Clinical Case Report

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Significant response of low-dose apatinib monotherapy in brain metastases of triple-negative breast cancer

A case report

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Abstract

Rationale: The potential efficacy of apatinib in patients with advanced triple-negative breast cancer (TNBC) has been observed in a previous phase II clinical study. However, there is no study to evaluate its efficacy and safety in TNBC patients with brain metastasis (BM). Here we report one case that apatinib exhibited excellent antitumor effects in a breast cancer patient with brain metastasis, with no serious treatment-associated with adverse event.

Patient concerns: In this case report, one Chinese woman who was diagnosed with stage IV TNBC with multiple bone, lung, and brain metastases was unable to tolerate chemotherapy and refused whole-brain radiation therapy (WBRT) due to her poor physical condition. She had previously undergone radical mastectomy and intravenous chemotherapy.

Diagnoses: Triple-negative breast cancer.

Interventions: The patient underwent left radical mastectomy with ipsilateral axillary lymph node dissection, and the following adjuvant chemotherapy, but developed multiple bone, lung, and brain metastases. Due to her poor physical condition, chemotherapy was not eligible for her. And she refused WBRT and chose to take low-dose apatinib (250 mg, oral, daily) monotherapy.

Outcomes: After 2 months of treatment, the symptom of headache and vomiting relieved and all the brain metastases (BMs) lesions disappeared.

Lessons: Low-dose apatinib monotherapy may be an alternative treatment for patients with poor physical condition. Preclinical and clinical studies should be conducted to further evaluate the mechanism and efficacy of apatinib in the treatment of BM from TNBC, as well as to explore the optimal dose of the drug.

Abbreviations: BBB = blood-brain barrier, BM = brain metastasis, BMs = brain metastases, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, PS = performance status score, TKIs = tyrosine kinase inhibitors, TNBC = triple-negative breast cancer, TNBC-BM = triple-negative breast cancer with brain metastasis.

Keywords: apatinib, brain metastasis, triple-negative breast cancer

1. Introduction

Triple-negative breast cancer (TNBC) is highly malignant and has a high tendency to metastasize to the brain. Data from the Dana-Farber Cancer Institute showed that nearly half of all metastatic TNBC patients experienced metastasis to the brain before death.[1] One recent Chinese study reported that the incidence of brain metastasis (BM) in metastatic TNBC patients was 29% (127/433).[2] TNBC-BM patients are intractable and usually have poor prognosis with a short median survival time of about half a year, even if they are treated with current standard treatment regimens.[1,2] And also many TNBC-BM patients are not tolerant to the toxicities resulting from traditional chemotherapy. The development of effective treatment regimens for TNBC-BM patients is urgent unmet medical needs.

Apatinib, an orally administered small-molecule targeted drug, has potential antiangiogenic and antineoplastic effects by blocking the intracellular ATP-binding site of VEGFR-2. The efficacy of this drug has been evaluated by phase II and III clinical trials,[3,4] and apatinib has been approved as third-line treatment for advanced gastric cancer patients in October 2014 in China. In recent years, a series studies have shown that apatinib shows encouraging antitumor activities in several solid tumors, including non-small cell lung cancer and breast cancer.[5–9] However, the efficacy of apatinib monotherapy in TNBC-BM patients has not been reported yet. Herein, we reported one

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TNBC-BM patient who responded to low-dose (250 mg, QD, oral) apatinib.

2. Case report

In June 2014, a 51-year-old Chinese woman underwent left radical mastectomy with ipsilateral axillary lymph node dissection in our hospital. The pathological diagnosis and stage was T1N1M0 stage IIA breast cancer. The genetic subtype was triple-negative. Two weeks after surgery, as adjuvant therapy, the patient received chemotherapy of paclitaxel combined with epirubicin four times. In December 2015, multiple metastases in the bone were detected by both whole-body bone scanning and computed tomography (CT), no local tumor recurrence or metastatic lesions in other organs was found. Then the patient received one cycle of gemcitabine and carboplatin chemotherapy. The patient reported that her pain was significantly relieved, but the treatment was stopped because of severe adverse events (experienced one grade four bone marrow suppression and one severe hepatic injury). The patients complained aggravated pain, in March 2016, she received tegafur and lumbar radiotherapy treatments (VMAT, 30 Gy/10F/3 Gy). The medical timeline is outlined in Figure 1.

In May 2016, the patient complained headache and frequent vomiting. BMs and surrounding edema were found by brain CT examination (Fig. 2A). At the same time, multiple lung metastases were also found by chest CT. Considering her poor physical condition (PS 4), we thought chemotherapy was not eligible for her, and recommended to receive whole-brain radiation therapy (WBRT) or targeted therapy. She refused WBRT and chose to take apatinib (250 mg, daily) since May 10, 2016. After 1 month of apatinib monotherapy, she reported that the severity of headache and vomiting relieved, and her performance status was also improved (PS 3). The brain CT examination showed that multiple brain lesions and the surrounding edema were either significantly reduced in size or disappeared (Fig. 2B). After 1 month of continued treatment, all the intracranial lesions disappeared (Fig. 2C). During the whole treatment period, no grade 3 or 4 adverse event was observed. Unfortunately, the patient died because of serious lung infections. Both overall survival (OS) and progression-free survival (PFS) were 3.5 months for this patient.

