

Long-term remission of hormone receptor-positive/HER2-positive metastatic breast cancer due to combined treatment with everolimus/trastuzumab/exemestane: A case report

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Abstract. The present case report describes a postmenopausal patient with hormone receptor (HR)⁺/human epidermal growth factor receptor 2 (HER2)⁺ metastatic breast cancer, who experienced progression of disease in bilateral lungs, lymph nodes and the liver under previous endocrine therapy and trastuzumab. Following the failure of two lines of endocrine-based treatment, the patient was administered the combined treatment of everolimus, trastuzumab and exemestane following surgical resection of the liver metastasis. A durable partial remission was achieved, which has continued for >27 months. This prominent clinical outcome in this patient demonstrates that the combined administration of endocrine therapy, trastuzumab and everolimus is clinically effective, and may induce long-term remission in patients with HR⁺/HER2⁺ metastatic breast cancer.

Introduction

Breast cancer is the most common type of cancer diagnosed in females between the ages of 30 and 59 years, and is the leading cause of cancer-associated mortality in females <45 years (1). Breast cancer is a heterogeneous disease with 5 molecular subtypes: Luminal A, luminal B, human epidermal growth factor receptor 2 (HER2)-enriched, normal-like breast cancer and basal-like breast cancer. Each of these subtypes exhibits important prognostic and predictive information which enables the appropriate treatment to be administered (2-4). Hormone receptor (HR) status serves a notable role in selecting systemic

hormonal therapy for patients with early and advanced breast cancer (5-7). Endocrine therapy is the preferred option for HR⁺ disease, even in the presence of visceral disease, unless there is an indication of endocrine resistance or rapidly progressive disease (8).

Estrogen receptor (ER) and/or progesterone receptor (PR) expression occurs in ~50% of patients with HER2⁺ breast cancer and patients with ER⁺/HER2⁺ metastatic disease typically obtain less benefit from endocrine therapy, compared with patients with HER2/HR⁺ disease (9-14). Previous studies have suggested that cross-talk between the ER and HER2 pathways is implicated in resistance to endocrine therapy and supports tumor progression (15-18). Furthermore, several clinical studies indicate that simultaneous inhibition of the HER2 and ER signaling pathways is more effective than ER inhibition alone (19-21). These studies suggest that a combination of endocrine therapy and HER2 inhibition may be the optimal treatment for HR⁺/HER2⁺ breast cancer; however, this remains unclear.

The interaction between the phosphoinositide 3-kinase (PI3K)-protein kinase B-mammalian target of rapamycin (mTOR) and ER signaling pathways is an additional emerging mechanism of endocrine resistance (22-24). mTOR is a downstream target in the HER2 signaling pathway and is associated with the activity of the ER signaling pathway. A number of clinical studies have identified the value of using allosteric mTOR inhibitors in combination with anti-estrogen therapy in advanced endocrine-resistant tumors. Everolimus, an mTOR inhibitor, is effective in treating tumors which exhibit increased activity of the mTOR signaling pathway and therefore is a potential agent for the reversal of endocrine resistance (25,26).

To the best of our knowledge, there have been no previous studies on the co-suppression of the ER, HER2 and mTOR signaling pathways. The present case report describes a patient with metastatic breast cancer who has received systemic treatment with a combination of an estrogen inhibitor, trastuzumab and everolimus. Progression-free survival (PFS) of the patient has currently extended to 27 months and continues at the time of writing. Thus, the inhibition of ER, HER2 and mTOR may produce an improved clinical outcome, suggesting a combination strategy for patients with HR⁺/HER2⁺ breast cancer.

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Case report

In March 2002, a 48-year-old female identified a mass in her right breast. The patient underwent a modified radical mastectomy with axillary lymph node dissection in the same month. Pathological examination revealed a 2x2 cm infiltrative ductal carcinoma that was ER⁺, PR⁺ and HER2⁻, with no metastases to the axillary lymph nodes at that time (pT1N0M0, using the pathological tumor-node-metastasis staging). The patient was administered adjuvant chemotherapy comprising cyclophosphamide (500 mg/m²), epirubicin (100 mg/m²) and 5-fluorouracil (500 mg/m²) every 3 weeks over 18 weeks (for 6 cycles). Subsequently, the patient received anti-estrogen therapy (tamoxifen at 20 mg/day) for 5 years and regular medical examinations.

