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ORIGINAL ARTICLE

Temozolomide chemotherapy combined with radiotherapy versus radiotherapy alone after surgery in patients with high-risk low-grade gliomas

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Summary

Purpose: *The purpose of this study was to compare the clinical efficacy and safety of temozolomide (TMZ) combined with three-dimensional conformal radiotherapy (3D-CRT) and radiotherapy alone after surgery in patients with high-risk low-grade gliomas (LGGs).*

Methods: *Patients (N=110) with LGGs were enrolled. Patients receiving TMZ chemotherapy combined with radiotherapy were considered as combination group (n=55), while those treated with radiotherapy alone were regarded as control group (n=55). The patients were followed up, and the overall survival (OS) and progression-free survival (PFS) were recorded. Finally, factors possibly affecting prognosis were analyzed.*

Results: *The follow-up results exhibited median OS [(67.4±8.8) months vs. (63.9±8.6) months] and median PFS [(51.1±7.6) months vs. (46.8±6.9) months] as well as three-year OS rate and three-year PFS rate in combination group and control group. Log-rank test indicated that the difference in OS was not statistically significant between the two groups of patients, and PFS in combination group was significantly superior to that in control group. The results of univariate and multivariate analysis displayed that age <40 years old and complete tumor resection were independent factors affecting the three-year OS of patients with high-risk LGGs. Besides, age <40 years old, complete tumor resection and TMZ chemotherapy combined with radiotherapy after surgery were independent factors affecting the three-year PFS of patients with high-risk LGGs.*

Conclusion: *TMZ chemotherapy combined with radiotherapy after surgery in patients with high-risk LGGs can prominently improve clinical efficacy, prolong PFS, and facilitate tolerance to adverse reactions, but not prolong the OS of patients. The OS is notably prolonged in patients aged <40 years old and receiving complete tumor resection.*

Key words: *TMZ, concurrent chemoradiotherapy, LGGs, high risk, clinical efficacy.*

Introduction

According to the 2007 WHO Classification of Nervous System Tumors, gliomas in grades I and II are considered to be low-grade gliomas (LGGs), of which grade I gliomas mostly occur in adults, including astrocytomas, oligodendrogliomas and oligoastrocytomas [1,2]. LGGs grow slowly but may transform into high-grade gliomas, and high-risk patients are prone to relapse, leading to high disability and mortality rates. LGGs, mainly occurring in young and middle-aged adults aged 30-45 years old, have enormous differences in prognosis, and the median overall survival (OS) is 5-12 years, which

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can be extended to about 20 years after effective treatment [3,4]. Hence, in terms of therapeutic strategies, it is necessary to control tumor growth rate, and prolong progression-free survival (PFS) and OS, and more attention should be paid to improving the quality of life of patients after treatment [5].

Maximum safe resection offers an important initial means for treating LGGs. For patients with high-risk LGGs, the supportive effect of surgery-based radiotherapy has been confirmed definitely, but the clinical efficacy of adjuvant chemotherapy remains unclear [6]. Characterized by the ability to pass through the blood-brain barrier, high efficiency and less adverse reactions, temozolomide (TMZ) is a new type of alkylating antineoplastic agent that can effectively ameliorate the treatment and prognosis of malignant gliomas [7,8]. In this study, the clinical data of patients with high-risk LGGs who underwent surgery were retrospectively analyzed, and the clinical efficacy and safety of TMZ combined with three-dimensional conformal radiotherapy (3D-CRT) and radiotherapy alone after surgery were investigated.

Methods

General data

A total of 110 patients with LGGs were enrolled as the research objects. The inclusion criteria were set as follows: a) patients who received complete tumor resection and pathologically diagnosed with WHO grade II gliomas, b) those with at least 3 high-risk factors, including age ≥40 years old, histological subtypes of astrocytomas, largest tumor diameter ≥6 cm, tumor crossing the midline, and neurological deficit before surgery, except for simple epileptic seizures, and c) those who had no radiotherapy or chemotherapy before treatment. The exclusion criteria involve: a) patients with severe cardiac, hepatic, renal or pulmonary insufficiency, b) those who could not cooperate in treatment due to neurological or mental diseases, or c) those with hematological diseases, endocrine system diseases or autoimmune diseases, or abnormal bone marrow reserve. After surgery, patients who received TMZ chemotherapy combined with radiotherapy were considered as combination group (n=55), while those treated with radiotherapy alone were regarded as control group (n=55), including 63 males and 47 females averagely aged (45.13±9.44) years old. The baseline data of the two groups of patients before treatment are shown in Table 1, and the differences were not statistically significant (p>0.05). This study complied with the *Declaration of Helsinki* and was approved by the Medical Ethics Committee of this hospital, and all enrolled patients were informed of the treatment options and signed the informed consent form.

