Clinical Case Report

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Efficacy and safety of bevacizumab treatment for refractory brain edema

Case report

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Abstract

Objective: This retrospective study investigated the efficacy and safety of bevacizumab treatment for refractory brain edema.

Methods: Between March 2009 and December 2015, bevacizumab was used to treat 59 cases of brain metastatic patients with refractory brain edema. The median dose of bevacizumab was 4.68 mg/kg (range 2.8–6.52 mg/kg). The clinical-pathological data, the efficacy, and the side effects of bevacizumab were recorded. Magnetic resonance imaging (MRI) was performed before and after bevacizumab treatment. Tumor and edema volumes were measured separately.

Results: The clinical symptoms of 50 out of 59 cases (84.74%) improved the day after the bevacizumab treatment, and the edema volumes of 55 (93.22%) cases were reduced after the bevacizumab treatment. The average edema volume was significantly reduced after bevacizumab treatment from 125,583.43 ± 14,093.27 to 71,613.42 ± 9473.42 mm^3 (Mann–Whitney rank test, $P < .01$), and the average edema index was significantly reduced from 25.66 ± 11.54 to 17.87 ± 6.87 (Mann–Whitney rank test, $P < .01$). One patient died from a hemorrhage due to a cancerous-ulcer of the maxillary sinus. The main complication observed was hypertension, which was observed in 11 cases (18.6%).

Conclusion: The effective rate of bevacizumab for refractory brain edema is 84.74%. Hypertension was the main side effect of the bevacizumab treatment. Bevacizumab is an effective and relatively safe treatment for brain edema.

Abbreviations: EI = edema index, IMRT = intensity-modulated radiation therapy, MRI = magnetic resonance imaging, PTBE = peritumoral brain edema, SBRT = stereotactic body radiation, VEGF-A = vascular endothelial growth factor A, WBRT = whole brain radiotherapy.

Keywords: bevacizumab, brain edema, brain metastasis

1. Introduction

Primary or metastatic brain tumors are often surrounded by extensive peri-tumoral brain edema (PTBE),[1] which could cause neurological symptoms, including dizziness and headache. Several medications such as mannitol, steroids, and diuretics, were frequently used to relieve brain edema. However, the effects of these drugs were limited in some patients with refractory edema. Vascular endothelial growth factor A (VEGF-A) promotes angiogenesis and vascular permeability. Therefore, it has been suggested that it plays an important role in cerebral edema associated with brain tumor. Recently, case studies or clinical trials[2–11] have shown that bevacizumab, a monoclonal antibody against VEGF-A, provides an effective treatment for brain edema.

Nevertheless, the pharmacokinetics and pharmacodynamics of bevacizumab was not fully understood and a dose–effect relationship has not yet been proven in vivo. Further improvement in therapeutic efficacy while minimizing side effects is needed, possibly by adjusting the dosage and timing of treatment.[12]

In the present study, we demonstrated significant effects of bevacizumab on refractory brain edema in 59 cases of brain metastases, and the safety of bevacizumab treatment was also evaluated.

2. Materials and methods

2.1. Patients

We collected the clinical data of 333 patients who were hospitalized between March 1, 2009, and December 1, 2015, and received bevacizumab treatment at the Affiliated Hospital of Academy of Military Medical Sciences in Beijing, China. The inclusion criteria included peritumoral brain edema was

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confirmed by magnetic resonance imaging (MRI) examination; the clinical symptoms were not relieved after more than 3 days of mannitol or glucocorticoid treatment; the purpose of bevacizumab treatment was to alleviate PTBE; and the clinical and pathological data were complete. Exclusion criteria were brain tumor size was below 3 mm; patients with complications related to other malignancies; and patients with complications related to cerebral infarction, epilepsy, cerebral hemorrhage, or other intracranial diseases. The academic and ethics committees of our hospital approved this study. All patients were provided written informed consent before the treatment of bevacizumab.

2.2. Measurement of tumor volume and peritumoral edema

A MRI was performed before and after bevacizumab treatment. Tumor volume and peritumoral edema volume were measured using the method described previously by Bitzer et al.[6] Tumor volumes were measured on postcontrast T1-weighted images, and edema volume was calculated according to the FLAIR and T2-weighted TSE sequence images.