In March 2010, the patient identified a hard lump in a right supraclavicular lymph node. The subsequent computed tomography (CT) scan of the chest revealed multiple nodules in the lungs (Fig. 1A and B). The subsequent excision biopsy revealed metastatic adenocarcinoma, and immunohistochemistry identified it to be ER⁺, PR⁻ and HER2⁺⁺-HER2⁺⁺⁺. Tumor sections were deparaffinized and stained with antibodies against ER, PR, HER2, using standard protocols (27,28). Fluorescent *in situ* hybridization (FISH) determined HER2 gene amplification. Docetaxel (75 mg/m² on day 1) and capecitabine (1,250 mg/m² twice daily on days 1-14) was administered in combination with trastuzumab (8 mg/kg loading dose, 6 mg/kg subsequently) every 3 weeks for 3 cycles until the patient developed hand-foot syndrome. The patient experienced reddening, desquamation and numbness of the palms of the hands and soles of the feet, due to the side effects of capecitabine. Subsequently, capecitabine was replaced by gemcitabine (1,000 mg/m² on days 1 and 8). The regimen was carried on for 3 cycles until August 2010, when a CT scan indicated partial remission of the pulmonary metastasis (Fig. 1C and D). Subsequently, the patient was administered anastrozole (1 mg/day) combined with trastuzumab (6 mg/kg) every 3 weeks. The administration of trastuzumab was stopped after 1 year for financial reasons.

In May 2012, the patient identified another lump in the right supraclavicular fossa; however, a CT revealed no progression of the lesions in the lungs. Radiation therapy of 24 Gy in 12 fractions was administered to the right supraclavicular lymph nodes with a complete response. Subsequently, the patient received endocrine therapy with fulvestrant (250 mg every 4 weeks) followed by stable disease for 19 months. In December 2013, a CT scan identified novel nodules in the lungs (Fig. 2) and a single 4x4 cm low-intensity lesion in the liver (Fig. 3). In addition, the level of the tumor marker CA153 was revealed to be >300 U/l. The pulmonary metastases were stable. The patient underwent surgical resection of the liver metastasis 1 week later and whole-exome sequencing was performed on a partially resected specimen of the liver. Postoperative pathology revealed liver adenocarcinoma derived from the breast; immunohistochemistry indicated that they were ER⁺, PR⁻ and HER2⁺⁺⁺ (Fig. 4). The patient was administered everolimus (5 mg/day) and exemestane (25 mg/day) in combination with trastuzumab every 3 weeks. After 5 months of treatment, there was partial remission of the lesions in the lungs and liver (Figs. 2B and 3B) with a marked decrease in levels of CA153. The patient currently remains on the combined regimen of

everolimus, trastuzumab and exemestane, and regular medical examinations have identified no recurrence or additional metastases for >27 months (Figs. 2C and 3C).

All procedures performed in the present case report were in accordance with The Declaration of Helsinki (1964) and its later amendments or comparable ethical standards. Written informed consent was obtained from the patient for inclusion in the present case report.

Discussion

Endocrine therapy is the fundamental treatment for patients with HR⁺ advanced breast cancer; however, a number of patients develop resistance despite experiencing an initial benefit (29,30). In the present case report, the regimens were administered on the basis of the recommendations of the National Comprehensive Cancer Network (31). For patients who are sensitive to endocrine medications, the three-sequential lines of endocrine-based therapy may be continued until accompanied symptomatic visceral diseases occur (31). Previous clinical studies have suggested that aromatase inhibitors (resulting in estrogen deprivation) may be more effective compared with tamoxifen in patients with ER⁺ tumors that overexpress HER2 (32,33). A previous clinical study demonstrated that first-line fulvestrant is at least as effective as anastrozole in exhibiting a clinical benefit response and objective response rate, and is associated with a markedly longer time to progression. Thus, first-line fulvestrant may offer longer-lasting disease control in the treatment of advanced breast cancer (34).

