CLINICAL VIGNETTE

A Case of Widely Metastatic HER2 Positive Breast Cancer - Now a Chronic Disease?

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Case Report

A 38-year-old woman underwent a left mastectomy for stage IIIA T3N2 ER+, PR+, HER2 positive breast cancer. Adjuvant systemic chemotherapy was administered on a research protocol with doxorubicin and cyclophosphamide at standard doses for 3 cycles, followed by high dose chemotherapy with doxorubicin, cyclophosphamide, and paclitaxel with autologous stem cell rescue. Adjuvant external beam radiation therapy was also given, followed by tamoxifen.

Eight months after the start of adjuvant tamoxifen, this patient developed a malignant pleural effusion as her first site of metastatic disease. She was treated with docetaxel and trastuzumab with a complete response. After 2.5 years on maintenance therapy with letrozole and trastuzumab, she then developed extensive metastatic disease in pleura, lung, lymph nodes and liver. She was treated with vinorelbine and trastuzumab with another complete response.
She was then placed on anastrazole and trastuzumab for nearly 3 years, at which time she progressed in her lung and her treatment was changed to fulvestrant with trastuzumab. After 1 year on this therapy, she developed intrathoracic adenopathy, and her therapy was changed to exemestane and trastuzumab, to which she responded and has remained in complete remission for 5 years.

Discussion

Metastatic breast cancer generally has a poor prognosis, with brain metastasis resulting in the worst survival statistically, followed by liver metastasis[1]. Metastatic breast cancer is heterogeneous, with the subtype of breast cancer also playing a role in prognosis. Triple negative breast cancer often results in the shortest survival[2].

The patient discussed here is alive with no clinical evidence of disease 13 yrs after her initial diagnosis of metastatic disease. The question arises as to why this patient is maintaining a complete remission for so many years? She was able to achieve a complete response with two different chemotherapies in combination with trastuzumab, with prolonged progression free intervals on maintenance endocrine therapy with concurrent trastuzumab.

Her initial systemic therapy was adjuvant high dose chemotherapy with autologous stem cell rescue, 7 years prior to the FDA approval of trastuzumab for use in the adjuvant setting. At the time, there was great optimism that the use of high dose chemotherapy would improve survival for high risk breast cancer patients, with phase II data suggesting improved outcomes[3,4]. However, subsequent phase III trials did not demonstrate a benefit in overall survival[5], and this method of treatment was generally abandoned.

Systemic treatment options in metastatic breast cancer are based upon the hormone receptor status and HER2 status of the disease. For patients such as discussed here with “triple positive” breast cancer – ER positive, PR positive, and HER2 positive- the widest treatment options are available, which include endocrine therapy, chemotherapy, and HER2 blocking agents, often used in combination.

Preclinical data reveal consistent interactions of trastuzumab with a variety of chemotherapeutic agents, resulting in additive or synergistic cytotoxic effects[6,7]. In the clinical setting, chemotherapy in combination with trastuzumab has improved survival in metastatic HER2 positive breast cancer[8,9]. Still, development of resistance remains an important issue and general practice is to change chemotherapeutic agents but to continue HER2 blockade after disease progression. In preclinical studies, continuation of trastuzumab had continued effect against cell growth, with rapid tumor regrowth after it was withdrawn[8,10]. In addition, clinical data support the use of continued HER2 suppressive therapy for treatment of metastatic HER2 positive breast cancer after progression[11,12]. The continuation of second line trastuzumab was

evaluated in patients who had received prior trastuzumab as a single agent, and were randomized to chemotherapy with capecitabine, with or without trastuzumab. Time to progression was improved with the addition of trastuzumab, as was overall survival (26 vs 20 months), although the latter was not statistically significant. Of note is that continued trastuzumab therapy on this study was not associated with increased toxicity.

There are now a variety of FDA approved HER2 targeted therapies. Lapatinib, pertuzumab, and trastuzumab emtansine (T-DM1) are all available for use in metastatic disease. Should this patient's disease progress through her current treatment, she potentially could be treated with one of these agents for continued HER2 directed therapy. Lapatinib has shown efficacy in combination with chemotherapy, endocrine therapy, and when used with trastuzumab. Pertuzumab as of now is indicated for first line therapy of metastatic disease in combination with docetaxel and trastuzumab, but is being studied in combination with other chemotherapeutic agents and endocrine therapy in the metastatic setting. Trastuzumab emtansine, an antibody-drug combination of trastuzumab with the microtubule inhibitor maytansine, improves overall survival in pretreated women with metastatic HER2 positive breast cancer.

For patients with hormone receptor positive breast cancer, endocrine therapy remains an additional form of systemic therapy to target metastatic disease. Generally better tolerated than chemotherapy, endocrine therapy is a preferred option for prolonged systemic treatment. In the patient discussed here, the combination of various endocrine therapies with trastuzumab has resulted in prolonged periods of progression free survival in which she maintained a good quality of life. She currently remains on exemestane and trastuzumab, with a good functional status and no evidence of active disease. She has not had any significant loss in bone density, as can potentially be seen with prolonged therapy with the aromatase inhibitors such as exemestane.

Regarding the chronic use of trastuzumab, our patient has not experienced any toxicity, despite the prolonged use. One concern with treatment with this agent is potential cardiac toxicity, which when it occurs generally is manifested by an asymptomatic decline in ejection fraction, with rare congestive heart failure. After trastuzumab is held, the cardiac toxicity is often reversible, and many patients can then be rechallenged and tolerate further therapy well. Of note is that one of the risk factors for cardiac toxicity is prior anthracycline therapy, but fortunately this patient who received prior doxorubicin has not had cardiac complications of the trastuzumab.

This patient demonstrates that prolonged survival is attainable for some patients with HER2 positive metastatic breast cancer. The variety of chemotherapeutic and endocrine therapies available which may result in additive or synergistic effects in combination with chronic HER2 blockade have changed the natural history of HER2 positive breast cancer to a much more favorable, potentially chronic disease.

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Disclosures: MT, none; PC, none

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Submitted on June 5, 2013