Original Article

Efficacy of Treatment With Carvedilol in Preventing Early-Stage Left Ventricular Dysfunction in Patients With Breast Cancer Candidated to Receive Trastuzumab Using 2D Speckle-Tracking Echocardiography

Maryam Moshkani Farahani[1], MD; Saeed Nourian*[1], MD;
Hamed Reza Jalalian[2], MD; Arezoo Khosravi[1], MD; Mahmmod Salesi[3], PhD

ABSTRACT

Background: Treatment-induced cardiotoxicity is one of the major side effects of trastuzumab treatment in patients with breast cancer. Left ventricular (LV) dysfunction is the leading cause of treatment-induced cardiotoxicity. The development of treatment-induced cardiotoxicity during cancer treatment may force patients to modify or quit the treatment. In this trial, we evaluated the prophylactic effects of carvedilol on LV dysfunction in patients with breast cancer receiving trastuzumab using 2D speckle-tracking echocardiography (2DSTE).

Methods: We conducted an open-label randomized clinical trial and enrolled 71 non-metastatic HER-2 positive patients with breast cancer candidated to receive trastuzumab. Carvedilol was administered concomitantly with the trastuzumab standard regimen at a dosage of 6.25 mg twice a day and up-titrated to the maximum tolerated dosage. The 2DSTE parameters to evaluate the LV systolic and diastolic functions were evaluated initially and 3 months thereafter.

Results: Thirty-six patients were randomly assigned to the carvedilol group and 35 patients to the control group. The mean left ventricular ejection fraction (LVEF) was not significantly different either in both groups or between the 2 groups (*P*=.61) during the follow-up. In contrast, the global longitudinal strain of the LV (GLS) (*P*=.000) and the strain rate of the LV systolic function (SRS) (*P*=.004) as markers of the LV systolic function were reduced in the control group. Furthermore, the LV strain rate of the early (SRE) and late (SRA) diastolic functions were preserved in the patients who received prophylactic carvedilol (*P*=.000 and *P*=.005, respectively).

Conclusions: Concomitant carvedilol treatment with a maximum tolerable dose in patients with non-metastatic HER2-positive breast cancer under treatment with trastuzumab might be effective on the reduction of systolic and diastolic echocardiographic findings other than the LVEF in patients with weak markers of heart failure. ***(Iranian Heart Journal 2019; 20(1):20-31)***

KEYWORDS: Cardioprotection, Carvedilol, Trastuzumab, Breast cancer

[1] Atherosclerosis Research Center, Baqiyatallah University of Medical Sciences, Tehran, IR Iran.
[2] School of Medicine, Baqiyatallah University of Medical Sciences, Tehran, IR Iran.
[3] Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Tehran, IR Iran.

***Corresponding Author:** Saeed Nourian, MD; Atherosclerosis Research Center, Baqiyatallah University of Medical Sciences, Tehran, IR Iran.
Email: S-nourian@razi.tums.ac.ir **Tel:** 09129215873

Received: July 8, 2018 **Accepted:** September 25, 2018

New chemotherapy regimens have improved the survival of cancer patients. [1] On the other hand, survivors will face the delayed side effects of anticancer drugs during their life. [2] The cardiovascular complications of chemotherapy include myocardial dysfunction and heart failure, which are often addressed as cardiotoxicity, and other 8 main categories. [3] Trastuzumab, a monoclonal antibody and anti-human epidermal growth factor-2 [HER2] chemotherapeutic agent, serves for metastatic and non-metastatic HER2-positive patients with breast cancer. [4]

Trastuzumab can be concomitantly or sequentially administered with anthracyclines, and previous studies have shown that the former has more cardiotoxicity effects. [5,6] A HERA trial concluded that patients in the trastuzumab arm had a more reduction in the left ventricular ejection fraction (LVEF) than did the control arm. [7] About 18% of the patients under treatment with trastuzumab with a leading cause of treatment-induced cardiotoxicity (TIC) may interrupt the treatment prematurely, which may increase the risk of cancer recurrence. [8] TIC is defined as a reduction in the LVEF to less than 45% or a reduction of 10% from the baseline to 45% or to 49%. A significant reduction in the global longitudinal strain (GLS) may be considered to be more than a 15% decline in the relative percentage from the baseline. [3] ERBB2 (HER2), a proto-oncogene, encodes a member of the transmembrane receptor tyrosine kinase and has a significant role in the development of cardiomyocytes. After the maturation of cardiomyocytes, an impaired ERBB2 signaling may cause dilated cardiomyopathy. Molecular studies have demonstrated that trastuzumab affects this type of tyrosine kinase inhibitors and leads to cardiotoxicity. [9] LV dysfunction induced by trastuzumab is usually asymptomatic, independent from the cumulative dose and reversible by heart failure treatment and medical interruption. [10-12]