Cross-talk between the ER and HER2 signaling pathways is implicated in resistance to endocrine therapy and therefore supports tumor progression (15,16). Massarweh *et al* (29) identified that tamoxifen resistance is mediated by the activation of HER family signaling which may be a result of increased expression of HER ligands and the release of membrane-bound HER ligands which act in an autocrine manner; however, this may be inhibited by the HER inhibitor gefitinib. In addition, Evans *et al* (35) demonstrated that AEE788, an epithelial growth factor receptor/HER2 inhibitor, increased ER-mediated transcription in HER2⁺/ER⁺ breast cancer cells. This indicated that letrozole in combination with AEE78 may be superior to letrozole alone for the treatment of acquired ER⁺/HER2⁺ endocrine-resistant breast cancer. A previous study provided a rationale for the dual inhibition of ER and HER2; for instance, the Trastuzumab and Anastrozole Directed Against ER-Positive HER2-Positive Mammary Carcinoma study, the first randomized Phase III study to combine a hormonal agent with trastuzumab without chemotherapy to treat HR⁺/HER2⁺ metastatic breast cancer, has identified that the combination of trastuzumab and anastrozole improves outcomes, compared with anastrozole alone (19). An additional study has demonstrated that the combination of letrozole and trastuzumab produces durable responses in HER2⁺ and ER⁺ advanced breast cancers: The median time to progression was 5.8 months and the duration of response was >20.6 months (9). These observations suggest that the optimal treatment for HR⁺/HER2⁺ breast cancers may be a combination of endocrine therapy and HER2 inhibitors (36). On the basis of the results of previous studies (9,19,35), endocrine therapy

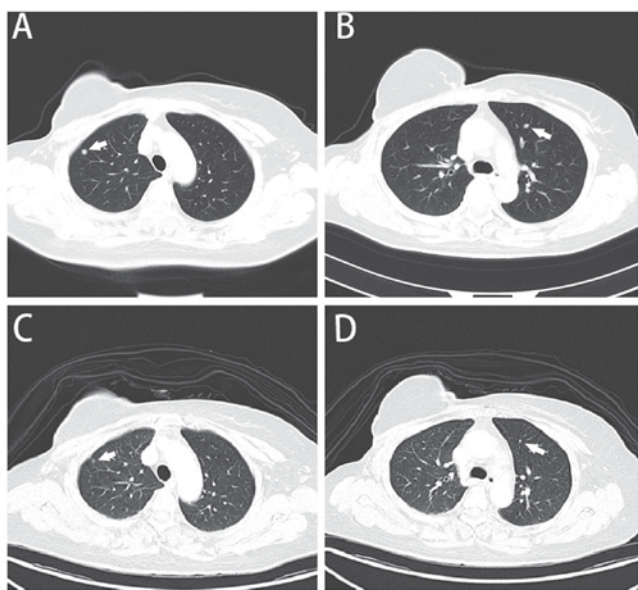


Figure 1. CT scan demonstrating lung metastasis. (A) CT scan of the chest demonstrating pulmonary metastases (March 2010). A metastatic lesion in the right lung (lesion 1) is indicated by an arrow. (B) CT scan of the chest demonstrating pulmonary metastases (March 2010). A metastatic lesion in the left lung (lesion 2) is indicated by an arrow. (C) CT scan of the chest demonstrating partial remission of lesion 1 (October 2010). (D) CT scan of the chest demonstrating the partial remission of lesion 2 (October 2010). CT, computed tomography.

