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Clinical safety study of temozolomide combined with radiotherapy after glioma resection.

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Abstract

The aims of this study were to investigate the efficacy and safety of radiotherapy combined with temozolomide (TMZ) after glioma resection. A total of 86 patients with glioma were randomly divided into two groups (n=43). Group A was treated with 3D conformal radiotherapy combined with TMZ (R-TMZ), and Group B was only treated with 3D conformal radiotherapy. The clinical efficacy, postoperative 1, 2 and 3-year survival rate, Karnofsky score, and side effects were compared and analysed. The objective response rate (ORR) and disease control rate (DCR) values in group A were 76.7% and 90.7% respectively, significantly higher than group B (55.8% and 74.4%, P<0.05). The Karnofsky scores of both groups were improved after treatment than before (P<0.05). The median survival period and postoperative 1, 2 and 3-year survival rates in group A were significantly higher than group B (P<0.05). There was no significant difference in the side effects between the two groups (P>0.05). R-TMZ is a safe and effective adjuvant therapy after glioma resection, which can improve short-term and long-term survival rate while not increase side effects.

Keywords: Glioma, Radiotherapy, Chemotherapy, Temozolomide.

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Introduction

High-grade malignant glioma is a primary malignant tumor in the brain tissue, and can be divided into undifferentiated glioma (undifferentiated astrocytoma, anaplastic oligodendroglioma, and undifferentiated oligodendroglioma tumor), and glioblastoma (GBM) according to patient's pathological features [1].

Glioma is a common primary intracranial malignancy, accounting for about 40% of all intracranial tumors. Because glioma can invade into surrounding brain tissues, pure surgery is difficult to completely remove it, so glioma is easy to relapse after surgery [1]. Presently, most scholars believe that radiotherapy after glioma resection can effectively improve patient's survival rate, but the effect is still not ideal [2]. According to statistics, the median survival time of the patients with post-resection radiotherapy is 9 to 12 months, the 2-year survival rate is only 8% to 12%, and the 5-year survival rate is less than 5% [3]. At the same time, because the blood-brain barrier and glioma cells can tolerate most chemotherapeutic drugs, it's still controversial whether postoperative radiotherapy combined with chemotherapy can further improve the efficacy [4,5]. In this study, the patients with glioma were treated with radiotherapy combined with temozolomide (R-TMZ) postoperatively, aiming to explore the efficacy and safety of this protocol for Chinese patients. Temozolomide combined with radiotherapy can extend the survival of glioblastoma from 12-14 months than radiotherapy alone [6]. O6-methylguanine-DNA methyltransferase (MGMT) is a DNA repair enzyme that can reduce the efficacy of temozolomide. The application of temozolomide combined with radiotherapy in the glioblastoma patients lacking the expression of methylated MGMT can improve their median survival period. However, the median survival in 55% of the patients applied temozolomide combined with radiotherapy was reported to be 12.7 months, and that in the patients with radiotherapy alone was only 11.8 months [3]. Temozolomide is a sensitizer for radiation therapy. As for human U251 glioblastoma cell lines, the radiation dose can be increased from 1.32 Gy/once 2 Gy/once, and increasing the radiation dose can also improve the survival [7].

Materials and methods

General information

A total of 86 glioma patients treated in the department of neurosurgery in our hospital from January 2009 to December 2012 were collected, including 51 males and 35 females, aging 24 to 67 years old (with the mean as 39.2 ± 4.6 years old).

Inclusion criteria: (1) confirmed pathologically and already performed craniotomy for the resection; (2) 18 to 80 years old, Karnofsky score >50 points, expected survival time ≥3 months.

Exclusion criteria: With chemotherapy or radiotherapy contraindications, or severe heart, liver, and kidney dysfunction.

Tumor sites: 34 cases in the frontal lobe, 22 cases in the temporal lobe, 19 cases in the occipital lobe, and 11 cases in the parietal lobe.

Pathological grading: 54 cases in WHO grade II, 21 cases in WHO grade III, and 11 cases in WHO grade IV. The patients were randomly divided into group A (R-TMZ) and group B (R). The two groups were comparable in the age, gender, pathological grade, and tumor sites (P>0.05). This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Beihua University. Written informed consent was obtained from all participants.