Various tools are available for the evaluation of the LV function such as nuclear imaging, echocardiography, and cardiac magnetic resonance. Among these, echocardiography is capable of providing further information on the LV tissue Doppler and the diastolic function as well as the systolic function. In this era, 2D-speckle tracking echocardiography (2DSTE) is a new angle-independent method to figure out early changes in the myocardial function even before a reduction in the LVEF. [1,3,13] An early detection of LV myocardial dysfunction and, thus, appropriate interventions may prevent overt irreversible TIC. [14-17] The risk factors for the development of TIC include a history of treatment with anthracyclines, heart failure, older age, and arterial hypertension. [18] As Sawaya et al [19] concluded, the GLS and cardiac biomarkers are useful parameters for detecting high-risk patients, who may develop heart failure in the future and the implementation of cardioprotective strategies to prevent heart failure should be considered. During chemotherapy, due heed should be paid to symptomatic/asymptomatic or reversible/irreversible reductions in the LVEF. Carvedilol, a vasodilator non-selective β adrenergic receptor blocker, is a mitogen-activated protein (MAP) kinase inhibitor, as well. [20] Protein kinase groups have at least 7 subgroups, and the dimerization of the HER2 receptor may lead to the activation of the MAP kinase receptor. [21] As was mentioned earlier, trastuzumab may cause LV dysfunction by the inhibition of the protein kinase pathway. To the best of our knowledge, no randomized trial study exists to determine the efficacy of beta-blockers in preventing subclinical LV dysfunction following trastuzumab therapy.

OBJECTIVE

We evaluated the prophylactic effects of carvedilol on LV dysfunction in patients with breast cancer receiving trastuzumab on the basis of the hypothesis the MAP kinase modulatory and antioxidant effects of carvedilol

on the heart may prevent subclinical LV dysfunction.

METHODS

Study Design

The present study was a 2-arm, single-center, phase 2, open-label randomized clinical trial, registered at the Iranian Registry of Clinical Trials (Ref. No: IRCT2017042433619N1). Eligible patients who gave informed consent were allocated to 2 groups using randomized permuted blocks 1:1 ratio. Group A did not receive any treatment, while group B received a generic product of carvedilol. The initial dose of carvedilol was 6.25 mg twice a day, and 6.25 mg was added to each serving every week to the maximum tolerated dose (ie, as long as no symptoms of bradycardia or hypotension occurred). The patients underwent both 2D echocardiography and 2DSTE at the beginning and 3 months later, and a pre-designed datasheet was filled during each interview. Every 3 weeks, a physician called the patients and asked them about their consumption of the medication and heart failure symptoms. During the follow-up, if a patient suffered heart failure symptoms (ie, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, or fatigue), 2D echocardiography was performed to estimate the LV systolic and diastolic functions. In the cases with LVEF reductions of greater than 10% to less than 50% or LVEFs of less than 45%, a more than 15% relative reduction in the GLS from the baseline, and impairment or deterioration of the diastolic function (ie, normal diastolic function impaired to mild diastolic dysfunction or mild diastolic dysfunction deteriorated to moderate diastolic dysfunction), the results were considered to represent significant changes.

