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Case series

Safety and feasibility of intra-arterial delivery of teniposide to high grade gliomas after blood–brain barrier disruption: a case series

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnis-2023-021055).

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Received 24 September 2023
Accepted 11 November 2023

ABSTRACT

Background This case series describes the safety and efficacy of superselective intra-arterial (IA) cerebral infusion of teniposide for the treatment of patients with glioma, to provide new ideas and methods for the treatment of high grade gliomas.

Methods 12 patients with glioma who were previously treated with standard therapy were treated with superselective IA cerebral infusion of teniposide. Patients received at least two cycles of treatment (one cycle: 150 mg/time, used for 1 day, repeated at 28 day intervals) after blood–brain barrier disruption. Patients received individualized treatment on the tumor location. The ophthalmic artery was bypassed during the superselective arterial infusion.

Results No significant differences in biochemical indexes and Karnofsky performance status (KPS) score were observed before and after treatment, and no evident adverse events occurred (P>0.05). In a recent response evaluation (August 2023), two (8%) patients presented with a complete response (16.7%), four had a partial response (33.3%), four had stable disease (33.3%), and two showed progressive disease (16.7%). The overall response rate and disease control rate were 50.0% and 83.3%, respectively. In addition, we described the detailed course of treatment in two patients. Case No 1 (recurrent tumor) and case No 2 (primary tumor) received six and three cycles of teniposide infusion, respectively. After treatment, the tumors of the patients were significantly reduced without evident adverse effects.

Conclusion This small series suggests that superselective IA cerebral infusion of teniposide may be a safe and effective therapy in the multimodal treatment of malignant glioma and warrants further study in larger prospective investigations.

To cite: Ruan J, Shi Y, Luo P, *et al*. *J NeuroIntervent Surg* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnis-2023-021055

INTRODUCTION

Gliomas originate from the neuroepithelium and are the most common tumors of the CNS.[1] In general, gliomas are derived from glial cells or precursor cells, and then develop into astrocytomas, oligodendrogliomas, or glioblastomas (GBMs), for example, among which GBMs are the most aggressive.[2 3] Morbidity and mortality from gliomas are increasing every year.[4] The average survival of patients with a glioma is <1 year, and the 5 year survival rate is <5%.[5] At present, the treatment of malignant gliomas (WHO grades 3 and 4) is primarily the Stupp regimen (postoperative radiotherapy and temozolomide concurrent chemotherapy, followed by temozolomide adjuvant chemotherapy for 6–12 months).[6] Studies have found that the average time for recurrence of malignant gliomas treated with the Stupp regimen is 7 months, and survival after recurrence is 6–7 months.[7] Once high grade gliomas recur, the prognosis is extremely poor.[8] Currently, there is no standard treatment for recurrent malignant gliomas. Thus finding new methods to improve the efficacy is urgently needed.

Teniposide (VM-26), an analog of podophyllotoxin (PTOX), binds and inhibits topoisomerase II, preventing the healing of DNA breaks that occur during cell replication and leading to apoptosis.[9] Teniposide plays an important role in brain metastases of glioma and other malignant tumors.[10] Teniposide has the characteristics of CNS permeability and lipophilicity, and the concentration of teniposide in CSF can reach up to 27% of the blood concentration.[11] However, the limitations of intravenous teniposide are also prominent, such as poor bioavailability, large side effects, and drug resistance.[12] Therefore, the development of new teniposide based therapeutics is necessary.

Intra-arterial (IA) delivery for the treatment of intracranial tumors began in the 1950s.[13] Superselective IA cerebral infusion is a method in which a catheter is selectively inserted into the artery supplying the tumor and drugs are injected into the tumor.[13] Compared with intravenous administration, superselective IA cerebral infusion of modern chemotherapeutics after blood–brain barrier disruption can reach the local drug concentration at the tumor, and the amount of drug consumption and systemic adverse reactions decrease. Thus this method is widely used in clinical practice.[14] Several studies have evaluated the safety and efficacy of IA delivery of bevacizumab and bevacizumab to GBMs.[15 16] However, the safety and feasibility of IA delivery of teniposide to gliomas have not been evaluated. In this study, we report the safety and efficacy of superselective IA cerebral infusion of teniposide for the treatment of 12 glioma patients, to provide new ideas and methods for the treatment of high grade gliomas.

