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Continuous Low-Dose Apatinib Combined With WBRT Significantly Reduces Peritumoral Edema and Enhances the Efficacy of Symptomatic Multiple Brain Metastases in NSCLC

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Abstract

Background: Symptomatic multiple brain metastases with peritumoral brain edema (PTBE) occur in non-small cell lung cancer patients (NSCLC) who are without driver mutations or are resistant to epidermal growth factor tyrosine kinase (EGFR-TKI) are often associated with an unfavorable prognosis. Whole brain radiation therapy (WBRT) which comes with many complications and unsatisfactory effects, is the only option for the treatment. Previous studies have shown that bevacizumab can reduce the volume of PTBE and improve efficiency of radiotherapy. This study evaluated the effects and safety of apatinib combined with WBRT in NSCLC patients with symptomatic multiple brain metastases and PTBE. **Methods:** We performed a retrospective review of 34 patients with symptomatic multiple brain metastases from NSCLC (number >4, and at least 1 measurable brain metastasis lesion with cerebral edema). Intracranial objective response rate (IORR), peritumoral edema and intracranial tumor volumetric measurement, Karnofsky performance status (KPS) and adverse events (AEs) were evaluated. Median intracranial progression-free survival (mIPFS) and median overall survival (mOS) were also analyzed. **Results:** Thirteen cases received apatinib (125 mg or 250 mg, QD, oral) combined with WBRT and 21 cases received chemotherapy combined with WBRT were inclued. Apatinib combination group can better reduce the volume of intracranial tumors and PTBE and total steroid dosage used. It was associated with a better IORR (84.6% vs 47.6%, $P = 0.067$), longer mIPFS (6.97 vs 4.77months; $P = 0.014$). There was no significant difference in mOS(7.70 vs 6.67 months; $P = 0.14$) between the 2 groups. The most common adverse events of apatinib combination WBRT included grade 1/2 nausea (4/13), fatigue (3/13), hypertension (2/13) and white blood cell decrease (2/13). No grade 3/4 AEs were observed. **Conclusion:** Apatinib plus WBRT is well tolerated and may be a potential choice for relapsed or drug-resistant advanced NSCLC patients with symptomatic multiple brain metastases and PTBE.

Keywords

apatinib, brain metastases, peritumoral brain edema, radiation therapy, whole brain radiotherapy, non-small cell lung cancer

Abbreviations

NSCLC, non-small cell lung cancer; EGFR-TKI, epidermal growth factor tyrosine kinase; WBRT, whole brain radiation therapy; IORR, intracranial objective response rate; AEs, adverse events; mIPFS, median intracranial progression-free survival; mOS,

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median overall survival; LSCC, lung squamous cell carcinoma; PTBE, peritumoral brain edema; TKIs, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ICR, intracranial complete response; IPR, intracranial partial response; ISD, intracranial stable disease; IPD, intracranial progressive disease; KPS, Karnofsky Performance Status

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Introduction

The survival of patients with NSCLC is extended due to progress in diagnosis and systemic treatment, however the incidence of brain metastases increases to 50%.[1] The significant cause of brain metastases is the failure of system treatment, with a median survival of 1-2 months.[2] Symptomatic brain metastases occur in 50% of NSCLC patients by mass effect and PTBE which contributes to increased intracranial pressure or focal neurologic dysfunction. This will impair quality of life and shorten survival time.

WBRT should be adopted actively when symptomatic multiple brain metastases occur and WBRT is still an important method of salvage therapy for symptomatic multiple brain metastases (having $\geq$4 lesions). However, brain metastases often recur after single application of WBRT, and the treatment often cannot achieve a satisfactory local control rate and survival time.[3] Patients with driver gene mutation as well as asymptomatic brain metastasis from NSCLC can benefit from therapy of tyrosine kinase inhibitors (TKIs), such as erlotinib, osimertinib, etc. The therapy can enhance radiosensitivity of metastasis and improve the intracranial response rate and survival time[4] However, how to apply WBRT to control NSCLC patients with symptomatic brain metastasis but no driver gene mutation or resistant to TKIs, remains a difficult problem in clinical practice.

Extensive brain edema is the most important feature of metastatic brain tumors, and it often leads to a reduction in the dose and sensitivity of radiotherapy.[5] Vascular endothelial growth factor (VEGF), also known as vascular permeability factor, is well documented to be able to increase vascular permeability[6] and induce growth of tumor arterial endothelial cells.[7] The up-regulation of VEGF expression in symptomatic multiple brain metastasis does not only promote the growth of intracranial tumors but also induces PTBE, which aggravates the mass occupying effect.[8] Radiotherapy can also induce high VEGF expression,[9] then aggravates PTBE and tumor hypoxia, as a result it reduces the sensitivity of radiation.[10] Therefore, reducing the expression of VEGF can decrease cerebral edematous volume and increase the sensitivity of radiotherapy.

