

Original Article

Continuous trastuzumab treatment for more than 9 years of metastatic breast cancer without cardiotoxicity: a case report

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Abstract: Trastuzumab is the backbone treatment of HER2-positive early breast cancer and metastatic breast cancer. Trastuzumab revolutionized clinical outcomes and prognosis of HER2-positive breast cancer patients. However, the potential cardiac side effects of trastuzumab was concerned, and any trastuzumab-related Adverse Events would lead to trastuzumab discontinuation. Here we report a case of HER2-positive metastatic breast cancer, a 53-years-old woman, who was diagnosed with ER-positive, PR-positive and HER2-positive metastatic breast cancer, treated with trastuzumab-based chemotherapy and hormone therapy for over 9 years, no significant cardiac dysfunction happened and the metastatic disease was well controlled. This long survival case indicated that in the metastatic setting, 10 years continuous of trastuzumab was well tolerated and trastuzumab should be used as maintenance therapy for HER2-positive metastatic breast cancer until disease progression.

Keywords: HER2-positive metastatic breast cancer, long survival, trastuzumab

Introduction

Trastuzumab (Herceptin) is a humanized monoclonal antibody inhibitor of human epidermal growth factor receptor 2 (Her2/neu). Her2/neu belongs to the epidermal growth factor receptor family of transmembrane tyrosine kinase receptors, which is highly expressed in about 20% of invasive breast cancer. Activation of HER2 has been shown to lead to tumor growth and progression. Trastuzumab alters the natural history of HER2 positive breast cancer, and the combination or monotherapy provides superior survival benefits compared with the basic treatment [1]. Because of the use of trastuzumab, the progression of HER2-positive disease was significantly improved, and the progression-free survival (PFS) and overall survival (OS) of HER2-positive disease were significantly higher than those of HER2-positive [2].

Trastuzumab is an effective targeted agent. However, the clinical concern regarding long-term use of trastuzumab is cardiac tolerability owing to the unexpected high incidence of cardiac

events reported by the early pivotal trials, particularly when associated with anthracyclines. Despite the introduction of trastuzumab, the majority of Her2-positive metastatic breast cancer patients treated with trastuzumab-based regimens on progress within one year, with only very few patients experiencing prolonged remission. It is not known whether continuing trastuzumab after progression improves the OS of women with metastatic breast cancer. Accordingly, the Phase III study did not demonstrate a significant survival benefit for treatment beyond progression with trastuzumab [3]. Here, we introduce the case of a postmenopausal woman with metastatic breast cancer, currently in complete remission, who received trastuzumab for more than 9 years, without any significant cardiac toxicity.

Case report

In October 1997, a 34-year-old woman, with no history of hormone therapy, smoking, drinking, or a family history of breast cancer, presented to a medical oncologist with a complaint of a

