

Detection of Early Sub-Clinical Trastuzumab-Induced Cardiotoxicity in Breast Cancer Patients

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Abstract

Background: Trastuzumab (TZB) is a recombinant humanized monoclonal antibody, used for the treatment of HER2-positive breast cancer, with recognized associated-cardiotoxicity. The methods for its early sub-clinical detection are not well defined.

Objective: To evaluate TZB-induced cardiotoxicity in patients (pts) with breast cancer followed for a 3-month period of treatment.

Methods: Prospective study of consecutive pts treated with TZB for advanced HER2-positive breast cancer enrolled between May-September/2010. A comparison of clinical, laboratory and echocardiographic data, prior to and at the 3rd month after starting TZB was performed. Left ventricular systolic function deterioration (Cardiac Review and Evaluation Committee criteria) and diastolic function (American Society of Echocardiography classification) were studied.

Results: Data were available for 51 women, mean age = 55.4 ± 14.0y. At the 3rd month, no patient had symptomatic heart failure. Left ventricular ejection fraction (LVEF) did not differ at 3 months (69.3 ± 7.4 vs. 67.1 ± 6.5%, p > 0.05), decreasing in 57.9% pts (only one to LVEF < 55%). There was a significant increase in the E/e' ratio (3.9 ± 0.8 vs. 8.0 ± 1.9, p < 0,001) due to an e' velocity reduction (0.19 ± 0.02 vs. 0.10 ± 0.03, p < 0.001). Other diastolic parameters remained unchanged. Both the left atrial and the left ventricular volumes remained unchanged. N-terminal pro-B type natriuretic peptide levels did not increase. During the follow up period two pts died and two were admitted to the hospital, all for non-cardiovascular causes.

Conclusion: During the first 3 months of TZB treatment none of the pts presented overt heart failure or significant LVEF deterioration. A significant reduction in the E/e' ratio was detected, but neither the loading parameters nor LVEF changed significantly (Arq Bras Cardiol. 2013;100(4):328-332).

Keywords: Immunosuppressive Agents; Breast Neoplasms / chemistry; Antineoplastic Agents / adverse effects; Heart Failure / chemically induced; Ventricular Dysfunction / chemically induced.

Introduction

Breast cancer remains one of the most common causes of death among women. However, adjuvant trastuzumab (TZB) therapy in association with conventional chemotherapy has revolutionized the treatment of the disease. TZB is a recombinant humanized monoclonal antibody used for the treatment of HER2-positive breast cancer, an overexpressed gene in 25-30% of cases¹⁻³. In the pivotal phase III trial, the addition of TZB to doxorubicin and cyclophosphamide or to paclitaxel chemotherapy resulted in improved time to recurrence and an overall increased survival in patients with metastatic disease⁴. Subsequently, several trials have shown that TZB reduce the risk of recurrence and early death⁵⁻⁷. In the HERA trial, TZB given after primary therapy reduced the rate of recurrence by approximately fifty percent⁸.

Serious adverse events after TZB, including anaphylaxis and death, are rare (0.25%)⁹. However, one of the possible deleterious side effects is cardiotoxicity which increases with anthracyclines exposure. It is believed that oxidative stress has a central role^{10,11}. Cardiotoxicity, being mostly reversible after drug discontinuation, may be symptomatic, with signs and symptoms of heart failure (1-4% in HERA trial) or asymptomatic, with a progressive reduction in left ventricular ejection fraction (LVEF). In the first cases TZB should be discontinued, although in the last ones controversy still exists concerning both the evaluation of the dysfunction and the appropriate time for discontinuation of treatment¹².

Several criteria are proposed to detect subclinical left ventricle dysfunction, although there is still no consensus towards the best imaging method and parameters of use. Echocardiography is proposed as the main non-invasive tool for cardiotoxicity monitoring. A baseline evaluation of LVEF is recommended with an every 3-month reassessment during therapy¹³. Because of the different criteria for the diagnosis of TZB cardiotoxicity, an independent Cardiac Review and Evaluation Committee

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was created to establish a set of criteria to confirm cardiac dysfunction, even if subclinical¹⁴. Nevertheless they are strictly based on LVEF changes and it is being recognized from more recent studies that some changes occur before this dysfunction, probably predicting it. Thus, our aim in this study was to evaluate early TZB-induced cardiotoxicity in patients with breast cancer receiving this antibody as an adjuvant therapy.

Methods

A prospective study including 51 breast cancer female patients undergoing adjuvant chemotherapy with TZB in a tertiary hospital - at the Oncology and Cardiology Departments, was conducted. Patients were enrolled during a 5-month period (May to September 2010), and were selected for TZB therapy according both to HER-2 positivity on the immunohistochemical study and at the discretion of the Oncology medical team. Women with prior history of cardiac events (stroke, acute myocardial infarction or heart failure) and chemotherapy, namely anthracyclines and TZB, were excluded.

