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SHORT COMMUNICATION

Clinical effect of erlotinib as first-line treatment for Asian elderly patients with advanced non-small-cell lung cancer

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Abstract
Purpose To evaluate the efficacy and toxicities of erlotinib as first-line treatment for Asian elderly patients with advanced non-small-cell lung cancer (NSCLC).
Patients and methods Untreated patients with advanced NSCLC were included in this study; erlotinib was orally administered at a dose of 150 mg daily until disease progression or intolerable toxicity or for other reasons.
Results A total of 35 patients were enrolled. Patient characteristics were as follows: mean age 75.6 years (ranged 70–81 years), 24 (68.6%) male, 16 (45.7%) former or current smokers, 13 (37.1%) adenocarcinoma, 18 (51.4%) squamous cell carcinoma and 4 (11.4%) bronchioloalveolar carcinoma. Out of 35 patients, 1 CR, 16 PR and 10 SD, resulting in an overall response rate (CR + PR) of 48.6% and disease control rate (DCR = CR + PR + SD) of 77.1%. The median TTP was 6.4 months, and the median OS was 12.7 months. The CBR was 80%, and the 1-year survival rate was 48.6%. The most common adverse event (AE) was mild skin rash and diarrhea (CTC AE 1/2). Among them, the female never smokers with a non-squamous cell carcinoma histology was superior to the male smokers with a squamous cell carcinoma in disease control rate, with significant differences ($P < 0.05$).
Conclusion The results suggest that erlotinib monotherapy is an effective and well-tolerated treatment option for Asian elderly patients with advanced NSCLC.

Keywords Erlotinib · Lung carcinoma · Non-small-cell lung cancer · Elderly patients

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Introduction

Lung cancer, predominantly NSCLC, has been the leading cause of cancer-related death in the world [1] mostly related to its advanced stages upon presentation. Treatment for these patients includes chemotherapy, radiotherapy, and best supportive care, with current guidelines recommending platinum-based combination regimens as first-line treatment [2]. Although improvement has been achieved over the last few decades, the prognosis for these patients remains poor, with response rates for first-line therapy of 20–40% and median survival times of 7–12 months [3, 4].

Moreover, as a result of an increasing life expectancy, the elderly population is experiencing a rise in the incidence of lung carcinoma. Data from the Surveillance, Epidemiology, and End Results (SEER) registry indicate that about 30% of advanced NSCLC are diagnosed in patients older than 70 years of age [5]. Elderly cancer patients often present with medical and physiologic challenges [6], which make the selection of their optimal treatment daunting. Meanwhile, aging is inextricably associated with physiologic changes in functional status, organ function, and drug pharmacokinetics. Aging is associated with decreases in marrow reserve, drug clearance, and lean body mass. Furthermore, concomitant comorbidities that affect functional status, general health, and tumor symptoms are frequently

present in this patient population [7]. As a result, treatment for these patients is often palliative in nature.

In recent years, selective epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) has emerged as an alternative treatment option for advanced NSCLC with distinct mechanism of action and safety profile. However, little is known about the efficacy and toxicities of erlotinib as first-line treatment, especially for elderly patients with advanced NSCLC. Therefore, we conducted a phase II study of erlotinib as first-line treatment in Asian elderly patients with advanced NSCLC.

Patients and methods

Eligibility criteria

Eligibility criteria were (1) over 70 years of age; (2) cytologically or pathologically proven stage IIIB/IV NSCLC, at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria; (4) no prior chemotherapy, life expectancy of more than 1 months and Karnofsky performance status (KPS) $\geq$50; (5) without typical interstitial pneumonia and pulmonary fibrosis, and (6) adequate bone marrow, hepatic, and renal function. The study was approved by the Institutional Review Board of Yichang Central People's Hospital, and a written informed consent was obtained from all patients.

Study design

Patients were treated with erlotinib at a dose of 150 mg daily. One dose reduction per patient was permitted from 150 to 100 mg, and erlotinib treatment could be interrupted for a maximum of 21 days. Therapy was continued until disease progression or intolerable toxicity or for other reasons.

