Apatinib combined with trastuzumab and albumin-bound paclitaxel for treatment of HER2+ breast cancer with brain metastases resistant to anti-HER2 TKIs: A case report

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Abstract. Although human epidermal growth factor receptor 2 (HER2)-targeted therapy significantly improves the prognosis of patients with HER2-positive breast cancer, most patients with advanced breast cancer eventually progress due to drug resistance. At present, there is no standard treatment after patients become resistant to HER2-targeted therapy. Previous studies have indicated that anti-angiogenesis drugs have potential efficacy in the treatment of advanced breast cancer. The present study reported on a case of a pretreated patient with HER2-positive advanced breast cancer with brain metastases who developed resistance to multiple lines of HER2-targeted treatment. The patient was treated with apatinib combined with trastuzumab and albumin-bound paclitaxel. The patient achieved partial response to the third-line treatment with a progression-free survival of 9 months. After combination treatment, the symptoms of headache and vomiting were relieved and all the brain metastases were significantly reduced. The present case indicated that apatinib may have anti-tumor activity in patients with HER2-positive breast cancer with HER2-targeted drug resistance. The present case provides valuable information and may offer a new possibility for the treatment of patients with breast cancer with brain metastases who progressed after clinical treatment with small-molecule anti-HER2 tyrosine kinase inhibitor drugs.

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Introduction

Among females, breast cancer is the most common malignancy worldwide and it is also the leading cause of cancer-associated death (1). Statistical results indicate that human epidermal growth factor receptor 2 (HER2)-positive breast cancer accounts for 15-20% (2) and this subtype of breast cancer accounts for 22.6% in China (3). HER2-positive breast cancer is comparatively more aggressive and has a poor prognosis (4). Although the use of anti-HER2 therapy has significantly improved the prognosis of HER2-positive advanced breast cancer, when drug resistance occurs, the treatment effect will be poor and the tumor will progress (5,6). Therefore, it is required to adopt new treatments to overcome drug resistance.

Tumor angiogenesis is closely related to tumor growth, invasion and metastasis. Therefore, anti-angiogenesis may be one of the effective methods to treat cancer (7-9). Bevacizumab, an anti-angiogenic monoclonal antibody, has demonstrated anti-tumor activity in advanced breast cancer (10-13). In addition, anti-angiogenic drugs have been applied in the treatment of advanced breast cancer (14-16).

Apatinib is a highly selective tyrosine kinase inhibitor (TKI) that targets vascular endothelial growth factor receptor-2 (VEGFR2). Apatinib was first used for the treatment of advanced gastric cancer (17). Two phase II clinical studies indicated that apatinib monotherapy had good efficacy in the treatment of pretreated advanced breast cancer (18,19). An observational study suggested that apatinib combined with chemotherapy has potential efficacy in the treatment of previously treated advanced breast cancer (20). However, studies on the use of apatinib for the treatment of HER2-positive advanced breast cancer with brain metastasis are scarce. In the present study, apatinib combined with trastuzumab and albumin-bound paclitaxel were used to treat a patient with refractory HER2-positive breast cancer with brain metastasis, and good efficacy was achieved. This case is reported below.

Case report

In April 2014, a 42-year-old Chinese female underwent radical surgery for left breast cancer at an external hospital

and the axillary lymph nodes on the same side were removed. Pathological inspection revealed invasive non-specific breast carcinoma (Grade III). The size of the tumor was 1.0x1.0 cm, 19 lymph node metastases were detected in 23 left axillary lymph nodes and the postoperative stage was pT1N3M0, stage IIIC. The immunohistochemistry results were as follows: Estrogen receptor (ER), 85%+; progesterone receptor (PR), 15%+; HER-2, 2+; Ki-67, 45%+; fluorescence *in situ* hybridization (FISH) detection, HER-2 gene amplification (+). The patient received six cycles of adjuvant chemotherapy with paclitaxel combined with lobaplatin, followed by one-month endocrine therapy with tamoxifen. The patient refused to receive adjuvant radiotherapy and anti-HER2 targeted therapy.

