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Original Article

Cardiotoxicity Associated with Trastuzumab Therapy in Taiwan: A Single Medical Center's 5-Year Experience

Che-Ming Chang[1], Fiona Tsui-Fen Cheng[2]*, Tsen-Long Yang[2], Wu-Chin Wen[3]

[1]*Division of Cardiology, Department of Internal Medicine, Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan*
[2]*Division of General Surgery, Department of Surgery, Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan*
[3]*Division of Hematology and Oncology, Department of Internal Medicine, Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan*

Abstract.

Introduction: Trastuzumab, a recombinant humanized monoclonal antibody, targets the external domain of HER2 to improve the efficacy of HER2-positive breast cancer treatment and inhibit carcinoma cellular proliferation. The purpose of this study was to identify early changes in cardiac function and dimensional changes in heart size in patients treated with trastuzumab.

Materials and Methods: Seventy three female patients with Her2/neu overexpression (IHC 3+/Fish +) in breast cancer underwent echocardiography before and after trastuzumab therapy.

Results: Cardiac complications developed in 14 patients (19.2%), including asymptomatic left ventricle systolic dysfunction (n = 12), symptomatic heart failure (n = 2), new asymptomatic left bundle branch block (n = 1), new negative T waves on electrocardiogram (n = 2), pericardial effusion (n = 1), and death (n = 1). No significant deterioration in diastolic function was noted, and right heart diameters and function did not change significantly. Most patients remained in an asymptomatic stage of cardiac disease. A significant decrease in left ventricular ejection fraction (LVEF) was observed in 14 patients (19.2%), and new mitral regurgitation (≥ grade 1) was noted after 3 months of trastuzumab therapy in 7 patients (9.6%).

Conclusions: Trastuzumab led to measurable decreases in LVEF (but only 2.7% was symptomatic heart failure) and new mitral regurgitation. Therefore, regular follow-up with echocardiography is essential for early detection and prevention of trastuzumab-induced cardiomyopathy.

Keywords **:** trastuzumab, cardiotoxicity, breast cancer, HER2 over expression

原著論文

乳癌治療用藥賀癌平 (Trastuzumab) 之心臟毒性：單一醫學中心之五年臨床經驗

張哲明 [1] 鄭翠芬 [2]* 楊圳隆 [2] 溫武慶 [3]

[1] *新光吳火獅紀念醫院 心臟內科*
[2] *新光吳火獅紀念醫院 一般外科*
[3] *新光吳火獅紀念醫院 腫瘤內科*

中文摘要

目的：本研究是研究乳癌病患在賀癌平(Trastuzumab)治療後之心臟功能及心臟大小之早期改變。

材料和方法：研究 73 位人類表皮生長因子受體 2（HER2）過度表現之乳癌女性病患在賀癌平治療前後之心臟超音波變化；研究期間於西元 2007 年 10 月起至 2013 年 9 月；心血管危險因子之分析包括年齡、身體質量比(BMI)、抽煙與否、有無高血壓、生活型態、有無乳癌家族史、有無高血脂、有無糖尿病、有無憂鬱、有無使用血管轉換抑制劑或血管張力素受體阻斷劑或乙型阻斷劑之使用。

結果：心臟相關之併發症發生於 14 位病患(19.2%)，包括無症狀之左心室收縮異常(n=12)，有症狀之心臟衰竭(n=2)，新發生無症狀之左束支傳導阻滯 (n=1)，心電圖上新發生之負 T 波變化(n=2)，心包膜積水(n=1)，和死亡(n=1)。而心臟舒張功能及右心室大小功能並無明顯變化。大部份乳癌病患經賀癌平治療後維持在無症狀之心臟功能狀態。明顯之左心室收縮功能下降發生於 14 位病患(19.2%)，和三個月後明顯的二尖瓣逆流(≥ grade 1) 發生於 9 位病患(9.6%)。

