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A pilot clinical study of apatinib plus irinotecan in patients with recurrent high-grade glioma

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Abstract

Background: Malignant glioma is the most common primary malignant brain tumor that displays high vascularity, making vascular endothelial growth factor receptors become promising targets. This study was conducted to evaluate the efficacy and safety of apatinib, a new potent oral small-molecule tyrosine kinase inhibitor targeted vascular endothelial growth factor receptor 2, combined with irinotecan, in patients with recurrent malignant glioma.

Methods: Ten patients with recurrent malignant glioma who were experiencing relapse after treatment of temozolomide were enrolled in this study. They received oral apatinib (500 mg qd) in conjunction with irinotecan (340 mg/m^2 or 125 mg/m^2 depending on use of enzyme-inducing antiepileptic drugs) for 6 cycles. After that the patients continued to take apatinib as maintenance. Dosage adjustment occurred in only 3 (30.0%) patients.

Results: Among the 10 patients, 9 were available for the efficacy evaluation. There were 5 with partial response, 2 with stable disease and 2 with progressive disease. The objective response rate and the disease control rate (DCR) were 55% (5/9) and 78% (7/9), respectively. The median progress free survival time was 8.3 months. As for safety analysis, the most 3 common adverse events were gastrointestinal reaction (31.8%), hypertension (22.7%), and myelosuppression (18.0%).

Conclusion: Apatinib combined with irinotecan seems to be a promising therapeutic option for recurrent malignant glioma patients. Perspective clinical studies with adequate sample size are required to validate our results.

Trial Registration: NCT02848794/Ahead–BG306.

Abbreviations: AEs = adverse events, CNS = central nervous system, CR = complete response, CTC AE = Common Terminology Criteria for Adverse Events, DCR = disease control rate, ECOG = Eastern Cooperative Oncology Group, GBM = glioblastoma, MDR = multidrug resistance, MG = malignant glioma, mOS = median overall survival, mPFS = median progress free survival time, MRI = magnetic resonance imaging, ORR = objective response rate, OS = overall survival, PD = progressive disease, PFS = progress free survival time, PR = partial response, SD = stable disease, TKI = tyrosine kinase inhibitor, TMZ = temozolomide, ULN = upper limit of normal, VEGF = vascular endothelial growth factor, VEGFR-2 = vascular endothelial growth factor receptor 2, VEGFRs = vascular endothelial growth factor receptors, WHO = World Health Organization.

Keywords: antiangiogenic agents, apatinib, recurrent malignant glioma, vascular endothelial growth factor receptor

1. Introduction

Malignant glioma (MG) is one of the most common primary tumors in the central nervous system (CNS). Glioblastoma (GBM) accounts for 55% of glioma and is nearly always fatal. Standard treatment for newly diagnosed MG is surgery followed by radiotherapy and temozolomide (TMZ) with additional maintenance TMZ.[1] The prognosis of MG is closely correlated with the pathological classification and World Health Organization (WHO) grade level. At the time of disease recurrence, tumors can progress to a more aggressive state and few treatment options are available. It was reported that survival after relapse and retreatment of MG was usually in the range of 6 to 8 months,[2] and the median time to the second progression was 14 weeks.[3] Treatment options for patients with recurrent GBM are limited and include repeat resection, RT, and systemic chemotherapy, such as TMZ, nitrosoureas, platinum-based regimens (carboplatin, cisplatin), cyclophosphamide, and irinotecan.[4] Thus, recurrent GBM remains a largely unmet medical need, which highlights the need for novel and effective therapies.

Significant progress has been made in understanding the molecular characteristics of MG and the potential of targeted therapeutic approaches to the disease. Grade IV glioma have long been associated with pathologic hallmarks of extensive tumor necrosis; intense

Editor: Eric Bush.

LW, LL, and TY contributed equally to this work.

This study was supported by the National Natural Science Foundation of China (grant NO. 81472792).

