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Research Article

Temozolomide Dose-Density Protocol Combined with Anti-Angiogenesis in the Treatment of Recurrent Glioma

Wang K, Ding Y, Ning Z, Huang J, Li Q* and Gu W *

Department of Radiation Oncology, The Third Affiliated Hospital of Soochow University, China

***Corresponding author:** Qilin Li, Department of Radiation Oncology, The Third Affiliated Hospital of Soochow University, Jiangsu, China and Wendong Gu, Department of Radiation Oncology, The Third Affiliated Hospital of Soochow University, Jiangsu, China

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Abstract

Background: There is no standard treatment modality for the recurrent high-grade glioma. Temozolomide (TMZ) resistance can be improved by increasing the TMZ dose and Bevacizumab is a monoclonal antibody to VEGF that inhibits angiogenesis. The combination of the two may bring new ideas to treatment. This study investigated the efficacy of different Dose-Dense TMZ (ddTMZ) combination with anti-angiogenesis after glioma recurrence.

Methods: A total of 14 patients with recurrent glioma were enrolled. Treatment after relapse: All patients received ddTMZ 7 days on/7 days off schedule, 100 mg/m^2, 4 patients were given apatinib, 500 mg/day; 10 patients were given bevacizumab, 5 mg/kg, every 2 weeks. These patients were followed up every 3months until the disease progression. The data was closed on September 1, 2020.

Results: Observation indicators: clinical remission rate, Progression Free Survival (PFS), Overall Survival (OS) and toxic side effects. Complete Remission (CR), Partial Remission (PR), Stability Disease (SD) and Progression Disease (PD) are based on the RECIST 1.1 standard. Of all, 2 patients SD during the study follow-up and 12 patients PR during treatment. Median PFS for 7 months, 6m-PFS 57.1%, 1y-PFS 28.6%; median OS 12.5 months, 6m-OS 78.6%, 1y-OS 50%.

Conclusion: ddTMZ-combing bevacizumab is effective at this stage. The main side effects are hypertension. This experiment needs more patients to be included in further research on efficacy and prognosis.

Keywords: Recurrent glioma; ddTMZ; Anti-angiogenesis; Chemotherapy

Abbreviations

CR: Complete Remission; ddTMZ: Dose-Dense Temozolomide; OS: Overall Survival; PD: Progression Disease; PFS: Progression-Free Survival; PR: Partial Remission; SD: Stability Disease

Introduction

Glioma is the most common malignant tumor of central nervous system in adults, accounting for about 81% of cerebral malignant tumor, of which 56.6% is Glioblastoma (GBM) [1].The standard treatment of newly diagnosed high-grade gliomas, which is highly malignant and extremely poor prognosis, is Stupp regimen [2]. First the resection of the gross lesion, followed by concurrent chemoradiation and adjuvant Temozolomide (TMZ). However, almost all patients with WHO III-IV grade glioma will relapse after a period of treatment [3]. Ammirati et al., reported that the time of mean relapse is 32~36weeks [4]. For patients with relapsed high-grade glioma, there is currently no definitive and effective salvage treatment option and the prognosis is even more poor. Weller et al reported that the Progression-Free Survival (PFS) is only 9~48% in 6 months [5]. The median PFS is about 10 weeks and the Overall Survival (OS) is 30 weeks in the research of Wong et al., [6]. The regular regimen of chemotherapy for the recurrent glioma is CPT-11 or TMZ [7]. Because most patients had used TMZ (Stupp regimen) during the first stage of treatment, TMZ resistance was a severe problem due to the presence of MGMT repair-protein [8]. In order to improve the efficacy of treatment, different Dose-Dense Temozolomide (ddTMZ) treatments can be chosen, which increases the concentration of TMZ [9].

