Clinical Case Report

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Apatinib in refractory radiation-induced brain edema

A case report

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Abstract

Rationale: Apatinib is a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor-2, which has observed to be effective and safe in refractory radiation-induced brain edema, like Avastin did. Till now, there is no case report after apatinib came in the market.

Patient concerns: Two patients who received brain radiotherapy developed clinical manifestations of brain edema, including dizziness, headache, limb activity disorder, and so on.

Diagnoses: Two patients were both diagnosed as refractory radiation-induced brain edema.

Interventions: Two patients received apatinib (500 mg/day) for 2 and 4 weeks.

Outcomes: Two patients got symptomatic improvements from apatinib in different degrees. Magnetic resonance imaging after apatinib treatments showed that compared with pre-treatment imaging, the perilesional edema reduced dramatically. However, the toxicity of apatinib was controllable and tolerable.

Lessons: Apatinib can obviously relieve the symptoms of refractory radiation-induced brain edema and improve the quality of life, which offers a new method for refractory radiation-induced brain edema in clinical practices. But that still warrants further investigation in the prospective study.

Abbreviations: AEs = adverse events, BBB = blood–brain barrier, CT = computed tomography, HIF-1α = hypoxia-inducible factor-1α, MR = magnetic resonance, NHL = non-Hodgkin lymphoma, OS = overall survival, PFS = progression-free survival, PR = partial response, RN = radiation necrosis, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor, VEGFR-2 = vascular endothelial growth factor receptor-2.

Keywords: apatinib, complication, edema, radiotherapy, treatment

1. Introduction

Radiation-induced brain injury is a late central nervous system complication for patients with head and neck neoplasms after radiotherapy. The main clinical manifestations are increased intracranial pressure caused by brain edema and localizing symptoms or signs caused by brain necrosis. An epidemiologic study in American showed that up to 40% of patients who were diagnosed with cancer every year would develop one or more brain metastases.[1] With improvements of radiotherapy and extension of survival, the complication of radiotherapy such as radiation-induced brain edema will prominently influence the quality of life, even survival. However, special and effective treatments for radiation-induced brain edema are still lacking. The traditional treatment strategy is the combination of dehydration (such as mannitol) and glucocorticoid. In vitro experiments conformed that glucocorticoid could improve the survival of patients, but was complicated by obviously side effects. The effective rate was just about 20%, and long-term or high-dose treatment might increase the risk of adverse reactions.[2,3] In the clinical practice, recurrence of symptoms and drug dependence were also observed in patients, so it was extremely urgent to find more effective strategies. Recently, some domestic and foreign researches showed that bevacizumab, an anti-angiogenic agent, had significantly therapeutic effects in the radiation-induced brain edema. However, it was too expensive to widespread use. Another anti-angiogenic agent was apatinib; its mechanism was also inhibition of angiogenesis, and there was no evidence to conform the efficacy of apatinib in radiation-induced brain edema. In the present study, apatinib was first used in clinical practice to treat 2 patients with refractory

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radiation-induced brain edema. Both of patients got good responses and obvious symptom improvements. The cases were summarized as follows.

2. Case presentation

Two patients who received brain radiotherapy developed clinical manifestations of brain edema, including dizziness, headache, limb activity disorder, and so on. T2-weighted magnetic resonance imaging (MRI) revealed large perilesional edema. Two patients were treated with cortisone drugs and mannitol for dehydration, and symptoms did not improve. With the informed consents of 2 patients and without obvious contraindication of apatinib, 2 patients received apatinib (500 mg/day) after meals (once a day, 2 tablets each time, successive administration, repeated every 4 weeks). The changes of clinical manifestation and MRI after apatinib treatment were prospectively observed and recorded.