Treatment options

A total of 110 patients underwent craniotomy microsurgery in neurosurgery, including 88 cases of complete tumor resection and 22 cases of partial tumor resection.

Radiotherapy: At one month after surgery, conventional radiotherapy was carried out by a linear accel-

Table 1. Baseline characteristics of the studied patients

	Combination group (n=55) *n (%)*	*Control group (n=55)* *n (%)*	*p*
Age (years old)	44.23±9.40	45.81±9.66	0.387
Gender (Male/ Female)	29/26	34/21	0.441
Histological type			0.208
Astrocytic glioma	32 (58.2)	38 (69.1)	
Oligodendroglioma	10 (18.2)	11 (20.0)	
Oligodendrocytoma	13 (23.6)	6 (10.9)	
Degree of resection			0.340
Complete excision	42 (76.4)	46 (83.6)	
Partial excision	13 (23.6)	9 (16.4)	
Tumor diameter			0.436
≥3 cm	31 (56.4)	35 (63.6)	
<3 cm	24 (43.6)	20 (36.4)	
Symptoms of epilepsy			0.171
Yes	30 (54.5)	37 (67.3)	
No	25 (45.5)	18 (32.7)	
KPS score (points)			0.229
≥70	39 (70.9%)	33 (60.0)	
<70	16 (29.1)	22 (40.0)	

KPS: Karnofsky performance status.

erator (6-10 MV X-ray beams). The patient's head was fixed with a head frame, followed by center positioning under the simulator, and continuous enhanced CT scanning (3 mm slice thickness) on the head. Then data were input into the computer system to delineate the target area occupied by the tumor, and then the gross tumor volume (GTV) and clinical target volume (CTV) were determined combined with the head T1-weighted magnetic resonance imaging (MRI) (plain scan + enhanced scan). Radiotherapy was performed at 1.8 Gy/day (54 Gy in total), 5 days/week for 6 weeks. During radiotherapy, intracranial pressure should be reduced in time when symptoms or signs of intracranial hypertension such as headache, dizziness and vomiting occurred.

Chemotherapy: TMZ (Temodal, Merck, 20 mg/capsule) was given at 75 mg/m^2/day simultaneously from the first day of radiotherapy for 6 weeks. Subsequently, the dosage was adjusted to 150-200 mg/m^2/day within D 1-5, repeated every 28 days, a total of 5 courses. Blood routine tests, blood biochemical tests and head MRI examination were performed once a week, and adverse reactions of patients were recorded. The general adverse reactions of TMZ, including bone marrow suppression and gastrointestinal reaction, could be tolerated or relieved by drug treatment in mild cases. Discontinuation referred to a serious adverse reaction that caused the patient's intolerance or disease progression during the medication.

Observation indicators

The follow-up period was 3 years in patients after surgery. Cranial MRI (plain scan + enhanced scan) was performed within 72 d after surgery, and head MRI (plain scan + enhanced scan) or head CT (plain scan + enhanced scan) was performed every 3-6 months after surgery to determine the therapeutic effect, presence or absence of progression and objective response rate.

The major toxic reactions (gastrointestinal reactions and hematological toxicity) should be monitored. TMZ could be taken when neutrophils >1.5×10^9/L and platelets ≥100×10^9/L. Conversely, the drug dosage should be halved. According to the grading standard assessed by the *National Cancer Institute* (version 3.0), toxicity is divided into 0-4 grades, of which Grades I and II indicate serious toxic reactions.

OS referred to the time from the day of surgery to the day of death or the most recent follow-up. PFS referred to the time from the day of surgery to the day of occurrence of disease progression or the most recent follow-up.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was adopted for statistical analysis. The measurement data were expressed as mean ± standard deviation, and t-test was used for comparison between groups. The enumeration data were analyzed by x^2 test or Fisher's exact probability test. The short-term efficacy and adverse reactions were compared according to one-way ordered rank data, and analyzed by Mann-Whitney U test. Kaplan-Meier method and log-rank test were used for survival analysis. Multivariate Cox's proportional hazard regression model was used to analyze the factors affecting the prognosis of patients. $p<0.05$ indicated that the difference was statistically significant.

