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Erlotinib intercalating pemetrexed/cisplatin versus erlotinib alone in Chinese patients with brain metastases from lung adenocarcinoma: a prospective, non-randomised, concurrent controlled trial (NCT01578668)

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ABSTRACT

Objective Erlotinib has a synergistic effect with pemetrexed for treating non-squamous non–small-cell lung cancer. We investigated the efficacy and safety of erlotinib (E) in combination with pemetrexed/cisplatin (E-P) in Chinese patients with lung adenocarcinoma with brain metastases.

Design Patients who were erlotinib-naïve or pemetrexed-naïve were assigned in parallel to receive either E or E-P. The primary endpoint was the intracranial overall response rate (ORRi).

Results Sixty-nine patients with lung adenocarcinoma with brain metastases received E (n=35) or E-P (n=34) from January 2012 to November 2014. Demographics and patient characteristics were well balanced between the two groups, including epidermal growth factor receptor (EGFR) status, sex, age, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, brain metastases and number of prior treatments. ORRi in the E-P arm was superior to that in the E arm (79% vs 48%, p=0.008). Compared with E as the first-line treatment, E-P was associated with better intracranial progression-free survival (PFSi, median: 9 vs 2 months, p=0.027) and systemic PFS (median: 8 vs 2 months, p=0.006). The most frequent E-related adverse events were higher in the combination arm. No new safety signals were detected. The side effects were tolerable, and there were no drug-related deaths.

Conclusion Our study suggests that the E-P combination may be effective in Chinese patients with lung adenocarcinoma with brain metastases, with improved PFS in treatment-naïve patients. Toxicities are tolerable, and there are more E-related side effects.

Key questions

What is already known about this subject?
► Radiotherapy and surgical therapy have been already known in brain metastases of lung cancer.

What does this study add?
► In our study, we find good response of erlotinib combined with chemotherapy in treating brain metastases of Chinese patients with lung adenocarcinoma.

How might this impact on clinical practice?
► It would provide a probable new strategy in treating brain metastases of lung cancer.

INTRODUCTION

Up to 30%–50% or more patients with brain metastases from lung adenocarcinoma present at the time of diagnosis or will develop brain metastases during treatment with poor overall survival (OS) of only 3–6 months.[1] Standard treatment options include whole brain radiotherapy with or without stereotactic radiosurgery; however, the median survival, ranging 2–4.8 months, remains disappointing.[2 3] Until recently, no effective strategy but radiotherapy shows instant alleviation of neurological symptoms, and systemic treatment in symptomatic brain metastases is limited.

The combination of erlotinib with pemetrexed has synergistic effects in vitro.[4 5] Clinical trials have shown that the two agents could achieve better response and survival than single-agent erlotinib or pemetrexed for treating lung adenocarcinoma as a second-line treatment.[6–8] Erlotinib accumulates in cranial tumour tissues and treats brain metastases of lung adenocarcinoma with epidermal growth factor receptor (*EGFR*)

mutation effectively.[9 10] Previously, we reported that pemetrexed could be detected in cerebrospinal fluid and that pemetrexed combined with platinum achieved a better intracranial response in brain metastases of non–small-cell lung cancer (NSCLC).[11 12] Therefore, erlotinib intercalating pemetrexed and platinum would theoretically improve the intracranial tumour response and survival in patients with lung adenocarcinoma.

In addition, it has been reported that *EGFR* mutations are present predominantly in Chinese patients with lung adenocarcinoma (about 50%–60%) and in patients of East Asian ethnicity.[13 14] In asymptomatic brain metastases from lung adenocarcinoma, erlotinib achieved an overall response rate (ORR) of 58% and a median intracranial progression-free survival (PFSi) of 10.1 months.[10] Accordingly, we designed a study to compare the intracranial response between erlotinib and intercalating erlotinib with pemetrexed plus low-dose cisplatin for intracranial tumour of lung adenocarcinoma.