Breast cancer treatment regimen

Following surgical and oncological staging, patients were selected for loco-regional therapy and adjuvant chemotherapy with anthracyclines and/or taxanes in addition to TZB. None of the patients received treatment with adriamycin/doxorubicin alone. When clinically justified, some patients were also given hormonal therapy. TZB was administered according to International Guidelines for breast cancer treatment: first dose at 8mg/kg followed by a 3-week schedule of 6mg/kg in 250ml of sodium chloride 0.9% (30' perfusion length)¹⁵. The mean cumulative TZB dose was 1.8 ± 0.4 g per patient.

Cardiotoxicity evaluation/surveillance

Before adjuvant treatment for breast cancer and in order to both assess risk and monitor chemotherapy-associated cardiotoxicity, all patients were asked to present a complete clinical past history (including previous hospital admissions for oncologic etiologies, heart disease and current and past medications) and cardiovascular risk factors (smoking, hypertension, diabetes mellitus, dyslipidemia and familiar history of cardiovascular disease); demographic data were also recorded (age and gender). A complete physical examination in search for signs of heart failure, biochemical markers of myocardial lesion (troponin I - Electys[®], cut-off value: 0.04 μ g/ml) and diastolic function by natriuretic peptide (N-terminal B-type natriuretic peptide - Nt-proBNP, cut-off value: 150pg/L) were assessed at baseline and three months after starting TZB therapy. Two transthoracic echocardiographic studies (*GE Vivid S6[®], Milwaukee*), at baseline and at the third month of follow-up, included the evaluation of: left ventricular (LV) M-mode dimensions and indexed mass; *Simpson* biplanar volumes and LVEF; transmitral spectral Doppler peak *E* and *A* velocities; *E* wave deceleration time; tissue Doppler *e'* and *a'* velocities at the septal and lateral mitral annulus; left atrial indexed volume; tricuspid annular plane systolic excursion (TAPSE); pulmonary artery systolic pressure (PASP); and inferior vena cava (IVC) dimensions. Pericardial effusion was qualified as mild, moderate or severe and mitral regurgitation was only quantified when more than mild. Echocardiographic acquisition was performed by one of the two cardiologists/echocardiographers participating in the

study. However, echocardiographic data recording was made at the discretion of their joint evaluation. All-cause mortality and admissions for cardiac and non-cardiac causes were recorded. Additional echo evaluation was performed in a non-programmed schedule every time left ventricular function deterioration or clinical signs of heart failure were suspected. At our institution, chemotherapy is interrupted when patients develop symptomatic heart failure and when left ventricular function becomes impaired (ejection fraction below 55% or a more than 10% decrease below the baseline ejection fraction).

Statistical analysis

Categorical variables are presented as number (percentage) and were compared by the *chi-squared* test. Continuous variables are expressed as mean \pm standard deviation and were compared by paired or unpaired *Student's t-test*, after the identification of a normal distribution for each continuous measure. A *p* value of <0.05 was considered statistically significant and all statistical tests were two sided. SPSS statistical package (version 18.0, SPSS[®], Inc., Chicago, IL, USA) was used for the statistical analysis.

Results

Of the 51 women included, mean age of 55.4 ± 14.0 years, 23 (45.1%) had at least one identified cardiovascular risk factor: hypertension 18 (35.3%), dyslipidemia 13 (25.5%), family history of cardiovascular disease 10 (19.6%), diabetes mellitus 6 (11.8%) and smoking 3 (5.9%). One patient had a past history of atrial fibrillation and one other had past radiation therapy to the right chest because of breast cancer. Family history of cancer was present in 18 patients (35.4%). The mean body mass index was 25.9 kg/m² (obesity in six patients - body mass index > 30 kg/m²). Twelve patients (23.5%) were under angiotensin converse enzyme inhibitors or angiotensin II receptor blockers and two patients (3.9%) were on beta-blockers. All of these medications were used for blood pressure treatment. Thirteen patients (25.5%) were treated with statins for dyslipidemia and diabetics (11.8%) were on aspirin. One patient was on warfarin for atrial fibrillation. None of the patients were under diuretics or aldosterone antagonists.

At the third month, there was no record of symptomatic heart failure. Clinical and biochemical data were not statistically different at baseline and after three months of TZB therapy (Table 1). However, on echocardiographic evaluation there were differences in diastolic parameters after TZB. A statistically significant difference in the *E/e'* ratio at baseline and at the 3rd month of follow-up was observed, and this was strictly due to a decrease in the *e'* myocardial velocity as assessed by tissue Doppler (Table 2, Figure 1). No differences were observed in the transmitral *A* wave measurements or in the indirect loading/volemia parameters, such as LA indexed volume, IVC diameter and PASP.

