The Importance of Early Monitoring and Identification of Cardiotoxicity of Trastuzumab Treatment in Breast Cancer: Case Report

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A Importância do Monitoramento e da Identificação Precoce de Cardiotoxicidade do Tratamento com Trastuzumabe no Câncer de Mama: Relato de Caso

La Importancia del Monitoreo y de la Identificación Temprano de la Cardiotoxicidad del Tratamiento con Trastuzumab en el Cáncer de Mama: Informe de Caso

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Abstract

Introduction: Breast cancer represents the most common neoplasm among women, with elevated morbimortality. With the appearance of new drugs, there has been an increase of global survival; however, trastuzumab, a monoclonal antibody used in the treatment, may promote cardiotoxicity that should be evaluated and monitored during treatment. The aim of this article is to describe a case report of a patient presenting trastuzumab-associated cardiotoxicity and the importance of monitoring and early identification of cardiotoxicity through echocardiography (ECHO). **Case report:** A 63-year-old female patient, hypertensive, obese, with breast cancer, presented trastuzumab-associated cardiotoxicity, reduced left ventricular ejection fraction (LVEF), who developed diabetes after the treatment. The patient underwent regular echocardiography follow-up during treatment and this process was essential for early detection and appropriate management of trastuzumab-associated cardiotoxicity. An algorithm was used to determine the causality. **Conclusion:** This study shows the importance of LVEF follow-up with ECHO in patients undergoing cardiotoxic chemotherapy, and the monitoring of possible metabolic changes after oncologic treatment.

Key words: Cardiotoxicity; Breast Neoplasms; Trastuzumab; Drug Therapy.

Resumo

Introdução: O câncer de mama representa a neoplasia mais frequente entre as mulheres, com elevada morbimortalidade. Com o advento de novos medicamentos, houve um aumento na sobrevida global; entretanto, o trastuzumabe, um anticorpo monoclonal utilizado no tratamento, pode promover cardiotoxicidade, que deve ser avaliada e monitorada durante o tratamento. O objetivo deste artigo é descrever um relato de caso de paciente que apresentou cardiotoxicidade associada ao uso de trastuzumabe e a importância do monitoramento e da identificação precoce da cardiotoxicidade por meio do monitoramento pelo ecocardiograma (ECO). **Relato do caso**: Paciente, sexo feminino, 63 anos, hipertensa, obesa, com câncer de mama, apresentou cardiotoxicidade associada ao uso de trastuzumabe, com redução da fração de ejeção do ventrículo esquerdo (FEVE) e desenvolveu diabetes após o tratamento. A paciente fez acompanhamento regular pelo ECO durante o tratamento, tendo sido esse processo fundamental para a detecção precoce e o manejo adequado da cardiotoxicidade associada ao uso do trastuzumabe. Foi utilizado um algoritmo na determinação da causalidade. **Conclusão**: Este estudo mostra a importância do acompanhamento da FEVE pelo ECO em pacientes submetidas à quimioterapia cardiotóxica e do monitoramento de possíveis alterações metabólicas após o tratamento oncológico.

Palavras-chave: Cardiotoxicidade, Neoplasias da Mama; Trastuzumab; Tratamento Farmacológico.

Resumen

Introducción: El cáncer de mama representa el cáncer más común entre las mujeres, con alta morbilidad y mortalidad. Con el advenimiento de nuevos medicamentos, ha habido un aumento en la supervivencia general, sin embargo, trastuzumab, un anticuerpo monoclonal utilizado en el tratamiento, puede promover la cardiotoxicidad, que debe evaluarse y monitorearse durante el tratamiento. El objetivo de este trabajo es describir un informe de caso de un paciente que presenta cardiotoxicidad asociada con el uso de trastuzumab y la importancia del monitoreo y la identificación temprana de la cardiotoxicidad a través del monitoreo ecocardiográfico (ECHO). **Relato del caso:** Una paciente de 63 años, hipertensa, obesa, con cáncer de mama, tenía cardiotoxicidad asociada con trastuzumab, fracción de eyección ventricular izquierda (FEVI) reducida y diabetes después del tratamiento. El paciente se sometió a un seguimiento ecocardiográfico regular durante el tratamiento y fue el proceso fundamental para la detección temprana y el manejo adecuado de la cardiotoxicidad asociada con el uso de trastuzumab. Se utilizó un algoritmo para determinar la causalidad. **Conclusión:** Este estudio muestra la importancia del seguimiento ECHO de la FEVI en pacientes sometidos a quimioterapia cardiotóxica, y el monitoreo de posibles cambios metabólicos después del tratamiento del cáncer.