PATIENTS AND METHODS

Study design and patients

This prospective, open-labelled, non-randomised concurrent controlled trial was undertaken at the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China. Eligible patients had histologically or cytologically confirmed lung adenocarcinoma (American Joint Commission on Cancer/International Union Against Cancer version 7) with brain metastases diagnosed by MRI. Patients had to be pemetrexed and erlotinib naïve. Patients could receive no more than three treatment regimens, including two chemotherapy regimens or gefitinib. Patients with poor performance status (PS, score 2–3) were included, but the poor PS had to have been caused only by neurological symptoms of the intracranial tumour. The online supplementary data detail the inclusion and exclusion criteria. It is not a randomised trial, because this is not possible in this patient population (symptomatic brain metastases). The patients were divided according to age, sex, *EGFR* status, Eastern Cooperative Oncology Group (ECOG) status, brain metastases, previous chemotherapy and the patient's will. The Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University approved the protocol, and all patients provided written informed consent for participation in the study and the provision of tumour samples (NCT01578668). Eligible patients were assigned (1:1) to receive erlotinib (E) or erlotinib combined with pemetrexed/cisplatin chemotherapy (E-P). Patient characteristics such as *EGFR* status, sex, age, smoking status, previous treatment and brain metastases status were balanced between the two groups.

Procedures

Eligible patients (PS score of no more than 3) were assigned in parallel to receive 150 mg/day erlotinib or erlotinib on days 4–21 plus 500 mg/m^2 pemetrexed on day 1 and 20 mg/m^2 cisplatin on days 1–3 (if PS<2) or 30 mg cisplatin on days 1 and 2 (if PS 2 or 3) every 21 days for up to 6 cycles and subsequent oral 150 mg/day erlotinib until progressive disease or unacceptable toxicity occurred. All patients in the E-P arm received vitamin B_{12} Centrum supplementation and dexamethasone prophylaxis. Target lesions were assessed by CT or MRI. Tumour response and disease progression were assessed by investigators together with one radiologist independently using Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1. Adverse events (AEs) were assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Tumour assessment was performed every other cycle except for brain MRI scanning, which was performed before the second cycle initially and then repeated every other cycle. After discontinuation of chemotherapy in the E-P arm, patients were followed up every 2 months. The primary endpoint was intracranial ORR (ORRi); the secondary endpoints included systemic ORR, PFSi and PFS, safety and OS.

EGFR mutation analysis

Genomic DNA was extracted from formalin-fixed, paraffin-embedded (FFPE) tissues using a QIAamp DNA FFPE Tissue Kit and RNeasy FFPE Kit (Qiagen, Germany) at first diagnosis. *EGFR* mutations were detected using commercially available kits from Amoy Diagnostics (Xiamen, China), which were based on amplification refractory mutation system real-time PCR technology. The analysis detects 29 mutations in exons 18–21, including T790M, L858R, L861Q, S768I, G719S, G719A, G719C, three insertions in exon 20 and 19 deletions in exon 19. All detections were performed following the manufacturer's protocol.

Statistical analysis

Our previous data showed that about 56% of erlotinib-treated patients and 78% of patients treated with erlotinib plus chemotherapy achieved ORRi. To detect a difference between the two arms with 70% power at a two-sided alpha of 5%, we estimated a required minimum sample size of 65, which was assigned in a 1:1 ratio. The planned patient number was increased to 72 to allow a 10% dropout rate. The study is a non-randomised controlled design, as it is impractical to perform random allocation due to the complexities of brain metastases severity.

A χ^2 test or Fisher's exact test was used to detect the difference in baseline patient characteristics or ORR between the two groups. We used Kaplan–Meier methods to assess time-to-event endpoints and log-rank tests to compare time-to-event endpoints between two groups.