Case 1, male, 70-year-old, admitted to hospital due to "lung shadow for 1 year, chest pain for half year." The admitting diagnosis was lung adenocarcinoma with brain, bone, and pleura metastases (cT4N3M1b stage IV). The pathological result of the right supraclavicular lymph node biopsy showed adenocarcinoma with lymph nodes metastasis and EGFR activating mutation. After chemotherapy of pemetrexed and nedaplatin for 2 cycles, chemotherapy was stopped, because the side effects could not be tolerated. He received icotinib (125 mg tid) from August. After he received radiotherapy of the left temporal and parietal metastases (DT = 42 Gy/6 Gy/7 F), which was supplemented by mannitol and dexamethasone for dehydration from August 2015, those symptoms disappeared. Computed tomographic (CT) scan (November 2015) indicated that compared with the previous one (July 2015), the masses in the right lung and the lymph nodes metastasis were obviously smaller, and partial lesion disappeared. The therapeutic evaluation was partial response (PR). In December 2015, the patient was admitted to hospital again due to "right weakness progressively aggravated." Conventional administration with mannitol and dexamethasone for dehydration improved his symptoms. However, the symptoms relapsed after these drugs were discontinued and the patient could not get off the treatment of mannitol and dexamethasone. T2-weighted MRI of cranial (January 2016) revealed that compared with the previous one (November 2015), the perilesional edema of the left temporal and parietal was larger. Patient received apatinib (500 mg/day) and stopped icotinib from January. After 2 weeks, the weakness symptoms were obviously improved, and dizziness and