Palabras clave: Cardiotoxicidad; Neoplasias de la Mama; Trastuzumab; Tratamiento Farmacológico.

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INTRODUCTION

Breast cancer is the most frequent neoplasm among women in the Western world and in Brazil, where new 59.700 breast cancer cases are anticipated for each year of 2018-2019, with estimated risk of 56.33 cases for every 100 thousand women, representing the main cause of death by cancer in women[1].

The appearance of new drugs for breast cancer treatment lead to the extension of the global survival, with emphasis to trastuzumab, a monoclonal antibody utilized in breast cancer HER2 positive, which significantly increased the survival; however, patients treated with trastuzumab can suffer cardiac dysfunction[2]. This toxicity is frequently characterized by an asymptomatic reduction of the left ventricular ejection fraction (LVEF)[2].

Cardiotoxicity represents one of the most feared complications of the cancer treatment, and cardiac insufficiency with ventricular dysfunction stands out[2,3]. Cardiotoxicity according to LVEF can be measured by several methods and represents a parameter utilized to verify the myocardial injury of the chemotherapeutics[3].

The objective of this article is to describe a case report of a patient who presented reduction of LVEF and emphasize the relevance of regular follow up of LVEF with echocardiogram (ECHO) for early detection of cardiotoxicity associated to trastuzumab in patients with breast cancer.

CASE REPORT

Female, 63 years old, brown, hypertensive, using captopril and hydrochlorothiazide, obese grade I, tobacco addicted, sought for medical consultation in 2015, complaining of nodule in the left breast. In May 2015, a histopathological test revealed infiltrating ductal carcinoma in the left breast, segmentectomy in June 2015 and six cycles of fluorouracil, doxorubicin and cyclophosphamide (FAC). From April to June 2016, underwent radiotherapy (50 Gy) in the left supraclavicular fossa. Initiated tamoxifen in August 2016 and trastuzumab isolated in November of the same year. Did ECHO prior to trastuzumab, presenting LVEF equal to 68%, and normal echocardiogram. After the third cycle of trastuzumab, in February 2017, the patient went to the emergency with progressive dyspnea, fatigue at small efforts and dizziness. She remained hospitalized for five days and did a new ECHO, presenting moderate global systolic dysfunction of the left ventricle and LVEF equal to 44%. Initiated treatment with furosemide, spironolactone, amlodipine, acetylsalicylic acid, carvedilol and kept captopril. Echo Doppler, after one month, revealed important moderate dysfunction of the left ventricle and LVEF equal to 38%. Trastuzumab was discontinued due to cardiac insufficiency and the patient was referred to the cardiologist. After 2017, the patient developed *diabetes mellitus* and initiated metformin. The ECHO of 2018 revealed diastolic dysfunction of the left ventricle grade I with increase of pressures of the left atrium and LVEF equal to 56%. In November 2019, the patient was well and improved the cardiac insufficiency. The patient is under follow up with Clinical Oncology and Nutrition.

The Institutional Review Board approved the report on February 14, 2019, number CAAE: 98429018.0.0000.5243. The patient read and signed the Informed Consent Form.

DISCUSSION

The initial evaluation revealed a patient with multiple previous risk factors as: gender (female), older than 60 years, arterial hypertension, obesity grade I, previous use of anthracyclines (doxorubicin), radiotherapy ≥50 Gy and tobacco addiction[4]. Developed diastolic dysfunction of the left ventricle and reduction of LVEF after chemotherapy, showing the importance of the stratification of the initial risk and serial follow up of ECHO for early identification of cardiotoxicity[4].

Some authors suggest the use of cardioprotective medications, but there are not yet safe evidences that show the benefit of the cardioprotective pharmacologic treatment[5].

Cardiovascular reactions, as ventricular dysfunction, reduction of LVEF, progressive dysfunction, fatigue at small efforts and dizziness were evaluated to determine the causality by the algorithm of Naranjo[6], considered possible for trastuzumab and doubtful for doxorubicin. According to the Guide of Notification of Adverse Reactions of the Brazilian Society of Oncology Pharmacists (SOBRAFO)[7], the reactions were considered severe.

