doi.org/10.36721/PJPS.2022.35.1.REG.077-084.1

Analysis of cardio-cerebrovascular adverse events in patients with brain metastasis from lung cancer treated with antiangiogenic drugs

Yuqing Zhang MA[1], Haitao Zhang[2] and Wenguang Song[3]*

[1]Department of Oncology, Tangshan Gongren Hospital affiliated to North China University of Science and Technology, Tangshan, Hebei Province, China
[2]Department of Infection, Tangshan Central Hospital, Tangshan, Hebei Province, China
[3]Department of Oncology, Tangshan Gongren Hospital, Tangshan, Hebei Province, China

Abstract: To observe the occurrence of cardio-cerebrovascular adverse events in patients with brain metastases from lung cancer treated with antiangiogenic drugs. A total of 182 patients with brain metastases from lung cancer were selected as the research objects. They were divided into patients receiving antiangiogenic drugs and those not receiving antiangiogenic drugs. The incidence of cardio-cerebrovascular adverse events was observed. The incidence of low-grade hypertension, cerebral haemorrhage, cerebrovascular accident, cerebrovascular arrhythmia and other cardio-cerebrovascular adverse events in patients with brain metastases from lung cancer after receiving antiangiogenic therapy was higher than in the group that did not receive anti-vascular therapy (P<0.05). The incidence of low-grade hypertension increased in patients with a previous history of hypertension after they received antiangiogenic drugs (P< 0.05). There were no statistically significant differences between cardio-cerebrovascular adverse event rates in patients treated with three different antiangiogenic drugs (P>0.05). Head radiotherapy did not increase the rate of cardio-cerebrovascular adverse events among patients treated with antiangiogenic drugs (P< 0.05), and the incidence of adverse events was lowest in the endost group combined with radiotherapy. The incidence of cardio-cerebrovascular adverse events in the combined gemcitabine + platinum (GP) and irinotecan + platinum (IP) regimen group was higher than that in the other combined chemotherapy regimen groups. Treatment of brain metastases from lung cancer using antiangiogenic drugs increases the incidence of low-grade cardio-cerebrovascular adverse events, but these drugs are safe and controllable and are worthy of clinical application.

Keywords: Antiangiogenic therapy, adverse drug reaction, brain metastasis, lung cancer, cardio-Cerebrovascular.

INTRODUCTION

Lung cancer is a type of malignant tumour that has shown one of the fastest increase rates in morbidity and mortality and that represents a high level of threat to human health and life.(Fenske *et al*, 2017) The common methods of treatment of brain metastases are radiotherapy, surgical treatment and supportive treatment; however, even after active treatment, prognosis is still poor. (Lukas *et al*, 2016; Bernhardt *et al*, 2017) Therefore, improving the survival time and quality of life of non-small-cell lung cancer (NSCLC) patients with brain metastases has become a new research direction for anti-tumour therapy. The formation of new blood vessels is one of the important steps in the growth of brain metastases. (Fox *et al*, 2011; Yongli *et al*, 2017) This paper deals with three antiangiogenic drugs for the treatment of lung cancer with brain metastases. The addition of anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody bevacizumab to systemic chemotherapy has long been the standard approach for first-line treatment of advanced NSCLC, and recent data indicate that bevacizumab is effective in patients with brain metastases from NSCLC. (Braganca *et al*, 2010; Besse *et al*, 2015; Masuda *et al*, 2019) Endostatin (ES) is an antiangiogenic drug developed independently in China. (Ling *et al*, 2007) It can both improve the hypoxic environment of tumours and inhibit VEGF and VEGF-2 pathways to reduce oedema around brain metastases. Anlotinib is a new type of small-molecule tyrosine kinase multi-target inhibitor that mainly inhibits tumour angiogenesis and tumour cell proliferation by inhibiting multiple receptors.(Qin *et al*, 2020) With the widespread clinical application of this treatment, reports of adverse reactions to antiangiogenic drugs, including hypertension, bleeding and proteinuria, are increasing. (Xu *et al*, 2019) However, the cerebrovascular adverse events in patients with brain metastases from lung cancer treated by antiangiogenic drugs are not clear. This article retrospectively analyses the observation of cardio-cerebrovascular adverse events in patients with brain metastases from lung cancer after receiving antiangiogenic drugs.

