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Original Article

Short- and long-term efficacy of sustained-release chemotherapy in tumor bed interstitium combined with surgical resection for recurrent malignant glioma

Longlong Wang, Zhifeng Wang, Zan Liang, Guojing Li, Shibo Duan, Yanguo Xi

Department of Neurosurgery, Cangzhou Central Hospital, Cangzhou 061000, Hebei, China

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Abstract: Objective: To discuss and analyze the short- and long-term curative effect of sustained-release chemotherapy combined with surgical resection on recurrent malignant glioma. Methods: The clinical data of 137 patients with recurrent glioma admitted to our hospital from March 2016 to July 2018 were retrospectively analyzed. Among them, 67 patients who received local chemotherapy with cisplatin slow-release polymer after surgical resection were included in the observation group, and the other 70 patients who did not receive chemotherapy after surgical resection were regarded as the control group. The short-term therapeutic efficacy, quality of life score before and after surgery, incidence of toxic and side effects, long-term recurrence rate and survival were compared between the two groups. Results: The total remission rate of clinical treatment in observation group was remarkably higher than that in control group ($P<0.05$). There was no statistically significant difference in quality of life score between the two groups before and after surgery ($P>0.05$). There was no significant difference in the incidence of postoperative side effects between the two groups ($P>0.05$). While the recurrence rates of the observation group at 12 and 24 months after surgery were significantly lower than those in the control group ($P<0.05$). The overall postoperative survival of observation group was obviously superior to that of control group ($P<0.05$). In patients who received sustained-release chemotherapy in tumor bed interstitium combined with surgical resection, older ones and the ones with partial surgical resection or pathological grade IV had worse long-term survival ($P<0.05$). Conclusion: The combined treatment of sustained release chemotherapy in tumor bed interstitium and surgical resection for recurrent malignant glioma can effectively improve the clinical efficacy, reduce postoperative recurrence rate and prolong the survival time of the patients.

Keywords: Sustained release chemotherapy, tumor bed interstitium, surgical resection, recurrent, malignant glioma, short-term efficacy, long-term efficacy

Introduction

Glioma is a tumor of the central nervous system. The incidence of glioma accounts for about 40% of all intracranial tumors, and malignant gliomas account for 77.5% of gliomas [1]. The biological behavior of malignant glioma is highly invasive, and its tumor cells can still remain in normal tissues after radical resection, so the patients usually have poor prognosis and high recurrence rate. Those with recurrence have a median survival time of only 3-9 months [2]. The local anti-tumor treatment technique is widely adopted for clinical recurrent malignant glioma, including tumor bed interstitial radiotherapy and local adaptive immunotherapy of LAK cells and recombinant cytokine IL-2 [3]. The most concerned is the use of implants with sustained-release tumor chemotherapeutic drugs for antitumor treatment in the stroma of tumor bed. Chemotherapy can prolong the survival of patients with malignant glioma to a certain extent, but conventional intravenous or intraarterial administration cannot substantially improve their survival [4]. The application of interstitial chemotherapy in tumor bed can maximize the exposure of tumor to chemotherapy drugs and reduce the adverse reactions caused by systemic chemotherapy [5]. There have been numerous human and animal studies that used intrastromal antitumor agents such as bleomycin, doxorubicin, cisplat-

in, methotrexate, and camustine, which make it feasible for local intratumoral bed interstitial chemotherapy in recurrent malignant glioma [6, 7]. This study aimed to explore and analyze the short- and long-term curative effect of sustained-release chemotherapy combined with surgical resection on patients with recurrent malignant glioma.

Data and methods

Clinical data

The clinical data of 137 patients with recurrent glioma admitted to our hospital from March 2016 to July 2018 were retrospectively analyzed. Among them, 67 patients who received local chemotherapy with cisplatin slow-release polymer after surgical resection were included in the observation group, and the other 70 patients who received routine postoperative radiotherapy and chemotherapy were regarded as the control group. This study was approved by the ethics committee of Cangzhou Central Hospital.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients underwent surgical treatment and were diagnosed with recurrent malignant glioma by postoperative pathological tests, such as CT, MRI; (2) Patients had first recurrence; (3) Patients previously received conventional tumor radiotherapy, with a total radiotherapy dose ≥5500 Gy; (4) Patients had their tumor confined to one hemisphere and a maximum diameter on enhanced MRI of less than 6 cm; (5) Patients voluntarily signed the informed consent forms.

