

Case Report

Dual HER2 Suppression with Lapatinib plus Trastuzumab for Metastatic Inflammatory Breast Cancer: A Case Report of Prolonged Stable Disease

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Keywords

Lapatinib · Trastuzumab · HER2 · Metastatic breast cancer · Inflammatory

Abstract

Background: Continuous therapy targeting human epidermal growth factor receptor 2 (HER2) is recommended until disease progression for patients with HER2-overexpressing (HER2+) metastatic breast cancer. Prolonged stable disease has been observed with such maintenance therapy using trastuzumab, but the frequency of these cases remains low. Whether combined maintenance therapy with two different HER2-targeted agents could improve the rates of durable progression-free survival compared with trastuzumab alone is under investigation. **Objectives:** To evaluate the efficacy of the combined HER2-targeted agents, trastuzumab and lapatinib, as maintenance therapy in one patient. **Methods:** We describe a patient with HER2+, hormone receptor-negative, inflammatory metastatic breast cancer who was previously treated with doxorubicin, cyclophosphamide, and zoledronic acid followed by paclitaxel and trastuzumab. After completion, the patient underwent a bilateral mastectomy and then enrolled into a Phase III open-label clinical trial of trastuzumab plus lapatinib. **Results:** The patient experienced long-term stable disease on combined lapatinib and trastuzumab maintenance therapy over 4 years. **Conclusions:** This case demonstrates that prolonged stable disease is possible with lapatinib plus trastuzumab, even in patients with the aggressive inflammatory subtype. Optimization of maintenance therapy could improve outcomes for patients with HER2+ metastatic breast cancer.

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Introduction

Approximately 5 in every 100,000 women in the US are diagnosed with human epidermal growth factor receptor 2 (HER2)-enriched (HER2-overexpressing [HER2+] and hormone receptor-negative) breast cancer [1]. The inflammatory subtype occurs in approximately 1–5% of all breast cancer cases, and represents extremely aggressive disease [2]. Initial treatment for HER2-enriched breast cancer is typically chemotherapy and HER2-targeted therapy [3–6]. In the case of metastatic disease, HER2-targeted therapy is continued as a form of maintenance therapy until disease progression [3–6]. Trastuzumab and lapatinib are two different HER2-targeted agents: trastuzumab binds the extracellular domain of HER2 and inhibits ligand-independent signaling; lapatinib binds the intracellular domain and blocks activation of downstream signaling [7–9]. A Phase III open-label trial (NCT00968968) is investigating the efficacy and safety of lapatinib in combination with trastuzumab versus trastuzumab alone as maintenance therapy after prior chemotherapy and trastuzumab in women with HER2+ metastatic breast cancer [10]. Here we present a case report of a patient with metastatic inflammatory breast cancer enrolled in this trial, who experienced prolonged stable disease on maintenance therapy with lapatinib plus trastuzumab.

Case Report

A 53-year-old Caucasian female presented with a chief complaint of “twisting” right breast pain, associated with the development of yellow-green bruising on the breast. The patient waited approximately 7 to 8 months before obtaining a mammogram and ultrasound of the right breast, which revealed a right breast mass and right axillary adenopathy (Fig. 1). A biopsy was significant for cancer within lymphatic vessels in the skin, and the breast tissue showed grade 2 invasive ductal carcinoma. The tumor was estrogen and progesterone receptor-negative (<1% each) and HER2+ (3+ by immunohistochemistry). During the initial visit, the patient complained of a productive cough with scant sputum production and mid-back pain for 2 months. The patient suffered from fatigue, and experienced night sweats for the past year with no weight loss. The patient admitted to noticing a change in breast shape and size, but no nipple discharge. The initial physical examination was significant for morbidly obese body habitus. The left breast was large, free of masses, and non-tender. The right breast was significantly larger compared with the left, and tender with a rash. A palpable 2-cm axillary lymph node on the right was appreciated. A positron emission tomography (PET)/computed tomography (CT) scan revealed hypermetabolism within the anterior aspect of the right breast consistent with inflammatory carcinoma, right axillary and supraclavicular lymphadenopathy, and several skeletal metastatic lesions predominantly within the cervical and thoracic spine. The primary tumor, regional lymph node, and distant metastasis (TNM) staging was T4b, N1, M1.

As indicated for the treatment of metastatic inflammatory breast carcinoma in a premenopausal patient, treatment was initiated with doxorubicin and cyclophosphamide every 2 weeks for 4 cycles. After the first week of chemotherapy, monthly zoledronic acid was added to the treatment regimen due to the presence of bone metastases. Treatment was then followed by paclitaxel and trastuzumab weekly for 12 weeks.

At the 5-month follow-up visit, a repeat PET/CT scan was significant for a positive response to treatment: the abnormal hypermetabolism within the right breast, axillary and supraclavicular nodes, and within the skeleton had resolved. At the 6-month follow-up visit, the

patient had completed the above chemotherapy followed by the paclitaxel plus trastuzumab treatment course. The patient underwent a bilateral mastectomy with reconstructive surgery. Post-operatively, the patient had residual 0.1 cm of focal invasive ductal carcinoma, intravascular carcinoma with deep resection margins, and isolated carcinoma cells in two axillary nodes. The patient was subsequently enrolled into the Phase III open-label clinical trial of trastuzumab plus lapatinib maintenance therapy (trastuzumab 6 mg/kg every 3 weeks plus lapatinib 1000 mg/day), and was randomized to receive the combination treatment.

At the 16-month follow-up visit, a CT scan of the abdomen, pelvis, and chest with intravenous contrast was significant for sclerotic changes within the lumbar spine, thoracic spine, and ribs, consistent with metastatic disease. Within 1 month later, after continued trastuzumab plus lapatinib treatment, a nuclear medicine whole-body bone scan revealed increased activity correlating with treated metastatic disease of the thoracic spine.