Results

Comparison of adverse reactions

After surgery, chemoradiotherapy-related adverse reactions including leukopenia, anemia, thrombocytopenia, nausea and vomiting, diarrhea, fatigue, fever, alopecia and neurotoxicity, mostly in Grade I-II, could be alleviated by symptomatic treatment, and no statistically significant difference was found in the incidence rate of adverse reactions ($p>0.05$). The incidence rate of Grade III-IV adverse reactions was low. Leukopenia occurred in 2 cases in combination group and 2 cases in control group, and nausea and vomiting occurred in 3 cases and 2 cases, respectively. The results indicated that adverse reactions were not significantly increased in patients treated with radiotherapy combined with TMZ chemotherapy after surgery (Table 2).

Table 2. Comparison of adverse reactions between the two groups of patients

	Combination group (n=55) *n (%)*	*Control group (n=55)* *n (%)*	*p*
Leukopenia	13 (23.6)	9 (16.4)	0.340
Anemia	8 (14.5)	11 (20.0)	0.449
Thrombocytopenia	6 (10.9)	10 (18.2)	0.279
Nausea and vomiting	19 (34.5)	16 (29.1)	0.539
Diarrea	14 (25.5)	10 (18.2)	0.356
Fatigue	16 (29.1)	13 (23.6)	0.516
Fever	5 (9.1)	3 (5.5)	0.463
Alopecia	4 (7.3)	6 (10.9)	0.507
Neurotoxicity	10 (18.2)	5 (9.1)	0.165

Follow-up survival data

All 110 patients were followed up until June 2020, and the follow-up period was 6-36 months. The follow-up results exhibited median OS [(67.4±8.8) months *vs.* (63.9±8.6) months] and median PFS [(51.1±7.6) months *vs.* (46.8±6.9) months], one-year OS rate [96.4% (53/55) *vs.* 92.7% (51/55)] and one-year PFS rate [87.3% (48/55) *vs.* 78.2% (43/55)], two-year OS rate [85.5% (47/55) *vs.* 80.0% (44/55)] and two-year PFS rate [76.4% (42/55) *vs.*

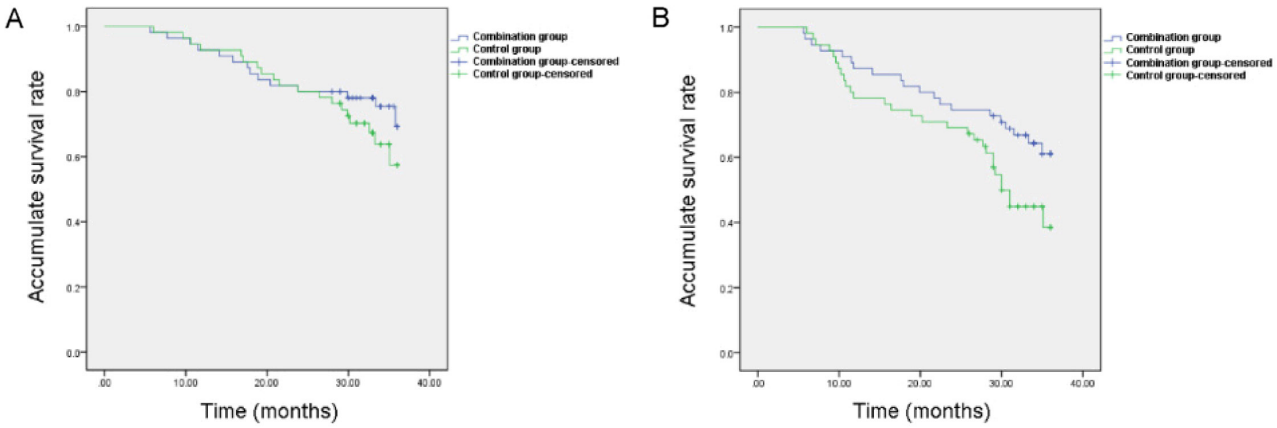

Figure 1. Kaplan-Meier survival curves of low-grade glioma patients. The difference in the overall survival rate **(A)** of patients between Combination group and Control group had no statistical significance (p=0.300). The PFS **(B)** of patients in Combination group was significantly higher than that in Control group (p=0.047).

Table 3. Univariate analysis of predictors for 3-year OS and 3-year PFS in low-grade glioma patients

