Thoracic Cancer
Open Access
Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Efficacy of pemetrexed and carboplatin with or without bevacizumab in lung adenocarcinoma patients with *EGFR* non-T790M mutations after progression on first-line EGFR-tyrosine kinase inhibitors

Zhansheng Jiang, Yu Zhang, Yinli Yang, Zhensong Yue & Zhanyu Pan

Department of Integrative Oncology, Tianjin Medical University Cancer Institute and Hospital; National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin; Tianjin's Clinical Research Center for Cancer, Tianjin, China

Keywords
Epidermal growth factor receptor (*EGFR*); T790M; lung adenocarcinoma; pemetrexed; bevacizumab.

Correspondence
Zhanyu Pan, Department of Integrative Oncology, Tianjin Medical University Cancer Institute and Hospital; National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin; Tianjin's Clinical Research Center for Cancer, Huanhuxi Road, Hexi District, Tianjin 300060, China.
Tel: +86 22 2334 0123
Fax: +86 22 2334 0123
Email: s0010027@163.com

Received: 3 June 2018;
Accepted: 21 June 2018.

doi: 10.1111/1759-7714.12814

Thoracic Cancer **9** (2018) 1151–1155

Abstract

Background: The purpose of this study was to compare the effects of pemetrexed and carboplatin plus bevacizumab (PC + B) versus pemetrexed and carboplatin (PC) in lung adenocarcinoma patients with *EGFR* non-T790M mutations after progression on first-line EGFR-tyrosine kinase inhibitors (TKIs).

Methods: Patients with *EGFR*-positive lung adenocarcinoma who had received second-line PC with or without bevacizumab harboring *EGFR* non-T790M mutations after progression on first-line EGFR-TKIs between April 2015 and 2017 at Tianjin Medical University Cancer Institute and Hospital were enrolled in the study. The primary endpoint was progression-free survival and secondary endpoints were overall survival, objective response rate, disease control rate, and safety.

Results: A total of 85 patients were eligible for the study: 55 and 30 cases were enrolled in the PC and PC + B groups, respectively. The median progression-free survival was prolonged with PC + B compared to PC (median 8.2 vs. 5.1 months; $P = 0.037$). The objective response rate was improved with PC + B compared to PC (46.7% vs. 25.5%; $P = 0.047$) and overall survival prolonged with PC + B compared to PC (median 26.3 vs. 19.2 months; $P = 0.012$). Safety was similar to previous studies of bevacizumab in non-small cell lung cancer: one patient experienced grade 3 hypertension and proteinuria but did not require the discontinuation of therapy.

Conclusion: The addition of bevacizumab to PC was superior to PC alone as second-line therapy in patients with advanced non-T90M *EGFR*-positive lung adenocarcinoma. However, this result needs to be confirmed by prospective clinical trials.

Introduction

Lung cancer is the leading cause of cancer-related death both in China[1] and worldwide,[2] and non-small cell lung cancer (NSCLC) accounts for 80–85%. *EGFR* mutations are the most common and important driver genes in NSCLC, particularly in an Asian population. The prospective PIONEER study demonstrated that 51.4% of Asian patients with advanced adenocarcinoma developed *EGFR* mutations.[3] Moreover, another retrospective study of early-stage and advanced-stage groups of Chinese patients exhibited similar *EGFR* mutation frequencies and types (53.6% vs. 51.4%, respectively).[4] To date, several EGFR-tyrosine kinase inhibitors (TKIs), including gefitinib, erlotinib, icotinib, afatinib, and osimertinib, have become standard first-line treatments for advanced *EGFR*-mutant NSCLC.

Despite high tumor response rates with first-line EGFR-TKIs, the majority of patients acquire resistance to first-generation EGFR-TKIs within a year.[5–7] It is estimated that

50–60% of patients develop T790M mutations.[8] For T790M positive patients, osimertinib is more effective than chemotherapy;[9] however, cytotoxic chemotherapy is still the best choice for T790M negative patients. In current clinical practice, pemetrexed plus carboplatin (PC) is the most commonly used treatment regimen for patients with *EGFR* non-T790M mutations. Bevacizumab combined with chemotherapy as first-line therapy has been proven to improve efficacy and prolong survival in patients with advanced or recurrent non-squamous NSCLC,[10] especially in Chinese populations.[11] Therefore, it is necessary to explore whether bevacizumab can further improve the efficacy of chemotherapy in patients with *EGFR* non-T790M mutations who have not received past chemotherapy.