The tumor and edema volume is assumed to be an elliptical sphere, per the spheroid volume formula: $V = \pi/6 \times abc$ computing volume, a, b, c are the largest perpendicular diameters of three directions. The "Edema index (EI)" was calculated per the equation of "edema index = (peri-tumoral edema volume+ tumor volume)/tumor volume."

2.3. Statistical analyses

The comparisons of brain edema volume, KPS score, and EI between pre-and post-treatment were performed using the Mann–Whitney rank test. An arbitrary level of 5% was used to indicate statistical significance. Our clinical data was analyzed using SPSS version 20.0 statistical software.

2.4. Results: patients' clinical and pathological characteristics

Fifty-nine patients with refractory PTBE satisfied the inclusion and exclusion criteria and were included in the study. Table 1 summarizes the clinicopathological characteristics of all the included patients. Twenty-four of them were male and 35 were female, with a median age of 52 years (range, 22–74 years). For majority of cases, the primary sites of tumor were glioma (n = 21), lung (n = 19), and breast (n = 14). Fifteen out of the fifty-nine patients (25.4%) received concurrent brain radiotherapy.

2.5. Bevacizumab administration

The treatment regimen of bevacizumab was adjusted depending on the neurological symptoms of patients, such as dizziness, fatigue, and headache. The median dose of bevacizumab was 4.68 mg/kg (range of 2.8–6.52 mg/kg). The median times of the bevacizumab treatment was 1 (range 1–4 times), with intervals of 2 to 12 weeks between treatments. The MRI examinations were conducted within 2 weeks before and 2 months after the bevacizumab treatment. Fifteen patients accepted brain tumor radiotherapy during the MRI tests. Eight patients received whole brain radiotherapy (WBRT), 4 patients received intensity-modulated radiation therapy (IMRT), and 3 underwent stereotactic body radiation (SBRT).

Table 1

Patients' clinicopathological characteristics.

Characteristic	n/N (%)
Age, y	
<50	24/59 (40.7%)
≥50	35/59 (59.3%)
Gender	
Male	24/59 (40.7%)
Female	35/59 (59.3%)
Primary tumor	
Glioma	21/59 (35.6%)
Lung cancer	19/59 (32.2%)
Breast cancer	14/59 (23.7%)
Cervical cancer	1/59 (1.7%)
Esophageal cancer	1/59 (1.7%)
Colon cancer	1/59 (1.7%)
Ampulla vater cancer	1/59 (1.7%)
Maxillary sinus cystadenocarcinoma	1/59 (1.7%)
Brain surgery history	
Yes	21/59 (35.6%)
No	38/59 (64.4%)
Brain radiotherapy history	
Yes	22/59 (37.3%)
No	37/59 (62.7%)
Pre-existing hypertension	
Yes	1/59 (1.7%)
No	58/59 (98.3%)
Concurrent brain radiotherapy	
Yes	15/59 (25.4%)
No	44/59 (74.6%)

2.6. Efficacy of bevacizumab

The clinical symptoms of 84.74% cases (50 out of 59) were significantly improved after the treatment of bevacizumab. PTBE, as determined by brain MRI, was significantly reduced with the average PTBE volume decreased from $125{,}583.43 \pm 14{,}093.27$ to $71{,}613.42 \pm 9473.42\,mm^3$ ($P < .01$) by bevacizumab treatment. Consistently, the average EI was significantly reduced from 25.66 ± 11.54 to 17.87 ± 6.87 by the treatment ($P < .01$) (Table 2, Fig. 1A, B).

Furthermore, in the group of 44 cases without radiation, the PTBE volume was significantly reduced from $135{,}810.77 \pm 16{,}643.51$ to $74{,}432.61 \pm 10{,}028.59\,mm^3$ by bevacizumab treatment ($P < 0.01$). Also, the EI was significantly reduced from 15.24 ± 2.81 to 13.05 ± 3.58 ($P < .01$) by the treatment (Table 2, Fig. 2A, B).

2.7. Adverse effects of bevacizumab

Hypertension was observed in 18.6% of cases (11 out of 59). The hypertension was successfully treated in all the cases using antihypertensives. One patient died from asphyxia after bleeding of the maxillary sinus wound. No other complication was observed.

3. Discussion

In this retrospective clinical study, we focused on the efficacy and adverse effects of bevacizumab treatment on refractory PTBE in 59 cases. This is the most comprehensive study with a relatively large population in this area. It may have significant clinical

Table 2

Refractory brain edema volume and edema index of pre-treatment and post-treatment of bevacizumab.