Neovascularization is the basis of tumor growth and metastasis [10]. Like other solid tumors, glioma growth and progression are also dependent on angiogenesis. It is reported that gliomas have a high angiogenic index [11]. A number of growth factor receptor pathways that promote tumor angiogenesis were reported in the studies of molecular mechanisms in recent years. Among them, the most studied and clearest signal transduction pathway is the Vascular Endothelial Growth Factor (VEGF) protein family and its receptor signal transduction pathway. Overexpression of VEGF is associated with grading and prognosis of glioma, and the average concentration of VEGF in high-grade glioma is 11 times more than that in the lower grades [12,13]. Reducing the expression of VEGF can inhibit the growth of glioma cell lines, so it is speculated that inhibition of VEGF function may control the growth tumors [14]. Bevacizumab is a monoclonal antibody to VEGF that inhibits angiogenesis, thereby deminshing the proliferation of GBM in animal models [15]. Apatinib is a highly effective, small molecule tyrosine kinase VEGFR-2 inhibitor with high affinity. It is reported that Apatinib is a good tumor growth inhibitory activity against glioma both *in vitro* and *in vivo* tests [16]. This study was designed to evaluate the efficacy

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Table 1: Clinical Characteristics and Therapeutic Effects of 14 Cases of Recurrent High-grade Gliomas.

No.	Gender	Age	Pathological grade	MGMTstatus	Adjuvant TMZ course of treatment	Curative effect	Antiangiogenic drugs	Living conditions	PFS (month)	OS (month)
1	Male	29	3	Methylation	6	PR	Apatinib	Survival	37	37
2	Male	33	4	NA	6	PR	Bevacizumab	Death	5	10
3	Male	51	3	NA	6	PR	Bevacizumab	Death	3	5
4	Female	22	3	NA	9	SD	Bevacizumab	Death	5	9
5	Male	46	4	Methylation	0	PR	Bevacizumab	Death	10	10
6	Male	39	4	NA	0	PR	Apatinib	Death	8	15
7	Male	72	3	Methylation	2	PR	Apatinib	Death	5	17
8	Male	51	3	Unmethylated	0	PR	Apatinib	Survival	20	38
9	Male	44	3	NA	6	PR	Bevacizumab	Death	8	16
10	Female	27	4	Methylation	0	SD	Bevacizumab	Survival	5	5
11	Male	25	4	Unmethylated	0	PR	Bevacizumab	Survival	27	27
12	Male	66	4	Unmethylated	1	PR	Bevacizumab	Survival	2	2
13	Male	46	3	NA	6	PR	Bevacizumab	Survival	6	6
14	Female	39	3	NA	10	PR	Bevacizumab	Survival	20	20

of ddTMZ combination with anti-angiogenesis for the recurrent glioma.

Materials and Methods

Enrollment criteria

Patients the high-grade glioma (WHO grade III-IV), whose pathological diagnose is high-grade glioma (WHO grade III-IV), received surgical removal of the tumor with subsequent concomitant radiation/temozolomide (STUPP regimen) and followed by regular follow-up. The relapse of these patients were confirmed by two senior physicians based on imaging (MRI, plain scan+enhancement+MRSI+PWI). KPS ≥70 and written information consent was obtained.

General clinical data

From September 2014 to June2020, a total of 14 patients with recurrent glioma were eligible for enrollment entered the study, included 11 males and 3 females; aged 22-72 years (median 42 years); the primary pathology was high-grade glioma, 8 cases of WHO III, 6 cases of IV-grade; 7 patients detected the status of MGMT (50%), methylation in 4 and unmethylated in 3patients. All patients underwent radiotherapy chemotherapy, irradiation dose: 50-60 Gy, routine segmentation and simultaneous TMZ (75 mg/m^2). 6 patients received TMZ adjuvant chemotherapy (150 mg/m^2) after chemotherapy and the number of cycle was 1-10 (median 6).

Recurrence

The interval from the date of surgery to recurrence by imaging diagnosis was 3-27 month in 14 patients (mean 12 months). The diagnosis of recurrence is based on the criteria of response assessment (RANO, response assessment in neuro-oncology) in neuro-oncology.