Study Population

Seventy-two patients who were referred from oncology clinics between March 2017 and December 2017 were randomly assigned. Our inclusion criterion was HER2/neu-positive non-metastatic patients with breast cancer who were treated with standard anthracyclines regimens and were candidated to receive trastuzumab. Patients with an LVEF of less than 50%, significant valvular heart disease, a glomerular filtration rate of 30 mL/h/m^2, hepatic failure, contraindications for receiving beta-blockers, and symptoms of heart failure were excluded from the trial. All the patients had been treated with doxorubicin and idarubicin before attendance in the study with maximum cumulative doses of less than 500 mg/m^2 and 100mg/m^2, respectively. They were candidated to receive the trastuzumab regimen at an initial dose of 4 mg/kg over 90 minutes, followed by an infusion of 6 mg/kg over 30 to 90 minutes every 3 weeks as the maintenance dose. All the patients were under a routine follow-up schedule of the oncology ward to detect any chemotherapy-induced complications throughout the study.

Echocardiography

Echocardiography was performed by a well-experienced echocardiologist. The left lateral decubitus position was the optimal position for acquiring echocardiography data with a commercial echocardiography machine (Philips EPIQ 7 Ultrasound System, Philips Healthcare, Eindhoven, the Netherlands, with a 2-4 MHz probe). During echocardiography, 1-lead electrocardiography monitoring with the optimal torso position was performed to obtain the highest P-wave. The echocardiologist was blinded to the study groups. The LVEF was measured with the modified Simpson method. All the measurements were performed in accordance with the guidelines of the American Society of Echocardiography (ASE). [22] The LV wall thickness and the LV mass were computed in the long-axis and the 4-chamber view, respectively. We measured the right ventricular (RV) diameter in the middle of the RV cavity, as well as the RV end-diastolic and end-systolic areas. Pulsed-wave Doppler was used to obtain peak mitral flow waves (E and A) via the apical

4-chamber view. The RV free wall peak myocardial motion velocity (s') was measured in the apical 4-chamber view using pulsed-wave tissue Doppler imaging. The myocardial motion velocity in the septum and the lateral wall of the LV at the level of the mitral annulus was obtained in the apical 4-chamber view using pulsed-wave Doppler with a sample volume of 4 mm. We did our best to reach the optimal alignment with these ventricular walls. The horizontal sweep rate and velocity scale rate were set 50 to 100 cm/s and -20 cm/s to +20 cm/s, respectively.

The longitudinal and circumferential functions of the LV were evaluated with 2DSTE. The principles of storing 3 consecutive cardiac cycles at the mid-cavity level of the short axis view and the apical 2-, 3-m and 4-chamber views at a frame rate of 40-80 f/s at the end of expiration were constituted during the 2DSTE study. The echocardiologist used the stored movies off-line to analyze the LV longitudinal and circumferential functions. The end-systolic time was determined automatically. The 2DSTE software determined both the endocardial and epicardial borders automatically. Afterward, the user reevaluated these regions of interest. If the automatically determined borders did not adjust to the LV thickness properly, then the operator manually defined the borders. Maximum effort was made to obtain the optimal data, and these processes were repeated to obtain the best data. If the quality of the myocardial signals was still poor after several attempts, the patient was omitted from the study. Finally, the longitudinal strain of the 2-, 3-, and 4-chamber views and the GLS of the LV were acquired individually. The short-axis view at the level of mid-cavity was used to determine the LV circumferential strain. The strain curve of the LV had a negative systolic peak. Otherwise, the curve of the LV strain rate consisted of 1 negative peak (strain rate systolic) and 2 positive peaks as the early and late diastolic strain rates. Inter- and intraobserver variabilities were evaluated by assessing the records of 12 patients at the end of the study by a cardiologist, who was blinded to the patients' previous findings.

Primary and Secondary End Points

The study's primary end point was to evaluate whether carvedilol could prevent the LV systolic function reduction (LVEF, GLS, and the strain rate of the LV systolic function [SRS]) while the patient was under treatment with trastuzumab. The secondary end point was the evaluation of the LV diastolic function and the filling pressure as the E/E', the SRE, and the SRA.

Statistical Analysis

All the analyses were performed using the IBM SPSS 23.0 software (IBM, Armonk, NY, USA). Frequencies (percentages) and means (SDs) were used to present the qualitative and quantitative variables. The normality of the quantitative variables was assessed with the one-sample Kolmogorov–Smirnov test. Within-group comparisons were conducted using the Wilcoxon test and between-group comparisons were made with the Mann–Whitney *U*-test, the χ^2 test, or the Fisher exact test—as appropriate. Statistical significance was defined as a *P* value of equal to 0.05.