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:49(e9053)

Received: 12 August 2017 / Received in final form: 9 October 2017 / Accepted: 11 November 2017

http://dx.doi.org/10.1097/MD.0000000000009053

vascular proliferation; and increased expression of angiogenic factors, the most notable of which is vascular endothelial growth factor (VEGF). VEGF is an important regulator of angiogenesis and has been implicated in pathologic angiogenesis associated with tumor growth.[5] It is highly expressed in GBM, and overexpression correlates with high-grade malignancy and poor prognosis.[6–8] Consistent with being hypoxia driven, VEGF expression is localized to regions of GBM that border areas of necrosis.[9–11]

Bevacizumab neutralizes the biologic activity of VEGF and inhibits the binding of VEGF to its receptors on the surface of endothelial cells. It was granted accelerated approval by the US FDA in 2009 as a single agent or combined with irinotecan for patients with GBM with progressive disease (PD) following prior therapy.[12] In the bevacizumab-alone and the bevacizumab-plus-irinotecan treatment, it was reported that estimated 6-month median progress free survival time (mPFS) rates were 42.6% and 50.3%, respectively; objective response rate (ORR) were 28.2% and 37.8%, respectively; and median overall survival (mOS) were 9.2 and 8.7 months, respectively.[13]

Apatinib (Hengrui Pharmaceutical Co, Ltd, P.R. China) is a small-molecule tyrosine kinase inhibitor (TKI) that highly selectively binds to and strongly inhibits vascular endothelial growth factor receptor 2 (VEGFR-2), which was approved for marketing in China in 2014 and admitted for the treatment of advanced gastric cancer patients who had failed after the second-line.[14] Apatinib has demonstrated a substantial potential to be a new therapeutic option in a variety of tumor types.[15] Given the current evidence for bevacizumab in recurrent GBM, we investigated the efficacy and safety of apatinib in combination with irinotecan in a pilot study in patients with recurrent MG who were experiencing relapse after treatment with TMZ.

2. Patients and methods

2.1. Study design

This multicentric single-arm, open-label, pilot phase II trial studied the efficacy and safety of apatinib plus irinotecan in high-grade recurrent MG.

The primary endpoint was PFS and secondary endpoints consisted of OS, ORR, and disease control rate (DCR). Complete response (CR), partial response (PR), stable disease (SD), and PD were measured by RECIST 1.1 criteria; PFS was defined as the time from the beginning of intervention treatment to PD or death from any cause; ORR = (CR + PR)/total number of cases × 100%; DCR = (CR + PR + SD)/total number of cases × 100%.

2.2. Eligible criteria

Eligible patients were ≥18 years old with histologically confirmed high-grade glioma (World Health Organization [WHO] Grade III or IV) for which they had received surgery and postoperative standard Stupp regimen, radiotherapy, or chemoradiotherapy. All experienced recurrence within 3 months and had measurable lesion by magnetic resonance imaging (MRI) confirmation. A minimum of 4 weeks was required from prior intracranial surgery, radiation, and other chemotherapeutic agents. Other key inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, acceptable cardiac, hematologic, hepatic and renal function (ie, hemoglobin ≥90 g/L, absolute neutrophil count $\geq 1.5 \times 10^9\ L^{-1}$, platelet count $\geq 80 \times 10^9\ L^{-1}$, bilirubin $< 1.5 \times$ the upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase $< 2.5 \times$ ULN or $5 \times$ ULN if hepatic metastases exited, serum creatinine $\leq 1.5 \times$ ULN or endogenous creatinine clearance rate >45 mL/min). A patient was excluded if there was evidence of ≥grade 2 pulmonary hemorrhage or ≥grade 3 hemorrhage anywhere else according to Common Terminology Criteria for Adverse Events (CTC AE) Version 3.0; the patient was a female who was pregnant or nursing; the patient with uncontrolled blood pressure with medication (>140/90 mm Hg); the patient receiving thrombolytics or anticoagulants; or the patient had any other condition that would make the treatment unsafe.

The study was approved by hospital ethics committee of the Affiliated Lianyungang Hospital of Xuzhou Medical University. All patients signed written informed consent before participating in the study.