In March 2021, multiple metastases in the bone and lymph node were detected by computed tomography (CT) and brain magnetic resonance imaging (MRI) revealed multiple brain metastases. The patient underwent left axillary lymph node biopsy and the pathological diagnosis was metastasis of breast cancer with the following immunohistochemical results: ER, 90%+; PR, 15%+; HER-2, 2+; Ki67, 60%+; and FISH detection, HER-2 gene amplification (+). The patient then received capecitabine plus pyrotinib for 8 months as the first-line treatment. The best tumor response of intracranial and extracranial lesions was stable disease based on CT and MRI examination. In November 2021, reexamination by brain MRI indicated that the left parieto occipital lobe metastatic tumor was enlarged and the evaluation indicated progressive disease. The patient received second-line treatment with pyrotinib plus trastuzumab (Herceptin®) and capecitabine. One month later, the brain metastases progressed again. Table I provides the medical timeline of the patient's treatment prior to presenting at our hospital.

In December 2021, the patient was admitted to our hospital, the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Shenzhen, China), for the first time, after having received second-line palliative chemotherapy at other hospitals. The patient complained of headache and vomiting. CT of the whole body revealed multiple lymph node and bone metastases, as well as suspected lung metastasis. Brain MRI indicated two huge brain metastases (one in the right temporooccipital parietal lobe and the other in the left occipital parietal lobe), involving adjacent meninges, accompanied by obvious edema; the midline structure shifted to the left and the right lateral ventricle and the third ventricle moved to the left under pressure.

As the brain metastases of this patient had progressed significantly after using small molecule anti-HER2 TKI drugs, the brain metastases were now huge and accompanied by obvious edema. After multi-disciplinary discussion, consideration was given to the following points: i) The radiotherapy department had no indication for radiotherapy, so it was recommended to perform a neurosurgery consultation to consider palliative surgery; ii) the neurosurgery department indicated that it may be able to perform palliative surgery, but the risk is relatively high and the patient's condition should be fully informed; iii) after careful consideration, the patient and the patient's family refused surgical treatment of the patient. Finally, the combined treatment plan of apatinib [250 mg per os (po) once per day (qd)] plus trastuzumab (Zercepac®) [6 mg/kg, intravenous drip, day 1 of every 3 weeks] and albumin-bound paclitaxel (130 mg/m^2, intravenous drip, days 1 and 8 of every 3 weeks) was formulated and the patient began to receive the third-line treatment from mid-December 2021. The patient also received conventional intervention with mannitol and dexamethasone for dehydration. After one cycle of combined treatment, the patient complained that the severity of the headache and vomiting had decreased. Brain MRIs are provided in Figs. 1-3. Brain MRI examination after 2 cycles of combination treatment indicated that peritumoral brain edema was significantly reduced (Fig. 1B) and two brain metastases were significantly reduced (Figs. 2B and 3B). After 4, 6 and 8 cycles of combination treatment, further reductions of peritumoral brain edema were found (Fig. 1C-E). The right temporooccipital parietal lobe metastasis (Fig. 2C-E) and the left occipital parietal lobe metastasis were further reduced after 4, 6 and 8 cycles of combination treatment (Fig. 3C-E), and the efficacy was rated as partial response. The patient tolerated the treatment well and no grade 3 or 4 adverse events were observed during the whole treatment period. In September 2022, brain MRI indicated progress in brain metastases and systemic CT suggested that extracranial metastases remained stable. The progression-free survival was 9 months for the third-line treatment.

When the brain metastases of this patient progressed again, neurosurgery and radiotherapy experts were invited for consultation again, but the patient and the patient's family still refused the surgery and did not consider radiotherapy for the time being. Therefore, the medical anti-tumor treatment plan was adjusted as follows: Apatinib (250 mg po qd) plus inetetamab (Cipterbin®, anti-HER2 recombinant human monoclonal antibody; 6 mg/kg, intravenous drip, day 1 of every 3 weeks, with 8 mg/kg for the first cycle) and oral vinorelbine (80 mg/m^2, po, days 1 and 8 of every 3 weeks, with 60 mg/m^2 for the first cycle). To date, three cycles of the aforementioned treatment with a combination of apatinib, inetetamab and oral vinorelbine have been performed and a comprehensive review and evaluation will be performed before the next cycle. At present, the patient has no obvious headache, vomiting or other complaints/symptoms.