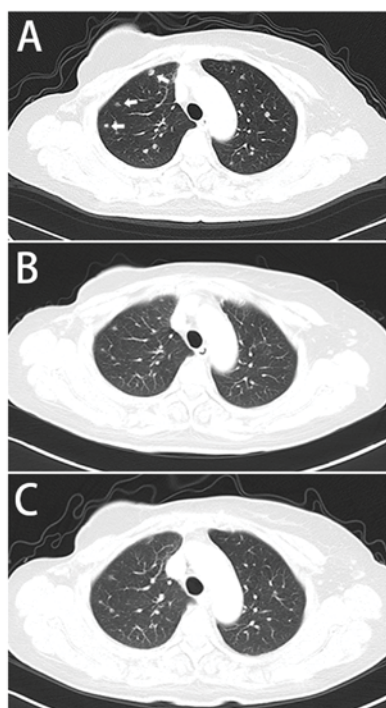


Figure 2. CT scan demonstrating the progression of the pulmonary metastases. (A) CT scan of the chest (December 2013) revealing increased number of nodules in the lungs, indicated by arrows. (B) CT scan (May 2014) revealing partial remission of the lesions in the lungs. (C) CT scan (December 2015) demonstrating stable disease. CT, computed tomography.

combined with trastuzumab in the first- and second-line treatment of advanced breast cancer was selected in the present

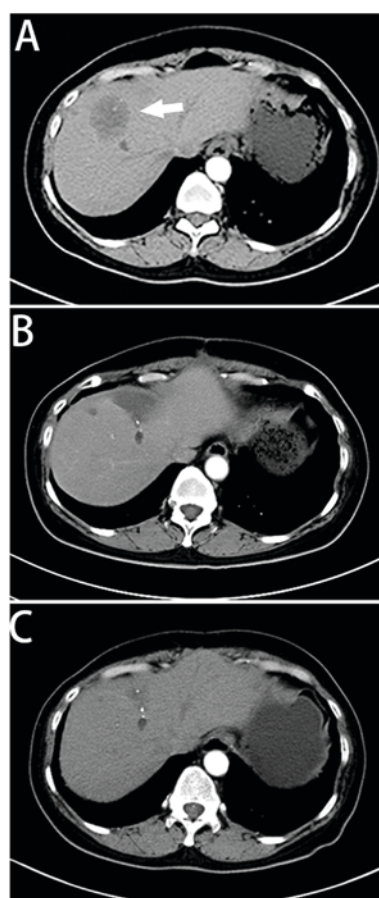


Figure 3. CT scan demonstrating liver metastasis. (A) CT scan (December 2013) of the abdomen revealing a single 4x4-cm low-density shadow in the right lobe. (B) CT scan (May 2014) of the abdomen demonstrating complete remission of the hepatic metastasis. (C) CT scan (December 2015) of the abdomen indicating no recurrence of the liver metastasis. CT, computed tomography.

case report. When the first progression was assessed in a right supraclavicular lymph node and the lungs, trastuzumab in combination with chemotherapy was recommended to control the disease. Subsequently, trastuzumab was combined with anastrozole for maintenance therapy. When the second progression was observed, following a complete response to radiation therapy, anastrozole was replaced by fulvestrant to stabilize the disease for a longer period of time. However, the combination of trastuzumab and endocrine therapy may only be recommended for patients with less extensive or asymptomatic metastatic disease. For young patients, or those with life-threatening or symptomatic disease, chemotherapy-based HER2-targeted combination therapy may be preferred.

In the present report, after 19 months of PFS, a single liver metastasis was identified by CT. Although liver resection in patients with breast cancer exhibiting extrahepatic metastases has been debated, a number of studies determining the role of therapeutic hepatic metastasectomy have demonstrated encouraging survival statistics for patients with tumors of low histological grade, long disease-free interval and patients with well-controlled extrahepatic metastases (37-39). Chua *et al* (40) identified a median survival time following partial hepatectomy of 40 months and a 5-year survival rate of 40%, which suggested that surgery for liver metastases,

