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Cardiac monitoring during trastuzumab therapy in metastatic breast cancer: early incidence of cardiac dysfunction

Francesco Perone[1,2], Pilar Zamora Auñon[3,4], Laura Rodríguez[1], David Vinal[3,4], Juan Caro-Codon[1], Ana Pertejo[3,4], Virginia Martínez Marín[3,4], Enrique Espinosa[3,4], Teresa López-Fernández[1]

[1]Cardiology Department, La Paz University Hospital, IdiPAZ Research institute, Madrid, Spain; [2]Cardiology Department, University of L'Aquila, Italy; [3]Oncology department, La Paz University Hospital, Madrid, Spain; [4]Translational Oncology Group, IdiPAZ, CIBERONC, Madrid, Spain

Abstract

Trastuzumab therapy has dramatically changed breast cancer prognosis. Consensus documents recommend a close monitoring during therapy, not always feasible, especially in metastatic breast cancer. The purpose of this study is to describe trastuzumab cardiotoxicity in metastatic breast cancer patients to understand how to improve cardiovascular monitoring. We retrospectively studied metastatic breast cancer patients scheduled for trastuzumab therapy (2001-2018). All patients underwent a baseline evaluation and monitoring during therapy. Cardiotoxicity was defined as symptomatic heart failure or asymptomatic decrease in left ventricular ejection fraction >10% from baseline and <53%. Ninety-two women were included, mean age 61 years (±14.43), median follow-up 42.5 months (IQR 26-74). Fourteen percent developed cardiotoxicity: two heart failure with preserved left ventricular ejection fraction, three heart failure with reduced left ventricular ejection fraction, and eight asymptomatic decreased in left ventricular ejection fraction. Eighty-one percent of cardiac dysfunction cases occurred within the first 4 years and on median of 31 months from trastuzumab initiation. Thus, in metastatic breast cancer patients, trastuzumab-mediated cardiotoxicity occurred more frequently during the first 4 years. These data should be considered to optimize follow-up protocols.

Correspondence: Dr. Francesco Perone, Cardiology Department, La Paz University Hospital, IdiPAZ Research institute, Madrid 28046, Spain.
E-mail: francescoperone1988@gmail.com

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Introduction

Breast cancer is a major public health problem, with great economic and social impact [1]. Human epidermal growth factor receptor-2 (HER2) protein overexpression and/or amplification of the gene is present in 20-25% of breast cancers, and translate in aggressive growth and poor prognosis. Trastuzumab has demonstrated to improve survival in patients with early and advanced HER2 positive breast cancer. Unfortunately, this therapy is associated with congestive heart failure (HF) or asymptomatic decrease in left ventricular ejection fraction (LVEF), linked to an increase of both cardiovascular and cancer-specific mortality, especially when they limit the patient's ability to complete effective treatments [2]. A comprehensive cardiovascular baseline assessment as well as serial cardiac function monitoring is critical during trastuzumab therapy to detect early cardiac dysfunction and to minimize cancer treatment interruptions [3,4].

In patients on HER2-targeted therapies, surveillance according to the product license includes echocardiography at baseline and every 3 months during therapy, and any patient who has new LVEF impairment will require cardio-oncology follow up assessment [5,6]. However, standard protocols do not take into account baseline cardiotoxicity (CTOX) risks or different cancer populations (early *vs* metastatic HER2 positive breast cancer) to define long term follow-up. Additionally, actual adherence to these pro-

tocols is poor, especially in the context of metastatic disease, with little evidence regarding the benefit-risk ratio [7-9].

The main objective of the present study is to describe the cardiovascular toxicity profile of trastuzumab in patients with metastatic breast cancer (MBC) to understand how to improve cardiovascular monitoring.

Material and Methods

Study design and population

A retrospective, observational, and single-institution study was performed. All metastatic breast cancer (MBC) patients treated with trastuzumab for at least 6 months, from 2001 to 2018, were included.

