowship expert.

Following findings were presumed as Left Ventricular Dysfunction (LVD)(20, 23):

- 1- Global LVEF decrease
- 2- Interventricular LVEF decrease
- 3- 5% or more decrease from basal LVEF or EF<55% in symptomatic patients
- 4- 10% or more decrease from basal LVEF or EF<50% in asymptomatic patients
- 5-

Carvedilol administration

Carvedilol was administered for the patients with the starting dose of 3.125 mg twice a day and started 7 days before trastuzumab administration. The dose has been increased in a three-week period to reach 12.5 mg twice a day and continued until the end of therapy. of note, many patients had normal blood pressure and could not tolerate this dose; in these patients, carvedilol has been administered in the maximum dose of tolerance.

Statistical analysis

Statistical analysis was performed by IBM SPSS version 23. Chi square test was used to determine the significance of correlation between categorical variables. Repeated measure ANOVA test was used to measure the significance of correlation between continuous variables as well. In all of the comparisons, p-value < 0.05 was assumed as a measure of significance. Linearity was tested by matrix scatter plot. Normality of continuous variables was measured using Kolmogorov-Smirnoff test.

RESULTS

We divided our patients into case and control groups. Age, EF, PAP, receptor status and other basic characteristics have been measured and no statistically significant difference was present among the case and control groups except for the PAP variable. Related data is summarized at Table 1.

Of note, metastasis was reported for two patients in the case group and one patient in the control group in the course of therapy; There was no need to exclude these subjects due to p-value> 0.05.

All the patients underwent a follow-up echocardiography in 3,6,9 and 12 months after initiation of their treatment and final echocardiography one month after the end of

treatment in order to evaluate the course of EF and PAP changes. Our results showed no significant difference in EF and PAP amounts of the case and control group (Table 2).

Table 1. Demographic and basic characteristics

	Intervention Group		Control Group		P
Age	47.6 ± 9.64		46.2 ± 8.59		0.555
Basal EF	55 ± 1.03		54.9 ± 0.45		0.423
Basal PAP	28.23 ± 4.56		25.13 ± 5.75		0.024
Estrogen Receptor	Positive	53.3%	Positive	50%	0.999
	Negative	46.7%	Negative	40%	
Progesterone Receptor	Positive	53.3%	Positive	46.7%	0.797
	Negative	46.7%	Negative	53.3 %	
Metastasis	2 (6.67%)		1 (3.33%)		0.999

Table 2. Course of EF and PAP changes

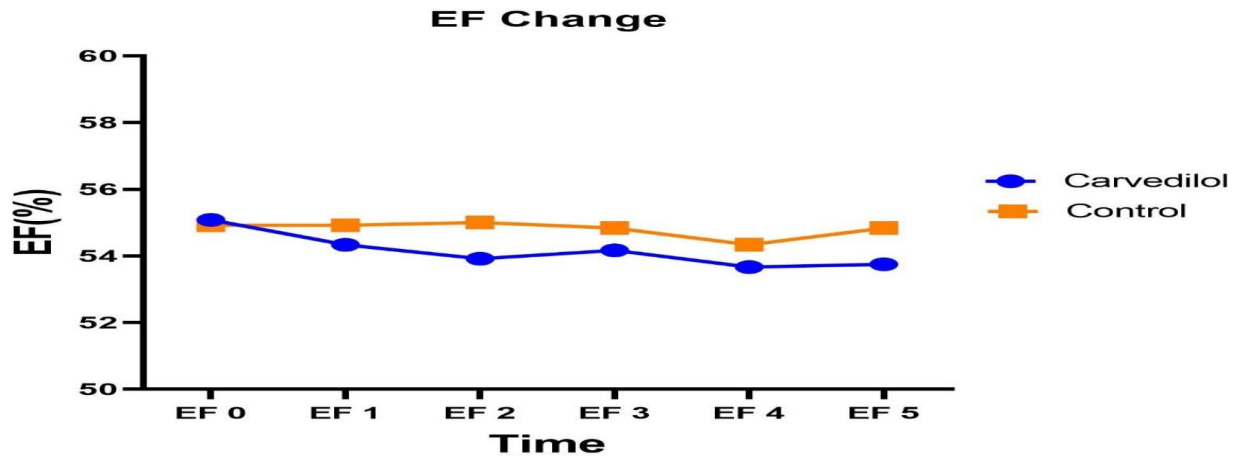
	Intervention Group	Control Group
EF-3months	54.33 ± 2.85	54.91 ± 1.39
EF-6months	53.91 ± 3.81	55 ± 0.00
EF-9months	54.16 ± 3.61	54.83 ± 0.91
EF-12months	53.66 ± 3.63	54.33 ± 4.14
Final EF*	53.75 ± 3.52	54.83 ± 4.25
PAP-3months	28.33 ± 3.65	25.60 ± 5.36
PAP-6months	28.76 ± 4.01	25.55 ± 5.30
PAP-9months	28.43 ± 4.20	25.50 ± 5.28
PAP-12months	28.70 ± 4.15	25.73 ± 6.49
Final PAP**	28.70 ± 4.15	25.03 ± 7.61