Discussion

At present, the treatment options for brain metastasis of breast cancer include local treatment, systematic treatment or combination of multiple treatments. Local treatment includes surgery, stereotactic radiosurgery (SRS) and whole-brain radiation therapy (WBRT). Systemic therapy includes chemotherapy and targeted therapy. Certain studies have indicated that surgery may improve the overall survival (OS) of patients with brain metastases from breast cancer, but it is usually only applicable to patients with obvious symptoms, good general condition and limited brain metastasis lesions (21,22). Most patients with brain metastases from breast cancer receive radiotherapy (23). Patients with good performance and localized brain metastases receive SRS, while patients with poor performance or extensive brain metastases usually receive WBRT (23). One study indicated that WBRT combined with SRS had no benefit regarding OS, while increasing the risk

Table I. Summary of the timeline of the patient's past medical history.

Treatment time	Therapy	Response evaluation	DFS or PFS
April 2014-October 2014	Radical surgery and adjuvant therapy (TP for 6 cycles, tamoxifen for 1 month)	-	83 months
March 2021-November 2021	Capecitabine + pyrotinib	SD	8 months
November 2021-December 2021	Herceptin + capecitabine + pyrotinib	PD	1 month

TP, Paclitaxel + Lobaplatin; DFS, disease-free survival; PFS, progression-free survival; SD, stable disease; PD, progressive disease.

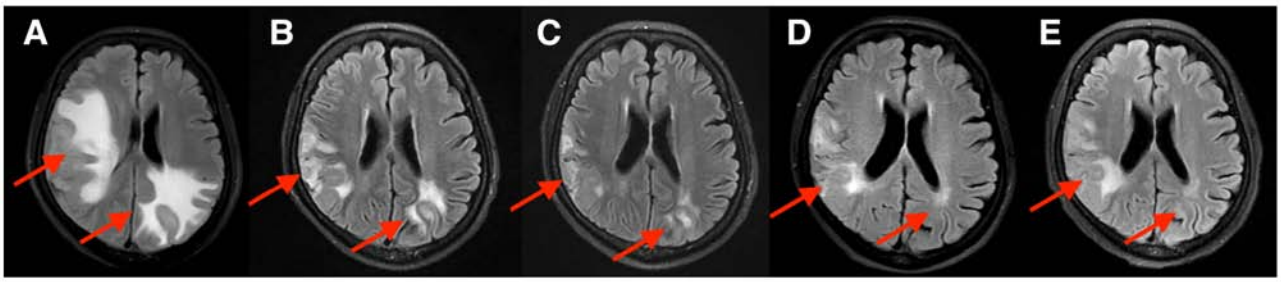

Figure 1. Brain MRIs of response in peritumoral brain edema to apatinib + trastuzumab + albumin-bound paclitaxel. (A) Prior to combination treatment (T2-weighted longTR FLAIR), (B) after 2 cycles of combination treatment (T2-weighted FLAIR), (C) after 4 cycles of combination treatment (T2-weighted FLAIR), (D) after 6 cycles of combination treatment (T2-weighted longTR FLAIR) and (E) after 8 cycles of combination treatment (T2-weighted FLAIR). The white areas indicated by arrows are peritumoral brain edema. MRI, magnetic resonance imaging. FLAIR, fluid attenuated inversion recovery; longTR, long repetition time.