	n (%) n=110	*3-year OS (%)*	*p-value*	*3-year PFS (%)*	*p*
Age (years)			0.012		0.010
<40	51 (46.4)	82.4		70.6	
≥40	59 (53.6)	59.3		42.4	
Gender			0.529		0.333
Male	63 (57.3)	73.0		50.8	
Female	47 (42.7)	66.0		61.7	
Histological type			0.216		0.438
Astrocytic glioma	70 (63.6)	64.3		51.4	
Oligodendroglioma	21 (19.1)	81.0		66.7	
Oligodendrocytoma	19 (17.3)	78.9		57.9	
Degree of resection			0.001		0.001
Complete excision	88 (80.0)	78.4		63.6	
Partial excision	22 (20.0)	36.4		22.7	
Tumor diameter			0.401		0.176
≥3 cm	66 (60.0)	66.7		50.0	
<3 cm	44 (40.0)	75.0		63.6	
Symptoms of epilepsy			0.451		0.243
Yes	67 (60.9)	67.2		50.7	
No	43 (39.1)	74.4		62.8	
KPS score (points)			0.002		0.002
≥70	72 (65.5)	80.6		66.7	
<70	38 (34.5)	50.0		34.2	
Postoperative treatment			0.406		
Temozolomide+Radiotherapy	55 (50.0)	74.5		63.6	0.047
Radiotherapy	55 (50.0)	65.5		47.3	

KPS: Karnofsky performance status; OS: Overall survival; PFS: Progression free survival.

Table 4. Multivariable Cox Regression analysis of predictors for 3-year OS and 3-year PFS in low-grade glioma patients

	HR value	*95% CI*	*p*
3-year overall survival rate			
Age <40 years	0.798	0.519-0.950	0.017
Tumor complete excision	0.892	0.655-0.976	0.011
KPS score ≥70 points	1.075	0.804-1.414	0.109
3-year progression-free survival rate			
Age <40 years	0.742	0.581-0.943	0.022
Tumor complete excision	0.788	0.656-0.971	0.014
KPS score ≥70 points	1.179	0.829-1.589	0.207
Postoperative Temozolomide+Radiotherapy	0.673	0.512-0.894	0.024

HR: hazard ratio; CI: confidence interval; KPS: Karnofsky performance status; OS: Overall survival; PFS: Progression Free Survival.

67.3% (37/55)], and three-year OS rate [74.5 (41/55) *vs.* 65.5% (36/55)] and three-year PFS rate [63.6% (35/55) *vs.* 47.3% (26/55)] in combination group and control group. Kaplan-Meier method was used to draw survival curves (Figure 1), and log-rank test indicated that the difference in OS was not statistically significant between the two groups of patients (p=0.300), and PFS in combination group was significantly superior to that in control group (p=0.047).

Univariate and multivariate analysis of factors affecting three-year OS and PFS in patients with high-risk LGGs

The factors that may affect OS and PFS in patients with high-risk LGGs, including age, gender, histological type, degree of tumor resection, tumor diameter, presence or absence of epileptic symptoms, Karnofsky performance status (KPS) score before treatment, and radiotherapy combined with TMZ chemotherapy or not, were included in the univariate analysis. The results displayed that the three-year OS rate was significantly higher in patients aged <40 years old, with complete tumor resection and KPS score ≥70 points before treatment than that in those aged ≥40 years old, with partial tumor resection and KPS score <70 points before treatment (p=0.012, p<0.001, p=0.002), and the three-year PFS rate was significantly higher in patients aged <40 years old, with complete tumor resection and KPS score ≥70 points before treatment than that in those aged ≥40 years old, with partial tumor resection, KPS score <70 points before treatment and radiotherapy without TMZ chemotherapy after surgery (p=0.010, p<0.001, p=0.002, p=0.047) (Table 3).

The factors with statistically significant differences in univariate analysis were included in the multivariate analysis, including age, degree of tumor resection, KPS score before treatment, and radiotherapy combined with TMZ chemotherapy or not, and the results indicated that age <40 years old and complete tumor resection were independent factors affecting the three-year OS of patients with LGGs [HR: 0.798, 95% confidence interval (CI): 0.519-0.950, p=0.017, HR: 0.892, 95% CI: 0.655-0.976, p=0.011]. Besides, age <40 years old, complete tumor resection and TMZ chemotherapy combined with radiotherapy after surgery were independent factors affecting the three-year PFS of patients with LGGs (HR: 0.742, 95% CI: 0.581-0.943, p=0.022, HR: 0.788, 95% CI: 0.656-0.971, p=0.014, HR: 0.673, 95% CI: 0.512-0.894, p=0.024) (Table 4).

Discussion

Currently, the treatment options for LGGs are still controversial, and most scholars agree that minimizing the tumor cell load (resection range >90%) can effectively improve the survival rate of patients [9]. According to the National Comprehensive Cancer Network (NCCN) Guidelines (2015), radiotherapy and/or chemotherapy is recommended after surgery [10]. Multiple studies have confirmed that postoperative radiotherapy is able to prolong the PFS and OS of LGGs, and the results of European Organization for Research and Treatment of Cancer (EORTC) 22845 trial have demonstrated that early radiotherapy significantly improves PFS (median PFS: 5.3 years *vs.* 2.4 years, HR: 0.59, p<0.0001) [11,12]. The reason why some researchers insist on rejecting radiotherapy is the abnormal cognitive function caused by radiotherapy. Patients were followed up for 12 years in a study by Douw et al [13], and it was found that obvious cognitive dysfunction occurred in 53% of those undergoing early radiotherapy and 27% of those in non-radiotherapy group, and the clinical symptoms were progressively decline in attention, memory and execution, and gait and balance disorders.