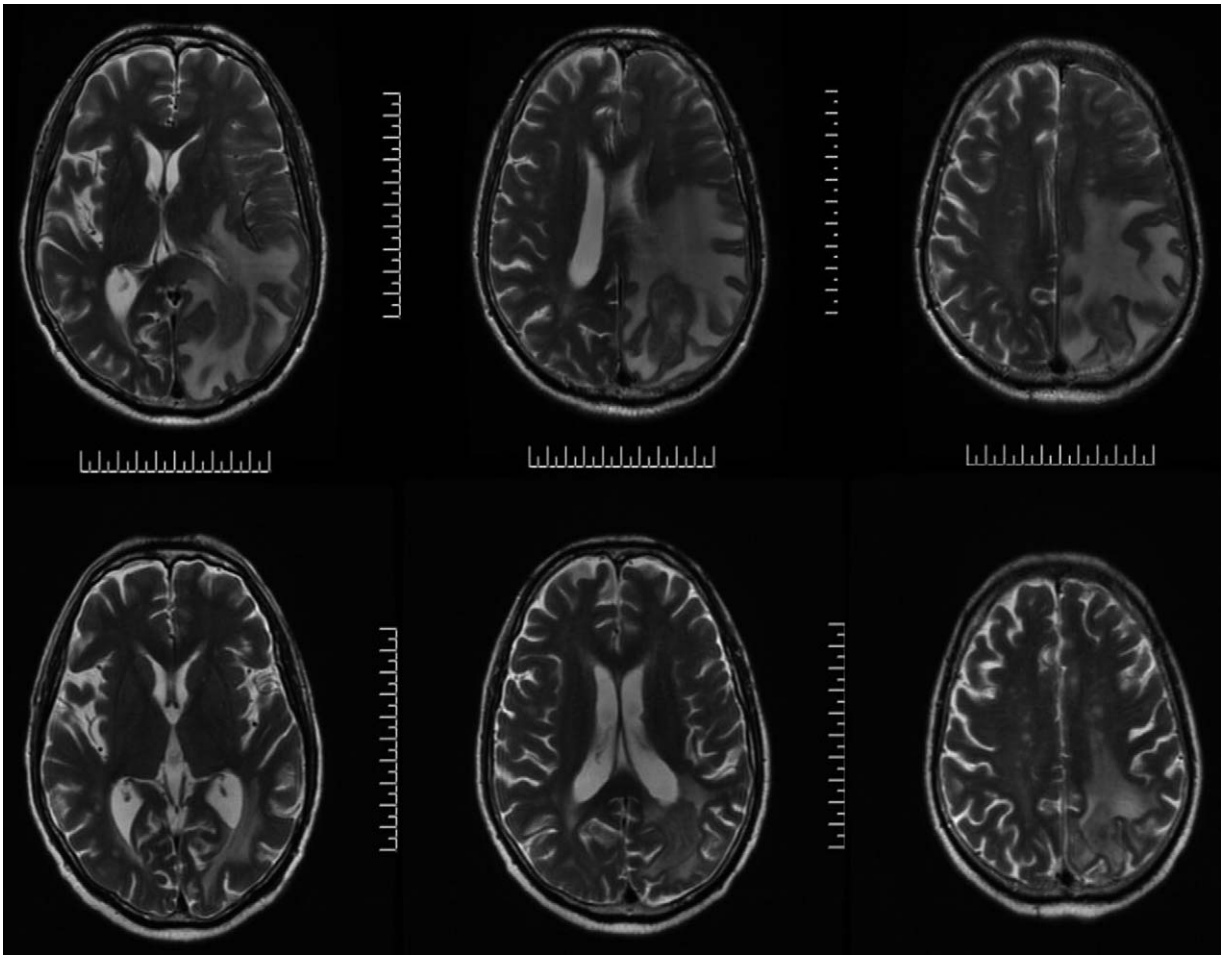

Figure 1. The 3 pictures above display T2-weighted MR of case 1 before treatment of apatinib, while the 3 pictures below indicate T2-weighted MR of case 1 after treatment of apatinib. Before apatinib administration, T2-weighted MR revealed large perilesional edema in the left parietal lobe. Four weeks after treatment with apatinib, T2-weighted MR showed that edema shrank obviously.

headache disappeared. Compared with the previous one (January 2016), T2-weighted MRI of cranial (February 2016) revealed that perilesional edema of the left temporal and parietal prominently shrank (Fig. 1).

Case 2, female, 45-year-old, admitted to hospital due to "headache and vomit" in February 2016. Imaging examinations showed intracranial mass. On February 2016, patient received neurosurgical resection of the space-occupying, and postoperational pathological examination indicated non-Hodgkin lymphoma (NHL). After surgery, in March 2016, she received whole brain radiotherapy (DT = 40 Gy/20 F) with the boost dose (DT = 10 Gy/5 F) in the left temporal and parietal. Cranial MRI after radiotherapy revealed that compared with previous one, the left parietal lobe, basal ganglia, and corpus callosum lesion decreased. In May 2016, patient was treated with high-dose methotrexate chemotherapy for 2 cycles. Two weeks after treatment, her right weakness gradually aggravated and progressed to right hemiplegia, muscle strength 0 level. She received conventional therapy of mannitol and dexamethasone for dehydration, but only got little symptomatic improvements. Cranial MRI indicated that compared with previous one (May 2016), the left parietal lobe edema was larger. In July 2016, the patient was treated with oral apatinib (500 mg/day). One month later, her right hemiplegia symptoms improved remarkably. Her muscle strength restored to normal and headache, nausea, and vomit disappeared (Fig. 2).

3. Discussion

In vitro experiments confirmed that the most prominent histopathological changes in radiation-induced brain injury were brain parenchyma injury, including demyelination of white matter, gliosis, and neural cell loss; and vascular endothelial damages that might cause altered permeability, hyalinosis, and fibrinoid deposits in the vessel walls in the acute and subacute phases. Vascular damages were significant segments in radiation-induced brain injury, and researches found that VEGF (vascular endothelial growth factor) was not only associated with late delayed effects but also with the development of vascular pathologies.[4] Animal models of the radiation-induced brain injury have confirmed that the radiation in mouse was associated with increased BBB (blood–brain barrier) permeability, elevated levels of VEGF in cerebral cortex, and brain parenchyma injury.[5] Radiation could cause the vascular endothelial damages, leading to the BBB breakdown. The local microcirculatory disorders resulted in the vascular system hypoxia, and stimulated the vascular endothelial and astrocyte to secrete the VEGF. There were 2 prominent biological characteristics for VEGF, one was a vasoactive peptide, causing pathological angiogenesis and angiotelectasis, and the other was increasing the vascular permeability, leading to the perilesional edema.[6] Nonoguchi et al[7] conducted histological and immunohistochemistry analyses in clinical specimens of patients with symptomatic radiation necrosis (RN). The results of H&E staining showed remarkable revascularization, proliferation of reactive astrocytes, and the prominent telangiectasis. In immunohistochemistry analysis, HIF-1α (hypoxia-inducible factor-1α) was strongly expressed and perinecrotic area was surrounded by a lot of VEGF-positive reactive astrocytes. This strongly suggested that VEGF secreted by the positive astrocytes in the perinecrotic area might be the prominent causes of the endothelial proliferation in the perinecrotic area and radiation-induced brain edema.

