ORIGINAL ARTICLE

# Cardiotoxicity Alerts during Treatment with Trastuzumab in Breast Cancer at Four-year Follow-up

## *Alertas de cardiotoxicidad en el tratamiento con trastuzumab en cáncer de mama, 4 años de seguimiento*

DANIEL A. SANTOS[1], MARÍA ESTELA TETTAMANTI[1], CAROLINA CHACÓN[2], JORGE NADAL[3], VICTORIA COSTANZO[3], ADRIÁN NERVO[3], FEDERICO LOSCO[3], REINALDO CHACÓN[3]

## ABSTRACT

**Background:** Adjuvant treatment of HER2+ breast cancer includes adriamycin and trastuzumab, a monoclonal antibody that produces cardiotoxicity. The actual epidemiologic impact of trastuzumab-related cardiotoxicity in unselected populations in Argentina remains unknown.
**Objectives:** The aim of this study was to evaluate the impact of trastuzumab-related cardiotoxicity during adjuvant treatment for breast cancer in an unselected population after >12 months of completing therapy.
**Methods:** Among 888 patients prospectively evaluated for breast cancer, 231 (38%) were HER2+ and received adjuvant therapy with adriamycin and trastuzumab. Left ventricular ejection fraction was evaluated before treatment, after completing adriamycin and then every 3 months during follow-up. Cardiotoxicity was defined as a decline in left ventricular ejection fraction >10%, according to the definition of the American College of Cardiology and was compared with the definitions of the B-31 trial and the MD Anderson Cancer Center.
**Results:** A decline in left ventricular ejection fraction >10% from baseline values occurred in 65% (n=150) of the patients during a mean follow-up of 48±12 months. In the per group analysis, patients included in the B-31and MD Anderson Cancer Center vs. the American College of Cardiology definitions presented greater percent fall in left ventricular ejection fraction during treatment: 20% vs. 20% vs. 16%, respectively (p <0.04) and ended treatment with left ventricular ejection fraction <50% in 42% vs. 41% vs. 33% of cases, respectively (p=0.01).
**Conclusions:** In the population treated with trastuzumab under cardio-oncology surveillance during 48±12 months:
1- Left ventricular ejection fraction was significantly decreased in more than 60% of patients.
2- Different guidelines show different cardiotoxicity risks which demands continuous cardio-oncological monitoring.

**Key words:** Cardiotoxicity - Trastuzumab - Breast cancer

## RESUMEN

**Introducción:** El tratamiento adyuvante de cáncer de mama Her2+ incluye adriamicina y trastuzumab, un anticuerpo monoclonal con efecto cardiotóxico del que no se conoce el verdadero impacto epidemiológico de toxicidad cardíaca en poblaciones no seleccionadas en la Argentina.
**Objetivos:** Conocer el impacto cardiotóxico del tratamiento con trastuzumab en adyuvancia en cáncer de mama en una población no seleccionada a más de 12 meses después de finalizado su tratamiento.
**Material y métodos:** Sobre 888 pacientes prospectivos con cáncer de mama, 231 p. (38%) presentaban cáncer de mama Her2+, en tratamiento adyuvante con adriamicina + trastuzumab. Las pacientes fueron evaluadas mediante fracción de eyección ventricular izquierda, en pretratamiento, fin de adriamicina y cada 3 meses en el seguimiento. Se definió cardiotoxicidad a la caída de la fracción de eyección ventricular izquierda > 10% según la Sociedad Estadounidense de Cardiología, se subanalizó con algoritmos del estudio B-31 y MD ANDERSON.
**Resultados:** Presentaron caída de la fracción de eyección ventricular izquierda > 10%: 150/231 p. (65%) respecto del basal con un seguimiento medio de 48 ± 12 meses. En el análisis por grupo, las pacientes incluidas en el B-31 vs. MD Anderson vs. Sociedad Estadounidense de Cardiología presentaron mayor pérdida porcentual de la fracción de eyección ventricular izquierda durante el tratamiento: 20% vs. 20% vs. 16% con p < 0,04, finalizaron el seguimiento con fracción de eyección ventricular izquierda < 50%: 42% vs.41% vs. 33% con p = 0,01, respectivamente.
**Conclusiones:** En la población con trastuzumab bajo control cardioncológico, se observó luego de un seguimiento medio de 48 ± 12 meses:
1- Caída significativa de la fracción de eyección ventricular izquierda en más del 60% de la población.
2-Las distintas guías muestran diferentes riesgos cardiotóxicos lo que requiere un monitoreo continuo cardioncológico.

