Echocardiographic signs of right ventricle changes after Trastuzumab treatment in breast cancer patients with erb-2 overexpression

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Abstract

Objective: Left ventricular (LV) dysfunction after trastuzumab treatment in erb-2 breast cancer cases has been fully investigated. However, there is not enough data about the effect of trastuzumab treatment on right ventricular (RV) functions. This study is designed to evaluate the right heart changes by performing echocardiography after trastuzumab treatment in patients with erb-2 breast cancer.

Methods: Forty-two consecutive breast cancer patients with erb-2 overexpression mean age 50.4±11.6 years who were decided to receive trastuzumab treatment were enrolled. Echocardiographic examinations including 2-D, spectral, and tissue Doppler measurements were performed at the baseline (T1) and repeated after 6 months (T2).

Results: Tricuspid annular plane systolic excursion (TAPSE) was decreased, RV myocardial performance index (RVMPI) and tricuspid E/e' ratio was increased after trastuzumab treatment (1.84 vs. 2.14; p<0.01) (0.46 vs. 0.56, p<0.01) (4.4±1.07 vs. 5.08±1.46; p=0.04). Median serum NT-ProBNP levels, troponin I, and hs-CRP levels were similar between the groups. LVEF and TAPSE were negatively correlated with dosage of trastuzumab (r=-0.392, p=0.04; r=-0.522, p=0.006). There was a stepwise decrease in LVEF when trastuzumab used with anthracyclines however this not reached statically significant (62.4±2, 60±4.5; p=0.06).

Conclusion: In our study; we observed a trend of RV deterioration after trastuzumab treatment. These preliminary RV changes were demonstrated by using TAPSE, RV tissue Doppler imaging derived MPI and E/e' ratio parameters by echocardiography and these parameters could also use as markers of trastuzumab toxicity in this population. *(Anatolian J Cardiol 2015; 15: 143-8)*

Key words: breast cancer, trastuzumab, tricuspid annular plane systolic excursion, right ventricle, myocardial performance index

Introduction

Breast cancer is the most frequent cancer in women and the leading cause of cancer-related death (1). In 20-30% of invasive breast cancers, overexpression of human epidermal growth factor receptor type 2 (HER2), which is related to the aggressive type and poor prognosis, occurs (2). HER-2/neu is included in the family of four transmembrane receptor tyrosine kinase, which mediates cell growth, differentiation, and survival (3). Trastuzumab is a monoclonal antibody against the HER2/erbB2 receptor, which is an important new treatment for breast cancer patients with HER2 protein overexpression (4).

Trastuzumab predominantly affect cardiac metabolism (mitochondrial dysfunction) and contractile proteins, leading to transient contractile dysfunction (4). Although trastuzumab is generally well tolerated; the cardiac toxicity is encountered as a rare, but potentially serious complication limiting its use in cancer patients. Early detection of trastuzumab induced cardiac toxicity is important, because it may be useful in heart failure prevention. Left ventricular ejection fraction (LVEF) (5) and Doppler derived echocardiography parameters (6) have been the most commonly used data to detect the cardiac dysfunction. However, the relationship between the right ventricle (RV) function and performance with trastuzumab treatment has not been studied enough. This study is designed to evaluate the right heart changes by performing echocardiography after trastuzumab treatment in patients with erb-2 breast cancer.

Methods

Forty-two consecutive breast cancer patients with erb-2 overexpression, who were decided to receive trastuzumab