RESULTS

Patients and treatment

A total of 72 patients were assigned to the E and E-P arms in a 1:1 ratio. In total, 69 patients received at least two doses of trial medication and comprised the response and safety

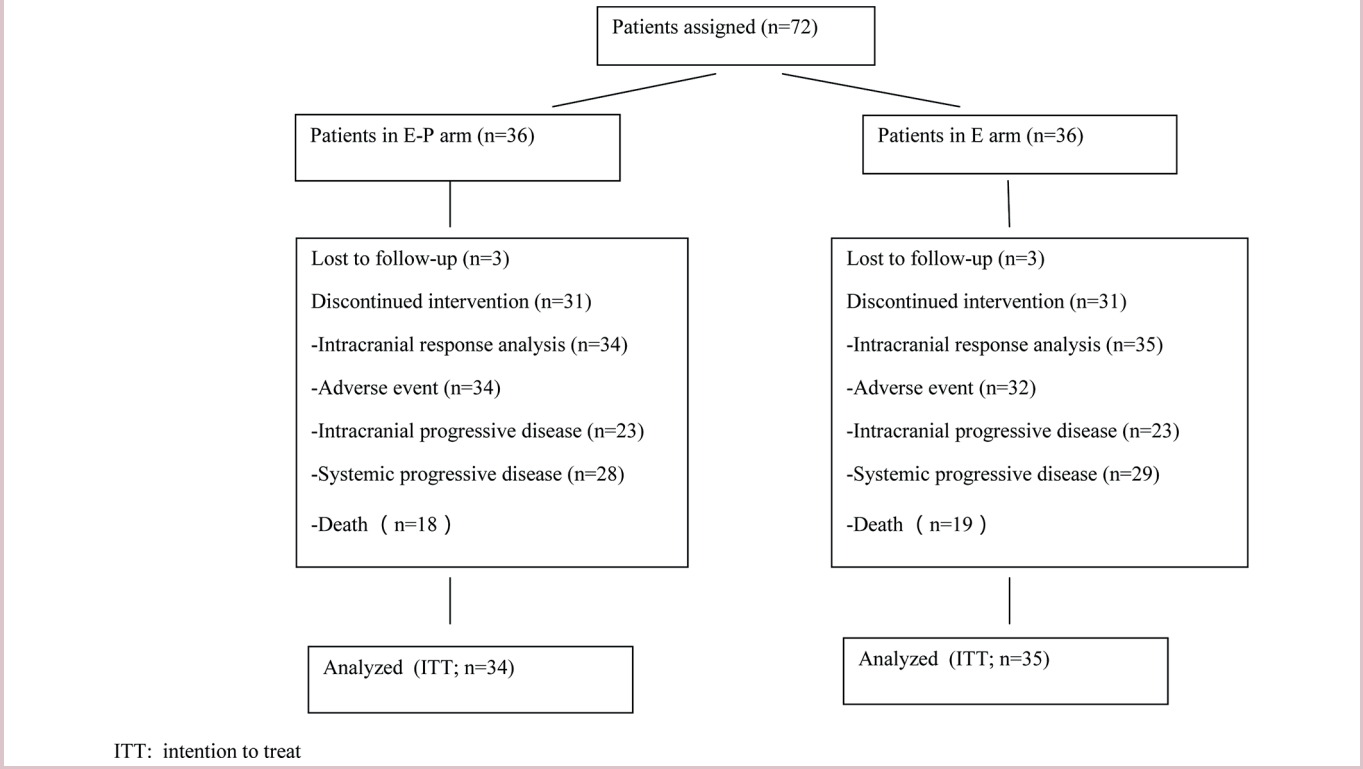

Figure 1 Consort diagram.

analysis set (figure 1). Fifty patients had available *EGFR* status: 32 (32/69, 46%) had *EGFR*-sensitive mutation and 18 (18/69, 26%) were wild type. Baseline demographics and disease characteristics were well balanced between the two treatment groups. Significantly fewer patients in the E arm than in the E-P arm had received previous gefitinib treatment (p=0.01). Patients with poor PS (PS 2–3) were included in the study: 13 in the E arm and 16 in the E-P arm (table 1). In the E arm, 50% of patients received the pemetrexed regimen after erlotinib failure, and 40% of patients in the E-P arm received chemotherapy after disease progression.