MATERIALS AND METHODS

Information

A sample was selected of 182 patients with brain metastases from lung cancer admitted to Tangshan

**Corresponding author:* e-mail: songwenguang2020@126.com

Workers' Hospital from September 2012 to September 2020 who were diagnosed by histopathological or cytological examinations. The sample was divided into a group of 80 patients who received antiangiogenic drug treatment and a group of 102 who did not receive this type of treatment.

Exclusion criteria

(1) Renal insufficiency: creatinine clearance < 60 ml/min;

(2) History or test results suggest inherited bleeding disorders or coagulopathy;

(3) urine test results of proteinuria <2+, patients with a 2+ or greater urine dipstick reading at baseline should undergo further assessment with a 24-hour urine collection, and include when proteinuria is <1 gram per 24 hours;

(4) Uncontrolled hypertension (systolic blood pressure > 150 mmHg and/or diastolic blood pressure >100 mmHg) or clinically significant (e.g., active) cardiovascular disease (6 months prior to enrollment), myocardial infarction (6 months prior to enrollment), unstable angina pectoris, congestive heart failure of NYHA class II or above, or severe arrhythmia that cannot be controlled with drugs or has a potential impact on the experimental treatment;

(5) Patients with severe medical diseases, including abnormal heart function or a history of related conditions such as myocardial infarction or severe arrhythmia;

(6) Patients using anticoagulant drugs and antiplatelet drugs;

Ineligible criteria

(1) Those who do not use drugs regularly;
(2) Patients with absence of treatment information.

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tangshan Gongren Hospital.

STATISTICAL ANALYSIS

Statistics regarding patient age, gender, past medical history, metastatic location, driver gene type, lung cancer type, history of anti-vascular treatment before brain metastasis, antiangiogenic drug dosage, combined treatment plan, incidence and severity of cardio-cerebrovascular adverse events, etc. were analysed.

The US National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 classifies adverse events into grades 0-IV. Grade 0 indicates no adverse events, while grade I refers to mild adverse events, grade II to moderate adverse events, grade III to severe adverse events and grade IV to life-threatening or loss-of-function adverse events.

STATISTICAL ANALYSIS

SPSS 17.0 software was used for data processing. General data were described by frequency. The differences between the groups were tested by χ^2. The test level was α =0.05 and P<0.05 indicated a statistically significant difference.

RESULTS

Basic patient information

We reviewed the information of 182 patients with brain metastases from lung cancer treated by Tangshan Workers' Hospital from September 2012 to September 2020. Of the patients in the sample, 31.3% were >65 years old, while 68.7% were <65 years old. The ECOG performance status of the patients was patients were male (58.2%) and female (41.8%). ECOG PS is 0-2 (94.0%). At the baseline examination, 30.2% of cases had a history of hypertension, 9.3% had a history of diabetes, and 13.7% had other conditions in their medical history. In addition to brain metastases, 24.2%, 17.0% and 6.0% of the patients showed bone metastases, liver metastases and metastases to other sites at baseline examination. The types of cancer in the sample were lung adenocarcinoma (56.0% of patients), lung squamous cell carcinoma (9.3%) and small-cell lung cancer (34.6%). In terms of gene mutations, 19.2% of patients were EGFR mutation positive and 2.7% were ALK mutation positive. Before brain metastasis occurred, 86.3% of patients had not received antiangiogenic therapy and 38.5% had received anti-vascular therapy. Overall 61.5% of the sample patients received radiotherapy (table 1).

Antiangiogenic drug dosage and combined treatment plan

Among the treatment group, 36 patients received bevacizumab (7.5mg/kg) once every three weeks, 15 patients received endost (15mg) (continuous administration on days 1-14) and 29 patients received anlotinib (12mg once per day) for two consecutive weeks, stopped the drug for one week, and then received the same dosage again for 21 days.