**Palabras claves:** Cardiotoxicidad - Trastuzumab - Cáncer de mama

Rev Argent Cardiol 2019;87:105-110. http://dx.doi.org/10.7775/rac.v87.i2.13799

SEE RELATED ARTICLE: Rev Argent Cardiol 2019:87:91-93. http://dx.doi.org/10.7775/rac.v87.i2.14606

SEE RELATED ARTICLE: Rev Argent Cardiol 2019;87:94-95 http://dx.doi.org/10.7775/rac.v87.i2.14985

*Address for reprints:* Dr. Daniel Santos: dsantos@alexanderfleming.org /danielsantos.md@gmail.com. Instituto Alexander Fleming, Crámer 1180 (C1426ANZ) - Ciudad Autónoma de Buenos Aires, Argentina.

Instituto Alexander Fleming, Buenos Aires, Argentina.
[1] Department of Cardio-oncology, Instituto Alexander Fleming
[2] Department of Radiotherapy, Instituto Alexander Fleming
[3] Department of Clinical Oncology, Instituto Alexander Fleming
This study won the 2018 Dr. Pedro Cossio Foundation Award at the Argentine Congress of Cardiology.

## Abbreviations

| | |
|---|---|
| **ACC** | American College of Cardiology |
| **LVD** | Left ventricular dysfunction |
| **LVEF** | Left ventricular ejection fraction |

## INTRODUCTION

Breast cancer is the most common malignancy among women worldwide, accounting for 2.4 million new cases and 523,000 deaths yearly. (1, 2) Approximately 23–30% of cases are HER2-positive (HER2+) and can be treated with trastuzumab, a monoclonal antibody against the HER2 receptor that was approved in 2001. The incidence of cardiotoxicity with adjuvant trastuzumab after chemotherapy with adriamycin is >25%. (3-6). Trastuzumab-related cardiotoxicity is reversible after removing the agent. This has led to the development of protocols for monitoring left ventricular ejection fraction (LVEF) and to publications as safety guidelines with different limits to define cardiotoxicity that have not been validated in the general population. (4, 6-9)

The goal of the present study was to know the impact of trastuzumab-related cardiotoxicity in breast cancer with adjuvant therapy on an unselected and prospective population by comparing three different definitions of cardiac injury. The secondary objective was to evaluate the impact on the clinical outcome of cardiac monitoring during treatment with trastuzumab and the degree of left ventricular dysfunction reversibility.

## METHODS

Between January 2010 and May 2018, all patients with breast cancer undergoing adjuvant therapy were prospectively included. The treatment regime consisted of adriamycin 60 mg/m2 + cyclophosphamide 600 mg/m2 (4 cycles) + paclitaxel 80 mg/m2 once weekly for 12 weeks + radiotherapy. Patients with HER2+ also received trastuzumab during one year. All the patients were evaluated by a cardio-oncology team in a center specialized in oncology.