2.3. Study treatment

Between May 2015 and November 2016, 10 patients were enrolled. Here we reported these treatment response and safety data (Table 1). The patients received irinotecan 125 mg/m^2 or 340 mg/m^2 depending on use of enzyme-inducing antiepileptic drugs of every 21-day cycle concurrently oral apatinib in the first 6 cycles and then apatinib maintenance therapy. The initial apatinib dose was 500 mg. If grade 3 or 4 toxicity occurred, the dose was adjusted to 250 mg. The majority of the patients had received prior surgery (90%). Half of patients had received concurrent chemoradiotherapy. After that 90% of them had received TMZ treatment.

3. Statistical methods

The method of Kaplan-Meier was used to estimate the distribution of survival. Statistical analyses were performed using SPSS version 16.0 (IBM, Armonk, NY).

Table 1

The clinical characteristics of 10 high-grade malignant gliomas patients treated with apatinib plus irinotecan.

Patients	Gender	Age	Glioma WHO Grade	Surgery before enrollment	Concurrent chemoradiotherapy before enrollment	Radiotherapy before enrollment	Chemotherapy before enrollment	ECOG Status	Initial apatinib dose, mg	Irinotecan dose, mg*	Efficacy	PFS, mo	OS, mo
1	Male	40	IV	Yes	Yes	No	TMZ	1	500	230	SD	13	19
2	Female	54	III	Yes	Yes	No	TMZ	0	500	280	PR	10	11
3	Female	49	IV	Yes	No	Yes	TMZ	0	500	200	PR	11	12.8
4	Male	50	III	No	No	Yes	TMZ	1	500	160	PD†	3.5	SA
5	Male	46	III	Yes	No	Yes	TMZ	0	500	280	PR	8.3	11
6	Male	61	IV	Yes	Yes	No	No	1	500	200	NA	NA	NA
7	Male	46	IV	No	No	No	TMZ	1	500	220	PD	2	2.3
8	Male	51	IV	Yes	Yes	No	TMZ	0	500	250	SD	5	6.5
9	Female	66	IV	Yes	Yes	No	TMZ	2	500	200	PR	ST	SA
10	Male	27	III	Yes	No	Yes	TMZ	1	500	200	PR	5	SA

ECOG = Eastern Cooperative Oncology Group, NA = not applicable, OS = overall survival, PD = progressive disease, PFS = progress-free survival time, PR = partial response, SA = still alive, SD = stable disease, ST = still in treatment, TMZ = temozolomide.

* Calculated based on body surface area.

† Stopped treatment after 1 cycle due to severe hypertension.

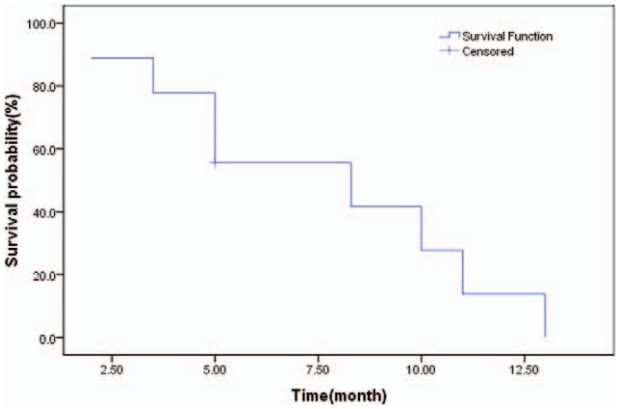

Figure 1. The efficacy evaluation of apatinib in high-grade malignant gliomas patients: PFS curve of apatinib combined with irinotecan therapy. PFS = progress free survival time.

4. Results

4.1. Efficacy

Tumor assessments were performed at baseline, and the response to therapy was determined by MRI and neurologic examination after 12 weeks until disease progression. The investigators utilized the MacDonald criteria to evaluate the MRI. Eight of 10 patients received at least 12 weeks of apatinib treatment and were eligible for the first efficacy analysis, and a patient, who had hypertension history, stopped treatment after 1 cycle of treatment due to severe hypertension. After reviewing the data of these 9 glioma patients, we found the mPFS was 8.3 months. Survival curves for PFS were estimated using the Kaplan-Meier method (Fig. 1). In total, there were 5 with PR, 2 with SD, and 2 with PD. Three patients were still alive, 1 patient was not applicable, and 1 patient was in treatment at the time of analysis. The ORR was 55% (5/9) and the DCR was 78% (7/9).