Subsequent CT and bone scan imaging over the next 3 years reflected stable metastatic disease, consistent with healed skeletal metastatic disease, and was unchanged. The patient continued to be treated with trastuzumab plus lapatinib, and at the 4-year follow-up visit (while still on trastuzumab plus lapatinib), the most significant complaint from the patient was chronic diarrhea (which was controlled with diphenoxylate plus atropine tablets 3 times a day) and a single syncopal episode (a magnetic resonance imaging scan revealed no acute infarct, hemorrhage, or mass).

Discussion/Conclusion

Prolonged stable disease has been reported with trastuzumab-based maintenance therapy in a small number of patients with HER2+ disease [6, 11, 12]. Here we describe a patient with stable metastatic inflammatory breast cancer for 4 years on trastuzumab plus lapatinib maintenance therapy. As of June 2018, the patient still had stable disease and continued to receive trastuzumab plus lapatinib. This patient had a remarkably good response to the pre-surgery chemotherapy and a successful mastectomy, which may have contributed to the prolonged response to trastuzumab and lapatinib.

Inflammatory breast cancer is an aggressive subtype, with a historically shorter median survival (2.9 years) compared with locally advanced breast cancer (6.4 years; cases diagnosed between 1988 and 2000) [13]. Survival has improved with the advent of HER2-targeted therapies for HER2+ disease (trastuzumab was first approved in the US in 1998) [8], with a retrospective study reporting a 5-year survival rate of 53% for patients diagnosed between 1989 and 2011 with primary stage III, hormone receptor-negative, HER2+ inflammatory breast cancer who received neoadjuvant chemotherapy and underwent definitive surgery ($n = 122$) [14]. A smaller, single-institution retrospective study in France reported a 5-year survival rate for patients diagnosed between 2003 and 2012 with non-metastatic inflammatory breast cancer of 74% for all subtypes ($n = 67$), and 89% for HER2+ disease ($n = 21$); all patients were treated with high-dose chemotherapy with autologous hematopoietic stem cell transplantation in the neoadjuvant setting, in addition to other therapy (including trastuzumab for HER2+ tumors from 2005) [15]. Optimization of maintenance therapy after neoadjuvant treatment and surgery should continue to improve treatment outcomes.

The addition of lapatinib to trastuzumab maintenance therapy could be a promising therapeutic option to extend disease-free survival of patients with HER2+ metastatic breast cancer. The ongoing Phase III open-label trial of lapatinib plus trastuzumab (NCT00968968)

is investigating the benefit of this combination HER2-targeted therapy compared with trastuzumab alone.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.L. conceived the idea for the case report. All authors drafted and revised the case report. All authors read and approved the final case report.

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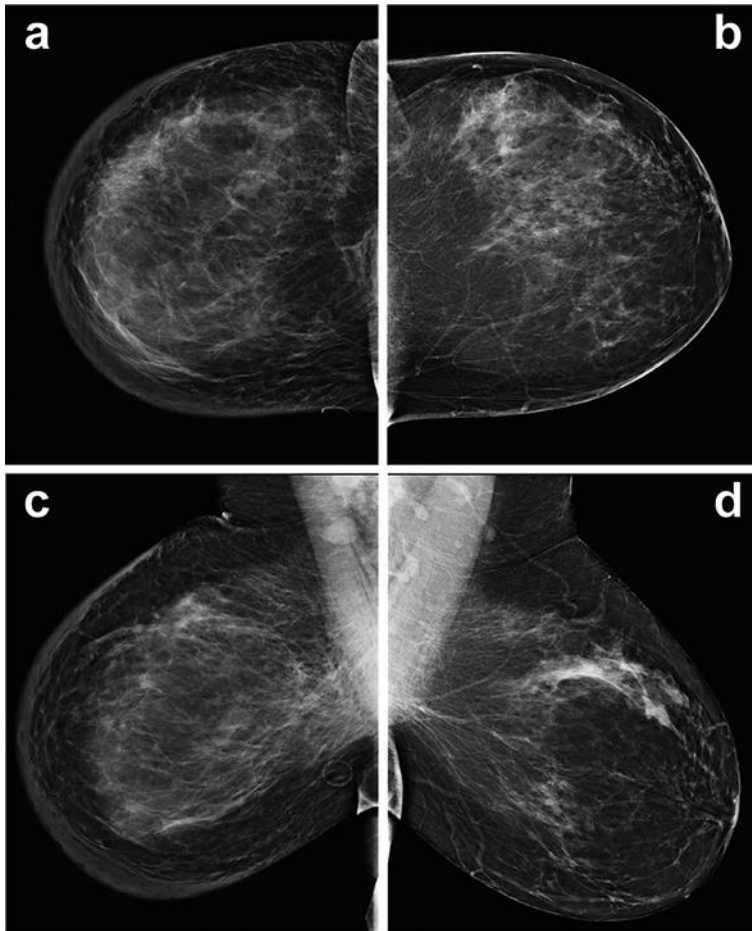


Fig. 1. Diagnostic digital bilateral mammogram. Views are (a) right craniocaudal, (b) left craniocaudal, (c) right mediolateral oblique, and (d) left mediolateral oblique. The images revealed scattered benign-appearing calcifications that limited the evaluation, and heterogeneously dense breast tissue that may have lowered the sensitivity of the mammography. Images of the right breast indicated skin thickening, more than 10 suspicious segmental calcifications in the upper outer quadrant anterior to posterior, and axillary adenopathy. A skin lesion on the right breast was consistent with a nevus. Intramammary lymph nodes were present in the left breast.