Some studies showed that anti-VEGF biological agents such as bevacizumab combined with localized radiation modalities (WBRT or SRS) can reduce the volume of the edema, and ensure the safety of radiotherapy. Bevacizumab can also enhance radiosensitivity by normalizing tumor vessels and improving tumor hypoxia.[11,12] Apatinib is a noval antiangiogenic agent. Compared with large-molecule bevacizumab, apatinib, a small-molecule vascular endothelial growth factor receptor 2 (VEGFR 2) tyrosine kinase inhibitor, has significant advantage over oral administration and cost control, and it has been approved for the third-line treatment of advanced gastric adenocarcinoma or gastric-esophageal junction adenocarcinoma in China.[13] Furthermore, studies have found that apatinib monotherapy has a encouraging curative effect and a dosage safety in advanced triple-negative breast cancer,[14] non-squamous NSCLC,[15] hepatocellular carcinoma[16] and other solid tumors. Several case reports indicated that apatinib significantly reduces the volume of PTBE and cerebral metastases, relieved the symptoms of central nervous system and extended the survival time.[17,18] A retrospective study indicated that apatinib combined with chemotherapy or EGFR-TKI showed higher activity than apatinib monotherapy in patients with BMS from NSCLC.[19] However, there is no study that has ever investigated the combination of apatinib and WBRT in NSCLC patients with symptomatic brain metastases so far.

Methods

Patient Selection

We enrolled consecutive patients with symptomatic multiple brain metastases from advanced NSCLC in the Department of Oncology of The Second People's Hospital of Yibin, from February 2018 to October 2019. The main inclusion criteria were as follows: (1) Patients with pathological histology confirmed as NSCLC, (2) More than 4 brain metastases lesions and at least 1 measurable brain metastasis lesion with cerebral edema confirmed by contrast-enhanced CT, (3) no driver gene mutations or resistance to EGFR-TKIs; (4) WBRT as local radiotherapy; (5) Oral apatinib as a single agent or combined with chemotherapy alone during WBRT course. The major exclusion criteria were as follows: (1) Combined with other cranial local radiotherapy or surgery, (3) Systemic therapy combined with immunotherapy or any other anti-angiogenesis therapy, (4) No post-treatment cranial contrast-enhanced CT. Patients who received treatment of apatinib combined with WBRT provided informed consent in the present study.

Treatment

Apatinib (125 mg or 250 mg once a day) was administered until the progress of intracranial tumors, unacceptable toxicity or death, and WBRT was initiated within half a month. In 2 groups, the device used for WBRT was Elekta instruments (synergy2560, Sweden). The total dose was both 30 Gy, with a dose/fraction of 3 Gy for 10 fractions, and steroid treatment was used during the treatment.

Assessments

Before the treatment, all patients had undergone a contrast-enhanced CT of the brain to establish a baseline imaging. AEs were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 5.0). Health status were evaluated by the Karnofsky performance status (KPS). The responses of the tumors were evaluated based on response evaluation criteria in solid tumors (RECIST version 1.1), including intracranial complete response (ICR), intracranial partial response (IPR), intracranial stable disease (ISD), intracranial progressive disease (IPD), and IORR = ICR + IPR, IDCR = ICR + IPR + ISD. IPFS was defined as the time between the beginning of treatment and the intracranial disease progression or death. OS was defined as the time from the start of the application of apatinib to the date of death or last follow-up (for any cause). The baseline imaging and the post-treatment cranial contrast-enhanced CT imaging were imported into the eclipse treatment planning system (Varian) target area delineation system. and the target area was delineated layer by layer (Window width 80 Hu ~ 100 Hu, Window level 35 Hu ~ 45 Hu). The volumes of a measurable intracranial tumor and the maximum brain edema were calculated based on the system (Figure 1).

Statistical Analysis

All statistical analyses were performed by SPSS version 19.0 software. The difference of baseline categorical variable between different treatment groups was compared using the χ^2 test or Fisher exact test. The difference of baseline continuous variables and comparisons of measurement data between both groups were performed by the Wilcoxon signed-rank test and t-test. IPFS and OS curves were analyzed by the Kaplan-Meier method and Log-rank tests. $P < 0.05$ was considered statistically significant.