MATERIALS AND METHODS

Clinical data

Retrospective analysis was conducted on 12 patients with malignant gliomas who were treated at the Department of Neurosurgery, Chongqing

University cancer hospital, from June 2022 to July 2023. Inclusion criteria were: (1) age >18 years; (2) patients with pathologically confirmed high grade gliomas; (3) Karnofsky performance status (KPS) score >60 (predicted postoperative survival time is >3 months)[17]; and (4) no contraindications to radiotherapy or chemotherapy, and no other brain lesions. Exclusion criteria were: (1) patients with severe heart, liver, or kidney dysfunction; and (2) patients who were treated with superselective intracranial arterial infusion less than two times.

The Stupp protocol was used for postoperative treatment. General data for the patients were collected, including sex, age, lesion location, pathological type, and other clinical information. Biochemical indicators before and after infusion of chemotherapy were collected, including white blood cells, neutrophils, hemoglobin, platelets, aspartate aminotransferase, alanine aminotransferase, and D-dimer.

Therapeutic method

Superselective intracranial arterial infusion of teniposide was performed in patients with high grade gliomas who completed the Stupp protocol. Seldinger puncture was performed on the right femoral artery, and a 6 F artery sheath (6F-11CM 402–606X; Cordis, Miami, Florida, USA) was inserted. Blood–brain barrier disruption was carried out by rapid intravenous infusion of 125 mL of 20% mannitol. The 6 F guided catheter (670-258-00; Cordis) was used to conduct bilateral common carotid artery angiography. After systemic heparinization (80 U/kg), the Enchelon10 microcatheter (Covidien, Mansfield, Massachusetts, USA) was superselected into the A1/M1/P2/C7 segment under the guidance of the AVIGO microguide wire. Superselective microangiography showed that the tube tip was in a suitable position. Teniposide (150 mg) was mixed with normal saline (250 mL), and the micropump was continuously pumped at a rate of 5 mL/min.[18] One cycle of infusion of chemotherapy was administered as follows: 150 mg each, administered for 1 day, repeated at 28 day intervals.

After completion of the interventional chemotherapy, angiography showed that the intracranial vessels were unobstructed and no obvious abnormalities were observed. Patients received individualized treatment. Based on the cerebral vascular supply area of the tumor site, the microcatheter was beyond the ophthalmic artery. Arterial infusion of chemotherapy was also performed by superselective placement of the anterior cerebral artery (ACA) A1 segment, middle cerebral artery (MCA) M1 segment, posterior cerebral artery P2 segment, or the end of the C7 segment of the internal carotid artery. In this study, all 12 patients received at least two cycles of treatment.

Assessment of patients' functional status and adverse events

KPS was assessed before and after the first treatment with superselective intracranial arterial infusion of teniposide.[19] The specific scoring criteria were: 100 points=no symptoms or signs; 90 points=can perform normal activities with minor symptoms or signs; 80 points=barely performing normal activities with some symptoms or signs; 70 points=can take care of themselves but cannot maintain normal life and work; 60 points=can take care of most of their own life, but occasionally need help from others; 50 points=often need to be taken care of by others; 40 points=cannot take care of themselves and need special care and help; 30 points=cannot take care of themselves; 20 points=severe illness requiring hospitalization and active supportive care; 10 points=severe risk and near death; and 0 points=death. Adverse events of infusion of chemotherapy were observed and recorded.

Table 1 Baseline characteristics of 12 glioma patients

Characteristics	Glioma patients (n=12)
Age (years) (mean±SD)	47.8±11.1
Sex	
Men	5 (41.7)
Women	7 (58.3)
Height (cm) (mean±SD)	161.9±7.2
Weight (kg) (mean±SD)	61.4±10.7
Body mass index (kg/m^2) (mean±SD)	23.4±3.7
Smoking history	3 (25.0)
Drinking history	1 (8.3)
Comorbidities	
Hypertension	1 (8.3)
Diabetes	1 (8.3)
Family history of glioma	0 (0.0)
Tumor number	
Unifocal	12 (100.0)
Multifocal	0 (0.0)
Treatment before Teniposide	
Surgery	12 (100.0)
Chemoradiotherapy	12 (100.0)
Type of surgery	
Total resection	6 (50.0)
Partial resection	6 (50.0)
Pathological classification	
WHO grade 3	1 (8.3)
WHO grade 4	11 (91.7)
Outcome after chemoradiotherapy	
Partial response	12 (100.0)
Tumor type	
Primary	8 (66.7)
Relapsed	4 (33.3)

Values are number (%) unless indicated otherwise.

