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Case Report,

Pertuzumab-Related Cardiotoxicity: A Case Report

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Abstract
About 20% of patients with breast cancer overexpress or have amplification of the HER-2 oncogene, and the advent of anti-HER2 therapy has changed the natural history of the disease. Cardiotoxicity resulting from treatment with dual anti-HER2 blockade is a matter of considerable debate. Trastuzumab-related cardiac dysfunction is well recognized, but the cardiotoxic effect of pertuzumab has so far been less documented. We report a case of pertuzumab-related cardiotoxicity in the treatment of a young patient with metastatic HER2-positive breast cancer. The identification of such an adverse effect and the multidisciplinary management allowed us to safely maintain single anti-HER2 blockade with trastuzumab, which provided the patient with a good result in terms of oncologic disease control. This case illustrates that undesirable pertuzumab-related effects on the cardiovascular system may occur and require early identification, adequate multidisciplinary management, and better understanding of its safety profile.

Keywords: breast cancer, treatment, heart failure, ventricular dysfunction, cardiotoxicity

Introduction:
Breast cancer is the most diagnosed neoplasm and the leading cause of cancer death in women. For patients with human epidermal growth factor receptor 2 (HER2)-positive disease, the wide availability of several agents that target the HER2 receptor has resulted in improved survival over the past few decades. However, improved results have increased the need for understanding adverse events associated with treatment, with cardiotoxicity as a major cause of concern.

Pertuzumab has improved patient outcomes when given in combination with trastuzumab and chemotherapy in the early[1] and metastatic setting.[2,3] The cardiotoxicity of trastuzumab is well recognized in the literature, but the cardiotoxic effect of pertuzumab has so far been less documented.[4] We report a case of documented pertuzumab-related cardiotoxicity in the treatment of metastatic HER2-positive breast cancer.

Case Report:
A 36-year-old black woman was diagnosed with invasive ductal carcinoma of the right breast in 2011. Pathology characteristics revealed a grade 3 tumor, hormone receptor-positive, with overexpression of HER2 (immunohistochemical score of 3+) and 40% Ki67 positivity. Partial mastectomy with sentinel lymph node biopsy (pT1cpN0) was performed in November 2011, followed by adjuvant chemotherapy (doxorubicin + cyclophosphamide) and radiation therapy. Administration of adjuvant tamoxifen was started in December 2012. In August 2016, she developed metastasis to the lung, bone, and liver and started first-line metastatic systemic therapy with docetaxel and zoledronic acid. Because of a delay in the national coverage and access to dual anti-HER2 blockade in Brazil, only in July 2017 the patient was able to start dual anti-HER2 blockade with trastuzumab and pertuzumab combined with

endocrine therapy (anastrozole) and inhibition of ovarian function with leuprorelin.

After starting dual blockade, she developed important cardiac toxicity, with a reduction in ejection fraction from 55% to 31% (Figure 1), evolving to symptomatic acute pulmonary edema, requiring hospitalization for management. During hospitalization, the patient was seen by the oncology and cardiology department, and treatment with parenteral vasodilator (sodium nitroprusside) and intravenous furosemide was started. At hospital discharge, the patient was instructed to use the following medications: carvedilol, enalapril, spironolactone, isosorbide dinitrate, hydralazine, furosemide and digoxin. Dual blockade was then discontinued, and only anastrozole was maintained. The patient was followed by the cardiology team every 2 months, with periodic evaluation of cardiac function by echocardiogram. In April 2018, due to recovery of cardiac function, the patient was re-exposed to dual anti-HER2 blockade. The patient again developed cardiotoxicity, requiring the discontinuation of cancer treatment, with subsequent improvement.

In September 2018, after recovery of cardiac function, we decided, in multidisciplinary tumor board discussion together with the cardio-oncology team, to discontinue pertuzumab and restart trastuzumab alone. Since then, the patient has maintained stable ventricular function (Figure 1).