The combined chemotherapy treatment plans were mainly comprised of pemetrexed + platinum (AP), gemcitabine + platinum (GP), albumin paclitaxel + platinum (TP), docetaxel + platinum (DP), etoposide + platinum (EP) and irinotecan + platinum (IP). The dosage of each chemotherapeutic drug was calculated according to the surface area of the human body in accordance with the drug description and the chemotherapy administration time was determined according to National Comprehensive Cancer Network guidelines and patient tolerance status. Every 21 days constituted a cycle, and at least two cycles were undertaken. Use of the regimen was continued for stable patients for whom the therapy was proving effective. Targeted therapy mainly consisted of

Table 1: Patient and disease characteristics at baseline

	Antiangiogenic treatment group (n=80)	Non-antiangiogenic treatment group (n=102)	Total (N=182)
Age n (%)			
>65 years old	16(20%)	41(40.2%)	57(31.3%)
<65 years old	64(80%)	61(59.8%)	125(68.7%)
Gender n (%)			
Male	48(60%)	58(56.9%)	106(58.2%)
Female	32(40%)	44(43.1%)	76(41.8%)
ECOG score, n (%)			
0-2	76(95%)	95(93.1%)	171(94.0%)
3-4	4(5%)	7(6.9%)	11(6.0%)
Past history n (%)			
No	47(58.8%)	58(56.9%)	105(57.0%)
Hypertension	26(32.5%)	29(28.4%)	55(30.2%)
Diabetes	7(8.8%)	10(9.8%)	17(9.3%)
Others	10(13%)	15(14.7%)	25(13.7%)
Metastasis n (%)			
Brain	80(100%)	102(100%)	182(100%)
Bone	18(22.5%)	26(25.5%)	44(24.2%)
Liver	10(12.5%)	21(20.6%)	31(17.0%)
Others	6(7.5%)	5(4.9%)	11(6.0%)
Types of lung cancer n (%)			
Adenocarcinoma	48(60%)	54(52.9%)	102(56.0%)
Squamous cell carcinoma	5(6.3%)	12(11.8%)	17(9.3%)
Small Cell Lung Cancer	27(33.8%)	36(35.3%)	63(34.6%)
Driver gene n (%)			
No	64(80%)	78(76.5%)	142(78.0%)
EGFR gene mutation positive	14(17.5%)	21(20.6%)	35(19.2%)
ALK gene mutation positive	2(2.5%)	3(2.9%)	5(2.7%)
Anti-vascular treatment before brain metastasis n (%)			
No	64(80%)	93(91.2%)	157(86.3%)
Yes	16(20%)	9(8.8%)	25(13.7%)

gefitinib (250mg orally per day), erlotinib (150mg per day), crizotinib (250 mg twice a day) and osimertinib (80 mg per day), administered until the disease progressed or until the patient could no longer tolerate the treatment (table 2).

A total of 80 of the sample patients were treated with antiangiogenic drugs. Among these, 23 were treated with first-line treatment, 15 with second-line treatment, 22 with third-line treatment and 20 with posterior-line treatment.

Occurrence of adverse events

In the antiangiogenic drug treatment groups, 36 cases (45.0%) of cerebrovascular adverse events of hypertension occurred, of which 3 cases were grade III/IV. Adverse events occurred at the same time as drug treatment, suggesting that the progress of the events was related to the antiangiogenic drugs. After antihypertensive treatment, the symptoms of adverse events disappeared. There were 6 cases of cerebral haemorrhage (7.5%), 1 case of transient cerebral ischemia, 1 case of cerebral infarction, 3 cases of cerebrovascular accident and 1 case of epilepsy (not related to treatment, resulting in death). The other 10 patients had no sequelae after symptomatic treatment. There were 13 cases of arrhythmia (16.3%), of which 8 cases were in the anlotinib group and 1 case of angina. In the group that did not receive antiangiogenic treatment, 27 cases (26.4%) had hypertension of any grade (I–IV), and 3 cases (2.9%) had arrhythmia. There were statistical differences between the incidence of adverse events of the low-grade hypertension, cerebral haemorrhage, cerebrovascular accident and arrhythmia types (P<0.05). There was no statistically significant difference between cardio-cerebrovascular adverse events in the bevacizumab, endost and anlotinib groups (P>0.05) (see tables 3 and 4). The relative incidence rates of different types of adverse event in the antiangiogenic drug treatment group were as follows: Bone-marrow suppression = endost group >bevacizumab group >anlotinib group; fatigue =bevacizumab group >anlotinib group >endost group and gastrointestinal reaction = bevacizumab group > anlotinib group > endost group. The most frequent types of adverse event in the group that did not receive antiangiogenic drug treatment were bone-marrow suppression (38.2%), fatigue (24.5%) and gastro-

