

Efficacy of erlotinib and celecoxib for patients with advanced non-small cell lung cancer

A retrospective study

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Abstract

This study evaluated the efficacy and toxicity of erlotinib and celecoxib (EC) for treating Chinese patients with advanced non-small cell lung cancer (ANSCLC) and epidermal growth factor receptor (EGFR) wild type.

Totally, 75 subjects with ANSCLC and EGFR wild type were included. They all underwent EC treatment. The outcome measurements consisted of progression-free survival (PFS), overall survival (OS), complete response (CR), partial response (PR), stable disease (SD), progress disease (PD), and disease control rate (DCR). Additionally, adverse events were also documented.

Two-year CR, PR, SD, PD, and DCR were 4.0%, 6.7%, 42.6%, 46.7%, and 53.3% respectively. The median PFS was 3.4 months, the median OS was 10.0 months. Additionally, acceptable toxicities were recorded in this study.

The results showed that EC may be efficacious for patients with ANSCLC and EGFR wild type only, and acceptable toxicity among the Chinese Han population.

Abbreviations: ALT = alanine transaminase, ANSCLC = advanced non-small cell lung cancer, AST = aspartate transaminase, COX-2 = cyclooxygenase-2, CR = complete response, DCR = disease control rate, EC = erlotinib and celecoxib, EGFR = epidermal growth factor receptor, NSCLC = non-small cell lung cancer, OBD = optimal biological dose, OS = overall survival, PD = progress disease, PFS = progression-free survival, PGEM = prostaglandin E2, PR = partial response, RECIST = response evaluation criteria in solid tumors, SD = stable disease, sEC = serum-soluble E-cadherin, TKIs = tyrosine kinase inhibitors.

Keywords: advanced non-small cell lung cancer, celecoxib, efficacy, erlotinib, toxicity

1. Introduction

Lung cancer is one of the most common condition, which results in cancer death all over the world.^[1,2] It has been estimated that it is responsible for almost 20% death (1.59 million deaths, 19.4% of the total).^[3] Previous studies reported that the 5-year survival of non-small cell lung cancer (NSCLC) for all stages is approximately 15%.^[4,5] However, the majority of them are diagnosed with advanced or metastatic disease.^[6] Unfortunately, the relative 5-year survival rate among such kind of population is only 4%.^[7,8]

Targeted therapies have been reported to prolong survival for NSCLC,^[9–13] especially for epidermal growth factor receptor

(EGFR)-mutations by tyrosine kinase inhibitors (TKIs).^[14,15] However, these kinds of therapies are not eligible for about 80% patients with NSCLC.^[16] Although many tumors are reported not sensitive to single-agent intervention, combined treatment that targets multiple pathways may help to enhance clinical endpoint.

It is reported that the signaling pathways of EGFR and cyclooxygenase-2 (COX-2) presents a novel mechanism of EGFR TKI therapy resistance for NSCLC treatment.^[17,18] Additionally, it is responsible for tumor proliferation, invasion, and angiogenesis.^[19] Thus, combined EGFR and COX-2 may help to potentiate responses for NSCLC.

Although several studies have explored the efficacy of erlotinib combined celecoxib (EC) for the treatment of advanced non-small cell lung cancer (ANSCLC), no study specifically investigated the efficacy and safety of EC for ANSCLC patients with EGFR wild type alone.^[20–22] Thus, in the present study, we analyzed the efficacy and toxicity of EC in patients with ANSCLC and EGFR wild type only among the Chinese Han population.

2. Patients and methods

2.1. Ethic approval

This study has been approved by the Ethical Committee of the First Affiliated Hospital of Jiamusi University. All patients provided the informed written consent. It was operated at First Affiliated Hospital of Jiamusi University from May 2012 to June 2015.

2.2. Patients

Seventy-five patients with the confirmed diagnosis of stage IIIB and IV ANSCLC and tumor tissue were available for mutation

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Table 1
Characteristics of included patients.

Characteristics	Value
Mean age, yr	66.3 (13.1)
Sex	
Male	35 (46.7)
Female	40 (53.3)
Ethnicity (Chinese Han)	75 (100.0)
Occupation	
Employed	27 (36.0)
Unemployed	15 (20.0)
Retired	33 (44.0)
Histology	
Squamous cell carcinoma	16 (21.3)
Adenocarcinoma	59 (78.7)
ECOG	
0	36 (48.0)
1	39 (52.0)
Smoking	
Yes	55 (73.3)
No	20 (26.7)
Stage	
IIIB	11 (14.7)
IV	64 (85.3)
EGFR wild type	75 (100.0)
Number of previous treatments	
0	8 (10.7)
1	38 (50.7)
≥2	29 (38.6)

Data are present as mean ± standard deviation or number (%).

ECOG = Eastern Cooperative Oncology Group, EGFR = epidermal growth factor receptor.

analysis. All patients were ANSCLC with EGFR wild type.^[2,3] The status of Eastern Cooperative Oncology Group was 0 or 1.^[2,4] Patients had normal functions of hematology, kidney, and liver. Cases were excluded if the subjects were pregnancy or breastfeeding or previous received EGFR or COX-2 inhibitor, gastrointestinal ulceration, bleeding or perforation, and severe psychological disorders that affected the treatments.

