

Received:
27 May 2022

Revised:
25 April 2023

Accepted:
30 April 2023

Published online:
16 May 2023

<https://doi.org/10.1259/bjr.20220550>

Cite this article as:

Pan H, Zhou X, Shen L, Li Y, Dong W, Wang S, et al. Efficacy of apatinib+radiotherapy vs radiotherapy alone in patients with advanced multiline therapy failure for non small cell lung cancer with brain metastasis. *Br J Radiol* (2023) 10.1259/bjr.20220550.

FULL PAPER

Efficacy of apatinib+radiotherapy vs radiotherapy alone in patients with advanced multiline therapy failure for non small cell lung cancer with brain metastasis

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Objective: Lung cancer is the leading cause of cancer-associated mortality worldwide. Central nervous system (CNS) metastasis is a prevalent and serious complication. The most common treatment for brain metastasis (BM) is still radiation therapy (RT). An increasing number of drugs have been shown to have intracranial activity or to sensitize tumours to radiotherapy.

Methods: Consecutive advanced multiline therapy failure in patients with non-small-cell lung cancer (NSCLC) with BM at the authors' hospital were retrospectively reviewed. Eligible patients were divided into two groups: Apatinib+RT group and RT group. Intracranial progression-free survival (PFS) and overall survival (OS) were analysed using the Kaplan-Meier method.

Results: The median intracranial PFS for the RT group and Apatinib+RT group was 5.83 months and 11.81 months ($p = 0.034$). The median OS for the RT group and

Apatinib+RT group was 9.02 months and 13.62 months ($p = 0.311$). The Apatinib+RT group had a better intracranial PFS, but there were no significant differences between the two arms in OS. The Apatinib+RT group had significantly reduced symptoms caused by BM.

Conclusion: RT combined with apatinib could help to control intracranial metastases. The Apatinib+RT group had significantly reduced symptoms caused by BM and improved quality of life for patients, the safety of the two treatments was similar.

Advances in knowledge: Here, we propose that RT combined with apatinib can significantly relieve brain symptoms and tolerate side-effects without affecting OS in patients with BM following failure of multiline therapy for NSCLC. Of course, this paper is a retrospective origin study, and more powerful evidence is needed to demonstrate.

OBJECTIVES

Lung cancer is the leading cause of cancer-associated mortality worldwide, and in China, non-small-cell lung cancer (NSCLC) represents approximately 80–85% of all lung cancers.^{1,2} Central nervous system (CNS) metastasis is a prevalent and serious complication, with negative effects on quality of life (QoL) and overall survival (OS).³ More than 10% of NSCLC patients present with brain metastasis (BM) at their first visit to hospital,^{4,5} and approximately 30–40% of patients with NSCLC develop BM during the course of their disease, with a poor prognosis and a median survival of 1–4 months, without any

treatment.⁶ There are many therapeutic methods for BMs, including surgery, chemotherapy, targeted therapy and radiotherapy. Chemotherapy alone has been shown to extend survival by only 2–3 months in patients for whom immune or targeted therapy is not available.⁷ There have some studies shown that with targeted therapy or immunotherapy could prolong survival to approximately 3–8 months. However, some patients eventually develop drug resistance after a median of 8–13 months of disease control.⁸ Surgical resection or radiosurgery (SRS) combined with adjuvant WBRT prolong survival to approximately 8–11 months.⁹

At present, the most common treatment for BM is still radiation therapy (RT), including stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT). WBRT is the most common method for the treatment of BMs because it is suitable for most patients and can rapidly relieve cranial nerve symptoms, with an effective rate of 70%.¹⁰ This may be because BMs are often accompanied by brain oedema, and radiotherapy usually aggravates the oedema of the normal brain tissue to some extent.¹⁰ Local approaches, such as surgery and SRS, are indicated in solitary or oligometastatic disease. Several chemotherapy drugs in combination with WBRT fail to improve survival because of the impenetrability of the blood–brain barrier (BBB).¹¹ Along with chemotherapy, many targeted agents have been developed to improve the typically dismal outcome associated with NSCLC. Irrespective of the origin and the site of metastases, the growth and survival of tumour cells depend on the establishment of an adequate blood supply,¹² which is mainly supported by neo-angiogenesis. Angiogenesis is regulated by several pro- and anti-angiogenic factors. Among pro-angiogenic factors, vascular endothelial growth factor (VEGF) is the most extensively studied and stimulates angiogenesis primarily through activation of vascular endothelial growth factor receptor-2 (VEGFR-2),¹³ and both are commonly expressed in NSCLC.¹⁴ The primary goal for using anti-angiogenic therapies is to block the development of malignant neovasculature, to reduce oxygen availability in the tumour and to decrease its growth. Apatinib is an oral tyrosine kinase inhibitors (TKIs) with anti-angiogenic properties, and it is currently approved for the treatment of advanced gastric cancer. In addition, many studies have demonstrated that apatinib is effective in the treatment of advanced NSCLC,¹⁵ and some studies suggest that apatinib has some synergistic effects with RT.¹⁶ However, the mechanism of action of apatinib combined with RT for better control of BM is not completely clear.