Table 2: Combined treatment plan after brain metastasis

	Number of cases in the group receiving anti-angiogenesis treatment			Number of cases in the group not receiving anti-angiogenesis treatment	Total (N=182)
	Bev	Endost	Anlotinib		
Chemotherapy					
AP	23	9	0	29	61
GP	3	6	0	5	14
TP	6	0	0	8	14
EP	0	0	19	15	34
IP	0	0	10	21	31
Targeted therapy					
EGFR inhibitor	3	0	0	21	24
ALK inhibitor	1	0	0	3	4
Received head radiation therapy	27	12	15	58	112
What line of treatment after brain metastasis?					
First line	16	7	0	21	44
Second line	7	4	4	20	35
Third line	4	2	16	33	55
Posterior line	9	2	9	28	48

Bev for bevacizumab group; endost for endost group; anlotinib for anlotinib group; AP for pemetrexed + cisplatin; GP for gemcitabine + cisplatin; TP for paclitaxel + cisplatin; EP for etoposide + cisplatin; IP for irinotecan + cisplatin.

Table 3: Adverse reactions after treatment of brain metastases from lung cancer

Adverse events	Antiangiogenic drug treatment group (N=80)						Not receiving anti-angiogenic drug treatment (%) (N=102)		X^2	*P*
	Bev group (%) (N=36)		Endost group (%) (N=15)		Anlotinib group (%) (N=29)		All grades	3/4 grades		
	All grades	3/4 grades	All grades	3/4 grades	All grades	3/4 grades				
Hypertension	16(44.4)	2(5.6)	7(46.7)	0	13(44.8)	1(3.4)	24(25.5)	1(1)	9.353	0.002
Cerebral hemorrhage	3(7.4)	1	1(6.7)	0	2(6.9)	0	0	0	7.911	0.005
Transient cerebral ischemia	1(2.8)	0	0	0	0	0	0	0	1.282	0.258
Cerebral infarction	1(2.8)	0	0	0	0	0	0	0	1.282	0.258
Cerebrovascular accident	2(5.6)	1	1(6.7)	0	0	0	0	0	5.215	0.022
Arrhythmia	4(11.1)	0	1(6.7)	0	8(27.9)	0	3(2.9)	0	9.904	0.002
Angina pectoris	1(2.8)	0	0	0	0	0	0	0	1.282	0.258
Anemia	6(16.7)	2(5.6)	4(26.7)	1(6.7)	5(17.2)	2(6.9)	13(12.7)	3(2.9)	1.242	0.265
Leukopenia	12(33.3)	4(11.1)	5(33.3)	2(13.3)	2(6.9)	0	18(17.6)	5(4.9)	1.031	0.310
Thrombocytopenia	10(27.8)	4(11.1)	5(33.3)	1(6.7)	2(6.9)	0	24(23.5)	6(5.9)	0.133	0.715
Liver damage	3(8.3)	0	2(13.3)	1(6.7)	3(10.3)	0	14(13.7)	5(4.9)	5.663	0.017
Proteinuria	6(16,7)	1(2.8)	2(6.7)	1(6.7)	4(13.8)	1(3.4)	3(2.9)	1(1)	8.621	0.003
Bleeding	13(36.1)	1(2.8)	3(20)	0	2(6.9)	0	0	0	25.469	0.000
Fatigue	15(41.7)	0	4(26.7)	2(13.3)	9(31.0)	0	25(24.5)	0	2.390	0.122
Rash	0	0	1(6.7)	0	2(6.9)	0	7(6.8)	2(2)	0.837	0.360
Hand-foot syndrome	0	0	0	0	7(24.1)	1(3.4)	6(5.9)	1(1)	0.556	0.456
Gastrointestinal reaction	12(33.3)	5(13.9)	4(26.7)	1(6.7)	8(27.6)	2(6.9)	26(25.5)	3(2.9)	0.458	0.499

Table 4: Influence of hypertension at baseline on adverse events of hypertension after treatment with antiangiogenic drugs

		Number of cases of hypertension in the antiangiogenic drug group		X^2	*P*
		Yes	No		
Hypertension after receiving antiangiogenic drugs	With hypertension	18	18	9.138	0.003
	Without hypertension	8	36		

