

Comparison of erlotinib and pemetrexed as second-/third-line treatment for lung adenocarcinoma patients with asymptomatic brain metastases

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Objective: Brain metastases occur in one-third of all non-small-cell lung cancer patients. Due to restrictive transport at the blood–brain barrier, many drugs provide poor control of metastases in the brain. The aim of this study was to compare erlotinib with pemetrexed as second-/third-line treatment in patients with lung adenocarcinoma with asymptomatic brain metastases.

Methods: From January 2012 to June 2014, all lung adenocarcinoma patients with asymptomatic brain metastases who received treatment with erlotinib or pemetrexed as second-/third-line treatment were retrospectively reviewed. Chi-square and log-rank tests were used to perform statistical analysis.

Results: The study enrolled 99 patients, of which 44 were positive for *EGFR* mutation. Median progression-free survival (PFS) in months was not significantly different between the erlotinib- and pemetrexed-treated groups (4.2 vs 3.4 months; 95% confidence interval [CI]: 2.01–6.40 vs 2.80–5.00, respectively; $P=0.635$). Median PFS was found to be significantly longer in *EGFR* mutation-positive patients in the erlotinib-treated group (8.0 months; 95% CI 5.85–10.15) compared to the pemetrexed group (3.9 months; 95% CI: 1.25–6.55; $P=0.032$). The most common treatment-related side effect was mild-to-moderate rash and the most common drug-related side effects in the pemetrexed-group were vomiting and nausea.

Conclusion: Erlotinib and pemetrexed may be used as second-/third-line treatment in lung adenocarcinoma patients with asymptomatic brain metastases, and detection of *EGFR* mutation status is very important in these patients. *EGFR* mutation-positive lung adenocarcinoma patients with asymptomatic brain metastases showed longer PFS when treated with erlotinib as opposed to pemetrexed.

Keywords: erlotinib, pemetrexed, lung adenocarcinoma, *EGFR*, asymptomatic brain metastases

Introduction

Lung cancer continues to be the primary cancer-related cause of death worldwide.^{1–3} In majority of cases, lung cancers reach metastatic stage by the time of diagnosis. Brain is one of the most common metastatic sites of lung cancer.⁴ Patients with brain metastases have poor prognoses despite treatment with whole-brain radiotherapy (WBRT).^{5,6} Apart from WBRT, few treatment options are currently available for brain metastases. Most of the potential chemotherapy agents cannot effectively penetrate the blood–brain barrier (BBB).⁷ Therefore, more effective, less toxic treatments are urgently needed for lung adenocarcinoma patients with brain metastases.

Epidermal growth factor receptor tyrosine kinase inhibitors (*EGFR*-TKIs) have been widely used in the treatment of advanced non-small-cell lung cancer (NSCLC).^{8–10}

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Patients treated with erlotinib survived longer than those who received best supportive care in second-/third-line therapy.¹¹ Many reports have demonstrated that brain metastases of lung adenocarcinoma can respond to *EGFR*-TKIs.^{9,12}

Some clinical trials have also shown that pemetrexed may be effective against brain metastases. Pemetrexed is a third-generation drug that inhibits multiple folate-dependent enzymes.^{13–15} It has been suggested that concomitant treatment of pemetrexed and cisplatin (AP) and WBRT is well tolerated, with promising effects in lung adenocarcinoma patients with brain metastases.¹⁵

Few studies have compared the therapeutic effects of erlotinib versus pemetrexed in the treatment of lung adenocarcinoma with asymptomatic brain metastases. This study, therefore, aimed to evaluate the efficacy of erlotinib compared with pemetrexed as second-/third-line therapy in lung adenocarcinoma patients with asymptomatic brain metastases.

Patients and methods

Patients

From January 2012 to June 2014, 99 patients were enrolled into the study. Eligible patients were confirmed with stage IV lung adenocarcinoma (Union for International Cancer Control classification version 7) with a confirmed activating mutation of *EGFR* (exon 19 deletion or an exon 21 L858R mutation). Patients were all in second-/third-line chemotherapy treatment and had platinum-based doublet chemotherapy as first-line therapy. All patients also had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), an Eastern Cooperative Oncology Group performance status of 0–2, adequate hematological, biochemical, and organ function, and were above 18 years old. This research was approved by the Ethics Committee of Shanghai Pulmonary Hospital, Tongji University, and written informed consent was obtained from all of the enrolled patients.

Treatment

Patients' data include medical history and physical examination, hematologic and biochemical testing, and chest and abdomen computed tomographic scans before second-/third-line treatment. Assessments of toxic effects and quality of life were obtained. Patients received erlotinib, 150 mg daily, or pemetrexed, 500 mg/m² day 1, which was repeated every 3 weeks until disease progression or intolerable side effects occurred. Toxicity was assessed according to National Cancer Institute Common Toxicity Criteria (version 4.0). Patients were evaluated every 3 weeks, at which time hematology

and blood chemistry assessments were performed; tumor measurements were made every 6 weeks.

