Original Article

Efficacy and safety of bevacizumab combined with chemotherapy in symptomatic brain metastases from lung adenocarcinoma: a retrospective analysis

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Background: Currently, the treatment of symptomatic brain metastases from lung adenocarcinoma has remained difficult. Bevacizumab combined with chemotherapy is one of the standard treatments of lung adenocarcinoma. This study was designed to investigate the efficacy and safety of bevacizumab combined with chemotherapy in symptomatic brain metastases from lung adenocarcinoma that are not suitable for local treatments, and to explore the predictive value of baseline serum vascular endothelial growth factor (VEGF) for the treatment.

Methods: We retrospectively reviewed 14 consecutive patients, between Jan 2015 and Jul 2017, with brain metastases from lung adenocarcinoma who received bevacizumab and chemotherapy to determine efficacy and toxicity. Kaplan-Meier method was used to estimate survival curves, and univariate and multivariate analyses were performed by Cox proportional hazard model. The primary endpoints were objective response rate (ORR) and intracranial ORR (iORR). The secondary endpoints were progression-free survival (PFS), intracranial PFS (iPFS), overall survival (OS) and disease control rate (DCR).

Results: The efficacy of 12 patient was evaluated. Overall ORR was 25% (3/12) and the iORR of brain lesions was 33.3% (4/12). DCR was 75% (9/12). The median OS was 18.3 months, the median PFS was 6.7 months, and the median iPFS was 12 months. After 2 cycles of bevacizumab, 10 patients showed improved symptoms of central nervous system (CNS), and the symptom control rate was 83.3% (10/12). Head MRI showed that edema in the brain was greatly reduced in 6 patients, resulting in the lessened usage of dexamethasone. iPFS was significantly shorter in high VEGF group (3.6 *vs.* 8.0 m, P=0.02), and multivariate analysis showed a significant correlation between iPFS and serum baseline VEGF level (P=0.023). The most commonly adverse events of bevacizumab included leukopenia [5 (35.7%)], fatigue [3 (21.4%)], thrombocytopenia [3 (21.4%)], anemia [2 (14.3%)], which were mostly degree I and II.

Conclusions: This study showed bevacizumab combined with chemotherapy could effectively control intracranial lesions, relieve symptoms, and improve the quality of life and survival of patients with brain metastases from lung adenocarcinoma. Serum baseline VEGF may be a predictor of efficacy of bevacizumab plus chemotherapy in the treatment of brain metastases from lung adenocarcinoma.

Keywords: Symptomatic brain metastases; lung adenocarcinoma; bevacizumab plus chemotherapy; vascular endothelial growth factor (VEGF)

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Introduction

The brain is one of the most common metastatic sites of non-small cell lung cancer (NSCLC), occurring about 50% of lung adenocarcinoma during the course of the disease. NSCLC patients with brain metastases, which are one of the major causes of treatment failure or even deaths, have a poor prognosis with a median overall survival (OS) of approximately 1–2 months (1,2). The usage of tyrosine kinase inhibitor (TKI), such as gefitinib, osimertinib, crizotinib and ceritinib, has improved the intracranial response rate and survival of driver-gene-mutant patients with brain metastases from lung adenocarcinoma (3). However, for patients without driver mutations or that resistant to TKI, especially with symptoms of central nervous system (CNS), there are no more effective treatment beside chemotherapy or radiotherapy, which efficacy remains dissatisfactory.

Bevacizumab is a recombinant humanized monoclonal lgG1 antibody, which has anti-tumor activity by inhibiting vascular endothelial growth factor (VEGF). Bevacizumab combination with chemotherapy could significantly improve survival of nonsquamous NSCLC, so the combination therapy was approved for the treatment of NSCLC as the first-line treatment (4-6). Bevacizumab provides a new choice for treatment of NSCLC patients with brain metastases (7-9). A phase II clinical trial assessing bevacizumab in nonsquamous NSCLC with asymptomatic brain metastases showed a median progression-free survival (mPFS) of 6.7 months and a median overall survival (mOS) of 16.0 months (10). Bennouna *et al.* (11) reported that nonsquamous NSCLC with or without brain metastases treated by bevacizumab combination with chemotherapy had similar mPFS (6.5 *vs.* 6.9 months, P=0.54) and mOS (14.5 *vs.* 12.5 months, P=0.33).