Exclusion criteria: (1) Patients with coagulation function, history of intracerebral hemorrhage, cerebral embolism, severe intracranial infection or severe hypertension; (2) Patients with severe heart, lung, kidney, liver or other organ dysfunction; (3) Patients who had received antiglioma therapy in 4 weeks prior to the study.

Methods

Surgical methods and interstitial sustained-release chemotherapy: The surgical procedures were the same for both groups of patients, i.e., microsurgery under yellow fluorescence after general anesthesia. Fluorescein sodium skin test was performed 30 min before operation by intravenous injection of 5 mL fluorescein sodium (5-10 mg/kg, diluted from 0.5 mL). The patients were observed for 15 min, and if the skin test was confirmed negative, surgical treatment was performed. The location of the tumor was fully exposed after routine craniotomy. Under the fluorescence microscope with a wavelength of 560 nm, the dura mater was cut. Yellowish-green fluorescent tumor was seen in the parenchyma of the tumor, and the surrounding area was light yellow. But there was no fluorescent yellow staining in normal brain tissue. The tumor was resected later. YE560 fluorescence mode was used to monitor the whole excision process. If the patient was bleeding, hemostasis treatment was performed when the microscope was switched to the normal white light mode. When the brightness of the tumor in the surgical field was consistent with that of normal brain tissue under YE560 fluorescence mode, the normal light mode was adjusted. The outermost layer of tumor tissue and brain tissue without yellow staining were removed for fluorescence staining and sent to the monitoring room for frozen section pathological examination. We strived to remove the recurrent tumor tissue to the maximum extent under the microscope on the premise of protecting nerve function. In the observation group, cisplatin slow-release implant was placed after tumor resection. The implant was a polymer tablet with a size of 1.5 cm × 1.5 cm, and the concentration of cisplatin was 1 mg/cm^2. Each patient received 20 tablets of cisplatin slow-release polymer implanted to fill the remaining tumor bed stroma.

Postoperative radiotherapy and chemotherapy methods: Both groups of patients received conventional treatments including oral phenytoin to prevent epilepsy, 20% mannitol to lower intracranial pressure, and glucocorticoid therapy to alleviate side effects. Both groups received radiotherapy for 2-3 weeks after operation, once a day and 5 days/week. The daily dose was 2 Gy, and the total dose of cranial irradiation was 20 Gy. Subsequently, the enhanced tumor bed irradiation was performed once/day and 5 days/week. The daily dose was 2 Gy, and the total dose of tumor bed irradiation was 60 Gy.

Quality of life evaluated by Karnofsky scale

The quality of life of patients was scored using Karnofsky scale before and after treatment

Table 1. Comparison of clinical data between the two groups

Group	Number of cases	Sex		Age (years, $\bar{x}\pm s$)	BMI (kg/m^2, $\bar{x}\pm s$)	DRFI (years, $\bar{x}\pm s$)
		Male	Female			
Observation group	67	41	26	50.24±7.30	23.18±2.31	1.39±0.45
Control group	70	40	30	49.53±8.56	22.89±2.54	1.48±0.51
t/x^2	-	0.233		0.521	0.698	1.093
P	-	0.630		0.603	0.486	0.276

BMI: Body mass index, DRFI: Recurrence time.

Table 2. Comparison of Karnofsky quality of life scores before and after treatment between the two groups (points, $\bar{x}\pm sd$)

Group	Number of cases	Before treatment	After treatment	t	*P*
Observation group	67	65.49±7.89	73.42±9.21	5.352	0.000
Control group	70	64.32±8.47	72.95±7.90	6.099	0.000
t	-	0.834	0.321	-	-
P	-	0.405	0.749	-	-

with a score ranged from 0 to 100 points. Higher score referred to a better quality of life.

Adverse reactions

The assessment of the adverse reactions of anti-cancer drugs was based on the National Cancer Institute: I (mild): no influence on normal life; II (moderate): life threatening but tolerable; III (severe): great impact on life and intolerable; and IV (serious): endangering life.

Follow-up visits

The two groups of patients were followed up via hospital visits, outpatient, telephone, WeChat and door-to-door approaches. The deadline for follow up was June 1, 2021, and the overall survival (OS) was recorded with deadline or death as the end event.

Statistical analysis

Data processing and analysis were performed by statistical software SPSS 25.0. The comparison of measurement data was conducted by t-test, and that of counting data was conducted by X^2 test. Kaplan-Meier survival curve was drawn to reflect the two groups' survival, and log-rank test was used for the comparison. *P<0.05* was considered as statistically significant difference.

