

A case report of targeted therapy with apatinib in a patient with recurrent high grade glioma

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Abstract

Rationale: Despite the approval of antiangiogenic therapy for high grade glioma (HGG) patients, survival benefits are still limited. New treatment plans have always been developed to improve the survival.

Patient concerns: A 26-year-old woman was admitted to our hospital for distending pain of head and eye.

Diagnoses: Resonance imaging (MRI) revealed a large spherical heterogeneously enhancing, mixed cystic and solid mass in the right frontal region, and the midline shifted.

Intervention: The patient received apatinib therapy for positive vascular endothelial growth factor.

Outcomes: A partial response was observed after 4 weeks and remains sustained until now.

Lessons: It suggests that apatinib might be a feasible option for the treatment in advanced HGG patients or patients with poor physical condition.

Abbreviations: HGGs = high grade gliomas, HIF-1= hypoxia inducible factor-1, MRI = magnetic resonance imaging, TKI = tyrosine kinase inhibitor, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor 2.

Keywords: angiogenesis, apatinib, bevacizumab, high grade glioma, vascular endothelial growth factor

1. Introduction

High grade gliomas (HGGs), especially glioblastoma, is the most frequent and malignant primary tumor of the central nervous system in adults. Despite the availability of aggressive therapies, 1- and 2-year survival rates of HGG are only 50% and 25%, respectively,^[1] and the median survival rates of it range from 12 to 15 months, and <3% of patients survive >5 years.^[2] The difficulty in treating HGG attributes to its aggressive characteristics, including diffused infiltration, rapid progression, resistance to radio- and chemotherapy, and ineffective drug delivery.^[3,4] This tumor displays the most angiogenic features and the highest degree of vascular proliferation and endothelial cell hyperplasia. Angiogenesis is a key pathologic event in HGG and necessary for the progression of a localized neoplasm to be a highly aggressive

tumor.^[5] Many efforts have been made to develop effective therapeutic strategies to improve the survival.

Vascular endothelial growth factor receptor 2 (VEGFR-2), as one of the VEGFR subtypes, is most commonly implicated in the vascular endothelial growth factor (VEGF), which induces pathological formation of a leaky vasculature.^[6] Internalization of vascular endothelial-cadherin can be induced by VEGF/VEGFR-2 signaling, then the endothelial junction complexes is disassembled.^[7] Apatinib (Hengrui Pharmaceutical Co. Ltd, Shanghai, China) is a novel receptor tyrosine kinase inhibitor (TKI) that selectively targets VEGFR-2.^[8] By binding to VEGFR-2, apatinib inhibits not only the effects of VEGF binding and subsequent VEGFR-2 auto-phosphorylation, but also the downstream phosphorylated extracellular signal-regulated kinase. Preclinical studies have shown that apatinib significantly reduced tumor growth in several established human tumor xenograft models by inhibiting tumor-induced angiogenesis.^[9] Moreover, apatinib has been demonstrated to have antitumor activity in patients with gastric cancer and other solid tumors.^[8,10] Until now, few studies have reported the efficacy of apatinib for HGG. In this study, we aim to present our initial clinical experience of a case of HGG in which apatinib produced an excellent tumor response and acceptable toxicity.

2. Case report

A 26-year-old female patient went to hospital for her 1-week distending pain of right head and eye in May 2015. Magnetic resonance imaging (MRI) revealed a large (8 cm × 6 cm × 5 cm), spherical heterogeneously enhancing, mixed cystic and solid mass in the right frontal region, and the midline shifted (Fig. 1A). The diffusion of the mass suggested high grade tumor activity. A stereotactic right frontal craniotomy was performed, and the tumor was successfully and completely resected (Fig. 1B). Upon histopathologic review, the tumor consisted of a diffusely

