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ORIGINAL ARTICLE

Therapeutic effect of thalidomide combined with temozolomide and three-dimensional conformal radiotherapy for patients with high-grade gliomas after operation

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Summary

Purpose: *To investigate the clinical therapeutic effect and safety of thalidomide combined with temozolomide (TMZ) and three-dimensional conformal radiotherapy for patients with high-grade gliomas after operation.*

Methods: *The clinical data of 108 patients with high-grade gliomas undergoing operation were retrospectively analyzed, of which 54 received thalidomide combined with TMZ and three-dimensional conformal radiotherapy (thalidomide group) and 54 received TMZ combined with three-dimensional conformal radiotherapy (control group). The clinical data of all patients were collected. Thereafter, the level of serum immune factors of the patients was recorded, and the overall survival (OS) rate and progression-free survival (PFS) rate of the patients were followed up and recorded.*

Results: *The therapeutic effect was evaluated in all the patients at 1 month after treatment. It was found that the overall response rate (ORR) in thalidomide group [68.5%] was markedly higher than that in control group [44.4%] (p=0.012). After treatment, the scores of 36-Item Short Form Health Survey (SF-36) evaluating the quality of life in thalidomide group were higher than that in control group (p=0.028). Following treatment, the levels of vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) were statistically significantly different between the two groups (p<0.001). Besides, the incidence rate of drowsiness of the patients in thalidomide group was notably lower than that in control group (p=0.029), but the difference in the incidence rate of other manifestations was not statistically significant (p>0.05). Additionally, the follow-up results manifested that the mean OS was 16.1±3.6 months, and 12.8±3.9 months, respectively, and the mean PFS was 9.0±3.2 months and 12.3±3.4 months, respectively, in thalidomide group and control group. Furthermore, log-rank test revealed that the patients in thalidomide group had longer OS (p=0.025) and PFS (p=0.040) than those in control group.*

Conclusions: *The application of thalidomide combined with TMZ and three-dimensional conformal radiotherapy for high-grade glioma patients after operation can prominently enhance the clinical therapeutic effect, improve patient quality of life, prolong survival, and produce tolerable adverse reactions.*

Key words: *thalidomide, temozolomide, three-dimensional conformal radiotherapy, glioma, high-grade, therapeutic effect*

Introduction

Gliomas are primary intracranial tumors in the central nervous system caused by environmental carcinogens, chronic inflammation, heredity, cell metabolic abnormalities, viruses and other factors, taking up about 40-50% of all intracranial tumors. They often occur in young and middle-aged people (30-40 years old) [1,2]. According to the World Health Organization (WHO) grading standards, malignant gliomas (grade III-IV gliomas) account for 36% of primary tumors in the nervous system.

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Surgical resection is the first choice for the treatment of malignant gliomas, but tumor cells show infiltrating growth, and the prognosis of patients receiving only surgery is poor [3,4].

In radiotherapy, cancer cells are killed by radioactive rays, and the effectiveness of killing is better in tumor cells. Postoperative radiotherapy has become routine treatment method for high-grade gliomas (WHO grade III-IV), and it should be supplemented after operation regardless of postoperative residues [5]. Three-dimensional conformal radiotherapy is a kind of high-precision radiotherapy, in which computed tomography (CT) images are mainly used to reconstruct the three-dimensional tumor structure, and irradiation fields are set in different directions to enable the target area to receive high-dose irradiation, thus minimizing the irradiation dose of tissues around the lesion, effectively killing tumor cells and protecting the normal tissue around the tumor to the largest extent at the same time [6]. Temozolomide (TMZ) has strong anti-tumor activity, and combined with radiotherapy offers a crucial treatment method for gliomas at present [7,8]. Thalidomide is able to suppress the proliferation of blood vessels in tumor tissues, which is a currently hot spot of anti-angiogenic research, but its therapeutic effect on gliomas has rarely been reported [9]. In this study, the postoperative clinical data of patients with high-grade gliomas after operation were retrospectively analyzed, and the clinical therapeutic effect and safety of thalidomide combined with TMZ and three-dimensional conformal radiotherapy for such patients were explored.