Further to the score evaluation, the patient recovered LVEF and improved her clinical condition, which matches the cardiotoxicity type II assigned to trastuzumab, where the damage to the myocardial is reversible[3].

As proposed by some authors, patients during the treatment with trastuzumab should go through an initial assessment for stratification of risk factors and LVEF evaluation[3,8].

Although there are different definitions for the diagnosis of the ventricular dysfunction associated to cancer treatment, one of the most utilized definitions is the reduction of LVEF below 53% or reduction of 10% of the baseline value, with or without symptoms and repeating the test two or three weeks later[4]. Pursuant to the

Brazilian Guideline of Cardio-Oncology of the Brazilian Society of Cardiology, the ventricular dysfunction of LVEF represents a value under 55% or reduction of 10% to 20% or symptomatic cardiac insufficiency[3].

In 2017, the Brazilian National Health Surveillance Agency (ANVISA) issued a note about the importance of cardiac monitoring during treatment with trastuzumab to reduce the frequency and severity of left ventricular dysfunction and congestive cardiac insufficiency[9].

In this note the authors suggest that cardiac evaluations should be done in the beginning of the treatment and repeated every three weeks during the treatment and, in case of reduction of LVEF in ten percentage points or below 50% of the baseline test, the treatment with trastuzumab must be discontinued and LVEF evaluated within nearly three weeks[9]. Anthracyclines and trastuzumab should not be administered concomitantly with the adjuvant treatment of breast cancer according to the recommendations[9].

For patients who used anthracyclines and trastuzumab, additional monitoring is recommended annually for until five years from the last administration of the drug, reinforcing the evaluation of LVEF as required method for cardiac monitoring[9].

The case report is described in details in Figure 1 through a timeline since the diagnosis of breast cancer in 2015, until follow up by Clinical Oncology and Nutrition in 2019.

The regular follow up of LVEF by the patient complied with the recommendations of the literature; however, the evaluation after three months occurred because of worsening of the patient clinical status who sought for emergency services. The ideal would be to follow up LVEF after three months regularly and avoid cardiovascular complications[3].

Although there are in the literature other predictive methods of cardiotoxicity, regular evaluation of LVEF through ECHO represents a safe, easily applicable, low-cost method that can help the monitoring of patients in treatment with cardiotoxic drugs as trastuzumab[8].

The patient developed also *diabetes mellitus* after breast cancer treatment, which may suggest an association between the use of tamoxifen and the appearance of metabolic alterations[5]. Tamoxifen is associated to changes of the lipid profile as reduction of the total cholesterol and increase of triglycerides[5].

Tamoxifen can increase the incidence of *diabetes mellitus* by the inhibitor effect of the estrogen[10]. In a study involving 14,360 patients, breast cancer survivors, older than 65 years, 10% of the patients developed *diabetes mellitus* along 5.2 years follow up, indicating the necessity of monitoring and counseling for *diabetes mellitus* prevention of patients with breast cancer who received treatment with tamoxifen[10].

CONCLUSION

The case reported showed the importance of follow up with ECHO in patients submitted to cardiotoxic treatment. The use of algorithms may contribute to