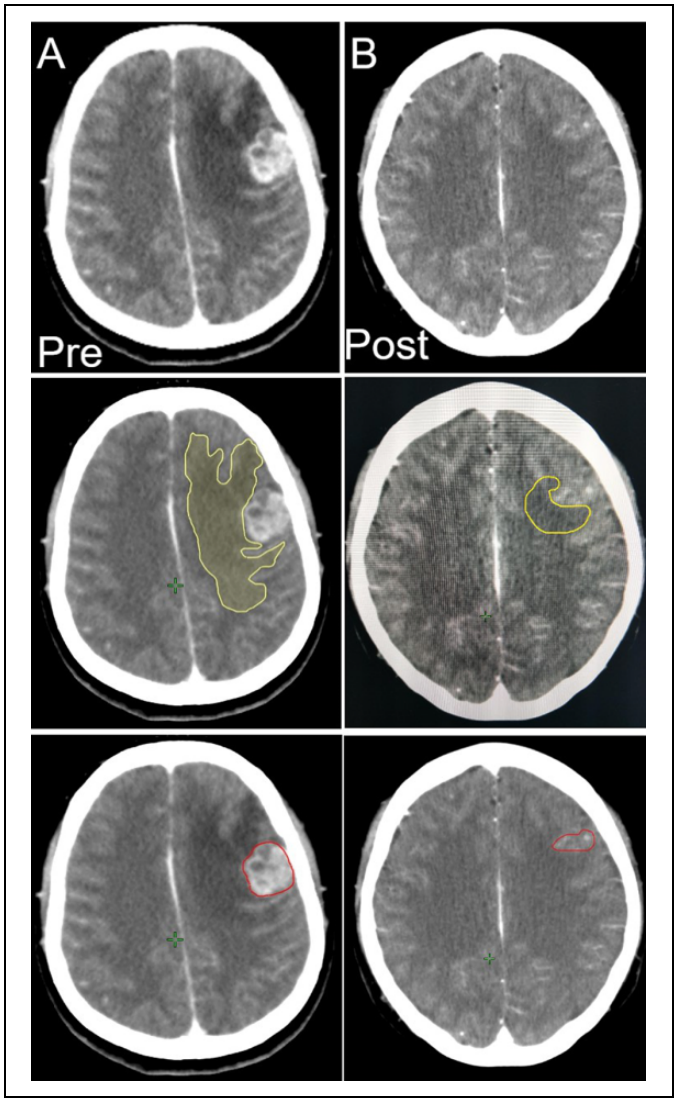

Figure 1. Contours demonstrating volumes of tumor (red) and PTBE (yellow) on CT images obtained pretreatment (A) and post-treatment (B).

Results

Patient Characteristics

Thirty-four cases who received either apatinib plus WBRT or WBRT alone as treatment were enrolled into the final analysis. Among them, 13 (38.24%) patients in the combined group received a dose of 125 mg or 250 mg once a day of apatinib. Apatinib combined with WBRT was used as a salvage treatment for patients with NSCLC symptomatic brain metastasis, and it didn't include other anti-cancer drugs during WBRT course. Four cases had failed 1 line and 9 patients had failed 2 lines of prior systemic treatment. 2 cases had previously received chemotherapy combined with bevacizumab. One patient had previously received chemotherapy combined with endostatin. Their detailed clinical diagnosis and treatment process is shown in Figure 2. Four (11.76%) males and 9 (26.47%) females were included, with a median age of 56 years and a median KPS score of 60 points. Eleven (32.36%) patients had metastasis lesion besides the brain and 6 (17.64%) patients without EGFR mutation. The symptoms of the patients from brain metastasis include increased intracranial pressure (35.30%) and focal neurologic dysfunction (17.65%). Twenty-one (61.76%) patients received chemotherapy combined with WBRT as a salvage treatment for advanced NSCLC with symptomatic multiple brain metastases, and it didn't include immunotherapy or anti-angiogenesis therapy. Among them, 6 (17.65%) patients received chemotherapy as first-line