Patients were followed by the first trastuzumab administration until October 2018 or death. Every patient underwent a comprehensive cardiovascular assessment and LVEF monitoring before cancer therapy and every 3 months during therapy. Clinical variables included age, sex, cardiovascular risk factors, previous cardiovascular diseases (congenital heart disease, ischemic heart disease, valvular heart diseases or permanent atrial fibrillation), previous cancer treatments, and current cancer diagnosis and treatment. Echocardiograms were obtained following current recommendations for cardiac chamber quantification in adults [10,11]. We define CTOX as the presence of symptomatic HF or the decrease in LVEF >10% and <53% [12-15]. The severity of HF symptoms was graded according to the New York Heart Association (NYHA) functional classification (I–IV) [16]. The reversibility of left cardiac dysfunction was defined according to ASE/EACVI criteria [12]. Patients who developed CTOX were referred to the cardiology or cardio-oncology clinic and a multidisciplinary discussion decided when to stop and resume trastuzumab treatment.

The study was conducted in accordance with the Declaration of Helsinki and its later amendments.

Statistical analysis

All analyses were performed using SPSS software (version 17; SPSS Inc.). Continuous variables are reported as mean and standard deviation if normally distributed, median and interquartiles if not normally distributed. They were compared with *t*-test if normally distributed and with Mann Whitney U if not. Categorical variables are reported as absolute number (n) and percentage (%) and were compared with the Chi-square or with the Fisher's exact test. Data were compared for individual patients using the paired *t*-test and instead for groups of patients using repeated measures of analysis of variance. A p-value <0.05 was considered statistically significant. A Kaplan-Meier curve was used to show the cumulative incidence of the first event of left ventricular dysfunction (LVD).

Results

A total of 92 female breast cancer patients were included. Patient baseline characteristics are detailed in Table 1. Mean age was 61 years (±14.43). Thirty-four patients (36.9%) were ≥60 years. Forty-three patients (46.7%) had at least one cardiovascular risk factor and 12 (13%) at least two. Forty-nine patients (45.7%) were previously treated with anthracyclines and 15 (16.3%) with taxanes. Baseline LVEF was within the normal limits in all patients. Patients received trastuzumab for a median of 42.5 months (IQR 26-74). Thirteen patients (14.1%) presented CTOX during follow-up: two patients developed symptomatic HF with preserved LVEF (HFpEF), three patients developed symptomatic HF with LVD (mean LVEF 44±3.61%), and eight experienced an asymptomatic decrease in LVEF (mean LVEF 45.7±4.89%). We did not find significant differences in the LVEF values of patients with symptomatic or asymptomatic LVD (p=0.601).

The median time between the start of treatment and the development of cardiac dysfunction was 31 months (IQR 16, 44) with 81.8% of events occurring during the first 4 years (Figure 1). The CTOX event was not influenced by any of the classic cardiologic or oncologic risk factors (Table 2, p>0.05). During the treatment 53 patients died (57.6%) from disease progression, but none due to cardiac events.

Ten of 11 patients developed LVD before 2014 and after a multidisciplinary discussion temporarily treatment interruption was recommended in patients with clinical HF and those who developed a LVEF <40%. One patient developed asymptomatic LVD after 2014 and trastuzumab therapy was continued under HF therapy. Except in patients with specific contraindications (n=6), patients with any degree of CTOX started angiotensin-converting enzyme (ACE) inhibitors and / or beta-blockers treatment. At follow-up, everyone recovered LVEF to limits similar to baseline (n=11, mean LVEF 60.6±4) (Figure 2, p<0.0001) without recurrence of cardiovascular events when trastuzumab was resumed.

Table 1. Baseline clinical and echocardiographic characteristics.

Variable	Total
Age (years), mean ± SD	61 ± 14.43
Arterial hypertension, n (%)	22 (23.9)
Diabetes mellitus, n (%)	10 (10.9)
Dyslipidemia, n (%)	12 (13)
Previous heart disease[a], n (%)	3 (3.2)
Smokers, n (%)	11 (12)
Past smokers, n (%)	8 (8.7)
Time to trastuzumab (months) median ± IQR	42.5 (26. 74)
Previous radiotherapy, n (%)	54 (58.7)
Previous anthracycline, n (%)	34 (37)
Previous taxanes, n (%)	9 (9.8)
Previous anthracycline + taxanes, n (%)	15 (16.3)
LVEF (%), mean ± SD	61.6 ± 4.37
LV telediastolic diameter (cm), mean ± SD	4.40 ± 0.58
Left atrial area (cm^2), mean ± SD	15 ± 3.1
Peak E-wave velocity (cm/s), mean ± SD	72.12 ± 19.45
E/A ratio, mean ± SD	0.97 ± 0.28
Lateral e' velocity (cm/s), mean ± SD	10.62 ± 3
Medial e' velocity (cm/s), mean ± SD	8.16 ± 2.15
Lateral E/e' ratio, mean ± SD	7.47 ± 2.07
Medial E/e' ratio, mean ± SD	9.48 ± 2.32
TAPSE (mm), mean ± SD	25.16 ± 5.87
sPAP (mmHg), mean ± SD	23.05 ± 3.27
Valvulopathy[b], n (%)	0 (0)