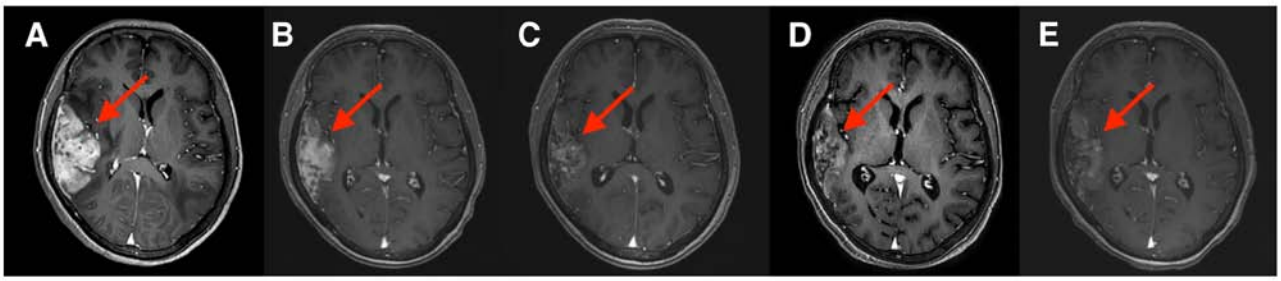

Figure 2. Brain MRIs of response of metastasis of right temporooccipital parietal lobe to apatinib + trastuzumab + albumin-bound paclitaxel. (A) Prior to combination treatment (T1-weighted enhancement), (B) after 2 cycles of combination treatment (T1-weighted BRAVO enhancement), (C) after 4 cycles of combination treatment (T1-weighted BRAVO enhancement), (D) after 6 cycles of combination treatment (T1-weighted enhancement) and (E) after 8 cycles of combination treatment (T1-weighted BRAVO enhancement). The white areas indicated by arrows are right temporooccipital parietal lobe metastases. MRI, magnetic resonance imaging. BRAVO, brain volume imaging.

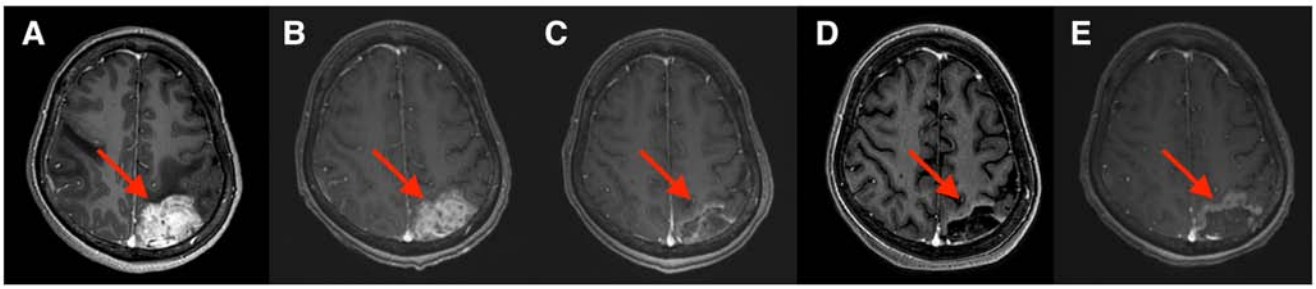

Figure 3. Brain MRIs of response of metastasis of left occipital parietal lobe to apatinib + trastuzumab + albumin-bound paclitaxel. (A) Prior to combination treatment (T1-weighted enhancement), (B) after 2 cycles of combination treatment (T1-weighted BRAVO enhancement), (C) after 4 cycles of combination treatment (T1-weighted BRAVO enhancement), (D) after 6 cycles of combination treatment (T1-weighted enhancement) and (E) after 8 cycles of combination treatment (T1-weighted BRAVO enhancement). The white areas indicated by arrows are left occipital parietal lobe metastases. MRI, magnetic resonance imaging. BRAVO, brain volume imaging.

of neurocognitive toxicity compared with SRS alone (24). Therefore, the latest consensus guidelines recommend complete resection or SRS for limited brain metastases, and adjuvant WBRT should not be conducted subsequently (25). In terms of systematic treatment, the application of chemotherapy in brain metastasis from breast cancer is limited. However, due to the use of anti-HER2 therapy in HER2-positive subtypes, systematic therapy has achieved good results. The exploratory study on central nervous system metastasis in the EMILIA phase III study shows that T-DM1 may prolong the OS of patients with brain metastasis of breast cancer (26). The subgroup analysis of the DESTINY-Breast 01 study on brain metastasis of breast cancer indicated that trastuzumab deruxtecan (T-DXd, DS8201) has achieved encouraging therapeutic benefits for patients with brain metastasis of breast cancer (27).

Small-molecule anti-HER2 TKI drugs, such as lapatinib, neratinib, tucatinib and pyrotinib, may also be used for the systematic treatment of brain metastases in patients with HER2-positive breast cancer. However, the treatment of HER2-targeted drug-resistant patients is an important clinical challenge. The present study reported a case in which the combination of apatinib with trastuzumab and albumin-bound paclitaxel effectively controlled refractory brain metastases after the failure of pyrotinib therapy. The reduction of the brain metastases from breast cancer and alleviation of the brain edema lasted 9 months.