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treatment at the Medical Oncology department of our Tepecik Research and Training were included the study. The study was conducted according to the recommendations of Declaration of Helsinki on Biomedical Research involving human subjects and was approved by the local Ethics Committee of our Hospital. Written informed consent was obtained from each participant. The inclusion criteria were defined in line with the clinical guidelines (7) and both invasive HER2 positive breast cancer and LVEF ≥60% were histologically confirmed. The patients were excluded if they had symptoms of heart failure and/or depressed LVEF (<60%). We also did not involve patients who had inadequate echocardiographic view. Other exclusion criteria were coronary artery diseases, uncontrolled arrhythmia, hypertension, and valvular heart disease more than trivial. All patients were diagnosed with histologically confirmed, completely excised invasive breast cancer with HER2 overexpression and fulfilling criteria for adjuvant and neoadjuvant therapy with trastuzumab. HER2 status was determined by immune histochemical staining (3+) or in case of HER2 result 2++ amplification of the HER2 gene was evaluated using the fluorescence in situ hybridization (FISH) method. In 34 patients (86%) trastuzumab treatment was initiated as an adjuvant therapy after total or partial mastectomy operation and in 8 patients (14%) trastuzumab was used as a neoadjuvant therapy. Participants received trastuzumab as a single agent with the loading administration dose was 8 mg/kg of body weight, and the maintenance dose was 6 mg/kg once in every 3 weeks (52 weeks of therapy). During and following doxorubicin + cyclophosphamide (AC) or fluorouracil +epirubicin+ cyclophosphamide (FEC), Trastuzumab received with initial dose: 4 mg/kg IV infusion over 90 minutes then 2 mg/kg.

All participants have undergone cardiovascular system evaluation (history, cardiovascular risk factors and blood pressure), anthropometrical measurements, electrocardiography, blood sampling and echocardiography at baseline (T1) and repeated after 6 months (T2).

Blood samples were obtained for serum NT-proBNP, hs-CRP and troponin I levels determination. An electrochemiluminescence immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany) was used for the determination of serum NT-proBNP measurement which had a reference range between 0 and 125 pg/mL. Serum hs-CRP levels were evaluated by nephelometry and troponin I was assessed by Spectral Cardiac STATus troponin I rapid test (Spectral Diagnostics, Toronto, Canada).

In 14 (33%) patients, anthracycline-containing regimens were used as the adjuvant or neoadjuvant chemotherapy, and trastuzumab was initiated after completion of these regimens (8 patients received AC, 6 patients received FEC). Of patients, 28 (66%) were newly diagnosed, and did not receive anthracycline-containing regimens. Radiotherapy was administered in 12 (28%) patients.

Anthropometry, blood pressure measurement

The body surface area (BSA) was calculated using DuBois formula $BSA=71.84\ W^{.425}\ H^{.725}$, (8) where W is weight in kg and H is height in cm. Waist circumference (in centimeters) was measured from the midpoint between the lowest rib and the iliac crest while the subject was standing up. After a 30-minute resting period, blood pressure (BP) was measured twice in both arms while sitting down by using a mercury sphygmomanometer with the appropriate cuff size. The average of two of the highest BP measurements was used to calculate systolic and diastolic BP.

Echocardiography

Echocardiography examinations were performed at baseline (T1) and repeated after 6 months (T2) according to American Society of Echocardiography recommendations (9) with a Vivid 7 instrument (General Electric, Horten, Norway) and a 2.5 MHz transducer. Measurements were made on 3 representative beats and mean of the results was taken. Standard echocardiography analysis included two-dimensional, M-mode, and Doppler flow measurements. All Echo-Doppler studies were carried out by the same observer, who was blinded for the clinical data. Each examination was recorded and two other cardiologists blinded for chemotherapeutic condition of patients interpreted the results off-line. Inter and intraobserver variability was calculated by using correlation analysis method and inter observer variability was found <5%.

LVEF was measured from the apical four-chamber view using biplane Simpson's rule, and other echocardiography measurements were assessed according to American Society of Echocardiography guidelines (10).

