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Trastuzumab-induced cardiotoxicity in patients with HER-2 positive breast cancer

Cardiotoxicidade induzida por trastuzumabe em pacientes com câncer de mama HER-2 positivo

Cardiotoxicidad inducida por trastuzumab en pacientes con cáncer de mama HER-2 positivo

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Abstract
Introduction: Trastuzumab is a humanized monoclonal antibody precursor of HER-2 positive inhibitors. Cardiotoxicity is one of the most important adverse reactions from a clinical point of view, associated with trastuzumab use. Studies show that 12.6% of patients treated with the HER-2 inhibitor had cardiotoxicity. Objective: To identify the presence of trastuzumab-induced cardiotoxicity in patients with HER-2 positive breast cancer. Method: The study was cross-sectional and retrospective, carried out in a philanthropic cancer hospital in the city of Salvador, Bahia, Brazil. Data were collected through electronic medical records. Patients with a diagnosis of HER-2 positive breast cancer, female, over 18 years of age, who used trastuzumab from September to December 2020, were included in the study. The variables analyzed were: age, comorbidity, combination of chemotherapy (monotherapy, associated) and type of therapy (adjuvant, neoadjuvant). Results: 159 patients were included in the study. 10 (6%) of them had cardiotoxicity during treatment, most of them aged between 40-59 years (70%). Regarding comorbidities, 6 (60%) patients were hypertensive. 7 of the patients (70%) were on trastuzumab monotherapy. All patients use transtuzumab as an adjuvant treatment. Conclusion: In the present study, it was possible to identify the presence of cardiotoxicity in patients who used trastuzumab. Thus, it is essential to pay special attention to the monitoring of cardiac function, as well as the clinical follow-up of these patients to identify, early on, signs and symptoms presented and thus prevent possible damage. In future research, new monitoring parameters should be studied to identify trastuzumab-induced cardiotoxicity early.
Keywords: Breast neoplasm; Trastuzumab; Cardiotoxicity; Oncology.

Resumo
Introdução: Trastuzumabe é um anticorpo monoclonal humanizado precursor de inibidores HER-2 positivos. A cardiotoxicidade é uma das reações adversas mais importantes do ponto de vista clínico, associada ao uso de trastuzumabe. Estudos mostram que 12,6% dos pacientes tratados com o inibidor de HER-2 apresentaram cardiotoxicidade. Objetivo: Identificar a presença de cardiotoxicidade induzida por trastuzumabe em pacientes com câncer de mama HER-2 positivo. Método: O estudo foi transversal e retrospectivo, realizado em um hospital filantrópico oncológico da cidade de Salvador, Bahia, Brasil. Os dados foram coletados por meio de prontuários eletrônicos. Foram incluídos no estudo pacientes com diagnóstico de câncer de mama HER-2 positivo, do sexo feminino, maiores de 18 anos, que utilizaram trastuzumabe no período de setembro a dezembro de 2020. As variáveis analisadas foram: idade, comorbidade, combinação de quimioterapia (monoterapia, associada) e tipo de terapia

(adjuvante, neoadjuvante). Resultados: 159 pacientes foram incluídas no estudo. 10 (6%) deles apresentaram cardiotoxicidade durante o tratamento, a maioria com idade entre 40-59 anos (70%). Quanto às comorbidades, 6 (60%) pacientes eram hipertensos. 7 dos pacientes (70%) estavam em monoterapia com trastuzumabe. Todos os pacientes usaram trastuzumabe como tratamento adjuvante. Conclusão: No presente estudo, foi possível identificar a presença de cardiotoxicidade em pacientes que utilizaram trastuzumabe. Assim, é fundamental uma atenção especial ao monitoramento da função cardíaca, bem como ao acompanhamento clínico desses pacientes para identificar, precocemente, os sinais e sintomas apresentados e, assim, prevenir possíveis danos. Em pesquisas futuras, novos parâmetros de monitoramento devem ser estudados para identificar precocemente a cardiotoxicidade induzida pelo trastuzumabe.
Palavras-chave: Neoplasia da mama; Trastuzumabe; Cardiotoxicidade; Oncologia.

