A Case Report on Prolonged Response with Trastuzumab Emtansine (T-DM1) in Recurrent Advance Breast Cancer Setting

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Abstract: Breast cancer holds the dubious distinction of being the most prevalent malignant tumor among women worldwide the 5 year survival rate for patients with advanced or metastatic forms of the disease is estimated at a mere 23%, with approximately 20% of cases exhibiting an amplification of the human epidermal growth factor receptor 2 (HER2). HER2 overexpression was linked to a dismal prognosis prior to the advent of targeted HER2 therapies. The introduction of ado-trastuzumab emtansine (T-DM1) has emerged as one of the standard treatment options for HER2-positive breast cancer patients who experience a recurrence or progression of the disease. This case concerns a patient with recurrent metastatic breast cancer who achieved an unusually extended period of time without the disease progressing while on T-DM1 treatment. After experiencing disease progression on multiple treatment lines involving trastuzumab, the patient achieved a nearly complete clinical remission (cCR) with T-DM1 therapy. The availability of cost-effective biosimilars has expanded access to advanced biologic therapies, which were previously limited to a small segment of the population due to the cost barrier.

Keywords: T-DM1, biosimilar, prolonged response, recurrent cancer, breast cancer, HER2-positive.

INTRODUCTION

Breast cancer is the most prevalent form of cancer among women, and the five-year survival rate for patients with metastatic disease is estimated to be 23% [1]. It has the highest incidence among malignant tumors affecting women worldwide, with approximately 20% of patients showing amplification of the human epidermal growth factor receptor 2 (HER2). Historically, HER2 overexpression in breast cancer was associated with a poor prognosis prior to the development of HER2 targeted therapies [2].

The introduction of targeted therapies has led to a significant transformation in the prognosis of HER2-positive metastatic breast cancer [3]. Ado-trastuzumabemtansine (T-DM1) emerged as one of the standard therapyoptions for HER2-positive breast cancer patients who experience disease recurrence or progression after receiving taxane and trastuzumab-based treatment. T-DM1 is an antibody-drug conjugate (ADC) that combines trastuzumab with the microtubule-inhibitory agent emtansine (DM1). It was the first ADC agent approved for the treatment of HER2-positive breast cancer [4].

In this report, we present a case of recurrent metastatic breast cancer in which the patient achieved an exceptionally long progression-free survival (PFS) on T-DM1. After experiencing disease progression on multiple lines of trastuzumab-containing regimens, the patient attained nearly complete clinical remission (cCR) with T-DM1 therapy.

CASE DESCRIPTION

The patient is a 73-year-old female with metastatic left breast cancer and multiple bone metastases and a fungating breast mass. She had a history of a lump in her left breast for the past year and was initially on an alternative therapy. The patient presented in August, 2017 with pain in her right hip and was diagnosed with a pathological subtrochanteric fracture of the right hip. She underwent CRIF (closed reduction internal fixation) with PFN (proximal femoral nail) and biopsy, which confirmed the diagnosis of invasive duct carcinoma, grade 2, with a MBR score of 7. The immunohistochemistry (IHC) results showed ER-negative (2/8), PR-negative (1/8), and HER2-positive (3+). The Ki67 proliferation index was 20-24%.

In October, 2017 the patient was started on palliative chemotherapy with paclitaxel and trastuzumab on a weekly basis. After completing four cycles of this regimen, a post-chemotherapy PET-CT scan was done which showed a near-complete metabolic response. She continued further with a total of six cycles of paclitaxel and trastuzumab till January, 2018.

Considering the advanced nature of the disease and poor prognosis with limited survival benefit on palliative treatment, patient was then continued further with maintenance trastuzumab monotherapy (3-weekly)

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along with 3weeklyzoledronic acid and letrozole in view of weak ER, PR positivity. Patient received nearly 19 cycle of trastuzumab along with zoledronic acid till September, 2018. During the treatment course, PET-CT scan in November, 2018 revealed that there was increased FDG (fluorodeoxyglucose) activity in the left parieto-temporal lobe region with perilesional edema with midline shift towards right and skeletal Mets. Subsequent MRI of the brain confirmed a metastatic lesion measuring approximately 2.3 x 2.2 cm in the left posterior temporal region.

The patient further received cranial radiation therapy with Stereotactic radio surgery (SRS) in November 2018, to December, 2018. Post-surgical treatment continued with trastuzumab and letrozole there after till January, 2019 and the option of adding pertuzumab was discussed further with patient and relatives but not pursued due to personal reasons.