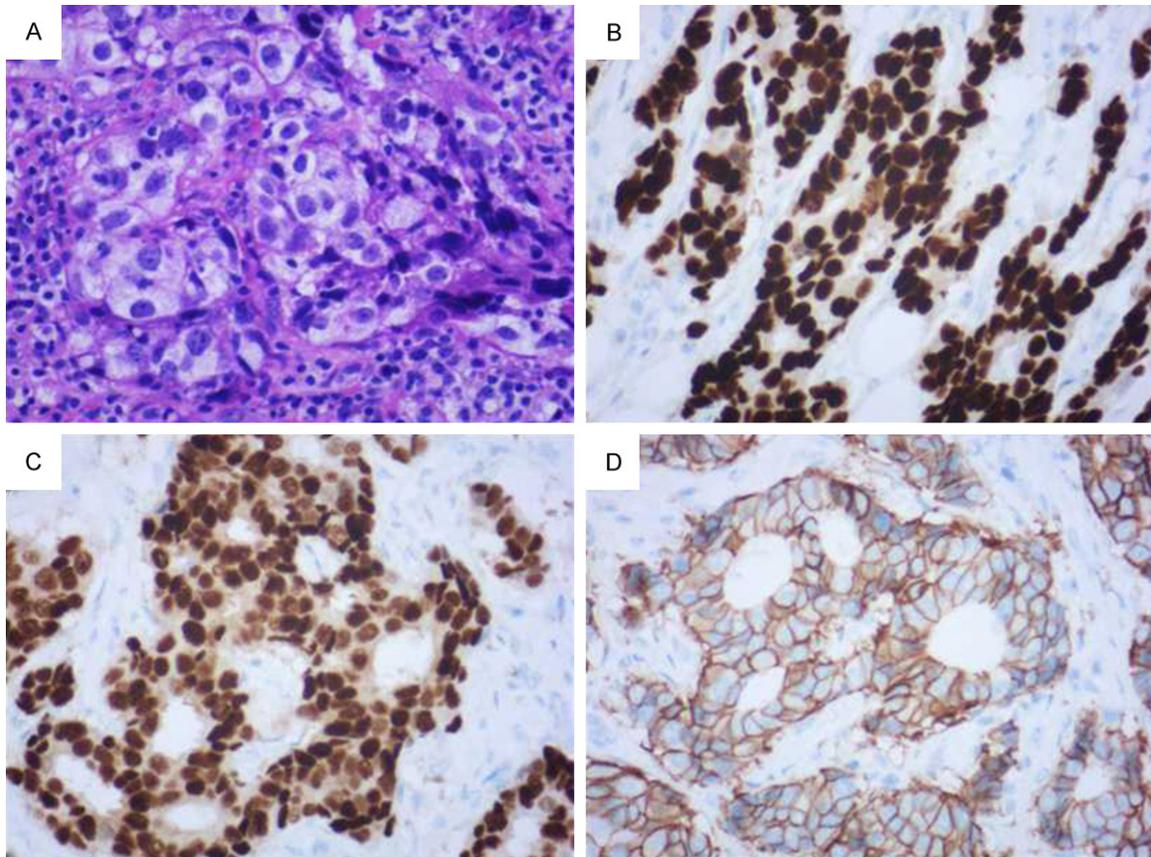


Figure 1. The biopsy of the resected specimens.

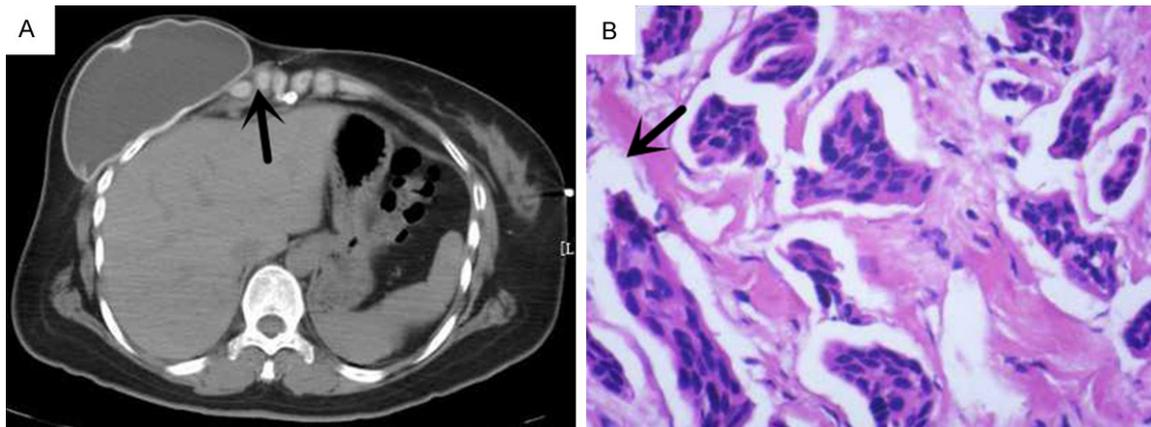


Figure 2. The biopsy and CT scan of the chest wall metastasis.