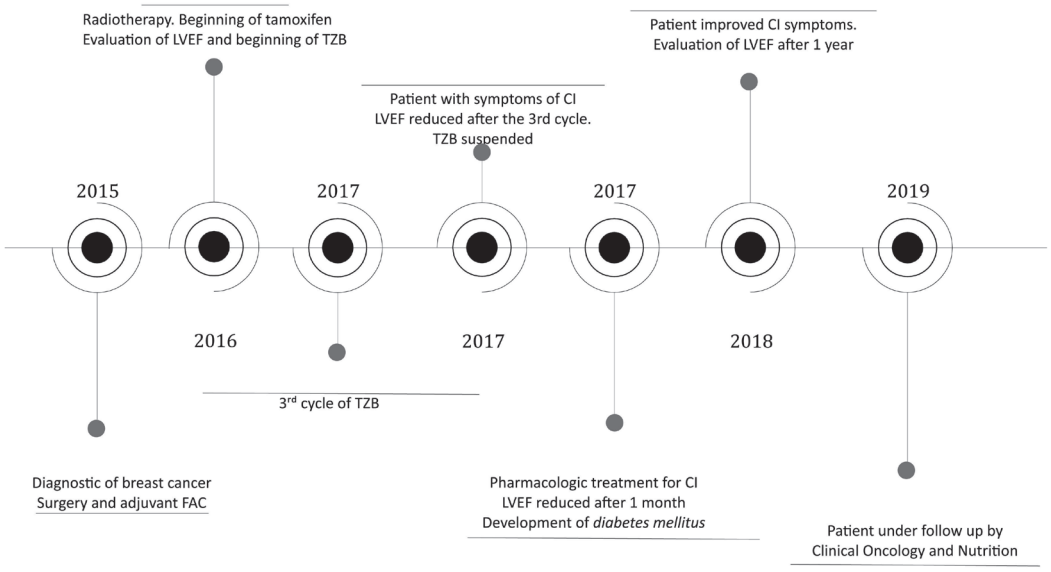

Figure 1. Timeline for treatment and follow up of cardiotoxicity of the clinicl case

Captions: FAC: fluorouracil, doxorubicin and cyclophosphamide; LVEF: reduced left ventricular ejection fraction ; CI: cardiac insufficiency; TZB: trastuzumab.

determine the causality of cardiovascular reactions. Monitoring and counseling to prevent *diabetes mellitus* in patients with breast cancer treated with tamoxifen should be encouraged. Monitoring and early detection of cardiotoxicity are essential to promote the precocious identification for the cardiologist and avoid cardiovascular complications.

CONTRIBUTIONS

Patricia Marques Soares Valente, Wolney de Andrade Martins and Selma Rodrigues de Castilho contributed substantially for the conception, planning, analysis and interpretation of the data, wording, critical review and elaboration of the final version. Eduardo Pinho Braga, Thamires Lopes da Silva, Thamires Ferreira Neves and Walter Claudino Pires de Souza contributed substantially for the analysis and interpretation of the data. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

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REFERENCES

1. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2018: incidência de câncer no Brasil. [Internet]. Rio de Janeiro: INCA; 2019. [acesso 2019 ago. 10]. Disponível em: https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//estimativa-incidencia-de-cancer-no-brasil-2018.pdf
2. Adão R, Keulenaer G, Leite-Moreira A, et al. Cardiotoxicidade associada à terapêutica oncológica: mecanismos fisiopatológicos e estratégias de prevenção. Rev Port Cardiol. 2013;32(5):395-409.doi: https://doi.org/10.1016/j.repc.2012.11.002
3. Kalil Filho R, Hajjar LA, Bacal F, et al. I Diretriz Brasileira de Cardio-Oncologia da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol. 2011;96(2 Supl 1):1-52.
4. Plana JC, Galderisi M, Barac A, 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;27(9):911-39. doi: https://doi.org/10.1016/j.echo.2014.07.012
5. Leite AM, Macedo AVS, Jorge AJL, et al. Terapia antiplaquetária em pacientes com câncer de mama em uso de terapia hormonal: mitos, evidências e potencialidades – Revisão Sistemática. Arq Bras Cardiol. 2018;111(2):205-12. doi: http://dx.doi.org/10.5935/abc.20180138
6. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45. doi: https://doi.org/10.1038/clpt.1981.154
7. Sociedade Brasileira de Farmacêuticos em Oncologia; Agência Nacional de Vigilância Sanitária. Guia para notificação de reações adversas em oncologia. 2. ed. São Paulo: Conectfarma Publicações Científicas; 2011.
8. Ribeiro ML, Jorge AJL, Nacif MS, et al. Detecção precoce e monitoramento da disfunção ventricular esquerda secundária à quimioterapia do câncer pelos métodos de imagem. Arq Bras Cardiol. 2019;112(3):309-16. doi:http://dx.doi.org/10.5935/abc.20190022
9. Anvisa: Agência Nacional de Vigilância Sanitária [Internet]. Brasília, DF: Anvisa; [2000]. Comunicado do Serviço de Informações Rocher, recomendações de monitoramento cardíaco durante o tratamento com Herceptin* (trastuzumab) para redução da frequência e severidade de disfunção ventricular esquerda e insuficiência cardíaca congestiva (ICC); 2017 jun. 12 [acesso 2019 ago. 10]; [3 telas]. Disponível em: http://portal.anvisa.gov.br/cartas-aos-profissionais-de-saude/-/asset_publisher/6Qk8g2SPhy9v/document/id/3522820/contato
10. Lipscombe LL, Fischer HD, Yun L, et al. Association between tamoxifen treatment and diabetes: a population-based study. Cancer. 2012;118(10):2615-22. doi:https://doi.org/10.1002/cncr.26559

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