Table 5: Comparison of cardio-cerebrovascular adverse events among three different antiangiogenic drugs after brain metastasis from lung cancer

	Number of cases in the group receiving antiangiogenic drugs (n=80)			X^2	*P*
	Bev	Endost	Anlotinib		
Hypertension					
Yes	16	7	13	0.22	0.989
No	20	8	16		
Cerebral hemorrhage					
Yes	3	1	2	0.066	0.967
No	33	14	27		
Arrhythmia					
Yes	4	1	8	4.449	0.108
No	32	14	21		

Table 6: Comparison of adverse cardio-cerebrovascular events after receiving head radiotherapy with different antiangiogenic drugs

			Number of cardio-cerebrovascular adverse events after receiving different antiangiogenic drugs		X^2	*P*
			Yes	No		
Head radiotherapy in antiangiogenic drug groups	Bev Group	Yes	16	11	0.600	0.439
		No	4	5		
	Endost Group	Yes	6	6	0.268	0.605
		No	2	1		
	Anlotinib Group	Yes	10	5	0.279	0.597
		No	8	6		

Table 7: Incidence of cardio-cerebrovascular adverse events in patients receiving antiangiogenic drugs combined with different chemotherapy regimens

	Number of cardio-cerebrovascular adverse events after receiving different antiangiogenic drugs	
	Yes	No
AP	19(59.4%)	13(40.6%)
GP	6(66.7%)	3(33.3%)
TP	3(50.0%)	3(50%)
EP	11(57.9%)	8(42.1%)
IP	6(60.0%)	4(40.0%)

intestinal reactions (25.5%). There were statistically significant differences in bleeding and proteinuria between the antiangiogenic drug treatment group and the non-antiangiogenic-drug-treatment group ($P<0.05$) (table 3).

Patients with a history of hypertension at baseline showed an increased incidence of hypertension under treatment with antiangiogenic drugs after brain metastasis compared with patients with no such history, and the difference was statistically significant ($P<0.05$) (table 5). After brain metastasis from lung cancer, the patients in the antiangiogenic drug treatment group who received head radiotherapy did not show an increased incidence of cardio-cerebrovascular adverse events ($P>0.05$); meanwhile, the incidence of cardio-cerebrovascular events in the endost group decreased after receiving head radiotherapy (40%) (table 6). The highest incidences of cardio-cerebrovascular adverse events were seen in patients in the antiangiogenic drug treatment group receiving GP (66.7%) and IP (60.0%) (table 7).

DISCUSSION

High incidence of brain metastases and poor prognosis have become difficult issues in lung cancer treatment. With the gradual recognition of the role of vascular endothelial growth factor (VEGF), targeted therapies that interfere with neovascularisation have emerged. Bevacizumab is a recombinant human monoclonal IgG antibody that induces the degeneration of existing blood vessels and inhibits tumour growth. (Bernhardt *et al*, 2017) Endost is a new type of recombinant human endostatin that has been developed independently in China. It is a small-molecule protein with multiple targets (Peng *et al*, 2020) inhibit angiogenesis and tumour growth. (Besse *et al*, 2015) The national multi-centre ALTER-0303 study confirmed that Anlotinib increases

both progression-free and overall survival rates in patients with brain metastases from lung cancer. (Cheng *et al*, 2020).

The current study summarises cardio-cerebrovascular adverse events in 182 patients with brain metastases from lung cancer in Tangshan Workers Hospital from 2012 to September 2020. The results indicate an increased incidence of cardio-cerebrovascular adverse events after the use of antiangiogenic drugs, The findings regarding other adverse events (fatigue, bone-marrow suppression, bleeding, proteinuria, etc.) are similar to previous results. (Reck 2009; Reck *et al*, 2010).

In the present study, there were 31 cases of hypertension in the anti-angiogenesis treatment group. With 14 cases in the bevacizumab group, 5 cases in the endost group and 12 cases in the anlotinib group, there was no statistical difference between the three drugs (P>0.05). Of these 31 cases, 91.7% were low-grade hypertension adverse events and symptoms were relieved after antihypertensive treatment. The incidence of hypertension increased after receiving anti-angiogenic treatment for patients with a history of hypertension (P<0.05). There were 27 cases of hypertension in the group not receiving anti-angiogenesis treatment, representing a statistically significant difference from the group who did receive anti-angiogenesis treatment (P<0.05).

