Complete response of brain metastases from breast cancer after therapy with lapatinib plus capecitabine: case report

Mariko Kikuchi, Yoshimasa Kosaka, Norihiko Sengoku, Yoko Kohno, Hiroshi Nishimiya, Mina Waraya, Hiroshi Katoh, Takumo Enomoto, Hirokazu Tanino, Masaru Kuranami, Masahiko Watanabe

Department of Surgery, Kitasato University School of Medicine

A 60-year-old postmenopausal woman presented with a lump in her right breast. Physical examination revealed a 3-cm breast tumor and right axillary lymphadenopathy. The patient was diagnosed with breast cancer in the right breast and underwent mastectomy and right axillary lymphadenectomy. The pathological findings were: 1.5 cm tumor, invasive ductal carcinoma (Grade 3 [poorly differentiated]), lymph node metastases (+) estrogen receptor (-) progesterone receptor (-) HER2 (3+) T1N2M0 and stage IIIA. Multiple bone metastases were detected 24 months after surgery, for which the patient underwent radiation therapy. In addition, trastuzumab monotherapy was initiated. Multiple brain metastases were detected 32 months after surgery, and whole brain radiation therapy was administered. Metastases to the lung, liver, and spleen were simultaneously detected. The brain metastases became worse 41 months after surgery. Therefore, combination therapy consisting of lapatinib plus capecitabine was initiated. There was complete resolution of the brain metastases after 4 months of therapy. We described a HER2-positive breast cancer patient with metastatic disease, who achieved complete response of her brain metastases due to lapatinib plus capecitabine therapy.

Key words: HER2-positive metastatic breast cancer, lapatinib, capecitabine, brain metastases, complete response

Introduction

Molecularly targeted drugs have improved the prognosis of patients with human epidermal growth factor receptor-2 (HER2)-positive breast cancer. Lapatinib is a specific inhibitor of tyrosine kinase activity in both the epidermal growth factor receptor (EGFR) and HER2. A phase III clinical study of lapatinib combined with capecitabine (EGF100151) for women with advanced breast cancer that had progressed on trastuzumab revealed that the response rate (RR) and clinical benefit rate (CBR) were 23.7% and 29.3%, respectively, which indicated that this combination was more effective than capecitabine alone, with a RR of 13.9% and CBR of 17.4%. Patients with HER2-positive breast cancer frequently develop brain metastases, which have poor prognosis. Therefore, appropriate treatments for patients with HER2-positive breast cancer metastatic to the brain are needed. Although several studies of treatments for patients with metastatic breast cancer have indicated that lapatinib provides favorable responses, only a few studies have shown that lapatinib achieved complete response (CR) in patients with brain metastases.

Here, we report a patient with brain metastases from HER2-positive breast cancer who was successfully treated using lapatinib plus capecitabine (LC).

Case Report

The patient was a 60-year-old Japanese postmenopausal woman who presented with a lump in her right breast. Physical examination revealed a 3-cm tumor in her right breast and right axillary lymphadenopathy. The patient was diagnosed with invasive ductal carcinoma (T1N2M0, stage IIIA) and underwent a mastectomy with axillary lymph node dissection.

The histopathologic findings included a 1.5-cm invasive ductal carcinoma (Grade 3 [poorly differentiated]) and axillary lymph node metastases (5/22). Immunohistological analysis showed a HER2-type breast...
cancer (negative for expression of estrogen and progesterone receptors and positive for expression of HER2). The patient refused postoperative adjuvant therapy and was closely observed. A compression fracture of the cervical spine occurred 24 months after surgery, and multiple bone metastases were found. She received radiation therapy to her cervical spine (total dose, 30 Gy) and trastuzumab monotherapy. Seven months after initiation of trastuzumab therapy, multiple metastases in the brain, lung, liver, and spleen were discovered. The patient’s only symptom was vertigo without paralysis.

Since multiple brain metastases were observed, the patient underwent whole brain radiotherapy (WBRT), receiving a total dose of 20 Gy. She continued to receive trastuzumab therapy, and 9 months after WBRT, the brain metastases had increased in size, and the patient’s tumor-marker levels (including carcinoembryonic antigen [CEA] and cancer antigen 15-3 [CA 15-3]) had also increased. LC was then initiated as a second-line treatment.

Lapatinib was administered at a dose of 1,250 mg/day orally and capecitabine was given at a dose of 2,000

---

**Figure 1.** Head CT

A. Three metastatic brain tumors (maximum, 1.2 cm) in both frontal lobes, and 6 tumors (maximum, 1.5 cm) in the cerebellar hemispheres, were revealed by computed tomography (CT) before radiation therapy and **lapatinib plus capecitabine** combination therapy.