Resumen
Introducción: Trastuzumab es un anticuerpo monoclonal humanizado precursor de los inhibidores de HER-2 positivos. La cardiotoxicidad es una de las reacciones adversas clínicamente más importantes asociadas con el uso de trastuzumab. Los estudios muestran que el 12,6% de los pacientes tratados con el inhibidor de HER-2 tenían cardiotoxicidad. Objetivo: Identificar la presencia de cardiotoxicidad inducida por trastuzumab en pacientes con cáncer de mama HER-2 positivo. Método: El estudio fue transversal y retrospectivo, realizado en un hospital oncológico filantrópico de la ciudad de Salvador, Bahía, Brasil. Los datos fueron recolectados a través de historias clínicas electrónicas. Se incluyeron en el estudio pacientes con diagnóstico de cáncer de mama HER-2 positivo, sexo femenino, mayores de 18 años, que usaron trastuzumab de septiembre a diciembre de 2020. Las variables analizadas fueron: edad, comorbilidad, combinación de quimioterapia (monoterapia, combinación) y tipo de tratamiento (adyuvante, neoadyuvante). Resultados: 159 pacientes fueron incluidos en el estudio. 10 (6%) de ellos presentaron cardiotoxicidad durante el tratamiento, la mayoría con edades entre 40-59 años (70%). En cuanto a las comorbilidades, 6 (60%) pacientes eran hipertensos. 7 de los pacientes (70%) estaban en monoterapia con trastuzumab. Todos los pacientes utilizaron trastuzumab como tratamiento adyuvante. Conclusión: En el presente estudio fue posible identificar la presencia de cardiotoxicidad en pacientes que utilizaron trastuzumab. Por ello, es fundamental prestar especial atención a la monitorización de la función cardiaca, así como al seguimiento clínico de estos pacientes para identificar precozmente los signos y síntomas que presentan y así prevenir posibles daños. En futuras investigaciones, se deben estudiar nuevos parámetros de monitoreo para identificar la cardiotoxicidad temprana inducida por trastuzumab.
Palabras clave: Neoplasia de mama; Trastuzumab; Cardiotoxicidad; Oncología.

1. Introduction

Breast cancer ranks first in both incidence and mortality among women (Do et al., 2021). Breast cancer can be classified according to its histological and molecular characteristic. Each subclassification expresses a behavior with distinct particularities of cancer, and it is important to understand them to direct a more assertive treatment (Tsang & Tse, 2020). Overexpression of HER-2 receptors is a molecular classification that affects about 15 to 25% of the total number of breast cancer cases and is characterized by a poor prognosis and aggressive proliferation (Arias et al., 2017). It is the second most relevant target in the treatment of breast cancer, behind treatments aimed at estrogen receptors (Piccart et al., 2021).

Trastuzumab is a humanized monoclonal antibody precursor of HER-2 positive inhibitors (Bradley et al., 2021). It was approved in 1998 and was the first targeted therapy for breast cancer approved by the FDA (Food and Drug Administration) (DuMond et al., 2021). The mechanism consists of the binding of these receptors, causing the growth of this tumor to stabilize (Buzatto et al., 2017).

Drugs agents used in the treatment of breast cancer can be classified as type I and type II. They are classified as type I when they cause irreversible damage to cardiac cells. This category includes anthracyclines and alkylating agents. Type II drugs, such as trastuzumab, cause reversible damage (Geralda et al., 2021; Negishi et al., 2018).

Cardiotoxicity can be identified and confirmed through some criteria, such as: cardiomyopathy with reduced left ventricular ejection fraction (LVEF) measurement; symptoms and signs related to heart failure; reduction in LVEF compared to baseline from at least 5% to less than 55%, with concomitant signs or symptoms of heart failure, or reduction in LVEF in the range of at least 10% (Pina et al., 2019; Siddiqui et al., 2022). The possible pathologies associated with the use of trastuzumab

are related to the development of cardiac arrhythmias, congestive heart failure, angioedema and left ventricular diastolic diameter (Esteva et al., 2019; Nemeth et al., 2017)

Left ventricular ejection fraction (LVEF) is an important indicator in monitoring cardiotoxicity (Oikonomou et al., 2019). Before complete ventricular deterioration actually occurs, left ventricular diastolic involvement occurs, which can be measured by echocardiography from the LVEF value (Barron et al., 2019; Pereira Vaz et al., 2016).

Monitoring is done before starting treatment to identify possible cardiac pathologies or predisposition, during treatment every three months and after completion of treatment for two years, every six months (Curigliano et al., 2019). Patients who experience cardiac toxicity after the use of trastuzumab present an asymptomatic reduction in LVEF, being treated with the suspension of the antibody and initiation of standard treatment for left ventricular dysfunction (Eiger et al., 2020; Florido et al., 2017).

The patient is monitored until recovery of ventricular function. If this function is recovered, trastuzumab can be reintroduced. If the patient, after reintroduction, presents ventricular alterations again, the drug should be definitively discontinued (Mohan et al., 2018). Thus, it is extremely important to know the incidence of patients who developed cardiotoxicity, as well as their clinical characteristics to provide the development of strategies related to their monitoring and management in order to prevent possible damage.