At present, we understand that the mechanism of hypertension associated with antiangiogenic drugs may inhibit the effect of VEGF, (Ferrara, 2004; Rini *et al*, 2005) which may in turn lead to a decrease of endothelial cell renewal ability and an increase of apoptosis. (Yao *et al*, 1992) At the same time, this process interferes with endothelial cells to produce vasodilators such as nitric oxide and prostacyclin, causing vasoconstriction. In addition, hypertension may be related to increased peripheral vascular resistance due to sparse blood vessels and a functional reduction in the number of arterioles and capillaries (De Graaf *et al*, 1992; Ian 2001). Severe complications of hypertension can include hypertensive encephalopathy, central nervous system haemorrhage, reversible posterior leukoencephalopathy and congestive heart failure. Application of anti-vascular drugs prior to brain metastasis may produce superimposed adverse conditions, potentially including hypoxia, which can increase the incidence of adverse events of hypertension. (Lu and Kang 2010) Therefore, both clinicians and patients should be aware of the risks of hypertension, and these risks should be monitored and treated in a timely and appropriate manner.

Table 3 shows that there were 3 cases of cerebral haemorrhage in the bevacizumab group, 1 case in the endost group, 1 case in the anlotinib group; therefore, the highest incidence was in the bevacizumab group. Previous studies have shown that bevacizumab inhibits VEGF, which reduces the ability of endothelial cells to regenerate and causes endothelial defects. Endothelial cells are exposed to the phosphorous or basic matrix of the plasma membrane cavity to promote blood clotting, leading to thrombosis and bleeding. Some researchers have raised the issue of the safety of bevacizumab in patients with brain metastases. (Dansin *et al*, 2010) However, to the best of our knowledge, no bleeding above grade II was found in the PASSPORT and ATLAS studies. (Lynch *et al*, 2014) Additionally, the findings of a previous evidence-based review of the risk of central nervous system haemorrhage in patients with brain metastases from non-small-cell lung cancer with antiangiogenic drugs indicate that antiangiogenic drug treatment does not significantly increase the risk of central nervous system haemorrhage. (Sandler *et al*, 2012) Antiangiogenic drugs may hinder any increase in the expression of pro-inflammatory genes and may accelerate in-situ thrombosis and affect interpretation of a higher incidence of adverse events in arteries and veins, including cardiac and cerebral ischaemia. Adverse events associated with bevacizumab were mentioned in E4599 and AVAiL studies, and similar adverse events, such as hypertension, were observed in this article, (Reck 2009; Reck *et al*, 2010) the use of bevacizumab and incidence of common, controllable adverse events, such as hypertension, proteinuria, fatigue and other adverse events were observed in this study.

Radiotherapy is currently the primary method for the treatment of brain metastases from lung cancer, but the curative effect on intracranial tumour recurrence is not satisfactory. Ma Honglian *et al*., (2017) have reported that combining antiangiogenic drug treatments with radiotherapy can improve their efficacy. In the current study, the adverse cardio-cerebrovascular events in the antiangiogenic drug group after head radiotherapy were not statistically significant (P<0.05). Six patients in the endost group had low-grade adverse events, which was a lower incidence than for the other two drugs. This may be because endost is an endogenous antiangiogenic drug. Generally, there are no new blood vessels in adults and the other two antiangiogenic drugs used in the patients in our sample inhibit both tumour blood vessels and the normal tissue vascular hematopoietic system. The specific mechanisms for these effects require further study.

