

Case Report

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Prolonged survival associated with anti-HER2 therapy: case report

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Abstract

Introduction: The advent of targeted therapy for human epidermal growth factor receptor 2 (HER-2), introduced by trastuzumab, represented a significant advancement in the treatment of breast cancer, impacting the survival of patients who overexpress this protein. Long-term survival (> 5 years) remains rare according to the literature, with an average of 25%. **Case Report:** This is a single-case observational report of a patient with extended survival in HER-2+ breast cancer treatment with trastuzumab combined with other medications. Clinical, pathological, treatment history, and survival data were retrospectively collected from the medical records. Patient, female, 37 years old, premenopausal, without associated comorbidities, physically active, no history of smoking or alcohol consumption, diagnosed in March 2015. She underwent intravenous chemotherapy for palliative purposes, achieving a maximal response. Trastuzumab was continued, combined with anastrozole, and she currently presents stable disease and extended survival (> 5 years). Targeted therapies significantly improve survival outcomes for HER2+ breast cancer patients. Recent studies demonstrate that clinical outcomes are better for triple-positive patients (ER, PR, and HER-2 positive), highlighting how this therapy has altered the natural course of the disease. There is evidence that the continuation of targeted therapy after disease progression results in clinical benefit, however, there is no consensus on the duration of treatment. **Conclusion:** This case, of a young patient diagnosed with HER2+ metastatic breast cancer, with long-term survival exceeding that described in the literature, demonstrates that the extended use of targeted therapy with trastuzumab, in combination with various chemotherapy and hormone-therapies regimens, can lead to the prolongation and improvement of the quality of life for patients whose prognosis at diagnosis was discouraging. This fact may assist in future decision-making regarding the use of targeted therapy after disease progression, filling this gap in knowledge.

Keywords: Breast neoplasms; Trastuzumab; Survival; Case reports.

Sobrevida prolongada associada à terapia anti-HER2: relato de caso

Resumo

Introdução: A terapia direcionada para o receptor tipo 2 do fator de crescimento epidérmico humano (HER-2), introduzida pelo trastuzumabe, representou grande avanço no tratamento do câncer de mama, impactando na sobrevida de pacientes que com alta expressão dessa proteína. A sobrevida a longo prazo (maior que cinco anos) ainda é rara (em torno de 25%), segundo a literatura. Há evidências de que a manutenção da terapia-alvo após progressão de doença resulta em benefício clínico, todavia, não há consenso sobre a duração do tratamento. **Relato Do Caso:** Trata-se de relato de observação única de paciente com sobrevida prolongada em tratamento de câncer de mama HER-2+ com trastuzumabe associado a outros medicamentos. Dados clínicos, patológicos, histórico de tratamento e de sobrevida foram coletados do prontuário, de forma retrospectiva. Paciente, sexo feminino, 37 anos, pré menopausa, sem comorbidades associadas, praticante de exercícios físicos, sem histórico de tabagismo ou etilismo, diagnosticada em março de 2015. Realizou tratamento quimioterápico venoso (Docetaxel) com finalidade paliativa, obtendo resposta máxima. O trastuzumabe foi mantido, associado ao anastrozol, apresentando atualmente doença estável e sobrevida prolongada (superior a oito anos). Estudos recentes demonstram que resultados clínicos encontrados são melhores para pacientes triplo positivo (RH e HER-2 positivos), sugerindo que essa terapia pode modificar o curso natural da doença. **Conclusão:** Este relato de paciente jovem com diagnóstico de câncer de mama HER2+, metastático ao diagnóstico e prognóstico desfavorável descreveu o uso de terapia-alvo prolongada com trastuzumabe, em associação a diferentes esquemas quimio e hormônioterápicos no qual se observou sobrevida em longo prazo, acima da descrita em literatura, e aumento da qualidade de vida. Sugere-se a realização de estudos de coorte com um grupo maior de pacientes para análise de dados de vida real que apoiem a tomada de decisão da equipe sobre o uso de terapia-alvo após progressão de doença.

Palavras-chave: Câncer de mama; Trastuzumab; Sobrevida; Relatos de casos.



Introduction

Breast cancer is considered to be the most common cancer among women, impacting health systems. For the triennium 2023-2025, around 74,000 new cases per year are estimated in the Brazilian population¹⁻².

Epithelial cell carcinoma is histologically more common and includes *in situ* and invasive lesions, with the infiltrating ductal subtype being more prevalent, comprising around 80 to 90% of cases². The luminal A molecular subtype (in which there is ample hormone receptors expression) has a better prognosis and lower recurrence risk, while the subtype defined by greater HER-2 expression is associated with a high relapse risk, greater aggressiveness and a higher mortality rate³⁻⁴.