Capecitabine and Zoledronic acid-based therapy was planned as the next treatment option. Zoledronic acid was started and continued in view of bone metastases. The patient completed seven cycles of capecitabine till June, 2019 and continued to be used till March, 2020. Then it was discontinued due to severe hand and foot syndrome. Trastuzumab (dose-262 mg) monotherapy was continued. The treatment with monthly denosumab (dose-120 mg) was started in the patient due to rising creatinine level with zoledronic acid.

Patient had a pathological fracture in Right femur, which got operated in July 2020 and an ipsilateral iliac crest bone grafting was done. PETCT Scan in November, 2020 showed metabolically active lesion along segment-IV of liver-not appreciated previously-along with metabolically active mediastinal and hilar lymphnodes**.** Same therapy was continued further as there was no evidence of abnormal activity elsewhere in the body and there was also good overall response in terms of therapy.

PETCT Scan in September, 2021 indicate resolved liver lesion and a new lesion in left breast (Figure **1**) which was tested further. USG Guided Biopsy of left breast mass in April, 2021 confirms it as a Mucinous Carcinoma. Grade-2, MBR Score-7/9. Carcinoma in Situ-Absent. Lymphovascular invasion-Present, 2. (IHC) results showed ER-negative (0/8), PR-positive (5/8), and HER2-strongly positive (3+). The Ki67 proliferation index was 30-35%.

CEMRI of Brain in October, 2021 indicates almost complete resolution of left temporal region with possible development of gliotic area in this region. The patient received multiple doses of trastuzumab till then and now considering the disease advancement started on treatment with T-DM1 as the next line of therapy. As the patient had access to an approved biosimilar option available in our country, the same was selected and the first dose of T-DM1 biosimilar (UJVIRA^{TM}, dose-160 mg) was infused on October, 2021.

Various PET-CT scans were performed at a regular duration of six to eight months to monitor the treatment response, which revealed good treatment response and no significant interval changes observed. 2D Echo was also performed regularly at every four-six cycle to monitor the LVEF % and to track putative toxicity of the continued T-DM1 therapy (Figure **2**). Based on the good treatment response, patient was continued on

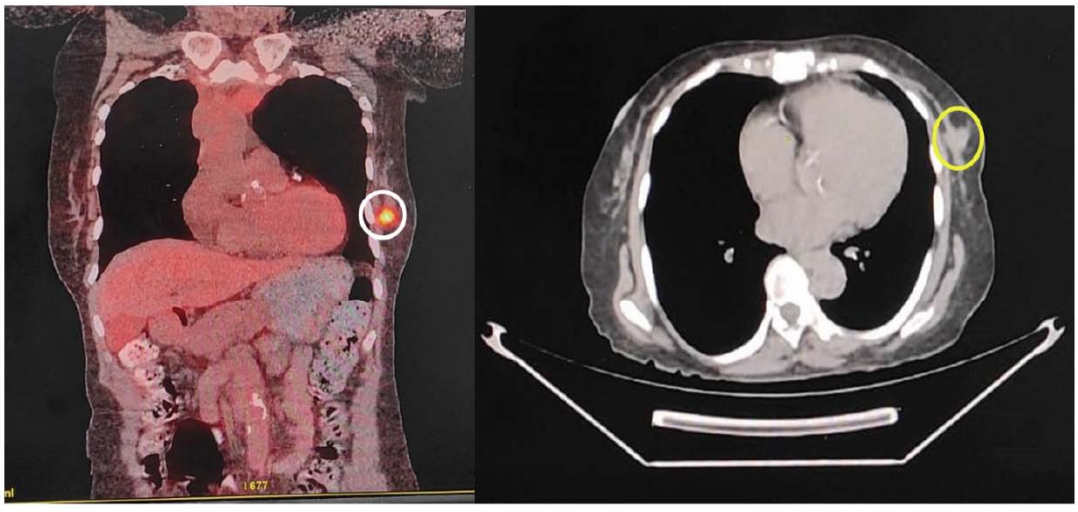

Figure 1: FDG avid mass with speculated margins measuring 1.7x1.4x1.5 cm, left breast lower outer quadrant suggestive of new lesion.