Methods

General data

A total of 108 patients with high-grade gliomas subjected to operation in our hospital from September 2014 to December 2016 were collected. Inclusion criteria: 1) patients who were firstly pathologically diagnosed with grade III-IV gliomas and had postoperative residual evaluable lesions shown in magnetic resonance imaging (MRI) examination; 2) those with Karnofski performance status (KPS) >60 points, expected survival time >3 months and no obvious contraindications of radiotherapy and chemotherapy; 3) those receiving no chemoradiotherapy before treatment; 4) those with no dysfunction in the heart, liver, kidney, lung and other important organs; and 5) those with no bleeding tendency and no history of severe hypertension and anticoagulant therapy. Exclusion criteria: 1) patients with severe dysfunction of vital organs; 2) those complicated with neurological and psychiatric diseases who cannot cooperate in the treatment; 3) those who were treated with antibiotics or traditional Chinese medicine in the past 3 months; 4) those complicated with hematological diseases, endocrine system diseases, autoimmune diseases, or abnormal bone marrow reserve function; or 5) those complicated with other primary tumors.

Table 1. Baseline characteristics of the studied patients

Characteristics	*Thalidomide group (n=54)*	*Control group (n=54)*	*p value*
Age (years)	54.9±10.1	56.4±9.8	0.435
Gender (Male/ Female)	29/25	33/21	0.560
Pathological type, n (%)			0.685
Neuroastrocytoma	36 (66.7)	32 (59.3)	
Oligodendroglioma	10 (18.5)	11 (20.4)	
Mixed gliomas	8 (14.8)	11 (20.4)	
Tumor location, n (%)			0.391
Frontal lobe	14 (25.9)	18 (33.3)	
Parietal Lobe	19 (35.2)	11 (20.4)	
Temporal lobe	13 (24.1)	16 (29.6)	
Others	8 (14.8)	9 (16.7)	
Pathological grading, n (%)			0.304
III	39 (72.2)	34 (63.0)	
IV	15 (27.8)	20 (37.0)	
Tumor diameter (cm)	4.22±1.10	4.35±0.94	0.511
KPS score (points)	67.78±4.76	69.11±5.49	0.182
Systemic diseases, n (%)			
Hypertension	19 (35.2)	14 (25.9)	0.296
Diabetes mellitus	10 (18.5)	8 (14.8)	0.606

KPS: Karnofsky performance status

The patients were divided into thalidomide combined with TMZ and three-dimensional conformal radiotherapy group (thalidomide group, n=54) and TMZ combined with three-dimensional conformal radiotherapy group (control group, n=54) according to the different treatment methods. There were 62 males and 46 females with mean age 55.8±9.9 years. The baseline data of the two groups of patients before treatment showed no statistically significant differences (p>0.05) (Table 1). This study was approved by the Ethics Committee of Qingdao Municipal Hospital. All patients enrolled in the present study complied with the Declaration of Helsinki, were informed of the experimental protocol and signed the informed consent.

Treatment regimen

Three-dimensional conformal radiotherapy: Precise Plan Release 2.16 (Elekta Co., Ltd., Sweden) treatment plan system was applied. The patients were in supine position, with heads fixed with thermoplastic masks, and underwent CT scan from the calvarium to the upper neck. Then, CT localization scan images were transmitted to the treatment plan system workstation, and the radiotherapy target area was delineated by combining preoperative and postoperative MRI. The postoperative residual tumor represented the gross tumor volume (GTV), and 2-3 cm at the edematous region edge or the entire tumor surgical cutting edge was defined as the clinical target volume (CTV). After the total CTV irradiation dose reached 54 Gy/27 f, the irradiation field was reduced to the GTV expanded by 0.5-1 cm, and then irradiation was continued until the total GTV irradiation dose reached 60 Gy/30 f. 3-5 irradiation fields were designed.

Control group: The patients took orally TMZ at a dose of 75 mg/(m^2•d) during radiotherapy, after which they received 6 cycles of conventional TMZ treatment [150 mg/(m^2•d)×5 d, q28d]. Thalidomide group: In addition to TMZ concurrent chemoradiotherapy or TMZ adjuvant chemotherapy, patients took orally thalidomide (200 mg per night, Changzhou Pharmaceutical Factory Co., Ltd., Changzhou, China) simultaneously. Mannitol and dexamethasone were given to prevent and treat cerebral edema during chemoradiotherapy, and symptomatic treatments such as anti-nausea treatment, gastric protection treatment, liver protection treatment were routinely performed during chemotherapy.