Results

Comparison of clinical data

The observation group included 41 males and 26 females, with an average age of 50.24±7.30 years, body mass index (BMI) of 23.18±2.31 kg/m^2 and recurrence time of 1.39±0.45 years. The control group consisted of 40 males and 30 females, with an average age of 49.53±8.56 years, BMI of 22.89±2.54 kg/m^2 and recurrence time of 1.48±0.51 years. There was no statistically significant difference in clinical data between the two groups (*P>0.05*) (**Table 1**).

Comparison of quality of life scores

The score of quality of life in the observation group was 65.49±7.89 points before treatment and increased to 73.42±9.21 points after treatment. The score of the control group was 64.32±8.47 points before treatment and 72.95±7.90 points after treatment. The post-treatment quality of life scores of the two groups were significantly higher than those before treatment (*P<0.05*), and there was no significant difference between the two groups before and after treatment (P>0.05) (**Table 2**).

Comparison of toxic and side effects

In the observation group, there were 3 cases of edema, 1 case of seizure and 5 cases of leukopenia. In the control group, there were 4 cases of edema, 3 cases of seizure and 4 cases of leukopenia. There was no significant difference in the incidence of postoperative toxic and side effects between the two groups (*P>0.05*). The side effects of the two groups of patients were

Table 3. Comparison of toxic and side effects between the two groups [n (%)]

Group	Number of cases	Edema	Seizures	Leukopenia	Total
Observation group	67	3 (4.48)	1 (1.49)	5 (7.46)	9 (13.43)
Control group	70	4 (5.71)	3 (4.29)	4 (5.71)	11 (15.71)
X^2	-	-	-	-	0.143
P	-	-	-	-	0.705

Table 4. Comparison of postoperative recurrence rates between the two groups [n (%)]

Group	Number of cases	6 months after surgery	12 months after surgery	24 months after surgery
Observation group	67	19 (28.36)	24 (35.82)	35 (52.24)
Control group	70	24 (34.29)	37 (52.86)	51 (72.86)
X^2	-	0.559	4.023	6.228
P	-	0.455	0.045	0.013

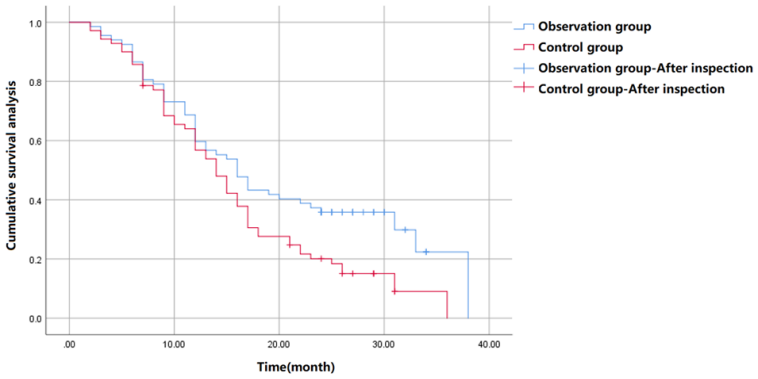

Figure 1. Comparison of survival between the two groups.

both grade I to II, and there were no patients with grade III to IV side effects (**Table 3**).

Comparison of postoperative recurrence rates

In the observation group, recurrence was shown in 19 cases within 6 months after surgery, in 24 cases within 12 months after surgery, and in 35 cases within 24 months after surgery. In the control group, recurrence was shown in 24 cases within 6 months after surgery, in 37 cases within 12 months after surgery, and in 51 cases within 24 months after surgery. There was no statistical significance in the 6-month recurrence rate between the two groups (*P>0.05*). The 12-month and 24-month recurrence rates in the observation group were notably lower than those in the control group (*P<0.05*) (**Table 4**).

Comparison of survival

The median survival time was 18.72 months in the observation group and 14.28 months in the control group. The general postoperative survival of the observation group was obviously superior to that of the control group (*P<0.05*) (**Figure 1**).

Factors influencing the survival time of patients with tumor bed interstitial sustained release chemotherapy

The factors influencing the survival time of patients were analyzed. For patients with tumor bed interstitial sustained release chemotherapy combined with surgical resection, worse long-term survival showed in older patients (*P<0.05*, **Figure 2B**), patients with partial surgical resection (*P<0.05*, **Figure 2C**) and those with pathological grade IV (*P<0.05*, **Figure 2D**), while sex and tumor diameter were not associated with long-term survival (*P>0.05*, **Figure 2A**, **2E**).