Angiogenesis is closely related to HER2 signal transduction at the molecular level (28). A previous study indicated that VEGFR2-positive stromal vessel counts were higher in HER2-positive breast cancer compared with other subtypes. These data indicate that the influence of HER2 on tumorigenesis may be partially mediated by the stimulation of angiogenesis, which provides a strong theoretical basis for the use of anti-angiogenic drugs in HER2-positive breast cancer (29). In another preclinical study, the authors observed that HER2 overexpression was associated with upregulation of VEGF in human breast cancer cell lines (30). Several clinical studies suggested that trastuzumab combined with bevacizumab was effective in the treatment of HER2-positive advanced breast cancer (31-33). In addition, a phase II study suggested that lapatinib combined with bevacizumab was effective in patients with HER2-positive advanced breast cancer (34).

Due to the existence of the blood-brain barrier (BBB), which has low permeability and strong expression of multiple specific efflux transporters, the entry of numerous drugs into the brain is limited (35). Therefore, numerous anti-tumor drugs cannot achieve any therapeutic effects on brain metastases.

Apatinib is a highly selective and effective VEGFR TKI, which has high affinity for VEGFR2. The molecular weight of apatinib is small, and thus, it may easily pass through the BBB and its potential effect on brain metastasis may be better than that of other agents. Furthermore, apatinib is administered orally, which avoids injection, reduces hospitalization and the drug is taken orally every day to maintain a stable blood concentration. Two phase II clinical studies demonstrated the efficacy of apatinib in patients with advanced triple negative and non-triple negative breast cancer (18,19). Of note, three patients with brain metastasis were included in the study of triple negative breast cancer above, but the therapeutic effect on brain metastasis with apatinib was not described in detail. The mechanism of apatinib penetrating the BBB remains elusive and there is also a lack of large randomized controlled studies to confirm its efficacy in patients with breast cancer with brain metastasis. However, in certain cases, the beneficial effect of apatinib on brain tumors has been reported. Apatinib has been reported to be effective in the treatment of brain glioma (36). One case report indicated that apatinib was effective in the treatment of brain edema caused by brain metastases (37). In addition, two case reports demonstrated the efficacy of apatinib monotherapy or in combination for the treatment of brain metastases of advanced triple negative breast cancer (38,39). However, to the best of our knowledge, no previous case report on apatinib for the treatment of a patient with HER2-positive breast cancer with brain metastasis, particularly after anti-HER2 treatment resistance, has been published to date.

The present case was a patient with HER2-positive advanced breast cancer that was progressing with small molecule anti-HER2 TKI drugs, with a heavy brain metastasis load and obvious brain edema. The radiotherapy department was unable to perform brain radiotherapy, the neurosurgery department determined that the operation was risky and the patient and the patient's family refused the operation. It was only possible to treat the brain metastases by using drugs. Compared with standard paclitaxel, albumin-bound paclitaxel has better efficacy and higher safety in the treatment of advanced breast cancer (40). A study indicated that albumin is able to penetrate the BBB and drugs conjugated with albumin can also penetrate the BBB, and thus, anti-tumor drugs conjugated with albumin may serve a role in the treatment of intracranial tumors (41).

Considering the molecular subtype, brain metastases and previous resistance to small-molecule TKI drugs of the patient of the present study, the regimen of apatinib combined with trastuzumab and albumin-bound paclitaxel was finally adopted. Surprisingly, this combination regimen produced remarkable results. After two courses of treatment, the patient's headache and vomiting symptoms were significantly diminished, brain MRI indicated that brain metastases were significantly reduced and brain edema was significantly alleviated. This may be due to the synergistic anti-tumor effect of apatinib and albumin-bound paclitaxel through the BBB.

In conclusion, the present study reported on the treatment of apatinib combined with trastuzumab and albumin-bound paclitaxel for a patient with HER2-positive advanced breast cancer with brain metastases who developed resistance to anti-HER2 drugs. The curative effect of the combined treatment of this patient is good. The symptoms of headache and vomiting were significantly improved and the brain metastases were significantly reduced. This case demonstrates the therapeutic effect of apatinib on brain metastases of HER2-positive breast cancer. In the future, further large-scale clinical trials are needed to clarify the role of apatinib in patients with refractory brain metastasis of breast cancer and HER2-targeted drug resistance.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JH and CD designed the study and wrote the manuscript. JH, XC and LS confirmed the authenticity of all the raw data analyzed and interpreted the data. XC and JG obtained medical images (MRI scans) and analyzed patient data. YM and HZ contributed to the study conception, overall design and quality control. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of the case report, including publication of all clinical details and diagnostic images.

Competing interests

The authors declare that they have no competing interests.

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