DNA extraction and *EGFR* mutation analysis

All *EGFR* mutational analyses were performed by Amplification Refractory Mutation System in Tongji University Medical School Cancer Institute (Shanghai, People's Republic of China), as described previously.¹⁶

Statistical analysis

The chi-square test was used to analyze the association between hepatic metastases, clinical data, and disease control rate. For the survival analysis, patients were censored at the last date at which they were known to be alive. All time-to-event outcomes, such as progression-free survival (PFS), were estimated using the Kaplan–Meier method and compared across groups with the log-rank test or the Cox proportional hazards model. The SPSS statistical package for Windows version 17.0 (SPSS Inc., Chicago, IL, USA) was used. All *P*-values were two-sided, and statistical significance was defined as *P*<0.05.

Results

Patient characteristics

A total of 99 lung adenocarcinoma patients with asymptomatic brain metastases with known *EGFR* mutation status were enrolled into the study. Of these patients, 68 received erlotinib and 31 received pemetrexed. The median age was 56 years, and 36 (36.4%) were males and 63 (63.6%) were females. Among all patients, 44 (47.1%) had an *EGFR* positive mutation. Among patients with a positive *EGFR* mutation, 32 patients were treated with erlotinib and 12 patients with pemetrexed. None of the patients had received WBRT before enrolling into the study. Table 1 summarizes the characteristics of the eligible patients.

Therapeutic effects

In the erlotinib-treated group (n=68), the objective response rates of cerebral and extracerebral lesions were found to be similar (29.4% vs 26.5%; *P*=0.134). In the pemetrexed-treated group (n=31), no statistical difference was observed between the response rates of cerebral and extracerebral lesions (12.9% vs 16.1%; *P*=0.525; Table 2). In the erlotinib-treated group (n=68), the objective control rates of cerebral and extracerebral lesions showed significant difference (*P*=0.000; Table 3).

Table 1 Characteristics of eligible patients

Sex, n (%)	
Male	36 (36.4)
Female	63 (63.6)
Age, median	56
Smoker, n (%)	40 (40.4)
Performance status (ECOG), n (%)	
0	2 (2.0)
1	77 (77.8)
2	20 (20.2)
T stage, n (%)	
1	3 (3.0)
2	27 (27.3)
3	19 (19.2)
4	50 (50.5)
N stage, n (%)	
0	2 (2.0)
1	15 (15.2)
2	59 (59.6)
3	23 (23.2)
EGFR mutation, n (%)	44 (44.4)
Exon 19 deletion	24 (54.5)
Exon 21 mutation	20 (45.5)
Number of brain metastases, n (%)	
≤3	42 (42.4)
<3	57 (57.6)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Association between EGFR mutation and clinicopathological features

EGFR-positive mutations were more prevalent in nonsmokers (33 patients, 33.3%) than smokers (11.1%) ($P=0.005$). No significant difference was observed between male and female patients ($P=0.582$).

Survival analysis

Figure 1 shows the Kaplan–Meier curve for PFS. Median PFS was not different between the groups treated with erlotinib and pemetrexed (4.2 vs 3.4 months; 95% confidence intervals [CI]: 2.01–6.40 vs 2.80–5.00, respectively; $P=0.635$) (Figure 1).

Table 2 Therapeutic effect in different tumor lesion (PD + SD versus PR + CR)

Therapy	Extracerebral lesions	Cerebral lesions, n (%)		P-value
		PD + SD	PR + CR	
Erlotinib	PD + SD	38 (55.9)	12 (17.6)	0.134
	PR + CR	10 (14.7)	8 (11.8)	
Pemetrexed	PD + SD	23 (74.2)	3 (9.7)	0.525
	PR + CR	4 (12.9)	1 (3.2)	

Abbreviations: PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

Table 3 Therapeutic effects in different tumor lesion (CR + PR + SD versus PD)

