



Case Report

A case of leptomeningeal metastases of human epidermal growth factor receptor 2-positive breast cancer that responded well to lapatinib plus capecitabine

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ABSTRACT

Background: Leptomeningeal metastases (LM) pose the most difficult form of cancer metastasis to treat and portend a poor prognosis. Standard treatment has yet to be established, and intrathecal chemotherapy and whole-brain radiotherapy are administered on an empirical basis.

Case Description: We report on a 46-year-old woman with LM from human epidermal growth factor receptor 2 (HER2)-positive breast cancer. She was suffering from intractable headaches, severe nausea and vomiting, and cerebellar ataxia. Contrast-enhanced magnetic resonance imaging (MRI) revealed diffuse enhancement of the meninges, mainly in the posterior cranial fossa, and compression of the cerebellum by the profoundly thickened meninges. The first step in the treatment was decompression of the posterior cranial fossa to relieve intracranial hypertension. After surgery, her symptoms immediately improved. The second step was treatment with lapatinib at 1250 mg and capecitabine 1200 mg, which dramatically improved her symptoms and disappeared diffuse abnormal signal enhancement on MRI.

Conclusion: We treated a patient with LM from primary HER2-positive breast cancer who responded well to lapatinib plus capecitabine.

Keywords: Breast cancer, Capecitabine, Human epidermal growth factor receptor 2, Lapatinib, Leptomeningeal metastases

INTRODUCTION

Leptomeningeal metastases (LM) occur when cancer cells invade the pia mater, arachnoid mater, subarachnoid space, and cerebrospinal fluid of the central nervous system.^[1] The incidence of clinically diagnosed LM in patients with solid tumors is approximately 5%, but the incidence of undiagnosed or asymptomatic LM may be as high as 20% or more in certain solid tumors, as confirmed by autopsy series.^[1] By primary cancer type, LM are most commonly found in with breast cancer, representing 12%–35% of cases.^[1,11] Frequency of LM is 5% in the whole breast cancer.^[11] The prognosis of LM is poor, and survival in untreated patients is short with periods of only 4–6 weeks reported.^[11] The main forms of antitumor treatment are radiotherapy, mainly by means of whole-brain radiotherapy, and intrathecal chemotherapy. However, even with active

treatment, survival remains <8 months on average, and the development of new treatment options and the establishment of a standard therapy are both urgent tasks.^[11] Herein, we report a case of the patient with LM from human epidermal growth factor receptor 2 (HER2)-positive breast cancer who responded well to systemic chemotherapy with lapatinib plus capecitabine.

CASE PRESENTATION

A 46-year-old woman had undergone mastectomy for breast cancer (estrogen receptor 2+, progesterone receptor 3+, and HER2 3+) 5 years before presentation and had subsequently remained under observation without any postoperative adjuvant therapy. Multiple lung, liver, and bone metastases were identified in year 3 postoperatively, and systemic chemotherapy was introduced. The chemotherapy regimen included docetaxel, trastuzumab, pertuzumab, and bisphosphonates, and radiotherapy for lumbar spinal bone metastases (20 Gy/5 Fr). However, she developed multiple brain metastases (BM) 1 year later, which were treated with whole-brain radiotherapy (30 Gy/10 Fr) and placement of a ventriculoperitoneal shunt for hydrocephalus. The systemic chemotherapy regimen was subsequently switched to trastuzumab emtansine, but further LM developed, and the patient was referred to our hospital.

At the time of referral, Eastern Cooperative Oncology Group (ECOG) performance status was 4, level of consciousness as assessed by Glasgow coma scale score was E3V4M6, and she was suffering from intractable headaches, severe nausea and vomiting, and cerebellar ataxia. T1-weighted gadolinium-enhanced magnetic resonance imaging (MRI) revealed diffuse contrast enhancement of the meninges, mainly in the posterior cranial fossa, with compression of the cerebellum by the significantly thickened meninges [Figure 1a,b]. In light of the clinical course, treatment options were limited, and best supportive care was presented as an option.

However, the patient requested further therapy, and given her good karnofsky performance status (KPS), an aggressive treatment strategy was pursued. The first step in the treatment

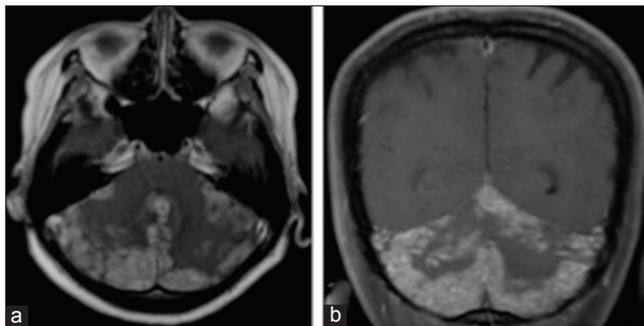


Figure 1: Magnetic resonance imaging images (a,b) Pre-treatment T1-weighted gadolinium-enhanced MRI (axial and coronal images)

was to relieve intracranial hypertension, and decompression of the posterior cranial fossa was performed [Figure 2]. After surgery, headaches, nausea, and vomiting were immediately improved and her performance status improved.