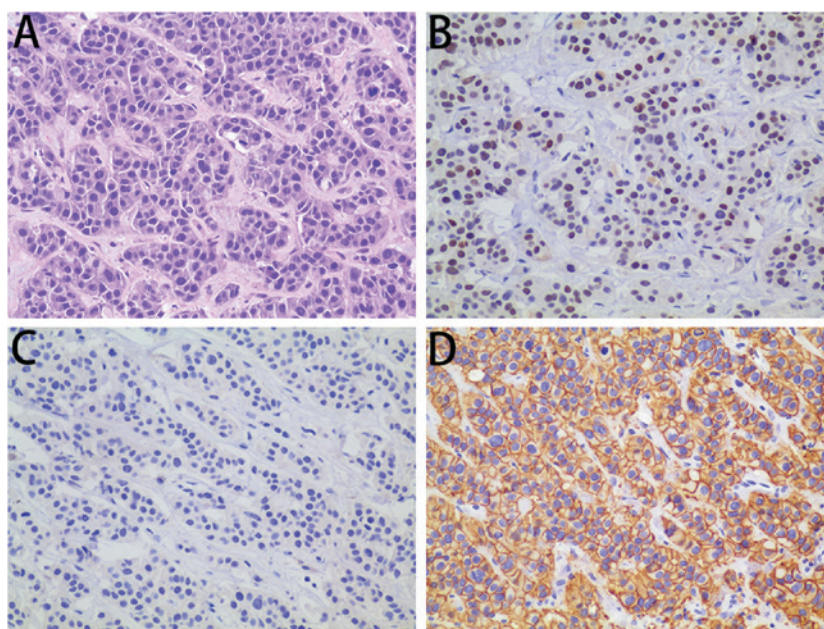


Figure 4. Pathological results of liver metastasis using the labeled streptavidin-binding technique. (A) Metastatic adenocarcinoma, consistent with origin from the breast. (B) ER⁺ cells (25%). (C) PR⁻ cells (0%). (D) HER2⁺ cells (score 3+). Magnification, x200.

due to breast cancer, may be an effective therapeutic strategy. However, a number of studies have demonstrated that hormone-refractory liver metastasis is a negative predictor of overall survival rate (38,41). Therefore, continued treatment following the resection of liver metastases is of importance.

The question remains whether, following long PFS owing to dual inhibition of ER and HER, there is a way of improving the regimen for patients confronted with progression. An emerging mechanism of endocrine resistance is the interaction between the PI3K-protein kinase B-mTOR and ER signaling pathways (22-24). In a previous study involving patients with newly diagnosed breast cancer, neoadjuvant everolimus combined with letrozole improved the clinical response rate and decreased tumor cell viability, compared with letrozole alone (42). The Tamoxifen Plus Everolimus randomized Groupe d'Investigateurs Nationaux pour l'Etude des Cancers de l'Ovaire et du Sein trial (43) identified an improved time to progression: 4.5 months with tamoxifen alone vs. 8.6 months with tamoxifen plus everolimus. The Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study (44) revealed that the addition of everolimus to exemestane markedly improved PFS; the median PFS time, on the basis of central assessment, was 10.6 and 4.1 months, respectively (hazard ratio, 0.36; 95% confidence interval, 0.27-0.47; $P < 0.001$). Notably, everolimus was additionally identified to reverse trastuzumab in metastatic breast cancer. The results of the BOLERO-3 study (26) demonstrated that the addition of everolimus to trastuzumab with vinorelbine markedly prolonged PFS time in patients with trastuzumab-resistant and taxane-pretreated HER2⁺ advanced breast cancer; however, their hormone receptor status was not assessed. Patients with ER⁻ breast cancer exhibit an increased benefit compared with patients with ER⁺ breast cancer, indicating the importance of dual inhibition of the HER2 signal and the ER signaling pathway. Patients with a loss of phosphatase

and tensin homolog (PTEN) and mutations to phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit- α isoform (PIK3CA) have a greater sensitivity to everolimus; although next-generation sequencing of the resected liver specimen revealed no loss of PTEN and or PIK3CA mutations, it remains likely that the patient would benefit from everolimus (45,46).

The patient was recommended to continue to follow the principle of dual inhibition of ER and HER2. Everolimus was introduced into the regimen on the assumption that it may strengthen the therapeutic effect. Although there was no clinical evidence of the efficacy of exemestane with everolimus and trastuzumab, the patient provided written informed consent for the treatment. The patient's response was continually monitored during treatment. The patient achieved a long-term remission and is in good health at the time of writing.

The combined regimen of exemestane with everolimus and trastuzumab may be used for similar cases. To the best of our knowledge, the present case report is the first in which the patient's PFS reached >27 months. Additional observation has been undertaken and case series or small-scale clinical trials would be welcome to increase understanding on this topic.

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