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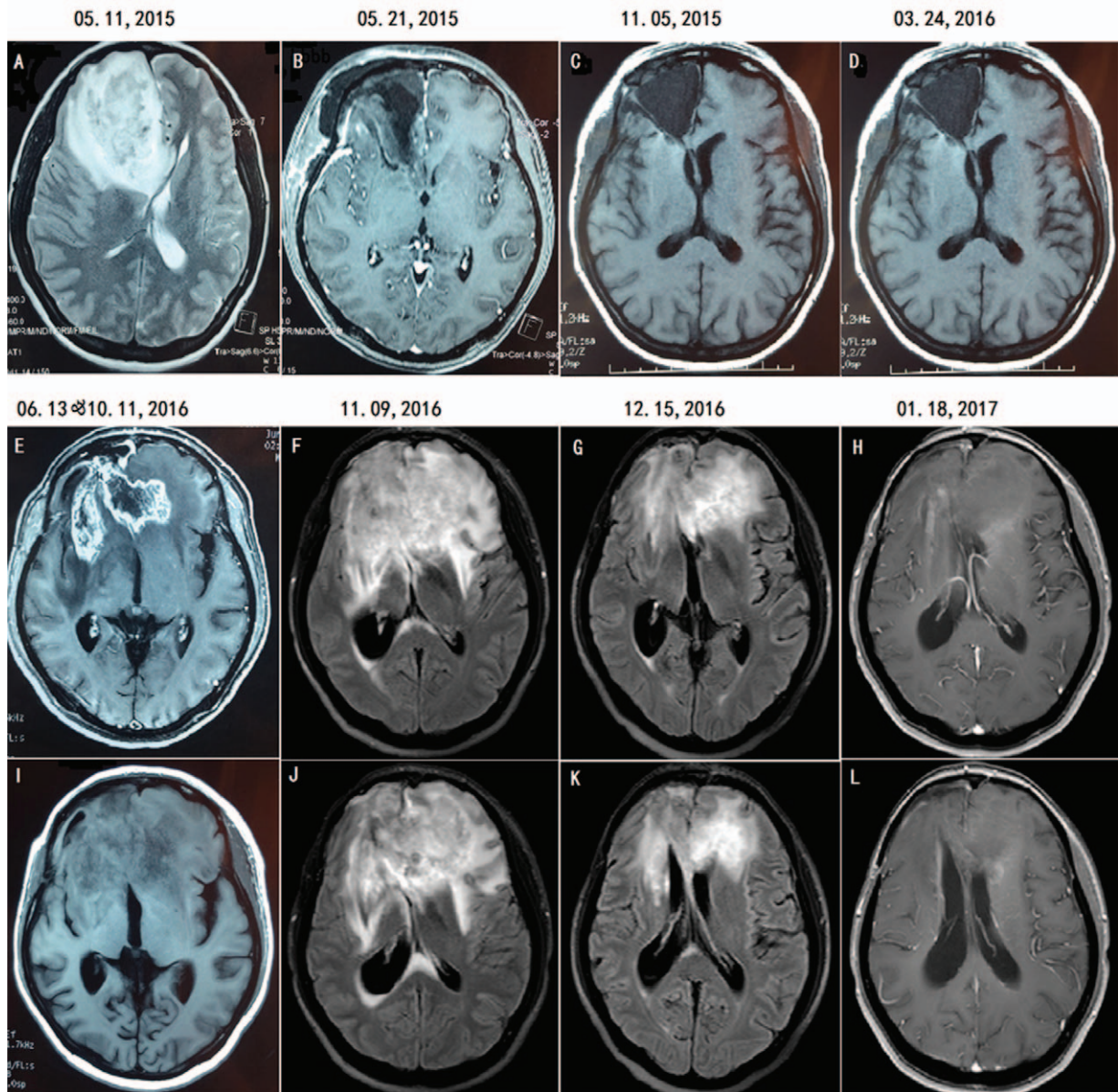


Figure 1. Chronological changes on magnetic resonance imaging (MRI) document the tumor recurrence and response. Coronal MRI contrast were taken at the following times: (A) diagnosis, (B) postoperatively, (C, D) after radiation therapy and while adjuvant chemotherapy, (E) 13 months after operation, (I) after bevacizumab therapy, (F, J) after 1 month without treatment and start of apatinib therapy, (G, K) after 1 month of apatinib therapy, and (H, L) after >2 months of apatinib therapy.