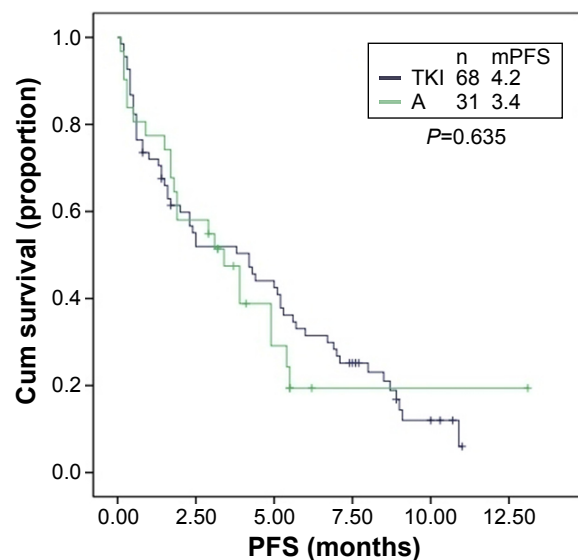
Therapy	Extracerebral lesions	Cerebral lesions, n (%)		P-value
		PR + CR + SD	PD	
Erlotinib	PR + CR + SD	43 (63.2)	6 (8.8)	0.000
	PD	7 (10.3)	12 (17.6)	
Pemetrexed	PR + CR + SD	19 (61.3)	10 (32.3)	0.142
	PD	0 (12.9)	2 (6.5)	

Abbreviations: PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

In the erlotinib-treated group, median PFS in EGFR mutation-positive patients was 8.0 months, whereas it was 1.3 months in EGFR mutation-negative patients (95% CI: 5.85–10.15 vs 0.26–2.35; $P<0.001$) (Figure 2). The median PFS in EGFR mutation-positive patients was 8.0 months in the erlotinib-treated group, whereas it was 3.9 months in the pemetrexed-treated group (95% CI: 5.85–10.15 vs 1.25–6.55; $P=0.032$). These two sentences are repetitive regarding PFS in mutation-positive patients with erlotinib.

Treatment-related side effects

The most frequent treatment-related side effects observed with erlotinib therapy were mild-to-moderate skin toxicity (48.5%), diarrhea (27.9%), and increased levels of alanine aminotransferase (23.5%). Patients experienced grade 3–4 events including two cases of anemia, three cases of skin rash, one case of increased alanine aminotransferase levels, and two cases of fatigue. The most common drug-related side effects observed in the pemetrexed-treated group were

**Figure 1** Association between therapeutic effect and PFS in patients.

Abbreviations: PFS, progression-free survival; TKI, erlotinib; A, pemetrexed; mPFS, PFS (month).

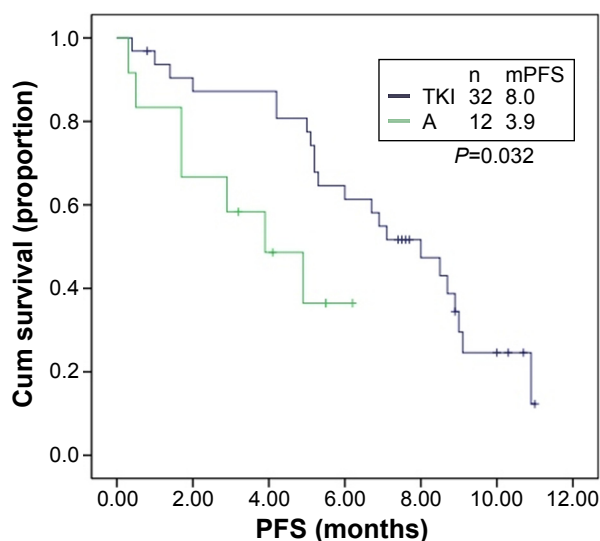


Figure 2 Association between therapeutic effect and PFS in *EGFR* mutation-positive patients.

Abbreviations: PFS, progression-free survival; TKI, erlotinib; A, pemetrexed; mPFS, PFS (month).

vomiting or nausea (9.7%), and one patient experienced grade 3 fatigue (Table 4).

Discussion

This study investigated the efficacy of erlotinib compared with pemetrexed as second-/third-line treatment in lung adenocarcinoma with asymptomatic brain metastases in Chinese patients. We found that these drugs may be used as second-/third-line treatment in these patients. In *EGFR* mutation-positive patients with lung adenocarcinoma and asymptomatic brain metastases, treatment with erlotinib yielded longer median PFS.

The brain is a common site of NSCLC metastases: 50% of patients with lung cancer eventually experience

brain metastases.¹⁷ Available therapeutic approaches for brain metastases include WBRT, stereotactic radiosurgery, surgery, and supportive treatment.^{18–20} Despite advances in NSCLC treatment, survival rates for brain metastases patients are still poor.¹⁹ Most brain metastases from NSCLC are not treatable by surgery when they are diagnosed,²¹ so WBRT represents the standard treatment. The treatment of NSCLC patients with brain metastases remains a significant challenge.