Treatment with lapatinib at 1250 mg and capecitabine 1200 mg was started on postoperative day 14. As early as 2 weeks later, the diffuse abnormal signal enhancement across her tissues shrunk dramatically on T1-weighted gadolinium-enhanced MRI after starting this new regimen [Figure 3a,b]. Further imaging revealed that the LM had almost disappeared on MRI by 2 months of therapy [Figure 3c,d]. At present, no recurrence has been observed more than 1 year after the treatment. The patient is continuing to attend our hospital unit for treatment under the same regimen and currently remains well with an ECOG Performance Status 1.

DISCUSSION

Recently, a number of cases have been reported of BM responding to systemic chemotherapy, particularly using molecular-targeted drugs. With lung cancer treatment, good therapeutic outcomes have been reported with the use of molecular-targeted drugs not only for BM but also for LM.^[4,5,7,10] As a result, we are now in an era when the central nervous system may also be a target of systemic chemotherapy. In breast cancer treatment, a number of regimens have been explored; several agents are under investigation.^[12] Trastuzumab is now available for HER2-positive patients, in hopes that this agent might also have antitumor effects on the central nervous system. However, the high molecular weight of this agent means that it cannot easily pass through the blood-brain barrier, and this treatment has not proven effective for tumors of the central nervous system.^[6]

Lapatinib has now succeeded trastuzumab as a new drug targeting HER2 and epidermal growth factor receptor, and its low molecular weight compared with trastuzumab gives

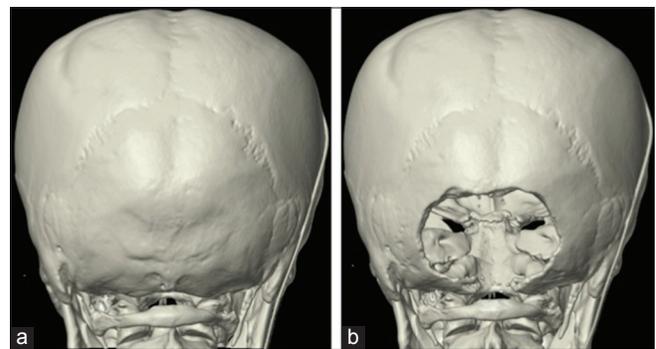


Figure 2: (a) Preoperative three-dimensional computed tomography. (b) Postoperative three-dimensional computed tomography. The occipital bone has been removed, and the foramen magnum has been opened.

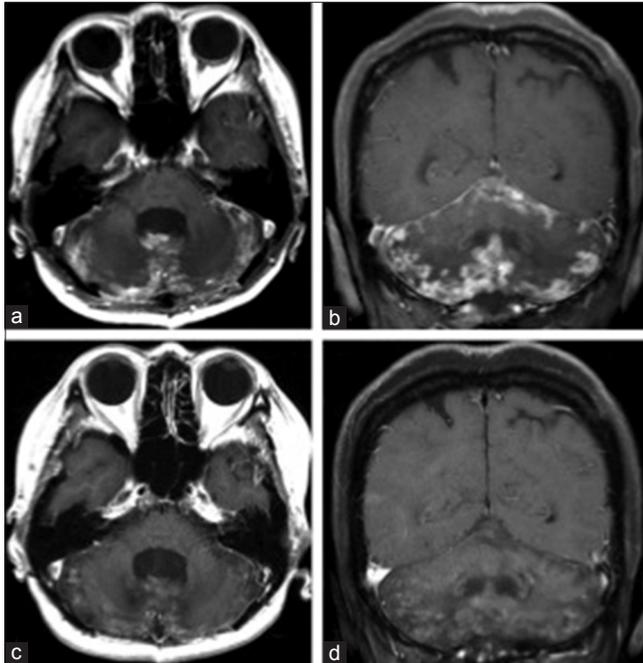


Figure 3: Magnetic resonance imaging images (a,b) T1-weighted gadolinium-enhanced MRI (axial and coronal images) after 2 weeks. Diffuse enhancement of the meninges has improved markedly. (c,d) T1-weighted gadolinium-enhanced MRI (axial and sagittal images) after 2 months. Diffuse enhancement of the meninges has almost disappeared.

support to the notion of greater efficacy against central nervous system lesions. We have reported herein a case in which LM responded well to combination therapy with lapatinib plus capecitabine. Although our patient had undergone decompression surgery to relieve symptoms of intracranial hypertension, the effects were certainly expected to be temporary only, and hence the second step treatment with lapatinib plus capecitabine was added. The effects of this combination of chemotherapy were rapidly apparent, and a good outcome for the patient was achieved.

The response rate with lapatinib monotherapy for recurrent BM after treatment with trastuzumab and radiotherapy is 2.6%–6.0% and this rate is further improved in combination therapy with capecitabine.^[8,9] The LANDSCAPE study, a Phase 2 trial of lapatinib plus capecitabine combination therapy for BM, achieved good therapeutic outcomes, with a tumor regression rate $\geq 50\%$ obtained in 65.9% of patients and the median time to central nervous system progression of 5.5 months.^[2]

The response assessment in a neuro-oncology working group recently proposed guidelines for the diagnosis and response assessment of LM.^[3] The treatment result for LM using these evaluation criteria will be reported in the future. As a result, new therapeutic strategies for LM seem highly likely to be developed.

CONCLUSION

We treated a patient with LM from primary HER2-positive breast cancer who responded well to lapatinib plus capecitabine.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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None.

Conflicts of interest

There are no conflicts of interest.

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