### Echocardiographic evaluation

Transthoracic echocadiography was performed with digital image capture ultrasound machines and analyzed with GE system FIVE EchoPAC software from January 2010 to April 2016, and thereafter with Vivid T8 until the end of the recruitment period. The same operator, using the same equipment, was responsible for data collection, echocardiographic evaluation, LVEF variability monitoring and cardiotoxicity alert throughout the follow-up period. Echocardiographic assessment included M-mode, two-dimensional and color-Doppler measurements. (8) Left ventricular EF was estimated with the Simpson method from 2-chamber and 4-chamber volume measurements, using the same technique for each patient (manual contour tracing or automated edge detection from the apex) before treatment, every 3 months during 18 months and every 4 months during follow-up. (4) The evaluations were open-label, and the images before treatment were always available to the operator and used as reference to compare changes due to toxicity. Each patient was used as self-witness to define cardiotoxicity according to the fall in LVEF reference values during follow-up. (3-5) Events were confirmed by the cardio-oncology committee before giving the information to the attending oncologist.

Cardiotoxicity events: Echocardiographic monitoring of trastuzumab therapy was established by the institutional Tumor Committee in 2010, which considered cardiotoxicity as a fall in LVEF >10% from the baseline value, requiring temporary or permanent discontinuation of trastuzumab, as applicable, following the recommendations of the American College of Cardiology (ACC) and the Food and Drug Administration (FDA), the regulatory agency of the United States. (6) Patients with persistent fall in LVEF despite trastuzumab discontinuation according to our institutional toxicity criteria (those of the ACC) were evaluated following other guidelines with less strict criteria to define cardiotoxicity:

ACC criterion: LVEF decline >10% from pretreatment value and not below the lower normal limit of 55%. (6)

B-31 trial criterion: LVEF decline >15%. (4)

MD Anderson Cancer Center criterion: Up to 40% decline in LVEF during treatment. (7)

When the MD Anderson Cancer Center criterion of a tolerated 40% decline in LEVF was evaluated, we changed it to a limit not <45%, as none of the patients reached this value. (7) Each patient presented only one cardiotoxicity event with the maximal fall in LVEF attained in this study. In each group, changes in the following LVEF variables during treatment with trastuzumab were compared: lowest LVEF reached, months to peak decline, LVEF at the end of treatment, percentage of patients with complete recovery: difference in LVEF <5% from the pretreatment value, and percentage of patients without total recovery: LVEF <50% at the end of follow-up.

The cardiotoxic event was evaluated in general and for each criterion, and the cardiological and oncological decisions made regarding trastuzumab therapy were reported.

### Statistical analysis

This was a prospective, longitudinal, analytic, open-label, single center study, representative of daily clinical practice. Continuous variables were expressed as mean ± standard deviation. Discrete variables were expressed as frequencies and percentages. Qualitative variables were analyzed using the chi-square test or Fisher's exact test. Continuous variables were compared using Student's t test for independent data or the Wilcoxon rank sum test, as applicable. A p value <0.05 was considered statistically significant. All the calculations were performed using Epi Info 7.2.

### Ethical considerations

The study was approved by the institutional Ethics Committee.