B. The tumors resolved after 4 months of lapatinib plus capecitabine combination therapy.

**Figure 2.** Chest CT

A. Multiple metastases to the lung were detected on CT prior to treatment.

B. The sizes of the tumors in the lung decreased after treatment.
Complete response of brain metastases from breast cancer

Figure 4. Bone scintigraphy

A. Abnormal accumulation of $^{99m}$technetium in the skull, sternum, vertebral body, bilateral pelvic bones, and femurs was detected on bone scintigraphy prior to treatment.

B. $^{99m}$Technetium accumulation at the metastatic sites disappeared after treatments.

Figure 3. Ultrasonography

A. A 1.3-cm metastatic tumor in S5 of the liver was detected on ultrasonography (US) prior to treatments.

B. The liver tumor decreased to 0.6 cm after treatments.

C. A 4.2-cm metastatic tumor in the spleen was detected on US prior to treatments.

D. The splenic tumor decreased to 2.4 cm after treatments.
mg/m²/day for 14 days of a 21-day cycle. Four months after the initiation of LC therapy, computed tomography showed complete resolution of the brain metastases and a partial response (PR) of the lung metastases (Figures 1 and 2, respectively). Abdominal ultrasonography and bone scintigraphy revealed PR of the liver, spleen, and bone metastases (Figures 2-4, respectively).

The levels of CEA and CA 15-3 increased with the appearance of the bone metastases and then decreased after trastuzumab initiation. The levels increased again after exacerbation of the brain metastases but decreased after the initiation of LC therapy (Figure 5).

Discussion
The prognosis of breast cancer patients has improved with advances in cancer therapeutics. However, 25%-34% of patients develop brain metastases.7 In particular, patients with HER2-positive breast cancer have a high risk of brain metastases.8,9 One-third of patients with HER2-positive metastatic breast cancer who are being treated with trastuzumab develop brain metastases, which occur within 2 years.3,10-15 Trastuzumab and chemotherapy are effective against metastases to extracranial organs in patients with HER2-positive breast cancer.16-19 However, these drugs have a limited effect on brain metastases because they cannot penetrate the blood-brain barrier (BBB). Therefore, trastuzumab and chemotherapy are not first-line treatments for brain metastases.

Small tumors and a low number of metastatic foci in the brain should be treated using surgery and stereotactic radiosurgery (SRS).20 In the patient in the present study, WBRT was administered because she had multiple brain metastases. Additionally, trastuzumab, a recombinant humanized monoclonal antibody against HER2, was administered as a systemic therapy. WBRT induced stable disease, but the brain metastases increased 9 months after RT, and there were increases in tumor marker levels. LC was then chosen as the subsequent therapeutic regimen.

Lapatinib is a small-molecule inhibitor (943 Da) of the intracellular tyrosine kinase domains of both EGFR and HER2. Data indicate that it penetrates the BBB, whereas trastuzumab, with a high molecular mass (148,000 Da), does not efficiently cross the BBB, which accounts for its poor efficacy against brain metastases.

Lapatinib is used for advanced or metastatic HER2-positive breast cancer resistant to anthracyclines, taxanes,
and trastuzumab and is recommended for combined use with capecitabine. Lin et al. conducted a phase II clinical study of lapatinib for patients with brain metastases from HER2-positive breast cancer. PR was achieved in 10 (20%) of 50 patients who received LC therapy. Of these 50 patients, the tumor sizes of 11 (22%) patients were decreased more than 50%, and those of 20 (40%) patients were decreased more than 20%.

Although Lin et al. have also conducted several lapatinib clinical trials on patients with HER2-positive breast cancer metastasizing to the brain, CR was not achieved in any patient. Ro et al. administered LC to patients with HER2-positive breast cancer metastasizing to the brain. CR was achieved in 2 of 47 patients who received WBRT. Abboud et al. reported 1 patient with brain metastases from HER2-positive breast cancer who achieved CR after LC. Because there have been few case reports on patients with CR of brain metastases from breast cancer after LC therapy, the present study provides additional support for the efficacy of LC. The present study suggests that LC therapy may have a significant efficacy for brain metastases from breast cancer.

Diarrhea, hand-foot syndrome, nausea, vomiting, and skin eruption have frequently been reported as adverse effects of lapatinib therapy. Serious adverse events such as interstitial pneumonia and cardiac disorders have also been reported. Serious adverse events did not occur in the patient in the present study.

The efficacy of pertuzumab for metastatic breast cancer, an anti-HER2 humanized monoclonal antibody that inhibits receptor dimerization, was recently reported. The therapeutic options for patients with HER2-positive breast cancer will likely, therefore, increase in the near future. We reported a patient with brain metastases from HER2-positive breast cancer, who achieved complete response to lapatinib plus capecitabine combination therapy.

References