LGGs grow slowly and are blocked by the blood-brain barrier, so they are considered as chemotherapy-insensitive tumors. However, multiple studies have confirmed that LGGs have a certain sensitivity to chemotherapy. The prospective randomized controlled trial RTOG9802 of the cooperative group of the American Society for Radiological Oncology has demonstrated that postoperative adjuvant radiotherapy can significantly prolong the PFS rather than OS of LGGs [14]. At the 2014 American Society of Clinical Oncology (ASCO) Annual Meeting, Buckner announced the further long-term follow-up results of the trial (the results of the trial were published in the New England Journal of Medicine in 2016), suggesting that compared with radiotherapy alone, radiotherapy combined with procarbazine, lomustine and vincristine (PCV) chemotherapy can significantly prolong the median survival (13.3 years *vs.* 7.8 years, p=0.03), median PFS (10.4 years *vs.* 4.0 years, p=0.002) and OS (p=0.003). It can be seen that radiotherapy-based chemotherapy may prolong survivals [15]. Therefore, radiotherapy combined with chemotherapy has been mostly used for patients with relapse after radiotherapy. Traditional PCV chemotherapy and current dominant TMZ are commonly utilized at present. In recent years, a number of retrospective studies and small-sample prospective clinical trials have displayed that TMZ has a certain objective response rate for both newly diagnosed and recurrent LGGs, with good tolerance [16,17]. Van den Bent and Field [18,19] reported that although chemotherapy efficacy of PCV and TMZ regimens for LGGs has not been compared, TMZ characterized by oral administration, predisposition to pass through the blood-brain barrier and less side effects is preferred over PCV.

The results of this study showed that the three-year OS rate of patients receiving radiotherapy combined with TMZ chemotherapy after surgery was 74.5%, which was 65.5% in patients undergoing radiotherapy alone, and the difference was not statistically significant (p=0.300), while the three-year PFS rate was significantly higher in combination group (63.6%) than that in control group (47.3%) (p=0.047), consistent with literature reports. The adverse reactions included leukopenia, anemia, thrombocytopenia, nausea and vomiting, diarrhea, fatigue, fever, alopecia and neurotoxicity. In this study, the results indicated that adverse reactions were not significantly increased in patients treated with radiotherapy combined with TMZ chemotherapy after surgery. Although adverse reactions are ameliorated after symptomatic treatment, without affecting the administration of TMZ, there is a potential risk of TMZ regimen in standardized treatment in the treatment of high-risk LGGs. Therefore, the response of patients during concurrent chemoradiotherapy should be paid more attention to, and it is necessary to regularly complete the blood routine tests to prevent serious complications. A previous study revealed a high incidence rate of Grade IV hematological toxicity in elderly patients during the concurrent chemoradiotherapy, and shortening the course or reducing the dosage of TMZ in the concurrent chemoradiotherapy still needs further research [20].

Bauman et al [21] reported that although the pathological grade is low, the tumor aggressiveness in older patients is greater than that in younger patients. Studies have confirmed that the average malignant transformation time of tumors is (44.2±17) months in patients aged <40 years old and (7.5±5.7) months in patients aged >40 years old, and the older the patient, the less satisfactory the survival time and quality of life. Leighton et al [22] reported that the survival is notably shortened in patients with epileptic seizures and neurological deficits. The results of this study displayed that age, degree of tumor resection, KPS score before treatment, and radiotherapy combined with TMZ chemotherapy or not were independent factors affecting the three-year OS of patients with LGGs.

This study was a single-center retrospective study with certain limitations, such as a small sample size, short follow-up period, and less comprehensive follow-up content. TMZ chemotherapy has been previously confirmed to be unsuitable for patients with IDH1/2 mutations accompanied by 1p/19q co-deletion. Therefore, the guiding significance of molecular typing for chemotherapy still needs further research.

Conclusions

TMZ combined with radiotherapy after surgery in patients with high-risk LGGs can prominently improve clinical efficacy, prolong PFS, and facilitate tolerance to adverse reactions, but not prolong the OS of patients. The OS is notably prolonged in patients aged <40 years old and receiving complete tumor resection.

Conflict of interests

The authors declare no conflict of interests.

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