Efficacy

In primary efficacy analysis, the E-P group had superior ORRi compared with the E group. The ORRi in the E arm and E-P arm was 48% (95% CI 32% to 65%) and 79% (95% CI 63% to 93%) (p=0.008), respectively (table 2). Regardless of *EGFR* gene status, the ORRi of subgroups in the E-P arm was higher than that in the E arm, despite there being no significant statistical difference due to the small sample size (figure 2). In the E-P arm, the combined medication relieved clinical neurological symptoms to improve PS after the first treatment in 94% of patients (17/18) with symptomatic brain metastases.

In treatment-naïve and *EGFR*-negative patients, the E-P combination achieved much better ORRi (78% vs 44%, p=0.08; 64% vs 14%, p=0.066) than erlotinib alone.

For the systemic ORR analysis, there were 27 and 31 evaluable patients in the E arm and E-P arm, respectively. Twelve patients were not evaluable for systemic ORR, because they had no extracranial lesions or their intracranial lesions progressed too quickly for extracranial tumour response to be assessed due to limited time. Patients in the E-P arm tended to achieve better extracranial response rates than those in the E arm (table 2).

Survival

The overall median PFSi was 6 months, as was the median PFS. The median PFSi of the E-P arm was 9 months (95% CI 7.5 to 10.4) versus 7 months (95% CI 4.0 to 9.9) for the E arm (p=0.30). The median PFS was 7 months (95% CI 4.9 to 9.1) in the E-P arm versus 5 months (95% CI 1.8 to 8.2) in the E arm (p=0.22). In particular, patients treated with E-P compared with E as the first-line treatment were associated with better PFSi (9 vs 2 months, p=0.027; HR=0.32, 95% CI 0.13 to 0.92) (figure 3A) and systemic PFS (8 vs 2 months, p=0.013; HR=0.35, 95% CI 0.15 to 0.83) (figure 3B). Treatment-naïve patients with *EGFR* mutation in the E-P arm had longer PFSi than those in the E arm (9 vs 5 months, p=0.13) and longer systemic PFS (8 vs 4 months, p=0.12) (figure 4A and B). At a median follow-up of 11 months (range, 5–36 months), 37 patients had died (E-P arm: 18; E arm: 19). The median OS was 22 months in the E-P arm versus 16 months in the E arm, and the OS between the two groups was not significantly different (p=0.78).

Adverse events

The AEs are summarised in table 3. The incidence of AEs was not significantly different between the E and E-P arms (91% vs 100%, p=0.25). More cases of grade 2 or 3

Table 1 Baseline demographics and characteristics

	Patients (n=69)		
	E arm (n, %)	**E-P arm (n, %)**	**p Value**
Age (years)			0.39
≥60	18, 51	14, 49	
<60	17,49	20, 51	
Sex			0.88
Male	14, 40	13, 38	
Female	21, 60	21, 62	
EGFR status			0.49
Mutation	18, 50	14, 41	
Wild type	7, 20	11, 32	
Unknown	10, 30	9, 27	
ECOG			0.40
0-1	22, 63	18, 53	
2-3	13, 37	16, 47	
Diameters of cranial lesions*			0.78
≥3 cm	9, 26	8, 23	
<3 cm	26, 74	27, 77	
Neurological symptoms			0.26
Yes	10, 29	18, 53	
No	25, 71	16, 47	
Leptomeningeal metastases			0.72
Yes	7, 20	8, 24	
No	28, 80	26, 76	
Smoking status			0.46
Yes	11, 31	8, 24	
No	24, 69	26, 76	
Previous chemotherapy			0.55
No	16, 46	18, 53	
One or two regimens	19, 54	16, 47	
Previous cranial radiotherapy			0.31
Yes	11, 31	7, 21	
No	24, 69	27, 79	
Previous gefitinib treatment			*0.01*
Yes	5, 14	14, 41	
No	30, 86	20, 59	