結論：賀癌平之使用可能會導致左心室收縮功能下降(但僅 2.7% 會產生有症狀的心臟衰竭)和明顯的二尖瓣逆流，故在治療期間定期心臟超音波監測是必要的。

***關鍵字*:** 賀癌平、相關之心臟毒性、乳癌、人類表皮生長因子受體 2

INTRODUCTION

Breast cancer is the most common cancer in women and the leading cause of cancer-related deaths worldwide. Up to 25% of women with early breast cancer have human epidermal growth factor receptor 2 (HER2)-positive disease, which is associated with aggressive disease, a higher chance of recurrence after initial treatment, and a poor prognosis [1,2].

Trastuzumab is a recombinant humanized monoclonal antibody which targets the external domain of HER2 to improve the efficacy of HER2-positive breast cancer treatment and inhibit carcinoma cellular proliferation. Four large multicenter randomized trials revealed that trastuzumab in HER2-positive breast cancer added to anthracycline, cyclophosphamide, or paclitaxel chemotherapy resulted in a 50% reduction in 3-year risk of recurrence and a reduction of over a 30% in mortality [4,5]. Those benefits were recently confirmed by longer follow-up studies [6].

Contrary to the irreversible cardiomyocyte damage caused by anthracycline, trastuzumab-mediated cardiotoxicity seems to be reversible [7]. The observation of cardiac functional recovery after exposure to trastuzumab led to the description of “chemotherapy-related cardiac dysfunction” or CRCD [8]. Cardiovascular toxicity following breast cancer treatments with trastuzumab may manifest as hypertension, rhythm disturbances, ischemic heart disease, thromboembolic events, or congestive heart failure (CHF). The incidence of cardiotoxicity was highest in patients receiving concurrent trastuzumab and anthracycline (27%), with a lower risk in patients receiving trastuzumab and either paclitaxel (13%) or trastuzumab alone (3-7% in metastatic disease) [9].

Monitoring of the left ventricular ejection fraction (LVEF) is the current standard for detection of trastuzumab-induced cardiotoxicity, and trastuzumab-induced cardiotoxicity was defined as a decrease in LVEF of ≥ 15% or to a value < 50%. A clinically significant decrease in LVEF was observed in 28.6% of women receiving trastuzumab therapy [9].

***Corresponding author:** Fiona Tsui-Fen Cheng M.D.

*通訊作者：鄭翠芬醫師

Tel: +886-2-28332211 ext.2086

Fax: +886-2-28389404

E-mail: breastsection@hotmail.com

Table 1. Risk factors in the overall patient population and in patients either with or without cardiac complications [#]

Risk factors	Overall patient population (n=73)	No cardiac complications (n=59)	Cardiac complications (n=14)	P value*
Age (years)	54.7 ± 11.9	50.1 ± 10.9	65.5 ± 13.5	0.06
Hypertension	15 (20.54%)	11 (18.64%)	4 (28.57%)	0.82
Diabetes mellitus	7 (9.59%)	5 (8.47%)	2 (14.29%)	0.89
Smoking	7 (9.59%)	5 (8.47%)	2 (14.29%)	0.89
Hypercholesterolemia	22 (30.14%)	18 (30.51%)	4 (28.57%)	0.78
Sedentary life style	46 (63.01%)	38 (64.41%)	8 (57.14%)	0.91
Body mass index (BMI, kg/m^2)	26.81 ±4.52	26.92 ±4.63	27.33 ±4.41	0.95
Overweight (BMI between 25 to 30)	9 (12.33%)	6 (10.17%)	3 (21.43%)	0.66
Obesity (BMI ≥ 30)	6 (8.22%)	4 (6.78%)	2 (14.29%)	0.65
Depression	8 (10.96%)	6 (10.17%)	2 (14.29%)	0.94
Positive family history	25 (34.25%)	18 (30.51%)	7 (50.00%)	0.88
ACE-I/ARB (at baseline)	12 (16.38%)	10 (16.95%)	2 (14.29%)	0.92
β-Blockers (at baseline)	9 (12.33%)	6 (10.17%)	3 (21.43%)	0.71