Using apical four-chamber views and pulse wave recordings at the level of tricuspid leaflet tips-annulus, we evaluated RV diastolic function as follows: Tricuspid inflow velocity during early diastolic filling (E) and late diastolic filling velocity due to atrial contraction (A) were measured. E/A ratio and E wave deceleration time (DTE) were also calculated. Using a 5 mm sample volume placed in the lateral tricuspid annulus, maximum systolic (S_m), early (e'), and late (a') diastolic velocities and isovolumetric contraction (IVC) and relaxation (IVR) times were measured. Moreover RV E/e' ratio (meaning the ratio of the E wave of tricuspid inflow to e' wave obtained from tissue Doppler at the lateral tricuspid annulus) was calculated (10). Standard Doppler and tissue Doppler imaging measurements were also obtained for the left ventricule (LV). Myocardial performance index (MPI) was calculated as the sum of isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) divided by ejection time (ET) (11). To determine the motion and excursion of tricuspid annulus (TAPSE), an M-mode cursor was placed at the junction of the tricuspid valve plane with the RV free wall, using the images of the apical four-chamber view (12).

Statistical analysis

Statistical analysis was performed using SPSS 11.0 for Windows. Parametric test conditions were tested for the continuous variables. Data are presented as mean±standart deviation or median (minimum-maximum). The Shapiro-Wilk test was used to determine whether the continuous variables were normally dis-

tributed. While the mean differences between measurement times were compared by repeated measures of ANOVA; the Friedman test was applied for comparisons of the median differences. When the p values from ANOVA or Friedman's test statistics were statistically significant, Bonferroni's adjusted multiple comparison test or Bonferroni's adjusted Wilcoxon's sign-rank test was used to determine which measurement time differs from which others. The correlations of continuous variables were analyzed by Spearman correlation analysis. A probability value of $p<0.05$ was considered as significant.

Results

Table 1 shows the baseline characteristics of the study population. The mean age of the patients was 50.4±11.6 years. All of the patients remained in sinus rhythm. Table 2 shows the echocardiography measurements and the blood test results.

The average dosage of trastuzumab (indexed with BSA) was 1777.07±829.5 mg/m ^{2}. LVEF and TAPSE were negatively correlated with trastuzumab dosage (Table 3). There was a stepwise decrease in LVEF when trastuzumab used with anthracyclines however this not reached statically significant (62.4±2, 60±4.5; p=0.06). Other echocardiography parameters were not different when adjuvant trastuzumab was used with anthracyclines [LVMPI (0.57±0.14, 0.54±0.18; p=0.65), RVMPI (0.59±0.11, 0.53±0.13; p=0.14) and TAPSE (1.81±1, 1.85±2; p=0.47)]. RT was given to 13 patients prior to chemotherapy, and no significant difference was detected with the non-RT receiver group [LVEF (61.1±3.2, 62.5±1.3; p=0.15), LVMPI (0.57±0.17, 0.58±0.14; p=0.87), RVMPI (0.53±0.11, 0.60±0.10; p=0.13) and TAPSE (1.84±1.6, 1.8±1.3; p=0.44)].

TAPSE was correlated with RVMPI (r=-0.556, p<0.01), mitral e' (r=0.235, p=0.04), mitral IVRT (r=0.24, p=0.04) and hs-CRP (r=-0.279, p=0.03). RVMPI was correlated with LVMPI (r=0.258, p=0.03) and hs-CRP (r=0.342, p<0.01). The other LV function and blood test parameters were not correlated with TAPSE or RVMPI.

Discussion

Detrimental effects of trastuzumab on LV systolic and diastolic functions have been reported in previous studies (13). However RV deterioration is a novel finding in these patients. In our study; we observed a trend of RV deterioration after trastuzumab treatment. These preliminary RV changes were demonstrated by using TAPSE, RV TDI-derived MPI and E/e' ratio parameters by echocardiography.