2.3. Treatment schedule

Patients often orally taken erlotinib 150 mg once daily, and celecoxib 200 mg trice daily for a total of 600 mg daily within 30-day cycle. All patients were given the above medication for up to 12 months. Then, patients kept on taking erlotinib orally until the disease progression or unacceptable toxicity achieved.

2.4. Outcome measurements

The outcome measurements included progression-free survival (PFS), overall survival (OS), complete response (CR), partial response (PR), stable disease (SD), progress disease (PD), and disease control rate (DCR). Moreover, toxicity was also

documented, which was assessed based on the common terminology criteria for adverse events (V3.0).^[2,5]

2.5. Statistical analysis

In this study, all included patients were monitored and recorded daily for the treatment-related toxicity. The tumor size measurement was performed by using the standard of response evaluation criteria in solid tumors (RECIST) 1.1.^[2,6] CR was defined as the total tumor disappearance. PFS was set as the time to receive the study medication to disease progression based on the RECIST. OS was calculated at the beginning of study medication applied to the date of death with any reasons. PFS and OS were evaluated by the Kaplan–Meier method. All data were analyzed by using SPSS software 18.0 (IBM Corp, Armonk, NY).

3. Results

The characteristics of all included patients are presented in Table 1. The mean age was 66.3 years old. All 75 included patients were Chinese Han ethnicity and were diagnosed as ANSCLC with EGFR wild type. Of them, 35 (46.7%) subjects were males. As for histology, 16 (21.3%) patients were squamous cell carcinoma, and 59 (78.7%) patients were adenocarcinoma. As for stage, 11 (14.7%) patients were IIIB, and 64 (85.3%) patients were IV.

The CR, PR, SD, PD, and DCR of 2-year follow-up were 4.0% (3/75), 6.7% (5/75), 42.6% (32/75), 46.7% (35/75), and 53.3% (52/75), respectively (Table 2). The median PFS was 3.4 months (Fig. 1), and the median OS was 10.0 months (Fig. 2).

The toxicity-related treatment is summarized in Table 3. All toxicities were acceptable. No death was found related to the study medication. The most common toxicities were rash 68.0% (51/75), diarrhea 61.3% (46/75), fatigue 64.7% (41/75), dry skin 53.3% (40/75), and aspartate transaminase (AST)/alanine transaminase (ALT) 46.7% (35/75).

4. Discussion

Several published studies have explored the efficacy and toxicity of EC for ANSCLC, and achieved some promising outcome results. A phase II trial assessed the efficacy and toxicity of EC for advanced NSCLC.^[2,1] It concluded that there was not significant difference between EC and erlotinib alone in unselected patients with NSCLC.^[2,1] However, it may benefit in the patient's subset with longer FPS.^[2,1] The other trial explored the EGFR and COX-2 inhibition for NSCLC.^[2,0] Its results demonstrated that EC failed to enhance outcome conditions in unselected patients, except the EGFR wild-type.^[2,0] Other study also explored the tumor response to EC combined treatment in patients with NSCLC. It has an association with a low baseline matrix metalloproteinase-9 (MMP-9) and a decrease in serum-soluble E-cadherin (sEC).^[2,7] The results found that serum sEC, MMP-9, tissue inhibitors of

Table 2
Response rate of all included patients.

Value	CR	PR	SD	PD	DRR
Response rate	4.0% (3/75)	6.7% (5/75)	42.6% (32/75)	46.7% (35/75)	53.3% (52/75)

CR = complete response, DRR = disease control rate, PD = progress disease, PR = partial response, SD = stable disease.

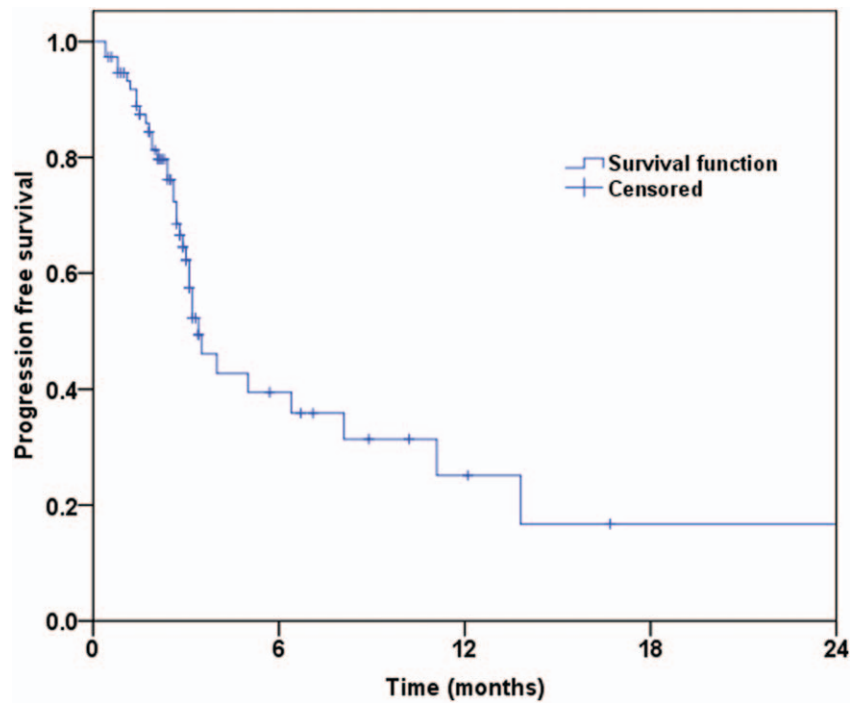


Figure 1. Progression-free survival.