*Final EF was the EF measured 1 month after the end of treatment

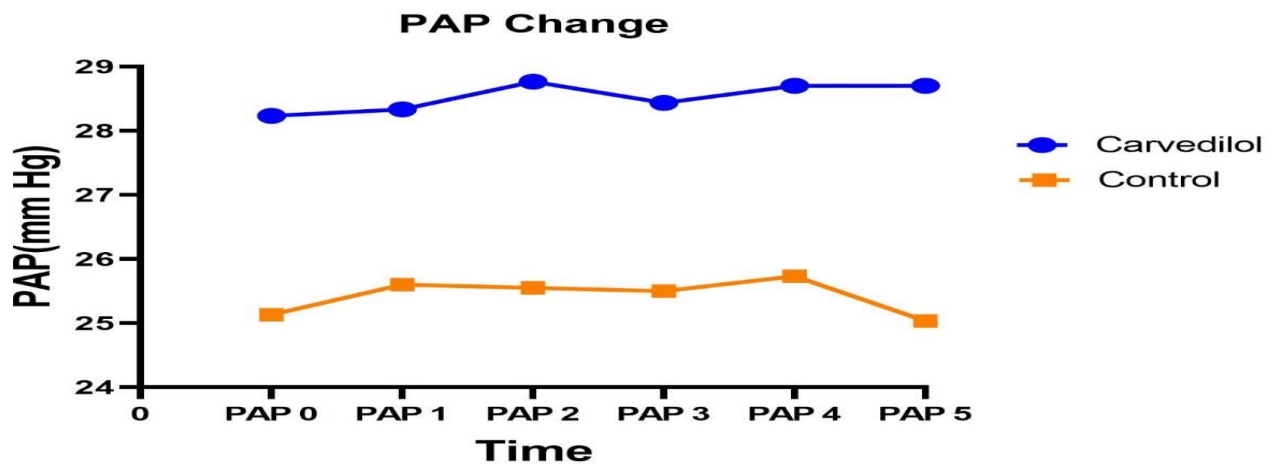
**Final PAP was the PAP measured 1 month after the end of treatment

According to repeated measure ANOVA test, EF and PAP changes for both groups had no significant changes during the course of treatment with Trastuzumab (p-value = 0.628 and p-value = 0.723, respectively). In more details, 7 patients (23.3%) in the intervention group and 2 patients (6.7%) in the control group presented with EF decrease (Final EF <

Basal EF) which was not statistically significant with p-value = 0.07. Also, 8 patients (26.7%) in the intervention and 9 patients (30%) in the control groups showed PAP increase (Final PAP > Basal PAP) which was not statistically significant as well, with p-value = 0.774 using Chi square test. Figure 1 illustrate the course of EF and PAP changes in both groups.



a) Figure 1- a- Mean EF values in both groups in 0,3,6,9 and 12 months of trastuzumab treatment, basal EF was indicated as EF0 and final EF as EF5 which was measured one month after the end of treatment.



b) Figure 1-b-Mean PAP values in both groups in 0,3,6,9 and 12 months of trastuzumab treatment, basal PAP was indicated as PAP0 and final PAP as PAP5 which was measured one month after the end of treatment.
 EF: Ejection Fraction; PAP: Pulmonary Artery Pressure

DISCUSSION

Trastuzumab-induced cardiotoxicity (TIC) is rarely associated with overt symptomatic heart failure (24); However, it is mainly associated with asymptomatic decline in EF in about 10-12 percent of patients and typically appears as a reversible complication of trastuzumab neoadjuvant or adjuvant therapy.(7, 25, 26) Risk factors for TIC are still under debate; but age, history of anthracycline use , basal left ventricle EF, Hypertension and Diabetes mellitus are among the most evident risk factors.(23, 27-29).

In our study, most patients well tolerated Trastuzumab and showed no EF decline and PAP rise during the course of therapy, whereas about 25% of the intervention group and 7% of the control group presented with EF reduction. This difference was not significant (p-value = 0.07) also, the EF values among the intervention group and the case group showed no significant difference at the end of therapy.

In addition, 27% of the intervention group and 30% of the control group showed PAP rise during the course of study. This difference was not significant as well (p-value = 0.774). However, we were not able to evaluate the PAP difference among the case and control group at the end of therapy because they showed a significant difference since the beginning.

In 2019, Sherafati et al. showed significant improvement in echocardiographic markers such as left atrium volume index, Tei index, Tricuspid Annular Plain Systolic Excursion (TAPSE) and Lateral Longitudinal Strain (LLS) but Left ventricle ejection fraction did not show a significant difference(30). Another study conducted by Farahani et al. also reported no significant difference in the EF of the case and control groups, while both global longitudinal strain (GLS) and strain rate of systolic function (SRS) was significantly lower in control group who received placebo instead of carvedilol (31). On the other hand, carvedilol protective effects against anthracycline-related agents is thoroughly confirmed by numerous studies (19, 32, 33) and hypothetically, this may play a crucial role in improvement of echocardiographic markers. For more evident information about carvedilol impact on TIC, further investigations with longer follow-up period may be needed.

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