Trastuzumab treatment usually causes asymptomatic cardiac complications which should be closely monitorized (14). The incidence of LV dysfunction was reported in various ranges 3-24% (15). Systolic and diastolic LV functions after trastuzumab chemotherapy are well studied, but RV involvement during or after trastuzumab have not been studied adequately. Trastuzumab has inhibitory effect on antibody against ErbB2. The NRG/ErbB signaling axis system is expressed equally by left and right ventricles cardiomyocytes and is located in T-tubule system and

Table 1. Baseline characteristic of study group

	Mean (n=42)
Age, years (range)	50.4±11.6 (26-77)
Smokers (n), %	15 (36)
Type 2 DM (n), %	4 (10)
HT (n), %	12 (29)
Weight, kg (range)	70.8±11.9 (37-102)
Height, cm (range)	158.8±4.9 (140-169)
Body area, m^2 (range)	1.75±0.1 (1.2-2.06)
Waist circumference (range), cm	97.9±12.1 (70-128)

HT - hypertension; Type 2 DM - type 2 diabetes mellitus

Table 2. Comparison of echocardiographic parameters and blood test results

	Group T1 Mean	Group T2 Mean	*P*
LVEF, %	62.4±4.2	61.2±3.4	0.2
Mitral E/A	1.02±0.22	0.97±0.28	0.4
Mitral DEC T, ms	208.5±36.7	207.9±27.1	0.94
Mitral e', cm/s	0.11±0.03	0.11±0.04	0.8
Mitral a', cm/s	0.1±0.02	0.1±0.02	0.67
Mitral sm', cm/s	0.08±0.02	0.09±0.02	0.27
Mitral E/e'	7.2±3.5	6.9±3.6	0.75
Mitral Ivrt, ms	70.4±19.8	65.8±15.6	0.29
Mitral Ivct, ms	71.6±19.5	70.2±18.5	0.75
Mitral ET, ms	267.7±31.7	248.8±43.5	0.03
LV MPI	0.52±0.14	0.57±0.15	0.13
Tricuspid E/A	0.93±0.09	0.95±0.16	0.72
Tricuspid E/e'	4.4±1.07	5.08±1.46	0.04
Tricuspid e', cm/sn	0.11±0.03	0.11±0.02	0.3
Tricuspid a', cm/sn	0.16±0.04	0.16±0.04	0.96
Tricuspid sm', cm/s	0.13±0.02	0.14±0.02	0.85
Tricuspid ivrt, msn	65.6±19.9	70.7±17.8	0.26
Tricuspid ivct, msn	63.3±15.5	68.0±20.4	0.26
RV MPI	0.46±0.10	0.56±0.12	<0.01
TAPSE, mm	2.14±2.6	1.84±1.5	<0.01
NT-Pro BNP, pg/mL	37.3±42.4	31.6±2.7	0.52
Troponin I, ng/mL	0.01±0.01	0.03±0.1	0.2
hs-CRP, ng/mL	0.64±0.51	1.25±2.3	0.17

DEC T - decelaration time; ET - ejection time; ivrt - isovolemic relaxation time; ivct - isovolemic contraction time; LVEF - left ventricular ejection fraction LV; MP - left ventricular myocardial performance index; Mitral E - mitral early diastolic velocity; Mitral A - mitral late diastolic velocity; Mitral e' - mitral annular early diastolic velocity; Mitral a' - mitral annular late diastolic velocity; Mitral sm' - mitral annular systolic velocity; RV MPI - right ventricular myocardial performance index; Tricuspid E - tricuspid early diastolic velocity; Tricuspid A - tricuspid late diastolic velocity; Tricuspid e' - tricuspid annular early diastolic velocity; Tricuspid a' - tricuspid annular late diastolic velocity; Tricuspid sm' - tricuspid annular systolic velocity; TAPSE - tricuspid annular plane systolic excursion

Table 3. Correlations of the clinical, echocardiographic and blood test parameters with trastzumab dose

Spearman correlation analysis	r	*P*
Age, years	0.02	0.95
LVEF, %	-0.392	0.04
Mitral E/A	-0.216	0.3
Mitral E/e'	0.128	0,54
Mitral DEC T, msn	-0.216	0.29
LV MPI	0.218	0.28
RV MPI	0.245	0.22
Tapse, cm	-0.522	0.006
Tricuspid E/A	0.145	0.47
Tricuspid E/e'	-0.019	0.88

