

## Trastuzumab and Chemotherapy after the Treatment Failure of lapatinib for HER2-positive Metastatic Breast Cancer

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We describe a patient with human epidermal growth factor receptor type 2 (HER2 / *c-erbB-2*)-positive metastatic breast cancer who survived for approximately 6 years after the initiation of combination therapy with trastuzumab and varying types of chemotherapeutic agents. The patient was a 48-year-old postmenopausal female who underwent partial mastectomy with axillary node dissection for cancer of the right breast in March 1994. She developed lung metastases 2 years thereafter, but survived free of relapse for 8 years following chemotherapy and pulmonary lobectomy. The patient failed to respond to lapatinib, a HER1 (EGFR) / HER2 tyrosine kinase inhibitor, received during the course of her treatment but then again responded to subsequently administered trastuzumab. Primary treatment with trastuzumab and paclitaxel was initiated in April 2004 when the patient developed hepatic metastases 8 years after undergoing surgery for lung metastases. Long-term combination therapy with continued trastuzumab and a variety of chemotherapeutic agents was administered for 6 years without any significant adverse events.

We discuss the treatment strategies for HER2-positive breast cancer and the role of lapatinib, a recently approved anticancer drug.

**Key words:** Breast cancer, trastuzumab, lapatinib, HER2

### INTRODUCTION

Trastuzumab is the first available anti-human epidermal growth factor receptor type 2 (HER2 / *c-erbB-2*) humanized monoclonal antibody for treating metastatic breast cancer with HER2 overexpression.

Developed by Genentech of the United States, clinical studies found trastuzumab to be clinically useful by, extending survival, improving response, and extending time to progression when used in combination with chemotherapy in comparison to chemotherapy alone [1-8]. Trastuzumab was approved by the American Food and Drug Administration (FDA) in 1998, and covered by Japan's national health insurance program in 2001. Trastuzumab is now used extensively to treat all grades of, i.e., early to metastatic, breast cancer. The advent of trastuzumab has revolutionized the treatment of HER2-positive breast cancer.

No definitive conclusions have been reached as to whether to continue or discontinue trastuzumab administration when treatment-failed, recurrent HER2-positive breast cancer stops responding to trastuzumab as a first-line treatment. In clinical practice, however, caregivers continue to administer trastuzumab with alternating concomitant chemotherapy.

This case report describes a patient who failed to respond to the tyrosine kinase inhibitor lapatinib, which binds to the HER1 (EGFR) / HER2 intracellular domain, but subsequently achieved a partial response when resumed on trastuzumab in combination with gemcitabine. Trastuzumab has been reported to have a

direct tumor-growth suppressing effect to contribute to antibody-dependent cell-mediated cytotoxicity (ADCC). The patient underwent long-term combination therapy for 6 years with trastuzumab and various chemotherapeutic agents, which contributed to her long-term survival. Attributing her survival to the synergistic effect achieved with trastuzumab and chemotherapeutic agents and the contribution of ADCC, the authors document this case and present a brief discussion.

### CASE REPORT

A 48-years-old woman underwent partial mastectomy with axillary node dissection in March 1994. The results of the microscopic pathological examination revealed invasive ductal carcinoma measuring 18 × 12 mm in size. Axillary node metastasis was noted. Immunohistochemical study revealed ER-negative, PgR-negative and HER2-positive (3+) characteristics. She underwent adjuvant chemotherapy with 2 cycles of cyclophosphamide / adriamycin / 5-FU (CAF). Two years after surgery, left pulmonary metastasis was detected. She was administered chemotherapy with 2 cycles of CAF. After the chemotherapy, video-assisted thoracic surgery (VATS) was performed in January 1997 and again in October 2000. Furthermore, in June 2001, left lower lobectomy of the lung was performed because of progressive disease. The patient was treated to this point at another medical institution.