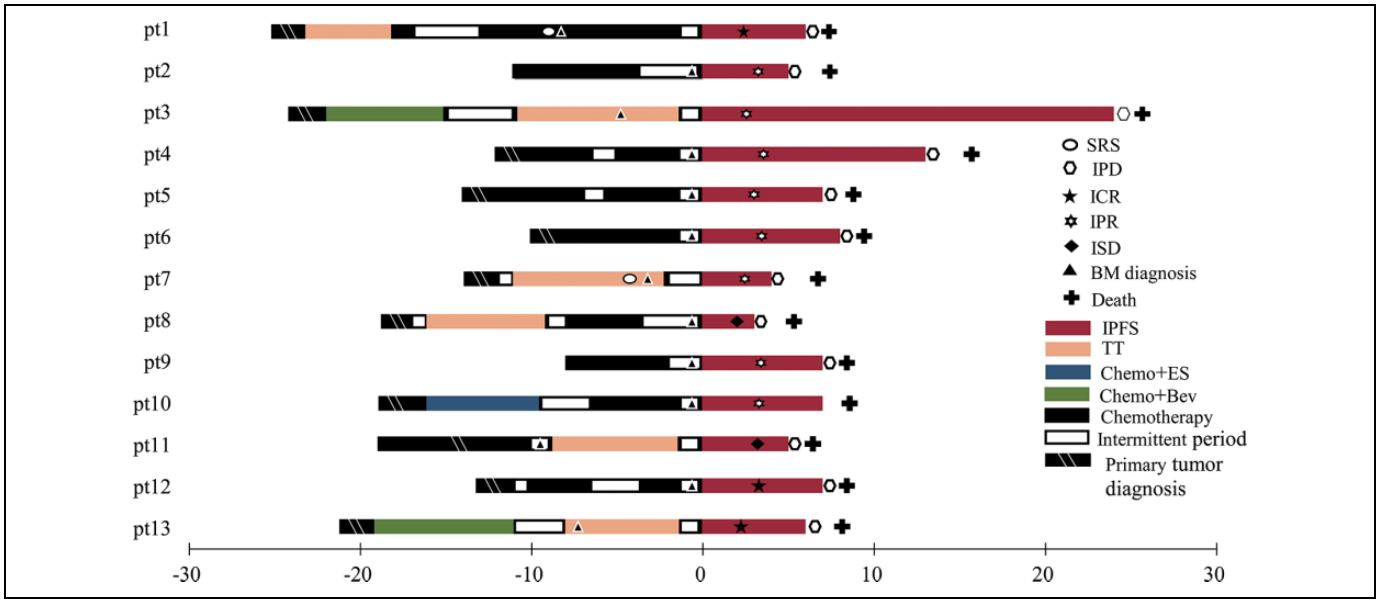

Figure 2. Timelins showing the clinical course of diseases of patients in the apatinib combined with WBRT. Each row represents a patient. The time point of WBRT is set to 0. The primary tumor is demonstrated on the left, and previous therapies are listed below. SRS, radiosurgery; TT, EGFR-TKIs; Chemo+ES, chemotherapy combined with endostatin; Chemo+Bev, chemotherapy combined with bevacizumab; BM, brain metastasis.

setting. 9 (26.47%) cases had failed 1 line and 6 (17.65%) patients had failed 2 lines of prior systemic treatment. The median age was 59 years and a median KPS score of 70 points, 13 (38.24%) were male, 9 (26.47%) were smokers, 19 (55.88%) had adenocarcinoma, 3 (8.82%) had EGFR exon 19 deletion mutation, 4 (11.76%) had EGFR exon 21 Leu858Arg mutation, 13 (38.24%) had no driver gene mutations, 16 (47.06%) had metastasis lesion besides the brain. The symptoms of the patients from brain metastasis include increased intracranial pressure (55.88%) and focal neurologic dysfunction (26.47%). Baseline characteristics of the included patients are summarized in Table 1. There was a statistical difference in prior systemic treatment between the 2 groups ($P = 0.031$), and no statistical difference between other clinical variables.

Efficacy and Safety

Until the last follow-up in August 2020, the median treatment duration of apatinib was 138 days. In the apatinib plus WBRT group, 2 patients died due to the progression of intracranial tumors, and the other 11 died of extracranial causes. In the apatinib combination treatment with WBRT group, the efficacy of intracranial tumor evaluation based on RECIST 1.1 was ICR in 3 patients, IPR in 8 patients, ISD in 2 patients. In the chemotherapy combined with WBRT group,10 cases were IPR, and 11 cases were ISD. Compared with chemotherapy, apatinib combined with WBRT had higher IORR (84.6% vs 47.6%, $P = 0.067$) (Table 2). We observed a significant decrease in the intracranial tumor volume (16.7 ± 15.2 cm^3 VS 4.1 ± 5.4 cm^3; $P = 0.001$) and edematous volume (55.7 ± 23.2 cm^3 VS 8.3 ± 7.7 cm^3; $P = 0.001$) in the apatinib plus WBRT group after treatment. We aslo observed significant decrease in the intracranial tumor volume(10.7 ± 13.6 cm^3 VS 4.5 ± 4.3cm^3; $P = 0.000$) and edematous volume(59.2 ± 35.6 cm^3 VS 36.6 ± 27.5cm^3; $P = 0.000$) in the chemotherapy plus WBRT group after treatment (Figure 3). There was a statistical difference in intracranial tumor ($P = 0.013$) and edematous volume reduction ($P = 0.004$) and total steroid dosage used ($P = 0.005$) before and after treatment between apatinib combination group and chemotherapy combination group in total population (Table 3). The average KPS scores of the 2 groups increased from 62.3 ± 12.4 to 82.3 ± 9.3 ($P = 0.001$) and 69.1 ± 10.0 to 77.1 ± 7.2 ($P = 0.002$), respectively. Statistical significance was found between cases with apatinib combination treatment and cases with chemotherapy combination treatment with regard to mIPFS [6.97 (95%CI 4.78-9.16) vs 4.77 months (95%CI 4.12-5.42); HR = 0.46, $P = 0.014$]. Two groups had mOS as 7.70 months (95%CI 6.64-8.78) vs 6.67 months [(95%CI 5.66-7.67); HR = 0.61, $P = 0.14$] (Figure 4).