Relapse treatment

Treatment options oral ddTMZ combined antiangiogenic. Instructions for use of ddTMZ is 100 mg/m^2, 7 days on/7 days off. Antiangiogenic drug are apatinib and bevacizumab. In the 4 patients, apatinib was selected, 500 mg/day; 10 patients were treated with bevacizumab, 5 mg/kg, every 2 weeks.

Observation indicators

Including clinical remission rate, Progression Free Survival (PFS), Overall Survival (OS) and toxic side effects. Complete Remission (CR), Partial Remission (PR), Stability (SD) and Progression (PD) are based on the RECIST 1.1 standard. PFS is defined as the time from start treatment until PD or death for any cause after relapse and OS is defined as the time from the start of treatment to the death of any cause after relapse.

Statistical methods

The database was established by SPSS17 0 software and the survival rate was calculated by Kaplan-Meier method.

Results

Follow-up

The patients were followed up in the way of telephone and outpatient review. The deadline of follow-up time was September 1, 2020. There were no patients who were lost to follow-up. The follow-up rate was 100% (Table 1).

Short-term efficacy and survival

MRI (flat scan+enhancement+MRSI+PWI) was reviewed every 3 months during the treatment. According to the RECIST 1.1 standard, overall 14 patients,12 patients PR and 2 patient SD. Median PFS for 7 months, 6m-PFS 57.1%, 1y-PFS 28.6%; median OS 16 months, 6m-OS 78.6%, 1y-OS 50 % (Figure 1).

Toxic side effects

8 of 14patients had different degrees of toxic and side effects, except for 2 grades of Grade 3, both grades 1 to 2. The most common side effect is elevated blood pressure, there are 6 cases, of which 2 cases are grade 3; especially in patients with apatinib, the incidence of hypertension is 4/4, including 2 cases of grade 3 hypertension; followed by myelosuppression There were 4 cases; 4 cases of fatigue;

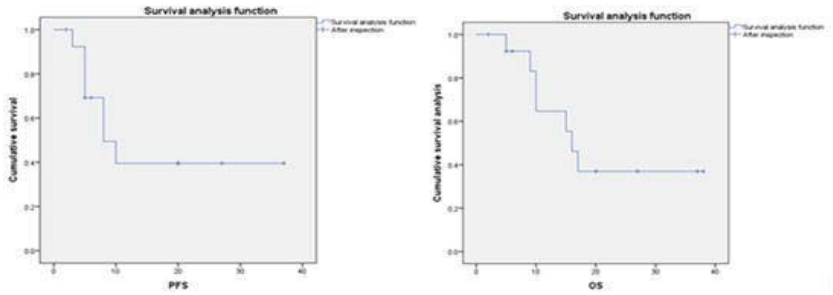

Figure1: Survival analysis (PFS, OS) of 14 patients with recurrent glioma treated with antiangiogenesis plus ddTMZ, the left picture is the PFS survival curve, the right picture is the OS survival curve.

Table 2: Treatment-related Adverse Reactions.

	Grade 1	Grade 2	Grade 3	Total
Hypertension	1	3	2	6
Myelosuppression	2	2		4
Gastrointestinal reaction	1	1		2
Hand and foot syndrome	1	1		2
fatigued	2	2		4
Nasal mucosal bleeding	1			1
Sore throat	1			1

2 cases of gastrointestinal reaction, 2 cases of hand-foot syndrome; 1 case of nasal mucosal hemorrhage and 1 case of sore throat (Table 2).