right breast mass. The axillary and neck lymph nodes were not palpably enlarged. After breast biopsy, radiography of the chest and ultrasound of the abdomen, the patient underwent a right radical mastectomy. Pathologic examination of the resected specimens revealed invasive ductal carcinoma (**Figure 1A**). The size of the primary tumor was 2 × 2.5 × 3 cm. The tumor was

found to be estrogen receptor-(ER) positive (80%-90%) (**Figure 1B**), progesterone receptor-(PR) positive (80%-90%) (**Figure 1C**), and Her2/neu positive (immunohistochemistry 3+) (**Figure 1D**).

The patient was treated with adjuvant chemotherapy, eight cycles of methotrexate, 5-fluoro-

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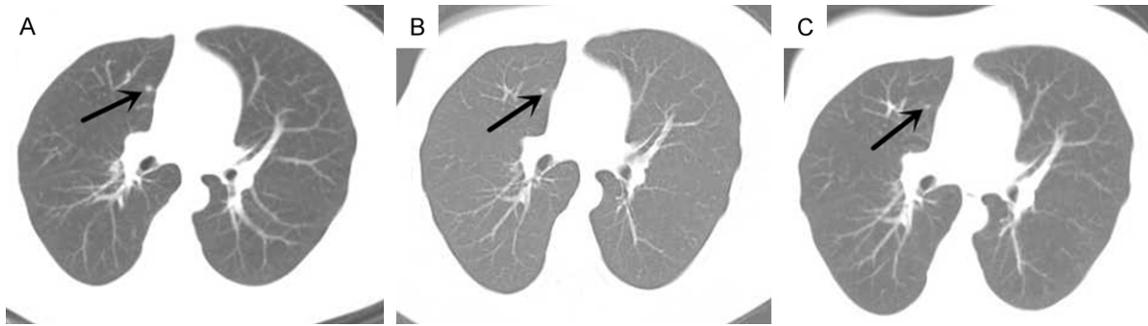


Figure 3. CT scans of the lungs.

Table 1. Process of therapy

| Time | Treatment | Response |
|----------------|--|----------|
| 1997/10/1 | Modified radical right mastectomy | / |
| 1997/11-1998/6 | 8 cycles of methotrexate, 5-fluorouracil and cyclophosphamide (40 mg/m ² d1, 8, 500 mg/m ² d1, 8, and 600 mg/m ² d1, 8, respectively) | / |
| 1998/7-2003 | Tamoxifen (20 mg/d) | PD |
| 2005/11-2006/3 | 8 cycles of docetaxel (75 mg/m ²) every 3 weeks, in combination with weekly trastuzumab (2 mg/kg) | PR |
| 2006/4-2014/5 | Letrozole (2.5 mg orally per day) and goserelin (3.6 mg subcutaneously every 28 days) in combination with weekly trastuzumab (2 mg/kg) | PR |

uracil and cyclophosphamide (40 mg/m² d1, 8, 500 mg/m² d1, 8, and 600 mg/m² d1, 8, respectively). Then, the patient received tamoxifen (20 mg/d) for more than 5 years, until 2003. A reevaluation of the lesion by radiography and CT followed regularly thereafter and showed a stable disease. In October 2005, after computed tomography (CT), the patient presented with lung and chest wall metastasis (**Figures 2A and 3A**). The chest wall metastasis was biopsied and the biopsy results revealed adenocarcinoma (**Figure 2B**).

At that time, CA 15-3 level increased to 239.5 U/ml. The patient was treated for eight cycles of docetaxel (75 mg/m²) every 3 weeks, in combination with weekly trastuzumab (2 mg/kg), with good clinical response. In March 2006, the chest wall mass was biopsied and the biopsy result was found to be cancer-free. The patient continued to be received trastuzumab (6 mg/kg) every 3 weeks for more than 7 years, until December 7, 2012. CT scans of the lungs performed in 2008 and 2013 have shown stable pulmonary metastatic disease for 8 years (**Figure 3B and 3C**).