VEGF was closely associated with the perilesional edema and radiation-induced brain injury. Researches indicated that anti-VEGF therapy could normalize BBB function, thereby providing theoretical foundation for treating the brain edema and radiation-induced brain injury. Bevacizumab, a recombinant

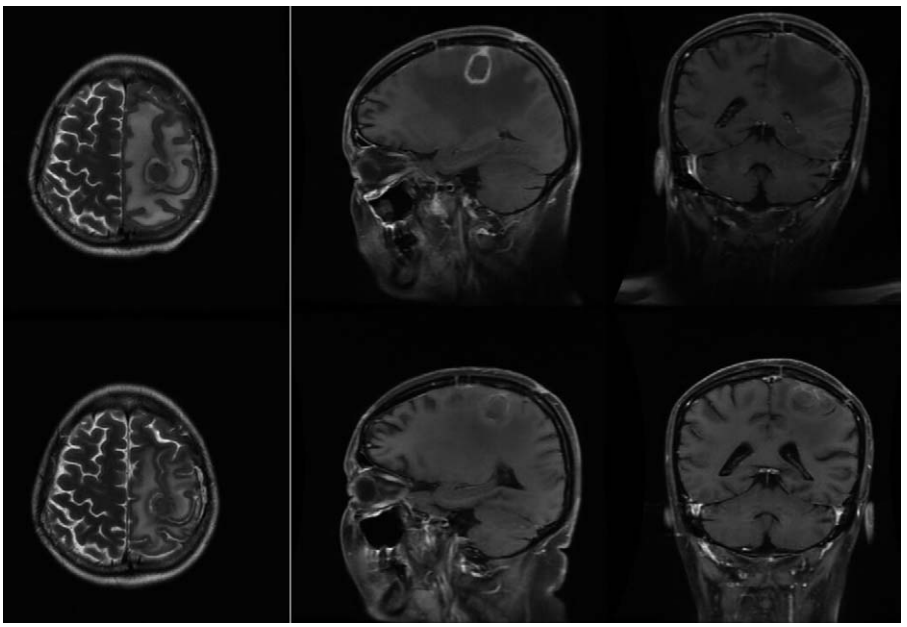

Figure 2. The 6 pictures are the cranial MRI images before and after apatinib treatment of case 2 who do not get benefits from conventional therapy of mannitol and dexamethasone for dehydration. Compared with the MRI images before apatinib treatment, horizontal plane of T2-weighted MR after apatinib treatment revealed that the large perilesional edema in the left frontal and parietal shrank obviously. In the vertical plane and coronal plane of T1-weighted MR, after apatinib treatment, the perilesional edema in the left parietal and oppression of the surrounding tissue improved, and structure of the left side of the third ventricle could be observed again.