Targeted therapy for the HER-2 receptor, introduced by the monoclonal antibody trastuzumab, marked a breakthrough in the treatment of this subtype, bringing benefits in overall progression-free survival⁴. Despite the new therapies, trastuzumab remains the treatment's backbone in several scenarios⁵.

In metastatic cancer, whose most common organs of distant involvement are bone, liver, lung, and brain, trastuzumab is indicated as the first line of treatment, resulting in a mean overall survival of 2 to 3 years. Long-term survival (over five years) is still low, at 25%⁶. Studies show that median survival is better in patients with metastatic breast cancer positive for hormone receptor and HER-2, when compared to cases in which patients are only positive for hormone receptor⁷.

The purpose of this paper is to report the case of a 37-year-old patient diagnosed with visceral metastatic breast cancer, with pulmonary involvement, HER-2 overexpression, under treatment with the monoclonal antibody trastuzumab, who had an overall survival of more than 5 years.

This study was submitted to and approved by the Research Ethics Committee (CEP) of the educational institution under No. 47531521.9.0000.5243 and the co-participating institution under No. CAAE: 47531521.0.3001.5274. The Informed Consent Form was obtained.

Case report

Patient, female, 37 years old, self-described brown, married, housewife, premenopausal, no associated comorbidities, regular physical exercise, no history of smoking or alcoholism, menarche at 12 years old, single pregnancy at 25 years old, 4 months of breastfeeding, use of oral contraceptives for around 10 years, diagnosed with breast cancer in March 2015, one year after noticing a lump in the right breast. Family history of maternal grandmother with cervical cancer, maternal aunt, and cousin with breast cancer, both aged 38 and deceased.

The patient was referred through the Unified Health System (SUS) vacancy regulation system to a federal public administration institute that is a reference in cancer treatment, located in Rio de Janeiro, Brazil. The patient presented a report showing a 5.5 cm solid nodule in the right breast, not adherent to the planes, without thickening or papillary effusion, with a suspicious lymph node, initially classified as stage IIIb (T4bN1M0) according to the TNM classification system².

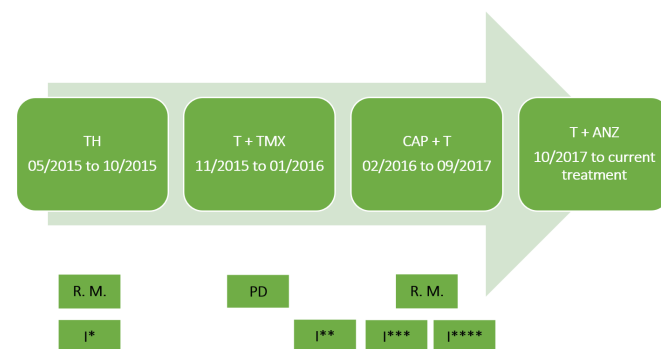
She underwent a core biopsy and complementary exams whose pathology report identified invasive ductal carcinoma, histological grade II, positive hormone receptors (estrogen 100% and progesterone 2%), HER2 receptors (+++) overexpressed and tumor marker for proliferation Ki-67 at 30%. A complementary CT scan in May 2015 showed pulmonary nodules with various opacities, compatible with secondary implants, resulting in the initial staging being changed to stage IV due to distant metastases.-

Initial chemotherapy treatment was carried out for palliative purposes, 6 cycles of docetaxel (TXT) associated with trastuzumab every 21 days. Due to a shortage of the antibody, two cycles of TXT alone were carried out. After 8 cycles, between May and October 2015, the medication TXT was discontinued due to maximum response, evidence of lung disease absence and good local clinical response. Treatment with trastuzumab every 21 days was maintained, with endocrine therapy associated with tamoxifen in November 2015. A new shortage in November 2015 led to the antibody being discontinued.

In January 2016, the patient showed local progression of the disease, and in February she began treatment with capecitabine and trastuzumab. Approximately one year after diagnosis, she started menstruating again and underwent surgical oophorectomy in June 2016.

Between June 2016 and June 2017, there were further shortages of trastuzumab, interrupting treatment in June and July 2016 and from October 2016 to July 2017, when it was reintroduced in association with capecitabine until maximum response in September of the same year. After discontinuing capecitabine, endocrine therapy with anastrozole was started in October 2017 (figure 1), and target therapy with trastuzumab in monotherapy was maintained.

Figure 1. Treatments' timeline carried out between 05/2015 and 03/2023.