Discussion

For patients with recurrent high-grade glioma, the effectiveness of optional treatments and range of outcomes are far from satisfactory. Treatments include re-surgery, radiation therapy, salvage chemotherapy, and/or anti-angiogenic therapy [7]. The advantages of surgery include obtaining the pathological diagnosis and distinguishing the recurrent glioma from radioactive brain necrosis. At the same time, testing some genes to enable clinicians to select potential targeted treatments. If the recurrent tumor evaluated preoperatively can be completely excised, reoperation should be the first choice of treatment due to the best curative effect [17]. However, reoperation is subject to many restrictions. The indications are limited to those patients [18] who are young (<70 years old) and generally good (KPS >80%), have small recurrent tumor volume (<50 cm^3), so that only 25% of recurrent glioma patients have the opportunity of reoperation. Moreover, compared with the non-surgical treatment, it was reported that reoperation does not show a better survival advantage [19]. Van Linde et al., [20] retrospectively analyzed 299 patients with salvage therapy after relapse of GBM, including chemotherapy, reoperation, re-radiation and optimal supportive care. The results showed that although the median OS of the surgical group was the highest (11.0 months) which was a statistical difference compared with the best supportive care (3.1 months), there was no significant survival benefit compared with re-radiation (9.2 months) or chemotherapy (7.3 months). It must be taken into consideration that the general condition of the patients in the surgery group was significantly better than the other treatment groups: 96.4% of patients in the surgery group had a KPS >70%, which may lead to selective bias to some extent.

Re-radiation is also an optional palliative treatment. Van Linde et al., [20] found a median OS of 9.2 months in the re-radiotherapy group, which was significantly better than proper supportive care. Schernberg et al. [21] studied re-radiotherapy combined with bevacizumab for the treatment of recurrent glioma and found a median OS of 10.5 months and a PFS of 6.7 months. Although re-radiation is effective, radioactive brain necrosis is more likely to occur [22]. In order to reduce this serious complication, Scoccianti et al. [23] suggested that the dose of re-irradiation (EQD2) should be adjusted according to the volume of the recurrent tumor that if the tumor volume is <12.5 ml, EQD2 <65 Gy is safe; The dose of EQD2 should be reduced to <50 Gy between 12.5 ml and 35 ml ; the volume is >35 ml, EQD2 should not exceed 36 Gy; and the tumor volume is >50 ml, then re-radiation may not be appropriate. In the view of Scherberg et al., [21], it is showed that the higher the dose of re-radiation, the better the treatment effect, the authors suggest that EQD2 must be >50Gy to meet satisfactory results. In fact, that only patients with smaller tumors have the opportunity to receive higher dose, re-radiation may be suitable just for patients with small recurrent lesions and good general condition. In addition, the shape of the tumor after recurrence is extremely irregular and the boundary of the target area is difficult to define, which increase difficulty of accurately portraying GTV when re-radiation [24].

Van Linde et al. [20] studied the median OS of the chemotherapy group was 7.3 months, the effect is not inferior to surgery and radiotherapy groups. Franceschi et al. [25] studied the re-application of TMZ (Stupp regimen) chemotherapy after recurrence of high-grade glioma and found that efficacy was closely related to Treatment-Free Interval (TFI). With TFI ≥5 months, or <5 months, the median PFS was 7.7 and 4.9 months respectively and the OS was 10.4 and 6.6 months respectively. Since MGMT protein can repair DNA damage caused by alkylating agents, an important factor ultimately leads to the failure of TMZ to treat GBM [8]. The dose-density protocol for increasing the unit dose can theoretically increase the depletion of MGMT repair-protein, which seems to be a feasible solution to solve the problem of TMZ resistance [9]. However, for the newly diagnosed GBM, the result of RTOG 0525 does not show the survival advantage of ddTMZ regimen in adjuvant therapy [26]. The reason may be that patient who was newly diagnosed has a certain sensitivity for the first exposing to TMZ treatment and there is no additional benefit in increasing the unit dose. For recurrent GBM, the dose density protocol (7 days on/7 days off) was superior to the conventional protocol in both PFS and OS and there was no additional increase

in toxic side effects, the 12-m PFS of relapsed GBM was 11.8-15.5 %, 12-m OS is 30.7-40.6 % [27].