Assessment of treatment response

The response to infusion chemotherapy was assessed in accordance with the response assessment in neuro-oncology (RANO) criteria.[20] Patients were followed for 8–19 months, with a mean follow-up of 12 months. The objective response rate (ORR) included complete response (CR) and partial response (PR). The disease control rate included CR, PR and stable disease (SD).

Statistical method

SPSS 22 was used for statistical analysis. Data are expressed as mean±SD. Biochemical indicators are expressed as median (IQR). Differences in biochemical indices and KPS scores before and after treatment were analyzed by a paired sample Wilcoxon test. $P<0.05$ was considered statistically significant.

RESULTS

This study included 12 patients with high grade gliomas, including 11 WHO grade 4 and one WHO grade 3 gliomas (table 1). One patient with relapsed diffuse astrocytoma, WHO grade 3, was enrolled in the study because resistance developed after treatment with temozolomide. A total of five

Table 2 Comparison of biochemical indices and Karnofsky performance status score before and after chemotherapy infusion

Parameter	Pre-infusion chemotherapy	Post-infusion chemotherapy	P value
WBC ($\times 10^9$/L)	4.6 (3.8–5.7)	5.5 (3.5–8.2)	0.182
Neutrophils ($\times 10^9$/L)	2.8 (2.3–3.7)	4.7 (2.3–7.1)	0.071
Hemoglobin (g/L)	136.0 (110.0–143.0)	141.0 (117.0–144.0)	0.223
Platelets ($\times 10^9$/L)	172.0 (163.0–251.0)	176.0 (156.0–203.0)	0.695
AST (U/L)	22.0 (11.0–45.0)	26.0 (11.0–40.0)	0.859
ALT (U/L)	18.0 (17.0–23.0)	18.0 (16.0–27.0)	0.574
D-dimer (mg/L)	0.4 (0.2–0.6)	0.5 (0.2–1.2)	0.331
KPS score (mean±SD)	75.6±13.3	72.2±14.8	0.195

All values are median.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; KPS, Karnofsky performance status; WBC, white blood cells.

men and seven women were included in our study, with an average age of 47.8±11.1 years. Eight patients had primary high grade gliomas and four had recurrent high grade gliomas. Before treatment with teniposide, all patients had undergone surgery and chemoradiotherapy (100.0%). Complete resection was achieved in 50% of patients and partial resection in 50%. Molecular detection was performed in eight patients, and data were not available for four patients because of surgery in other hospitals (online supplemental table 1). All patients had a PR after chemoradiotherapy.

All 12 patients had a single lesion, and the lesions were located in the callosum (n=1), right frontal lobe (n=2), right parietal lobe (n=1), right frontal–parietal lobe (n=1), right frontal temporal parietal lobe (n=1), right temporo-occipital lobe (n=1), left frontal–parietal lobe (n=1), left frontal lobe (n=1), both bilateral frontal lobe and callosum (n=1), and both callosum and right frontal lobe (n=1) (online supplemental table 2). The superselected vessels included the right posterior cerebral artery (n=1), right ACA (n=1), right MCA (n=3), distal right internal carotid artery (n=3), left ACA (n=1), and left MCA (n=3). The mean number of treatment cycles was 3.9±1.6. Patients who received one treatment session were not enrolled. Patients voluntarily gave up continuing treatment due to financial reasons, and the treatment was stopped after the doctor's advice was not taken.

Biochemical indices (white blood cells, neutrophils, hemoglobin, platelets, aspartate aminotransferase, alanine aminotransferase, and D-dimer) were higher after infusion of chemotherapy than before infusion, but the differences were not statistically significant (table 2). In addition, no significant difference in KPS scores was observed before and after infusion of chemotherapy (table 2). Of the 12 patients, 10 had no adverse reactions (online supplemental table 3). One patient had nausea and vomiting, and one had a skin allergy on the back. These results indicated that the new treatment had few toxic side effects and was effective in controlling tumor progression.