Note: TH - Docetaxel associated with Trastuzumab; T + TMX - Trastuzumab associated with Tamoxifen; CAP + T - Capecitabine associated with Trastuzumab; T + ANZ - Trastuzumab associated with Anastrozole; MR - Maximum response; DP - Disease progression. I* - Treatment interruption (Sept to Oct/15); I** - Treatment interruption (Dec/15 to Feb/16); I*** - Treatment interruption (Jun to Jul/16); I**** - Treatment interruption (Oct/16 to Jun/17). Source: Prepared by the authors.

During the follow-up period, there were numerous shortages of trastuzumab, purchased with the institution's own resources at the time, since it was not incorporated into the country's Unified Health System for the metastatic breast cancer treatment, which occurred in June 2017.

Monotherapy with trastuzumab was maintained, with 98 administrations carried out up to March 23. On this date, the patient had stable disease, with no pulmonary disease evident in the imaging tests carried out regularly and a good clinical response in the breast.

Discussion

This report showed a prolonged survival time in a young patient with metastatic breast cancer, positive for hormone receptor and HER-2 overexpression, treated with protocols involving endocrine therapy, chemotherapy, and target therapy.

It is well described in the literature that therapies targeting the HER-2 receptor significantly improve survival outcomes for patients with this subtype of cancer. More recent studies reveal that the clinical results found are even better for patients characterized as triple positive (HR and HER-2 positive) compared to those positive only for the hormone receptor, showing that the therapy has modified the natural course of the disease⁷.

The established treatment standard for metastatic disease with HER-2 amplification is to administer trastuzumab every 21 days until the disease progresses. However, some studies, such as the one carried out by Arciénega et al, have suggested that maintaining treatment with anti-HER2 therapy even after progression results in clinical benefit for the patient⁸.

Research carried out at the Royal Marsden Hospital has shown that continuing with the monoclonal antibody beyond progression is a positive factor in treatment⁹. However, in cases where the individual achieves complete metastasis' remission, there is still no evidence to indicate the ideal duration of administration of the therapy in question¹⁰.

Overall survival (OS) for patients with HER2-overexpressing metastatic breast cancer is estimated at 25 months and progression-free survival (PFS) at approximately 7.4 months^(3,6). However, in our report we observed an OS of 98 months (approximately 8 years) and a PFS of approximately 73 months, despite the four periods of interruption, totaling 16 months of treatment with trastuzumab during the observation.

As there is no consensus on the treatment length for patients with stable disease, this observation raises the discussion, already suggested by some authors, about the possibility of patients with metastatic disease achieving better long-term outcomes as a result of treatment with trastuzumab⁽¹¹⁻¹²⁾.

The case reported corroborates data in the literature, in which patients can achieve long periods of disease stability, even with intervals without treatment with trastuzumab, regardless of the reason for the interruption¹³. However, the decision to discontinue treatment with trastuzumab for a prolonged period in patients with stable disease remains a huge challenge⁽¹¹⁻¹⁴⁾.

In this study, it was not possible to evaluate molecular characteristics, specific biomarkers or clinical pathological findings that could justify the overall survival above the mean described and disease-free survival as a secondary endpoint. However, the characterization and determination of some of these parameters could benefit and direct the treatment of patients with similar characteristics and disease profile^(12,15).

A limitation of this study is the fact that it is a single specific case

report, with retrospective data over a long period of time.

However, we reiterate the relevance of describing the experience observed in a young patient's treatment, diagnosed in a metastatic setting, with overall survival above the expected mean, with stable disease and no new metastases. In view of the above, there is a need for further investigation into possible molecular and individual characteristics of patients with unusual outcomes, in order to guide possible targeted therapies and individualized therapeutic choices with a better prospect of outcome.

Conclusion

The trastuzumab antibody represents a milestone in the prognosis of breast cancer patients who overexpress HER2. There is no consensus in the palliative scenario about stopping treatment in patients with apparent disease control. There is an undeniable need to identify possible characteristics in patients who have an overall survival rate above the overestimated mean, given the impact of the morbidity profile related to breast cancer.

This report of a young patient diagnosed with HER2+ breast cancer, metastatic at diagnosis, with long-term survival above that described in the literature, suggests that the use of prolonged target therapy with trastuzumab, in association with different chemo- and hormone-therapy regimens, can result in prolonged and increased quality of life for patients whose prognosis at diagnosis was dismal. This may help in making future decisions about the use of target therapy after disease progression, filling this knowledge gap.

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Contributions

P R P A contributed substantially to the design and planning of the study, in obtaining, analyzing and interpreting the data, as well as in the writing and critical review. L A A F and M P F R contributed substantially to the project and conception, writing and critical revision. All the authors approved the final version to be published.

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Conflict of interest declaration

The authors declare no conflict of interest in relation to this article.

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