With the development of targeted therapy and immunotherapy, an increasing number of drugs have been shown to have intracranial activity or to sensitize tumours to radiotherapy. Therefore, finding a highly efficient and relatively nontoxic radiosensitization drug is crucial to improving the therapeutic effects of radiotherapy for BMs. Our study aims to demonstrate the clinical efficacy of apatinib combined with radiotherapy vs radiotherapy alone in the treatment of patients with advanced multiline failure for non-small-cell lung cancer with BM.

METHODS

Patients

Consecutive advanced multiline therapy failure in patients with NSCLC with BM at the authors' hospital from January 2016 to August 2020 were retrospectively reviewed. The eligibility criteria for this study were as follows: BM occurred in patients with NSCLC after failure of >2 lines of treatment; patients were historically diagnosed with NSCLC and new BM were confirmed by MRI; they had >3 measurable BM according to the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1; patients were diagnosed without a mutation in endothelial growth factor (EGFR), anaplastic lymphoma kinase (ALK), repressor of silencing 1 (ROS1), the RET and MET proto-oncogenes etc.; they had no serious dysfunction of major organs (e.g. heart failure or

uraemia); and they had adequate haematologic function (absolute neutrophil $\geq 1.5 \times 10^9 \text{ l}^{-1}$ or platelet count $\geq 100 \times 10^9 \text{ l}^{-1}$).

Study design

Eligible patients were divided into two groups: Apatinib+RT group and RT group. In the Apatinib+RT group, patients with NSCLC received radiation to BM at the same time that apatinib was used to treat lung cancer or other metastatic lesions. Patients in this group continue to take apatinib unless the disease progresses or severe adverse events occurred, and the mean duration of apatinib treatment was 7.25 months. In the RT group, patients only received RT to BM.

All patients were evaluated weekly during RT. Evaluation included a complete history, neurologic examination, blood counts, and biochemistry profile. Evaluation during follow-up was done monthly, including physical examination, neurologic examination, a complete blood count measurement, liver function test, and chest CT scan. Brain CT with and without contrast, abdominal CT, or bone scan, as well as MRI if necessary, was performed when there were relevant symptoms.

Statistical analyses

Pearson's χ^2 or Fisher's exact test was used to compare the baseline characteristics between the apatinib+RT group and RT group. Tumour response was assessed according to RECIST 1.1. OS was defined as the interval from the date of initial BM diagnosis to the date of death. Intracranial PFS was defined as the interval between the WBRT initiation and the date of confirming CNS progression or death from CNS progression if death had occurred within 60 days of the last CNS assessment date. If the complete survival time of a patient was impossible to obtain or the disease did not progress, the patient's status was assumed to be the last known survival and/or contact date. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v. 4.0.

Intracranial PFS and OS were analysed using the Kaplan–Meier method. Differences between groups were compared by the log-rank test. The Cox proportional hazards model was used for uni- and multivariate analyses to identify the independent prognostic factors for PFS and OS. Statistical analyses were carried out with SPSS 22.0 software. Tests were two-sided. A p -value < 0.05 was considered statistically significant, and robust estimates of the standard error were used in all regression analyses.

RESULTS

Patient characteristics

Among the total of 63 NSCLC patients with advanced BM after undergoing multiline therapy in hospital from January 2016 to August 2021, 31 (49.2%) were in the RT group and 32 (50.8%) were in the Apatinib+RT group.