In a recent curative effect evaluation (August 2023), two (8%) patients presented with CR (16.7%), four had PR (33.3%), four had SD (33.3%), and two showed PD (16.7%). The ORR and DCR were 50.0% and 83.3%, respectively (figure 1).

Patients received individualized treatment: the relevant feeding artery was on the basis of the tumor site, and the microcatheter was beyond the ophthalmic artery. The drug was pumped through a micropump.

Figure 1

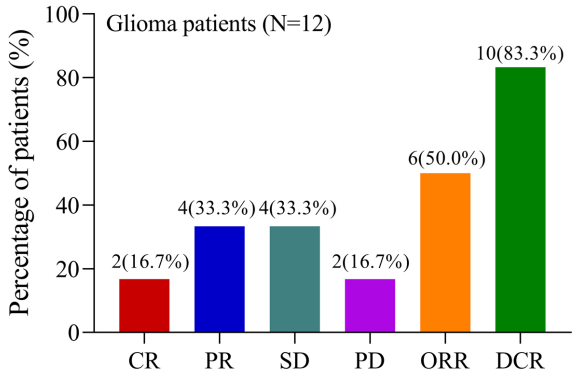

Figure 1 Tumor response after infusion of chemotherapy. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate.

Example case No 1

Case No 1 (patient No 7) was an adult patient who underwent intracranial glioma resection at another hospital 13 years previously (January 2010) and was diagnosed with grade 2 glioma by postoperative pathology. The patient received one chemotherapy session after surgery and was not re-examined. In July 2022, the patient presented with headache, nausea, and occasional vomiting without evident regularity. The patient underwent frontal lobe lesion resection with neuronavigation computer assisted surgery and CSF leakage repair in August 2022. Postoperative recovery was good. Postoperative pathology revealed diffuse astrocytoma, IDH mutation (online supplemental table 1), and CNS WHO grade 4. One month later (September 2022), the patient was treated with standard chemoradiotherapy. The treatment response was PR. The patient received superselective intracranial arterial infusion of chemotherapy (six cycles) in November 2022. Recurrent tumor was located in the corpus callosum region, and the microcatheter was superselected to the A1 segment of the ACA (figure 2A–B). Due to the opening of the ACA, chemotherapy drugs could reach the bilateral A2 segments, and the contralateral recurrent tumor regressed significantly. During chemotherapy, no nausea, vomiting, or other gastrointestinal discomfort was reported (figure 2C). At present, the patient's condition is stable without discomfort.

Example case No 2

Another adult patient (patient No 8) presented with headache, dizziness, and limb twitching in March 2022. In April 2022, the right parietal lobe lesion was resected in another hospital, and the postoperative pathology was consistent with GBM (IDH−, MGMT+, WHO grade 4, online supplemental table 1). The patient was treated with standard chemoradiotherapy in June 2022 and showed a PR. The patient developed left limb numbness in July 2022 and was admitted to our hospital for treatment in August 2022. The patient received three cycles of infusion of chemotherapy in November 2022. The tumor lesion was in the right parietal region, so the microcatheter was superselected into the M1 segment of the right MCA (figure 2D–F). Tumor regression was observed after infusion of chemotherapy. These results indicated that when the microcatheter superselected the artery distal to the ophthalmic artery, a good therapeutic effect can be obtained.