## RESULTS

Between January 2010 and May 2018, 884 patients

**Table 1.** Baseline characteristics of the population

| Baseline variables | N with T | Definition of cardiotoxicity ACC LVEF >10% | B-31 LVEF≥15% | MD Anderson LVEF not <45% | p= |
|---|---|---|---|---|---|
| Total number of patients/ Ctx patients | 231/150 | 81/231p. (35%) | 45/231 p. (19%) | 24/231 (11%) | |
| Age (years) | 51±11 | 53.3±12 | 54±12 | 57±12 | 0.4 |
| Sex (female) | 100% | 100% | 100% | 100% | |
| Follow-up (months) | 48±12 | 44±18 | 50±20 | 48±20 | 0.12 |
| HR (bpm) | 72±6 | 71±11 | 72±6 | 72±8 | 0.3 |
| SBP (mmHg) | 114±18 | 116±12 | 114±18 | 118±10 | 0.3 |
| DBP (mmHg) | 71±12 | 74±8 | 71±12 | 76±10 | 0.7 |
| History of dyspnea | 0 | 0 | 0 | 0 | |
| BSA (m2) | 1.7±0.11 | 1.68±0.10 | 1.7±0.11 | 1.66±0.11 | 0.55 |
| **Cardiovascular risk factors** | | | | | |
| HT (mmHg) | 42/231 (18%) | 15/81(18%) | 8/45 (17%) | 4/24 (16%) | 0.3 |
| Current smoker | 27/231(12%) | 8/81(10%) | 5/45(11%) | 3/24(12%) | 0.5 |
| Obesity | 35/231(15%) | 10/81 (12%) | 8/45 (17%) | 3/24 (13%) | 0.3 |
| Diabetes mellitus | 14/231(6%) | 5/81(6%) | 2/45(4%) | 2/24(8%) | 0.3 |
| Dyslipidemia | 44/231 (19%) | 14/81 (17%) | 8/45 (17%) | 4/24 (16%) | 0.4 |
| **Previous treatment** | | | | | |
| ACEI | 27/231 (12%) | 6/81 (14%) | 5/45 (11%) | 2/24 (12%) | 0.3 |
| Carvedilol | 14/231(6%) | 8/81 (10%) | 4/45(8%) | 2/24 (8%) | 0.4 |

T: Trastuzumab. ACC: American College of Cardiology. LVEF: Left ventricular ejection fraction. p: patients. HR: Heart rate. bpm: Beats per minute. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. BSA: Body surface area. HT: Hypertension. ACEI: Angiotensin-converting enzyme inhibitor.

**Table 2.** Neoplasm characteristics

| Oncological-related variables | N with T | Definition of cardiotoxicity ACC LVEF >10% | B-31 LVEF≥15% | MD Anderson LVEF not <45% | p= |
|---|---|---|---|---|---|
| Total number of patients/Ctx patients | 231/150 | 81/231p. (35%) | 45/231 p. (19%) | 24/231 (11%) | |
| Age (years) | 51±11 | 53.3±12 | 54±12 | 57±12 | 0.4 |
| Left breast cancer | 118/231(51%) | 39/81(48%) | 22/45(49%) | 12/24(50%) | |
| Right breast cancer | 113/231(49%) | 42/81(52%) | 23/45(41%) | 12/24(50%) | 0.12 |
| Left breast-conserving surgery | 88/118(74%) | 28/39(72%) | 16/22(73%) | 18/24(74%) | 0.3 |
| Right breast-conserving surgery | 78/113(69%) | 26/42(62%) | 15/23(65%) | 16/24(69%) | 0.3 |
| Adriamycin cumulative dose ( mg) | 400.54±68 | 392.44±22 | 411.01±11 | 409.28±33 | 0.7 |
| RT mean heart dose (Gy) | 2.2±0.12 | 2.1±0.10 | 2.0±0.09 | 2.2±0.02 | 0.55 |

ACC: American College of Cardiology. LVEF: Left ventricular ejection fraction. T: Trastuzumab. p: patients. RT: Radiotherapy. Gy: Gray.

with breast cancer were treated in the department of cardio-oncology of our institution; 26% (n=231) of these patients received adjuvant therapy with trastuzumab. The clinical and tumoral characteristics of the population are presented in Tables 1 and 2.

Analysis of the general population treated with trastuzumab: mean age of the female population was 51±11 years. A decline in LVEF >10% occurred in 65% (n=150) of the patients over a mean follow-up of 48±12 months (Table 3).

Echocardiographic variables of cardiotoxicity during follow-up: mean LVEF before treatment was 61±4.7% and at the end of the follow-up period, LVEF had decreased by 9.9±6.9% due to the oncological treatment. Only 45% of patients had complete LVEF recovery at the end of the follow-up period and 27% remained with LVEF <50%. Trastuzumab was temporarily discontinued in 17% (n=39) of patients and was permanently discontinued in 12% (n=28) due to cardiotoxicity (Table 3).