humanized monoclonal IgG1 antibody could specifically block the combination of VEGF and VEGFR (VEGF receptor), and decrease the proliferation of endothelial and angiogenesis, leading to the reduction of permeability and the normalization of vasculature. Due to the prominent anti-angiogenesis effect, it had remarkable advantages in anti-tumor therapy and improvement of perilesional edema.[8] Recently, bevacizumab had been reported to effectively improve the radiation-induced brain edema and RN by experts from multiple cancer centers in Europe and America. The potential beneficial effect of treatment with bevacizumab on 15 patients with RN was first reported by Gonzalez et al.[9] The result showed radiographic improvement with an average of 60% reduction in FLAIR MRI and 8.6 mg reduction in daily dexamethasone requirements. The research also indicated that bevacizumab could decrease the capillary leakage and improve the brain edema, and established the role of bevacizumab in the treatment of radiation-induction brain edema. Levin et al[10] conducted a randomized, double-blind, placebo-controlled trial, which enrolled 14 patients with symptomatic RN who were treated with bevacizumab. Results showed that all treatment group patients got decreases in RN and improvements in neurological symptoms or signs. At a median of 10 months follow-up after the last treatment of bevacizumab, only 2 patients experienced a recurrence of radiation-induction brain injury. The trial suggested that bevacizumab had a certain therapeutic effect in the treatment of radiation-induction brain injury. Then, Wang et al[11] reported the beneficial effect of the combination of bevacizmab and CyberKnife treatment for 8 patients with brain metastasis and extensive cerebral edema. Bevacizumab therapy was administrated 3 to 10 days after completion of CyberKnife treatment. T2-weighted MRI of cranial indicated average of 63.4% reduction in brain edema. Seven patients showed significant neurological improvements and 5 patients discontinued dexamethasone treatment 4 weeks after bevacizumab initiation.[11] After 3 to 8 months, the primary lesions of all patients were under control and no recurrence of edema or emerging RN was observed. Jiang et al[12] conducted a research to qualify the effectiveness of bevacizumab in the treatment of radiation-induction brain edema. The results of HE stain in mouse model showed that there were statistical differences between the bevacizumab-treated group and the control group in the vascular telangiectasia, hemorrhage, loss of neurons, and edema. Both of MRI findings and histologic assessment confirmed that bevacizumab could dramatically improve the late-onset radiation-induction brain edema.[12] Boothe et al[13] retrospectively researched 11 patients with brain edema who received bevacizumab. At a mean of 1 month, the mean percentage decrease in RN volume was 64.4%. After bevacizumab treatment, steroid requirement dramatically decreased in all patients and most patients had improvements in radiation-associated symptoms.[13] Although bevacizumab demonstrated prominent advantages in the treatment of radiation-induction brain edema, there were some unavoidable bevacizumab-related adverse events, including hypertension, hemorrhage, proteinuria, gastrointestinal perforation, thromboembolism, and wound healing syndrome. It was known that radiotherapy unavoidable injury the vascular endothelial, leading to platelet adhesion, macrophage activation, proliferation of vascular smooth muscle cell, and thickening of the blood vessel wall. Large and medium sized vessels were damaged, including vessel rupture, vascular stenosis, and vessel occlusion.[14]

Apatinib is a novel tyrosine kinase inhibitor targeting VEGFR-2 (Fig. 3). By highly selective inhibiting the VEGFR-2 tyrosine kinase and blocking the signal transduction of VEGF binding, apatinib could suppress the tumor angiogenesis (Fig. 4). At present, there was no research focused on the effect of apatinib in radiation-induced brain edema. However, in our clinical practice, several cases showed obvious efficacy of apatinib in refractory radiation-induced brain edema. In this study, 2 patients with refractory radiation-induced brain edema were treated with apatinib and were observed. The results showed that apatinib could dramatically reduce the area of brain edema, eliminate the oppression and occupied effect, and improve the clinical symptoms and quality of life. The effect was lasting and no recurrence was observed in follow-up after apatinib treatment. By analyzing the 2 patients, there was a dramatic reduction of the area of edema in T2-weighted MRI. As for the efficacy of apatinib in the treatment of multiple tumors, especially in gastric cancer, the results of the phase III clinical trial indicated that apatinib could significantly improve the median overall survival (OS) and progression-free survival (PFS).[15] In the present study, primary disease of case 1 progressed after 10 months. However, the lesion of cranial was stable and patient did not have brain edema symptoms, including nausea, vomit, dizziness, headache, and so on. The quality of life for the patient was obviously improved. One month after apatinib treatment, cranial MRI of case 2 revealed that compared with previous one, lesion on the left side of the basal ganglia expanded modestly, lesion on the left side of the frontal and parietal lobe reduced slightly, and area of the left frontal parietal lobe edema shrank. After apatinib treatment, right hemiplegia symptoms improved remarkably. Patient could walk by herself without nausea, vomiting, and so on, and the mental and physical were significant better than the previous condition.