3. Discussion

The multicenter phase II study that was conducted to explore therapeutic doses of apatinib indicated that a dose of 500 mg/day, rather than 750 mg/day, should be recommended for heavily pretreated metastatic TNBC patients because of toxicity.[7] However, treatment with the lower dosage of apatinib (500 mg, daily) did not reduce the toxicities, the rates of drug interruption and dose reduction were 25.4% and 32.2%, respectively.[7] It is still pertinent to find the best dose of apatinib in the treatment of TNBC, especially for patients with poor physical condition. To the best of our knowledge, this is the first report to describe the successful use of low-dose apatinib (250 mg, daily) monotherapy to treat TNBC-BM patient with poor physical condition. In this report, 250 mg apatinib treatment exhibited obvious efficacy for the BM lesions.

Most conventional chemotherapeutic drugs and humanized monoclonal antibodies are not effective at treating patients with BM due to the presence of the blood-brain barrier (BBB).[10–12] For example, trastuzumab is one type of macromolecular agent that has difficulty crossing the BBB in vitro models of brain metastases from breast cancer, with low concentration in the cerebrospinal fluid and rare antitumor activity for intracranial lesions in patients with human epidermal growth factor receptor (HER2)-positive breast cancer.[13,14] As is known, antiangiogenesis has become one of the important modules of current cancer therapy. Antiangiogenic drugs targeting vascular endotheliocytes may avoid the obstacle of the BBB. Bevacizumab, an antiangiogenic monoclonal antibody with a large molecular weight, has shown efficacy when combined with chemotherapy in the treatment of patients with NSCLC and asymptomatic untreated brain metastases, with an overall response rate (ORR) of 61.2% in intracranial lesions, a median PFS of 6.7 months [95% confidence interval (CI), 5.7–7.1] and a median overall survival (OS) rate of 16 months.[15] Similarly, as an inhibitor of the VEGF/VEGFR pathway in vascular endothelial cells, apatinib achieved good results in the treatment of metastatic TNBC patients with BM that have been exhibited in another document[16] and our present report.

Compared with traditional chemotherapy drugs, tyrosine kinase inhibitors (TKIs) have a low molecular weight and could permeate the BBB.[17] The epidermal growth factor receptor TKIs (eg, gefitinib, erlotinib, afatinib, and Osimertinib) have shown activity in the treatment of brain metastases in patients with NSCLC, achieved response rates of 60%–80% and a complete response rate as high as 40%.[18,19] Besides the activity in antiangiogenesis, as one of the small molecule TKIs, apatinib was proven to be able to induce tumor cells apoptosis in vitro tests.[20–23] When used for the treatment of intracerebral tumors, apatinb may pass through the BBB easily and then directly induce neoplastic cell apoptosis.

Evidence revealed that metastatic cancer cells could produce VEGF, which binding to VEGFR2, and induce the disruption of the BBB, facilitate a series of physiological changes including edema. Blocking of this signaling pathway could decrease clinical severity and tissue damage.[12,24–26] One case reported that apatinib can obviously reduce refractory radiation-induced brain edema.[26] In this present report, apatinib also showed activity for elimination of multiple BMs, as well as the surrounding edema after short-term treatment. We speculate that apatinib might have the ability to repair the BBB by blocking the intracellular ATP-binding site of VEGFR2.

In conclusion, low-dose apatinib monotherapy exerted excellent efficacy in the treatment of symptomatic BMs in one TNBC patient, the possible mechanism might be through antiangiogenesis, pro-apoptosis of tumor cells, and BBB repair. This suggests that low-dose apatinib monotherapy may be an efficient alternative for patients with poor physical condition. Preclinical and clinical studies should be developed to further explore the mechanism, efficacy, and appropriate dose of apatinib in treating brain-metastasized breast cancer.