Patients with brain metastases were excluded in the early phase clinical trials of bevacizumab. Although several recent retrospective studies and small clinical trials included patients with brain metastases, most of subjects were asymptomatic (8-11). Nevertheless, the NSCLC patients with symptomatic brain metastases are more common in the real world. Neurosurgical resection, intracranial stereotactic radiosurgery (SRS), and whole brain irradiation (WBRT) are main treatment options for patients with symptomatic brain metastases, whereas for patients who are ineligible to receive surgery or refuse local therapy because of radiation-induced neurotoxicity, drug therapy plays a key role in disease control and symptom improvement. Cerebral edema could be controlled by corticosteroids, but long-term use of corticosteroids may result in serious adverse events such as Cushing syndrome and reduced quality of life. Previous clinical studies demonstrated that bevacizumab-based treatment could effectively improve symptoms of patients with glioblastoma, allowing lessened usage of corticosteroids (12,13). Furthermore, a case reports showed that bevacizumab led to alleviation of cerebral edema and reduced dosage of corticosteroids in brain-metastatic breast cancer (14).

We conducted the retrospective study to investigate the efficacy and safety of bevacizumab combined with chemotherapy in symptomatic brain metastases from lung adenocarcinoma, and to explore the predictive value of baseline serum VEGF for the treatment.

Methods

Patient characteristics

In this retrospective study, we enrolled consecutive patients with symptomatic brain metastases from lung adenocarcinoma at Department of Oncology, Huashan Hospital (Shanghai, China), from January 2015 to July 2017. We included patients aged at least 18 years; a histologically confirmed diagnosis of lung adenocarcinoma; brain metastases or leptomeningeal metastases confirmed by CT or MRI, and/or histologically confirmed diagnosis of brain metastases or cerebrospinal fluid (CSF) cytology positive; no EGFR-sensitizing mutation or ALK translocations, or progression after an appropriate TKI for those with a sensitizing EGFR mutation or ALK gene rearrangement; with symptoms of CNS, but without brain metastases crisis (15); ineligible for or refuse of local therapy (surgery or radiation) for intracranial lesion, or interval time between end of brain irradiation and beginning of the treatment with bevacizumab >3 months; clinical indication for chemotherapy, including normal peripheral hemogram, no abnormalities of heart, liver and kidney function, normal electrocardiograph, no severe hypertension (blood pressure <150/100 mmHg) or hemorrhagic disease; no albuminuria (>2 g/24 h); and no unhealed wound. All study participants provided informed written consent. The protocol was approved by the Institutional Review Board Committee of Huashan hospital, Shanghai, China (No. KY2017-010). Participants were followed up every month and the last date of follow-up was June 30, 2018.

Treatment

Participants received bevacizumab 7.5 mg/kg intravenously every 3 weeks. Double platinum chemotherapy was given to those with ECOG performance status of 0 or 1. The chemotherapy agent for the patient with PS of 3 was pemetrexed. The two of patients with PS of 2 received pemetrexed plus cisplatin, and the other three received docetaxel and pemetrexed, respectively. The third generation chemotherapy agents which were previously effective or unused were chosen as the chemotherapy program. Chemotherapy agents were administered as follow: paclitaxel 135 mg/m², intravenously; pemetrexed 500 mg/m², intravenously; docetaxel 75 mg/m², intravenously; cisplatin, 75 mg/m², intravenously.

Assessments

Chest and abdomen CT and head MRI were performed every 6 weeks. The response to treatment was assessed according to RECIST (version 1.1) (16), including complete remission (CR), partial remission (PR), stable disease (SD) and progression disease (PD). Intracranial lesion was assessed according to RANO-BM (Response Assessment in Neuro-Oncology Brain Metastases) (17,18), consisting of intracranial CR (iCR), intracranial PR (iPR), intracranial SD (iSD), and intracranial PD (iPD). PFS was defined as time between beginning of bevacizumab treatment and disease progression or death. Intracranial PFS (iPFS) was defined as time between beginning of bevacizumab treatment and intracranial disease progression or death. OS was defined as time between beginning of bevacizumab treatment and death or last follow-up. All adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (19).