Eight years after undergoing removal of lung metastases she was referred to our medical institution with suspected liver metastases. As a systemic search revealed no distant metastases in the lungs, bone, or

brain, a diagnosis of hepatic metastases alone was made. Combination therapy with trastuzumab and paclitaxel was initiated as an initial treatment for HER2-positive metastatic breast cancer. After 24 weeks of treatment, the patient achieved a partial response (PR) that was maintained for 29 months. Time to progression (TTP) was 33 months. Combination therapy with trastuzumab and capecitabine was subsequently initiated, bringing about a PR as the best response. TTP was 13 months. Trastuzumab was then continued in combination with vinorelbine, which brought about stable disease as the best response with a TTP of 10 months. The patient developed no serious adverse events at any time during the treatments.

With disease progression, the patient was discontinued from trastuzumab treatment and participated in a phase II clinical trial of monotherapy with lapatinib in Japan, an epidermal growth factor receptor (EGFR or HER1) / HER2 dual tyrosine kinase inhibitor. She failed to respond to lapatinib monotherapy, and progressive disease was diagnosed based on a rapid increase in hepatic metastases (Fig. 1 and 2). Treatment with trastuzumab was resumed in combination with gemcitabine, which resulted in a rapid decrease in tumor markers. Hepatic metastases shrank substantially after 12 weeks of treatment (Fig. 3). PR was the best response, and the TTP was 24 weeks.

Subsequent disease progression brought general deterioration. The patient suffered acute aggravation of liver metastases despite combination therapy with trastuzumab and cyclophosphamide / methotrexate / 5-FU (CMF) or carboplatin and died of hepatic failure. Treatment was long term, continuing for 11 years after onset of disease and 6 years after the initiation of trastuzumab, but was always administered on an outpatient basis and brought about no serious adverse events (Fig. 4). It is concluded that trastuzumab in the treatment of HER2-positive breast cancer contributes to survival without affecting the patient's quality of life and is very useful in treating HER2-positive breast cancer.

## DISCUSSION

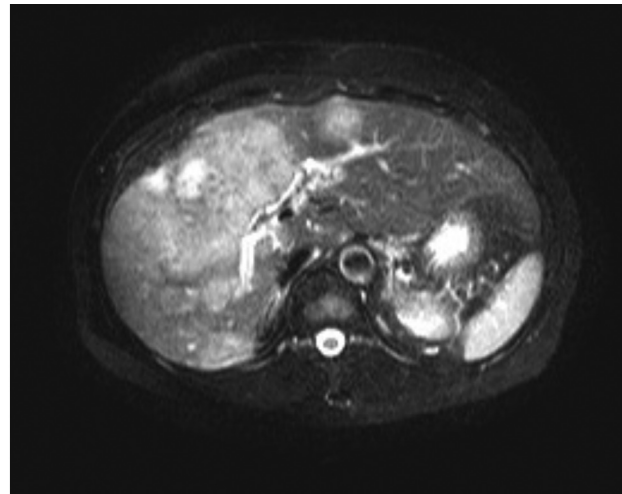
HER2/*c-erbB-2* is a member of the HER family, taking the form of a homodimer or a heterodimer with other HER family members. HER2 promotes the phosphorylation of intracellular tyrosine kinase, activating the signal transmission activity of PI3K/Akt downstream and Ras/MAPK growth stimulation to promote tumor growth.

Trastuzumab is the first anti-HER2 humanized monoclonal antibody for treating metastatic breast cancer with HER2 overexpression and has greatly improved the prognosis of HER2-positive breast cancer patients, which accounts for 25%–30% of all breast cancer patients, and has revolutionized the treatment of this disease.

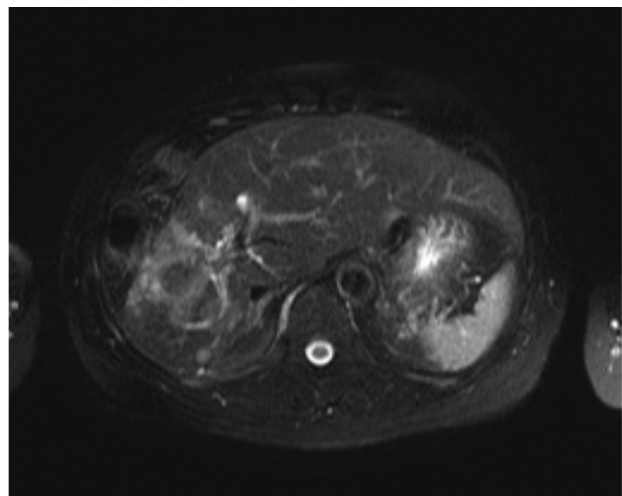
Trastuzumab derives its anticancer effects by binding to HER2 to suppress intracellular growth signals via the HER2 receptor, induces p27 to halt the cell cycle in G1, and otherwise directly inhibit tumor growth. Additionally, trastuzumab as an antibody binds to HER2 on the surface of tumor cells so that effector cells bind to the Fc portion of the antibody via recep-