The aim of the present study was to determine the incidence of cardiotoxicity in HER-2 positive breast cancer patients treated with trastuzumab in a philanthropic cancer hospital in the city of Salvador, Bahia, Brazil.

2. Methodology

A cross-sectional, retrospective and descriptive study was carried out in patients diagnosed with HER-2 positive breast cancer who used trastuzumab as part of their treatment from September to December 2020 and presented cardiotoxicity as an adverse reaction.

The data necessary for the research were collected through the analysis of electronic medical records, extracting information related to the sociodemographic and clinical characteristics of the patients, such as: age, comorbidity, chemotherapy combination (monotherapy, associated), type of therapy (adjuvant, neoadjuvant) and drug-related adverse reaction, such as cardiotoxicity, determined based on a fall in ejection fraction by 10% of the original value or based on a fall in the ejection fraction below the normal value. Patients with a diagnosis of HER-2 positive breast cancer, female and over 18 years of age, were included in the study. Male patients with breast cancer were excluded. The study was carried out at a philanthropic cancer hospital in the city of Salvador, Bahia, Brazil.

From September to December 2020, 175 patients diagnosed with HER-2 positive breast cancer were using trastuzumab. Of these, 16 were excluded from the study due to insufficient information in the electronic medical record. Thus, 159 patients were included in the research. The present study was approved by the Ethics and Research Committee of the Universidade do Estado da Bahia (UNEB), with opinion number: 4,958,225.

3. Results

Regarding the participants of the present study, it was possible to identify sociodemographic and clinical characteristics that contribute to and increase the probability of developing an adverse reaction related to cardiotoxicity. 52% were aged between 40 and 59 years, as shown in Table 1. Among the comorbidities, 29% had systemic arterial hypertension and 8% had type 2 diabetes mellitus. 62% of the patients underwent treatment in the monotherapy modality and 38% with therapy that combined trastuzumab with other chemotherapeutic agentes.

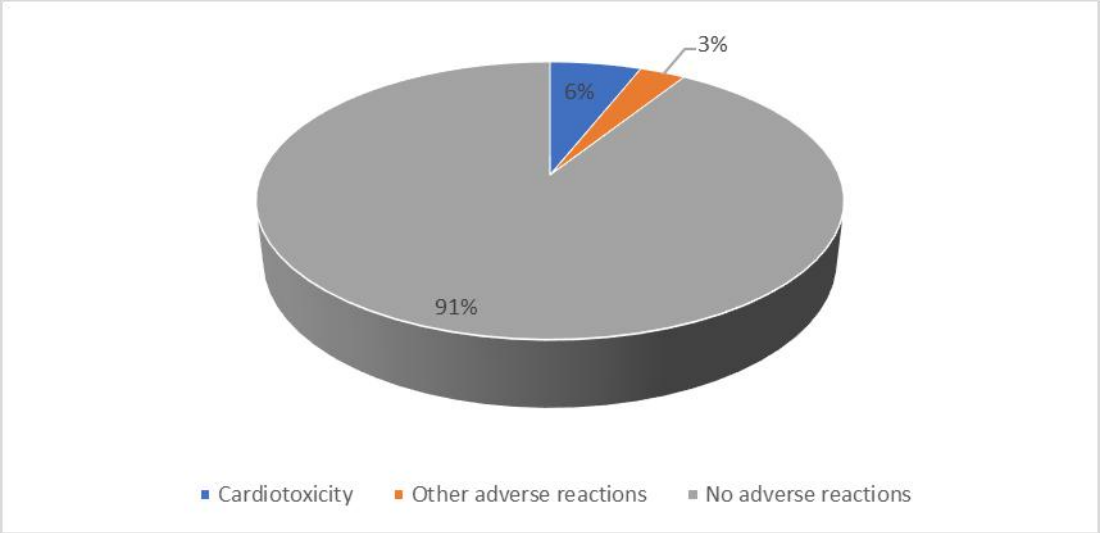
Table 1 – Characteristics of patients who used trastuzumab in a philanthropic oncology hospital in the city of Salvador, Bahia, Brazil.

VARIABLES	*n*	*%*
AGE		
≥60	56	35
40-59	82	52
<40	21	13
COMORBIDITY		
Hypertension	46	29
Diabetes Mellitus	12	8
Other Comorbidities	5	3
No comorbidities	95	60
THERAPY MODALITY		
Monotherapy	98	62
Combination	61	38

Source: Authors.