Observational indexes

Both groups of patients were reexamined via MRI 1 month after treatment, and the therapeutic effect was evaluated according to the evaluation criteria of solid tumor therapeutic effect as follows: complete response (CR): tumor lesions completely disappear for more than 4 weeks, and no new lesions appear. Partial response (PR): The product of the two maximum vertical diameters of the tumor is reduced by over 50% more than 4 weeks compared with that before treatment, and no new lesions appear. Stable disease (SD): The product of the two maximum vertical diameters of the tumor is increased by less than 50% or increased by less than 25% compared with that before treatment, without appearance of new lesions. Progressive disease (PD): The product of the two maximum vertical diameters of the tumor is increased by more than 25% compared with that before treatment or new lesion(s) appear [10]. Thereafter, the overall response rate (ORR) and disease control rate (DCR) were calculated according to the following formulas: ORR = (CR +PR)/total number of cases ×100%, DCR = (CR+PR+PD)/total number of cases × 100%.

During treatment, the occurrence time and grade of adverse reactions were recorded in detail, and acute radiation reactions were evaluated according to the standards stipulated by the United States Radiotherapy Oncology Group (RTOG). In addition, the safety of treatment was assessed by NCI CTCAE v4.0 for TMZ-related adverse reactions. Subsequently, the levels of serum inflammatory factors such as hepatocyte growth factor (HGF), tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-17, vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) before and after treatment were detected using ELISA kits. Thereafter, 36-Item Short Form Health Survey (SF-36) was utilized to assess the quality of life of the patients at 3 months after treatment. This scale scores 8 aspects, and the higher the score is, the better the quality of life will be.

Overall survival (OS) and progression-free survival (PFS) were used as the survival observational indexes. OS was defined as the time interval from the start of treatment to the patient's death or last follow-up, and PFS was defined as the time from the start of treatment to the time when the patient suffers from disease progression or dies with no progression.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was adopted for statistical analyses. Measurement data were expressed by mean±standard deviation, and the comparison between two groups was conducted using the t-test. The clinical data were compared by x^2 test or Fisher exact probability test. Besides, the short-term therapeutic effect and adverse reactions were compared as one-way ordered ranked data via Mann-Whitney U test. Furthermore, Kaplan-Meier curve was applied for survival analysis, and log-rank test was performed to assess statistical differences between 2 groups. P<0.05 showed statistically significant difference.

Results

Comparison of short-term therapeutic effects

At 1 month after treatment, the therapeutic effect was evaluated for all patients. In the thalidomide group, there were 11 cases (20.4%) of CR, 26 (48.1%) of PR, 13 (24.1%) of SD, and 4 (7.4%) of PD, with ORR 68.5% (37/54) and DCR 92.6% (50/54). In the control group, there were 6 cases (11.1%) of CR, 18 (33.3%) of PR, 21 (38.9%) of SD

and 9 (16.7%) of PD, with ORR 44.4% (24/54) and DCR 83.3% (45/54). The ORR in the thalidomide group was remarkably higher than in the control group, showing a statistically significant difference (p=0.012), but no statistically significant difference was observed in the DCR between the two groups (p=0.139) (Table 2).

Comparison of the score of SF-36 evaluating the quality of life between the two groups of patients

After treatment, the scores of SF-36 evaluating the quality of life in the thalidomide group were higher than in the control group, in which the physical function score showed a statistical-

Table 2. Clinical effective rates of the two studied groups

	Thalidomide group (n=54) *n (%)*	*Control group (n=54)* *n (%)*	*p value*
CR	11 (20.4)	6 (11.1)	
PR	26 (48.1)	18 (33.3)	
SD	13 (24.1)	21 (38.9)	
PD	4 (7.4)	9 (16.7)	
ORR	37 (68.5)	24 (44.4)	0.012
DCR	50 (92.6)	45 (83.3)	0.139

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ORR: overall response rate, DCR: disease control rate

Table 3. Comparison of posttreatment quality of life SF-36 scale scores of the studied patients in two different groups

	Thalidomide group (n=54)	*Control group (n=54)*	*p value*
Physical pain	73.28±9.41	70.09±9.09	0.076
Physical function	79.34±5.44	77.11±4.95	0.028
Health condition	76.90±6.86	75.90±6.21	0.429
Vitality	81.23±7.73	80.38±6.81	0.546
Physical role	77.28±6.54	76.81±5.98	0.698
Emotional role	70.13±7.74	68.96±8.49	0.456
Social function	80.91±7.65	79.14±6.90	0.210
Psychological function	79.89±10.25	78.21±10.66	0.406