E, erlotinib; E-P, erlotinib combined with pemetrexed/cisplatin; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor.
*Sum of the longest diameters of the largest three intracranial tumour.

skin rash (p=0.017), paronychia (p=0.038) and appetite loss (p=0.14) were seen in the E-P arm. Haematological AEs in patients treated with E-P were not severe, and the most commonly reported was grade 1 or 2 neutropenia (52.9%). There was no febrile neutropenia. AE resulting in erlotinib dose reduction occurred in seven patients (20.6%) in the E-P arm and four patients (11.4%) in the E arm (p=0.299).

DISCUSSION

The median survival of brain metastases of lung cancer ranges from 2 months to 8 months based on age, Karnofsky performance status, primary tumour status, volume or number of intracranial lesions and with occurrence of leptomeningeal metastases or *EGFR* gene mutation.[15 16] In China, Wu *et al* reported that more than 50% of patients with lung adenocarcinoma with asymptomatic

Table 2 Intracranial or extracranial ORR in subgroups of patients between the E arm and the E-P arm

	Group (n)	ORRi (n) (%) (95%CI)	Group (n)	Extracranial ORR (n) (%)
Total patients	E (35)	17 (48) (32–65)	E (27)	10 (37)
	E-P (34)	27 (79) (63–93)	E-P (31)	18 (58)
p value		*0.008*		0.11
EGFR mutation	E (18)	10 (56) (33–79)	E (15)	9 (60)
	E-P(14)	12 (86) (68–100)	E-P (13)	9 (69)
p value	0.124		0.70	
EGFR negative	E (7)	1 (14) (0–39)	E (4)	1 (25)
	E-P (11)	7 (64) (36–92)	E-P (10)	4 (40)
p value		*0.066*		1.0
EGFR unknown	E (10)	6 (60) (30–90)	E (8)	3 (38)
	E-P (9)	8 (88) (67–100)	E-P (8)	5 (63)
p value	0.303		0.619	
First-line treatment	E (16)	7 (44) (16–72)	E (10)	3 (30)
	E-P (18)	14 (78) (58–98)	E-P (16)	11 (69)
p value		*0.08*		0.10

E, erlotinib; E-P, erlotinib combined with pemetrexed/cisplatin; EGFR, epidermal growth factor receptor; ORR, overall response rate.

brain metastases responded to erlotinib.[10] However, no further trials have shown how patients with poor PS caused by cranial metastatic tumour can be treated except with cranial radiotherapy. In our study, there was no difference between the E and E-P arms in terms of the severity of brain metastases, *EGFR* gene status, sex, age, smoking status and previous treatment (p>0.05). Moreover, almost 50% of patients had severe brain metastases or poor PS because of leptomeningeal metastases or large tumour. However, to our surprise, the ORRi of the E-P arm was 79% compared with 48% in the E arm. Although it appears that, regardless of *EGFR* gene status, all subgroup populations could benefit from the combined therapy, the small sample size meant that only the *EGFR* wild-type population or patients with first-line treatment in the E-P arm had better ORRi (p<0.1). Interestingly, the extracranial ORR was not as good as the ORRi in this study (E arm: 37%; E-P arm: 58%). It may be caused by much higher local erlotinib concentration and longer function time in a relatively closed cranial environment.