DEC T - decelaration time; LVEF - left ventricular ejection fraction; LV MPI - left ventricular myocardial performance index; Mitral E - mitral early diastolic velocity; Mitral A - mitral late diastolic velocity; Mitral e' - mitral annular early diastolic velocity; RV MPI - right ventricular myocardial performance index; TAPSE - tricuspid annular plane systolic excursion

intercalated discs in close proximity to the system components of excitation-contraction coupling (16). The importance of the NRG/ErbB signaling axis at the cardiovascular level became evident after trastuzumab treatment, which could lead to ventricular dysfunction and had higher risk of cardiomyopathy (17). Considering this mechanism trastuzumab induced cardiotoxicity could be observed in right heart functions along with the left heart (18). However, choosing the echocardiographic methods to evaluate right heart functions is crucial. Transthoracic echocardiography is an easy and important method to evaluate cardiac changes associated with trastuzumab treatment (19). Assessment of noninvasive RV function is very limited in clinical practice, because of complex RV chamber geometry and suboptimal RV endocardial definition (20). According to previous data RV shortening occurs primarily along its longitudinal axis or from base to apex, whereas the LV shortens relatively symmetrically in the transverse and longitudinal planes (21). Systolic displacement of the tricuspid annulus toward the RV apex, referred to as TAPSE, closely correlates with right ventricule ejection fraction and has been found to be highly reproducible and practical (22, 23). In our study we demonstrated that TAPSE was decreased with the trastuzumab treatment (Fig. 1) and negatively correlated with dosage of trastuzumab. However it was not reached the cut-off point (TAPSE<16) for RV failure (23). Nevertheless it can be said that there is a trend towards RV deterioration with trastuzumab treatment. There is evidence that TAPSE may reflect abnormal LV function (24). In our study LVEF was negatively correlated with Trastuzumab dose and LV changes could also affect TAPSE measurements. However, only few LV functional parameters were found correlated with TAPSE.

MPI has been described as a noninvasive TDI-derived Doppler measurement of global (systolic and diastolic) ventricle. It has been previously used in some studies to evaluate the