Cardiac therapy due to the presence of cardiotoxicity was prescribed to 54% of the patients but was not tolerated by 10% due to hypotension (Table 3).

The subgroup analysis by tolerated LVEF decline showed that among 65% of patients, 35% developed cardiotoxicity according to the AAC definition, 19%

**Table 3.** Echocardiographic variables and changes during follow-up

| Variables | N with T | Definition of cardiotoxicity ACC LVEF >10% | B-31 LVEF≥15% | MD Anderson LVEF not <45% |
|---|---|---|---|---|
| Total number of number of patients/Ctx patients | 231/105 | 81/231p. (35%) | 45/231p. (19%) | 24/231p. (11%) |
| Baseline LVEF* | 61.3±4.7% | 60±6.6% | 57±12% | 56±7.3% |
| Minimal LVEF with trastuzumab* | 54±7.1% | 48±5.6% | 45.3±5 | 39± |
| Final LVEF at 24 m** | 56.66% | 52±8% | 50±8% | 49±8.2% |
| Months to peak decline | 18±4 m | 20±6m | 29±13m. | 23±15 m. |
| LVEF decline % *** | 9.9±6.9%* | 15.1±4%* | 20.6±4%* | 20,7±5,4%* |
| With total recovery | 104 p (45%) | 33 (41%)* | 19 (42%)* | 11(54%)* |
| Without total recovery | 231 (55%) | 48(59%) | 45(58%) | 13(46%) |
| Final LVEF <50% at 24 months | 63/231(27%) | 27 /81 (33%) | 19/45 (42%) | 10/24 (41%) |
| **Cardiac medication** | | | | |
| Carvedilol | 45 (19%) | 25 (34%) | 18 (40%) | 8 (33%) |
| ACEI | 45 p (19%) | 41 (50%) | 16(35%) | 10 (42%) |
| Both | 37 (16%) | 7 (9%) | 6 (13%) | 4(16%) |
| Intolerance | 22 (9%) | 8(10%) | 5(11%) | 2 (8%) |
| **Trastuzumab discontinuation** | | | | |
| Transient** | 39 (17%)** | 4/81 (4.9%)** | 11 (26%)** | 10 (41%)** |
| Permanent** | 28 (12%)** | 10/81 (8.1%)** | 4 (9%)** | 13 (50%)** |

T: Trastuzumab. ACC: American College of Cardiology. LVEF: Left ventricular ejection fraction. p: patients m: months. ACEI: Angiotensin-converting enzyme inhibitor. * p < 0.004; **<0.0001; *** p < 0.005

according to the B-31 trial and 11% according to the MD Anderson Cancer Center.

ACC criterion: the percent decline in LVEF was significantly greater compared with that of the general population (treated with trastuzumab), (15.1±4% vs. 9.9±7%, p=0.001), with no significant differences in the number of women with LVEF <50% by the end of follow-up (33% vs. 27% p=ns). The need for temporary discontinuation of trastuzumab was significantly lower (5% vs. 17%, p=0.004), with no difference for permanent discontinuation (12%).

Analysis of the B-31 trial and the MD Anderson Cancer Center versus the ACC criteria: The percent decline in LVEF during treatment was higher when the criteria of the B-31 trial and the MD Anderson Cancer Center were used: 20% vs. 20% vs.16% for the ACC criterion (p < 0.04), and more women presented LVEF decline <50% by the end of treatment (42% vs. 41% vs. 33%, p <0.01), and required transient discontinuation (26% vs. 41% vs. 5%, p=0.0001) and permanent discontinuation (9% vs. 50% vs. 8 %, p=0.0001) of trastuzumab.

There were no significant differences in the number of women receiving cardiac therapy among the three groups, and >80% of the patients were medicated (Table 3).