Erlotinib and gefitinib have been widely used in advanced NSCLC.^{8–10} However, not all patients are sensitive to the *EGFR*-TKIs. The response rate is from 10% to 40%.^{22,23} Patients of East Asian ethnicity, nonsmokers, and those with adenocarcinoma may benefit more from the *EGFR*-TKIs treatment.²⁴ Our study results concur with former studies,^{16,25} which showed that *EGFR*-positive mutations were more prevalent in nonsmokers than smokers.^{26,27}

Some scientists have reported high concentrations of erlotinib in the cerebrospinal fluid and subsequent regression of brain metastases with the treatment of erlotinib.^{28–30} Erlotinib passes into the cerebrospinal fluid in concentrations sufficient to cause brain metastasis regression.^{31–36} Regression of both the primary lung tumor and brain metastases in *EGFR* mutation-positive patients was reported in a positron emission tomography study using C11 erlotinib.³⁰ Weekly high-dose “pulses” of erlotinib could increase the concentration of erlotinib in the cerebrospinal fluid.^{35,36} Meanwhile, several studies concluded that the presence of *EGFR* mutations is an independent predictor of response to WBRT in brain metastases of lung adenocarcinoma.^{31–33} *EGFR*-TKIs might have an incomplete penetration through the BBB and its effectiveness for the treatment of brain metastasis may depend on the disruption of the barrier.^{32,33} The CTONG-0803 Phase II study showed that treatment with erlotinib resulted in significantly longer median time to progression within the brain and longer median overall survival among patients with *EGFR* mutation-positive NSCLC.⁹

Pemetrexed is a third-generation agent that inhibits multiple folate-dependent enzymes.^{13–15,37} It was reported that pemetrexed treatment could reduce the risk of developing brain metastases as the first site of disease progression. The findings suggested a potential beneficial effect of pemetrexed-based treatments for the control of brain metastases.³⁷ A prospective study demonstrated overall pulmonary and brain clinical benefits when irradiation-naïve patients received pemetrexed as second- or

Table 4 Treatment-related side effects

Toxicity	Erlotinib		Pemetrexed	
	Any grade, n (%)	Grade 3 or 4, n (%)	Any grade, n (%)	Grade 3 or 4, n (%)
Neutropenia	3 (4.4)	0 (0.0)	2 (6.5)	0 (0.0)
Thrombocytopenia	4 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	4 (5.9)	2 (2.9)	2 (6.5)	0 (0.0)
Infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin rash	33 (48.5)	3 (4.4)	0 (0.0)	0 (0.0)
Diarrhea	19 (27.9)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	9 (13.2)	0 (0.0)	1 (3.2)	0 (0.0)
Paronychia	10 (14.7)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting or nausea	7 (10.3)	0 (0.0)	3 (9.7)	0 (0.0)
Increased ALT	16 (23.5)	1 (1.5)	2 (6.5)	0 (0.0)
Fatigue	11 (16.2)	2 (2.9)	2 (6.5)	1 (3.2)

Abbreviation: ALT, alanine aminotransferase.

later-line treatment.³⁸ Another study reported 41.9% and 34.9% response rates on brain metastases and extracranial disease when pemetrexed plus cisplatin was received as the first-line therapy for NSCLC patients with brain metastases.³⁹ Recently, some Phase I and II clinical trials have demonstrated that pemetrexed plus cisplatin can be given concurrently with thoracic radiotherapy at full dose with tolerated toxicities. This combined modality therapy of AP chemotherapy with WBRT was generally well tolerated by most patients.^{13,14} Most side effects were well controlled by supportive care.¹⁵

Our study found no significant difference in response rates between patients with cerebral and extracerebral lesions. We hypothesize that both erlotinib and pemetrexed pass through the BBB. Patients with *EGFR* mutation-positive NSCLC who received erlotinib had a higher disease overall response rate and longer PFS than those who received pemetrexed.

In the erlotinib-treated group, the main side effects were rash and diarrhea. Patient's response to erlotinib was correlated with the grade of rash, in agreement with several previous trials.^{9,34} The most common drug-related side effects reported during pemetrexed therapy were vomiting and nausea. *EGFR* mutation-positive patients with lung adenocarcinoma and asymptomatic brain metastases treated with erlotinib had longer PFS than those who were treated with pemetrexed.

Conclusion

In conclusion, this study suggests that erlotinib or pemetrexed monotherapy is a potentially promising option with relatively modest side effects for second-/third-line treatment of lung adenocarcinoma patients with asymptomatic brain metastases. In *EGFR* mutation-positive patients with these symptoms, treatment with erlotinib resulted in longer PFS compared with pemetrexed. Also pemetrexed compared with erlotinib was found to be the better choice of treatment in these patients, in whom *EGFR* mutation status is also very important to be considered. Further study is needed to compare the overall survival of these patients when treated with erlotinib and pemetrexed.

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Disclosure

The authors report no conflict of interest in this work.

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