RESULTS

Of the 80 consecutive patients eligible for study enrollment, ultimately, 72 patients were included in the study and were randomly assigned to each of the groups. One patient was lost to follow-up and was, therefore, excluded. Thereafter, 36 patients were included in the carvedilol group and 35 patients in the control group (Chart 1).

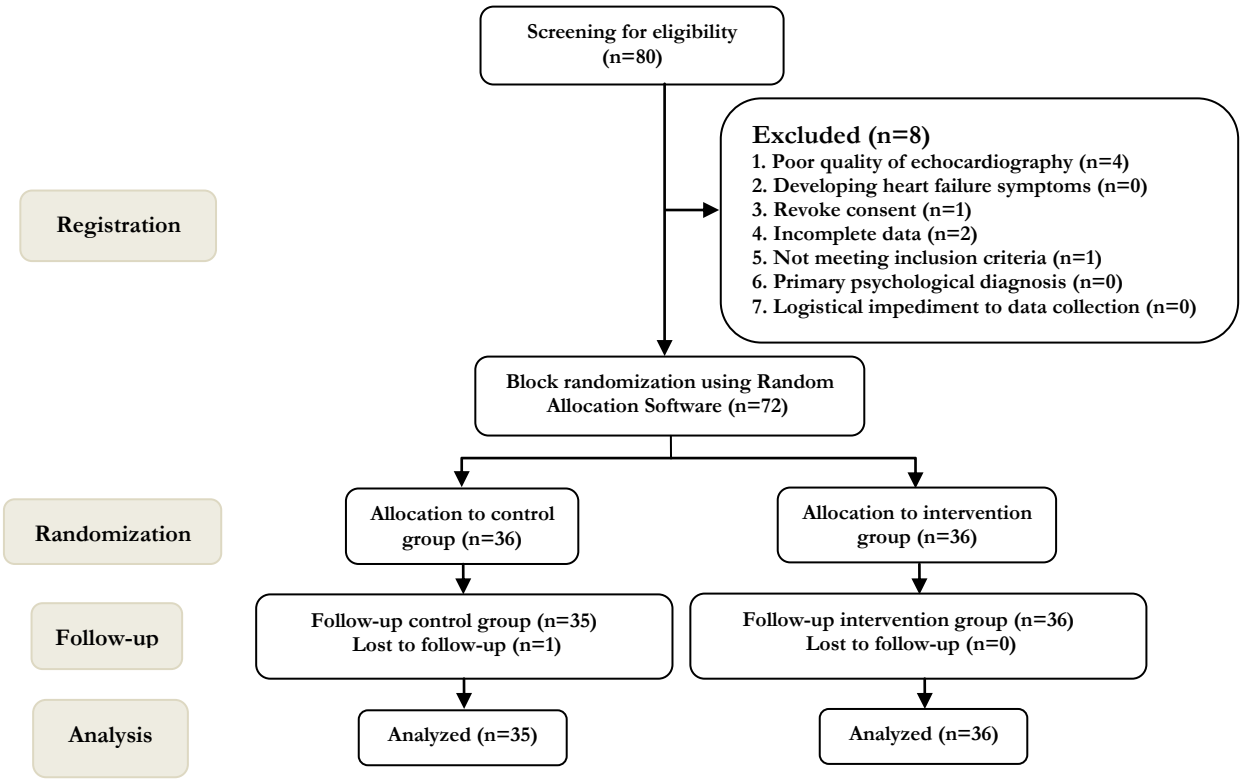

Chart 1. Flowchart of patient enrollment

The patients' demographics and baseline characteristics were similar between the carvedilol and control groups (Table 1). The maximum tolerated dose of carvedilol in the intervention group was 12.5±3.125 mg twice a day. The percentage of having a positive history of coronary artery disease was completely similar between the groups (0.0% vs 0.0%; *P*=0.999). The percentage of a cumulative anthracycline dosage of less than 450 mg administered before participation in the study was similar between the groups (39.4% vs 39. 3%; *P*=0.993), as was the patients' mean age (57.3±7.3 y vs 57.4±8.8 y; *P*=0.904).