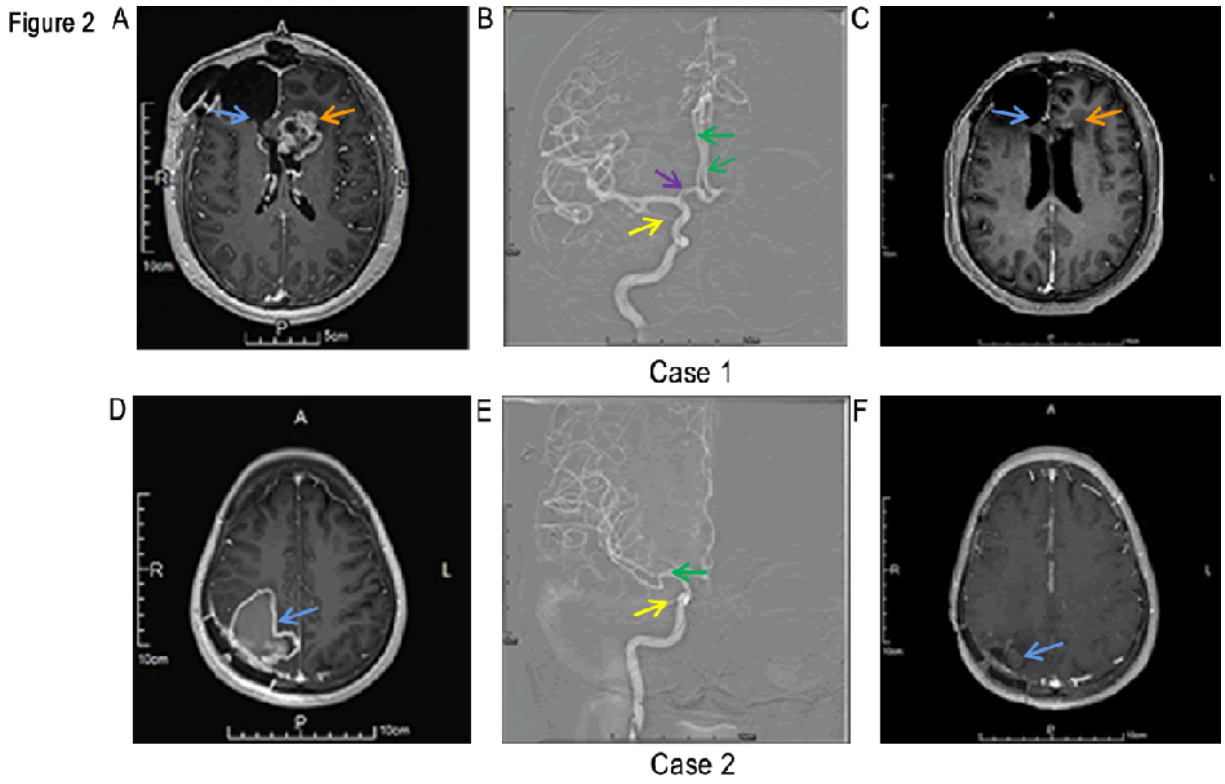

Figure 2 Course of treatment in two patients. (A) MRI image of the recurrent tumor before chemotherapy; blue represents the primary tumor area and orange represents the recurrent tumor area. (B) Catheter was superselected to the A1 segment of the anterior cerebral artery (ACA) for infusion of chemotherapy; yellow represents the ophthalmic artery, purple represents the A1 segment of the ACA, and green represents the A2 segment of the ACA. (C) MRI image of recurrent tumor after infusion of chemotherapy; blue represents the primary tumor area and orange represents the recurrent tumor volume reduction. (D) MRI image of the tumor before infusion of chemotherapy; blue represents the primary tumor area. (E) The microcatheter was superselected into the M1 segment of the right middle cerebral artery; yellow represents the ophthalmic artery,and green represents the M1 segment of the middle cerebral artery. (F) MRI image of the tumor after infusion of chemotherapy; blue represents the primary tumor volume reduction.

DISCUSSION

At present, surgical resection remains the main treatment for high grade gliomas. However, given the invasive growth of the tumor, completely removing the tumor by surgery is difficult, and recurrence is almost inevitable.[21] Chemotherapy drugs can block and kill residual tumor cells with different proliferation cycles after surgery.[22] However, considering the existence of the blood–brain barrier, brain glial cells are resistant to most chemotherapy drugs. Superselective arterial chemotherapy has attracted increasing attention because of its advantages of relatively low total drug dosage, high local drug concentration, and less systemic reactions and side effects.[23] Therefore, superselective IA cerebral infusion of teniposide for the treatment of glioma patients may be a safely tolerated and feasible strategy.

To date, an ideal second line treatment for glioma is lacking, and new treatment modalities are needed to improve the survival rate of patients with gilomas.[24] Teniposide is a highly sensitive drug for gliomas.[17] In previous reports, teniposide was commonly used for the treatment of gliomas by intravenous infusion. Considering the existence of the blood–brain barrier, the intravenous drug requirement is large, but the amount of drug that reaches the brain tissue is limited, thereby causing functional damage to other organs.[25] In this study, superselective intracranial arterial infusion of teniposide was used to treat primary and recurrent gliomas after opening the blood–brain barrier. No significant differences in biochemical indices or KPS score were observed before and after treatment. These results indicated that the treatment had few toxic side effects in controlling glioma progression.