Treatments

All the patients were performed 3D conformal radiotherapy within one month after resection: after fixed with one thermoformed mask and CT-simulated body marking, each patient was applied TPS for designing the radio therapeutic field and evaluating the dosage. The target radio therapeutic area was sketched in turn in computed tomography (CT) images, including gross tumor volume (GTV), clinical tumor volume (CTV), and planned tumor volume (PTV), among which CTV was +2.5~3 cm more than GTV, and PTV was +0.5~1 cm more. Meanwhile, the shapes and positions of sensitive tissues or organs around the tumor that needed protection were also mapped so as to ensure 95% of prescription dose was kept in the whole target area. All the patients were treated with high-dose radiotherapy, 2 Gy/time toward the target area, 1 time/day, 5 times/week, using 6-MVX linear accelerator (Siemens, Germany) with the total dose reaching 60~70 Gy within 5 to 7 weeks. Group A was orally applied 5-day TMZ (Tasly, Tianjin, China) on this basis at the same time, 50~75 mg/(m^2d) during radiotherapy, 150 mg/(m^2d) in the first cycle after radiotherapy, and 200 mg/(m^2d) in the second cycle (28 days as one cycle, for 4 to 6 cycles). Patient's blood routine was tested once each week during treatment so as to timely treat severe bone marrow suppression. Meanwhile, blood cell producing drugs were also orally administrated, and the patients with radiotherapy responses were performed symptomatic treatment.

Efficacy determination and observation indicators

(1) Referring to the diagnostic criteria of Response Evaluation Criteria In Solid Tumors (RECIST) complete remission (CR): the lesion disappeared and remained for more than 4 weeks; partial remission (PR): the lesion reduced more than 50% and maintained for more than 4 weeks; stable (SD): the lesion reduced less than 50%, or increased less than 25%; progression (PD): the lesion increased more than 25%, or new lesion appeared [8]. The objective response rate (ORR) was calculated by CR+PR, and the disease control rate (DCR) was calculated by CR+PR+SD after the end of treatment; (2) The 1, 2 and 3-year survival rates were recorded through clinic or telephone follow-up; (3) The Karnofsky scores before and after treatment were used to evaluate patient's life quality; (4) The safety assessment was performed according to the Common Terminology Criteria for Adverse Events by NCI, which were divided into grade 0-IV.

Statistical analysis

SAS8.0 software was used for the analysis. The count data were analysed by the $\chi 2$ test or rank sum test, with $P<0.05$ considered as statistically significant.

Results

Short-term effects

There was no treatment-related death during chemo radiotherapy in both groups. The ORR and DCR values in group A were 76.7% and 93.0%, respectively, and those in group B were 55.8% and 74.4%, respectively (P<0.05) (Table 1).

Table 1. *Comparison of ORR and DCR between the two groups.*

Group	n	CR	PR	SD	PD	ORR (%, 95%CI)	DCR (%, 95%CI)
A	43	3	30	6	4	76.7 (64.1%~89.3%)	93.0 (88.4%~93.0%)
B	43	2	22	9	10	55.8 (51.9%~59.7%)	74.4 (70.4%~78.4%)
$\chi 2$						4.21	3.95
P						0.0401	0.0467

Quality of life

Before treatment, the Karnofsky scores between the two groups had no significant difference (P>0.05); after treatment, the Karnofsky scores were improved in both groups, and that in group A was statistically significantly higher than group B (P<0.05) (Table 2).

Table 2. *Comparison of life quality scores before and after treatment ($\bar{x} \pm s$).*

Group	n	Before	After	t	P
A	43	51.34±5.44	64.54±7.81	4.67	0
B	43	52.36±6.75	57.48±9.37	1.54	0.0046
t		0.47	4.09		
P		0.4425	0.002		

Follow-up

The median survival period was 15.5 months in group A and 11.3 months in group B; the median survival period difference between the two groups was statistically significant (P=0.042). The postoperative 1, 2 and 3-year survival rate in group A was

statistically significantly higher than group B (P<0.05) (Table 3).

Table 3. Comparison of postoperative 1, 2, 3-year survival rate in the two groups.