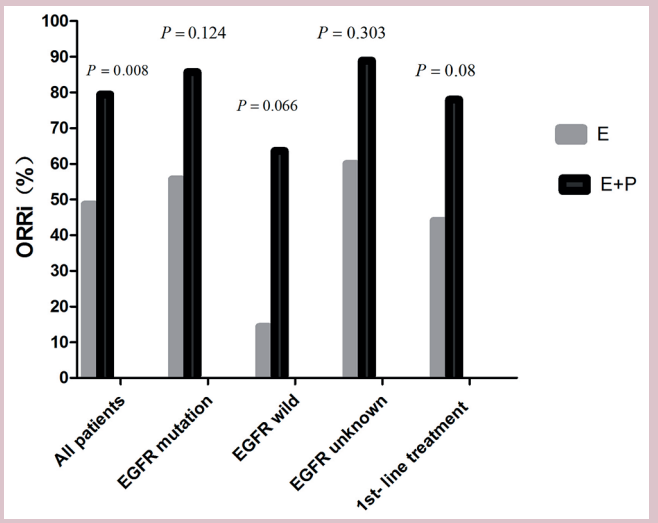

Figure 2 ORRi in subgroups of patients between the E arm and the E-P arm. E, erlotinib; E-P, erlotinib combined with pemetrexed/cisplatin; *EGFR*, epidermal growth factor receptor; ORRi, intracranial overall response rate.

Although there are more patients (41%) with previous gefitinib treatment in the E-P arm, it did not affect the superior response rate of the combination therapy. We did not detect the *EGFR*–tyrosine kinase inhibitor (*TKI*) resistance gene following gefitinib resistance, so consequently, we do not know if *EGFR* T790M mutation influenced the results. Furthermore, the result is in accordance with our previous report of successful treatment of patients with leptomeningeal metastases after gefitinib failure.[17] Therefore, it may be a good choice for patients with adenocarcinoma with gefitinib resistance to change their therapeutic strategy to erlotinib combined with pemetrexed.

The stronger effect of the E-P combination on the ORR compared with single-agent erlotinib (51.2% vs 30.1%) in East Asian patients is better than that in non–East Asian patients.[6] Although the *EGFR*–*TKI*–cisplatin combination reduces the anti-tumour activity of platinum in vitro,[18] the E-P combination in our study resulted in a similar ORR for extracranial lesions and possibly better control of intracranial tumours. In lung cancer chemotherapy, platinum plays a more important role in the sensitisation to pemetrexed than an antitumour role.[19] Moreover, Lee *et al* suggest that a low-dose erlotinib–cisplatin combination exerts its antitumour activity by targeting angiogenesis by modulating the c-MYC/hypoxia-inducible factor