An important reason for poor prognosis and prone to recurrence of high-grade glioma is neovascularization, which characterized by increasing expression of VEGF and microvascular infiltration. Anti-angiogenesis is an effective treatment. The BRAIN study [28] showed that bevacizumab alone or in combination with CPT-11 was used to treat relapsed glioma with PFS-6m of 42.6% and 50.3%, respectively, with a median OS of 9.2 and 8.7 months. BELOB [29] is a phase II clinical controlled study to compare the efficacy of lomustine with or without bevacizumab in the treatment of relapsed high-grade glioma. The results showed that the 9-month OS was 63% in lomustine combined with bevacizumab group, while in the single-agent lomustine was 43%. After adding anti-angiogenic drugs, the benefits were significant. However, the subsequent EORTC 26101 [30] III clinical study showed that the median OS of the single-agent lomustine and lomustine combined with bevacizumab group was 8.6 and 9.1 months, respectively and the median PFS was 1.5 and 4.3 months. The combination therapy only showed PFS benefits and there is no statistical difference in OS benefits. As a high-efficiency VEGFR2 small molecule tyrosine kinase inhibitor, it is very convenient to take apatinib, which can not only relieve refractory cerebral edema [31], but also have a certain role in the treatment of recurrent glioma [32].

Anti-angiogenic therapy can normalize abnormal blood vessels, increase regional blood flow, reduce edema and interstitial pressure, and contribute to absorption of TMZ drugs [33]. Moreover, sustained TMZ exposure can produce anti-angiogenic properties [34,35] by acting on endothelial cells. The combination of TMZ and anti-angiogenic therapy has a synergistic effect in theory. TAVAREC study [36] compared the efficacy of TMZ and TMZ combined with bevacizumab, and the dosage of TMZ was the Stupp regimen (150-200 mg/m^2, 5 days on/23 days off), showed that the median OS of the monotherapy group and the combined treatment group were 14.8 and 12.9 months respectively and the median PFS was 6.3 and 5.91 months, with no statistically significant difference. However, target population of TAVAREC's research is limited to patients with grade 2 or grade 3 glioma recurrence without lost 1p/19q heterozygote. RTOG 0625 study [37,38] reported the efficacy of bevacizumab combined with ddTMZ regimen (75-100 mg/m^2, 21 days on/7 days off). The results showed that 6m-PFS was 39%, median PFS PFS 4.7 months and median OS was 9.4 months. Peters et al., [38] added a histone deacetylase inhibitor, vorinostat, to the combination of anti-angiogenesis (bevacizumab, 10 mg/kg and every two weeks) and ddTMZ (50 mg/m^2, per day) for treating recurrent high-grade glioma. The results showed that the median PFS and OS were 6.7 and 12.5 months respectively, and the 1-year PFS and OS were 20.5% and 51.3%. In the above three studies, the dosage of TMZ in TAVAREC study [36] is the Stupp regimen and are different dose density schemes in the other two studies. In fact, the therapeutic effects of different dose density regimens may not differ much: a phase II clinical study compared the therapeutic effects of 120 mg/m^2, 7 days on/7 days off and 80 mg/m^2, 21 days on/7 days off. Which showed that the median OS was 9.8 months and 10.6 months respectively and there was no significant difference between the two groups [39]. The ddTMZ scheme chosen in our study is 100 mg/m^2, 7 days on/7 days off, while the antiangiogenic drugs are bevacizumab and apatinib, with median PFS and OS of 7 and 12.5 months respectively, slightly better than the survival rate reported in literature.

In terms of toxic and side effects, except for 2 cases of grade 3 hypertension in our study, all of them are grade 1-2. However, in RTOG 0625 study [37], side effects included mainly grade 2 and 3 hematology and gastrointestinal reactions as in our study and there were no treatment-related deaths. This indicates that ddTMZ regimen combining with anti-angiogenic therapy is generally well tolerated.

To sum up, ddTMZ regimen combining with anti-angiogenesis provides a new research direction for the treatment of recurrent high-grade glioma. In view of the small sample size and without a control group in this study, the specific efficacy and toxicity need further study.

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