In the current study, in the group that did not receive anti-angiogenesis treatment, 21 cases used EGFR inhibitors and 3 cases used ALK inhibitors. Meanwhile, in the anti-angiogenesis treatment group, 3 cases used EGFR inhibitors and 1 case used ALK inhibitors. Despite the large differences between these figures, no curative effect analysis was carried out; this is to be considered in the next study. In our review, an increased incidence of the cerebrovascular adverse events of low-grade

hypertension, cerebral haemorrhage and arrhythmia was seen in patients with lung cancer using antiangiogenic drugs after brain metastasis. The incidence of adverse reactions was high, but it was still within the controllable range and tolerable; therefore, the treatment is suitable for further clinical practice. The three There was no significant difference between incidence rates of cardio-cerebrovascular adverse events for the three different antiangiogenic drugs (bevacizumab, endost and anlotinib). An increased incidence of hypertension after receiving antiangiogenic therapy was also seen in patients with a history of hypertension before baseline. In the anti-vascular treatment of patients with brain metastases from lung cancer, close attention should be paid to the potential occurrence of cardio-cerebrovascular adverse events when head radiotherapy or combined GP and IP regimens are being administered. Fatigue, myelosuppression, gastrointestinal adverse events, proteinuria and bleeding were also observed in this study. In clinical applications, doctors should balance the anti-tumour efficacy with the risk of adverse events and carry out effective monitoring and prevention to reduce the occurrence of adverse events as much as possible and improve the survival time and quality of life of patients.

REFERENCES

Bernhardt D, Adeberg S, Bozorgmehr F, Opfermann N, Hoerner-Rieber J, Konig L, Kappes J, Thomas M, Herth F, Heußel CP, Warth A, Debus J, Steins M and Rieken S (2017). Outcome and prognostic factors in patients with brain metastases from small-cell lung cancer treated with whole brain radiotherapy. *J. Neurooncol.,* **134**(1): 205-212.

Besse B, Le Moulec S, Mazieres J, Senellart H, Barlesi F, Chouaid C, Dansin E, Berard H, Falchero L, Gervais R, Robinet G, Ruppert A-M, Schott R, Léna H, Clément-Duchêne C, Quantin X, Souquet PJ, Trédaniel J, Moro-Sibilot D, Pérol M, Madroszyk AC, Soria JC (2015). Bevacizumab in Patients with Nonsquamous Non-Small Cell Lung Cancer and Asymptomatic, Untreated Brain Metastases (BRAIN): A Nonrandomized, Phase II Study. *Clin. Cancer Res.,* **21**(8):1896.

Braganca KCD, Janjigian YY, Azzoli CG, Kris MG, Pietanza MC, Nolan CP, Omuro AM, Holodny AI and Lassman AB (2010). Efficacy and safety of bevacizumab in active brain metastases from non-small cell lung cancer. *J. Neurooncol.,* **100**(3): 443-447.

Cheng JD, Chai LX, Zhao ZP, Hao YY and Li S (2020). Efficacy and Safety of Anlotinib for Patients with Advanced NSCLC Who Progressed After Standard Regimens and the Preliminary Analysis of an Efficacy Predictor. *Cancer Manag. Res.,* **12**: 5641-5650.

Dansin E, Cinieri S, Garrido P, Griesinger F, Isla D, Koehler M and Kohlhaeufl M (2012). MO19390 (SAiL): Bleeding events in a phase IV study of first-line bevacizumab with chemotherapy in patients with advanced non-squamous NSCLC. *Lung Cancer,* **76**(3): 373-379.

De Graaf JC, Banga JD, Moncada S, Palmer RM, Groot P G, Sixma JJ (1992). Nitric oxide functions as an inhibitor of platelet adhesion under flow conditions. *Circulation,* **85**(6): 2284-2290.

Fenske DC, Price GL, Hess LM, John WJ and Kim ES (2017). Systematic Review of Brain Metastases in Patients With Non-Small-Cell Lung Cancer in the United States, European Union, and Japan. *Clin. Lung Cancer,* **18**(6): 607-614.

Ferrara N (2004). Vascular endothelial growth factor: Basic science and clinical progress. *Endocr. Rev,* **25**(4): 581-611.

Fox BD, Cheung VJ, Patel AJ, Suki D, Rao G (2011). Epidemiology of metastatic brain tumors. *Neurosurg. Clin. N. Am.,* **22**(1): 1-6.

Ian Z (2001). Signaling mechanisms mediating vascular protective actions of vascular endothelial growth factor. *Am. J. Physiol Cell Physiol.,* **280**(6): C1375.

Ling Y, Yang Y, Lu N, You QD, Wang S, Gao Y, Chen Y, Guo QL (2007). Endostar, a novel recombinant human endostatin, exerts antiangiogenic effect via blocking VEGF-induced tyrosine phosphorylation of KDR/Flk-1 of endothelial cells. *Biochem. Biophys. Res. Comm*., **361**(1): 79-84.