The systolic and diastolic blood pressures during echocardiography were similar between the carvedilol and control groups (121.7±14.7 mmHg vs 125.2±11.8 mmHg; *P*=0.418 and 75.8±9.6 mmHg vs 74.4±8.6 mmHg; *P*=0.534, respectively).

The percentage of cancer stage II and III was similar between the carvedilol and control groups (47.2% vs 54.3% and 52.8% vs 45.7%; *P*=0.552, respectively), as was the trastuzumab dosage administration status before the study: no history of receiving a session (47.2% vs 37.1%), a history of receiving 1 session (33.3% vs 42.9%), and a history of receiving 2 sessions (19.4% vs 20.0%) (*P*=0.653). Ultimately, the percentage of an LVEF of greater than 55% was similar between the carvedilol and control groups (44.4% vs 48.6%; *P*=0.727).

It is necessary to note that no valvular disease, whether regurgitation or stenosis, exacerbated or occurred during the study.

Signs and symptoms of heart failure

During the follow-up, none of the patients complained of exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea in the 2 groups. Physical examinations did not show any peripheral edema.

Table 1. Baseline characteristics of the 2 groups

Variable		Drug		*P*
		Carvedilol	Control	
Age (y)	Mean± SD	57.3 ± 7.3	57.4 ± 8.8	0.904‡
Body mass index (kg/m^2)	Mean± SD	28.9 ± 2.9	28.6 ± 3.2	0.501‡
Systolic blood pressure at echo time (mmHg)	Mean± SD	121.7 ± 14.7	125.2 ± 11.8	0.418‡
Diastolic blood pressure at echo time (mmHg)	Mean± SD	75.8 ± 9.6	74.4 ±8.6	0.534‡
Anthracycline dosage (g)	≤450	20(60.6%)	17(60.7%)	0.993†
	>450	13(39.4%)	11(39.3%)	
Cancer stage	II	17(47.2%)	19 (54.3%)	0.552†
	III	19(52.8%)	16(45.7%)	
History of radiotherapy	Yes	32(88.8%)	30(57.7%)	0.365†
	No	4(11.1%)	5(14.2%)	
Diabetes mellitus	Yes	1(2.8%)	2(5.7%)	0.614†
	No	35(97.2%)	33(94.3%)	
Hypertension	Yes	4(11.1%)	5(14.3%)	0.614†
	No	32(88.9%)	30(85.7%)	
History of coronary artery disease	Yes	0(0%)	0(0%)	0.999†
	No	36(100%)	35(100%)	
Left ventricular ejection fraction (%)	≤55	20(55.6%)	18(51.4%)	0.727†
	>55	16(44.4%)	17(48.6%)	
History of anemia	Yes	0(0%)	1(2.9%)	0.493†
	No	36(100%)	34(97.1%)	
LVEDD (mm)	Mean± SD	42.2±3.8	41.8±4.2	0.200‡
LVESD (mm)	Mean± SD	34.2±3.3	33.6±2.8	0.436‡
LV mass index (g/m2)	Mean± SD	63±8.9	61±11.1	0.080‡

† χ^2 test or Fisher exact test, ‡ Mann–Whitney test

Left ventricular systolic function

Apropos of the LV systolic function, there were significant differences between the changes of all the indices except the LVEF. The variable of the GLS exhibited a significant difference between the changes of the groups (*P*<0.0001) with an incremental value from the carvedilol group to the control group (-.32±0.8 vs .82±0.8). In addition, the changes were significant only in the control group (*P*<0.0001) and not in the carvedilol group (*P*=0.080), although the changes in the carvedilol group were close to the significance level.

The SRS had a significant difference between the changes of the groups (*P*=0.004) with an increasing value from the carvedilol group to the control group (-.10±0.3 vs -.07±0.1). Moreover, the changes were significant only in the control group (*P*=0.004) and not in the carvedilol group (*P*=0.090) (Table 2).

Left ventricular diastolic function

In regard to the LV diastolic function, there were significant differences between the changes of all the indices except the E/E′.

The E/A had a significant difference between the changes of the groups (*P*=0.022) with an increasing value from the carvedilol group to the control group (-.04±0.2 vs -.10±0.5). Moreover, the changes were significant only in the control group (*P*=0.022) and not in the carvedilol group (*P*=0.481).