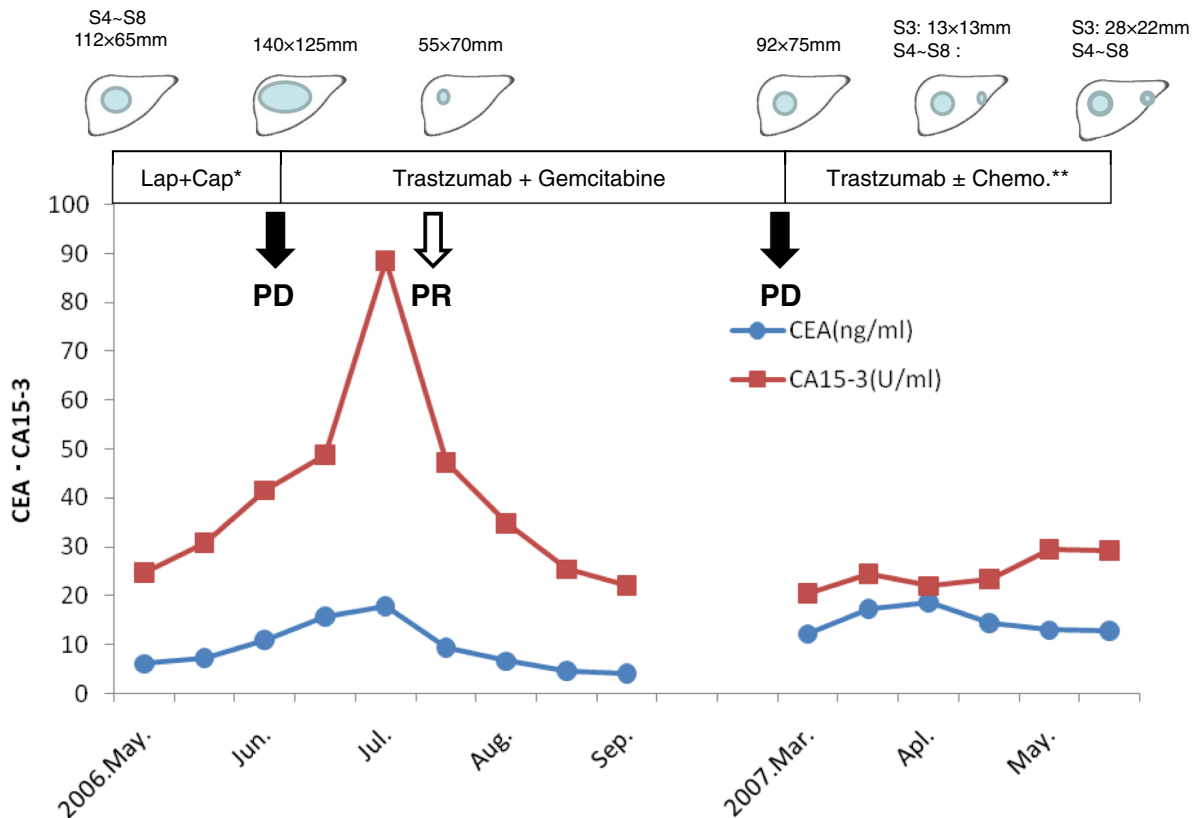
**Fig. 1** Magnetic resonance imaging shows the metastatic liver tumor before treatment with lapatinib. Lobulated and en-bloc tumor was observed, measuring 12 × 7 cm in size.



**Fig. 2** Two months after initiating treatment with lapatinib, the metastatic liver tumor rapidly upsized to 14 × 12 cm.