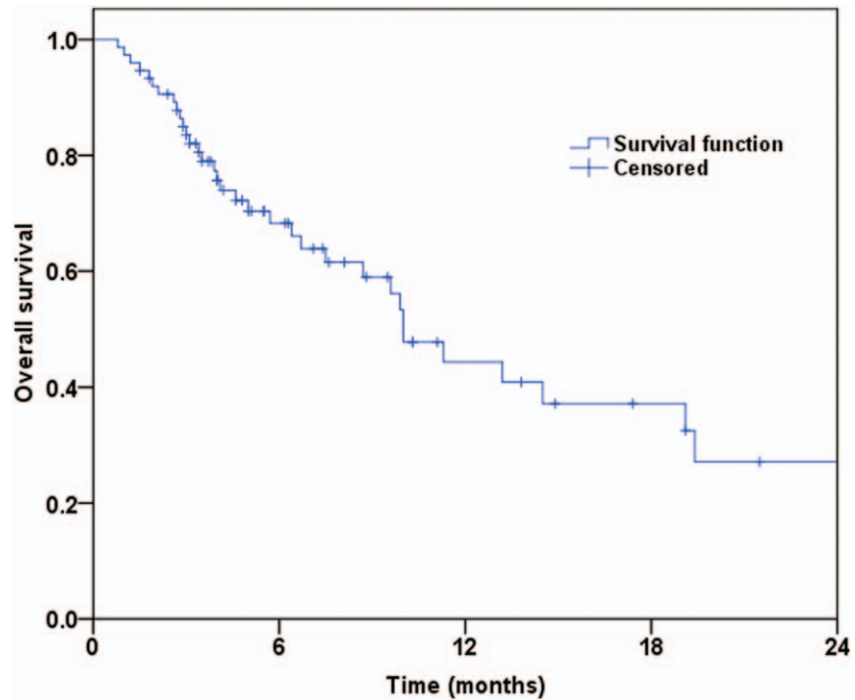


Figure 2. Overall survival.

matrix metalloproteinases, and C-C motif chemokine ligand 15 levels related to EC for NSCLC.^[27] Another study established the optimal biological dose (OBD), and toxicity profile of the combination of EC in patients with ANSCLC.^[22] Its results showed that objective responses with an acceptable toxicity

profile. In addition, it suggested the future trials using the OBD of celecoxib at 600 mg bid.^[22]

The results of the present study showed that the efficacy and toxicity of EC for Chinese patients with ANSCLC and EGFR wild type is encouraging. The 2-year median PFS and OS were 3.4 and

Table 3**Toxicities related to the treatment (all grades $\geq 10\%$).**

Toxicities	All grades $\geq 10\%$
Rash	68.0% (51/75)
Diarrhea	61.3% (46/75)
Fatigue	54.7% (41/75)
Dry skin	53.3% (40/75)
AST/ALT	46.7% (35/75)
Anorexia	38.7% (29/75)
Nausea	28.0% (21/75)
Hypoalbuminemia	25.3% (19/75)
Stomatitis	24.0% (18/75)
Anemia	18.7% (14/75)
Lymphopenia	14.7% (11/75)
Vomiting	12.0% (9/75)
Weight loss	10.7% (8/75)

ALT = alanine transaminase, AST = aspartate transaminase.

10.0 months, respectively. The DCF of 2-year follow-up was 53.3%. The total toxicity was mild without death related to the treatment. The most common toxicities included rash, diarrhea, fatigue, dry skin, and AST/ALT.

The present study has several advantages and limitations. As for advantages, this study first and specifically investigated the efficacy and safety of EC for Chinese patients with ANSCLC and EGFR wild type only, which may provide helpful evidence for the treatment of ANSCLC patients with EGFR wild type. In addition, all included patients were Chinese Han ethnicity, which may decrease the variability of study. As for limitations, first, this study included a quite small sample size, which may impact the results of the present study. Second, this study only investigated the patients with ANSCLC and EGFR wild type, thus patients with other EGFR types still need to be explored. Third, all included patients are Chinese Han ethnicity. Thus, the efficacy and toxicity of other ethnicities should still be explored in further study.

5. Conclusion

This study found that the efficacy of EC may benefit and its toxicity is acceptable for patients with ANSCLC and EGFR wild type only among the Chinese Han population.

Author contributions

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