#Cardiac complications included asymptomatic left ventricle dysfunction, symptomatic heart failure, significant changes of electrocardiograms, and pericardial effusion

*P value compares the groups with and without cardiac complications

The purpose of this study was to estimate trastuzumab-associated cardiac side effects in HER2 positive breast cancer patients after completion of trastuzumab therapy either in the adjuvant or neoadjuvant setting and with or without radiotherapy in Taiwanese women.

Materials and Methods

Study Design

This open-label, observational study was performed at a single medical center in Northern Taiwan to evaluate the cardiac safety of trastuzumab in women with HER2-positive breast cancer. All patients were diagnosed with histologically confirmed breast cancer with HER2 overexpression, Trastuzumab was used for adjuvant therapy in 11 patients and neoadjuvant therapy in 8 patients and there were also 13 patients who used trastuzumab when their disease had metastasized. The loading administration dose of trastuzumab was 8 mg/kg of body weight, and the maintenance dose was 6 mg/kg every 3 weeks for a total dose of 5,720 mg-6,600 mg. Trastuzumab was discontinued in patients who developed significant cardiotoxicity, which was defined as a potentially life-threatening cardiac event.

Anthracycline-containing regimens used as either adjuvant or neoadjuvant chemotherapy was AC (i.e., doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for four cycles). Docetaxel (60-75 mg/m^2) was administered three times weekly. Endocrine therapy was added as clinically indicated based on tumor biology behavior, and radiotherapy was administered concurrent with trastuzumab in 35 individuals (47.9%). All participants provided informed consent.

Patient Characteristics

This study included 73 consecutive patients with HER2 overexpression and who qualified for trastuzumab chemotherapy. Female patients ≥ 20 years of age who were treated at the Shin-Kong Wu Ho-Su Memorial Hospital beginning in October 2007 were eligible. The mean age at inclusion was 51.7 ± 12 years (range, 31-83 years). The sedentary lifestyle was defined as a type of lifestyle with no or irregular physical activity. Sedentary activities include sitting, reading, watching television, playing video games, and computer use for much of the day with little or no vigorous physical exercise.

Outcome Measures

The following cardiovascular risk factors were analyzed: age, body mass index (BMI) between 25 kg/m^2 and < 30 kg/m^2, BMI > 30 kg/m^2, smoking, hypertension, sedentary lifestyle, positive family history, hypercholesterolemia, diabetes mellitus, depression, positive family history, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE-I/ARB) and β-blocker usage (Table 1). Exclusion criteria included prior anti-HER2 treatment, prior adjuvant anthracycline-containing chemotherapy, prior high-dose chemotherapy with peripheral stem-cell transplantation, history of malignancy, serum creatinine > 1.5 upper limit of normal (ULN), bilirubin > 1.5 ULN, either transaminases or alkaline phosphatase > 2.5 ULN or > 5.0 ULN, respectively, in case of either liver or bone metastases, serum calcium > 512.0 mg/dL (3.0 mmol/L), pregnancy, lack of a reliable appropriate contraceptive method in women of child-bearing potential, or any medical condition likely to interfere with the conduct of the study. In addition, specific cardiovascular exclusion criteria were an LVEF < 55% determined by two-dimensional echocardiography at rest, prior treatment with cardiotoxic agents, valvular heart disease requiring treatment, cardiomyopathy, acute myocarditis, CHF, end-diastolic left ventricular diameter > 56 mm determined by M-mode echocardiography at rest, arrhythmias requiring treatment, poorly controlled arterial hypertension, or prior mediastinal irradiation. The breast cancer patients were regularly followed-up at the hospital's general surgery outpatient department after trastuzumab therapy was terminated every 3 months for at least 1 year.