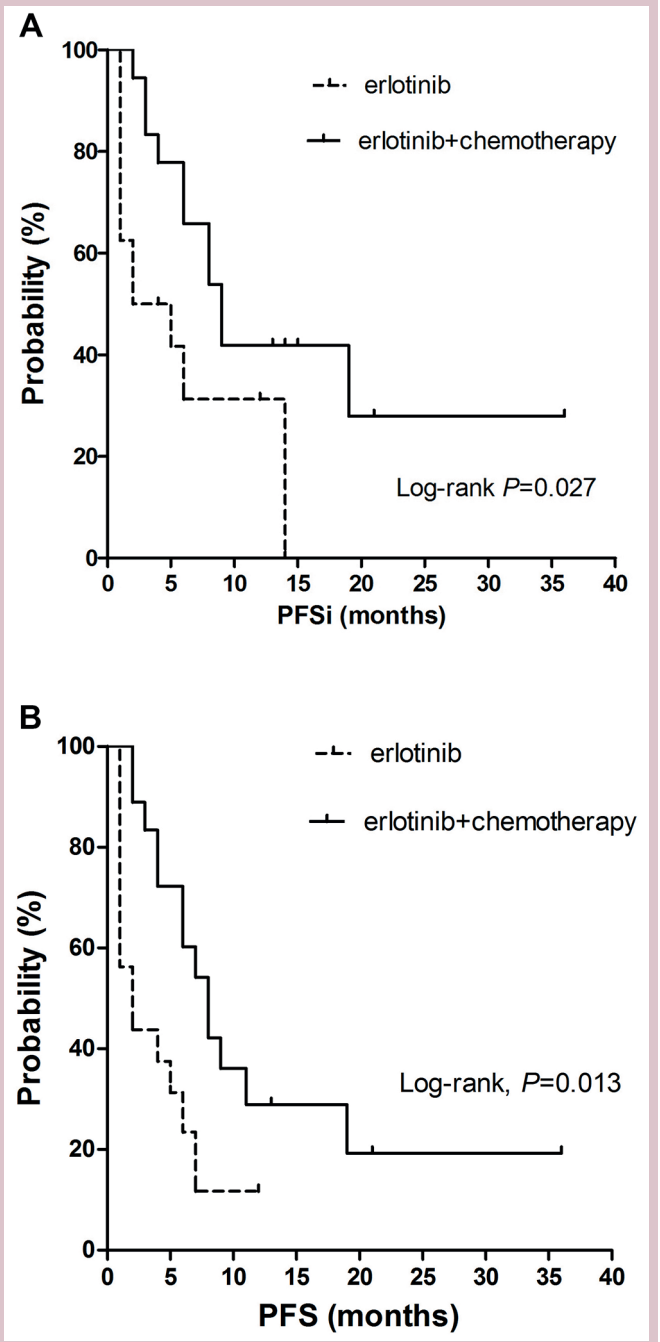

Figure 3 (A) PFSi according to the groups (E arm versus E-P arm) in treatment-naïve patients. (B) PFS according to the groups (E arm versus E-P arm) in treatment-naïve patients. E, erlotinib; E-P, erlotinib combined with pemetrexed/cisplatin; PFS, progression-free survival; PFSi, intracranial PFS.

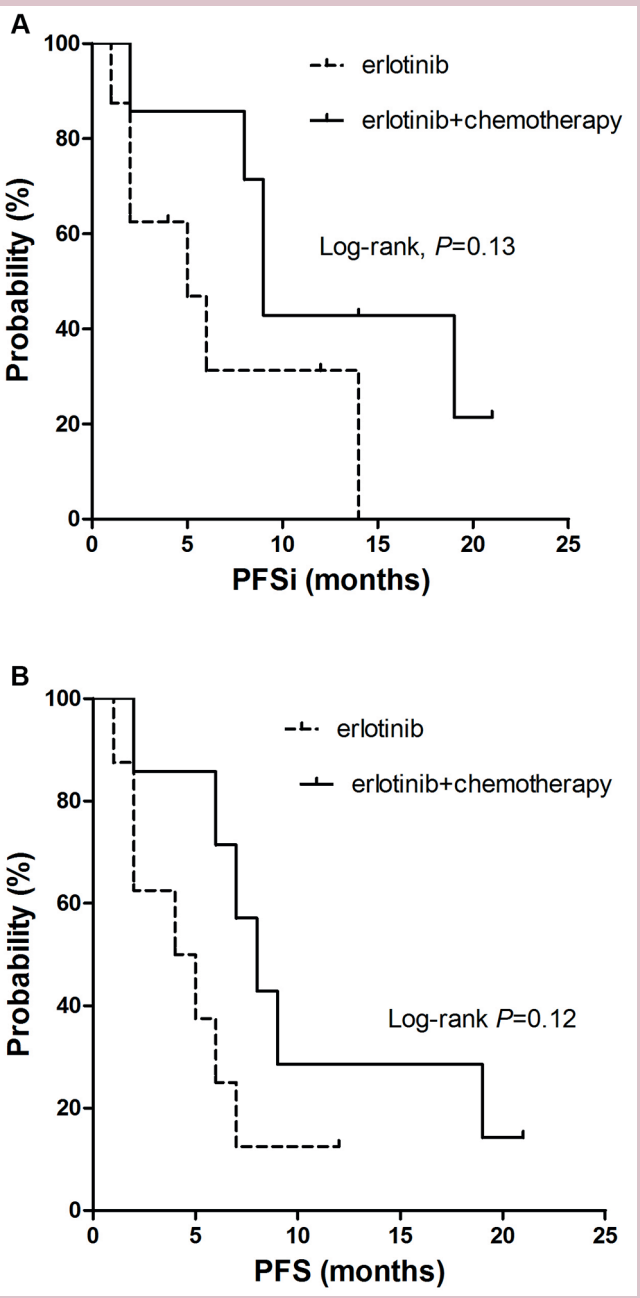

Figure 4 (A) PFSi according to the groups (E arm versus E-P arm) in treatment-naïve patients with EGFR mutation. (B) Systemic PFS according to the groups (E arm versus E-P arm) in treatment-naïve patients with EGFR mutation. E, erlotinib; E-P, erlotinib combined with pemetrexed/cisplatin; EFGR, epidermal growth factor receptor; PFS, progression-free survival; PFSi, intracranial PFS.