All of the treatment-related adverse reactions were shown in grades 1 or 2 (Table 4), including grade 1 proteinuria (1/13), fatigue (1/13), nausea (2/13), vomiting (1/13), platelet count decrease (1/13), white blood cell decrease (1/13) and lymphocyte count decrease (1/13). Grade 2 mucositis oral (1/13), palmar-plantar erythrodysesthesia syndrome (1/13), diarrhea (1/13), fatigue (2/13), nausea (2/13), hypertension (2/13) and white blood cell decrease (1/13). Grade 2 diarrhea occurred in 1 patient who stopped apatinib for 1 week, and the symptoms completely disappeared. Grade 2 mucositis oral and palmar-plantar erythrodysesthesia syndrome completely disappeared

Table 1. Baseline Characteristics of the Study Population (N = 34).

Variables	Apatinib + WBRT		Chemotherapy + WBRT		*P*-values
Total	13	38.24%	21	61.76%	
Median age, years	56 (interquartile ranged from 50.5 to 62.5)		59 (interquartile ranged from 51 to 66)		0.381
Sex					0.437
Male	4	11.76%	13	38.24%	
Female	9	26.47%	8	23.53%	
Smoking history					0.140
Yes	2	5.88%	9	26.47%	
No	11	32.35%	12	35.29%	
Tumor histology					1.000
Squamous cell carcinoma	1	2.94%	2	5.88%	
Adenocarcinoma	12	35.29%	19	55.88%	
Driver gene mutation					0.932
Exon 19 deletion	3	8.82%	3	8.82%	
Exon 21 Leu858Arg mutation	3	8.82%	4	11.76%	
No	6	17.65%	13	38.24%	
Unknown	1	2.94%	1	2.94%	
Prior systemic treatment					0.031
0	0	0	6	17.65%	
1	4	11.76%	9	26.47%	
2	9	26.47%	6	17.65%	
Clinical situation					1.000
Increased intracranial pressure	7	20.59%	12	35.29%	
Focal neurologic dysfunction	1	2.94%	2	5.88%	
Both	5	14.71%	7	20.59%	
Number of extracranial metastases					0.903
0	2	5.88%	5	14.71%	
1	5	14.71%	8	23.53%	
≥2	6	17.65%	8	23.53%	
Extracranial lesions control statuses					0.898
Partial response	3	8.82%	4	11.76%	
Stable disease	8	23.53%	12	35.29%	
Progressive disease	2	5.88%	5	14.71%	
Median karnofsky performance status	60 (interquartile ranged from 55 to 75)		70 (interquartile ranged from 60 to 80)		0.074
Baseline intracranial tumor volume($\bar{x} \pm s$, cm^3)	16.7 ± 15.2		10.7 ± 13.6		0.161
Baseline edematous volume($\bar{x} \pm s$, cm^3)	55.7 ± 23.2		59.2 ± 35.6		0.818

Table 2. Treatment Response (N = 34).

	Apatinib+ WBRT	Chemotherapy + WBRT	*P*
Response			
Intracranial complete response	3 (23.1)	0	0.021
Intracranial partial response	8 (61.5)	10	
Intracranial stable disease	2(15.4)	11	
Intracranial objective response rate	84.6%	47.6%	0.067
Intracranial disease control rate	100%	100%	

in 2 patients after the dose of apatinb reduction. No serious adverse events such as cerebral hemorrhage, cardiotoxicity, and thrombosis were observed.

Discussion

The present study is the first trial to evaluate apatinib combined with WBRT in symptomatic brain metastasis from NSCLC. In our study, we observed that long-term oral low-dose apatinib (125/250 mg) in combination with WBRT reduce PTBE and intracranial tumor volume, which was better than that of chemotherapy plus WBRT. In the apatinib combination group resulted in the significantly higher IORR and longer IPFS than chemotherapy combination group.