The primary endpoints were objective response rate (ORR) and intracranial ORR (iORR). The secondary endpoints were PFS, iPFS, OS and disease control rate (DCR).

Detection of baseline serum VEGF

Peripheral blood (5 mL) was collected from every participant before bevacizumab treatment. Blood samples were centrifuged at 4,000 r/min for 10 min, and the serum samples were stored at –20 ℃. The level of VEGF was evaluated using the enzyme-linked immunosorbent assay (ELISA) (human VEGF ELISA Kit, BioVision) and detected utilizing fully automated electrochemiluminescence (Elecsys 2010, Roche).

Statistical analysis

All statistical analyses were conducted using Statistical Package for the Social Sciences for Windows, software version 18.0 (IBM Inc., Armonk, NY, USA). Continuous data are presented as the mean ± standard deviation. PFS and OS curves were analyzed using the Kaplan-Meier method, with P value determined by a log-rank test. Hazard ratios (HRs) and 95.0% confidence intervals (CIs) were calculated. Univariate and multivariate analyses were performed by Cox proportional hazard model. In multivariate analyses, the clinicopathological characteristics with $P<0.1$ in univariate analysis were included to identify independent prognostic factors. A two-sided $P<0.05$ was considered statistically significant.

Results

Patients characteristics

From January 2015 to July 2017, a total of 14 patients with symptomatic brain metastases from lung adenocarcinoma were enrolled. Detailed clinicopathological data the cohort is shown in *Table 1* and *Table S1*. In brief, 7 patients (50%) had metastasis lesion besides brain, and 50% patients with drive genes mutation (EGFR or ALK), who received fist-line treatment with EGFR-TKI or ALK-TKI, such as erlotinib, gefitinib, osimertinib, ecotinib, or crizotinib. Eleven patients (78.6%) received pemetrexed plus cisplatin or paclitaxel plus cisplatin as chemotherapy program. The median courses of bevacizumab treatment cycles was 2.5 (range, 1–15).

Efficacy

Up to the last follow-up, all participants received a total of 102 cycles of bevacizumab treatment, and the median number of bevacizumab treatment cycles was 6 (range, 1–19). A proportion of 35.7% patients (5/14) received more than 10 cycles of bevacizumab, and two patients were still receiving bevacizumab at the time of data cutoff. Two patients received only one dose of bevacizumab because of adverse events or economic problems, which were excluded from efficacy analysis.

At the time of analysis, all of 12 patients had discontinued

Table 1 Clinical characteristics

Clinical characters	No. of patients (n=14)
Median age, years [range]	60.5 [42–71]
Sex	
Male	10
Female	4
ECOG PS	
1	8
2	5
3	1
Metastases outside the CNS	
Yes	7
No	7
Driver-oncogene status	
EGFR	7
ALK fusion	1
None	6
Chemotherapy	
Pemetrexed plus cisplatin	8
Paclitaxel plus cisplatin	3
Pemetrexed	1
Docetaxel	2
Baseline VEGF	
High VEGF group	6
Control group	6
N/A	2

VEGF, vascular endothelial growth factor; CNS, central nervous system; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

treatment (*Figure 1*). Assessments of best response according to RECIST 1.1 were PR in 3 patients, SD in 6 patients, and PD in 3 patients (*Table 2*). ORR was 25% (3/12) and DCR was 75% (9/12). Assessments of intracranial lesion according to RANO-BM were iPR in 4 patients, iSD in 5 patients and iPD in 3 patients. iORR of brain lesions was 33.3% (4/12) and iDCR was 75% (9/12). The median OS was 18.3 months (95% CI, 14.1–22.4 m), the median PFS was 6.7 months (95% CI, 4.5–11.65 m), and the median iPFS was 12 months (95% CI, 6.6–16.3 m, *Figure 2*).

Before treatment of bevacizumab combined with chemotherapy, the main symptoms of CNS included limb headache (41.7%), weakness (33.3%), dizziness (25.0%) and dysphasia (16.7%), and four patients needed mannitol ± dexamethasone to control these symptoms. After two cycles of bevacizumab treatment, improved symptoms of CNS were observed in ten patients (*Table 2*), resulting in a symptom control rate of 83.3% (10/12). The median time to improve the CNS symptoms from beginning of bevacizumab treatment was 270 days (range, 30–570 days). Head MRI showed that edema in the brain was greatly reduced in 6 patients, resulting in the lessened usage of dexamethasone (*Figure 3*).