In the RT group, all patients received WBRT or SRS for BMs. According to the number of BMs, patients with three or fewer BMs received SRS which has been used Varian EDGE machine. For patients with BMs, single segmental SRS limited V12 Gy brain tissue (normal brain+target vol) to $\leq 10 \text{ cm}^3$. If brain tissue

(normal brain+target vol) V12 Gy >10 cm³, fractional SRS considered to reduce the risk of radiation necrosis. Patients with BMs diameter ≤2 cm were treated with single segmental SRS, 20–24 Gy (located in or near a non-functional area). Patients with 2 cm ≤ BMs diameter ≤3 cm were treated with single segment SRS, 18 Gy or fractionated SRS (27 Gy/3 fx or 30cGy/5 fx). For large lesions (usually BMs diameter > 3 cm), a single dose of SRS is difficult to achieve good local control, and the therapeutic toxicity is significantly increased, Patients were treated with FSRS (27 Gy/3 fx or 30cGy/5 fx). And patients with more than four lesions were treated with WBRT (30 Gy/10 fx or 20 Gy/5 fx). In addition, the protection of organ at risk cannot be ignored: Brain stem: maximum tolerated dose ≤54 Gy; Optic nerve and optic chiasma: maximum tolerated dose ≤60 Gy.; Crystal: maximum tolerated dose ≤9 Gy.; Temporal lobe: maximum tolerated dose ≤60 Gy.; Pituitary: maximum tolerated dose ≤50~54 Gy, and the maximum dose in hippocampus was limited to 9–16 Gy.¹⁷

In the Apatinib+RT group, patients received radiotherapy in the same way as in the RT group, but they also received apatinib (500 mg/d) targeted therapy at the same time, until the disease progressed by restaging MRI or CT scan. When patients developed intolerable side-effects, the dose was reduced to 250 mg/d.

Patients in the RT group and Apatinib+RT group were well balanced with regard to sex, age, smoking history, Karnofsky performance status (KPS), Lung Cancer Using Molecular Markers (Lung-molGPA), and histologic type (Table 1).

Outcomes stratified by group

The median intracranial PFS for the RT group and Apatinib+RT group was 5.83 months (95% CI, 2.99–8.67 months) and 11.81 months (95% CI, 8.31–16.50 months, $p = 0.034$), respectively, as shown in Figure 1. The median OS for the RT group and Apatinib+RT group was 9.02 months (95% CI, 6.30–11.70 months) and 13.62 months (95% CI, 8.13–16.80 months, $p = 0.311$), respectively, as shown in Figure 2. The Apatinib+RT group had a better intracranial PFS (11.81 vs 5.83 months, $p = 0.034$), but there were no significant differences between the two arms in OS (13.62 vs 9.02 months, $p = 0.311$). The above results suggest that RT combined with apatinib could help to control intracranial metastases and delay the progression of intracranial metastases, but there was no significant effect on overall survival.

Multivariate analysis and toxicities

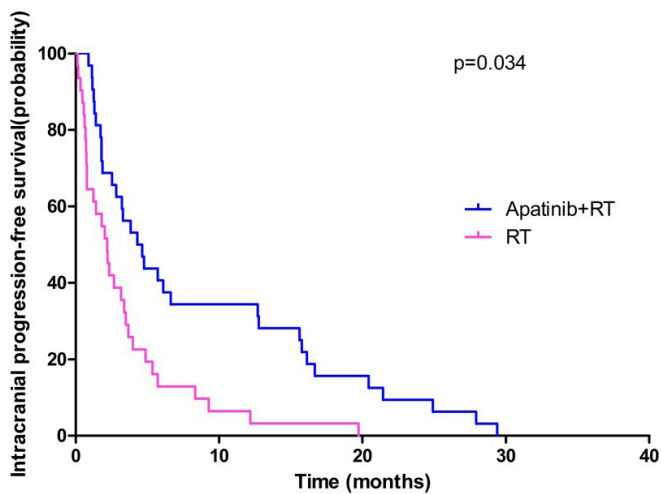
Multivariate analysis of intracranial PFS and OS for all NSCLC patients and for the RT group and Apatinib+RT group is shown

