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

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

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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 China1 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. For T790M positive patients, osimertinib is more effective than chemotherapy; 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, especially in Chinese populations. 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 lesions 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/m² 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,
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 + B versus the PC group (\( P = 0.012 \); 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...
Bevacizumab plus CT in \textit{EGFR} non-T790M

Z. Jiang et al.

Bevacizumab plus CT in EGFR non-T790M

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      |             |                 |                |                |
| 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,\textsuperscript{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.\textsuperscript{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%.\textsuperscript{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.\textsuperscript{13} Another study showed that a bevacizumab plus pemetrexed regimen was superior to pemetrexed monotherapy, even as third-line therapy in patients with \textit{EGFR} mutated lung adenocarcinoma (median OS 38.76 vs. 36.22 months, respectively; \(P = 0.04\)).\textsuperscript{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.\textsuperscript{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 \textit{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 \textit{EGFR} mutations. The JO25567 study showed that first-line therapy of bevacizumab plus erlotinib could prolong PFS compared to erlotinib alone in \textit{EGFR} mutation-positive NSCLC patients (16.0 and 9.7 months, respectively).\textsuperscript{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.\textsuperscript{17,18} The phase III BEVERLY trial comparing bevacizumab plus erlotinib versus erlotinib alone as first-line treatment for patients with \textit{EGFR}-mutated advanced non-squamous NSCLC is currently being conducted.\textsuperscript{19} Recently, a study in China found first-line bevacizumab plus chemotherapy followed by EGFR-TKIs may provide a favorable prognosis for \textit{EGFR}-mutant patients compared to first-line EGFR-TKIs followed by bevacizumab plus chemotherapy.\textsuperscript{20} Thus, the order in which bevacizumab plus chemotherapy and EGFR-TKIs are administered to patients harboring \textit{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 \textit{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.

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