Adverse events

Adverse events were assessed in all of 14 patients (*Table 3*). Most treatment-related adverse events were grade 1 or 2, including leukopenia [5 (35.7%)], fatigue [3 (21.4%)], thrombocytopenia [3 (21.4%)], anemia [2 (14.3%)], etc. Grade 3 leukopenia occurred in 2 patients (14.3%), who recovered following treatment with granulocyte-colony stimulating factor (G-CSF). One patient (7.1%) had grade 1 hypertension and blood pressure returned to normal after treatment with nifedipine sustained-release tablets. One patient, who had albuminuria (<2 g/24 h) before treatment, discontinued bevacizumab treatment because of increasing albuminuria (>2 g/24 h) after one cycle of bevacizumab. No grade 4 or 5 occurred. No hemoptysis, intracerebral hemorrhage or thrombotic diseases occurred in the patients.

The baseline serum VGFR and the efficacy of bevacizumab combined with chemotherapy

In efficacy analysis set of 12 patients, the median level of baseline serum VEGF was 61.3 pg/mL (3.2–281.9 pg/mL). We defined the patients with higher VEGF than the median level of VEGF as high VEGF group, and the other patients as control group. Survival curve showed that iPFS was significantly shorter in high VEGF group (3.6 *vs.* 8.0 m, P=0.02, *Figure 4*). Compared with control group, high VEGF was also associated with shorter PFS (5.8 *vs.* 12.1 m) and OS (12.8 *vs.* 18.4 m), but neither had significantly difference (P=0.4 and 0.08, respectively, *Figure 4*).

Univariate analyses showed that age, ECOG performance status, and baseline VEGF were associated with iPFS (P=0.005, *Table 4*). In multivariate logistic

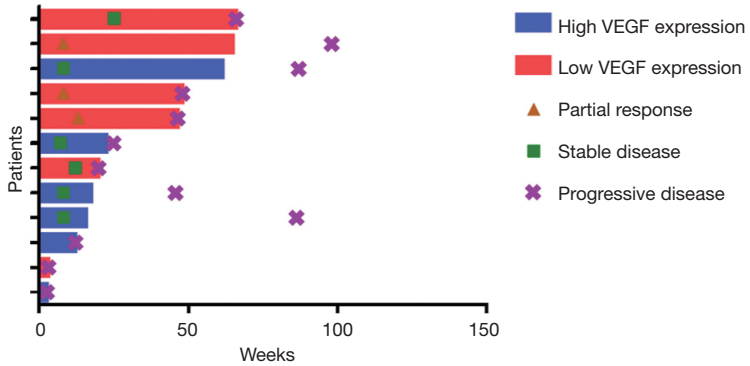

Figure 1 Treatment exposure and response duration. The length of each bar represents the treatment exposure of bevacizumab.

Table 2 Efficacy of bevacizumab

Response evaluation (n=12)	No. (% or 95% CI)
Response according to RECIST v1.1	
PR	3 (25.0)
SD	6 (50.0)
PD	3 (25.0)
Intracranial response	
iPR	4 (33.3)
iSD	5 (41.7)
iPD	3 (25.0)
Symptom of CNS	
Improved	10
No change	1
Increased	1
PFS (m)	6.7 (4.5–11.65)
iPFS (m)	12 (6.6–16.3)
OS (m)	18.3 (14.1–22.4)

CI, confidence interval; CNS, central nervous system; m, months; PR, partial response; SD, stable disease; PD, progression disease; PFS, progression-free survival; iPR, intracranial partial response; iSD, intracranial stable disease; iPD, intracranial progression disease; iPFS, intracranial progression-free survival; OS, overall survival.

regression including age, ECOG performance status, and baseline VEGF, the association between baseline VEGF and iPFS remained significant (P=0.023, *Table 5*). These results indicated that baseline serum VEGF could serve as a promising biomarker to predict the efficacy of bevacizumab combined with chemotherapy in symptomatic brain metastases from lung adenocarcinoma.