## DISCUSSION

Trastuzumab has opened a new modality of medicine based on the development of target-specific drugs, such as HER2+ breast cancer, which did not have a specific therapy. In 2005 the approval of adjuvant treatment with trastuzumab was a turning point in the treatment of this condition. (4)

Oncology has started a new stage of therapeutic resources, improving breast cancer survival in women by 33% at 3 years with the administration of trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2+ protein that is overexpressed in the tumor cells. (4-6) Between 23% and 30% of women with breast cancer receive this therapy and those who complete treatment with trastuzumab show greater benefit. (10, 11) As cardiotoxicity was reported with the use of trastuzumab in the phase III B-31 trial and in other studies, a standardized protocol for cardiac monitoring was developed to detect trastuzumab-related cardiotoxicity. This protocol established the evaluation of LVEF before treatment and every 3 months to ensure cardiac health outcomes, since initially reported trastuzumab cardiotoxicity was grade III-IV heart failure (HF) in 2.7% of the cases and asymptomatic left ventricular dysfunction (LVD) in 19%. (4) This modality of monitoring improved the final benefit on long-term survival. In a meta-analysis of studies with similar design that included 9,500 age-selected patients without history of cardiovascular disease, it was necessary to treat 40 patients with trastuzumab to save one life at 3 years, 30 patients to generate a case with symptomatic HF and only 5 to develop an asymptomatic LVD. (12, 13)

Thanks to this screening method, the cardiology community replaced endomyocardial biopsy by LVEF monitoring with echocardiography or nuclear medicine. (4, 9, 14) Cardio-oncology centers were created, still scarcely developed, where cardiologists and oncologists could implement this monitoring in the women treated to reduce cardiac morbidity. However, 19 years after the drug was introduced in the community and with more than 690,000 new cases per year of women with HER2+ breast cancer worldwide, publications show that cardiologists did not focus on monitoring LVEF in unselected populations. Instead, they were dedicated to the search of cardiotoxicity predictors by echocardiographic strain rate or troponins, which have an uncertain impact due to the low number of patients reported with these biomarkers worldwide. In addition, the use of cardioprotective premedications to prevent oncological treatment cardiotoxicity has not produced significant clinical outcomes to justify their systematic implementation. (15, 24-26).

Several expert or scientific society guidelines have been published without validating the results in the general population. (6, 8, 9, 14) Most of them have extended the range of LVEF decline produced by trastuzumab due to its potential reversibility or type 2 cardiotoxicity (1, 8, 14) but have not reported the outcomes to support this recommendation.

This study is based on the experience gained over more than 10 years in our cardio-oncology center, which provides a program of care for women with breast cancer, particularly for those treated with trastuzumab and other cardiotoxic drugs requiring cardiac monitoring. Our program is based on a model of care established by oncologists and cardiologists of our institution, consisting in measuring LVEF before treatment and every 3 months during follow-up, and defining cardiotoxicity as a decline in LVEF >10%. (2, 6) Using this value as a criterion of cardiotoxicity, 65% of the population presented a reduction in LVEF >10% and 17% (n=39) met criteria for temporary discontinuation of trastuzumab. A significant finding is that, despite the drug was stopped when LVEF declined >10%, it continued falling in 46% (n=69) of the patients, demonstrating the dynamic toxicity of the drug as a biological phenomenon that depends on each woman and that is not self-limiting or reversible in a high percentage of cases, as it has been postulated. (6, 7, 9, 14)

The recommendation of the ACC is the most appropriate as a result of the balance between considering cardiotoxicity as asymptomatic LVD and trastuzumab discontinuation, and it is also the most conservative in terms of limiting the fall in LVEF compared with the baseline value. Using this limit, 8% of the patients had to stop trastuzumab due to a cardiotoxic event compared with 50% of the patients who discontinued the drug when the absolute lower limit of LVEF was achieved, as recommended by the MD Anderson Cancer Center. (6, 7) Eighty percent of the patients with a reduction in LVEF received cardiac medication, and 10% of the women did not tolerate them due to hypotension.