Table 1. Clinical characteristics of patients

Characteristics	All patients N(%)	RT group N(%)	Apatinib+RT group N(%)	<i>p</i>
All patients	63(100)	31(100)	32(100)	
Gender				
Female	21 (33.3)	15 (48.4)	9 (28.1)	
Male	42 (66.7)	16 (51.6)	23 (71.9)	0.098
Age				
<65	49 (77.8)	24 (77.4)	25 (78.1)	
≥65	14 (22.2)	7 (22.6)	7 (21.9)	0.946
Smoking				
Never	30 (47.6)	19 (61.3)	12 (37.5)	
Current/former	33 (52.4)	12 (38.7)	20 (62.5)	0.059
KPS				
<70	18 (28.6)	8 (25.8)	10 (31.2)	
70–100	45 (71.4)	23 (74.2)	22 (68.8)	0.633
Lung-molGPA				
0–1.5	42 (66.7)	22 (71.0)	20 (62.5)	
2–3	21 (33.3)	9 (29.0)	12 (37.5)	0.476
Histology				
Adenocarcinoma	39 (61.9)	22 (71.0)	17 (53.1)	
Non-adenocarcinoma	24 (38.1)	9 (29.0)	15 (46.9)	0.145
WBRT/SRS				
WBRT	28 (44.4)	16 (51.6)	12 (37.5)	
SRS	35 (55.6)	15 (48.4)	20 (62.5)	0.260

Lung Cancer Using Molecular Markers: Lung-molGPA; Radiation RT: radiation therapy; Karnofsky Performance Status: KPS.

Figure 1. Intracranial progression-free survival of patients between RT group and Apatinib+RT group. RT, radiation therapy.

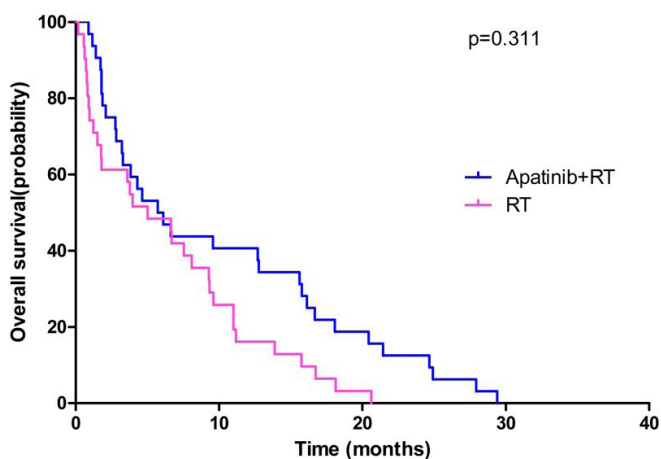


in Table 2. Among all patients, sex (0.008), KPS (0.006), Lung-molGPA (0.038) and smoking history (0.008) were associated with OS. Within the Apatinib+RT group, sex (0.012) was associated with intracranial PFS, and sex (0.006) and smoking history (0.027) were associated with OS. In the RT group, no significant factors affected the intracranial PFS and OS.

In the Apatinib+RT group, the disease control rate (DCR) and object response rate (ORR) were 56.3% ($N = 18$) and 38.7% ($N = 12$), respectively. In the RT group, the DCR and ORR were 19.4% ($N = 6$) and 37.5% ($N = 12$), respectively. The DCR and ORR were both higher in the Apatinib+RT group than in the RT group, but there were no statistically significant differences between the two groups ($p = 0.163$ and 0.111).

The Apatinib+RT group had significantly reduced symptoms caused by BM, mainly headache (21.9 and 19.4%) and vomiting (28.1 and 16.1%). Toxicities were reported in all patients in the RT group and Apatinib+RT group, such as headache (54.8 and

Figure 2. Overall survival of patients between RT group and Apatinib+RT group.



28.1%, respectively), nausea (67.7 and 37.5%) and vomiting (61.3 and 34.4%) (Table 3). Myelosuppression was also one of the more common adverse reactions in both groups, manifesting as anaemia (51.6 and 50.0%, respectively), neutropaenia (45.2 and 53.1%) and thrombocytopenia (45.2 and 46.9%) in the RT group and Apatinib+RT group.

Most patients tolerated the side-effects well. Overall, all toxicities were generally brief, reversible, and manageable. They were well tolerated after symptomatic treatments.