Discussion

As an antiangiogenic agent, bevacizumab could make blood vessel normal, enhance vascular permeability and improve tumor microenvironment (20,21). Fischer *et al.* (22) observed that microvascular density in tumors was decreased and vascular morphology was normalized after bevacizumab treatment. A preclinical study demonstrated that inhibiting VEGF could prevent brain metastases in mouse model (23). A retrospective analysis showed bevacizumab combining with chemotherapy significantly reduced the incidence of brain metastasis from lung compared with chemotherapy alone (14% *vs.* 31%, P<0.05) (24). On the other side, peritumoral edema often happens when incomplete vascular endothelium and increased vascular permeability cause fluid and serum protein to leak into nearby tissues. Increasing VEGF expression is associated with peritumoral edema, so anti-VEGF therapy could effectively control peritumoral edema and improve symptoms of CNS (25-27).

Unlike other studies, we enrolled the patients with symptomatic brain metastases, including some patients with worse ECOG performance status (≥2, 42.9%). Compared with previous studies of asymptomatic brain metastases, we observed similar OS and PFS. What's more, intracranial efficacy was remarkable, including high iORR and iDCR (33.3% and 75%, respectively). More than 90% patients obtained improved symptoms of CNS, resulting in lessened usage of dexamethasone and improved quality of life. Our results suggest that bevacizumab combination with chemotherapy could offer a choice to the patients with

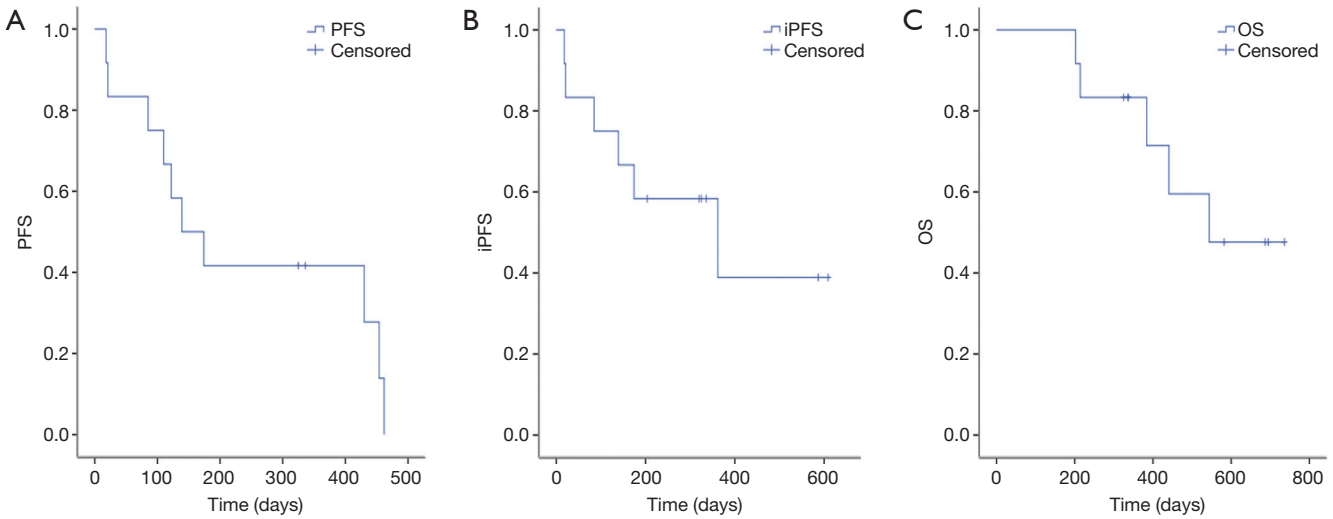

Figure 2 Kaplan-Meier estimates of progression-free survival (A), intracranial progression-free survival (B) and overall survival (C).