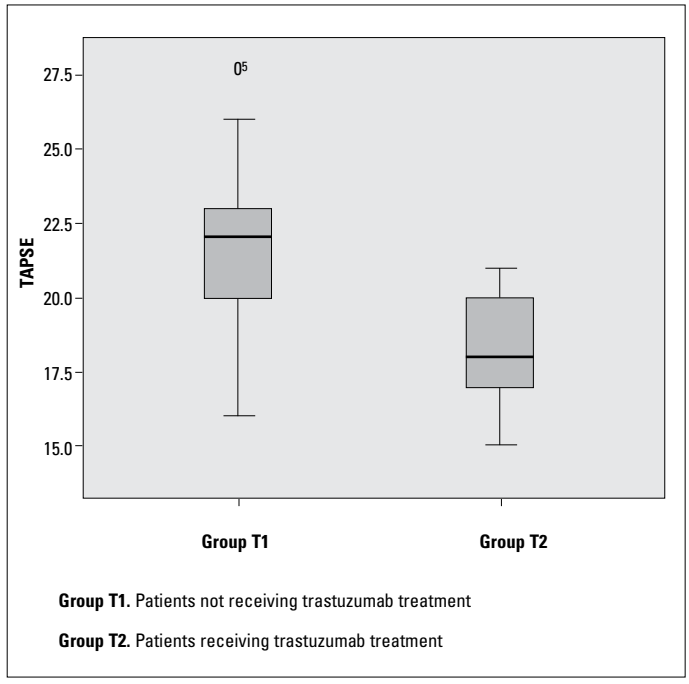

Figure 1. TAPSE was decreased with trastuzumab treatment

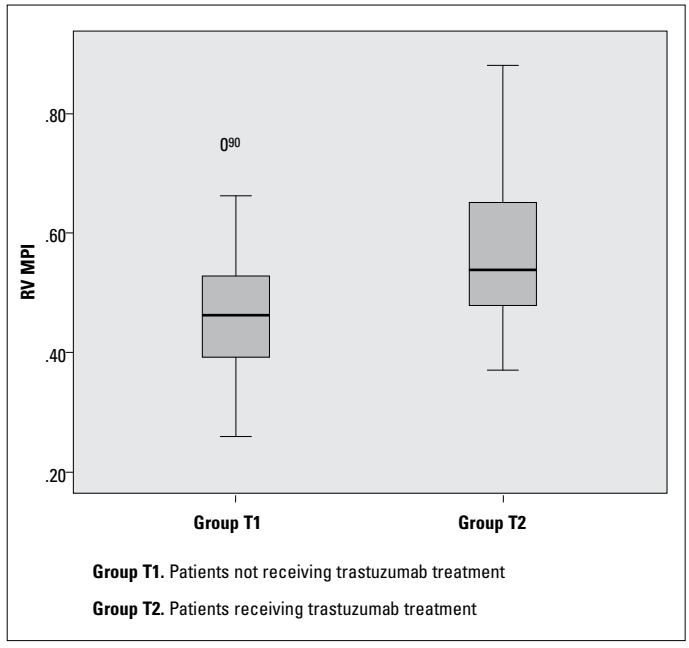

Figure 2. Right ventricular myocardial performance index was increased with transtuzumab treatment

chemotherapy induced cardiac toxicity (25). Although MPI is a good predictor of RV systolic and diastolic functions, it has not been used to evaluate RV functions after trastuzumab treatment. In our study RVMPI was higher with trastuzumab treatment and negatively correlated with TAPSE (Fig. 2). E/e' ratio is a reliable marker in assessing RV diastolic function. Increased E/e' values correspond to increased RV filling pressures. It has been shown by right heart catheterization studies that there is a direct correlation between E/e', right atrial volume and RV diastolic filling pressures (26). In our study, E/e' ratio was increased after

trastuzumab treatment. This could reflected the trend towards RV systolic and diastolic dysfunction. However RV performance cannot be interpreted independently from the LV.

In our study, there was a stepwise decrease in LVEF when trastuzumab used with anthracyclines. However this not reached statically significant. The time interval between the administration of the anthracycline and the start of trastuzumab was suggested to be related with cardiotoxic myocardial damage and concomitant administration was reported to be associated with the highest incidence of cardiotoxicity. According to this previous data the total dose of antracycline is important for the cardio toxicity (27). When the interval between anthracycline and trastuzumab therapies was more than 3 months, the cardiotoxicity incidence was reported as low as the treatment without including anthracycline therapy (27). Since follow up period was 6 months in our study, we could not observe significantly the additting cardiotoxic effect of anthracycline.

In this study we have detected that right heart could be affected with trastuzumab treatment. RVMPI, TAPSE and E/e' ratio were determined to be useful parameters, and could be indicators of cardiac deterioration caused by trastuzumab treatment in breast cancer patients. However, since RV adapts better to volume overload and may tolerate volume overload for a long time without any significant symptoms (28), symptoms related to RV failure may appear later than the signs of LV failure. Although, RV deterioration did not change the treatment regimen of the patient, it should be important to understand that trastuzumab could affect both ventricles. Decreased TAPSE, increased E/e' ratio and RVPMI values could also used as markers of trastuzumab toxicity in this population.

Study limitations

The major limitation of this study is the small number of participants and short follow-up period; however, the purpose is to assess the RV function in the short-term period, during ongoing chemotherapy. Finally RV was evaluated with standard echocardiography analysis included two dimensional, M-mode, and Doppler flow measurements. 3-D, strain- echocardiographic recordings or cardiac magnetic resonance imaging might give more appropriate results.

Conclusion

In conclusion, to the best of our knowledge, this study is the first one showing that RV is prone to toxic effects of trastuzumab treatment. Further prospective, randomized and placebo-controlled clinical studies are needed to investigate the value of TAPSE, RV MPI, E/e' ratio and the follow-up of the ventricular function in patients with subclinical cardiac damage.

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