Original Article

Apatinib plus docetaxel or pemetrexed shows promising activities against non-small cell lung cancer with brain metastasis: a retrospective analysis

Jing Tang[1], Hui Jiang[1], Zhengkai Xiang[2], Xianmin Zhu[1], Rong Xie[1], De Wu[3], Li Peng[4], Xiaobing Li[4]

[1]Department of Lymphoma, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [2]Department of Thoracic Surgery, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [3]The Centre of Molecular Diagnosis, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [4]Department of Thoracic Oncology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Contributions: (I) Conception and design: X Li; (II) Administrative support: H Jiang; (III) Provision of study materials or patients: Z Xiang, X Zhu; (IV) Collection and assembly of data: R Xie, D Wu, L Peng; (V) Data analysis and interpretation: J Tang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Xiaobing Li, MD, PhD. Department of Thoracic Oncology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 116, Zhuodaoquan South Road, Hongshan District, Wuhan 430079, China. Email: lixiaobing0629@126.com.

Background: So far, the treatment options for most advanced non-small cell lung cancer (NSCLC) with brain metastasis have been limited. Apatinib, an oral tyrosine kinase inhibitor (TKI) with anti-angiogenesis properties, has been approved for advanced gastric cancer in China. Clinical studies have demonstrated that apatinib also displays anticancer effects against several other human cancers, including NSCLC. We have observed that apatinib combined with pemetrexed or docetaxel shows promising efficiency for advanced NSCLC patients who have previously undergone two or more lines of treatment, we would like to further perform a retrospective efficiency analysis of apatinib combined with pemetrexed or docetaxel in advanced NSCLC patients with multiple brain metastasis in this study.

Methods: A total of 35 patients, between 18 and 70 years old, who were clinically and pathologically confirmed as having advanced NSCLC were included in this study. All of the included patients had accepted two or more lines of treatment. These patients received apatinib combined with pemetrexed or docetaxel between January 2014 and November 2020 in Hubei Cancer Hospital.

Results: The results showed that apatinib combined with pemetrexed or docetaxel could effectively delay the disease progression of brain metastasis in advanced NSCLC, with an approximate overall response rate (ORR) for measurable and non-measurable lesions of 10% and 15%, respectively. The disease control rate (DCR) for intracranial lesions was 66%, the median progression-free survival (PFS) was 4.0 months, and the median overall survival (OS) was 9.0 months. The most common treatment-related toxicities, such as fatigue, decreased appetite, and hand-foot syndrome (HFS), were either mild or moderate and tolerable.

Conclusions: Since there is currently no effective treatment for patients with advanced NSCLC patients with brain metastasis who have already undergone two or more lines of treatment, the promising efficiency of apatinib combined with pemetrexed or docetaxel would be of great significance for these heavily ill patients. The real therapeutic value of this method against brain metastasis needs to be confirmed by large, random, and prospective clinical trials in the future.

Keywords: Apatinib; brain metastasis; non-small cell lung cancer (NSCLC)

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Introduction

Brain metastasis is a common phenomenon (1), which is most commonly seen in advanced non-small cell lung cancer (NSCLC) in preliminary diagnosis, during or after the treatment. The treatment for brain metastasis depends on the size, number, location, and other factors, such as Eastern Cooperative Oncology Group performance status (ECOG PS), age, and so on (2). Concretely, when there are less than three metastasis loci, surgery, or stereotactic radiosurgery (SRS) could be utilized with priority, whereas in the case of more than three loci, whole brain radiotherapy (WBRT) may be more advantageous. In the setting of precision medicine, progress has been made for the treatment of advanced NSCLC during the past decades, including the treatment for brain metastasis of NSCLC. For example, for patients with advanced NSCLC, with the application of a corresponding drug with a specific target, the prognosis improves obviously (3). It is widely accepted that small molecular drugs could effectively penetrate the blood-brain barrier (BBB) and exert promising efficiency for patients with brain metastasis (4). Unfortunately, due to the limited coverage of molecular targeted treatment, for example, only 20–30% rate for epidermal growth factor receptor (EGFR) mutation and 3–5% for anaplastic lymphoma kinase (ALK) 4 translocation in advanced NSCLC, there is still a lack of effective treatment means against most advanced NSCLC with brain metastasis (2).