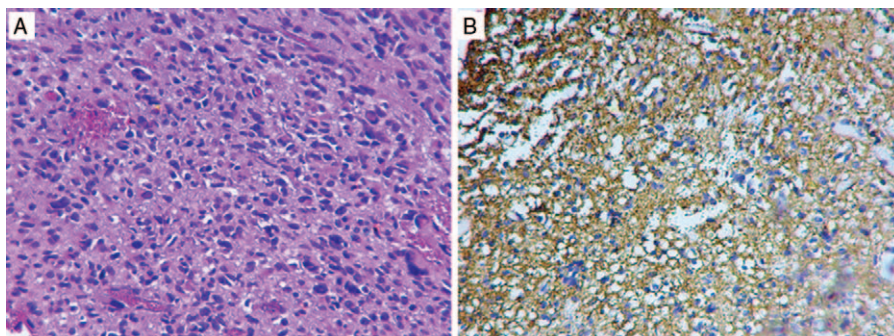


Figure 2. The pathological diagnosis and vascular endothelial growth factor (VEGF) result. (A) Pathological result of glioma (WHO grade III), (B) immunohistochemistry result of VEGF (+).

infiltrating glial neoplasm, fulfilling criteria for HGG (WHO grade III) (Fig. 2A). Immunohistochemistry results: MGMT (+30%), IDH-1 (-), VEGF (+) (Fig. 2B), S-100 (strong +), GFAP (+), Ki-67 (+5%).

After recovering from surgery, the patient was treated with the standard clinical management regimen. Focal radiation of 60 Gy/30f to the tumor bed was administered in combination with temozolomide (75 mg/m² daily) therapy over a 6-week period. After a 2-week break, she continued to receive temozolomide (150 mg/m² days 1–5, every 4 weeks) for another 12 cycles. Regular MRI scans showed no evidence of disease progression while she was on therapy (Fig. 1C and D). After a total of 13 months of therapy, an area of new enhancement in the margin of tumor bed became apparent (Fig. 1E). It was hard to distinguish the brain necrosis or relapse. Therefore, from July 2016, she began to be treated with bevacizumab 10 mg/kg on days 1 and 15 of 28-day cycles. Subsequent scans on October 11 showed progression (Fig. 1I). This patient refused treatment and was discharged from hospital. However, the left-sided weakness and headache got worse, and the MRI scans on November 9 showed the focus to be enlarging with increased perfusion, consistent with a recurrent and progressive tumor, and obvious edema around the tumor (Fig. 1F, J). Given the infiltrative nature of HGG and the location deep in the corpus callosum, surgical resection to remove all microscopic disease was impossible, and the patient refused biopsy. Therefore, after signing informed consent and confirmed by the hospital ethics committee approval, the patient started to take apatinib (500 mg/d) therapy. A week later, the symptoms of headache relieved a little. MRI scans indicated a partial response 4 weeks later, it showed the size of original lesion and edema were significantly decreased (Fig. 1G, K). Moreover, tumor shrinking was more obvious after another 4 weeks (Fig. 1H, L). The side effects included hypertension and skin rash of the whole body. Hypertension was controlled well by administration with antihypertensive drugs, while skin rash was treated with urea and vitamin E cream. The apatinib therapy was continued till now, and the patient was stable without other side effects.

3. Discussion

HGGs are rich in vessels and their size increases rapidly. Hypoxic and necrotic tissues in the tumor center can infiltrate the surrounding normal tissues and destroy the blood–brain barrier; thus, these tumors may relapse quickly even when they are completely resected. It is well recognized that VEGF is highly expressed in glioma cells,^[11,12] and the expression of VEGF in HGGs was significantly higher than that in low grade glioma.^[13] Bevacizumab, as a humanized monoclonal antibody, binds to VEGF-A, and then inhibits angiogenesis. By abrogating the reactive resistance mediated by VEGF and hypoxia inducible factor-1 (HIF-1), bevacizumab sensitizes both endothelial and cancer cells to therapy. However, it is effective mainly in combination with chemotherapeutic drugs and potentiates chemotherapy.^[14] Bevacizumab has been approved for recurrent glioblastoma because it can reduce brain edema, provide symptomatic relief. Yet unfortunately, no overall survival benefit has been demonstrated.^[15]

While apatinib, another anti-angiogenic agent, works through a different mechanism. As a TKI targeted VEGFR-2, apatinib downregulates the phosphorylation, and subsequent downstream signaling, inhibits the interaction of VEGF with VEGFR. Several studies have shown that selective VEGFR-2 TKIs

abrogated VEGF signaling pathways in neovascular endothelial cells, which significantly reduces edema and may substantially improve quality of life.^[16,17] As a result of VEGFR-2 inhibition, vascular normalizes and renders capillaries in brain tumors impermeable to MRI contrast agents by restoring the blood–brain barrier.^[18,19] Based upon all the information above, the patient was recommended to receive apatinib therapy.