Cardiovascular system evaluation (history, cardiovascular risk factors, blood pressure, and physical examination), electrocardiography, and echocardiography were performed at baseline and repeated every 3 months until trastuzumab termination. The evaluation was performed and interpreted by the same experienced cardiologists throughout the study period. Further, standard of care serial echocardiographic scans were performed to assess left ventricular contractile function at baseline and again 3 month and 6 month after trastuzumab initiation. Parasternal and apical views were obtained using a standard echocardiographic machine (Philips IE 33). The LVEF was determined from two-dimensional images according to established criteria, including the modified Simpson's method. For study purposes, clinically important cardiotoxicity was defined as a decrease in ejection fraction (EF) of ≥ 15% from baseline or to a value < 50%. All other patients were categorized as normal LVEF. Clinically relevant changes were treated via best clinical practice according to the managing general surgeon.

Tumor Characteristics

Tumor histology, stage, grading, receptor status (HER2 score), and antigen background (estrogen receptor, progesterone receptor) were recorded. Most patients had an invasive ductal growing pattern (98.6%). The majority of tumors at the time of discovery were at stage I~II and 65 patients (89%) were at Her2-neu receptor over-expression. Patients with a HER2 2+ (IHC score) underwent further fluorescent in situ hybridization test (FISH) (Table 2). HER2 status was determined using archived primary tumor

Table 2. Tumor characteristics in the study population

Tumor characteristics	Classification	No. of patients	%
Histology	Invasive ductal carcinoma	72	98.6%
	Invasive lobular carcinoma	0	0
	Others (mucinous carcinoma)	1	1.4%
Stage	T0	4	5.4%
	T1	11	15.1%
	T2	39	53.4%
	T3	14	19.2%
	T4	5	6.8%
Lymph node	N0	25	34.2%
	N1	23	31.5%
	N2	16	21.9%
	N3	9	12.3%
Distant metastasis	M1	13	17.8%
HER2 score	2+	8	11.0%
	3+	65	89.0%
Hormone receptor (+)	ER (+)/PR (+/-)	68	93.2%
Hormone receptor (-)		5	6.8%

ER, estrogen receptor; PR, progesterone receptor

samples and either a standard semi-quantitative immunohistochemistry test (DAKO HercepTest TM) or FISH analysis (Vysis or Ventana).

Chemotherapy before Adjuvant Trastuzumab Therapy

Seventy-three patients received adjuvant chemotherapy with different protocols before initiating adjuvant trastuzumab treatment. Twelve patients (16.4%) with advanced tumor were treated with trastuzumab and oral capcitamin (Xeloda). Taxotere was used in combination in 31 patients (42.5%), cyclophosphamide was part of a chemotherapy combination treatment in 29 patients (39.7%), and epirubicin was used in combination in 18 patients (24.7%). Both adjuvant and neoadjuvant were included in our study.

Trastuzumab Treatment

All patients received an initial infusion of trastuzumab (8 mg/kg body weight) dissolved in sodium chloride 0.9% over a 60 min period and followed infusions at 6 mg trastuzumab/kg body weight every 3 weeks.

On day 1, IV trastuzumab, epirubicin, and cyclophosphamide were administered according to standard prescribing information. Trastuzumab was withheld in the event of drug-related grade 3 or 4 non-hematologic toxicity until recovery to grade 2 or better. In the event of recurrence of grade 3 or 4 nonhematologic toxicity, trastuzumab was to be discontinued.