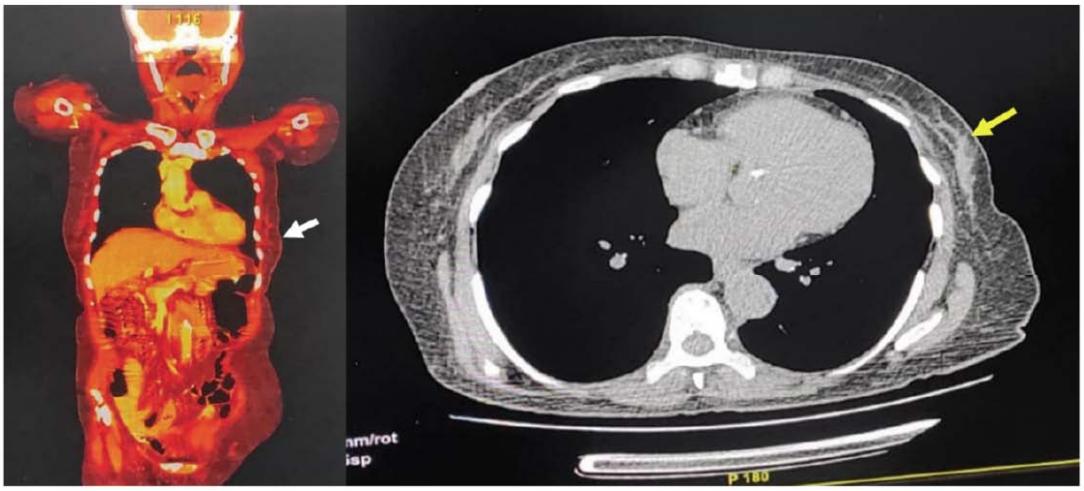

Figure 2: No active breast lesion was seen in PETCT is suggestive of good response to T-DM1.

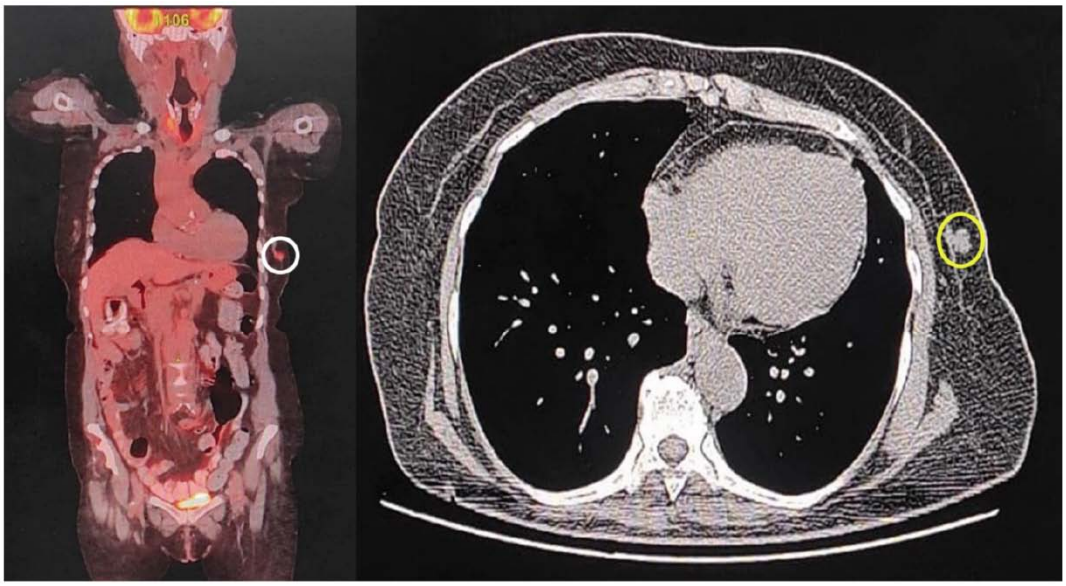

Figure 3: Left breast nodular lesion showed mild increased metabolic activity. No definite evidence of abnormal metabolic activity noted elsewhere, suggestive of maintained response overall.

long term therapy with T-DM1 and as of November 2023, the patient took 37th dose of T-DM1. The latest PET-CT scan indicated a good treatment response and stable disease (Figure **3**). The treatment with T-DM1 is still ongoing and patient is responding well to the therapy. In order to publish this clinical report, written informed consent was obtained from the patient as well as her legal guardian for the disclosure of images and the clinical details.

DISCUSSION

T-DM1, an antibody-drug conjugate, received FDA approval in 2013 for the treatment of HER2-positive, metastatic breast cancer based on data from the EMILIA trial [5]. The trial showed that T-DM1 resulted in better progression-free survival (PFS) of 9.6 months compared to 6.4 months for lapatinib plus capecitabine (P<0.001), as well as improved overall survival (OS) of 30.9 months compared to 25.1 months (P<0.001) after the failure of first-line anti-HER2 therapy [5, 6].