However, broadly speaking, all types of cancer possess targets, either specific or non-specific, represented by the former are EGFR and ALK (5), and by the latter is vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) (6). Considering the intrinsic advantage of small molecular drugs to cross the BBB and the wide recognition of anti-angiogenesis therapy in cancer treatment, applying small molecular drugs with anti-angiogenesis benefits would be a potential way to deal with advanced NSCLC with brain metastasis (7,8). In a clinical trial of apatinib against advanced gastric cancer, patients with brain metastasis with asymptomatic syndrome were also enrolled, implying that brain metastasis was not a contraindication for patients to receive apatinib treatment (9,10). Moreover, nintedanib (a VEGFR-2 inhibitor) plus docetaxel in advanced NSCLC with brain metastasis has been reported to display promising efficiency (11). Therefore, it is likely that apatinib plus pemetrexed or docetaxel may have therapeutic value for brain metastasis (12). However, no specific study on apatinib combined with pemetrexed or docetaxel treatment for such a specific population has been reported. Therefore, in this study, we focused on the efficiency analysis of the combination of apatinib and pemetrexed/docetaxel against advanced NSCLC with brain metastasis in patients who had already undergone two or more lines of treatment, aiming to seek for an effective way to approach this clinical dilemma. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1860/rc).

Highlight box

Key findings

- This is the first study reporting on the promising efficiency of apatinib and pemetrexed or docetaxel with tolerated toxicity against advanced non-small cell lung cancer (NSCLC) patients with brain metastasis.

What is known and what is new?

- Apatinib and pemetrexed or docetaxel had shown promising efficacy in treating brain metastases from advanced NSCLC.
- Apatinib and pemetrexed or docetaxel could play a synergistic effect against advanced NSCLC patients with brain metastasis.

What is the implication, and what should change now?

- This regimen may have the potential to become an effective treatment for NSCLC with brain metastasis. However, the real value of this regimen needs to be further confirmed.

Methods

Study design

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective trial was approved by the Ethics Committee of Hubei Cancer Hospital Affiliated to Tongji Medical College (Wuhan, China) (Ethical Number 2013HBCHEC1534), and patients or their families provided their informed consent form. A total of 35 advanced NSCLC patients with brain metastasis received the combined regimen of apatinib and docetaxel or pemetrexed in the second or above line treatment.

Source of patients

A total of 35 patients, who were clinically and pathologically confirmed as having advanced NSCLC were included. These patients received anti-tumor therapy between January 2014 and November 2020 in the Department of

Thoracic Oncology of Hubei Cancer Hospital.

Inclusion and exclusion criteria

Patients aged between 18 and 70 years old who had been clinically and pathologically confirmed as having advanced NSCLC were eligible for enrollment. The inclusion criteria included drug-resistance or intolerance to at least two previous chemotherapeutic treatments [including platinum-containing regimen and EGFR tyrosine kinase inhibitor (TKI) therapy]. The study also allowed for the recruitment of patients who were intolerant to second-line chemotherapy because these patients had no other therapeutic options. Other enrollment criteria included the following: an ECOG PS of 0 or 1; at least one measurable lesion defined by the Response Evaluation Criteria in Solid Tumors (RECIST) (12); and acceptable hematologic, hepatic, and renal function. Prior to enrolment, none of the patients had ever received immune checkpoint therapy such as anti-programmed death 1 (PD-1) or anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Exclusion criteria included uncontrolled hypertension, asymptomatic central nervous system (CNS) metastases, history of hemoptysis (a half teaspoon of bright red blood in the 3 months before enrolment) and tumors invading major blood vessels. The currently or recently using of full-dose anticoagulants or thrombolytic agents for therapeutic purposes was not permitted (first apatinib dose within 10 days), but prophylactic use of anticoagulants was permitted. The criteria for progression to third-line therapy (including chemotherapy or target therapy) were evaluated in terms of computed tomography (CT) and magnetic resonance imaging (MRI).

Gene detection

Most of the patients had received CT-guided needle aspiration for diagnosis. Once the diagnosis was confirmed pathologically, part of the sample was analyzed by multiple gene detection, such as *EGFR*, *ALK*, *C-Met*, and *K-RAS*. The detection was performed by standard assay.

