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Case Report

Surviving a Decade: Prolonged Survival in Metastatic HER2-Positive Breast Cancer through Continuous HER2 Blockade

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INTRODUCTION

HER2 receptor is overexpressed and/or amplified in 15-20% of malignant breast tumors, and this is associated with a more aggressive disease course [1]. Anti-HER2 therapy altered the course of early and metastatic disease with a significant reduction in relapse rates in curatively treated patients and also significantly prolonged survival in patients with metastatic disease [2,3]. With the development and application in clinical practice of new anti-HER2 agents after trastuzumab, this trend is even more pronounced. Despite increasing advances in adjuvant treatment, 20-30% of patients treated for non-metastatic disease still develop distant metastasis at some point, and 5-10% the disease debuts in the metastatic stage [4].

In recent years, a number of new anti-HER2 agents have been introduced into clinical practice, which has provided new treatment options for patients with advanced HER2-positive breast cancer [5]. At the moment, trastuzumab and pertuzumab are approved for use in metastatic disease as a first-line treatment, the drug conjugates trastuzumab deruxtecan and trastuzumab emtansine as a second-line treatment, as well as tucatinib, neratinib, lapatinib, margetuximab as subsequent therapeutic options [5]. A number of ongoing clinical trials are also investigating the effect of novel anti-HER2 molecules in metastatic disease. Accumulation of new data is constantly challenging current treatment standards, but at the same time questions are also being raised about what the optimal sequence of anti-HER2 therapies, what are the optimal combinations, and about the combination of endocrine therapy with anti-HER2 therapy in hormone receptor positive and HER2-positive tumors [5]. Last but not least are the challenges associated with the treatment of patients with brain metastases [5].

This case report is about the 11-year survival of a patient with metastatic HR+/HER2+ Breast Cancer (BC) who was treated with continuous anti-HER2 blockade.

CLINICAL CASE

A forty-six-year-old woman was diagosticized in May 2012 with multiple bone metastases, and biopsy of the right mammary gland demonstrated a low-differentiated (G3), Hormone-Receptor Positive (HR+) and HER2-positive breast cancer, with a high proliferative index Ki67-over 50%. The patient has ECOG PS 1, due to a pronounced pain syndrome, no accompanying diseases and without other distant spread of disease.

After a palliative radiation therapy for the pain syndrome, first-line treatment with docetaxel and trastuzumab was initiated, as well as osteomodulator administration. A partial response was observed after eight courses and treatment was continued as maintenance therapy with trastuzumab with the addition of endocrine therapy with an LHRH agonist and an antiestrogen. After 48 months of progression-free period (PFS1 = 48 months), there is CT and PET/CT evidence of tumor formations in both ovaries and new bone lesions. Total laparohysterectomy with bilateral adnexectomy and partial omentectomy was performed with histology for metastases from moderately differentiated HR+/HER2+ invasive ductal carcinoma, Ki 67-10%. We switched to second-line therapy with lapatinib and capecitabine, but after thirteen months a new progression was reported with a metabolically active lesion in the pelvis and new metabolically active bone foci (PFS2 = 13 months). After eight courses of third-line treatment with docetaxel in combination with trastuzumab and pertuzumab was achieved complete metabolic remission of the disease and the patient was left on maintenance treatment with trastuzumab and pertuzumab. After 23 courses, she again had PET/CT evidence of progression, with peritoneal involvement and a single new paracaval lymph node (28 months PFS3). The fourth line of treatment with lapatinib and letrozole was started, but after eleven months a new desease progression was reported in March 2021 with the appearance of metabolic activity in mediastinal lymph node, pelvic bones and in both adrenal glands (PFS4 = 11 months).

Fifth-line therapy with trastuzumab emtansine was initiated and was administered for 13 courses with partial response achieved, but a follow-up PET/CT in January 2022 showed evidence of metabolic and morphological progression of peritoneal lesions and metabolic progression in two bone foci (PFS5 = 10 months).