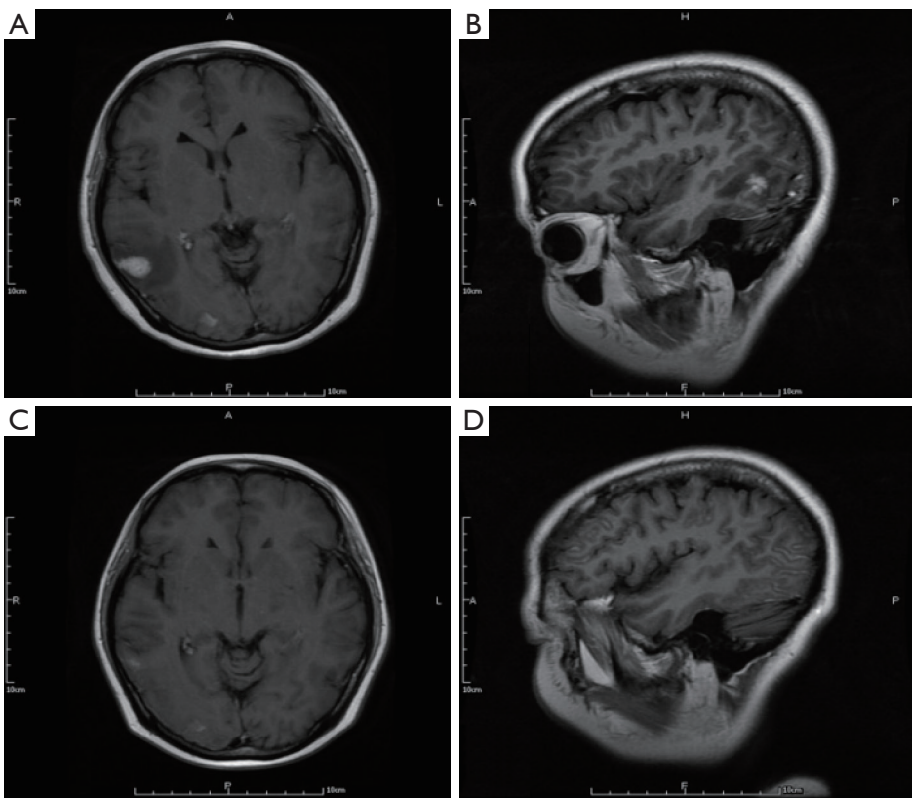

Figure 3 The brain MRI of a lung adenocarcinoma patient with brain metastasis before (A,B) and after (C,D) 2 cycles of bevacizumab.

symptomatic brain metastases who are ineligible to local therapy, even for the patients who are eligible to receive local therapy, bevacizumab combination therapy could improve symptoms and postpone local therapy.

Several studies also revealed bevacizumab combination with chemotherapy was a safe treatment for patients with brain metastasis from lung, with low incidence of intracerebral hemorrhage and other adverse events.

Table 3 Treatment-related adverse events

Adverse events, n=14	All grades, No. (%)	Grade 3[a], No. (%)
Leukopenia	7 (50.0)	2 (14.3)
Fatigue	3 (21.4)	0
Thrombocytopenia	3 (21.4)	0
Anemia	2 (14.3)	0
DVT	1 (7.1)	0
Hypertension	1 (7.1)	0
Albuminuria	1 (7.1)	1 (7.1)
Epistaxis	1 (7.1)	0
Creatinine increased	1 (7.1)	0
ALT increased	1 (7.1)	0

[a], there were no grade 4 or 5 treatment-related adverse events. ALT, alanine aminotransferase; DVT, deep vein thrombosis.