LV, left ventricle; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary artery pressure. [a]Congenital heart disease, ischemic heart disease or permanent atrial fibrillation; [b]stenosis or regurgitation of moderate degree or more.

Discussion

Trastuzumab therapy is essential in the management of metastatic HER2-positive breast cancer [6]. Current guidelines recommend a close monitoring of cardiac function in these patients including LVEF evaluation at baseline and every 3 months during therapy. However, we lack for evidence based recommendations in the setting of MBC and daily practice adherence is poor [7,8].

We present a series of HER2 positive MBC who received trastuzumab during a median time of 42.5 months (IQR 26, 74). This series is among the studies with the longest duration of trastuzumab administration investigating cardiac monitoring during long-term treatment. CTOX definition, in our study, includes the development of symptomatic HFpEF or LVD in patients receiving trastuzumab therapy. Indeed, the latest consensus statement on the definition of cardiovascular toxicities of cancer therapies defines the cardiovascular toxicity event as cardiac dysfunction or clinical HF [13]. Symptomatic HF is a major event, regardless of LVEF, and correlates with a worse prognosis. Specifically, patients with symptomatic HFpEF onset during cancer therapy are associated with a severe degree of cardiotoxicity [14,15].

Asymptomatic decrease in LVEF was more common than symptomatic HF (62 *vs* 38%) in patients who develop trastuzumab-related CTOX, similar to previous series [17-19]. Despite an increased risk of CTOX, none of the patients died from cardiac events and only two patients (1.8%) required hospitalization for acute HF.

Previous studies have identified several risk factors for the development of trastuzumab-mediated CTOX, such as advanced age, pre-existing arterial hypertension, and cumulative administra-

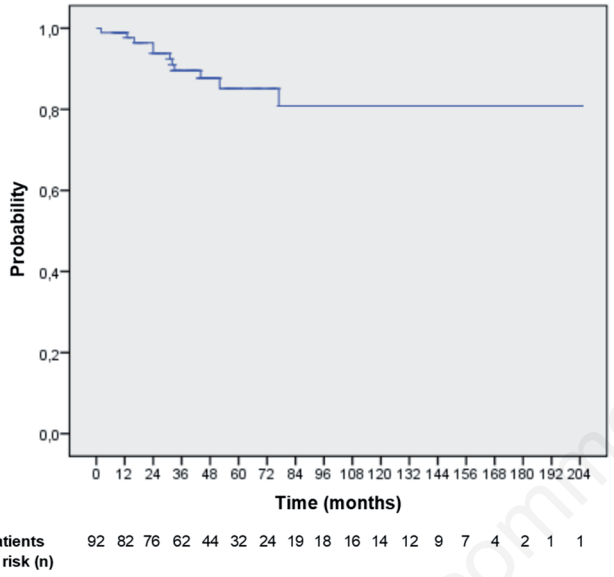

Figure 1. The cumulative incidence of cardiac dysfunction in the study population shown in Kaplan-Meier curve.

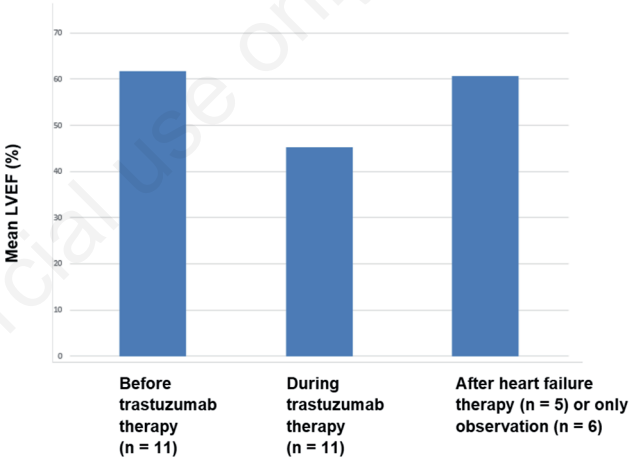

Figure 2. Changes in ventricular function in selected patients with cardiotoxicity due to reduced left ventricular ejection fraction (LVEF).