The detailed data of 2 typical cases (1 case with GBM and another one with anaplastic astrocytoma) were shown as follows. One 40-year-old male patient was first diagnosed to have GBM at the top left temporal (WHO grade IV) in April 2014. He was treated by tumor resection, 6 weeks of concurrent chemo-radiotherapy with TMZ 75 mg/m^2/d, then maintenance therapy with TMZ 150 mg/m^2/d. MRI examination showed disease recurrence in March 2015 (Fig. 2A). From March 2015 to June 2015 the patient was treated by combination of apatinib and irinotecan for 6 cycles (Table 1, No. 1) and maintenance with apatinib 500 mg/d until disease progress in April 2016. MRI

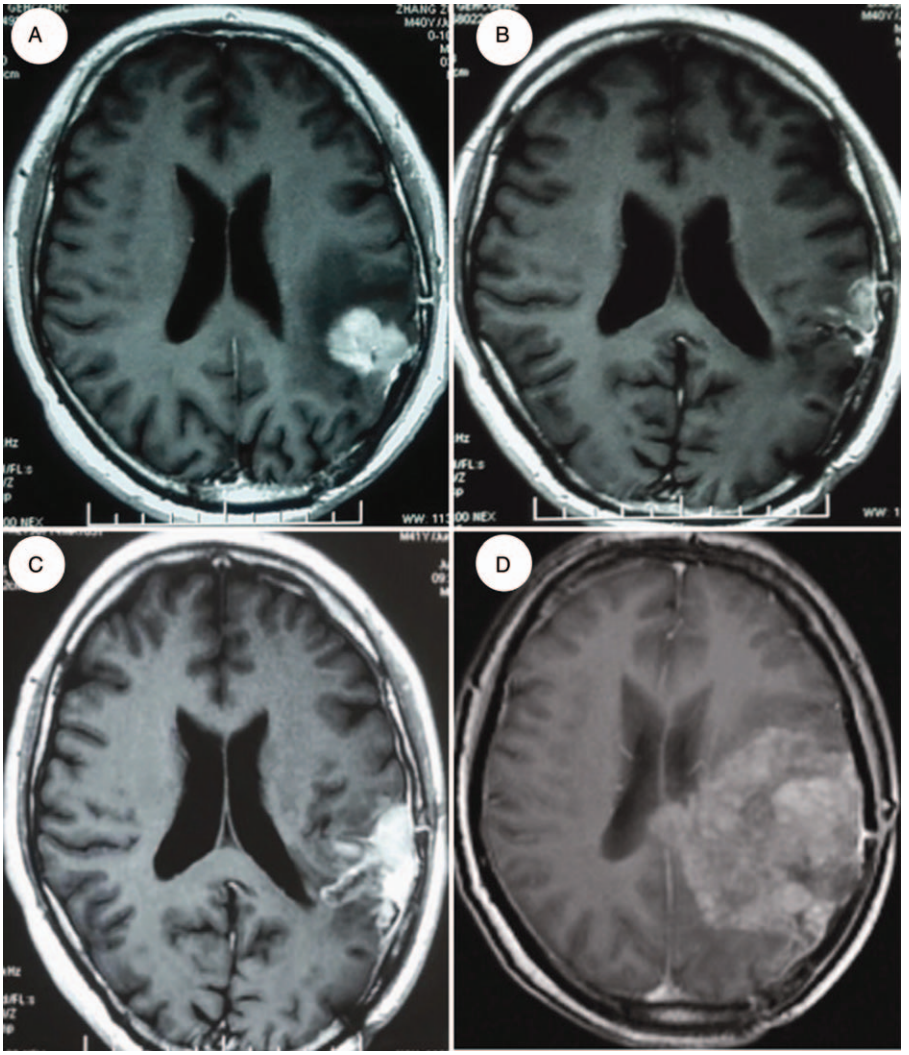

Figure 2. MRI of the patient (no. 1) with glioblastoma: (A) pretreatment MRI scan; (B) posttreatment MRI scan after 3 mo; (C) posttreatment MRI scan after 11 mo; (D) MRI scan of second relapse in April 2016. MRI = magnetic resonance imaging.