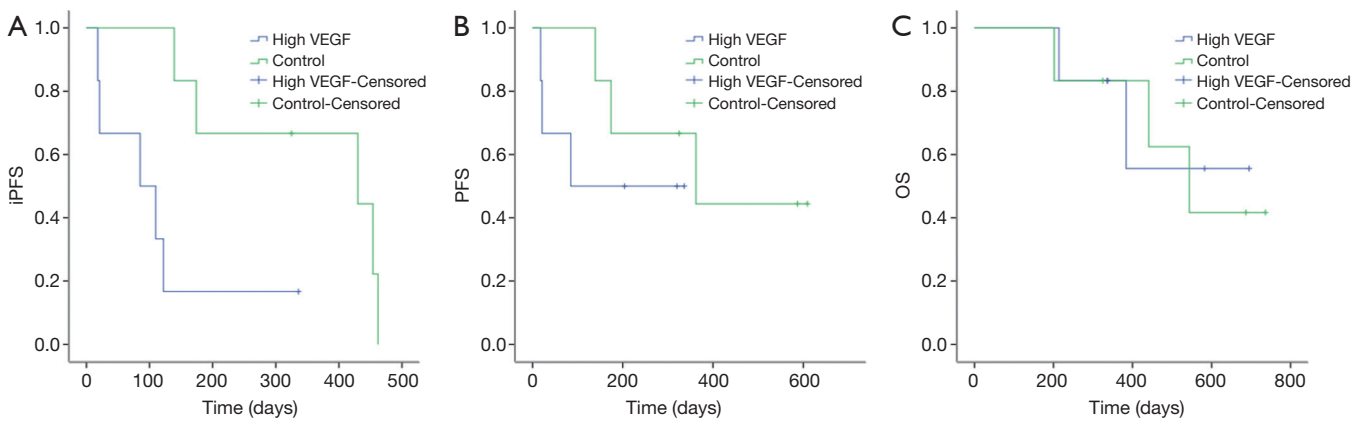

Figure 4 The baseline VEGF level and efficacy of bevacizumab combining with chemotherapy. (A) iPFS (high VEGF group *vs.* control group: 3.6 *vs.* 8.0 m, P=0.02); (B) PFS (high VEGF group *vs.* control group: 5.8 *vs.* 12.1 m, P=0.4); (C) OS (high VEGF group *vs.* control group: 12.8 *vs.* 18.4 m, P=0.08). VEGF, vascular endothelial growth factor; PFS, progression-free survival; iPFS, intracranial PFS; OS, overall survival.

PASSPORT study showed no grade 2 or more intracerebral hemorrhage occurred in brain metastasis patients treated with bevacizumab (28). A meta-analysis, including 8 clinical trials involving 8,713 patients with brain metastasis, found that the incidence of intracerebral hemorrhage was less than 1% after bevacizumab treatment (29). In the present study, more than 1/3 patients received more than 10 cycles of bevacizumab treatment. Most treatment-related adverse events were leukopenia, fatigue, thrombocytopenia, anemia, *et al.* Most adverse events were manageable, and no new safety signals were observed. Only one patient discontinued bevacizumab treatment because of increasing albuminuria (>2 g/24 h), and this patient had albuminuria (<2 g/24 h) before treatment.

Angiogenesis is thought to be associated with brain metastasis. VEGF is one of the most important factors to regulate angiogenesis, and play a role in recurrence, metastasis and death of patients with lung adenocarcinoma (24). Brain metastasis significantly reduce survival of lung adenocarcinoma patients, and symptoms of CNS caused by brain metastasis severely affect the quality of life. Therefore, it's crucial for patients with symptomatic brain metastases from lung adenocarcinoma to identify sensitive patients to antiangiogenic therapy through establishing effectively

Table 4 Univariate analyses of iPFS

Variable	n	iPFS (days)	P value
ECOG PS			0.093
>2	1	174	
≤2	11	298.9	
Age			0.069
≤60	6	124.1	
>60	6	340.6	
Metastases outside the CNS			0.891
Yes	6	273.8	
No	6	212.6	
EGFR/ALK status			0.725
Mutation	8	219.8	
Wild-type	4	289.3	
Baseline VEGF			0.005
High VEGF group	6	115.3	
Control group	6	351.2	

VEGF, vascular endothelial growth factor; CNS, central nervous system; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; iPFS, intracranial progression-free survival.

Table 5 Multivariate analyses of iPFS

Variable	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp (B)
Baseline VEGF	0.03	0.013	5.4	1	0.02	1.03	1.005–1.056
ECOG PS	–0.506	0.782	0.418	1	0.518	0.603	0.13–2.795
Age	–0.071	0.078	0.841	1	0.359	0.931	0.799–1.085

VEGF, vascular endothelial growth factor; iPFS, intracranial progression-free survival.

predictive biomarkers. The relationship between VEGF and efficacy of bevacizumab has remained ambiguous (30,31). Our results showed baseline serum VEGF was significantly associated with iPFS, indicating that VEGF could serve as a promising predictive biomarker.

This analysis is a retrospective, single-center clinical trial. Small sample size is the biggest limitation. So our conclusion need to be verified in randomized, multi-center trials. However, this is the first study to investigate the efficacy and safety of bevacizumab combined with chemotherapy in patients with symptomatic brain metastases from lung adenocarcinoma in China, and we provided a novel treatment choice for these patients. Furthermore, VEGF level, demonstrated to be a potential biomarker for bevacizumab treatment in this study, is convenient to be detected and has a promising clinical application value.

