

Relief Effect of Bevacizumab on Severe Edema Induced by Re-irradiation in Brain Tumor Patients

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INTRODUCTION

Brain edema is a serious clinical event and could cause various neurological symptoms such as dizziness and headache. Drugs frequently used to relieve brain edema include steroid, dehydrant (e.g., mannitol), and diuretics. But the effects of these drugs were limited in patients with severe edema. Bevacizumab has been applied in the treatment of cerebral radiation necrosis.^[1] Case studies have reported on the application of bevacizumab in the treatment of severe brain edema.^[2] In the present study, we describe significant effects of bevacizumab on severe brain edema in patients with re-irradiation.

MATERIALS AND METHODS

All 10 patients received re-irradiation for brain tumors in the same position. The use of mannitol and hormones could not relieve the severe edema, and the quality of life was poor for these patients. Bevacizumab was administered to treat the severe edema for them. We received written informed patient consent for this procedure. The dosage of bevacizumab was given $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{time}^{-1}$. Magnetic resonance imaging (MRI) was performed before and after the use of bevacizumab.

The extent of edema was measured using the method of Williamson *et al.*^[3] Three maximum edema diameters were measured in the X, Y, and Z directions in T2-weighted MRI images. The volume was estimated using the oblate spheroid formula ($\pi/6 \times XYZ$).

Equipment: The “moon God” gamma knife manufactured by Shenzhen ET Medical Group of China was used for

stereotactic radiosurgery (SRS) of single-fraction irradiation. A CyberKnife manufactured by Accuray in America was used for fractionated stereotactic radiotherapy of 3–5 fractions irradiation. A 23EX medical linear accelerator manufactured by Varian in America was used for intensity-modulated radiotherapy and whole brain radiotherapy.

Statistics: Paired *t*-test was used to conduct the Karnofsky Performance scale (KPS) score and edema volume between before and after treatment.

RESULTS

From February 2012 to November 2012, 10 patients with severe brain edema were treated with bevacizumab. The patients' characteristics are shown in Table 1.

New tumor lesions were found in 2 patients more than 60 weeks. Severe brain edema may have been induced by both the tumor and re-irradiation in 2 patients. Dexamethasone and mannitol had been administered before bevacizumab to patients for long time. The median time of follow-up was 6.5 months (3–18 months) for the survivors. There were 4 patients died include 2 from extracranial disease progression, 1 from intracranial disease progression, and 1 from bleeding of the wound surface in nasal cavity.

Administration and the efficacy of bevacizumab

The median times of bevacizumab treated for each patient was 3 times (range: 2–4 times). The median time between the initial use of bevacizumab and the 1st day (day 1) of the re-irradiation was 8.3 weeks (0.6–61 weeks). The symptoms and physical signs improved significantly after treatment of bevacizumab. No. 1 patient died before the MRI re-examination. The KPS scoring and edema size were not

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included in the statistical analysis. MRI re-examination was carried out in the other patients after received bevacizumab. The median KPS scores before and after bevacizumab were 40 (30–60) and 70 (50–80), respectively (paired *t*-test $P = 0.0002$). Cerebral MRI indicated significant relief of edema. The median volume of the edema region on T2-weighted images before and after medication was 300.1 ml (116–382.5 ml) and 33.2 ml (7.2–321 ml), respectively (paired *t*-test $P = 0.005$). The results are shown in Table 2.

Bevacizumab significantly relieved severe edema induced by SRS using the CyberKnife to treat the recurrent disease for no. 5 patient. The CyberKnife treatment was 0.2 weeks and 19.1 weeks after the check time of the first MRI. Bevacizumab was given at 3.1 weeks, 6.5 weeks, 11 weeks, and 20.4 weeks.

The edema volume before the initial use of bevacizumab was 382.5 ml and declined significantly after treatment each times: 323.1 ml (5.1 weeks), 97.8 ml (8.7 weeks), 171.7 ml (12.7 weeks), 79.0 ml (18.6 weeks), and 22.5 ml (21.7 weeks) [Figures 1 and 2].

Major toxicity

No. 1 patient dead from bleeding of the maxillary sinus wound. The effect of bevacizumab on edema was significant for the 1st time in this patient. Bevacizumab was administered 28 days later. The drug caused sudden large bleeding from the maxillary sinus wound the next morning and the patient died from asphyxia.