Discussion

Glioma is one of the most common intracranial tumors. It is invasive and difficult to be completely removed. Chemotherapy is an effective and important method to kill residual tumor cells and prevent recurrence [8]. However, most chemotherapeutic agents are difficult to cross the blood-brain barrier to achieve an effective therapeutic concentration in intracranial region. In addition, systemic administration has considerable toxic and side effects, including bone marrow transplantation, liver fibrosis, liver dysfunction, etc., and the half-life of intravenous administration in plasma and brain tissue is as short as 15 min [9]. Many scholars have explored the methods and pathways of administration in order to increase the local drug concentration and reduce side effects. In the view that 90% postoperative recurrences

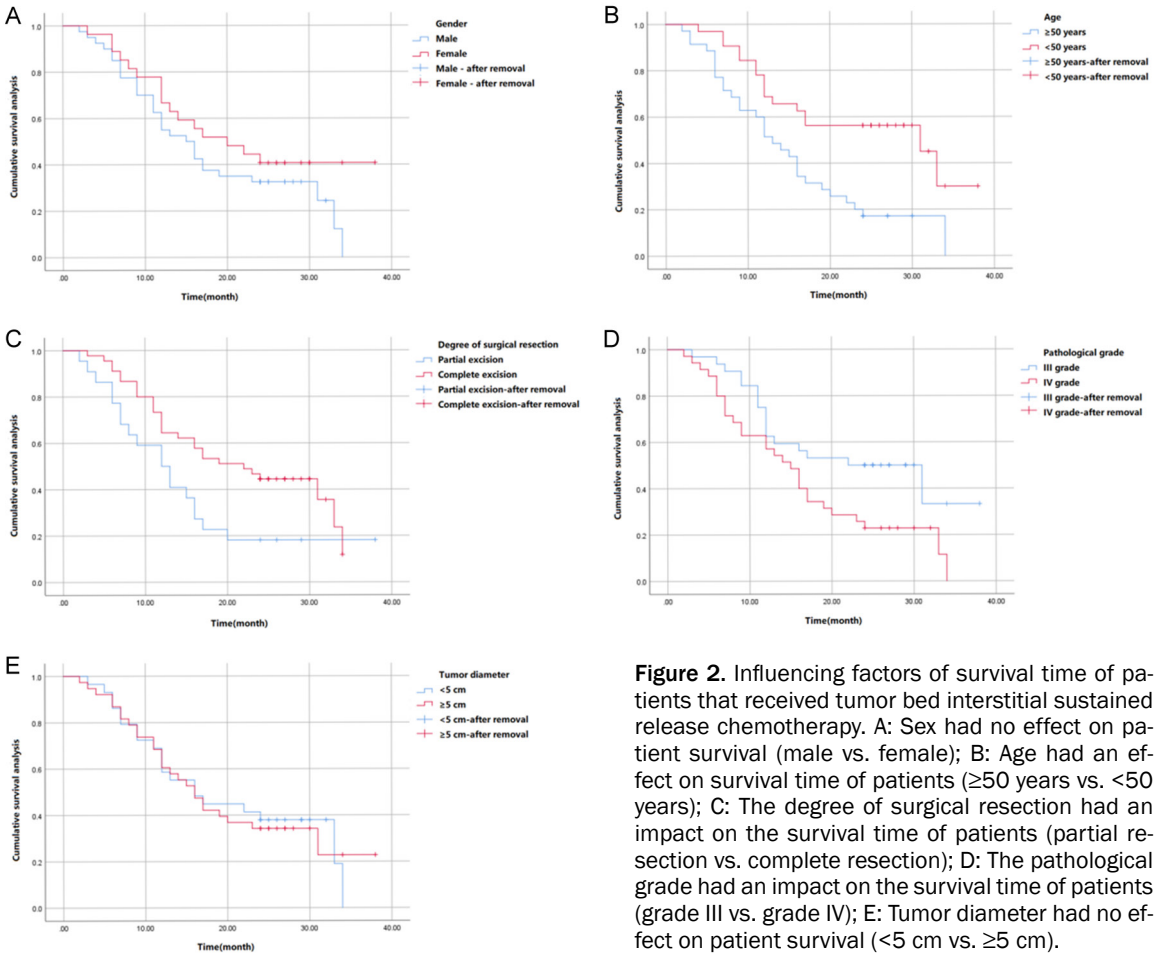

Figure 2. Influencing factors of survival time of patients that received tumor bed interstitial sustained release chemotherapy. A: Sex had no effect on patient survival (male vs. female); B: Age had an effect on survival time of patients (≥50 years vs. <50 years); C: The degree of surgical resection had an impact on the survival time of patients (partial resection vs. complete resection); D: The pathological grade had an impact on the survival time of patients (grade III vs. grade IV); E: Tumor diameter had no effect on patient survival (<5 cm vs. ≥5 cm).

