

Original Article

Efficacy of timorazolamide combined with three-dimensional conformal radiotherapy on residual disease after surgery of glioblastoma

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Received January 12, 2018; Accepted February 21, 2018; Epub March 15, 2018; Published March 30, 2018

Abstract: Objective: To evaluate the efficacy and safety of combination timorazolamide (TMZ) with three-dimensional conformal radiotherapy on residual disease after treatment of glioblastoma. Methods: Fifty-eight patients with residual disease after treatment of glioblastoma were enrolled in this study from October 2013 to September 2015. The patients were randomly divided into TMZ plus radiotherapy group and control group (29 cases in each group) using the random number table. Three-dimensional conformal radiotherapy was performed in both groups. Based on the body surface area, optimal dosage of TMZ was used in TMZ plus radiotherapy group simultaneously. The short-term efficacy, long-time survival rate and adverse reactions were recorded. Results: The overall response rate in TMZ plus radiotherapy group (72.41%) was significantly higher than that in control group (37.93%, $P < 0.05$). The median survival time in TMZ plus radiotherapy group and control group were 28.3 and 11.2 months, respectively. The two-year survival rates in TMZ plus radiotherapy group and control group were 51.72% and 13.79%, respectively. There was significant difference between two groups through Log Rank test ($X^2 = 4.664$, $P = 0.028$). The treatments in two groups were tolerated in patients. There were less adverse reactions in both groups, and normally mild and moderate reactions (grade I-II). Conclusion: The postoperative residual disease after treatment of glioblastoma was significantly improved by TMZ combined with three-dimensional conformal radiotherapy. This treatment could prolong the survival time of patients with good safety. Moreover, this treatment increased the overall response rate and survival rate, and could be adapted in other studies in the future.

Keywords: Glioblastoma, timorazolamide, three-dimensional conformal radiotherapy, short-term efficacy, long-term survival rate

Introduction

With the highest incidence and the most difficult in treatment, glioma accounts for 13%-26% in intracranial tumors and 21.2%-51.6% in glioblastoma [1]. Based on the high degree of malignancy and invasive growth features, the prognosis of glioma is still poor even after excision. There is great difficulty in complete surgical resection of the glioma, which may cause residual remaining. As the primary therapy for the patients with residual disease, who have lost chance for surgical treatment, combination radiotherapy with chemotherapy were employed and resulted in certain efficacy [2]. As a second-generation alkylating agent containing 4-oxoimidazo, TMZ was employed in treatment of glioma in the end of 20th century. The

absorption of TMZ was fast and complete through oral administration. As a lipophilic molecule, the bioavailability of TMZ was nearly 100%, and distributed widely in whole body without liver metabolism. The TMZ also could pass the blood-brain barrier, and gather in the tumor tissue of brain in priority [3, 4]. In recent years, temozolomide (TMZ) has been shown to increase the sensitivity of glioma cells to radiation [5]. Until now, there was no study on combination of TMZ and chemotherapy for the treatment of residual disease after the operation of glioblastoma.

In order to explore the efficacy and safety on residual disease after treatment of glioblastoma, and provide evidence for the further applications, combination of TMZ with three-dimen-

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Table 1. Participant information

Item	Control group	TMZ plus group	χ^2	P
Age	45.87±3.69	44.35±3.14	0.025	0.993
Gender			0.013	1.000
Male	16	17		
Female	13	12		
Tumor site			0.055	0.968
Frontal lobe	11	10		
Temporal lobe	9	10		
Parietal lobe	5	6		
Occipital lobe	3	2		
Other sites	1	1		
Average volume of tumor (cm ³)	8.11±0.76	8.02±0.71	0.611	0.763

Note: TMZ, timorazolamide.

sional conformal radiotherapy was employed in this study.

Materials and methods

Patient information

This study has got approval from local ethical committee. Fifty-eight patients with residual disease after treatment of glioblastoma at China-Japan Union Hospital of Jilin University were recruited in this study from October 2013 to September 2015.

The inclusion criteria consisted of (A) meeting the pathology diagnostic criteria for grade III and IV of primary glioblastoma, (B) ranging from 26 to 78 years-old, (C) definite diagnosis of residual disease through magnetic resonance imaging (MRI) after surgery, (D) survival time longer than three months after evaluation, (E) stable vital signs, good communication ability, understanding doctor's advice, (F) Karnofsky functional status score above 70, (G) the patients and family members understanding and signing the informed consent.

The exclusion criteria consisted of (A) severe functional insufficiency of heart, liver, kidney or other important organs, (B) performing chemotherapy or radiotherapy in past treatment, (C) already participating in another clinical trial.