Evaluation of response and adverse events

Baseline evaluations included a complete medical history, physical, and radiologic examinations, examination, KPS, complete blood count (CBC) and biochemistry within 2 weeks prior to entry onto the study. Evaluation of treatment response by computed tomography scan was repeated every 4 weeks according to RECIST. Disease control was defined the best tumor response of complete response (CR), partial response (PR), or stable disease (SD) that was confirmed and sustained for 8 weeks or longer. In terms of clinical benefit response (CBR), KPS, weight change and pain were considered according to Burris et al. [8]. If the pain medicine reduced $\geq$50%, KPS improved $\geq$20 or weight gain $\geq$7% and maintain at least 4 weeks, the patient will be determined beneficial for the CBR. The time to progression (TTP) was calculated from the initiation of therapy to the date of the disease progression, while overall survival (OS) was measured from the initiation of therapy to the date of the last follow-up or death. Adverse events were evaluated every cycle according to the National Cancer Institute Common Toxicity Criteria for adverse event (version 3.0).

Statistical analysis

The primary objective was to assess the DCR of erlotinib therapy. The secondary objectives were overall response rate, TTP, CBR, survival, and safety.

A two-stage optimal design proposed by Simon was used to decide the sample size of phase II study. We set a response rate of 30% as the target activity level and 10% as the lowest response rate of interest. With $\alpha = 0.05$ and $\beta = 0.2$, the upper limit for a first-stage treatment rejection was 2 response among 18 evaluable patients, the upper limit of second-stage rejection was 6 responses among 35 evaluable patients.

Response rates and control rate were analyzed by the Fisher's exact test. Survival curves were constructed using the Kaplan–Meier method. Two-sided P values less than 0.05 were considered significant. All statistical tests were conducted using the computer software SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 35 patients were enrolled in this study. Among them, 24 (68.6%) were men and 11 (31.4%) were women; mean age 75.6 years (range 70–81 years); 19 (54.3%) former or current smokers and 16 (45.7%) patients never smokers; 13 (37.1%) adenocarcinoma, 18 (51.4%) squamous cell carcinoma and 4 (11.4%) bronchioloalveolar carcinoma.

Efficacy

All patients were included in the response assessment.

Out of 35 patients, 1 CR, 16 PR and 10 SD, resulting in an overall response rate of 48.6% and DCR of 77.1%. Among them, the DCR was significantly higher in female patients than in male patients (100.0% versus 66.7%, $P = 0.037$), in patients with non-squamous cell carcinoma than in patients with squamous cell carcinoma (94.2% versus 61.1%, $P = 0.041$), and in never smokers than in ever smokers (93.8% versus 63.2%, $P = 0.047$). However, the overall response rate was not significantly associated with gender, histology, or smoking history (Table 1).

Table 1 Prognostic factor analysis

Variable	Patients(*n*)	Overall response rate (%)	*P* value	Disease control rate (%)	*P* value
Gender					
Male	24	37.5 (9/24)	0.075	66.7 (16/24)	0.037
Female	11	72.7 (8/11)		100.0 (11/11)	
Histological type					
Squamous cell carcinoma	18	33.3 (6/18)	0.094	61.1 (11/18)	0.041
Non-squamous cell carcinoma	17	64.7 (11/17)		94.2 (16/17)	
Smoking history					
Yes	19	42.1 (8/19)	0.505	63.2 (12/19)	0.047
No	16	56.3 (9/16)		93.8 (15/16)	

The symptoms and quality of life for 28 patients were improved significantly. They showed alleviated cough and asthma, disappeared hemoptysis, relieved pain, as well as improved general condition including appetite and physical strength. The CBR was 80% (28/35). However, the quality of life for another 7 patients was not improved significantly. Two patients had aggravated pain, and 5 patients had intensified cough, shortness of breath, and hemoptysis.