Thirty patients (57.9%) showed a decrease in LVEF, and only one patient had a value under 55% (LVEF 52%). In this case TZB was suspended despite the absence of symptoms. Three (5.9%) patients developed pericardial effusion (no more than mild in all of them). During the observation period two patients died and two others were admitted to the hospital, none of them for cardiovascular causes.

Table 1 - Mean values of clinical and biochemical data

Variables	Baseline	3-months TZB	p value
Systolic blood pressure (mmHg)	132.9 ± 15.9	124.9 ± 17.0	0.157
Diastolic blood pressure (mmHg)	75.9 ± 11.6	72.33 ± 12.0	0.337
Heart rate (bpm)	80.1 ± 11.0	78.3 ± 14.2	0.518
Troponin I (µg/L)	0.028 ± 0.002	0.040 ± 0.004	0.391
NT-proBNP (pg/ml)	87.4 ± 37.8	90.6 ± 77.0	0.930

* Values are based on single measurements at clinical evaluation. TZB: Trastuzumab

Table 2 - Comparison of echocardiographic parameters evaluated at baseline and at the 3rd month of TZB therapy

Variables	Baseline	3-months TZB	p value
Diastolic LV dimension (mm)	46.1 ± 5.4	46.5 ± 3.8	0.576
Systolic LV dimension (mm)	27.2 ± 4.2	34.2 ± 34.1	0.234
LVEF (%)	69.2 ± 7.4	67.1 ± 6.5	0.197
LA indexed volume (ml/m ²)	23.3 ± 9.1	21.3 ± 5.2	0.496
E transmitral wave (ms)	0.8 ± 0.2	0.8 ± 0.1	0.589
A mitral wave (ms)	0.8 ± 0.1	0.8 ± 0.2	0.977
Deceleration time (ms)	172 ± 19	184 ± 16	0.437
E/A	1.16 ± 0.39	1.21 ± 0.48	0.607
e' (cm/s)	0.19 ± 0.02	0.10 ± 0.03	0.001
E/e'	3.87 ± 0.84	8.04 ± 1.89	< 0.001
IVC (mm)	15.5 ± 4.0	14.1 ± 2.5	0.121
PASP (mmHg)	27.3 ± 9.9	25.0 ± 9.3	0.213
TAPSE (mm)	21.4 ± 3.2	21.5 ± 4.4	0.946

TZB: Trastuzumab; LV: Left ventricle; LVEF: Left ventricular ejection fraction; LA: Left atrium; IVC: Inferior vena cava; PASP: Pulmonary artery systolic pressure; TAPSE: tricuspid annular plane systolic excursion.

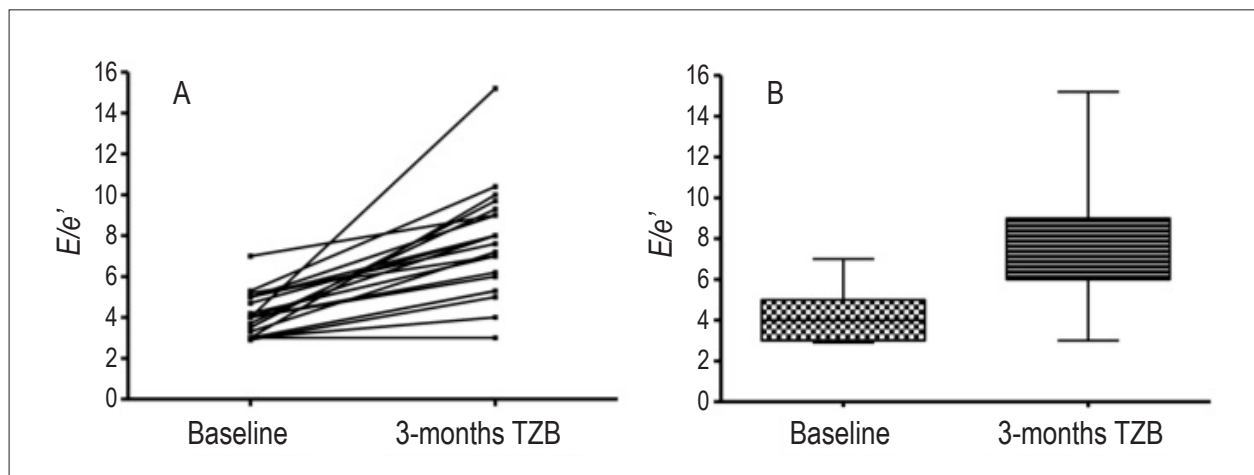


Figure 1 - Comparison of E/e' at baseline and after three months of TZB: A - change of the E/e' ratio in a single patient B - mean E/e' ratio values for the whole group of patients.