Drug application

All the patients had previously received two or more lines of treatment. Once disease progression or drug resistance had been clinically confirmed, the schemed chemotherapy was performed by using standard dosage, namely, the dosage of pemetrexed and docetaxel of 500 and 75 mg/m^2, respectively. For apatinib, the recommended dosage was 250 mg per os (p.o.) once a day (qd). If toxicities of degree 3 or 4 occurred, drug interruption or drug discontinuation could be performed for a period of no more than 1 week. For drug reduction, the dosage was gradually reduced from 250 to 125 mg, and the minimum dosage for apatinib was 125 mg p.o. qd. Apatinib was administered simultaneously with chemotherapy. A total of 28 days was regarded as one cycle.

Efficiency evaluation

All the patients had received at least one cycle of treatment. The efficiency evaluation was performed every 4 weeks based on lung CT and brain MRI. The main criterion was RECIST 1.0.

Statistical analysis

All analyses were performed by using SPSS 13.0 (IBM Corp., Chicago, IL, USA). Progression-free survival (PFS) was defined as the time from the first administration of the apatinib plus docetaxel or pemetrexed regimen to the date of confirmation of disease progression or death. Overall survival (OS) was defined as the time from the first administration of the apatinib plus docetaxel or pemetrexed regimen until death. Data for patients with unavailable information regarding death or disease progression were censored at the date of the last assessment. PFS and OS were summarized descriptively, and two-sided 95% confidence intervals (CIs) were presented. PFS and OS were estimated using the Kaplan-Meier method. The corresponding figures were drawn by using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA). Differences were assumed to be significant when a P value of 0.05 was achieved.

Results

Patient characteristics

In our study, 35 patients with advanced NSCLC were included. All of them had received two or more lines of treatment. The main pathological type was adenocarcinoma, followed by lung squamous cell carcinoma and adenosquamous carcinoma. Some 60% of the brain metastasis could be measured by MRI or CT scanning.

Table 1 Baseline clinical characteristics of the study cohort

Characteristics	Value (n=35)
Age (years), median [range]	65 [47–75]
Gender, n (%)	
Male	19 (54.29)
Female	16 (45.71)
Smoking history, n (%)	
Never smoker	12 (34.29)
Former smoker	23 (65.71)
Histology, n (%)	
Adenocarcinoma	21 (60.00)
Squamous carcinoma	14 (40.00)
ECOG PS score, n (%)	
0–1	22 (62.86)
≥2	13 (37.14)
Previous radiotherapy, n (%)	
Yes	10 (28.57)
No	25 (71.43)
Bone metastasis, n (%)	
Yes	8 (22.86)
No	27 (77.14)
Liver metastasis, n (%)	
Yes	5 (14.29)
No	30 (85.71)
Stage, n (%)	
IIIB/IIIC	4 (11.43)
IV	31 (88.57)

ECOG PS, Eastern Cooperative Oncology Group performance status.

The ECOG PS of the patients was 0 or 2. Among all the 35 patients, 16 were female, 19 were male. Most of the male patients were heavy smokers, the female patients were all non-smokers. The average age was 65 years. Most of these patients were EGFR wild type; three patients with EGFR mutation had disease progression after first-line TKI treatment (see *Table 1*).

Previous treatment

Most patients with EGFR wild type had at least received two lines of treatment of chemotherapy: the first line chemotherapy regimen was pemetrexed plus platinum, the priority regimen for second line was docetaxel or gemcitabine. Some 28% of them had received prior WBRT, the interval before enrollment was no less than 3 months. All the EGFR-mutated patients had received TKI treatment in first line. The concrete gene mutations of these patients were exon 19 del (one patient) and exon 21 L858R mutations (two patients). The drug for first line treatment was gefitinib, erlotinib, or icotinib. After the confirmation of disease progression, all these patients had received extra multiple gene detection; one patient with T790M mutation had directly received osimertinib treatment, the other two patients had chosen chemotherapy. The chemotherapeutic regimens were mainly similar to those of the EGFR wild type patients (see *Table 1*).

Efficiency

All the patients had received at least one cycle of treatment, and the mean treatment line of apatinib plus pemetrexed or docetaxel was the third. Our efficiency analysis indicated that no patient achieved complete response (CR), nine patients achieved partial response (PR), 14 patients achieved stable disease (SD), 12 patients had progressive disease (PD). For un-measurable brain metastasis lesions, the overall response rate (ORR) was 15%. As for measurable brain metastasis lesions, the ORR was 10%, and the disease control rate (DCR) was about 66%. The median PFS and OS were 4.0 and 9.0 months, separately (see *Table 2* and *Figures 1*,*2*).