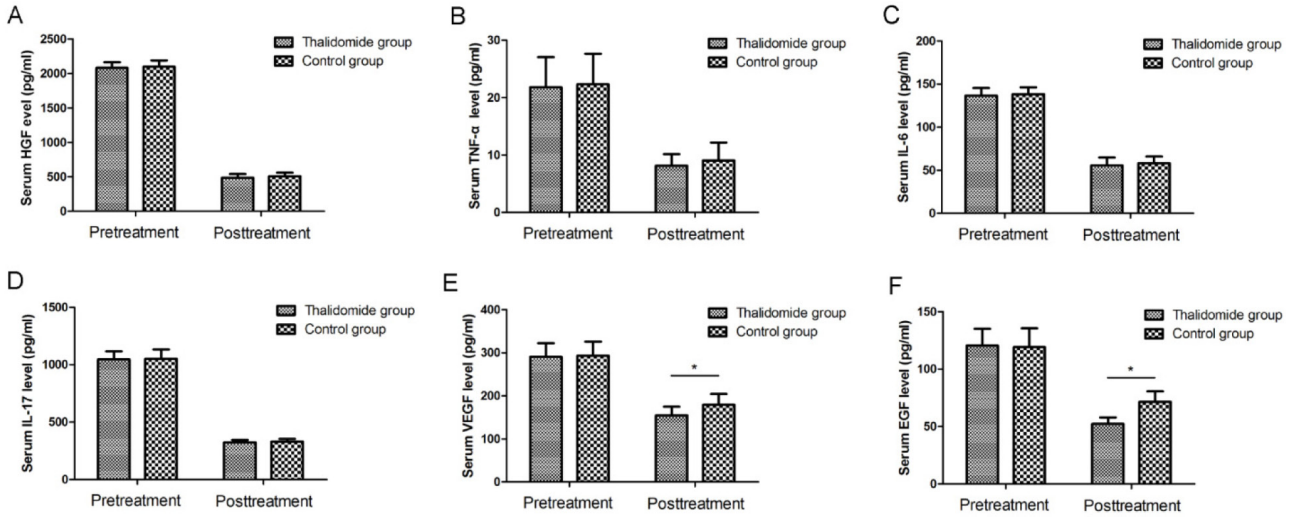

Figure 1. Comparison of pretreatment and posttreatment serum markers of the studied patients. The difference between pretreatment serum HGF **(A)**, TNF-α **(B)**, IL-6 **(C)**, IL-17 **(D)**, VEGF **(E)** and EGF **(F)** levels of patients in the Thalidomide and the Control group had no statistical significance (p>0.05). Serum HGF **(A)**, TNF-α **(B)**, IL-6 **(C)**, IL-17 **(D)**, VEGF **(E)** and EGF **(F)** levels of patients were significantly decreased after treatment (p<0.05). Posttreatment serum VEGF **(E)** and EGF **(F)** levels of patients in the Thalidomide group were significantly lower than those of the Control group (*p<0.001).

ly significant difference between the two groups (p=0.028), whereas the scores of the other items were not statistically significantly different between the two groups (p>0.05) (Table 3).

Comparisons of serological indexes between the two groups of patients

There were no statistically significant differences in the levels of HGF, TNF-α, IL-6, IL-17, VEGF and EGF between the two groups of patients prior to treatment (p>0.05). Following treatment, the mean levels of HGF, TNF-α, IL-6, IL-17, VEGF and EGF were decreased to 488.23±52.79 pg/mL, 8.14±2.02 pg/mL, 55.65±8.98 pg/mL, 323.84±21.72 pg/mL, 154.54±20.23 pg/mL and 52.35±5.65 pg/mL, respectively in the thalidomide group and to 469.69±51.91 pg/mL, 9.05±3.13 pg/mL, 58.01±7.87 pg/mL, 330.80±23.63 pg/mL, 179.12±25.03 pg/mL and 71.57±9.04 pg/mL, respectively in the control group. After treatment, the mean levels of HGF, TNF-α, IL-6, IL-17, VEGF and EGF in the thalidomide group were lower than those in the control group. Besides, the differences in the levels of HGF, TNF-α, IL-6 and IL-17 (p=0.069, p=0.076, p=0.149, p=0.114) were not statistically significant, but opposite results were detected in the levels of VEGF and EGF (p<0.001) (Figure 1).