Quality of life

QOL refers to the subjective feeling and total satisfaction of human beings in physical, psychological, spiritual and social aspects. American medical doctor Wenger think QoL is composed of three parts: 1. Functional state, *i.e.* patients with a variety of daily life ability and whether they can carry out normal people need a variety of routine activities, including the ability of daily life, social work ability, intelligence, emotional state that is the economic status of the five aspects. 2. The perception state, that is, the patient's own evaluation of the above cognition varies from person to person. 3. Symptoms can be changed by symptoms caused by the disease itself and adverse reactions caused by various treatments. Therefore, survival therapy, as a response to the physical function, psychological state, social adaptation and environmental factors of patients, can fully reflect the health level of patients.^{18,19}

According to the tumour patient QoL score standard scores in China 1990, from loss of appetite, spirit, sleep, fatigue, pain, understanding and co-operation with family, understand and co-operate with colleagues, self-understanding of cancer, attitude towards treatment, daily life, treatment side-effects, facial expression Grade 12 aspects, full marks for 60 min, 51–60 was divided into excellent, 41–50 was divided into good, 31–40 is divided into general, 21–30 divided into poor, divided into terrible less than 20.¹⁹ The results were shown in Table 4. There was no significant difference between the RT group and Apatinib+RT group. The score of most patients was 31–50. Patients enrolled in this study were NSCLC with BM after the failure of multiline therapy, so most patients were physically weak, while a few patients with a score less than 20 were in very poor condition, mainly due to long-term bed rest caused by serious adverse reactions. The mean score of RT group was 33.8, and the mean score of Apatinib+RT group was 38.1, which was significantly higher than that of RT group. The proportion of patients with 31–50 scores in Apatinib+RT group (78.1) was significantly higher than that in RT group (67.7%), mainly because the symptoms related to BM were reduced.

Discussion and conclusions

CNS metastasis is a prevalent and serious complication of NSCLC, with negative effects on quality of life and OS.³ BM from NSCLC remains a difficult problem in clinical practice. The purpose of this study was to investigate the clinical efficacy of apatinib added to RT in patients with BM after failure of multiline therapy.

Table 2. Multivariate analysis of factors affecting intracranial PFS and OS in the patients

Factors	Intracranial PFS			OS		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
All patients						
Gender	0.393	0.141–1.101	0.076	0.242	0.085–0.692	0.008
Age	1.190	0.545–2.601	0.663	1.260	0.593–2.678	0.548
KPS	1.065	0.979–3.357	0.057	1.950	0.370–5.349	0.006
Lung-molGPA	0.721	0.496–1.048	0.086	0.665	0.452–0.978	0.038
Smoking	0.430	0.180–1.026	0.057	0.297	0.121–0.728	0.008
Histology	0.875	0.457–1.674	0.686	0.637	0.337–1.205	0.166
RT group						
Gender	0.824	0.221–3.071	0.773	0.464	0.100–2.161	0.328
Age	1.751	0.576–5.317	0.323	1.748	0.529–5.774	0.360
KPS	1.232	0.707–6.050	0.171	1.178	0.901–7.202	0.072
Lung-molGPA	0.664	0.376–1.170	0.156	0.623	0.345–1.125	0.117
Smoking	0.261	0.063–1.085	0.065	0.242	0.054–1.088	0.064
Histology	0.502	0.183–1.375	0.180	0.675	0.229–1.992	0.476
Apatinib+RT group						
Gender	0.050	0.005–0.519	0.012	0.083	0.014–0.494	0.006
Age	0.895	0.310–2.586	0.838	1.185	0.442–3.176	0.736
KPS	1.587	0.708–3.555	0.262	1.300	0.941–4.622	0.068
Lung-molGPA	0.737	0.437–1.243	0.252	0.691	0.411–1.162	0.163
Smoking	0.463	0.139–1.536	0.208	0.277	0.089–0.862	0.027
Histology	0.874	0.335–2.281	0.784	0.774	0.321–1.867	0.569

progression-free survival: PFS; overall survival: OS; hazard ratio: HR; confidence interval: CI; Karnofsky Performance Status: KPS.