A combination of epirubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) administered every 3 weeks for six cycles then for four to six cycles at a higher dose level (epirubicin at 90 mg/m^2 and cyclophosphamide at 600 mg/m^2). Epirubicin was administered intravenously over 30 minutes and was followed by intravenous cyclophosphamide over 30 minutes. The first dose of chemotherapy was administered 3

Table 3. Left ventricular ejection fraction (LVEF) in the total patient population and in patients either with or without cardiac complications at particular time points

Time of measurement	Total patient population LVEF (%) (73 p't)	No cardiac complications LVEF (%) (59 p't)	Cardiac complications LVEF (%) (14 p't)	P value*
Baseline	67.36 ± 7.27	66.08 ± 6.76	72.31 ± 6.87	0.77
3 months	61.47 ± 9.46	64.98 ± 6.60	46.64 ± 3.33	0.01
6 months	61.42 ± 9.52	65.18 ± 6.61	46.69 ± 1.64	< 0.01

* P value compares the groups with and without cardiac complications

hours after trastuzumab, and subsequent doses were administered immediately after trastuzumab if the initial dose was well tolerated. Patients were scheduled to receive all cycles of chemotherapy at the same dose. Treatment could be postponed for a maximum of 1 week only in the event of severe hematological and/or nonhematologic toxicity. If there was no improvement in toxicity during that period, chemotherapy was discontinued.

Palliative and supportive care for disease- and treatment-related symptoms (e.g., analgesics, paracentesis, premedication and hydration) was offered to all patients when indicated, and palliative radiotherapy was permitted if it did not compromise evaluation of disease response Any drug, except antineoplastic drugs/agents, dextrazoxane, or prophylactic granulocyte colony-stimulating factor (G-CSF) could be administered concomitantly.

Clinical Assessment

Prior to trastuzumab treatment and every 3 months thereafter, each patient obtained a complete medical assessment. Symptoms of heart failure were assessed, and during the follow-up examination, patients were asked about clinically relevant worsening of cardiac function, especially dyspnea, palpitations, and edema.

LVEF was measured by two-dimensional echocardiography, examinations were recorded, and the long-axis view was used to assess EF in all patients. For the echocardiograms, all patients underwent a transthoracic two-dimensional echocardiography according to the guidelines of echocardiography [10]. To determine diastolic function, pulsed Doppler tracings of mitral inflow, pulsed Doppler tracings of the right upper pulmonary vein, and tissue Doppler imaging (TDI) records of the mitral valve annulus were obtained. The Simpson rule was used to calculate LVEF and LV systolic and diastolic volumes [11]. The fractional shortening (FS) was also used for estimating LVEF. All echocardiographic examinations were performed with a conventional echocardiographic system (Philip IE33 and a cardiac transducer 1.5-4.0 MHz).

Cardiac Monitoring and Cardiotoxicity

A physical examination, cardiac questionnaire, electrocardiogram (ECG), and an assessment of LVEF by echocardiography were executed at baseline and 3 months and 6 months and when clinically required (Table 3).

Patients with completely excised HER2-positive breast cancer were eligible for the study if they had completed at least four cycles of a standard (neo) adjuvant chemotherapy regimen and radiotherapy (if applicable).

Significant cardiotoxicity was regarded as a potentially life-threatening cardiac event and was defined using the following criteria: absolute decrease of LVEF > 15% [12], absolute reduction in LVEF < 50% [13], and any symptoms/signs of heart failure. As other events occurring in the cardiovascular system during trastuzumab treatment are rare and not well known, patients were carefully evaluated by both the cardiol-

Table 4. LA size and mitral regurgitation status in the total patient population and in patients either with our without cardiac complications at particular time points

Variable and time of measurement	Total patient Population (73 p't)	No cardiac complications (59 p't)	Cardiac complications (14 p't)	P value*
Left atrial size				
Baseline (mm)	35.15 ± 5.17	34.75 ± 5.26	36.57 ± 4.45	0.85
3 months (mm)	38.13 ± 5.31	35.51 ± 5.42	42.50 ± 5.49	0.67
6 months (mm)	40.34 ± 5.23	37.12 ± 6.68	45.31 ± 3.58	0.61
Mitral regurgitation				
Baseline (% and number of patients)	24.66% (18/73)	20.33% (12/59)	42.85% (6/14)	0.08
3 months (% and number of patients)	34.24% (25/73)	22.03% (13/59)	85.71% (12/14)	< 0.001
6 months (% and number of patients)	33.84% (22/65)	18.86% (10/53)	91.66% (11/12)	< 0.001