The ORR and DCR were 50.0% and 83.3%, respectively. In particular, two patients achieved CR after treatment. Traditional IA chemotherapy can cause retinal damage and vision loss, which can be avoided by superselective chemotherapy.[26] Based on the cerebrovascular characteristics of different tumor sites, we performed personalized infusion of chemotherapy beyond the ophthalmic artery to avoid damage to the retina. The drug was distributed in the blood vessels around the tumor, and the drug concentration was maintained at the tumor site to achieve better therapeutic effect and reduce drug toxicity. Arterial interventional therapy avoids systemic medication, as well as reduces the frequency and total amount of medication, so improving the efficacy of drugs and reducing side effects.[27] These findings indicated that superselective arterial infusion of teniposide might be effective and safe in glioma patients.

In conclusion, this small series suggests that superselective IA cerebral infusion of teniposide may be a safe and effective therapy in the multimodal treatment of malignant gliomas and warrants further study in larger prospective investigations. However, this study had some limitations. The sample size was small, and future studies with large samples are necessary for further verification. Progression free survival and overall survival data were lacking because patients responded well and are still in follow-up. Thus prospective and multicenter studies must be

conducted in the future to further explore whether this therapy can prolong the survival of glioma patients.

Contributors HY and JR contributed to the study concept and design. YS, PL, LL, JH, and JC contributed to acquisition and analysis of the data. JR drafted the manuscript. HY revised the manuscript. All listed authors contributed to the work and approved the final manuscript.

Funding This project was supported by the Chongqing University Cancer Hospital Scientific Research Starting Foundation and the Chongqing Health Appropriate Technology Promotion Project (Grant number: 2024cyjstg006).

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study was approved by the ethics committee of Chongqing University Cancer Hospital (CZLS2021077-A). Informed consent was obtained from the enrolled patients. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary table 1. The molecular information of the tumors

Patients	Molecular detection
Patient 1	1p/19q-;TERT C228T; IDH-; BRAF V600E-; MGMT-
Patient 2	1p/19q-;TERT-;IDH-;BRAF-V600E-;MGMT-
Patient 3	TERT-;IDH-;BRAF-V600E-;MGMT-
Patient 4	1p/19q-;TERT-;IDH1 R132H;MGMT+
Patient 5	1p/19q-;TERT C228T; IDH-; BRAF V600E-; MGMT-;p53-
Patient 6	TERT C228T;IDH-;MGMT+
Patient 7	IDH1 R132H;MGMT+
Patient 8	1p/19q-;TERT C228T; IDH-; BRAF V600E-; MGMT+;EGFR+
Patient 9	Not applicable
Patient 10	Not applicable
Patient 11	Not applicable
Patient 12	Not applicable

Supplementary table 2. Tumor location, super-selective vessel, and treatment cycles of the patients

Parameters	Glioma patients (N=12)
Tumor location, No. (%)	
Callosum	1 (8.3)
Right frontal lobe	2 (16.7)
Right parietal lobe	1 (8.3)
Right frontal-parietal	1 (8.3)
Right frontal temporal parietal	1 (8.3)
Right temporo-occipital lobe	1 (8.3)
Left frontal-parietal	1 (8.3)
Left frontal lobe	2 (16.7)
Bilateral frontal lobe	1 (8.3)
Callosum	1 (8.3)
Super-selected vessel, No. (%)	
Right posterior cerebral artery	1 (8.3)
Right anterior cerebral artery	1 (8.3)
Right middle cerebral artery	3 (25.0)
Distal right internal carotid artery	3 (25.0)
Left anterior cerebral artery	1 (8.3)
Left middle cerebral artery	3 (25.0)
Cycles of infusion chemotherapy, No. (%)	
Mean±SD	3.9±1.6
2 cycles, No. (%)	3 (25.0)
3 cycles, No. (%)	3 (25.0)
4 cycles, No. (%)	1 (8.3)
5 cycles, No. (%)	2 (16.7)
6 cycles, No. (%)	3 (25.0)

Supplementary table 3. Adverse events of infusion chemotherapy

Adverse events	Glioma patients (N=12)
Nausea and vomiting, No. (%)	1 (8.3)
Back skin allergy, No. (%)	1 (8.3)
No adverse events, No. (%)	10 (83.3)