Comparisons of adverse reactions

Adverse reactions were mainly manifested as myelosuppression, nausea and vomiting, constipation, liver function injury, drowsiness and neurotoxicity (grade I-II in most cases), which returned to normal after symptomatic treatment, with no significant differences in most cases (p>0.05). The incidence rate of grade III-IV adverse reactions was relatively low. Among them, leukopenia, nausea and vomiting and liver function injury occurred in 3, 2 and 3 cases, respectively, in the thalidomide group, and in 3, 4 and 4 cases, respectively, in the control group. As for common adverse reactions of the thalidomide, the incidence rate of drowsiness in thalidomide group [n=10 (18.5%)] was markedly lower than that in the control group [n=2 (3.7%)] (p=0.029), while the incidence rate of constipation [n=17 (31.5%)] in the thalidomide group was not statistically significantly different from that in the control group [n=14 (25.9%)] (p=0.523) (Table 4).

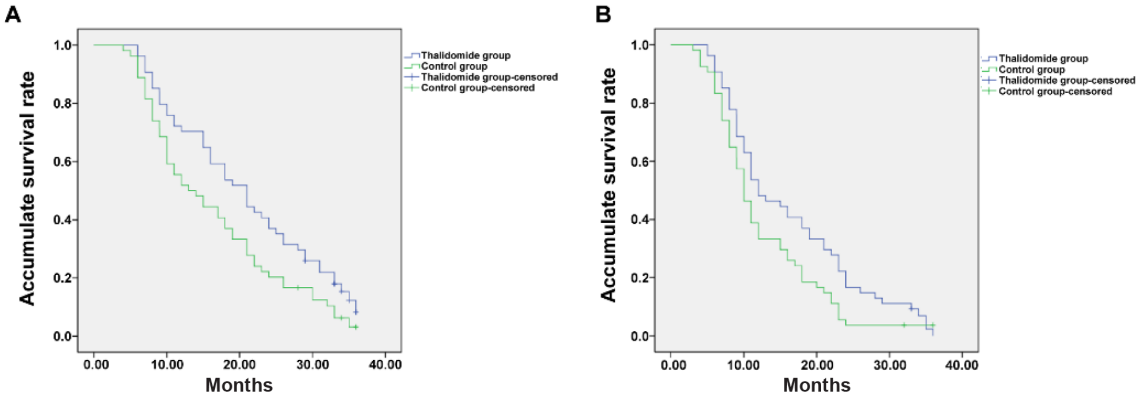

Figure 2. Kaplan-Meier survival curves of high-grade gliomas patients. The overall survival rate **(A)** and progression-free survival rate **(B)** of patients in the Thalidomide group were significantly higher than those of the Control group (p=0.025, p=0.040).

Table 4. Comparison of adverse reactions of patients in the two studied groups

Adverse reactions	*Thalidomide group (n=54)* *n (%)*	*Control group (n=54)* *n (%)*	*p value*
Leukopenia	20 (37.0)	16 (29.6)	0.414
Anemia	15 (27.8)	17 (31.5)	0.673
Thrombocytopenia	18 (33.3)	18 (33.3)	1.000
Nausea and vomiting	22 (40.7)	28 (51.9)	0.247
Liver function damage	13 (24.1)	11 (20.4)	0.634
Constipation	17 (31.5)	14 (25.9)	0.523
Drowsiness	10 (18.5)	2 (3.7)	0.029
Neurotoxicity	17 (31.5)	10 (18.5)	0.120

Follow-up results of patient survival

All the 108 patients were followed up for 6-36 months until December 2019. In the thalidomide and the control group, the mean OS was 16.1±3.6 months and 12.8±3.9 months, and the mean PFS was 9.0±3.2 months and 12.3±3.4 months, respectively. Besides, in the thalidomide and control group, the one-year OS was 70.4% (38/54) and 51.9% (28/54), two-year OS was 37.0% (20/54) and 20.4% (11/54), three-year OS was 13.0% (7/54) and 5.6% (3/54), one-year PFS was 48.1% (26/54) and 33.3% (18/54), and two-year PFS was 11.1% (6/54) and 3.7% (2/54), respectively. Kaplan-Meier method was applied to plot the survival curves of patients (Figure 2). Moreover, the log-rank test manifested that the thalidomide group had longer OS (p=0.025) and PFS (p=0.040) than the control group, displaying statistically significant differences.