ogist and oncologist during the course of the treatment. If significant cardiotoxicity developed, trastuzumab was discontinued early. The decision regarding termination of trastuzumab was made according to accepted guidelines [14,15] and following consultation with the supervising cardiologist. In the majority of cases of significant cardiotoxicity, trastuzumab was discontinued and heart failure (HF) treatment with ACE-I/ARB and/or β-blockers was initiated and adjusted to achieve the maximum tolerable doses. Additional cardiac treatment, including diuretics, anticoagulants, and antiarrhythmic drugs, was administered as required by the clinical situation, based on the current standard of care [16].

Statistical Analysis

Data were reported as mean ± standard deviation. Comparisons between groups were made using the unpaired Student's t test for continuous variables and by either the χ^2 test or Fisher exact test (as appropriate) for categorical variables. Univariate regression analysis was used to identify covariates of cardiotoxicity. A probability value of < 0.05 was considered statistically significant. SPSS release 17.0 (SPSS, Chicago, IL) was used for statistical analysis.

RESULTS

A total of 73 patients diagnosed with HER2-positive early stage breast cancer/metastatic breast cancer and eligible for trastuzumab adjuvant therapy were identified. All 73 patients reached the 3 month follow-up examination, and 65 patients reached the 6 month follow-up visit. Patients were divided into two groups based on observed cardiotoxicity, as defined above in terms of declining LVEF. The group with cardiac complication (n = 14) was older than group without cardiac complication (n = 59), but the difference was not statistically significant (65.5 ± 13.5 years vs 50.1 ± 10.9 years, p = 0.06, respectively) as described in Table 1. Most patients remained in an asymptomatic stage of cardiac disease. Only two patients developed dyspnea New York Heart Association II, and only three patients reported paroxysmal palpitations. In this study, 14 of the 73 women (19.2%) treated with trastuzumab experienced a clinically important decrease in LVEF following initiation of treatment. In the present study, we found that the patients with cardiac complication (n = 14) compared

with no cardiac complication (n = 59) had more depressed LVEF in the trastuzumab treatment in the 3rd month (46.64 ± 3.30 vs 64.98 ± 6.60; p = 0.01) and in the 6th month (46.69 ± 1.64 vs 65.18 ± 6.61; p <0.01).

Most patients with cardiac dysfunction recovered after 6 months. Patients with trastuzumab-associated cardiac dysfunction were treated with ACE-I/ARB and/or β-blockers, which were administered at the maximal tolerable dose [16]. Left atrial diameter geometry changed during the early periods of trastuzumab treatment. Specifically, the median left atrial diameter in the group of patients with cardiac complications increased compared to the group with the no cardiac complications after trastuzumab treatment (from 35.51 ± 5.4 mm to 42.5 ± 5.49 mm after 3 months, p = 0.67 and from 37.12 ± 6.68 mm to 45.31 ± 3.58 mm, p = 0.61 after 6 months of trastuzumab treatment), but that difference was not statistically significant (Table 4). In addition to the transformation of the left atrial geometry, an increased percentage of mitral valve regurgitation after trastuzumab treatment in the group of patients with cardiac complications was noted, which was statistically different between the two groups of patients after 3 months of trastuzumab treatment (22.0% vs. 85.7%, p < 0.001) and 6 months (18.9% vs. 91.7%, p < 0.001) as shown in Table 4.