Anti-angiogenesis is an important treatment strategy for NSCLC with cerebral metastasis. The largest retrospective study showed that compared with mono-EGFR-TKI, the first-line use of bevacizumab combined with EGFR-TKI can improve IORR, IPFS and OS in advanced non-squamous NSCLC with EGFR-mutant and multiple brain metastases.[20] In addition, A Nonrandomized, Phase II Study suggested that bevacizumab combined with chemotherapy or erlotinib

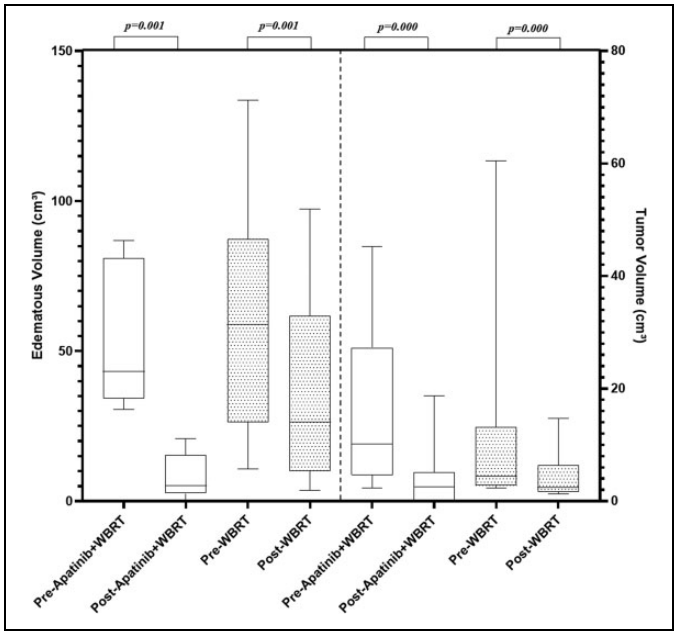

Figure 3. Box plots demonstrating the change in edematous, tumor volumes in the 2 groups.

Table 3. Comparison of Intracranial Tumor and Edematous Volume Reduction and Total Steroid Dosage Used Before and After Treatment in the 2 Groups.

	Apatinib+WBRT	Chemotherapy + WBRT	*P*
Tumor volume reduction ($\bar{X} \pm S$)	12.7 ± 11.9	6.2 ± 10.0	0.013
Edematous volume reduction ($\bar{X} \pm S$)	47.4 ± 21.9	22.6 ± 23.1	0.004
Total steroid dosage ($\bar{X} \pm S$)	100.8 ± 54.6	178.3 ± 96.1	0.005

provided a better control of intracranial metastasis of nonsquamous NSCLC with asymptomatic, untreated BMS compared to the control of extracranial lesion.[21] Ascha *et al* (2019) reported that bevacizumab reduced the hazard of mortality of NSCLC with brain metastasis by 0.75 times (95% CI: 0.59 ~ 0.96, $P = 0.020$), which was related to inhibit angiogenesis and improvement of vasogenic edema.[22] Therefore, the combined treatment model of anti-angiogenesis deserved to be further explored in NSCLC with multiple brain metastases. At present, only a few studies have focused on anti-VEGF therapy combined with WBRT in cerebral metastasis. For instance, in the phase I REBECA study, bevacizumab combining with WBRT had a synergistic effect and was a tolerable treatment for cerebral metastasis from different solid cancer, including from breast, ovary and lung cancer, an mIPFS of 7.1 months, an mOS of 13.3months[11] We look forward to the results of the ongoing further Phase II trial. Another randomized controlled study demonstrated that comparing with radiotherapy alone, recombinant human endostatin combining with radiotherapy can effectively reduce brain edema ($P < 0.05$) in NSCLC patients with cerebral metastasis and the ORR was increased in the patients with positive VEGFR (93% vs 67.7%, $P = 0.012$). The mOS of the combination and radiotherapy alone groups in total population was 9 months and 7 months, respectively.[23]

Apatinib is a novel small molecule vascular TKI of VEGFR 2 that inhibits tumor growth by blocking VEGF-induced endothelial cell migration and proliferation. Compared with intravenous bevacizumab, oral apatinib alone was effective as a salvage therapy in heavily pretreated solid cancer.[16,24,25] Our previous study suggested that 250 mg of apatinib daily monotherapy significantly reduced the volume of cerebral metastasis and PTBE in triple-negative breast cancer.[18] In addition, a retrospective study shows that apatinib combination with EGFR-TKI or chemotherapy can improve the DCR and survival time in patients with brain metastasis from NSCLC.[19] Ying *et al* first reported that a female case of lung adenocarcinoma with multiple brain metastases, and without driver gene mutation, 500 mg of apatinib daily monotherapy combined with WBRT plus simultaneous in-field boost, a partial response in intracranial and primary tumor was observed on the first day after finishing radiotherapy. Also, the volume of PTBE and neurological symptoms almost completely disappeared.[26]