Treatment for breast cancer HER2+ entails an unavoidable commitment of oncologists and cardiologists to achieve the best possible outcome of the patients with this condition, trying to reach the target of completing the treatment with minimal cardiac morbidity. In an exclusive scenario of cardio-oncology care, similar to the one presented in an unselected population and with long-term follow-up, during adjuvant treatment of breast cancer with trastuzumab, a patient might present a LVEF fall of 9.9±6.9% from the baseline value, 30% of the patients might remain with a LVEF <50% 4 years after ending treatment, 50% might receive carvedilol or angiotensin-converting enzyme inhibitors and only 8% might need to stop trastuzumab temporarily compared with the 20% reported in the literature. (3-5) These figures indicate that cardiac monitoring should be strict, as cardiotoxicity is not a self-limited phenomenon, but depends on each individual patient.

### Study limitations

Although the MD Anderson Cancer Center algorithm tolerates a LVEF fall of 40%, we changed to LVEF not < 45% because none of our patients reached such value. As the study was exclusively performed on women, we cannot extrapolate these results to men treated with trastuzumab. The decision to indicate cardioprotective medication was made by the cardio-oncology committee for each case of LVEF decline. The indication of cardiac medication as well as monitoring at fixed intervals do not allow the evaluation of the actual cardiotoxicity of the drug. None of the patients had to be hospitalized due to HF.

In the current field of oncology, trastuzumab is a pioneer in the development of therapeutics for diseases without treatment and with an impact on survival, confirming a message already provided by adriamycin: the treatment of cancer represents a cost for cardiac health. Women receiving this treatment are exposed to significant cardiotoxicity; thus, the development of new molecules for cancer treatment has, on the one hand, a positive and enthusiastic effect, but, on the other hand, it produces the negative impact of getting used to cardiovascular toxicity as a routine phenomenon. Trastuzumab needs to be monitored for women's health care; strict cardiac and oncologic control should be performed to achieve complete treatment without producing cardiac complications. A multidisciplinary teamwork with a shared understanding of goals is needed for the benefit of these patients.

## CONCLUSIONS

In the population of patients treated with trastuzumab, strict cardiac monitoring revealed a significant LVEF decline in more than 60% of the population by

the end of treatment. It was also seen that trastuzumab-related cardiotoxicity is not self-limited or reversible in a high percentage of patients and requires serial and continuous comparative monitoring. The resulting cardiotoxocity was statistically significant for all the definitions evaluated, and LVEF was < 50% in a high percentage of patients at the end of treatment. In view of this therapeutic scenario, an interdisciplinary team of cardio-oncologists and oncologists should take care of breast cancer patients.

### Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

## REFERENCES


**1.** Debiasi M, Polanczyk CA, Ziegelmann P, Barrios C, Cao H, Dignam JJ. Efficacy of AntiHER2 Agents in Combination With Adjuvant or Neoadjuvant Chemotherapy for Early and Locally Advanced HER2-Positive Breast Cancer Patients: A Network Meta-Analysis. Front Oncol 2018;8:156. Review. http://doi.org/gdk4gb

**2.** Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol 2010;55:213-20. http://doi.org/d8gqmt

**3.** Slamon, DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that over expresses HER2. N Engl J Med 2001;344:783-92. http://doi.org/c4sbf2

**4.** Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-84. http://doi.org/css67s

**5.** Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659-72. http://doi.org/cpxrkk

**6.** Food and Drug Administration. HERCEPTIN (trastuzumab) [package insert]. 2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf. accessed November 15, 2017.

**7.** Yeh E T H: MD Anderson Practices In Onco-Cardiology: https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/cardiology/research.html; Department of Cardiology at The University of Texas MD Anderson Cancer Center, Houston, Texas: 2016.