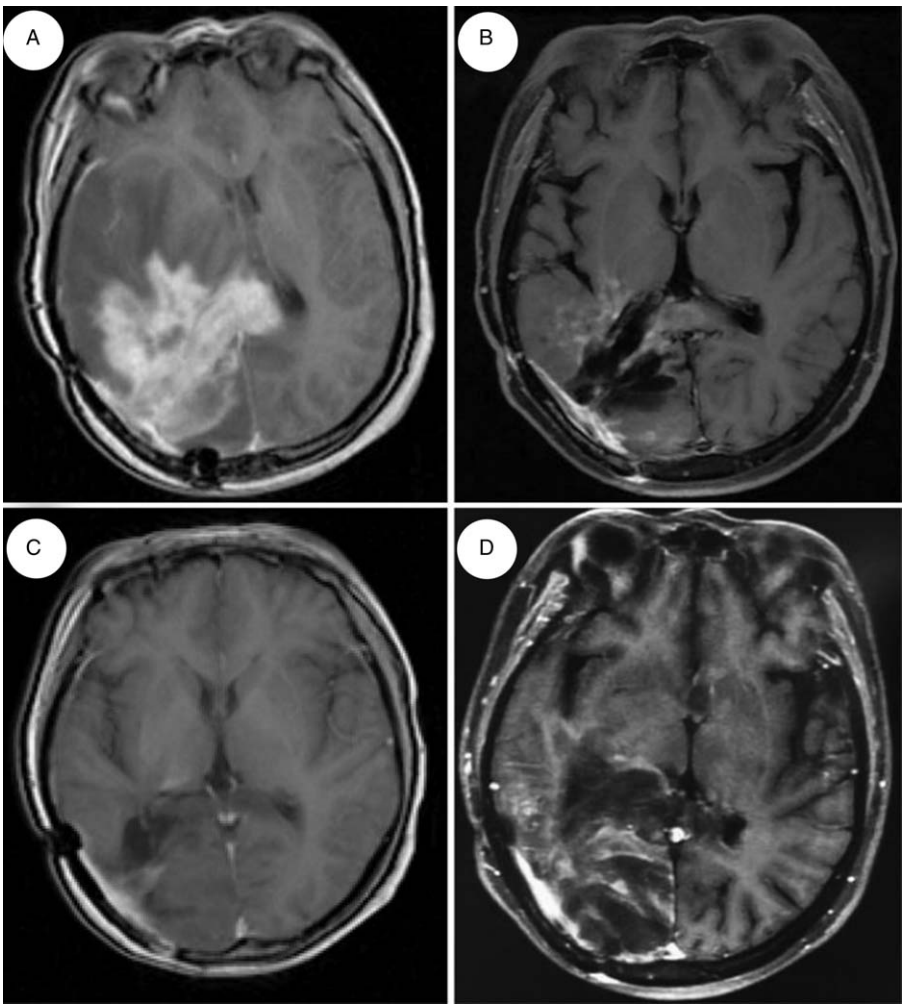

Figure 3. MRI of the patient (no. 2) with anaplastic astrocytoma: (A) pretreatment MRI scan; (B) posttreatment MRI scan after 3 mo; (C) posttreatment MRI scan after 4 mo; (D) posttreatment MRI scan after 9 mo. MRI = magnetic resonance imaging.

reviews in the follow-up showed SD (Fig. 2B–D). The patient died in October 2016, and he got 13 months of PFS and 19 months of OS. The second patient is a 54-year-old female who was diagnosed to have anaplastic astrocytoma at the top right frontal (WHO grade III) in October 2012. Also, she was treated by tumor resection and postoperative standard Stupp regimen. The patient was hospitalized again because of disease recurrence in May 2016 (Fig. 3A). From May 2016 to October 2016 the combination of apatinib and irinotecan for 6 cycles was administrated (Table 1, No. 2) and then apatinib 500 mg/d as maintenance. Three MRI scans showed significant reduction of lesions and the evaluation results are PR, almost achieved CR (Fig. 3B–D).