Against this background, a retrospective study was conducted to analyze the effect of PC with or without bevacizumab (B) in advanced NSCLC patients who experienced EGFR-TKI monotherapy failure and developed non-T790M mutations.

Methods

Patient eligibility

The records of patients with histologically or cytologically confirmed stage IIIB or IV lung adenocarcinoma with activating *EGFR* mutations (either exon 19 deletion or L858R in exon 21), treated at Tianjin Medical University Cancer Institute and Hospital between April 2015 and 2017, were reviewed. A total of 85 patients with NSCLC were included in the study. All patients had received first-line treatment of EGFR-TKIs (gefitinib, erlotinib, or icotinib) and were identified with progressive disease (PD). Acquired EGFR-TKI resistance in this study was defined as a prior radiographic response to EGFR-TKI therapy with later disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients were also required to have measurable legions as defined by the RECIST 1.1; an Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0 or 1; life expectancy ≥ 3 months; and adequate bone marrow, hepatic, and renal function. Major exclusion criteria were: Thr790Met mutations; hemoptysis (≥ 2.5 mL per event); a tumor invading the major blood vessels; a history of coagulation disorders or therapeutic anticoagulation; uncontrolled hypertension; a history of interstitial lung disease; or previous receipt of VEGF-related inhibitors. *EGFR* status was detected via next generation sequencing of blood or tumor tissue samples.

Treatment schedule

Patients received once cycle of pemetrexed 500 mg/m^2 and carboplatin AUC5 or AUC6 with or without bevacizumab 15 mg/kg via intravenous infusion every 21 days. Treatment continued until disease progression, the development of unacceptable side effects, or a request by either the patient or the physician to discontinue treatment. Patients received supplemental folic acid and vitamin B12 while participating in the study.

End points and evaluation

The primary endpoint was progression-free survival (PFS), which was defined as the duration from the start of treatment to tumor progression or the last follow up. Secondary endpoints were overall survival (OS), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs). OS was defined as the duration from the start of treatment to death or the last follow up. ORR was assessed by rate of patients with a complete response (CR) and partial response (PR). DCR was assessed by rate of patients with CR, PR, or stable disease (SD). AEs were evaluated by laboratory examination, questionnaires, and clinical observation according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. We performed baseline tumor assessments within 28 days after the initiation of treatment, with subsequent assessments performed every six weeks until objective disease progression. Brain imaging was only required in patients with known or suspected central nervous system metastases.

Statistical analysis

The final follow-up was performed in April 2018. Differences among subgroups stratified by gender, age, smoking status, disease stage, type of *EGFR* mutation, previous EGFR-TKI therapy, ORR, DCR, and AEs were analyzed by chi-square or Fisher's exact tests where appropriate. Kaplan–Meier plots were used to analyze PFS and OS and the median and 95% confidence intervals (CIs) were determined. All analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Two-sided P values of < 0.05 were considered statistically significant.

Results

Patients' clinical characteristics

Fifty-five patients received PC and 30 patients received pemetrexed/carboplatin plus bevacizumab (PC + B). The demographic and clinical characteristics of these patients are summarized in Table 1. The subsets contained similar proportions by year, ECOG PS, clinical stage, *EGFR* mutation, and first-line EGFR-TKIs. At the time of data cut off,

Table 1 Patient's baseline clinical characteristics

Characteristics	No. of patients (%)	
	PC (n = 55)	PC + B (n = 30)
Age, years		
Median	56	55
Range	31–75	35–74
Gender		
Male	23 (41.8%)	10 (33.3%)
Female	32 (58.2%)	20 (66.7%)
ECOG PS		
0	11 (20%)	5 (16.7%)
1	44 (80%)	25 (83.3%)
Smoking status		
Non-smoker	34 (61.8%)	21 (70%)
Former smoker	21 (38.2%)	9 (30%)
Clinical stage		
IIIB	13 (23.6%)	6 (20%)
IV	42 (76.4%)	24 (80%)
EGFR mutation status		
Exon 19 deletion	35 (63.6%)	20 (66.7%)
Exon 21L858R	20 (36.4%)	10 (33.3%)
First-line EGFR-TKIs		
Gefitinib	8 (14.5%)	4 (13.3%)
Erlotinib	7 (12.7%)	6 (20%)
Icotinib	40 (72.7%)	20 (66.7%)

B, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status; PC, pemetrexed/carboplatin; TKIs, tyrosine kinase inhibitors.

the median number of treatment cycles was 6 in the PC and 4 in the PC + B group.