of gliomas are within 2 cm of the primary tumor, interstitial sustained release chemotherapy has become a new approach for glioma chemotherapy in recent years [10, 11]. Interstitial sustained release chemotherapy refers to the combination of drugs and degradable polymer sustained release materials straight into postoperative tumor cavity for chemotherapy [12, 13]. Biodegradable polymer molecules have a certain spatial molecular structure, in which drugs are stored, and chemical drugs are released while degrading in vivo [14, 15].

This study is an exploration and analysis of the short-term and long-term efficacy of sustained-release chemotherapy combined with surgical resection in patients with recurrent malignant glioma. In this study, we used cisplatin sustained-release polymer for local chemotherapy in patients with recurrent glioma. There were no serious adverse reactions in the central nervous system or the whole body in the observation group, nor significant difference in the incidence of toxic and side effects between the two groups. This indicated that the clinical treatment scheme was safe and feasible, which is similar to previous research reports [16, 17]. Cisplatin is one of the commonly used drugs for chemotherapy of malignant glioma, but the blood-brain barrier severely inhibits the drug concentration in the tumor area. Studies [18-20] have shown that the clinical efficacy of systemic cisplatin chemotherapy in the treatment of glioma is largely limited by drug molecular therapy. The molecular weight of cisplatin is 300 u, while the maximum allowable molecular weight of blood-brain barrier is 200 u. In addition, systemic injection of a tolerable dose of cisplatin can only produce a drug concentration of 0.17 μg/kg in the brain tissue, which is far from enough to achieve the effect of antitumor. Bouvier et al. [21] applied stereotactic technology to place 16 microcatheters into a patient's brain tumor for the first time, and used a pump

syringe for cisplatin infusion, with a drug dose of 8.2 to 12.5 mg. During their 6 months of follow up, the patient did not have any serious complications.

The cisplatin sustained-release polymer used in this study is a mixture composed of cisdiamine dichloroplatinum and 6-carboxyl cellulose. The polymer was found 4-5 weeks after surgery by CT examination to observe the degradation of the polymer. In terms of short- and long-term efficacy, the remission rate of observation group was remarkably higher than that of control group, and the general postoperative survival of observation group was better than that of control group. This indicated that sustained-release chemotherapy within the tumor bed could significantly improve the short-term therapeutic effect of patients with malignant recurrent glioma and prolong their survival. We consider that within 4-5 weeks of the degradation of slow-release chemotherapeutic drugs in tumor bed interstitium, continuous chemotherapy may promote postoperative radiotherapy sensitization, play a synergistic anti-tumor effect, kill tumor cells to a great extent, achieve a high clinical remission rate and improve the long-term survival of patients [22-24].

After analyzing the factors influencing the survival of patients with interstitial slow-release chemotherapy combined with surgical resection, we found that the survival of older patients, patients with surgical partial resection and patients with pathological grade IV had poorer survival. This is basically consistent with the results of clinical speculation [25, 26], indicating that the function of patients with older age may be degenerative and the risk of complicated underlying diseases is increased, which may affect the survival and prognosis of the patients. If the tumor cells cannot be completely removed during surgery, the residual tumor cells in the body after partial resection are more likely to lead to postoperative recurrence and affect the prognosis of patients [27]. Pathological grade IV indicates that the patient's tumor is more aggressive, and therefore leads to a poorer survival [28, 29].

However, since the sample size included in this study was relatively small, and there was no exploration on the concentration of cisplatin intratumoral sustained-release chemotherapy drugs, it is suggested to further explore the impact of different drug concentrations on the curative effect in future study, and thus to acquire the optimal therapeutic dose and better clinical efficacy.

In summary, the combined treatment of sustained release chemotherapy in tumor bed interstitium and surgical resection for recurrent malignant glioma can effectively improve the clinical efficacy, reduce the postoperative recurrence rate in patients and prolong their survival time.

Disclosure of conflict of interest

None.

Address correspondence to: Yanguo Xi, Department of Neurosurgery, Cangzhou Central Hospital, No. 16 Xinhua West Road, Cangzhou 061000, Hebei, China. Tel: +86-18531701077; E-mail: xiyanguo0104@126.com

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