The efficacy of T-DM1 has also been supported by the THERESA trial, a multicentre phase III study. This trial demonstrated significantly improved median PFS (6.2 vs. 3.3 months, P<0.001) and OS (22.7 vs. 15.8 months, P=0.0007) with T-DM1 compared to physician's choice in patients who had progressed after at least two lines of HER2-targeted regimens for advanced breast cancer [7, 8].

It is important to note that the data on T-DM1 efficacy and long-term responses after previous lines of treatment are derived from several retrospective

studies, which vary in terms of design, patient characteristics, prior treatments, and prognostic factors. Therefore, caution should be exercised when interpreting these findings due to the potential for heterogeneity and bias.

Approximately 30-55% of patients with HER2-positive breast cancer are estimated to develop brain metastases (BMs) during the course of their disease. Traditionally, loco-regional therapies such as whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and surgery have been the mainstay of brain metastases treatment. However, the role of systemic therapies in this setting is still unclear due to limited penetration of the blood-brain barrier (BBB) by these treatments and the exclusion of patients with BMs from many clinical trials [9].

Nevertheless, T-DM1 has shown promise in improving overall survival in patients with trastuzumab-resistant advanced metastatic breast cancer and asymptomatic brain metastasis who have previously undergone local therapy, compared to lapatinib plus capecitabine [10]. Some case reports and small case series have also suggested favourable intracranial activity of T-DM1 in patients with asymptomatic BMs, with intracranial objective response rates ranging from 44% to 100% [9, 10]. Additionally, a study by de Vries *et al*. in 2018 reported CNS activity against symptomatic BMs [9].

The results of the EMILIA trial's exploratory analysis in patients with baseline CNS metastasis observes the PFS of 5.9 months, while in the KAMILLA analysis the Median PFS was 5.5 months (95% CI 5.3-5.6) in patients with baseline brain metastases suggesting that the PFS did not appear to be affected by line of treatment with T-DM1 [10, 11]. The results of the present case in terms of PFS is suggestive of a better long term response in terms of PFS as compared to the trials with favourable toxicity profile on long term therapy with T-DM1.

Multiple randomized clinical trials provide evidence for the survival benefit of continuing HER2 blockade in metastatic breast cancer patients who experience disease progression during or after anti-HER2 targeted therapies [2]. Current guidelines from the European Society for Medical Oncology and the American Society of Clinical Oncology recommend continuing HER2-targeted therapy until disease progression or the development of side effects [3]. However, there is no strong consensus on the duration of treatment after achieving a complete response in HER2-positive metastatic breast cancer patients.

There is no doubt that targeted therapy has a profound impact on the treatment of HER2-amplified metastatic breast cancer (MBC), leading to improved outcomes for women. However, it is important to recognize that HER2-positive breast cancer is a heterogeneous disease with diverse behaviour patterns. It remains uncertain whether a specific subset of HER2-positive breast cancer patients derives the maximum benefit from targeted therapies. Nonetheless, based on existing literature, if patients respond well to therapy and maintain a favourable clinical response, treatment with the targeted agent should be continued until disease progression.

It is crucial to consider individual patient characteristics, treatment response, and the overall clinical picture when making decisions about the duration of targeted therapy. The goal is to optimize the balance between treatment effectiveness and potential side effects. Ongoing monitoring of disease status, regular assessments, and close collaboration between the patient and healthcare team are essential to guide treatment decisions and ensure the best possible outcomes for HER2-positive breast cancer patients.

CONCLUSION

This case report represents the first documented instance from India of a patient experiencing a prolonged progression-free survival (PFS) benefit while receiving T-DM1 in breast cancer. The introduction of a cost-effective biosimilar in India has helped more patients to get the standard of care for patients who have exhausted early lines of treatment and for those who require long-term targeted therapy. It provides an opportunity to expand access to effective treatments and improve outcomes for HER2-positive BC patients with CNS involvement. This not only enhances the potential for improved disease control but also contributes to maintaining a favourable quality of life for patients.

AUTHOR CONTRIBUTIONS

Conception and design: P.S.B. Collection of patient data: M.W. Data assembly, analysis, and interpretation: all authors. Manuscript writing: all authors. Final approval of manuscript: all authors. Accountable for all aspects of the work: all authors. All authors have read and agreed to the published version of the manuscript.

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INFORMED CONSENT STATEMENT

Written informed consent has been obtained from the patient to disclose data and publish this paper.

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CONFLICTS OF INTEREST

The Author(s) declare(s) that there are no relevant financial or non-financial competing interests to report.

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