Toxicity

During the treatment, the common treatment-related hematological adverse events (AEs) were alopecia, nausea, fatigue, thrombocytopenia, vomiting, neutropenia, hypertension, and hand-foot syndrome (HFS), among others. Most of the side effects were of degree 1 or 2 and were tolerable. The mean dosage of apatinib was 250 mg p.o. qd. The AEs of degree 3 or 4 were fatigue, thrombocytopenia, neutropenia, HFS, anemia, and rash,

Table 2 Clinical activity of apatinib plus pemetrexed or docetaxel in advanced NSCLC with brain metastasis

Variables	Value (n=35)
CR, n (%)	0
PR, n (%)	9 (25.71)
SD, n (%)	14 (40.00)
PD, n (%)	12 (34.29)
Objective response (%)	25.71
Median PFS (months)	4.0
DCR (%)	66.03
Median OS (months)	9.0

NSCLC, non-small cell lung cancer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; DCR, disease control rate; OS, overall survival.

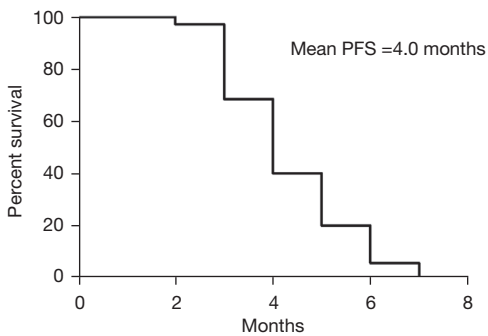

Figure 1 Overall PFS of these NSCLC patients with brain metastasis who had accepted the combination treatment of apatinib and pemetrexed or docetaxel in the second or above line treatment. PFS, progression-free survival; NSCLC, non-small cell lung cancer.

among others. The drug discontinuation rate of these patients was 30%. The serious AEs were alleviated or reduced by adopting corresponding support therapy (see *Table 3*).

Discussion

Brain metastasis is a common phenomenon observed

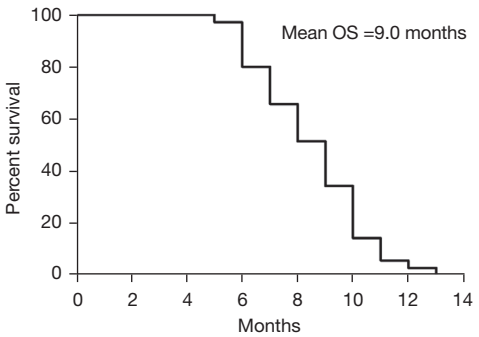

Figure 2 Overall OS of these advanced NSCLC patients with brain metastasis who accepted the drug combination of apatinib and pemetrexed or docetaxel in the second or above line treatment. OS, overall survival; NSCLC, non-small cell lung cancer.

Table 3 AEs of apatinib plus pemetrexed or docetaxel in advanced NSCLC with brain metastasis

AEs	Apatinib plus CT, n (%)	
	Any grade	Grade 3 or 4
Alopecia	22 (62.86)	2 (5.71)
Nausea	23 (65.71)	2 (5.71)
Fatigue	20 (57.14)	5 (14.29)
Thrombocytopenia	18 (51.43)	5 (14.29)
Vomiting	17 (48.57)	2 (5.71)
Neutropenia	16 (45.71)	8 (22.86)
Hypertension	16 (45.71)	3 (8.57)
HFS	15 (42.86)	5 (14.29)
Anemia	15 (42.86)	6 (17.14)
Proteinuria	12 (34.29)	4 (11.43)
Abnormal liver function	12 (34.29)	3 (8.57)
Rash	10 (28.57)	5 (14.29)
Diarrhea	8 (22.86)	2 (5.71)
Paronychia	7 (20.00)	2 (5.71)
Pruritus	6 (17.14)	2 (5.71)
Fluid retention	4 (11.43)	2 (5.71)
Hypomagnesemia	3 (8.57)	1 (2.86)

AEs, adverse events; NSCLC, non-small cell lung cancer; CT, chemotherapy; HFS, hand-foot syndrome.

in advanced cancer patients clinically (1). Since the past decades, progress has been achieved in the field of cancer treatment. The treatment of brain metastasis has also been affected. The application of local therapies, such as surgery and SRS, have been reported widely (13). However, only a minority of patients with brain metastasis has shown benefit. Considering the enormous population of patients with multiple brain metastases, effective approaches are eagerly needed at the present (14).