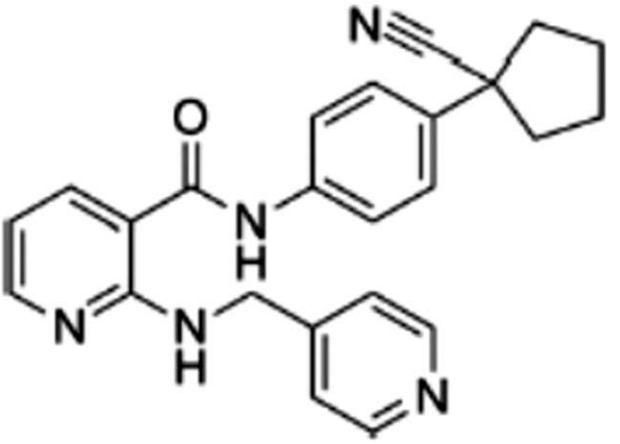

Figure 3. Chemical structure of apatinib.

The common side effects of apatinib (incidence ≥5%) included hematological toxicity (leukopenia, neutropenia, thrombocytopenia, and so on) and nonhematological toxicity (hypertension, proteinuria, hand-foot skin reaction, weak, diarrhea, and so on). Generally, most of AEs (adverse effects) could be controlled and reversed by drug discontinuation, reduction, and best support care.[15] In this study, 1 month after apatinib treatment, hand-foot skin reaction, anorexia, gastrointestinal reaction were observed in case 1, but no hematological toxicity occurred. Grade II myelosuppression with thrombocyte 72×10^9/L occurred in case 2 ten days after apatinib treatment, and no other AEs was observed. Although the dramatic effects of apatinib in

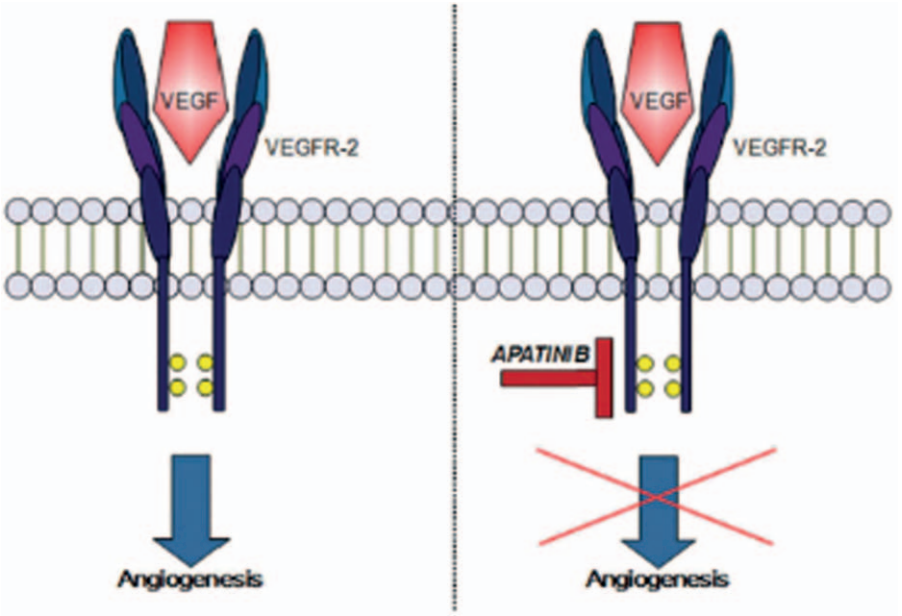

Figure 4. Mechanism of action of apatinib.

radiation-induced brain edema, the sample size of this study is small and more large researches are needed. Moreover, besides the complications, further analyses are required to determine the dosage and duration of apatinib in the treatment of refractory radiation-induced brain edema.

In conclusion, we first report that the effects of apatinib in treatment of radiation-induction brain edema are prominent. There are dramatic improvements in the occupied effect caused by brain edema. This study offers new methods for refractory radiation-induced brain edema in clinical practices, but more clinical studies are needed to complete the efficacy and safety data.

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