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Author contributions

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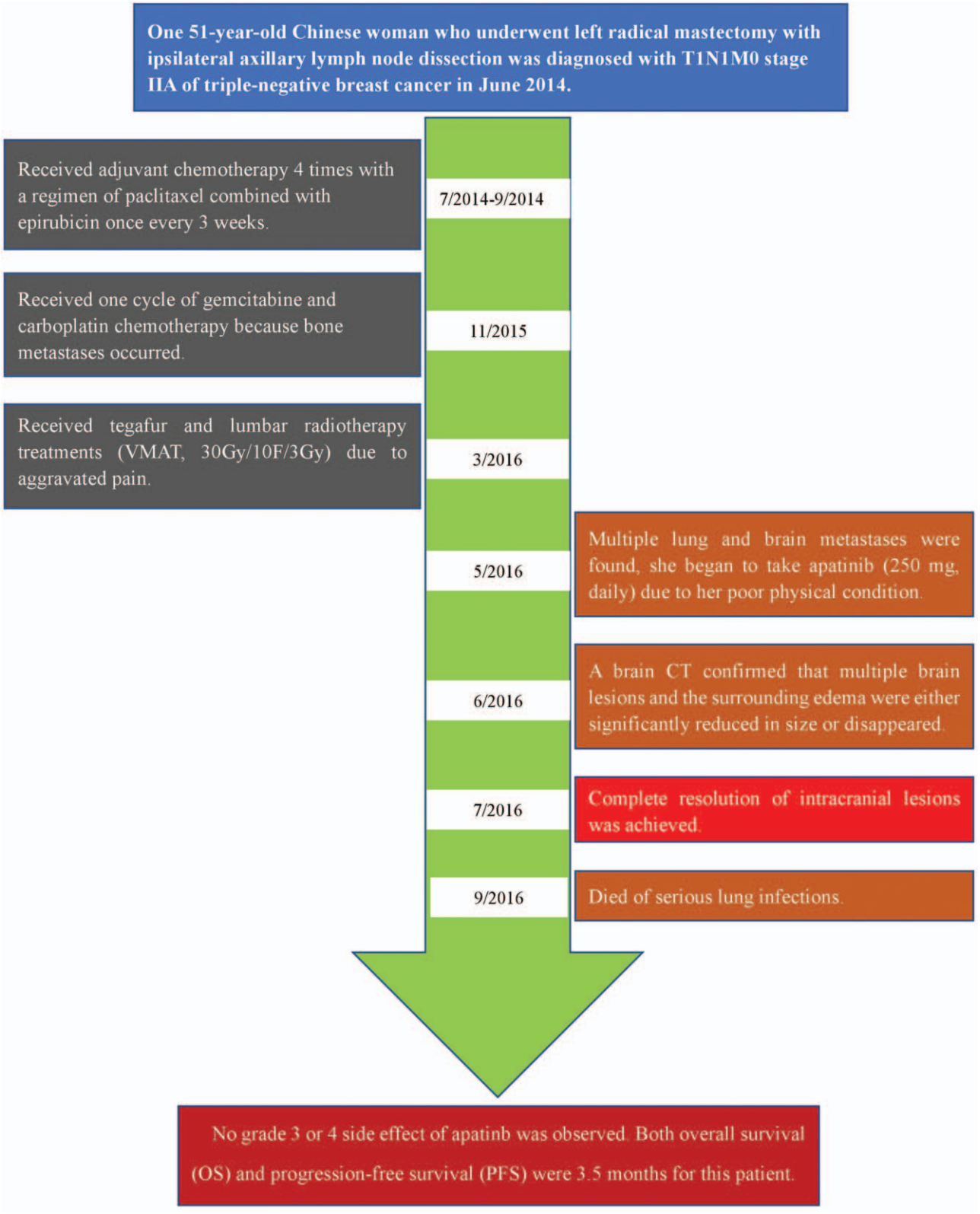

Figure 1. Timeline of interventions and outcomes.

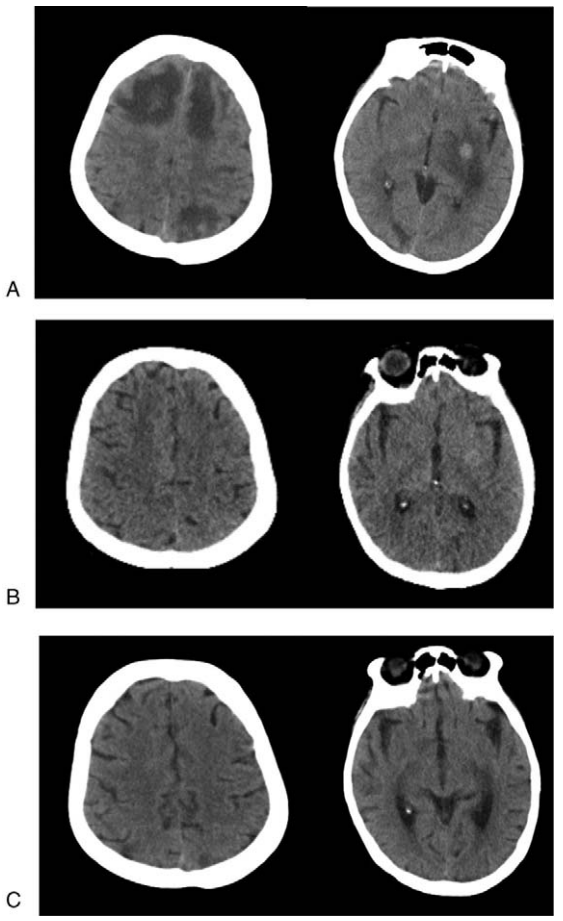

Figure 2. CT of response to apatinib monotherapy: (A) before single-agent apatinib, (B) after 1 month of single-agent apatinib, and (C) after 2 months of single-agent apatinib.

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