**8.** Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, JASE 2015;28:1-39.

**9.** Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2014;2:7911-39.

**10.** Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V. Breast Cancer Group: Regímenes con trastuzumab para el cáncer de mama temprano: https://www.cochrane.org/es/CD006243/regimenes-con-trastuzumab-para-el-cancer-de-mama-temprano.

**11.** Gyawali B, Niraula S. Duration of adjuvant trastuzumab in HER2 positive breast cancer: Overall and disease free survival results from meta-analyses of randomized controlled trials. Cancer Treat Rev 2017;60:18-23. http://doi.org/gcm7fr

**12.** Telli ML, Hunt SA , Carlson R W , Guardino AE: Trastuzumab-Related Cardiotoxicity: Calling Into Question the Concept of Reversibility: JCO 2007;25:3525-33.

**13.** De Azambuja E, Ponde N F, Procter M J, Rastogi P: Meta-analysis of the Cardiac Events in the Adjuvant Trastuzumab Trials; Cardio-Oncology Connection 07.16.2018. https://www.medpagetoday.com/clinical-connection/cardio-oncology/74044

**14.** Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R : The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Scientific Document Group. Eur Heart J 2016;37:2768-801. http://doi.org/czgt

**15.** Hare JL, Brown JK, Leano R, Jenkins C, Woodward N, Marwick TH. Use of myocardial deformation imaging to detect preclinical myocardial dysfunction before conventional measures in patients undergoing breast cancer treatment with trastuzumab. Am Heart J 2009;158:294-301. http://doi.org/cnzgxc

**16.** Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol. 2011;107:1375-80. http://doi.org/b4szxp

**17.** Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. Circ Cardiovasc Imaging 2012;5:596-603. http://doi.org/bx88

**18.** Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC, Marwick TH. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. J Am Soc Echocardiogr 2013;26:493-8. http://doi.org/f4xnkq

**19.** Poterucha JT, Kutty S, Lindquist RK, Li L, Eidem BW. Changes in Left Ventricular Longitudinal Strain with Anthracycline Chemotherapy in Adolescents Precede Subsequent Decreased Left Ventricular Ejection Fraction. J Am Soc of Echocardiogr 2012;25:733-40. http://doi.org/czgv

**20.** Sawaya H, Sebag IA, Plana JC, Januzzi J, Ky B, Cohen V. Early Detection and Prediction of Cardiotoxicity in Chemotherapy-Treated Patients. Am J Cardiol 2011;107:1375-80. http://doi.org/b4szxp

**21.** Hare JL, Brown JK, Leano R, Jenkins C, Woodward N, Marwick TH. Use of myocardial deformation imaging to detect preclinical myocardial dysfunction before conventional measures in patients undergoing breast cancer treatment with trastuzumab Am Heart J 2009;158:294-301. http://doi.org/cnzgxc

**22.** Tan TC, Bouras, Sawaya H, Sebag IA, Cohen V, Picard MH. Time Trends of Left Ventricular Ejection Fraction and Myocardial Deformation Indices in a Cohort of Women with Breast Cancer Treated with Anthracyclines, Taxanes, and Trastuzumab J Am Soc Echocardiogr 2015;28:509-14.

**23.** Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol 2014;63:2751-68. http://doi.org/f2skx8

**24.** Liu J, Banchs J, Mousavi N, Plana JC, Scherrer-Crosbie M, Thavendiranathan P, et al. Contemporary Role of Echocardiography for Clinical Decision Making in Patients During and After Cancer Therapy. JACC Cardiovasc Imaging. 2018;11:1122-31.

**25.** Avila MS, Ayub-Ferreira SM, de Barros Wanderley MR Jr, das Dores Cruz F, Gonçalves Brandão SM. Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity: The CECCY Trial. J Am Coll Cardiol 2018;71:2281-90. http://doi.org/gdk8pk

**26.** Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M. Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101-Breast): A Randomized Trial for the Prevention of Trastuzumab-Associated Cardiotoxicity. J Clin Oncol 2017;35:870-7. http://doi.org/f9t6qq