The SRA variable revealed a significant difference between the changes of the groups (*P*=0.005) with a decreasing value from the carvedilol group to the control group (.14±0.3 vs -.09±0.2). In addition, the changes were significant in both carvedilol (*P*=0.037) and control (*P*<0.023) groups.

The difference between the changes of the carvedilol group to the control group in terms of the SRE variable was significant (*P*<0.0001). In addition, the changes in both groups (*P*=0.006 and *P*=0.002, respectively) and the changes from the carvedilol group (.14±0.3) to the control group (-.09±0.2) followed from a decreasing value.

The difference in the E/E′ variable between the changes of the 2 groups was not significant

(*P*=0.388). The changes in the carvedilol group (-.28±1.9) to the control group (-.32±1.8) followed from a slightly decreasing value with nonsignificant changes in the former (*P*=0.399) and latter (*P*=0.388) groups (Table 2).

The global circumferential strain variable showed no significant difference between the changes of the carvedilol and control groups (*P*=0.649), but the difference was significant in the carvedilol group (.46±1.0; *P*=0.041) and in the control group (.44±0.7; *P*=0.001), separately. The changes in the values between the 2 groups exhibited a slightly decreasing value from the former group to the latter group.

With respect to the longitudinal time to peak SD, the RV fractional area change, and the LVEF, there were no significant differences between the changes of the carvedilol and control groups (3.97±22.00 vs 1.78±13.7; *P*=0.922 and -.02±6.2 vs -.39±7.9; *P*=0.872) and (.28±3.5 vs -.18±4.7; *P*=0.616), respectively (Table 2).

Figure 1 depicts the changes in the LV systolic and diastolic functions after 3 months between the carvedilol and control groups.

Table 2. Comparisons of the changes of the LV systolic and diastolic functions after 3 months between the groups

	Factor	Before	After	Change	*P* †	*P* ‡
Carvedilol	E/A	1.06±.2	1.02±.2	-.04±.2	.481	.022
	E/E'	9.03±2.3	8.75±1.9	-.28±1.9	.399	.461
	SRA	.68±.4	.82±.1	.14±.3	.037	.005
	SRE	.44±.3	.58±.1	.14±.3	.006	.000
	SRS	-.42±.3	-.52±.2	-.10±.3	.090	.004
	GLS	-17.22±1.8	-17.54±1.7	+.32±.8	.088	.000
	GCS	-16.64±2.3	-16.18±1.7	.46±1.0	.041	.649
	LTTPeak	38.89±19.4	40.86±18.8	3.97±22.00	.316	.922
	RVFAC	47.11±6.4	47.10 ±5.5	-.02±6.2	.883	.872
	LVEF	54.93±4.26	55.20 ±3.04	.28±3.5	.567	.616
Control	E/A	1.04±.2	.94±.3	-.10±.5	.022	.022
	E/E'	8.97±2.6	8.65±1.6	-.32±1.8	.388	.461
	SRA	.78±.22	.68±.2	-.1±.2	.023	.005
	SRE	.55±.16	.46±.1	-.09±.2	.002	.000
	SRS	-.49±.14	-.42±.2	.07±.1	.004	.004
	GLS	-17.17±1.5	-16.35±1.3	-.82±.8	.000	.000
	GCS	-15.76±1.0	-15.32±1.0	.44±.7	.001	.649
	LTTPeak	38.42±14.4	40.21±9.7	1.78±13.7	.456	.922
	RVFAC	46.53±7.7	46.13 ±5.4	-.39±7.9	.784	.872
	LVEF	54.32±5.32	54.51 ±2.89	.18±4.7	.461	.616

†Wilcoxon test for within-group comparisons, ‡Mann–Whitney test for between-group changes
SRA, Left ventricular strain rate late; SRE, Left ventricular strain rate early; GLS, Global longitudinal strain; GCS, Global circumferential strain; LTTPeak, longitudinal time to peak SD