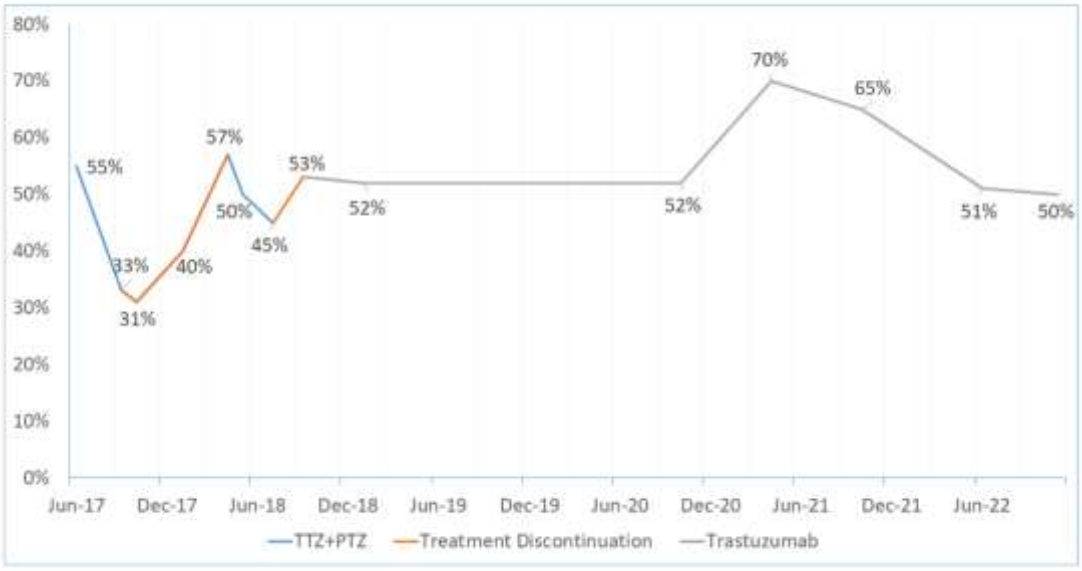

Figure 1. Change in ejection fraction during treatment.

TTZ, trastuzumab; PTZ, pertuzumab

The patient persisted with controlled systemic disease with trastuzumab, anastrazol and ovarian function suppression, developing isolated central nervous system (CNS) disease progression in 2019, 2020, and 2021, all of which were treated with brain-metastasis stereotactic radiosurgery. In July 2022, bone scintigraphy showed increased uptake in the femur and tibia regions bilaterally, requiring palliative radiation therapy at these sites. Subsequently, the hormonal therapy was changed to exemestane and HER2 blockade (trastuzumab) was maintained. The patient is currently on cycle 60 of trastuzumab, with computed tomography scans showing stable disease and echocardiogram with no signs of cardiotoxicity. Extra-CNS disease control has been maintained with the aforementioned anti-HER2 therapy.

Discussion:

Breast cancer is the most common malignancy and the leading cause of cancer death among women worldwide. In the United States, up to 5% of women diagnosed with breast cancer have metastatic disease at presentation, and up to 30% of patients with early-stage, non-metastatic breast cancer at diagnosis will develop metastatic disease.[5,6]

Approximately 20% of breast cancers overexpress HER2 and this overexpression is associated with an increased risk of disease recurrence and an overall poor prognosis. In this context, HER2-targeted therapies have become important agents in the treatment of metastatic breast cancer and have altered the natural history of the disease.[7] Dual blockade (trastuzumab and pertuzumab) plus chemotherapy was evaluated in the CLEOPATRA trial,[2,3] which showed a significant improvement in survival, with an absolute difference of 15.7 months compared with chemotherapy, trastuzumab, and placebo and median overall survival reaching up to 56.5 months.

Cancer treatment has evolved with the development of highly effective drugs. However, the side effects of antitumor therapy are still frequent and proper management is required. It is important to understand the different types and rates of adverse cardiac effects reported in the literature. Trastuzumab-related cardiotoxicity is widely recognized according to data published in clinical trials (Table 1), but data on pertuzumab-based treatments in daily clinical practice are less well documented (Table 2).

Table 1. Clinical trials of HER2-targeted therapy (trastuzumab) and its cardiac effects
TTZ, trastuzumab; CT, chemotherapy; CHF, congestive heart failure; LVEF, left ventricular ejection fraction.

Trastuzumab	
Outcome measure	**Cardiac safety data**
Cardiac dysfunction (symptomatic or asymptomatic) for patients receiving TTZ + CT vs CT.[8]	• 27% of patients receiving TTZ + anthracycline + cyclophosphamide vs 8% receiving anthracycline + cyclophosphamide. • 13% receiving TTZ + paclitaxel vs 1% receiving paclitaxel alone.
Cardiac dysfunction observed in a retrospective analysis of phase II and III clinical trials.[9]	• 27% of patients receiving TTZ + anthracycline + cyclophosphamide vs 13% receiving TTZ + paclitaxel vs 3%-7% receiving TTZ alone.
Meta-analysis of patients receiving TTZ for metastatic breast cancer.[10]	Significant increase in CHF for patients receiving TTZ (*P* 0.0009). Significant increase in LVEF decline for patients receiving TTZ (*P* 0.006).
Meta-analysis of patients receiving adjuvant TTZ in clinical trials.[11]	Significant increase in high-grade CHF for patients receiving TTZ ($P < 0.00001$).