In our study, the IORR (11/13, 84.6%) and IPFS (6.97 vs 4.77 months, $P = 0.014$) of apatinib combined with WBRT appear to be desirable and better than chemotherapy combined with WBRT. Continuous administration of apatinib and WBRT can inhibit intracranial tumor growth in a synergistic way, which may relate to the significant reduction of PTBE and the enhancement of the radiosensitivity. Moreover, small molecules apatinib may directly cross the blood-brain barrier to induce tumor cell apoptosis, while large molecules (such as bevacizumab) may not be able to cross the blood-brain barrier.[27] Our previous study showed that intracranial tumors responded well to apatinib monotherapy.[18] WBRT can probably increase the concentration of apatinib in cerebral spinal fluid, while it is still necessary to establish animal models verify this. One previous study had confirmed that WBRT can increase the concentration of small molecule targeted drugs (EGFR-TKI) in cerebral spinal fluid.[28] Compared with chemotherapy, apatinib combined with WBRT as a salvage treatment for patients with symptomatic brain metastasis from NSCLC, can significantly reduce the volume of PTBE and diminish the central nervous system symptoms. A combination of apatinib with WBRT can reduce the patients' dependence on steroid and no steroid-related complications occurred. Also, no acute radiation brain edema occurred in all patients during the treatment period to ensure the successful completion of radiotherapy. The total steroid dosage in the chemotherapy combination group was significantly higher than that in the apatinib combined treatment group. Among them, the dosage of steroids in 5 cases needs to be increased during WBRT, and the volume of PTBE increased in 2 cases after WBRT.

The mIPFS and mOS were 6.97 months and 7.70 months, which were lower than the mIPFS of 7.1 months and mOS of 13.3 months in the REBECA study. This outcome may be

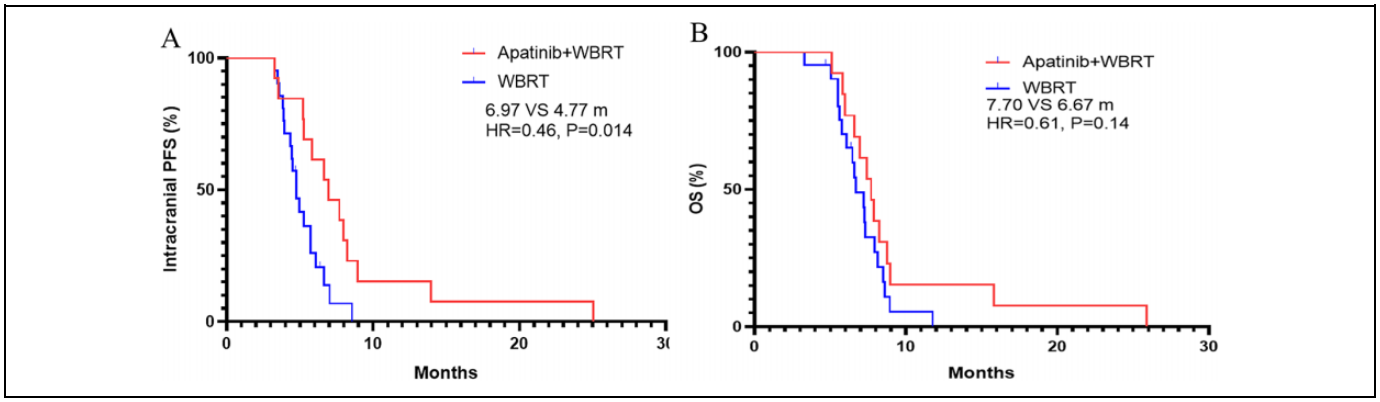

Figure 4. Kaplan–Meier intracranial progression-free survival (iPFS) and overall survival (OS) curves in 2 for peer review groups. (A) iPFS. (B) OS.

Table 4. Adverse Events Related to Treatment.