(HIF)-1α/vascular endothelial growth factor pathway in NSCLC with *EGFR* mutation.[20]

Given the small sample size, there was no significant difference in PFS between the E and E-P arms. However, a PFS benefit was observed in treatment-naïve patients treated with E-P ($p<0.05$) even in the *EGFR* mutation subgroup; despite the small sample size, the combined therapy as first-line treatment was associated with better PFSi compared with erlotinib alone (9 vs 5 months, p=0.13). Therefore, patients with treatment-naïve lung adenocarcinoma with *EGFR* mutation may have the most benefit from E-P treatment. Pemetrexed–erlotinib significantly improved PFS or OS compared with erlotinib or pemetrexed alone in non-squamous NSCLC, and superior results were observed often in non-smokers or East Asians harbouring *EGFR* mutation.[6–8 21] Unfortunately,

Table 3 Haematologic and non-haematologic (grade 2 or 3) adverse events

	Patients (n=69)		
	E arm (n, %)	E-P arm (n, %)	p Value
Grade 1 or 2 haematologic toxicities			
Anaemia	0	1, 2.9	
Neutrophil count decreased	0	18, 52.9	
Platelet count decreased	0	1, 2.9	
Grade 3 neutrophil count decreased	0	1, 2.9	
Grade 2 or 3 non-haematologic toxicities			
Appetite loss	2, 5.7	7, 20.6	0.140
Vomiting	1, 2.9	1, 2.9	1.00
Rash	7, 20.0	16, 47.1	0.017
Diarrhoea	1, 2.9	2, 5.9	0.534
Stomatitis	0	1, 2.9	1.00
Paronychia	0	3, 8.8	0.038
AST/ALT elevation	1, 2.9	1, 2.9	1.00
Erlotinib dose reduction	4, 11.4	7, 20.6	0.29

ALT, alanine transaminase; AST, aspartate transaminase.

these were all phase II trials. To our knowledge, we are the first to demonstrate that brain metastases of lung adenocarcinoma respond better to the E-P combination. This combination was well tolerated; we used low-dose platinum for pemetrexed sensitisation while avoiding severe myelosuppression. However, erlotinib-related side effects such as rash and paronychia were increased.

Given the difficulties of conducting clinical trials in symptomatic brain metastases, the shortcomings of this study are obvious and include the small sample size and non-randomised controlled design; therefore, there was insufficient test power for analysing survival. However, statistically significantly improved ORRi, PFSi and systemic PFS were noted in patients with treatment-naïve lung adenocarcinoma who received the erlotinib-combined chemotherapy, and numerically improved response was observed in all subgroup populations. Even in patients with EGFR wild-type mutation, a promising intracranial response (ORRi, 64%) was found in the E-P combination. Moreover, the combination chemotherapy relieved clinical neurological symptoms quickly and improved PS. In developing countries such as China, only 10%–20% lung adenocarcinoma could be detected with the *EGFR* gene status, and more are *EGFR* unknown patients.[22] It would provide a new probable strategy for patients with lung adenocarcinoma with brain metastases, regardless of *EGFR* gene status, in East-Asian low/middle-income countries.

In conclusion, our study suggests that the EP combination may be effective in Chinese patients with lung adenocarcinoma with brain metastases, with improved PFS in treatment-naïve patients. Toxicities are tolerable, and there are more erlotinib-related side effects. Certainly, we need further phase III clinical trials designed according to *EGFR* gene status to confirm the results.

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