4.2. Toxicity

Adverse events (AEs) encountered in the study were exhibited in Table 2. Overall, the grade 1 adverse reactions accounted for 45.4% of the total AEs. Grade 2, 3, and 4 AEs accounted for 27.3%, 22.7%, and 4.5%, respectively. Three patients experienced a reduction in the dose of the apatinib during the course of treatment for myelosuppression or hand-foot

Table 2

Adverse events in the combination therapy of apatinib and irinotecan.

Adverse events	Grade 1 (n, %)	Grade 2 (n, %)	Grade 3 (n, %)	Grade 4 (n, %)	Total
Myelosuppression	1 (4.5)	2 (9.0)	1 (4.5)	0	4 (18.0)
Gastrointestinal reaction	5 (22.7)	0	2 (9.0)	0	7 (31.8)
Hypertension	1 (4.5)	3 (13.6)	0	1 (4.5)	5 (22.7)
Hand-foot syndrome	0	0	2 (9.0)	0	2 (9.0)
Fatigue	2 (9.0)	0	0	0	2 (9.0)
Fecal occult blood	1 (4.5)	0	0	0	1 (4.5)

syndrome. One case of dose interruption occurred because of fecal occult blood (+). These AEs were quickly reduced and recovered after a dose reduction or interruption. So it is critical to detect the toxicity of the drug and adjust the dosage (from 500 mg to 250 mg as maintenance therapy) of the drug in time. The most frequently observed treatment-related AEs were as follows: gastrointestinal reaction (31.8%), hypertension (22.7%), and myelosuppression (18.0%) (Table 2). No drug-related AEs occurred in this study.

5. Discussion

This is the first clinical trial to investigate the safety and efficacy of apatinib combined with irinotecan in patients with recurrent MG. Our data demonstrated that apatinib in combination with irinotecan followed by single-agent apatinib maintenance was effective in PFS, ORR, and DCR, and were well tolerated in this Chinese population.

No standard treatment regimen has been proposed for recurrent MG so far. Treatment regimen was usually decided after the comprehensive assessments of general status of patients, location and size of recurrent tumor, and the efficacy of previous treatment. Single-agent irinotecan, which is a topoisomerase I inhibitor, is commonly used in the relapse setting with response rates of 15% or less, ORR is <10%, and mOS is 30 weeks or less.[16–19] Single-agent bevacizumab and bevacizumab in combination with irinotecan had been demonstrated to have notable antitumor activity in pretreated patients with GBM in first or second relapse and the observed 6-month PFS rate far exceeded the 15% rate assumed for salvage chemotherapy and irinotecan alone.[13]

Both of apatinib and bevacizumab are antiangiogenic agents. However, apatinib is oral small molecular TKI, and its target is intracellular domain of VEGFR-2. It has some advantages over bevacizumab. It was reported that apatinib could promote tumor cell apoptosis via intracellular autocrine VEGF signaling, while bevacizumab could not.[20,21] Moreover apatinib can reverse multidrug resistance (MDR) by inhibiting the function of multiple ABC transporters. P-glycoprotein (P-gp) is one type of ABC transporters, and its overexpression is common in cancer cells. It could actively efflux a wide variety of antineoplastic drugs including irinotecan. It had been demonstrated in vitro and in vivo that apatinib could reverse P-gp mediated MDR and increased efficacy of chemotherapeutic drugs.[22,23] Based on these study results, we thought the patients with recurrent MG who have experienced chemotherapy might benefit from combination of apatinib and irinotecan.

Our preliminary results meet our expectation. The adverse effects of apatinib were tolerant and controllable. The most common AEs were reported as leukopenia, neutropenia, hypertension, proteinuria, hand-foot skin reaction, fatigue, and diarrhea. Those were similar with our study. A patient showed grade 4 hypertension and withdrew from the study because he had hypertension history before enrollment.

In conclusion, this study provides supporting evidence that apatinib exhibits objective efficacy combined with irinotecan in high-grade MG with manageable toxicity. Given the sample size was small in this study, the efficacy and safety of apatinib combined with irinotecan in patients with recurrent MG also requires further investigation in a boarder population.