Discussion

Gliomas originate from neurogliocytes and are the most common primary intracranial tumors, whose main pathological type is astrocytomas [11]. In this study, there were 68 cases (63.0%) of astrocytomas, in consistency with the relevant literature. Gliomas are pathologically classified into grade I-IV, of which grade I-II represents low grade and grade III-IV means high grade, and high-grade gliomas account for 77.5% of all gliomas. Additionally, compared with low-grade gliomas, high-grade gliomas are characterized by high malignant behavior, faster proliferation of cancer cells and higher postoperative recurrence rate and metastasis rate [12]. At present, surgical resection is the preferred clinical treatment method for high-grade gliomas. However, owing to the disappearance of the boundary of cancer foci caused by the infiltration of cancer cells into surrounding tissues and the particularity and complexity of nervous system anatomy, the operation is extremely difficult, the cancer foci are hard to be completely removed, and residual cancer foci may lead to postoperative disease relapse [13]. Hence, postoperative adjuvant radiotherapy can further remove residual lesions, decrease tumor recurrence and prolong survival [14].

In the systematic evaluation of the therapeutic effect of chemotherapeutic drugs against gliomas, Tanabe et al [15] found that TMZ is obviously superior to traditional chemotherapeutic drugs in improving the therapeutic effect against gliomas, prolonging the survival period and reducing adverse reactions, and proposed that TMZ is the first-choice drug for glioma therapy. A study of Caragher et al [16] has pointed out that three-dimensional conformal radiotherapy combined with TMZ is safe and effective in the postoperative treatment of gliomas, and its clinical therapeutic effect is significantly better than that of radiotherapy. Adeberg et al [17] also demonstrated the above conclusions in the postoperative meta-analysis of patients with malignant gliomas treated by three-dimensional conformal radiotherapy combined with TMZ.

Gliomas are tumors rich in blood vessels. Neovascularization caused by endothelial cell proliferation has close associations with the biological invasiveness and malignancy of gliomas [18]. Increasingly more data have denoted that the combination of anti-angiogenesis and chemoradiotherapy may improve the therapeutic effect, but generally patients cannot afford it for its high price. According to a study, thalidomide combined with chemotherapy has achieved an obvious therapeutic effect in the treatment of multiple myelomas, and has good performance in the adjuvant treatment of liver cancer, neurogliocytoma, prostate cancer, lung cancer and malignant melanoma [19]. It may control tumor growth by inhibiting neovascularization caused by VEGFs and fibroblast growth factors, reducing angioedema, suppressing cyclooxygenase-2, and reducing micro-vessel density in the tumor [20]. An *in vivo* experiment has revealed that thalidomide is also able to increase the anti-tumor activity of chemotherapeutic drugs, such as temozolomide, irinotecan and paclitaxel, thereby jointly repressing tumors, reduce the incidence of adverse reactions to chemotherapy and improve the quality of life of patients [21].

In this study it was found that the ORR was 68.5% (37/54) and the DCR was 92.6% (50/54) in the thalidomide group. The ORR in the thalidomide group was evidently higher than in the control group (p=0.012), but there was no statistically significant difference in DCR between the two groups (p=0.139). In the thalidomide and control group, the mean OS was 16.1±3.6 months and 12.8±3.9 months, and the mean PFS was 9.0±3.2 months and 12.3±3.4 months, respectively. Follow-up results demonstrated that the OS (p=0.025) and PFS (p=0.040) in the thalidomide group were markedly longer than in the control group. With regard to adverse reactions, the incidence rates of nausea and vomiting in the thalidomide group were decreased, and the high incidence rates of drowsiness and constipation were also reduced after symptomatic treatment. Hence, the adverse reactions of thalidomide were mild and tolerable for the patients. Tumor patients often have psychological problems such as depression, anxiety and insomnia. Thalidomide has sedative, hypnotic and antiemetic effects, so combined with chemo-

radiotherapy improves the sleep, relieves the anxiety and improves the quality of life of patients. However, its mechanism remains largely unclear. A study has illustrated that thalidomide may exert immunomodulatory and anti-inflammatory effects by down-regulating TNF-α and IL-6, induce NF-κB inactivation, and reduce the levels of TNF-α and IL-6 *in vivo* [22].

This study is a single-center retrospective study with certain limitations. The sample size was not large enough, the follow-up time was short, and the follow-up content was not comprehensive enough. Therefore, a more rigorous, scientific and prospective multi-center randomized controlled study with a large sample size needs to be designed to confirm the conclusions of this study in the future.

Conclusions

The application of thalidomide combined with TMZ and three-dimensional conformal radiotherapy for high-grade glioma patients after operation can significantly increase the clinical therapeutic effect, improve patient quality of life, prolong survival, and produce tolerable adverse reactions.

Conflict of interests

The authors declare no conflict of interests.

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