Efficacy

The duration of PFS was significantly longer in the PC + B than in the PC group (median 8.2 vs. 5.1 months; P = 0.037) (Fig 1). The estimated PFS at six months was 63.3% in the PC + B group and 40% in the PC group. The secondary endpoint of OS was also prolonged in the PC +

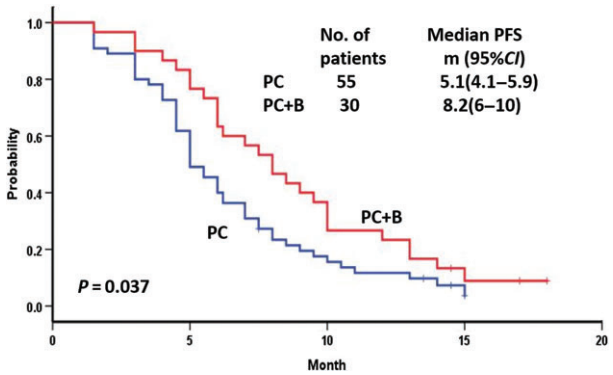

Figure 1 Kaplan–Meier curve of progression-free survival (PFS) in the two groups. B, bevacizumab; CI, confidence interval; PC, pemetrexed/carboplatin.

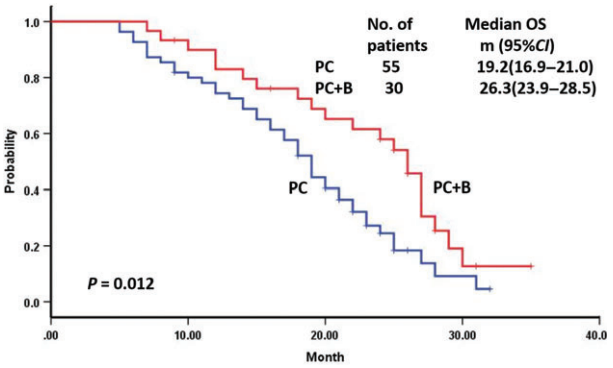

Figure 2 Kaplan–Meier curve of overall survival (OS) in the two groups. B, bevacizumab; CI, confidence interval; PC, pemetrexed/carboplatin.

B versus the PC group (P = 0.012); the median OS rates were 26.3 months (95% CI 23.9–28.5) versus 19.2 months (95% CI 16.9–21.0) for the PC + B and PC groups, respectively (Fig 2). CR was not observed in either group. ORR was improved with the addition of bevacizumab to chemotherapy, with an ORR of 46.7% in the PC + B versus 25.5% in the PC group (P = 0.047) (Table 2). DCR was similar in the PC + B and PC groups (83.3% vs. 80%, respectively; P = 0.707).

Safety

Hematological and non-hematological treatment-related toxicities are shown in Table 3. The most common AEs (incidence ≥ 30%, any grade) were hematologic and gastrointestinal-related disorders. The incidence of any grade and grade ≥ 3 AEs was comparable in both arms, except hypertension and proteinuria, which were both common AEs of bevacizumab.

Discussion

In this study, we found that advanced NSCLC patients with non-T790M mutations treated with PC + B achieved

Table 2 Response to treatment

Response	No. of patients (%)		P
	PC (n = 55)	PC + B (n = 30)	
CR	0	0	
PR	14 (25.5%)	14 (46.7%)	
SD	30 (54.5%)	11 (36.7%)	
PD	11 (20%)	5 (16.7%)	
ORR	14 (25.5%)	14 (46.7%)	**0.047**
DCR	44 (80%)	25 (83.3%)	0.707

Bold value indicates $P < 0.05$ are statistically significant. B, bevacizumab; CR, complete response; DCR, disease control rate; ORR, objective response rate; PC, pemetrexed/carboplatin; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3 Adverse events

Adverse event	PC (n = 55)		PC + B (n = 30)	
	Any grade N (%)	Grade ≥ 3 N (%)	Any grade N (%)	Grade ≥ 3 N (%)
Hematologic toxicity				
Leukopenia	28 (51)	6 (11)	16 (53)	3 (10)
Neutropenia	22 (40)	7 (13)	12 (40)	3 (10)
Anemia	16 (29)	5 (9)	8 (27)	2 (7)
Thrombocytopenia	12 (22)	2 (4)	6 (20)	1 (3)
Non-hematologic toxicity				
Hypertension	5 (9)	0 (0)	13 (43)	1 (3)
Bleeding	2 (4)	0 (0)	2 (7)	0 (0)
Proteinuria	6 (11)	0 (0)	8 (27)	1 (3)
Decreased appetite	20 (36)	2 (4)	11 (37)	2 (7)
Vomiting	11 (20)	2 (4)	7 (23)	1 (3)
Nausea	27 (49)	3 (5)	15 (50)	1 (3)
Fatigue	15 (27)	1 (2)	9 (30)	1 (3)
Constipation	20 (36)	5 (9)	10 (33)	3 (10)
AST increased	3 (5)	(0) 0	2 (7)	(0) 0
ALT increased	2 (4)	(0) 0	3 (10)	(0) 0
Mucositis	12 (22)	2 (4)	7 (23)	1 (3)