Cerebral infarction: Two patient with brain metastasis presented with slight to medium cerebral infarction. No. 2 patient had Colon cancer and brain metastasis and

Table 1: Patient's characteristics

Patient number	Sex	Age (years)	Diagnosis	Primary radiotherapy dose/fraction	Re-irradiation dose/fraction	Re-irradiation site and tumor size (cm)	Radiotherapy interval (weeks)	Began bevacizumab to re-irradiation day 1 (weeks)	Dexamethasone and mannitol before bevacizumab (weeks)*
1	Male	70	Adenoid cystic carcinoma	56 Gy/25 f	25 Gy/5 f	Temporal lobe (4×2.5)	103	25.6	7.1
2	Male	54	Colon cancer	40 Gy/20 f	16 Gy/1 f	Parietal lobe (1.5×1.2) Temporal lobe (1.2×1.0) Cerebella (1.0×1.0)	6	61	10.7
3	Female	64	Esophageal cancer	40 Gy/20 f	17 Gy/1 f	Occipital lobe (3.0×2)	26	0.6	3.4
4	Female	48	Glioblastoma	63 Gy/35 f	25/5 f	Frontal lobe (5.0×3.5)	138	18.1	11.7
5	Male	30	Anaplastic astrocytoma	59.4/33 f	24/5 f	Frontal horns of lateral ventricles (5.0×3.0)	283.3	1.3	4.1
6	Male	62	Glioblastoma	60 Gy/30 f	12 Gy/3 f	Occipital lobe (3.0×1.5)	13.7	4.9	6.6
7	Male	51	Glioblastoma	60 Gy/30 f	50.4 Gy/28 f	Frontal lobe (4.5×3.0)	112	4.6	1.9
8	Male	55	SCLC brain metastases	40 Gy/20 f	16 Gy/1 f	Parietal lobe (3.0×2.0)	38.4	11.7	9.3
9	Male	60	Anaplastic astrocytoma	60 Gy/30 f	24 Gy/5 f	Occipital lobe (3.5×3.2)	25.9	65.7	12.9
10	Male	74	Glioblastoma	50.4 Gy/28 f	10 Gy/1 f	Temporal insula (4.0×3.0)	7.3	3.1	2.1

*The dose of dexamethasone was 5 mg, 1–2 times/day, and the dose of mannitol was 125 ml, 2–4 times/day. SCLC: Small cell lung cancer.

Table 2: Dosage and effects of bevacizumab and follow-up

Patient	Weight (kg)	Bevacizumab dosage (mg)	Edema volume before bevacizumab (ml)	Minimum edema volume after bevacizumab (ml) and detection time (weeks)	KPS before bevacizumab*	KPS after bevacizumab*	Bevacizumab administration time (weeks)	Follow-up (months)	State
1	82	400	188.9	–	40	–	0.1, 4	1	Dead
2	58	300	116.0	7.2 (4)	60	80	1, 3	5	Dead
3	42	200	165.3	84.8 (4)	50	70	1.6, 3.6, 6	11	Dead
4	65	300	300.1	49.9 (9.7)	40	70	0.1, 2, 9.9	18	Alive
5	75	300	382.5	22.5 (25)	30	60	3.1, 6.5, 11, 20.4	14	Dead
6	83	400	379.8	32.1 (7.1)	30	70	0.1, 2, 1	10	Alive
7	78	400	377.1	321.0 (3.9)	30	50	0.3, 3.6, 8.2	4	Alive
8	70	400	254.4	33.2 (10.1)	40	80	3.3, 5.3, 9.1, 11.7	9	Alive
9	72	400	322.5	155.5 (6.7)	20	50	2.3, 7.7	4	Alive
10	62	300	245.8	168.7 (2.9)	20	40	0.6, 3	3	Alive

*Matched for the MRI detect time before and after bevacizumab. MRI: Magnetic resonance imaging; KPS: Karnofsky performance scale.

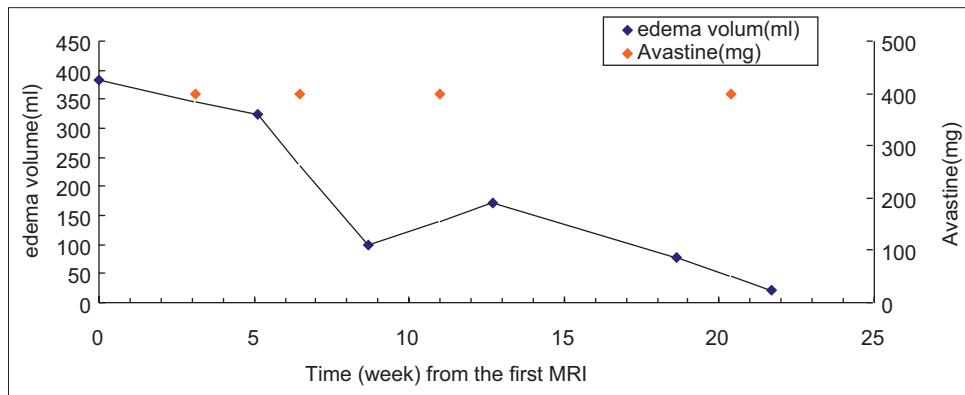


Figure 1: Edema volume and bevacizumab treatment time of no. 5 patient.