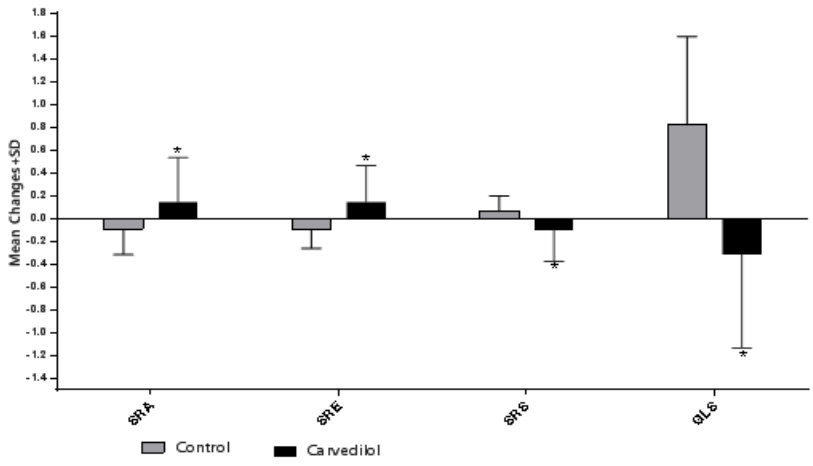

Fig. 1. Comparing the changes of LV systolic and diastolic function after 3 months between groups. (*p<0.05) show significant differences between the Carvedilol group and control group by Mann-Whitney Test. The data presented are mean change +SD.

DISCUSSION

As a result of the present study, we found that in patients with non-metastatic breast cancer who underwent adjuvant treatment with trastuzumab, carvedilol as a prophylactic agent offered protection against a reduction in the absolute value of the GLS, the SRS (a marker of the LV systolic function), the strain rate of the early diastole of the LV (SRE), the strain rate of the late diastole of the LV (SRA), and the E/A (markers of the LV diastolic function) during 3 months of follow-up. While the global circumferential strain decreased in each group significantly, there was no significant change during the follow-up between the groups. This may have happened because of the delayed impact of chemotherapy on the circumferential strain or the failure of the study to acquire the mid-ventricular circumferential strain at the base, mid, and apical sites of the LV for a better evaluation of the circumferential strain. The time to peak longitudinal strain did not change during the follow-up. This serves as a marker of ventricular dyssynchrony, and the unchanged results suggested that during the chemotherapy, no mechanical dispersion occurred.

All the patients underwent adjuvant therapy with doxorubicin (an anthracycline) with a cumulative dosage of less than 550 mg/m^2; however, there was no significant difference between the 2 groups. The patients who received carvedilol did not report any adverse drug reactions. Trastuzumab was administered at the beginning of data acquisition and carvedilol was begun before initiating trastuzumab. Trastuzumab treatment may cause CTI reversibly and it may not be dose-dependent as observed in Type II CTI. [23] Carvedilol as a beta-blocker agent can prevent subclinical LV dysfunction by the inhibition of tachycardia and hypertension, derived from catecholamine release. [24] The other impacts of carvedilol on heart failure are its acting as an anti-oxidant, the regulation of apoptosis, and the modulation of MAP kinase and ERBB2 signaling. [25,26]

In our study, none of the patients had overt heart failure (>10% LVEF reduction). This finding is compatible with the results of the FinHER trial, which concluded that patients under treatment with trastuzumab for less than 6 months had no significant LVEF reduction (median LVEF=65%). A significant reduction in the median LVEF (66% to 62%) was an exciting finding, which was concluded to have happened by chance. [27] Be that as it may, an overt decline in the LVEF may occur. Seidman et al, [28] in a retrospective study showed that patients who were on trastuzumab alone had a 3% to 7% increased risk of LV dysfunction. In a systematic review of 5 clinical trials, the pooled analysis showed that patients who had received trastuzumab for 1 year had an increased risk of severe heart failure, with the number needed to treat (NNT) of 62. Nevertheless, asymptomatic patients with a reduced LVEF had significant LV dysfunction and an NNT of 14. [29] A previous investigation evaluated the incidence of cardiomyopathy in elderly patients with early-stage breast cancer in a historical cohort and showed that the rate of the adjusted 3-year incidence of cardiomyopathy was high in the patients who received anthracycline concurrent with trastuzumab (49.1 per 100) in comparison with the patients who received trastuzumab with or without anthracycline (31.9 per 100). A cohort was conducted between July and December 2005 on 155 patients with breast cancer treated sequentially with trastuzumab after primary chemotherapy. Twenty-two (21.5%) patients had cardiac events (18 patients were asymptomatic and 4 patients had congestive heart failure) during a 9-month follow-up with echocardiography and history taking. [30] Meanwhile, we can conclude that carvedilol confers protective effects on the LV myocardial systolic function by increasing the GLS +.32±8% after 3 months of treatment, while in the control group, it was reduced to 16.35%