To our best knowledge, this is one of the few cases of successfully using apatinib to treat advanced HGG. Efficacy evaluation of promising response with manageable side effects indicated that apatinib was more effective than bevacizumab for this patient. It implied that apatinib might be a safe and effective oral targeted drug on patients with recurrent and progressive HGG, especially for those who experienced failure in chemoradiotherapy or with poor physical condition.

As a novel TKI of VEGFR-2, the efficacy of apatinib has been studied in the treatment of a variety of solid tumors. In this report, apatinib showed good efficacy and safety in the treatment of the recurrent and progressive HGG, which indicated that apatinib might be a feasible option for the treatment in advanced HGG patients or patients with poor physical condition. At present, a phase IIIa, single-arm study of apatinib and irinotecan in treating patients with recurrent HGG is under way, which aimed to evaluate the efficacy and safety of apatinib. It may provide some clinical evidence for the future use of apatinib for recurrent HGG.

Author contributions

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Formal analysis: Xiuping Ding.

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Methodology: Tingyong Fan.

Resources: Tingyong Fan.

References

- [1] Ohgaki H, Kleihues P. Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. *J Neuropathol Exp Neurol* 2005;64:479–89.
- [2] Galan-Moya EM, Le Guellec A, Lima Fernandes E, et al. Secreted factors from brain endothelial cells maintain glioblastoma stem-like cell expansion through the mTOR pathway. *EMBO Rep* 2011;12:470–6.
- [3] Paw I, Carpenter RC, Watabe K, et al. Mechanisms regulating glioma invasion. *Cancer Lett* 2015;362:1–7.
- [4] Weathers SP, de Groot J. VEGF manipulation in glioblastoma. *Oncology (Williston Park)* 2015;29:720–7.
- [5] Smith SJ, Tilly H, Ward JH, et al. CD105 (Endoglin) exerts prognostic effects via its role in the microvascular niche of paediatric high grade glioma. *Acta Neuropathol* 2012;124:99–110.
- [6] Weis SM, Cheresh DA. Pathophysiological consequences of VEGF-induced vascular permeability. *Nature* 2005;437:497–504.
- [7] Dejana E, Tournier-Lasserre E, Weinstein BM. The control of vascular integrity by endothelial cell junctions: molecular basis and pathological implications. *Dev Cell* 2009;16:209–21.
- [8] Roviello G, Ravelli A, Polom K, et al. Apatinib: A novel receptor tyrosine kinase inhibitor for the treatment of gastric cancer. *Cancer Lett* 2016; 372:187–91.
- [9] Tian S, Quan H, Xie C, et al. YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity in vitro and in vivo. *Cancer Sci* 2011; 102:1374–80.
- [10] Scott AJ, Messersmith WA, Jimeno A. Apatinib: a promising oral antiangiogenic agent in the treatment of multiple solid tumors. *Drugs Today (Barc)* 2015;51:223–9.

- [11] Ma C, Li Y, Zhang X, et al. Levels of vascular endothelial growth factor and matrix metalloproteinase-9 proteins in patients with glioma. *J Int Med Res* 2014;42:198–204.
- [12] Li Q, Qiao G, Ma J, et al. Downregulation of VEGF expression attenuates malignant biological behavior of C6 glioma stem cells. *Int J Oncol* 2014;44:1581–8.
- [13] Wang L, Zhang L, Shen W, et al. High expression of VEGF and PI3K in glioma stem cells provides new criteria for the grading of gliomas. *Exp Ther Med* 2016;11:571–6.
- [14] Blagosklonny MV. How avastin potentiates chemotherapeutic drugs: action and reaction in antiangiogenic therapy. *Cancer Biol Ther* 2005;4:1307–10.
- [15] Omuro A, DeAngelis LM. Glioblastoma and other malignant gliomas: a clinical review. *JAMA* 2013;310:1842–50.
- [16] Jain RK, di Tomaso E, Duda DG, et al. Angiogenesis in brain tumours. *Nat Rev Neurosci* 2007;8:610–22.
- [17] Verhoeff JJ, van Tellingen O, Claes A, et al. Concerns about antiangiogenic treatment in patients with glioblastoma multiforme. *BMC Cancer* 2009;9:444.
- [18] Claes A, Gambarota G, Hamans B, et al. Magnetic resonance imaging-based detection of glial brain tumors in mice after antiangiogenic treatment. *Int J Cancer* 2008;122:1981–6.
- [19] Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005;307:58–62.