Systemic therapies have been deemed ineffective in BM under the hypothesis that the BBB limits their delivery to the brain.¹¹ The BBB serves as a functional and structural barrier, limiting the passive diffusion of hydrophilic and charged compounds into the brain. Its tight junctions limit the passage of large molecules from the blood to the brain. Lockman et al suggested

that the BBB and the blood-tumour barrier present a significant obstacle in the treatment of BMs by limiting drug uptake to subtherapeutic levels.²⁰ RT is one of the most effective treatments for BMs.^{21–23} Here, the patients with three or fewer BMs received SRS,²¹ and patients with more than four lesions were treated with WBRT.²³ However, there are few studies on whether

Table 3. Toxicity profile for all patients

Side-effects	RT group (%) (N = 31)		Apatinib+RT group (N = 32)	
	All grades, N. (%)	Grade III/IV, N. (%)	All grades, N. (%)	Grade III/IV, N. (%)
Fatigue	17 (54.8)	3 (9.7)	18 (56.3)	4 (12.5)
Anorexia	13 (41.9)	2 (6.5)	13 (40.6)	2 (6.3)
Diarrhoea	3 (9.7)	0 (0)	3 (9.4)	1 (3.1)
Nausea	21 (67.7)	5 (16.1)	12 (37.5)	2 (6.3)
Vomiting	19 (61.3)	4 (12.9)	11 (34.4)	1 (3.1)
Headache	17 (54.8)	3 (9.7)	9 (28.1)	2 (6.3)
Anaemia	16 (51.6)	1 (3.2)	16 (50.0)	1 (3.1)
Neutropaenia	14 (45.2)	3 (9.7)	17 (53.1)	2 (6.3)
Thrombocytopenia	14 (45.2)	1 (3.2)	15 (46.9)	2 (6.3)

Radiation therapy: RT.

Table 4. QoL profile for all patients

QoL	All patients% (N = 63)	RT group % (N = 31)	Apatinib+RT group% (N = 32)
AVERAGE	36.0	33.8	38.1
51-60	3 (4.7)	1 (3.2)	2 (6.3)
41-50	21 (33.3)	8 (25.8)	13 (40.6)
31-40	25 (39.7)	13 (41.9)	12 (37.5)
21-30	10 (15.9)	6 (19.3)	3 (9.4)
< 20	4 (6.3)	3 (9.7)	2 (6.3)

Quality of QoL, quality of life.

VEGFR inhibitor combined with radiotherapy has better clinical efficacy. Our study showed that the Apatinib+RT group had a better intracranial PFS (11.81 vs 5.83 months, $p = 0.034$). RT combined with apatinib could help to control intracranial metastases and delay the progression of intracranial metastases, but it did not significantly extend OS. In addition, the safety of the two treatments was similar, and apatinib combined with RT did not increase the toxic effects or side-effects compared with RT alone. One point worth mentioning was that, there was no such toxicity facing the radiation oncologists, using Radiation alone. It was true that radiotherapy alone rarely causes myelosuppression. This phenomenon occurs because most of the patients included in this paper were patients who have failed multiline treatment, and the general condition of the patients was poor. Most of the patients have been treated with second-line or third-line chemotherapy, so many patients have myelosuppression.

Apatinib is an oral TKI with anti-angiogenic properties, and many studies have demonstrated that apatinib was effective in the treatment of advanced NSCLC.¹⁵ Tang et al demonstrated that apatinib combined with systemic cytotoxic chemotherapy had clinical efficacy in patients with disease-refractory metastatic NSCLC and provides evidence for further studies investigating apatinib-based combination regimens. Xu et al pointed out that apatinib was effective and well tolerated in patients with advanced NSCLC and had a good clinical effect in the treatment of BMs.²⁴ Xiaofang Ying et al reported the first case of apatinib combined with brain radiotherapy in EGFR Wild-Type and ALK-Negative Lung Adenocarcinoma With Multiple BMs, which achieved rapid clinical response. They propose that apatinib combined with brain radiotherapy may be an alternative treatment option for BM from NSCLC, especially for those without driver mutations.²⁵ In our study, when using apatinib for advanced NSCLC, we found that apatinib combined with RT for BM prolonged the intracranial PFS and significantly reduced the symptoms caused by BM and improved QoL for patients, such as intracranial oedema, severe headache, nausea and vomiting. Apatinib, a first-generation oral anti-angiogenic drug, selectively inhibits VEGFR-2, leading to decreased vascular endothelial cell proliferation and migration and tumour microvascular density.²⁴ Apatinib targets VEGFR-2, RET, platelet-derived growth factor- β (PDGFR- β), v-Src sarcoma viral oncogene homologue (c-Src), and stem cell factor receptor (c-Kit).²⁶⁻²⁸ Apatinib can effectively inhibit the proliferation, migration, and