Discussion

In this study, we sought to prospectively evaluate early subclinical cardiac changes as assessed by transthoracic echocardiography in a group of female patients undergoing TZB therapy and no previously known cardiovascular impairment.

Cancer therapy-associated cardiotoxicity has long been described, and is an issue for everlasting discussion. Since anthracyclines were first introduced, several efforts have been made in an attempt to identify patients at risk. Until now with the introduction of resources such as TZB into clinical practice, several mechanisms are proposed to describe anticancer agents-associated cardiotoxicity¹⁶. In fact, mechanisms explaining the cardiac deleterious effects are not yet fully understood.

Since pre-clinical signs of cardiac dysfunction are supposed to predict the development of future heart failure, several parameters of the diastolic and systolic functions have been proposed to evaluate this dysfunction¹⁷. However there is no consensus concerning both the best method and the best parameter of choice for the prediction of drug susceptibility and future clinical deterioration.

The development of systolic dysfunction during TZB therapy may be the hallmark for therapy discontinuation. However, it has been recognized that the deterioration of the cardiac function starts earlier during therapy despite normal values of LVEF, which is the accepted parameter for therapy withdrawal decision^{14,15}. Moreover, for patients in whom this therapy was discontinued due to LV impairment, it is suggested that, under appropriate medical interventions, TZB may be reintroduced once normal cardiac function has been restored^{12,18}. The detection of changes in cardiac parameters preceding LVEF reduction could theoretically allow the identification of patients who could benefit from early cardioprotective measures. Eventually these same patients might be maintained under TZB, with survival improvement.

In an attempt to evaluate pre-LVEF deterioration parameters, we evaluated the diastolic function in patients at the beginning of TZB therapy. In addition to conventional spectral Doppler evaluation we assessed mitral annular velocities by tissue Doppler imaging (TDI). This modality appears to offer important advantages over conventional echocardiographic parameters in the revealing of early signs of cardiotoxicity¹⁹. In fact, it is more sensitive than standard Doppler²⁰ in the study of diastolic function, and in our group of patients the E/e' ratio changed because of an e' velocity reduction. In mice, TDI can detect early LV dysfunction prior to changes in conventional echocardiographic indices, also predicting early mortality in those receiving doxorubicin plus TZB²¹. In a study of 42 patients, Fallah-Rad et al²² also showed pre-clinical changes in the left ventricular function using TDI and strain imaging before conventional changes in LVSF in patients receiving TZB in the adjuvant setting.

According to previous studies assessing both myocardial and functional changes, our findings, despite being limited for the evaluation of only one parameter of tissue behavior

– e' , suggest that structural changes occur before functional impairment. Not only the E/e' ratio was the single significant changed parameter, because of an e' velocity reduction, but also there were no changes in LVEF, loading parameters and biochemical markers such as Nt-proBNP. In a report from Sawaya et al²³, a decrease in the longitudinal strain, but not Nt-proBNP and diastolic parameters, was an independent predictor for the development of cardiotoxicity at six months of TZB therapy.

Nevertheless, this study was limited by the small sample size and particularly for the inability to correlate these early findings to the eventual development of LVEF reduction and/or heart failure in the subsequent patient follow-up. Furthermore, loading conditions may have been different, since the echocardiographic evaluation was not made exactly at the same time schedule among these patients. In fact, we should have also carried out a comprehensive echocardiographic evaluation to try to fully describe the left ventricular filling conditions, namely with pulmonary vein interrogation and E wave propagation velocity recording. Moreover, and in order to describe the myocardial behavior under TZB in this small group of patients, our aim should have been focused toward other parameters such as TDI derived strain and speckle tracking derived deformation.

Conclusion

We detected a very early change in a daily practice routine echocardiographic parameter (E/e') in patients under TZB therapy. Since several parameters assessing myocardial (dys) function are being described as impaired in TZB therapy for breast cancer, even before LVEF reduction, it should be included in the conventional cardiac monitoring of these patients in order to understand its clinical impact.

Author contributions

Conception and design of the research: Dores H, Abecasis J, Fonseca C, Arroja I, Martins A; Acquisition of data: Dores H, Abecasis J, Correia MJ, Gândara F, Azevedo J, Arroja I, Martins A; Analysis and interpretation of the data: Dores H, Abecasis J, Correia MJ; Writing of the manuscript: Dores H; Critical revision of the manuscript for intellectual content: Abecasis J, Fonseca C, Arroja I, Martins A, Mendes M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

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