Group	n	1-year		2-year		3-year	
		n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
A	43	32 (74.4)	(70.4%~78.4%)	23 (53.5)	(38.6%~68.4%)	19 (44.2)	(29.4%~59.0%)
B	43	21 (48.8)	(41.2%~56.4%)	14 (32.6)	(18.6%~46.6%)	10 (23.3)	(20.1%~26.5%)
χ^2		5.95		3.84		4.21	
P		0.0147		0.049		0.0401	

Side effects

The common side effects were such gastrointestinal reactions as nausea, vomiting, or diarrhoea, as well as such haematological toxicity as platelet and leukocyte reduction, anaemia and neurotoxicity, which were all self-limiting, and remitted by symptomatic treatment such as antiemesis and increasing white blood cells. There was no statistically significant difference in treatment-related adverse reactions between the two groups (P>0.05) (Table 4).

Table 4. Comparison of side effects between the two groups (n).

Adverse reactions	A				B				Z	P
	I	II	III	IV	I	II	III	IV		
Diarrhoea	4	3	1	0	5	3	0	0	0.6	0.5501
Nausea and vomiting	16	6	1	0	18	5	2	0	0.08	0.938
Platelet reduction	7	5	1	0	6	2	0	0	0.98	0.3288
Leukopenia	11	8	3	1	15	3	2	1	1.33	0.1826
Anaemia	14	3	2	0	11	4	2	0	0.51	0.6113
Neurotoxicity	12	3	1	0	9	4	0	0	0.2	0.8438

Discussion

Glioma is a malignant tumor with great invasiveness, and because it has no obvious boundary with normal surrounding brain tissue as well as often locates in important functional area, so it is difficult for complete resection. Therefore, postoperative adjuvant radiotherapy has become one of first-line clinical choices, which can effectively improve the treatment of glioma [9-11]. In recent years, tumor radiotherapy has been gradually developed into 3D conformal radiation, which can maximize the therapeutic dose against the target area and protect surrounding normal tissues and vital organs, so it has been widely used in a variety of solid tumors [12-14]. However, due to special brain anatomical structures and radiation dose limits, partial patients exhibit poor sensitivity to radiotherapy, so this technology can only extend their survival period. One meta-analysis has pointed out that glioma resection should be accompanied by simultaneous radiotherapy, chemotherapy, or other comprehensive treatment methods so as to control the shrunk tumor, prevent the proliferation, and further shrink the lesion [15].

The glioma cells can resist commonly used chemotherapeutic drugs, and the blood-brain barrier also greatly limits the application of chemotherapy. As a new oral alkylating agent, TMZ has rapid in vivo absorption and high bioavailability, and pass can through the blood-brain barrier and act on the central nervous system. Studies have shown that TMZ has inhibitory effects against tumor cells at all stage, and it can play its cytotoxic effects toward different pathological types of glioma [16,17]. The ORR and DCR values in group A were 76.7% and 90.7%, respectively, significantly higher than group B (55.8% and 74.4%, P<0.05). At the same time, the further follow-up also revealed that R-TMZ can significantly prolong the median survival of the patients, and the postoperative 1, 2 and 3-year survival rates were significantly improved (P<0.05), indicating that postoperative R-TMZ can improve the patient's short-term and long-term survival rates, which is considered to be related to the fact that radiotherapy can directly kill tumor cells and chemotherapy can trigger tumor cell's apoptosis [18]. Studies have shown that TMZ can induce the tumor cell cycle arrested in the G2-M period, thus synchronizing the cell cycle and playing the radiotherapy sensitization effects [19-21]. At present, chemotherapy is still controversial among the adjuvant

treatments of glioma, which is mainly focused on its efficacy, side effects, and drug resistance in patients [22]. The data in this study revealed that the postoperative quality of life in group A was significantly improved, which is considered to be related to the significant improvement of ORR and DCR; meanwhile, simultaneous chemo radiotherapy can reduce dose exposure in target-area-surrounding normal organs and tissues to a certain extent. Drug side effects were mostly grade I or II, and no patient quit the treatment due to side effects, indicating that the patients had good tolerance to TMZ. In short, R-TMZ is a safe and effective postoperative adjuvant treatment of glioma, can improve the short-term and long-term efficacy as well as the postoperative survival rate while does not increase toxic effects. In view of the small case number and short follow-up period in this study, the patient's long-term survival status and adverse reactions still need further follow-up and observation.

Conflicts of interest

The authors declare no conflict of interest.

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