ALT, alanine transaminase; AST, aspartate transaminase; B, bevacizumab; PC, pemetrexed/carboplatin.

a longer duration of PFS and OS and better response rates than those receiving PC alone after first-line EGFR-TKI therapy. Moreover, PC + B was well tolerated in the majority of patients, with only one patient experiencing grade 3 hypertension and proteinuria but did not require discontinuation of therapy.

It is well known that osimertinib is superior to chemotherapy in T790M positive patients;[9] however, the best second-line regimen for patients with non-T790M mutations has not been elucidated. The current National Comprehensive Cancer Network (NCCN) and Chinese Society of Clinical Oncology (CSCO) guidelines recommend the administration of platinum-based combination therapy in cases of progression after use of first-line EGFR-TKIs in patients with non-T790M mutations. A phase two trial compared the effects of pemetrexed and docetaxel as salvage chemotherapy after first-line EGFR-TKI failure, and suggested that pemetrexed was better tolerated.[12] Moreover, PC is the most common regimen for chemotherapy naïve non-squamous NSCLC patients in most regions of China. In the AURA3 trial, the median PFS and ORR in the PC group were 4.4 months and 31%.[9] Our results showed slightly better clinical efficacy with PFS of 5.1 months in the PC group; however, the characteristics of the two trials were different (T790M positive and negative). More importantly, PFS (8.2 months), OS (26.3 months), and ORR (46.7%) were improved when bevacizumab was added to chemotherapy in our study. A similar study in Japan also reported that PC + B achieved a PFS of 6.6 months and an ORR of 37% in patients who had experienced failure of first-line EGFR-TKIs.[13] Another study showed that a bevacizumab plus pemetrexed regimen was superior to pemetrexed monotherapy, even as third-line therapy in patients with *EGFR* mutated lung adenocarcinoma (median OS 38.76 vs. 36.22 months, respectively; $P = 0.04$).[14] In addition, in animal experiments, Furugaki *et al.* confirmed that bevacizumab could enhance antitumor activity in T790M negative rather than in T790M positive tumors.[15] These results suggest that bevacizumab combined with chemotherapy is a better choice than chemotherapy alone in patients with non-T790M mutations who have experienced first-line EGFR-TKI failure.

Bevacizumab plus chemotherapy is recommended as the first-line choice for *EGFR* wild type advanced non-squamous NSCLC. A number of studies have attempted to evaluate bevacizumab combined with EGFR-TKIs as first-line therapy for patients with *EGFR* mutations. The JO25567 study showed that first-line therapy of bevacizumab plus erlotinib could prolong PFS compared to erlotinib alone in *EGFR* mutation-positive NSCLC patients (16.0 and 9.7 months, respectively).[16] Meanwhile, the BELIEF Trial and the Okayama Lung Cancer Study Group Trial 1001 reported PFS rates of bevacizumab plus erlotinib or gefitinib as first-line therapy of 13.2 and 14.4 months, respectively.[17,18] The phase III BEVERLY trial comparing bevacizumab plus erlotinib versus erlotinib alone as first-line treatment for patients with *EGFR*-mutated advanced non-squamous NSCLC is currently being conducted.[19] Recently, a study in China found first-line bevacizumab plus chemotherapy followed by EGFR-TKIs may provide a favorable prognosis for *EGFR*-mutant patients compared to first-line EGFR-TKIs followed by bevacizumab plus chemotherapy.[20] Thus, the order in which bevacizumab plus chemotherapy and EGFR-TKIs are administered to patients harboring *EGFR* mutations may be significant.

There were some limitations to our study. First, this was a single center study with unmatched populations. Second, the baseline characteristics were not well balanced between the two groups. The ratio of women and non-smokers was higher in the PC + B than in the PC group. Third, our study was a retrospective analysis with a small sample size. These factors may lead to the relatively large discrepancies in the final results, especially in PFS and OS data because the tumor burden in the PC + B group was probably lower than in the PC group.