The patients were randomly divided into TMZ plus radiotherapy group and control group (29 cases in each group) using the random number table. There were 16 males and 13 females in control group. The age of patients was ranged

from 28 to 76 years old, and the average age was 45.87±3.69 years old. The residual tumor volumes were ranged from 6.4 to 11.2 cm³, and the average volume was 8.11±0.76 cm³. For the TMZ plus radiotherapy group, there were 17 males and 12 females. The age of patients was ranged from 26 to 78 years old, and the average age was 44.35±3.14 years old. The residual tumor volumes were

ranged from 6.1 to 10.9 cm³, and the average volume was 8.02±0.71 cm³. There was no significant difference in gender, tumor sites, and average tumor volume between two groups ($P>0.05$, **Table 1**).

Treatment program

Three-dimensional conformal radiotherapy was employed in both groups. The instrument for radiotherapy was Precise linear accelerator from Elekta (Sweden). The fractionated dose of GTV-P was 2.0-2.2 Gy at each time (once a day, five times per week). The overall dosage for tumor was around 60 Gy in 30 times.

In TMZ plus radiotherapy group, the TMZ (Tianshili, China) was employed based on the body surface area (75 mg/m², po), one time per day continuously in six weeks.

Outcome measures

For the evaluation of short-term efficacy, computed tomography (CT) or MRI for chest, or electronic gastroscope were performed two months after treatment. According to the solid tumor treatment guidance from World Health Organization for short-term efficacy, different clinical results were classified as follows: 1) The complete response (CR): no tumor lesion was observed at least 4 weeks; 2) Partial response (PR): above 50% of tumor lesion was reduced, and no new tumor lesion was observed at least 4 weeks; 3) Stable disease (SD): above 25%, and less than 50% of tumor lesion was reduced, no new tumor lesion was observed at least 4 weeks; 4) Progression disease (PD): above 25% tumor lesion was increased, or new tumor

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Table 2. Comparison of clinical efficacy between two groups

Item	Cases (n)	CR (n)	PR (n)	SD (n)	PD (n)	ORR (n, %)
Control group	29	4	7	12	6	11 (37.93)
TMZ plus group	29	7	14	6	2	21 (72.41)
χ^2						7.347
P						0.001

Note: CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, overall response rate; TMZ, timorazolamide.

lesion was observed; overall response rate (ORR)=(CR + PR)/amount of cases *100% [6].

For the adverse reaction, different grades were classified according to the National Institutes of Health (NCI-CTCAE, 3.0 version, NIH, US) as follows [7]. Grade I: mild adverse reaction, no influence for life; grade II: moderate adverse reaction, influence for life, but still tolerated; grade III: severe adverse reaction, cannot tolerated and need medication; grade IV: life-threatening or disabling adverse reaction. For the long-term efficacy evaluation, two-year survival rate was measured by continuous following-up until October 2017.

Statistical analysis

SPSS 21.0 software was employed for data analysis. The data was tested to accord with normal distribution, and expressed by mean \pm standard deviation (mean \pm SD). The comparison between groups was conducted with independent sample t test. The counting data was tested by χ^2 . The two-year survival rate was analyzed by Kaplan-Meier method. The significant difference of survival rate was evaluated by Log-Rank test. $P < 0.05$ indicated that the difference was statistical significant.

Results

Efficacy observation

Two months after chemotherapy and radiotherapy, the enhanced encephalic MRI were employed and analyzed for both groups. There was significantly higher ORR ($P < 0.05$) in TMZ plus radiotherapy group (72.41%) than that in control group (37.93%, **Table 2**).

Survival rate and survival time

The median survival times were 28.3 months in TMZ plus radiotherapy group, whereas 11.2 months in control group. The two-year survival

rates were 51.72% and 13.79% in TMZ plus radiotherapy group and control group, respectively. There was significant difference between two groups through Log Rank test ($\chi^2=4.664$, $P=0.028$, **Figure 1**).

Adverse reaction

There were adverse reactions with grade I/II in patients of both groups during the treatment. The incidence rates of adverse reaction were 41.38% and 34.48% in TMZ plus radiotherapy group and control group, respectively. No significant difference was observed for the incidence rates of adverse reaction between two groups in this study ($P > 0.05$, **Table 3**). The adverse reactions were relieved by symptomatic treatment. In this study, no patient was dropped out by severe adverse reaction.

Discussion

There is no obvious boundary between glioblastoma and normal peripheral brain tissue. Moreover, it was still difficult to remove tumor cells completely, and the rate of residual lesion was high [8]. As the one of important methods for tumor treatment, radiotherapy was employed in appropriate dosage. The tumor cells could be removed completely if the high enough dosage of radiotherapy was performed in theory. However, the dosage of radiotherapy was limited strictly in clinical study based on the maximum tolerance of normal tissues [9]. As an essential breakthrough in radiotherapy, three-dimensional conformal radiotherapy was performed to improve the irradiation from plane to three-dimensional. This treatment achieved the high dosage in tumor and low dosage in normal peripheral tissue. Although the continuous updates emerging on radiotherapy technology and accelerator, there was no obvious increasing in survival rate by the treatment using radiotherapy only. The three-dimensional conformal radiotherapy for medication of high-grade glioma was reported by Moinfar et al. [10]. The planning target volume (PTV) was 40 Gy/20 times, while the gross target volume (GTV) was 60 Gy/20 times. Moreover, the outside of PTV was 1.5 cm larger than GTV. The results showed 84% (21/25) PD, and 9.3 months of median survival time in all participants. In this study, the median survival time in control group was 11.2 months, the 1-year