(-.82±8). The absence of the development of symptomatic or overt heart failure during our study may be attributable to the short period of follow-up, which was 3 months in our study. Moreover, our patients had a lower prevalence of cardiovascular comorbidities.

In a cross-sectional study, HoE et al [31] evaluated 70 female survivors of breast cancer who underwent adjuvant chemotherapy with anthracycline with or without trastuzumab and showed that after 6 years of previous chemotherapy, the LVEF was not significantly different in comparison with the control group. In contrast, the peak mitral velocity E and the A, E' average at 6 points of the mitral annuli (as markers of the LV diastolic function) and the global longitudinal 2D strain of the LV had a reduction. Our study showed that the mitral inflow E/A ratio, the SRA, and the SRE were subclinically reduced during the 3 months of follow-up in the control group, with the difference between the 2 study groups constituting statistical significance. Nonetheless, the E/E' (a marker of the filling pressure) was not significantly different in the patients who received carvedilol. This finding is in contrast to the finding of the PRADA study, which showed that the E/E' increased in the metoprolol group and concluded that the rationale was the direct effect of beta-blockers on hemodynamics. [29] The circumferential strain tends to change later than does the longitudinal strain; accordingly, in our study, the mid-LV strain was not significantly different between the 2 groups.

Carvedilol has antioxidative and inflammatory effects by suppressing reactive oxygen species.[33] On the other hand, the MAP kinase modulation effect of this drug is efficacious in preventing LV dysfunction. Some small trials have investigated the effects of carvedilol in patients who receive anthracyclines as a primary cardioprotective agent. [34,35] In contrast, larger studies have not demonstrated any benefits for metoprolol. [32] The early results of a previous study showed that prophylactic treatment with angiotensin-converting enzyme inhibitor and beta-receptor blocker could prevent an LVEF decline by 3% and 1%, respectively. In that study, the LVEF was reduced by up to 5% in the placebo group according to cardiac magnetic resonance for the evaluation of the LVEF, and also bisoprolol significantly prevented a reduction in the LVEF during a 2-year follow-up in comparison with the placebo. [36]

Another important issue is whether or not prompt medication is useful to prevent the heart failure syndrome. Cardinale D et al [37] showed that 45% of their patients failed to respond to heart failure treatment and that heart failure treatment after chemotherapy offered fewer advantages and the treatment was ineffective. In a recently accepted study, 200 patients with breast cancer under treatment with anthracycline were randomly assigned to receive either carvedilol (a cardioprotective agent) or a placebo. The results showed concomitant carvedilol consumption failed to prevent the LVEF reduction. Meanwhile, the patients who received carvedilol had a lower incidence rate of diastolic dysfunction, which chimes in with our results. [38]

Non-metastatic breast cancer is a widespread disease in women. According to new diagnostic tools, early detection has conferred long-time survival, which underscores the significance of the measures to prevent and lessen comorbidities during cancer treatment.

The short period of follow-up in the present study is its salient limitation. A longer follow-up period may yield more reliable results vis-à-vis the heart failure syndrome and reductions in the LVEF. The small sample size of our study restricts the generalization of the findings.

CONCLUSIONS

Concomitant carvedilol treatment with a maximum tolerable dose in patients with non-metastatic HER2-positive breast cancer under treatment with trastuzumab might be effective

in the reduction of systolic and diastolic echocardiographic findings other than the LVEF in patients with weak markers of heart failure.

DECLARATIONS

Ethical Approval and Consent to Participate

The study was approved by the ethics committee of Baqiyatallah University of Medical Sciences (Tehran, IR Iran). Study participation was optional, and informed consent was obtained from the patients.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The authors have no conflict of interest to disclose.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

The authors wish to especially thank the patients and their families for their participation in the study.

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