Treatment continues with carboplatin/paclitaxel and trastuzumab with stable desease as determined by imaging, against the backdrop of an upward trend in tumor markers and with relatively severe patient tolerability. After eleven courses, PET/CT reports progression of peritoneal dissemination, with the formation of "omentum cake", the appearance of new metabolically active peritoneal deposits, as well as an increase in the volume of ascites fluid in the pelvis and perihepatic (PFS6 = 11 months) (Figure 1). At the same time, the patient has a clinical deterioration with the appearance of ascites and pronounced astheno-adynamic syndrome, thrombocytosis, anemia and hypoproteinemia, with an increase in the tumor marker (CEA: 31.26, CA 15-3: 538). Abdominal paracentesis and symptomatic treatment were performed and next (seventh) line with T-DXd was started.

The control PET/CT after 6 cycles of treatment showed partial therapeutic response in terms of size and metabolic activity of peritoneal carcinomatosis, a significant to complete reduction in the volume of ascites and peristension of the known multiple disseminated bone lesions, which were without significant morphological dynamics (Figure 2).

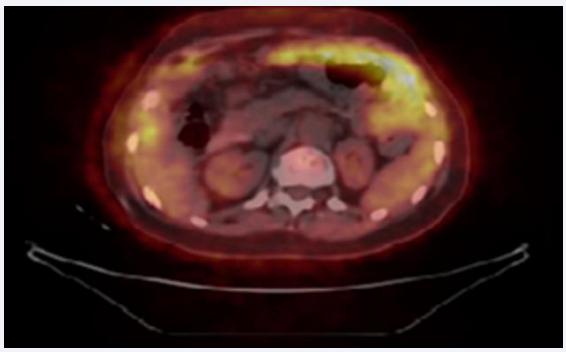

Figure 1 Progression of peritoneal carcinomatosis.

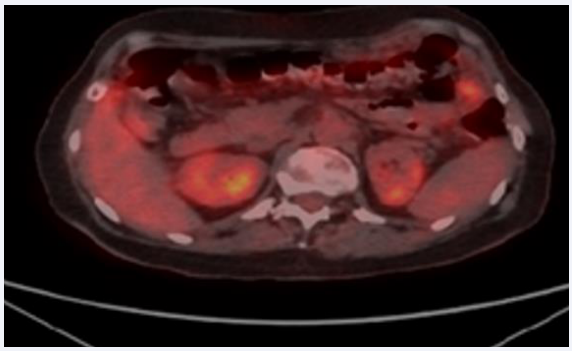

Figure 2 After six cycles seventh line.

There was also a significant improvement in the general condition of the patient, with complete resorption of the ascites, as well as a trend for a significant decrease in the values of tumor markers, as a result of which she returned to her normal daily life.

DISCUSSION

The present case illustrates the increasing survival rate achieved in patients with metastatic HER2-positive breast cancer. It is the result of targeted therapies targeting the HER2-signaling pathway that have significantly altered the natural course of HER2-positive disease, transforming it from a molecular subtype associated with very poor biology and prognosis to a disease in which median survival in the metastatic stage is now approaching five years. After many years the standard first-line treatment in these patients was the taxane and trastuzumab combination, the results of the CLEOPATRA clinical trial changed this and currently the trastuzumab/pertuzumab/taxane combination is still recommended as the first choice in patients with metastatic disease [6]. The positive results of the EMILIA clinical trial made trastuzumab emtansine (T-DM1) the standard for second-line treatment [7]. However, this changed with data from the DESTINY-Breast03 trial, which led Trastuzumab Deruxtecan (T-DXd) to replace trastuzumab emtazine as second-line therapy [8]. There are still no standard sequence recommendations for third and subsequent lines of treatment, but a number of options are available, including trastuzumab in combination with chemotherapy, lapatinib or margetuximab; lapatinib and capecitabine. Moreover, based on the results of the DESTINY-Breast01 study, trastuzumab deruxtecan is included in the treatment recommendations for pretreated patients treated with multiple lines of anti-HER2 therapy [9]. Another valid option is available in patients with hormone-positive and HER2-positive disease, namely the combination of anti-HER2-therapy with endocrine therapy, especially in patients who are not indicated for cytostatic treatment or as maintenance therapy.

Peritoneal metastasis in brest cancer is rare, has a very poor prognosis, and is associated with greatly reduced survival compared to other sites of distant metastasis, comparable in this respect to brain metastasis [10].

This clinical case provides further evidence that continuous HER2 blockade provides prolonged desease control and enables these patients to access subsequent novel and effective treatment options at the cost of acceptable toxicity and without significant impairment of quality of life.

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