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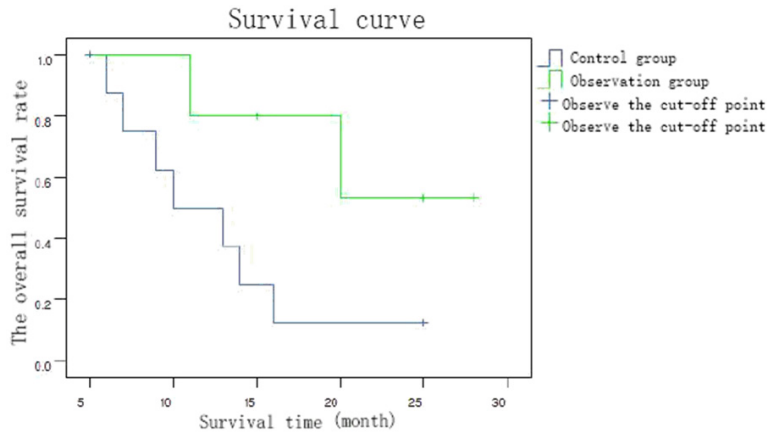


Figure 1. Comparison of survival rates between the two groups. The survival rates of 29 patients in each group were analyzed through Log Rank test. For the two-year survival rate, there was significant difference between two groups ($\chi^2=4.664$, $P=0.028$). Observation group indicated the TMZ plus radiotherapy group. + indicates the observation of cut-off value.

Table 3. Comparison of adverse reaction between two groups

Item	Control group	TMZ plus group
Cases	29	29
Nausea/vomiting		
I-II	4	4
III-IV	0	0
Leukopenia		
I-II	2	3
III-IV	0	0
Thrombocytopenia		
I-II	3	1
III-IV	0	0
Liver and kidney injury		
I-II	2	2
III-IV	0	0

Note: TMZ, timorazolamide.

and 2-year survival rate were 55.17% and 13.79%, respectively, whose results were similar with the previous study [10].

The ionizing radiation was widely used in tumor cells clearance. It could react with the molecules in tumor cells, then produce free radical to damage DNA and destroy tumor cells [11, 12]. However, the radiotherapy would induce three types damages for patients, including the potentially fatal damage, the sub-fatal damage, and the fatal damage. The potentially fatal damage and sub-fatal damage could be repaired in certain conditions. At the same

time, tumor cells were reproduced quickly. It induced the insufficient blood supply and emerging of hypoxic cells. Whereas the hypoxic cells were not sensitive to radiation, then the efficacy of medication was decreased [13, 14]. However, the chemotherapy could compensate for the deficiency of radiotherapy.

There was no direct antineoplastic activity in TMZ itself. It belonged to the precursor drug without hepatic metabolism. Under the condition of physiological alkaline pH, it was converted to active compound 5-(3-methyltriazen-1-yl)

imidazole-4-carboxamide (MTIC) through non-enzymatic pathway. Based on the cytotoxicity by methylation of O6 and N7 positions of guanine, the DNA double chain was ruptured which resulting in interference of the DNA synthesis. Finally, the cell was died through apoptosis [15, 16].

In addition, the TMZ induced the stagnate of tumor cells in G2/M phase, then improved the apoptosis [17, 18]. In this study, the median survival time in TMZ plus radiotherapy group (28.3 months) was significantly higher than that in control group (11.2 months). The two-year survival rate in TMZ plus radiotherapy group was also significantly higher than that in control group. Those results were conformed to the previous study [19]. The results indicated that combination TMZ with radiotherapy could significantly prolong the median survival time, and increase and two-year survival rate.

The main adverse reactions of TMZ were bone marrow suppression and gastrointestinal reaction. But the toxicity was relatively low without accumulation. The bone marrow suppression also could be reversed, which allowing continuous treatment [20]. In this study, the treatments in both groups were tolerated by patients. There were less adverse reactions in both groups, and the grades of adverse reaction were mainly I/II (mild/moderate). The adverse reaction was relieved after symptomatic treatment. Those results indicated that TMZ could not aggravate the toxicity and adverse

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reaction of radiotherapy, and the safety of TMZ was relatively high. The less patients and short length of follow-up limited the results in this research. More cases will be studied to confirm those results in the further research.

In conclusion, combination TMZ with three-dimensional conformal radiotherapy could significantly improve the residual disease after treatment of glioblastoma. This medication could prolong the survival time with high safety, also increase ORR and survival rate. This treatment could be adapted in other studies in the future.

Disclosure of conflict of interest

None.

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