**Fig. 3** Three months after initiating treatment with trastuzumab, the metastatic liver tumor downsized to 7 × 5.5 cm.



\*: Lap: Lapatinib, Cap: Capecitabine, \*\*: Chemo: CMF, CBDCA

**Fig. 4** The tumor marker decreased by trastuzumab with gemcitabine after the treatment failure of lapatinib.

tors present on the cell surface, activating antibody-dependent cell-mediated cytotoxicity (ADCC) to produce an antitumor effect through immune functions that heighten natural killer (NK) cell and macrophage functions [9]. Other hypothesized mechanisms include apoptosis, complement-dependent cytotoxicity (CDC), increased sensitivity to chemotherapeutic agents, damage to DNA repair function, and effects on cell adhesion.

Trastuzumab monotherapy and combination comprising with trastuzumab and chemotherapy have been established as standard therapies for treating HER2-positive metastatic breast cancer. The American NCCN Clinical Practice Guidelines in Oncology assigns a grade I recommendation to these treatments, strongly recommending them based on evidence.

Retrospective studies [10-12] have investigated whether trastuzumab treatment should be continued or chemotherapy with no trastuzumab should be administered in patients who stop responding to trastuzumab, these have concluded, similar to prospective clinical studies [13-14] that continuation of trastuzumab is beneficial. Therefore, it is now common practice to continue administering trastuzumab to patients who have been switched to chemotherapy after ceasing to respond to trastuzumab. Long-term combination treatment of trastuzumab and chemotherapy was possible in the patient described in this article.

Lapatinib inhibits EGFR and HER2 tyrosine kinase to reduce MARK-ERK1/2, a HER2 growth signal,

as well as AKT phosphorylation to inhibit cancer cell growth [15]. Lapatinib was found to be effective in the treatment of HER2-positive breast cancer when used in combination with capecitabine [16] or paclitaxel [17]. This patient participated in a Japanese phase II clinical trial of lapatinib monotherapy after ceasing to respond to combination trastuzumab and chemotherapy, but failed to respond to this drug. Cancer cells become resistant to trastuzumab when protein kinases cleave away the HER2 protein molecules present on the cell surface, removing the extracellular domain. Trastuzumab is then no longer able to bind to these cancer cells, which thereby gain resistance. The protein with the missing extracellular domain is detectable as p95 [18]. Lapatinib derives its efficacy by inhibiting HER2 protein tyrosine phosphorylation and disrupting intracellular signaling pathways and may therefore be effective in p95-expressing cells. Resistance to trastuzumab is achieved when AKT activation occurs following loss of PTEN [19]. The fact that trastuzumab resistance occurs with intracellular signaling changes suggests that lapatinib may have minimal efficacy in resistant patients.

Lapatinib is superior to trastuzumab in that it is taken orally and is effective in treating brain metastases. It is presently unclear, however, how lapatinib should be added to trastuzumab-based treatments or if the drug could prove a viable replacement to trastuzumab. Further research is essential for identifying presence of biomarkers other than HER2 that can predict efficacy

and for understanding the mechanism of lapatinib resistance.

The patient was switched to lapatinib after ceasing to respond to trastuzumab, which targets the HER2 protein, but failed to respond. She then responded when resumed on trastuzumab in combination with gemcitabine, making it an interesting case. Although the resistance to both drugs by the patient has not been thoroughly investigated, trastuzumab's ADCC activity continues as long as the drug can bind as an antibody to HER2 and likely derives its primary mechanism through working synergistically with chemotherapy, continued with another chemotherapeutic agent when a patient stops responding to trastuzumab and a given agent.

As has been discussed, continuing trastuzumab treatment while changing the chemotherapeutic regimen improves the patient quality of life and contributes to longer survival.

### CONCLUSION

Continuing trastuzumab with another chemotherapeutic agent when the patient stopped responding to trastuzumab and a given agent was found to again produce a therapeutic effect. Trastuzumab may be effective in patients that do not respond to lapatinib. These two drugs that target the HER2 protein will no doubt revolutionize breast cancer treatment. It appears important to continue suppressing HER2 signaling when treating HER2-positive breast cancer.

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