In April 2006, the patient was started on letrozole (2.5 mg orally per day) plus goserelin (3.6

mg subcutaneously every 28 days). In May 2014, the patient was found to have increased CA 15-3 level (179.5 U/ml). At that time, the patient was given trastuzumab (6 mg/kg) every 3 weeks. CA 15-3 level decreased to 25 U/ml in January 2015. In June 2015, scan of the CA 15-3 revealed a normal level, and her PET-CT scan did not show any evidence of active metastasis disease.

The foregoing indicates that, in this patient, continuous trastuzumab treatment was generally well tolerated. To summarize, more than 9 years of continuous trastuzumab treatment appears to be safe. The most recent echocardiogram performed in August 2015, was normal (ejection fraction: 61%). Process of therapy for the patients were shown in **Table 1**.

Discussion

MBC's clinical management is still a major therapeutic challenge because the oncologists balance the overall survival and improvement of patients' quality of life. Although after more than 30 years of researches, MBC is basically impossible to cure, the median survival time is about two years [4]. The therapy based on trastuzumab significantly improved the survival of

these HER2-positive MBC patients, and treatment continued at least until the disease progressed to its greatest benefit [5]. However, if trastuzumab is withdrawn, the disease may recur. Preclinical data suggest that if the trastuzumab withdrawal was withdrawn, previously inhibited tumor growth was rapidly restored [6]. Thus, the effective treatment of HER-2-positive diseases appears to require prolonged attenuation of HER-2 activity and it is difficult to define the time point beyond which trastuzumab may not provide additional benefit.

Furthermore, evidence in the literature supports the idea that continuing anticancer treatments as maintenance therapy in patients with stable disease may prolong the disease-free interval [7]. There are an increasing number of case reports describing patients who experienced long-term remission from HER-2-positive MBC while receiving Trastuzumab maintenance therapy [8].

In our case, after seven years treatments with trastuzumab the patient decided to stop the treatment despite being informed about the possible chance of relapse after trastuzumab withdrawal. Then, CA 15-3 level is increased within eleven months of withdrawal of trastuzumab maintenance therapy. CA 15-3 has been suggested as a marker of metastatic breast cancer. CA 15-3 might also be used in monitoring patients for the development of distant metastases during follow-up. In patients without metastasis, we observed a high incidence of early recurrence when initial CA 15-3 concentrations were high.

An important concern of many clinicians regarding long-term use of trastuzumab is cardiac tolerability owing to the unexpected high incidence of cardiac events reported by the early pivotal trials, particularly when associated with anthracyclines. It is therefore difficult to compare trials with different end points and eligibility criteria, however, the understanding of trastuzumab related cardiac events has since improved, and the majority of these events are manageable and reversible [9]. Extending trastuzumab treatment does not seem to be associated with an increased risk of cardiac dysfunction. In studies of trastuzumab treatment beyond progression, cardiac events appear to become relatively uncommon and mostly asymptomatic [10].

Conclusion

Chemotherapy and hormonal therapy play an essential role in the treatment of metastatic breast cancer. The debate on the continuation of secondary trastuzumab after initial progress has not yet been resolved, and our case suggests that this strategy may be beneficial for some patients. Trastuzumab combined with chemotherapy and hormone therapy may be synergistic, and may serve as the basis for different therapeutic agents. In the metastatic setting, the benefits of using trastuzumab in the forefront of the patient are obvious. In some HER2 positive metastatic breast cancer patients, such as our patient, long-term use of trastuzumab and careful cardiac monitoring, combined with chemotherapy and hormone therapy may help to achieve long-term survival or even cure.

Acknowledgements

Our study was approved by an independent ethical committee/institutional review board of Naval General Hospital of PLA, Beijing, China and patient.

Disclosure of conflict of interest

None.

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