In conclusion, our results suggest that bevacizumab combination with chemotherapy is effective and safe, and provides a new therapeutic option for the patients with symptomatic brain metastases. The baseline serum VEGF could serve as a promising biomarker to predict the efficacy of bevacizumab combined with chemotherapy in symptomatic brain metastases from lung adenocarcinoma.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The protocol was approved by the Institutional Review Board Committee of Huashan Hospital, Shanghai, China (No. KY2017-010).

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Supplementary

Table S1 Detailed clinical characteristics

No.	Sex	Age	PS	Extra-CNS metastases	Mum of BMs	Driver-oncogene	Therapy before BEV	Chemotherapy	Efficacy	Efficacy of CNS	Symptom of CNS	Improve of Sym	Num of Bev	Cause of withdrawal	Site of PD	Therapy after withdrawal
1	F	49	3	Bone	Multiple	EGFR 21 Exon L858r	Erlotinib, osimertinib	P	SD	SD	Limb weakness, dizzy	Yes	6	AE	N/A	BSC
2	F	70	1	None	Single	None	SRS	PP	PR	PR	Left limb weakness	Yes	12	PD	Lung, PBM(N)	BSC
3	M	52	1	None	Multiple	EGFR 19del	WBRT, chemotherapy, Gefitinib	TC	SD	SD	Headache	Yes	17	PD	LM	V-P shunt
4	M	71	1	Lymph node	Multiple	None	SRS	PP	N/A	N/A	N/A	N/A	1	ED	N/A	BSC
5	M	61	2	None	Multiple	None	N/A	PP	N/A	N/A	N/A	N/A	1	AE	N/A	BSC
6	M	49	1	None	Multiple	None	PC	TC	SD	SD	Limb weakness, foot numbness, dysuresia	Yes	5	PD	LM	BSC
7	M	69	1	Adrenal gland, lymph node	Multiple	EGFR 19del	chemotherapy, icotinib	TC	PD	PD	Limb weakness	No	2	PD	Lung, PBM(N+E)	Osimertinib, SRS
8	F	42	2	Lung, pericardium, bone	Multiple	EGFR 19del	Gefitinib	D	PD	PD	Headache, dizzy	No	1	PD	LM, PBM(N)	Osimertinib, SRS
9	F	60	1	None	Multiple	EGFR 21 Exon L858r	WBRT + SRS, erlotinib, osimertinib	PP	SD	SD	Dysphasia	Yes	15	PD	Liver	BSC
10	M	61	2	None	Multiple	None	N/A	PP	SD	SD	Memory loss, dysphasia, reading & writing difficulties	Yes	3	PD	Lung	GP, BSC
11	M	71	1	None	multiple	None	SRS	PP	PR	PR	Dysphasia, hearing loss, slow reaction	Yes	19	N/A	N/A	N/A
12	M	64	2	Lung	multiple	ALK fusion	Crizotinib	PP	SD	PR	Headache, dizzy	Yes	4	PD	Lung	BSC
13	M	52	1	Liver, bone	single	EGFR 20 Exon T790m	Surgery, osimertinib	PP	PR	PR	Headache	Yes	15	N/A	N/A	N/A
14	M	59	2	Lung, pleura	N/A	EGFR 19del	N/A	D	PD	PD	Headache, unconsciousness	No	1	PD	LM	Icotinib, osimertinib

Bev, bevacizumab; D, docetaxel; T, paclitaxel; PP, pemetrexed plus cisplatin; TC, paclitaxel plus cisplatin; GP, gemcitabine plus cisplatin; BSC, best support care; AE, adverse event; DVT, deep venous thrombosis; E, enlargement of existing lesions; ED, economic difficulties; F, female; LM, leptomeningeal metastases; M, male; N, new lesion; N/A, not applicable; P, pemetrexed; PBM, parenchymal brain metastases; PD, progressive disease; PR, partial remission; SD, stable disease; SRS, stereotactic radiosurgery; V-P shunt, ventriculoperitoneal shunt; WBRT, whole brain irradiation.