Table 2. Baseline characteristics of patients in absence or development of cardiotoxicity during trastuzumab therapy.

Variable	No cardiotoxicity (n=79)	Cardiotoxicity (n=13)	p-value
Age (years), mean ± SD	60 ± 14.02	64.77 ± 16.93	0.363
Arterial hypertension, n (%)	20 (25.3)	2 (15.4)	0.350
Diabetes mellitus, n (%)	9 (11.4)	1 (7.7)	0.571
Dyslipidemia, n (%)	10 (12.7)	2 (15.74)	0.535
Previous heart disease[a], n (%)	3 (3.8)	0 (0)	0.630
Smokers, n (%)	8 (10.1)	3 (23)	0.185
Past smokers, n (%)	6 (7.6)	2 (15.4)	0.315
Valvulopathy[b], n (%)	0 (0)	0 (0)	n.s.
Previous radiotherapy, n (%)	44 (55.7)	10 (77)	0.127
Previous anthracycline, n (%)	31 (39.2)	3 (23)	0.085
Previous taxanes, n (%)	7 (8.7)	2 (15.4)	0.373
Previous anthracycline + taxanes, n (%)	12 (15.1)	3 (23)	0.357
Mean LVEF, mean ± SD	61.7 ± 4.42	61.2 ± 4.18	0.711

LVEF, left ventricular ejection fraction. [a]Congenital heart disease, ischemic heart disease or permanent atrial fibrillation; [b]stenosis or regurgitation of moderate degree or more.

tion of anthracyclines [2]. In our study, 36.9% of patients were older than 60, however, traditional cardiovascular and oncologic risk factors have not been found associated with the CTOX development. These results could be explained by both the limited sample size and the use of cardioprotective therapies administered in patients with cardiovascular risk factors, such as ACE inhibitors and beta-blockers [20,21].

In our study, LVD occurred more commonly during the first 4 years of therapy. Our data agree with previous studies on MBC patients [17-19,22-24] who have documented a higher incidence of CTOX during the first years of treatment. Indeed, CTOX during prolonged trastuzumab therapy showed a plateau phenomenon characterized by a relatively early start of LVD. In the ROP study [25] (n=25) the safety profile of long-term administration of trastuzumab (≥5 years for breast cancer) was acceptable and no patients experienced an LVEF of <45% (range 47–63%).

Our data suggest that close trastuzumab therapy surveillance is needed in patients with MBC during the first years of therapy while a more relaxed protocol, based on individual patient's risk profiles, could be established after the fourth year of therapy [3]. Moreover, collaboration between cardiologist and oncologist is essential to minimize cancer treatment interruption in MBC patients. A recent study [19] documented high incidence of CTOX in MBC patients partly maximized by the absence of multidisciplinary work. Only 30% patients with LVD, and 50% of patients with HF symptoms, were referred to the cardiology clinic. In our study, all patients with CTOX were referred for multidisciplinary evaluation and patients who developed HF signs and/or symptoms promptly started HF therapy [5].

The main limitations to our study include the retrospective nature of the study with possibly intrinsic bias. Second, the data collected are dependent on the registration in the electronic cards of patients. Third, this study is represented by the sample size which would need to be increased to obtain greater statistical significance. Fourth, the patients were enrolled from 2001 to 2018, and definition and management of CTOX was carried out according to the recommendations of the year in which it occurred. Furthermore, we do not have baseline data for advanced echo quantification in the majority of patients to analyze these parameters during follow-up.

Conclusions

Trastuzumab-related CTOX in MBC is more common during the first 4 years of administration. This finding may be useful to reduce the need for follow-up in patients who require prolonged trastuzumab administration. Indeed, we can probably reduce the frequency of echo after 4 years of follow-up. Further randomized studies would be needed to confirm this hypothesis.

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