As shown in Graphic 1, 9% of the patients had some type of adverse reaction. 6% of these had cardiac toxicity. 3% had other adverse reactions such as chills, breast redness and headache.

Graphic 1 - Adverse reactions presented by patients who used trastuzumab in a philanthropic cancer hospital in the city of Salvador, Bahia, Brazil.



Source: Authors.

Among the patients who presented cardiotoxicity as an adverse reaction, 70% were aged between 40-59 years, as can be seen in Table 2. Regarding comorbidities, 60% had systemic arterial hypertension and 20% had diabetes mellitus. Regarding chemotherapy regimens, 70% were on monotherapy with trastuzumab and 30% in association of monoclonal antibody with other chemotherapeutic agents. Regarding the type of therapy, 100% were in adjuvant therapy.

Table 2 - Characteristics of patients who presented cardiotoxicity after the use of trastuzumab in a philanthropic oncology hospital in the city of Salvador, Bahia, Brazil.

VARIABLES	*n*	*%*
AGE		
≥60	3	30
40-59	7	70
COMORBIDITY		
Hypertension	6	60
Diabetes Mellitus	2	20
No comorbidities	2	20
COMBINATION		
Monotherapy	7	70
Associate	3	30
TYPE OF THERAPY		
Adjuvant	10	100

Source: Authors.

4. Discussion

Cardiotoxicity is one of the most important adverse reactions associated with the use of trastuzumab. In the respective article, 6% of the patients had cardiotoxicity associated with the use of trastuzumab, as shown in graph 1. It is an outcome with a lower value than that presented in a study carried out in the Netherlands, in which, among the 230 participants diagnosed with HER-2 breast cancer positive and who received treatment with trastuzumab, 12.6% had cardiotoxicity (Seferina et al., 2016). Similarly, in a study of 160 patients conducted in a hospital in Toronto, Canada, 21.3% had cardiotoxicity (Tang et al., 2017).

This potential to develop cardiotoxicity increases when patients undergo protocols that use anthracyclines and later use HER-2 inhibitors such as trastuzumab. Studies show that patients previously exposed to anthracycline were 1.6% more likely to develop cardiotoxicity compared to unexposed patients. Protocols that do not use anthracyclines have lower rates of cardiac dysfunction when compared to regimens that use trastuzumab plus anthracycline (El-Sherbeny et al., 2019). As shown in the BCIRG-006 study, in which the rates related to congestive heart failure and cardiac dysfunction were relatively higher in the group of patients who received a protocol that included doxorubicin as AC-T, compared to patients who received regimens that did not include anthracyclines (Slamon et al., 2011).

Among the patients who presented cardiotoxicity, it was observed that most of the patients used the classic treatment in monotherapy, as shown by the classic treatment protocols in Table 1. The result can be explained by the fact that the majority of the patients of the treatment containing anthracycline (Yang et al., 2022). Doxorubicin toxicity has a cumulative characteristic. Therefore, the later use of trastuzumab would increase its cardiotoxic potential, as both alone have the ability to trigger cardiac toxicity (Gabani et al., 2021).

According to the literature, some risk factors may increase the likelihood of developing cardiotoxicity, such as age over 50 years, the presence of comorbidities such as hypertension and previous use of anthracyclines (Bradley et al., 2021). The Brazilian Cardio-Oncology Guideline 2020 also adds to these factors the combined treatment with trastuzumab and anthracyclines. This can be seen in the present study, where the majority of patients who developed cardiotoxicity were aged between 40-59 years and had hypertension as a comorbidity (Koulaouzidis et al., 2021).

Thus, patients using trastuzumab should be monitored to identify possible complications generated by its use. This monitoring should be done: before the start of treatment, to identify possible pathologies or predisposition to cardiac toxicity; during treatment, every three months, to identify possible toxicities generated during treatment; and after the end of treatment,

for two years, every 6 months (Adão et al., 2013).

5. Conclusion

In the present study, it was possible to identify the presence of cardiotoxicity in patients who used trastuzumab. Being evidenced 6% of the patients diagnosed with breast cancer and who used the antibody. It is worth mentioning that there are characteristics that increase the probability of developing such a reaction, such as age, presence of comorbidities and previous exposure to chemotherapy.

Thus, it is essential to pay special attention to the monitoring of cardiac function, as well as the clinical follow-up of these patients to identify, early on, the signs and symptoms presented and, thus, prevent possible damage. In future research, new monitoring parameters should be studied to identify early trastuzumab-induced cardiotoxicity.

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