In conclusion, PC + B was superior to PC alone as second-line therapy in advanced NSCLC patients with *EGFR* non-T790M mutations after progression on first-line EGFR-TKIs. However, this treatment strategy needs to be confirmed by prospective clinical trials.

Disclosure

No authors report any conflict of interest.

References

1 Chen WQ, Zheng RS, Baade PD *et al*. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115–32.
2 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; **68**: 7–30.
3 Shi Y, Au JS, Thongprasert S *et al*. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol* 2014; **9**: 154–62.
4 Pi C, Xu CR, Zhang MF *et al*. EGFR mutations in early-stage and advanced-stage lung adenocarcinoma: Analysis based on large-scale data from China. *Thorac Cancer* 2018; **9**: 814–9.
5 Wu YL, Zhou C, Liam CK *et al*. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: Analyses from the phase III, randomized, open-label, ENSURE study. *Ann Oncol* 2015; **26**: 1883–9.
6 Maemondo M, Inoue A, Kobayashi K *et al*. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010; **362**: 2380–8.
7 Shi YK, Wang L, Han BH *et al*. First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVINCE): A phase 3, open-label, randomized study. *Ann Oncol* 2017; **28**: 2443–50.
8 Oxnard GR, Arcila ME, Sima CS *et al*. Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: Distinct natural history of patients with tumors harboring the T790M mutation. *Clin Cancer Res* 2011; **17**: 1616–22.
9 Mok TS, Wu YL, Ahn MJ *et al*. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* 2017; **376**: 629–40.
10 Sandler A, Gray R, Perry MC *et al*. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. (Published erratum appears in *N Engl J Med* 2007; **356**: 318). *N Engl J Med* 2006; **355**: 2542–50.
11 Zhou C, Wu YL, Chen G *et al*. BEYOND: A randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2015; **33**: 2197–204.
12 Dong L, Han ZF, Feng ZH, Jia ZY. Comparison of pemetrexed and docetaxel as salvage chemotherapy for the treatment for nonsmall-cell lung cancer after the failure of epidermal growth factor receptor-tyrosine kinase inhibitors. *J Int Med Res* 2014; **42**: 191–7.
13 Hattori Y, Satouchi M, Shimada T *et al*. A phase 2 study of bevacizumab in combination with carboplatin and paclitaxel in patients with non-squamous non-small-cell lung cancer harboring mutations of epidermal growth factor receptor (EGFR) after failing first-line EGFR-tyrosine kinase inhibitors (HANSHIN Oncology Group 0109). *Lung Cancer* 2015; **87**: 136–40.
14 Zhou CZ, Qin YY, Xie ZH *et al*. Efficacy of third-line pemetrexed monotherapy versus pemetrexed combination with bevacizumab in patients with advanced EGFR mutation-positive lung adenocarcinoma. *Chin J Cancer Res* 2014; **26**: 705–10.
15 Furugaki K, Fukumura J, Iwai T *et al*. Impact of bevacizumab in combination with erlotinib on EGFR-mutated non-small cell lung cancer xenograft models with T790M mutation or MET amplification. *Int J Cancer* 2016; **138**: 1024–32.
16 Seto T, Kato T, Nishio M *et al*. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): An open-label, randomised, multicentre, phase 2 study. (Published erratum appears in *Lancet Oncol* 2014; **15**: e475). *Lancet Oncol* 2014; **15**: 1236–44.
17 Rosell R, Dafni U, Felip E *et al*. Erlotinib and bevacizumab in patients with advanced non-small-cell lung cancer and activating EGFR mutations (BELIEF): An international, multicentre, single-arm, phase 2 trial. *Lancet Respir Med* 2017; **5**: 435–44.
18 Ichihara E, Hotta K, Nogami N *et al*. Phase II trial of gefitinib in combination with bevacizumab as first-line therapy for advanced non-small cell lung cancer with activating EGFR gene mutations: The Okayama Lung Cancer Study Group Trial 1001. *J Thorac Oncol* 2015; **10**: 486–91.
19 Gridelli C, Rossi A, Ciardiello F *et al*. BEVERLY: Rationale and design of a randomized open-label phase III trial comparing bevacizumab plus erlotinib versus erlotinib alone as first-line treatment of patients with EGFR-mutated advanced nonsquamous non-small-cell lung cancer. *Clin Lung Cancer* 2016; **17**: 461–5.
20 Chen RL, Chen HJ, Jiang BY *et al*. Bevacizumab plus chemotherapy for patients with advanced pulmonary adenocarcinoma harboring EGFR mutations. *Clin Transl Oncol* 2018; **20**: 243–52.