There was no significant difference between patients with normal and decreased LVEF based on either BMI or frequency of other known risk factors for cardiac dysfunction such as hypertension, diabetes, hypercholesterolemia, coronary artery disease, a sedentary life style, smoking, or use of antihypertensive medications (i.e., ACE-I/ARB, ß-blockers) as illustrated in Table 1. One patient (65 years old, stage T3N2M1, with radiation treatment and anti-hypertensive treatment) associated with trastuzumab-related death was noted during the 3rd treatment course (in the same night just after trastuzumab infusion 4 hours later). The other patient (63 years old, stage T4N2M1, with radiation treatment, with diabetic mellitus under oral hypoglycemic agents treatment) presented dyspnea discomfort after trastuzumab infusion (the 4th treatment course) and more dyspnea thereafter then developed small to moderate amount of pericardial effusion 1 week later, confirmed by echocardiogram, was treated by diuretic and recovery after 1 week later. Both of them were healthy and without heart disease history previously.

DISCUSSION

Cardiotoxicity, defined as a decrease in LVEF, has been observed following trastuzumab adjuvant treatment combined with standard chemotherapy in as many as 27-34% of patients [9,17,18]. Interestingly, the incidence of cardiotoxicity was lower in the current study, which found that only 19.2% of women (14/73) enrolled in this study who were treated with trastuzumab experienced a clinically significant decrease in LVEF. Rates of cardiotoxicity are somewhat lower in newer adjuvant trials of trastuzumab, but likely underestimate risk due to careful selection of patients to minimize cardiac events by excluding patients with underlying cardiac disease or abnormal baseline/postanthracycline treatment LVEF [17]. The highest incidence of cardiac side effects was observed in patients treated with a combination of anthracycline, cyclophosphamide, and trastuzumab (27%) followed by the group of patients treated with a combination of trastuzumab and paclitaxel (13%). In contrast, monotherapy with trastuzumab led to cardiac adverse events in only 4% of patients [19]. The clinical symptom of those cardiac adverse events was dyspnea and NYHA III or IV. In patients with adjuvant trastuzumab therapy subsequent to chemotherapy with anthracycline and cyclophosphamide, cardiac dysfunction occurred in only 9% of all patients [20]. The mechanisms of trastuzumab-related cardiotoxicity are still being discussed intensively, but appear to differ from those related to anthracyclines. Specifically, trastuzumab does not seem to cause myocyte loss. In patients with trastuzumab cardiac dysfunction, myocytes appear histologically normal, and changes can only be seen

via electron microscopy, consistent with a reversible cardiomyopathy [21]. That finding led to the classification of type II cardiotoxicity as opposed to the irreversible changes associated with anthracycline (type I cardiotoxicity). Unlike anthracycline toxicity, it has been shown that trastuzumab cardiotoxicity is not dose dependent, is reversible upon therapy withdrawal, and the drug can be safely re-administered after recovery of EF. In type I cardiotoxicity, the earliest damage is myofibrillar disorganization that is likely to progress to myocyte apoptosis and necrosis. When HF occurs, the clinical picture may stabilize, but the damage appears to be permanent and irreversible. Further, disease relapse months to years after type I cardiotoxicity can be correlated with sequential cardiac stress [8], whereas EF is likely to recovery in type II cardiotoxicity, and there is evidence of relatively safe re-administration after discontinuation. Unlike anthracyclines, there is a low likelihood of HF induced by sequential stress [22]. The Herceptin Adjuvant HERA trial demonstrated severe cardiotoxicity, including one cardiac death and nine patients with severe congestive heart failure in only 0.5% of women with adjuvant trastuzumab treatment for 12 months or 24 months [13]. More than 70% of patients received a chemotherapy combination with epirubicin in different study protocols before adjuvant trastuzumab treatment began.