Lukas RV, Kumthekar P, Rizvi S and Salgia R (2016). Systemic therapies in the treatment of non-small-cell lung cancer brain metastases. *Future Oncol.,* pp.1045-1058.

Lu X, Kang Y. Hypoxia and Hypoxia-Inducible Factors: Master Regulators of Metastasis. *Clin. Cancer Res.,* **16**(24): 5928-35.

Lynch TJ , Spigel DR , Brahmer J , Fischbach N, Garst J, Jahanzeb M, Kumar P, Vidaver R M, Wozniak A J, Fish S, Flick ED, Leon L, Hazard SJ, Kosty MP, Aries Study Investigators. Safety and Effectiveness of Bevacizumab-Containing Treatment for Non–Small-Cell Lung Cancer: Final Results of the ARIES Observational Cohort Study. *J. Thorac. Oncol,* **9**(9):1332-1339.

Ma HL, Hui ZG, Zhao LJ, Xu YJ, Zhai YR, Wu RY, Pang QS, Zhu GY, Li DM, Tang Y, Liang J, Kong Y, Chen M and Wang LH (2017). P2.02-025 Continuous Intravenous Pumping Endostar Combined with Radiochemotherapy in Unresectable Stage III Non-Small-Cell Lung Cancer: Topic: Clinical Outcome. *J. Thorac. Oncol,* **12**(1): S862.

Masuda C, Sugimoto M, Wakita D, Monnai M, Ishimaru C, Nakamura R, Kinoshita M, Yorozu K, Kurasawa M, Kondoh O and Yamamoto K (2020). Bevacizumab suppresses the growth of established non-small-cell lung cancer brain metastases in a hematogenous brain metastasis model. *Clin. Exp. Metastasis.,* **37**(1): 199-207.

Peng L, Wang Y, Fei S, Wei C H, Tong F, Wu G, Ma H, Dong XR (2020). The effect of combining Endostar with radiotherapy on blood vessels, tumor-associated macrophages, and T cells in brain metastases of Lewis lung cancer. *Transl. Lung Cancer* Res., **9**(3):745-760.

Qin TT, Liu ZJ, Wang J, Xia J L, Liu S C, Jia Y N, Liu H L and Li K (2020). Anlotinib suppresses lymphangiogenesis and lymphatic metastasis in lung adenocarcinoma through a process potentially involving VEGFR-3 signaling. *Cancer Biol. Med.,* **17**: 753-767.

Reck M, Von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, Leighl N, Mezger J, Archer V, Moore N and Manegold C (2010). BO17704 Study Group. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: Results from a randomised phase III trial (AVAiL). *Ann. Oncol.,* **21**(9): 1804-1809.

Reck (2009). Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. *J. Clin. Oncol.,* **27**(8): 1227.

Rini BI, Sosman JA and Motzer RJ (2005). Therapy targeted at vascular endothelial growth factor in metastatic renal cell carcinoma: Biology, clinical results and future development. *BJU Int,* **96**(3): 286-90.

Sandler A, Hirsh V, Reck M, Pawel JV, Akerley W and Johnson DH (2012). An evidence-based review of the incidence of CNS bleeding with anti-VEGF therapy in non-small cell lung cancer patients with brain metastases. *Lung Cancer,* **78**(1): 1-7.

Xu HF, Zhao GP, Yang JJ and Wen XP (2019). Advances in toxicity risk analysis and effective treatments for targeted antiangiogenic drugs. *Int. J. Clin. Exp. Med.,* **12**: 12020-12027.

Yao SK, Ober JC, Krishnaswami A, Ferguson J J, Anderson HV, Golino P, Buja LM and Willerson JT (1992). Endogenous nitric oxide protects against platelet aggregation and cyclic flow variations in stenosed and endothelium-injured arteries. *Circulation,* **86**(4): 1302-1309.

Yongli Z, Jigang D, Bo L, Maojiang L, Yan C and Xiaoxiao L (2017). The value analysis of blood brain barrier permeability in the treatment of multiple brain metastases patients with non-small cell lung cancer. *J. Mod. Oncol.,* **14**: 2238-2242.