Table 2. Clinical trials of HER2-targeted therapy (trastuzumab and pertuzumab) and its cardiac effects.
PTZ, pertuzumab; LVEF, left ventricular ejection fraction

Trastuzumab + Pertuzumab	
Outcome measure	**Cardiac safety data**
CLEOPATRA trial.[2,3]	• 27 patients (6.6%) in the PTZ group vs 34 patients (8.6%) in the placebo group had reduced LVEF over the course of the study.
APHINITY trial.[1,4]	17 patients (0.7%) in the PTZ group vs 8 patients (0.3%) in the placebo group had a primary cardiac event over the course of the study. With a median follow-up of 74 months: 83 patients (3.5%) in the PTZ group and 76 patients (3.2%) in the placebo group.

Cardiotoxicity related to cancer treatment should be understood as any treatment-induced alteration in the homeostasis of the cardiovascular system.[12] To understand the occurrence of ventricular dysfunction, it is necessary to understand the role of HER2 signaling in maintaining cardiovascular homeostasis. In cardiomyocytes, neuregulin-mediated HER2 receptor dimerization activates signaling pathways related to myocyte growth and survival. Blocking this pathway causes the breakdown of cardiovascular homeostasis by compromising repair mechanisms. Therefore, the main form of cardiotoxicity related to anti-HER2 agents is ventricular dysfunction, which can occur as an asymptomatic ventricular dysfunction or overt heart failure with reduced ejection fraction.[13,14] In the case reported here, the patient initially had an asymptomatic ventricular

dysfunction, but when it decreased to <40%, she required hospitalization for management of decompensated heart failure.

Current guidelines recommend that all pertuzumab-treated patients have their ejection fraction assessed at baseline and at regular intervals (every 3 months in the metastatic setting) during treatment. If the ejection fraction is <45%, or 45% to 49% with an absolute decline ≥10% below the pretreatment value, it is necessary to discontinue both pertuzumab and trastuzumab and repeat the assessment within approximately 3 weeks. Pertuzumab and trastuzumab should be discontinued if the ejection fraction does not improve or worsens, unless the benefits to the patient outweigh the risks. Furthermore, trastuzumab-related cardiotoxicity is reversible in most cases, and continuation or resumption of treatment after resolution of cardiac abnormalities may be safe in some women.

In the case reported here, despite the episode of grade 3 ejection fraction reduction, active cardiac monitoring and multidisciplinary management allowed the patient to maintain trastuzumab as monotherapy in view of the clinical/radiological benefit. The patient had a favorable outcome regarding the neoplasm and guideline-based medical therapy of heart failure, demonstrating that pertuzumab-related cardiotoxicity occurs and requires early identification, adequate treatment, and better understanding of its safety profile.

Reports on the cardiotoxic effect of pertuzumab are less well documented, as previously explained. A systematic review and meta-analysis aiming to determine the risk of cardiac events in patients with HER2-positive cancer receiving pertuzumab reported that the drug increased the risk of clinical heart failure but not of asymptomatic/minimally symptomatic left ventricular systolic dysfunction in patients with HER2-positive cancer.[15] In the present case, pertuzumab may have been the main trigger of the patient's cardiac toxicity, but the precise mechanism of this occurrence remains unknown. Therefore, further studies on the mechanisms underlying pertuzumab-related heart failure are needed to better understand its clinical spectrum of cardiotoxicity.

Conclusion:

There has been an increase in the number of agents available for the treatment of HER2-positive breast cancer and, despite the benefits in terms of disease control, these therapies are associated with some risks. Cardiovascular health is one such issue. Even though large, randomized trials have not shown an additive effect of pertuzumab on cardiac dysfunction, careful monitoring is of utmost importance in daily practice. In this case, cardiac monitoring aims to optimize therapy and minimize damage. We reported a case of a young patient developing pertuzumab-related cardiotoxicity in which an early identification and proper multidisciplinary management allowed the maintenance of trastuzumab monotherapy and proper disease control. Therefore, increased awareness of the effects of treatment-related cardiotoxicity and strategies for managing these situations is essential.

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