In the predominantly echocardiography-based study reported herein, the authors focused on systolic function and geometrical changes during the early months of trastuzumab treatment. In this study cohort, no patient had to interrupt the adjuvant therapy due to worsening of heart function and/or heart failure. During the observation period, only some patients developed symptoms of heart failure (i.e., NYHA I and II), yet no patient fulfilled the Cardiac Review and Evaluation Committee (CREC) criteria for discontinuing the adjuvant trastuzumab treatment, despite the fact that one patient died during trastuzumab treatment [9]. The study authors observed an increase in left atrial diameter index and an increase in mitral regurgitation identified by echocardiography.

The Framingham Heart Study revealed an association between increasing left atrial size and increasing age, left ventricle mass, hypertension, atrial fibrillation, congestive heart failure or myocardial infarction, mitral annular calcification, and diabetes. In addition, left atrial enlargement led to an increasing relative risk of death in both genders [24]. In hypertensive patients, left atrial (LA) enlargement is associated with higher incidence of cardiovascular death and stroke [25], and LA volumes increase to augment active LA emptying even in patients with mild hypertension [23]. Further, according to recently published data from the VALIANT echo study of patients after myocardial infarction, an independent association between LA volume index (LAVI) and the combined endpoints either death or hospitalization for heart failure and overall mortality was found [11].

In the present study, we found an increased degree of mitral regurgitation. It remained unclear if mitral regurgitation either induced LA enlargement or was a consequence of LA enlargement. However, a few signs, such as the unchanged reservoir function and the increasing mitral regurgitation from mild to moderate, pointed toward LA enlargement having developed earlier followed by mitral regurgitation. The diastolic heart functional values in the study cohort did not change significantly during the observation period.

Overall, nearly one in five patients will discontinue trastuzumab treatment due to cardiac complications, among which LV dysfunction is the most frequent abnormality. Although cardiac complications of trastuzumab therapy are frequent, they do not seem to be permanent. Instead, most cardiac complications are transient, asymptomatic, and reversible; however, there are reports of rare cases of progressive LV dysfunction and HF. Nevertheless, longer follow-up is needed to confirm that cardiotoxicity associated with trastuzumab therapy does not affect long-term outcome. Prior to institution of trastuzumab therapy, all

patients should be evaluated for cardiovascular status. As the majority of complications are asymptomatic, routine cardiac monitoring should be performed during trastuzumab treatment.

Major adverse cardiopulmonary events in our study were sudden death (1 patient) and pericardial effusion (1 patient). In our study, one patient developed dyspnea and small to moderate pericardial effusion was noted by echocardiogram 1 week later. In most case reports about trastuzumab related pericardial effusion [26,27], most case reports were small self-limiting and easy to medically control. There was a report about ventricular tachycardia associated with trastuzumab in a patient with preserved LV systolic function that resulted in sudden cardiac death [28].

An important limitation of this study was the small number of patients and the different therapeutic regimes used before starting the adjuvant trastuzumab treatment. Regardless, 24.7% of included patients received epirubicin in combination with different chemotherapeutics, and 39.7% of all treatment regimes included cyclophoshamide. Another major limitation of this study was the use of decreased LVEF as a surrogate for cardiotoxicity. In the United States, only 50% of patients diagnosed with heart failure actually had decreased LVEF [29-31], and the overall cardiac outcomes of heart failure patients with and without decreases LVEF were similar [31]. The long-term implication of asymptomatic changes in LVEF are unclear [17,32].

CONCLUSIONS

The blockade of Her2-neu receptors with trastuzumab in patients with breast cancer led to measurable changes in left ventricle systolic function, but most are clinically symptomless and not affected in their daily activities. These changes can occur early in the first 3 months after initiating treatment. For those patients with marked decrease LVEF in the first 3 months, echocardiography may be a necessary and strict follow-up (i.e. every 3 month). Symptomatic heart failure was noted in only 2.7% (n = 2) in our study. The cardiac complication group (n=14) seems older than the group without cardiac complication (n = 59), but not statistically significant (65.5 ± 13.5 vs 50.1 ± 10.9; p = 0.06). In that early period, an increased incidence of mitral regurgitation was also noted.

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