Acknowledgment

We thank the patients and all investigators.

References

[1] Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–96.
[2] Nieder C, Grosu AL, Molls M. A comparison of treatment results for recurrent malignant gliomas. Cancer Treat Rev 2000;26:397–409.
[3] Huncharek M, Muscat J. Treatment of recurrent high grade astrocytoma; results of a systematic review of 1,415 patients. Anticancer Res 1998;18:1303–11.
[4] Brem SS, Bierman PJ, Black P, et al. NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. J Natl Compr Canc Netw 2014;3:644–90.
[5] Ferrara N, Gerber HP, Lecouter J. The biology of VEGF and its receptors. Nat Med 2003;9:669–76.
[6] Lamszus K, Ulbricht U, Matschke J, et al. Levels of soluble vascular endothelial growth factor (VEGF) receptor 1 in astrocytic tumors and its relation to malignancy, vascularity, and VEGF-A. Clin Cancer Res 2003;9:1399–405.
[7] Jain HV, Nör JE, Jackson TL. Modeling the VEGF-Bcl-2-CXCL8 pathway in intratumoral agiogenesis. Bull Math Biol 2008;70:89–117.
[8] Godard S, Getz G, Delorenzi M. Classification of human astrocytic gliomas on the basis of gene expression: a correlated group of genes with angiogenic activity emerges as a strong predictor of subtypes. Cancer Res 2003;63:6613–25.
[9] Johansson M, Brännström T, Bergenheim AT, et al. Spatial expression of VEGF-A in human glioma. J Neurooncol 2002;59:1–6.
[10] Phillips H, Armani M, Stavrou D, et al. Intense focal expression of vascular endothelial growth-factor messenger-RNA in human intracranial neoplasms—association with regions of necrosis. Int J Oncol 1993;2:913–9.
[11] Majmundar AJ, Wong WJ, Simon MC. Hypoxia-inducible factors and the response to hypoxic stress. Mol Cell 2010;40:294–309.
[12] Cohen MH, Shen YL, Keegan P, et al. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. Oncologist 2009;14:1131–8.
[13] Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009;27:4733–40.
[14] Li J, Qin S, Xu J, et al. Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol 2016;34:1448–54.
[15] Zhang H. Apatinib for molecular targeted therapy in tumor. Drug Des Devel Ther 2015;9:6075–81.
[16] Friedman HS, Petros WP, Friedman AH, et al. Irinotecan therapy in adults with recurrent or progressive malignant glioma. J Clin Oncol 1999;17:1516–25.
[17] Cloughesy TF, Filka E, Kuhn J, et al. Two studies evaluating irinotecan treatment for recurrent malignant glioma using an every-3-week regimen. Cancer 2003;97(suppl 9):2381–6.
[18] Raymond E, Fabbro M, Boige V, et al. Multicentre phase II study and pharmacokinetic analysis of irinotecan in chemotherapy-naive patients with glioblastoma. Ann Oncol 2003;14:603–14.
[19] Prados MD, Lamborn K, Yung WK, et al. A phase 2 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: a North American Brain Tumor Consortium study. Neuro Oncol 2006;8:189–93.
[20] Peng S, Zhang Y, Peng H, et al. Intracellular autocrine VEGF signaling promotes EBDC cell proliferation, which can be inhibited by Apatinib. Cancer Lett 2016;373:193–202.
[21] Peng H, Zhang Q, Li J, et al. Apatinib inhibits VEGF signaling and promotes apoptosis in intrahepatic cholangiocarcinoma. Oncotarget 2016;7:17220–9.
[22] Tong XZ, Wang F, Liang S, et al. Apatinib (YN968D1) enhances the efficacy of conventional chemotherapeutical drugs in side population cells and ABCB1-overexpressing leukemia cells. Biochem Pharmacol 2012;83:586–97.
[23] Mi YJ, Liang YJ, Huang HB, et al. Apatinib (YN968D1) reverses multidrug resistance by inhibiting the efflux function of multiple ATP-binding cassette transporters. Cancer Res 2010;70:7981–91.