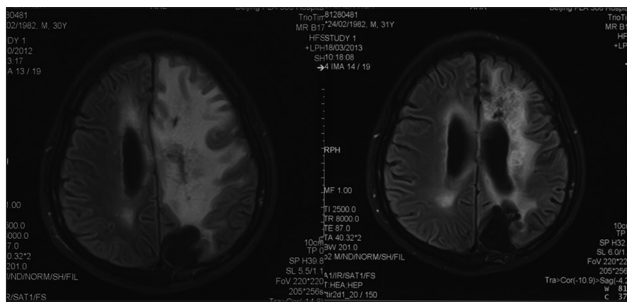


Figure 2: T2-weighted magnetic resonance imaging of no. 5 patient before bevacizumab treatment (left) and 25 weeks later (right).

received bevacizumab on July 6 and 20, 2012. A region of cerebral infarction measuring 2 cm × 4 cm appeared at the internal capsule on the left on July 29, 2012. Muscular strength of the right limb declined to Level 3 and then recovered to Level 4 1 month later. No. 3 patient received bevacizumab on July 6 and 30, 2012. On October 14, 2012, the patient lost consciousness and in a coma for 3 days. The brain MRI indicated a region of cerebral infarction measuring 3 cm × 3 cm in the right temporal lobe. After 1-week of symptomatic treatment, the patient recovered completely.

Hypertension and hyperthermia. No. 7 patient received bevacizumab 10 times for treating gliomas before re-irradiation. After each time, he experienced low fever with a maximum temperature of 37.5°C. The symptoms disappeared spontaneously after 3 days each time. The patient had no history of hypertension and did not develop hypertension during the treatment. After re-irradiation, bevacizumab was administered once more for severe edema and caused blood pressure increasing to 150–160 mmHg/100–110 mmHg. Blood pressure decreased spontaneously to 115 mmHg/85 mmHg 4 weeks later without using antihypertensive agents. Bevacizumab treated for edema again 4.6 weeks later, and blood pressure did not increase.

DISCUSSION

Wang *et al.*^[1] reported the significant efficacy of bevacizumab in the treatment of cerebral necrosis. The KPS of patients

improved, and the dosage of steroid was decreased, possibly because of the relieving effect of bevacizumab on brain edema. Williams *et al.*^[2] reported that bevacizumab had significant efficacy for treating brain edema after SRS in 1 patient. Our study included 10 patients who suffered severe brain edema after re-irradiation without the effect of steroid and mannitol. The treatment of bevacizumab quickly relieved the patients' symptoms, and improvements of the living status were significant on the 2nd day in our study. The treatment of bevacizumab allowed us to reduce the dosage of hormone and mannitol for patients with severe brain edema^[4] and improve their life quality.

For no. 1 patient, the efficacy lasted for 3 weeks after the first treatment of bevacizumab until the symptoms worsened. No. 4 patient received 2 times treatment of bevacizumab within 4 weeks, and the effect kept for 3–4 months until the neurological symptoms associated with cerebral edema began to worsen. For no. 5 patient, bevacizumab was given 4 times in 25 weeks, and the brain edema became very slight for a long time. The dose of bevacizumab in this paper was about 5 mg/kg with a relatively long interval.

The severe brain edema of 2/10 patients in our study may be caused by tumor and irradiation. Bevacizumab may have had an effect on both factors. Re-irradiation to the same site is the higher risk factor than irradiation for the 1st time that induced severe brain edema. Other factors that induced severe brain edema include irradiation dose, tumor size, tumor site and individual difference, etc. Anyway, bevacizumab could relieve the brain edema significantly in sorts of patients.

Toxicity

Authors reported that bevacizumab could cause various degrees of bleeding. Yoshida *et al.*^[5] reported the use of bevacizumab combined with chemotherapy treating 26 patients with unresectable or metastatic colorectal cancer 1 of whom experienced grade 3 cerebral hemorrhage. Nagane *et al.*^[6] reported bevacizumab treating 31 cases of recurrent malignant gliomas and only 1 case of asymptomatic cerebral hemorrhage with unnecessary treatment. In our study, 1 patient with adenoid cystic carcinoma of the sinus experienced fatal hemorrhage from the wound of nasal cavity after the administration of bevacizumab 2nd times indicating

that bevacizumab should be used with caution in all patients and banned for patient with wound.

There is a clear correlation between cerebral infarction and bevacizumab although the conclusion is based on individual cases.^[7] However, the large-sample-based data analyses by Campbell *et al.*^[8,9] indicated that the incidence of ischemic stroke was not significantly different between the bevacizumab treating group and control group. Fraum *et al.*^[10] analyzed 8 cases of ischemic stroke and concluded that the possible risk factors include hypertension, deep vein thrombosis, pulmonary embolism, arrhythmia, and dyslipidemia. In our study, no. 2 patient was diagnosed with diabetes while no. 3 patient without.

Other toxicity of bevacizumab

A meta-analysis by Amit *et al.*^[11] reported that the adverse reactions associated with bevacizumab also included proteinuria (risk ratio [RR] 7.08, $P < 0.00001$) and hypertension (RR 4.96, $P < 0.00001$). One patient in our study experienced hypertension, and none developed proteinuria.

In summary, the treatment of bevacizumab is effective on severe brain edema induced by re-irradiation. Bevacizumab is safe for patients whom without wounds. Our research suggests a new clinical indication of bevacizumab as treating for severe brain edema should be taken into account.

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