	Pre-treatment (x ± s)	Post-treatment (x ± s)	P
All (n = 59)			
Edema index	25.66 ± 11.54	17.87 ± 6.87	<.01
PTBE volume, mm^3	125,583.4 ± 14,093.3	71,613.42 ± 9473.42	<.01
Without radiotherapy (n = 44)			
Edema index	15.24 ± 2.81	13.05 ± 3.58	<.01
PTBE volume, mm^3	135,810.7 ± 16,643.51	74,432.61 ± 10,028.59	<.01
With radiotherapy (n = 15)			
Edema index	15.51 ± 7.10	9.02 ± 4.40	<.01
PTBE volume, mm^3	96,265.06 ± 25,725.07	63,533.66 ± 23,273.13	<.01

PTBE = peritumoral brain edema.

implications in salvage therapy and management for these patients.

A number of previous case studies with small sample sizes have shown that bevacizumab is effective for brain edema by blocking the binding of VEGF-A to its receptors.[7–10] Wang et al[11] reported that in 8 patients with brain metastasis and severe brain edema, using a combination therapy of bevacizumab and stereotactic radiosurgery (Cyberknife) decreased the edema area by 63.4% in MRI T2 images. Recently, our case series study of 10 patients showed that bevacizumab therapy effectively relieved serious brain edema associated with reirradiation in patients.[13] It was demonstrated that bevacizumab therapy benefited non-small-cell lung cancer patients with brain metastases symptomatically by consistently decreasing PTBE.[14] Our present study included 59 patients and showed bevacizumab therapy was effective with a response rate reaching 84.74%.

Bevacizumab could have a relatively large therapeutic window. Free serum VEGF concentrations were undetectable at bevacizumab administration for doses ≥0.3 mg/kg.[15] However, it was reported that a very low dose (0.125 mg/kg) of bevacizumab treatment was an effective method of controlling medically refractory epistaxis in patients with hereditary hemorrhagic telangiectasia.[16] Therefore, perhaps there is a wide window for choosing the dosage of bevacizumab for different treatments as needed. In this study, headache symptoms were alleviated significantly following the day of therapy with a dose of 2.8 mg/kg.

Bevacizumab therapy has a low risk for cerebral hemorrhage. In a study of patients with brain metastases, it was reported that the rate of cerebral hemorrhage was 0.8% to 3.3% in bevacizumab arms and 1.0% in non-bevacizumab arms. Khasraw et al[17] also reported that the cerebral hemorrhage rates of patients with glioma and brain metastases had little difference between bevacizumab and non-bevacizumab groups. In the current study, only 1 patient died of cerebral hemorrhage after bevacizumab therapy. Hypertension was observed in another 11 patients. A previous study has shown that patients with pre-existing hypertension, age, and BMI have a higher risk for serious anti-VEGF therapy-induced blood pressure elevation.[18] No other complications were found in this study.

There are some limitations to this study. First, the volume and index of edema may be affected by radiotherapy. However, the symptoms were significantly alleviated due to bevacizumab therapy before radiotherapy and could reflect the therapeutic effect of bevacizumab on PTBE. Second, further studies should be performed on the dosage of bevacizumab and the timing for the