	Grade		
Toxicity	1	2	Total
Non-hematologic			
proteinuria	1	0	1
Mucositis oral	0	1	1
Palmar-plantar erythrodysesthesia syndrome	0	1	1
Diarrhea	0	1	1
Fatigue	1	2	3
Nausea	2	2	4
Vomiting	1	0	1
Hypertension	0	2	2
Hematologic			
Platelet count decrease	1	0	1
White blood cell decrease	1	1	2
Lymphocyte count decrease	1	0	1

associated with all patients having central nervous system symptoms, and most patients were heavily pretreated for advance NSCLC and had poor KPS scores at baseline. In addition, the majority of patients with brain metastases in the REBECA study were from breast cancer. Our research also found that after the therapy of apatinib combined with WBRT, the symptoms of central nervous system of 12 patients disappeared and their KPS scores increased significantly, as a result, some patients were able to tolerate chemotherapy again. It implied that apatinib combined with WBRT may bring a survival benefit for NSCLC patients with brain metastasis. In the phase III BRAIN trial, the IORR of chemotherapy combined with WBRT was 40.9% in NSCLC with brain metastases harboring EGFR mutation, and the IPFS was 4.8 months, the mOS was 18 months.[29] The IORR and mIPFS of the chemotherapy combined with WBRT group in our study was 47.6% and 4.77 months, respectively, which was in line with BRAIN trial. Most chemotherapeutic drugs cannot penetrate the blood-brain barrier because of their large size (>150 kDa), hydrophilicity, ionization or protein-binding. Although the occurrence of brain metastasis leads to the destruction of the blood-brain barrier, they still cannot achieve therapeutic levels in intracranial.[30] Therefore, chemotherapeutic drugs have poor efficacy on intracranial tumors. Our research results also indicated that apatinib combined with WBRT was better than chemotherapy combined with WBRT in controlling intracranial tumors. The mOS in our 2 groups was shorter than the mOS of 18 months in BRAIN trial. The difference between our study's outcome with the former may be due to the fact that all patients were either on EGFR-TKI resistance before treatment start or did not harbor driver gene mutations. Notably, mOS between the 2 groups showed no statistical difference, which may have been caused by more effective systemic drugs and higher median KPS score in the WBRT group.

Because of the risk of cerebral hemorrhage caused by anti-angiogenic agents or the increased toxicity of the combination with WBRT, we usually applied a low-dose of apatinib (125-250 mg) in our study instead of the recommended dose of 850 mg in advanced gastric adenocarcinoma or 750 mg in advanced non-squamous NSCLC. In the phase II clinical trial, pretreated advanced non-squamous NSCLC patients received 500 or 750 mg apatinib daily, the incidence of Grade 3 AEs was 25%, including hand-foot-skin reaction (5.0%), hypertension (2.5%), thrombocytopenia (5%). The incidence of hand-foot-skin reaction, proteinuria, oral mucositis, fatigue, and hypertension was 30%, 27.5%, 22.5%, 20.0% and 17.5%, respectively.[15] In the phase III study, chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction oral apatinib 850 mg once daily, the incidence of Grade 3 to 4 AEs was 45.7%, the most common Grade 3 to 4 AEs including hand-foot-skin reaction (8.5%), proteinuria (2.3%) and hypertension (4.5%).[13] This retrospective study suggested that continuous administration of low-dose apatinib (125-250 mg) combined with WBRT was well tolerated in heavily pretreated advanced NSCLC with multiple symptomatic brain metastases, the treatment-related AEs were all grade 1 to 2, and no grade 3 to 4 AEs were observed. One study also reported that a low dosage of apatinib (250-425 mg/day) was also safe and effective in subsequent post-second-line treatment of 13 advanced LSCC (ORR

15.4%, DCR 46.2%, median PFS is 3.1 months), the main AEs were vomiting and experienced hypertension.[25] One LSCC patient with 250 mg of apatinib daily monotherapy did not develop pulmonary hemorrhage in our study. The present study suggested that a low-dose apatinib in combination with WBRT was effective and safe with no radiation-associated toxicities or cerebral hemorrhage. This was consistent with the results of prior studies.[11,23,26]

Although the results of our study had significant clinical value, several limitations were present in our study due to the small sample size and retrospective features. Therefore, large-scale research is still needed, especially prospective research. As far as we know, a randomized open controlled clinical trial of apatinib combined with brain radiotherapy for the treatment of brain metastases from NSCLC without driver gene mutations is ongoing.[31]

Conclusion

This is the first known retrospective study of apatinib concurrent with WBRT in NSCLC patients with symptomatic brain metastasis. In any case, it provides additional treatment option for patients with symptomatic brain metastasis from relapsed or drug-resistant advanced NSCLC, in the same time, a controlled study with enlarged sample size has been initiated (Registration number ChiCTR2000031785).

Authors' Note

Shan-bing Wang contributed equally to this work and is the co-first author of this article.All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Retrospective analysis of patient data was approved by the Ethics Committee of The Second People's Hospital of Yibin (Ethical approval documents number: 2020-019-01). Informed consent was obtained from all individual participants included in the study.

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Declaration of Conflicting Interests

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