tube formation of human umbilical vein endothelial cells, can block the budding of rat aortic rings and can inhibit the growth of several established human tumour xenograft models with little toxicity.²⁶ Previous studies reported that apatinib could reverse ATP-binding cassette transporter (ABC) subfamily B member 1 (ABCB1/MDR1/P-glycoprotein)- and ABC subfamily G member 2 (ABCG2/BCRP)-mediated multidrug resistance, which suggested the potential usefulness of combining apatinib with other chemotherapy drugs.^{27,29}

Some studies suggest that apatinib has some synergistic effects with RT.¹⁶ The mechanism through which apatinib combined with RT achieved better control of BM was not completely clear. It may be related to the following points. First, some studies suggest that VEGFR drugs can interfere with tumour metastasis pathways. Angiogenesis, which is mainly mediated by the VEGF pathway, is crucial for tumour survival, growth and invasion both in primary and metastatic brain lesions. As a primary driver of angiogenesis, VEGF is secreted by tumour cells in response to decreased vessel density and hypoxia. VEGF is highly expressed in breast, colorectal, and non-small-cell lung carcinomas.³⁰⁻³² Therefore, VEGFR inhibitors (such as apatinib) downregulate this pathway and reduce the number of tumour cells entering the brain, which may enhance the sensitivity to RT. Furthermore, several studies have shown that VEGFR promotes the normalisation of blood vessels, which can improve the delivery of drugs to the brain and play a role in RT sensitisation.^{33,34} Tong et al³³ indicated that inhibition of VEGF signalling by a monoclonal antibody that binds to the VEGF ligand, preventing receptor phosphorylation, has been shown to improve drug delivery through vascular normalisation. Jain et al³⁴ also found that VEGFR inhibition reduces tumour angiogenesis. In addition, a rationale for the use of VEGFR inhibition in BM was the concept of vascular normalisation.^{35,36}

Other studies have suggested that apatinib can penetrate the blood-brain barrier and play a synergistic role in radiotherapy.^{37,38} BM can induce neovascularisation, with leaky vessels, but can also co-opt existing brain vasculature, with a near-normal BBB, particularly in a tumour-infiltrated brain around tumour (BAT). Clinically, BMs can show highly variable permeability, and this has been recapitulated in haematogenous metastases in animal models.³⁶ Blocking VEGF signalling in systemic tumours produces a morphologically and functionally

normalised vasculature by pruning immature vessels and improving perivascular cell and basement membrane coverage and function.³⁸ It was hypothesised that normalisation of existing tumour vasculature will improve chemotherapy delivery and chemotherapy/radiotherapy efficacy. All of these mechanisms imply that an anti-angiogenic agent would always augment the response to radiation or chemotherapy.

There are some limitations to this study. First, this study was done retrospectively at a single institution, which may have led to inherent bias, and need more powerful evidence is needed to demonstrate. Second, the number of patients enrolled in this study may be insufficient. Factors that may impact the outcomes could not be fully evaluated. The follow-up period may not be long enough. External validation should be done using another large database to further evaluate the value RT combined with apatinib for patients with BM after failure of multiline therapy.

RT combined with apatinib could help to control intracranial metastases and delay the progression of intracranial metastases, but there was no significant effect on overall survival. The Apatinib+RT group had significantly reduced symptoms caused by BM and improved QoL for patients, mainly headache (21.9% and

19.4%) and vomiting (28.1% and 16.1%). In addition, the safety of the two treatments was similar, and apatinib combined with RT did not increase the toxic effects or side-effects compared with RT alone.

CONTRIBUTORS

HP, LS and XZ acquired and analyzed the data, XC and CX drafted the manuscript. YL and WD made contributions to follow up the patients. All authors read and approved the final manuscript.

FUNDING

The study was funded by Science and Technology Cooperation Project of Wenzhou Science and Technology Bureau. (grant number 2018H0003); The key R&D Project of the Department of Science and Technology of Zhejiang Province. (2020C03028); Major Project of Wenzhou Science and Technology Bureau. (2020ZY0013).

ETHICS APPROVAL

It has passed the review of Ethics Committee, and the code of ethics approval is KY2021-R127.

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