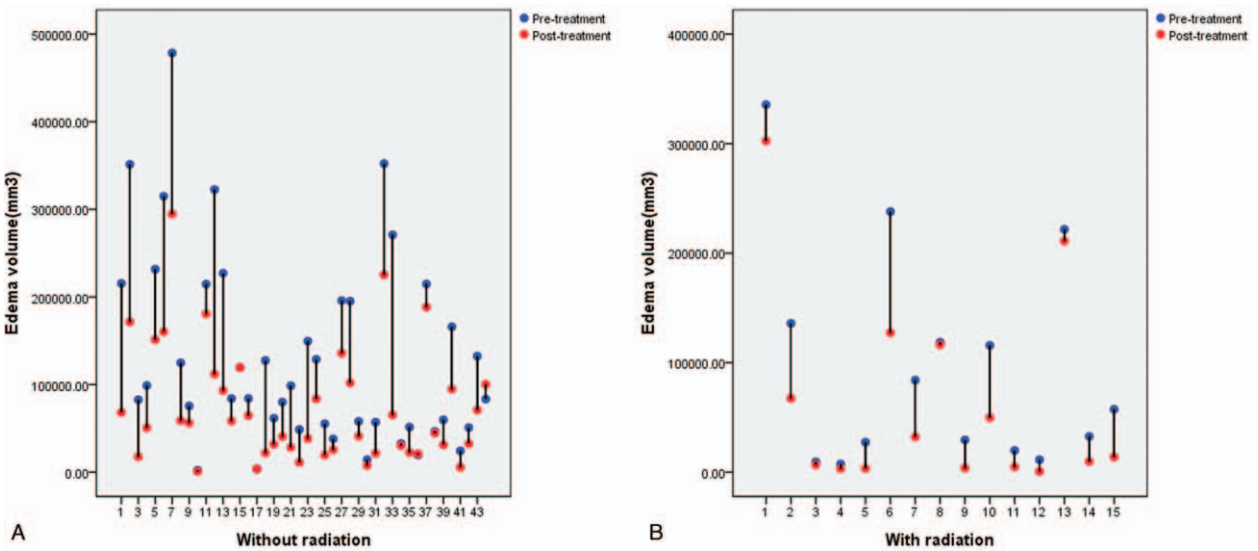

Figure 1. (A) Peri-tumoral brain edema volume of pre-treatment and post-treatment of bevacizumab without radiotherapy; (B) Peri-tumoral brain edema volume of pre-treatment and post-treatment of bevacizumab with radiotherapy.

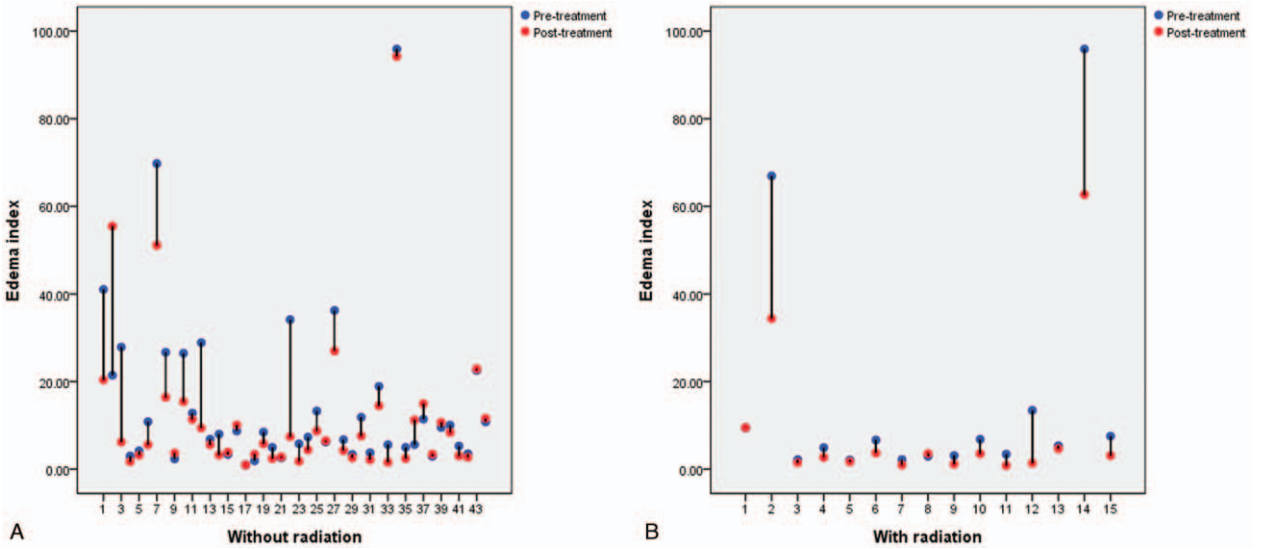

Figure 2. (A) Edema index of pre-treatment and post-treatment of bevacizumab without radiotherapy; (B) Edema index of pre-treatment and post-treatment of bevacizumab with radiotherapy.

combination of bevacizumab and radiotherapy. Also, further studies should be performed on individual differences of treatment for tumor edema with bevacizumab.

4. Conclusion

The present study focused on the therapeutic and adverse effects of bevacizumab in patients with severe brain edema in a large population. The patients responded very well to bevacizumab for refractory peritumoral edema (84.74%). Hypertension is a major adverse reaction of the bevacizumab treatment. Thus, bevacizumab is an effective treatment for cerebral edema that is relatively safe in brain tumor patients.

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