In this context, progress was made mainly by drug treatment in the past, besides molecular targeted therapy. One of the successful examples was consistent efficiency of molecular targeted therapy against advanced NSCLC with brain metastasis, such as *EGFR* mutation (15) and ALK translocation (16). Other drugs have also been found effective, such as immune checkpoint therapy (17) and anti-angiogenesis therapy (4). Although no big clinical trial has been performed on the efficiency against brain metastasis at present, subset analyses have demonstrated that these drugs could probably possess efficiency against brain metastasis, indicating the potential of these drugs/treatment for this specific population in the future (15,18-23).

Practically speaking, utilizing anti-angiogenic drugs to deal with multiple brain metastasis would be more reasonable (7,24,25). Many undetermined factors exist in immune checkpoint therapy (17), and the associated cost is very high at present. From the perspective of drug availability and cost-efficiency, it would be more reasonable to choose anti-angiogenesis therapy to seek further breakthroughs (6). Another reason is that we have previously observed that the combination of apatinib and single chemotherapy shows promising efficiency against advanced NSCLC, in a cohort that also involved patients with brain metastasis (12). Therefore, we chose apatinib, a small molecular inhibitor with anti-angiogenesis activity, as the main candidate, which has been approved in China since 2014 for the treatment of advanced gastric cancer or gastric-esophageal junction adenocarcinoma (26). Consistent with our expectation, we indeed observed that the combination of apatinib and single chemotherapy (pemetrexed or docetaxel) could effectively control or delay the brain metastasis progression of advanced NSCLC; the ORR was approximately 25% and the DCR for brain metastasis was about 66%, indicating the acceptable efficiency of such regimen against advanced NSCLC with brain metastasis. Moreover, most of the AEs, such as diarrhea, decreased appetite, fatigue, and HFS, were mild or moderate and could be tolerated (27,28). Since most of our patients had no specific target, such as *EGFR* mutation or ALK translocation, the amazing efficiency of this regimen was likely exerted by the reasonable combination of pemetrexed or docetaxel (29), as the single application of either drug had displayed limited or no efficiency, especially for patients with brain metastasis (30). Originally, apatinib was regarded as an anti-angiogenesis inhibitor against VEGFR-2, similar to drugs of a similar type, namely, sorafenib, sunitinib, and cabozantinib (31). Considering the limited efficiency of other anti-angiogenesis inhibitors, such as cediranib (32) in advanced NSCLC, it is rather possible that mechanism of apatinib may be different (33). Apatinib may also possess other targets, such as RET, FlT3, and so on (34). This direction is worthy of further exploration in the future.

To our knowledge, this is the first study to exhibit that the combination of apatinib and single chemotherapy (pemetrexed or docetaxel) shows promising efficiency against such a specific population with tolerable toxicity. However, due to the small size and retrospective observational nature of our study, it is still too early to make a confirmatory conclusion that such a regimen is effective at present. However, considering the practical requirement for the treatment of brain metastasis, this strategy would probably possess practical significance. With the increasing application of apatinib in cancer treatment, the authenticity of such a regimen requires further confirmation. Although many questions remain at present (6), with the rapid and deep development of anti-angiogenesis therapy, all the problems will gradually be resolved and more and more patients will be able to benefit.

Conclusions

As far as we know, our study is the first to describe the promising efficiency and tolerable toxicity of the regimen combined apatinib with pemetrexed or docetaxel in the second or above treatment line of advanced NSCLC with brain metastasis. However, due to the lack of a control group, small sample size, and retrospective design, there are still some issues that need to be further addressed, such as the mechanism of synergistic action, optimization of treatment modalities, and identification of predictive biomarkers for treatment efficacy. With further research and the accumulation of clinical experience, more lung cancer patients with brain metastases will benefit from treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1860/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1860/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1860/coif). 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 study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective trial was approved by the Ethics Committee of Hubei Cancer Hospital Affiliated to Tongji Medical College (Wuhan, China) (Ethical Number 2013HBCHEC1534), and patients or their families provided their informed consent form.

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