Survival data were followed up until the end of March 2010. At the time of analysis, there were 17 deaths (48.6%), and one patient lost to follow-up. The median TTP was 6.4 months, and median OS was 12.7 months (Fig. 1).The 1-year survival rate was 48.6%.

Adverse events

The major erlotinib treatment–related AE were grade 1/2 skin rash and diarrhea, which affected 82.9% (29/35) of patients. Only 1 case had dose decreased because of severe skin rash and diarrhea, but the patient had PR.

Discussion

Treatment of elderly patients with advanced NSCLC remains a challenge. Novel targeted agents such as inhibitors of histone deacetylase and multi-targeted tyrosine kinase inhibitor are currently an active area of research in NSCLC and will hopefully lead to improved treatment outcomes for patients. Erlotinib as a specific EGFR-TKI, which is currently approved for use as second-line or third-line therapy in patients with NSCLC, is based on the landmark BR.21 trial [9].

Several studies have observed that erlotinib as first-line treatment confers benefits in NSCLC elderly patients. A study by Jackman et al. [10] reported the efficacy of

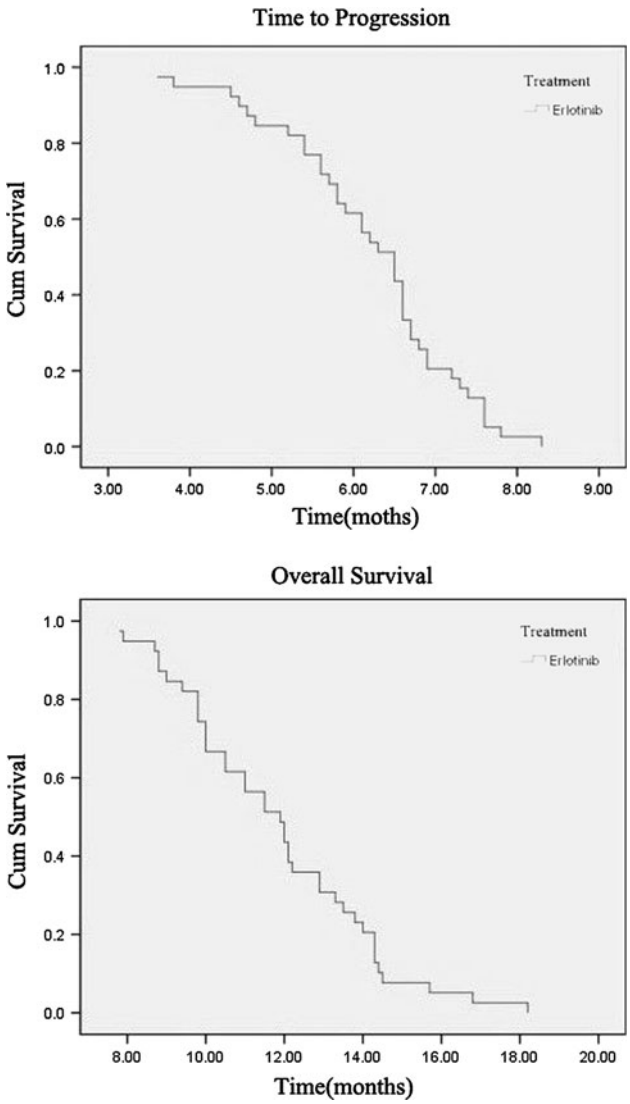

Fig. 1 Kaplan–Meier curve of time to progression and overall survival. The median TTP was 6.4 months, and median OS was 12.7 months 80 × 145 mm

erlotinib as first-line treatment in 80 unselected patients greater than 70 years of age with advanced NSCLC; the median TTP was 3.5 months, and the median OS was 10.9 months. A recent publication of an analysis of elderly patients in the large global TRUST study showed [11] a DCR of 77.2% in elderly patients treated with erlotinib, which compares favorably with the overall population DCR of 69%.

In our study, the DCR of erlotinib was similar to that in TRUST study and the CBR was 80%. The patients developed significant alleviation in cough, asthma, hemoptysis, pain and improvements in appetite, physical strength, and other general conditions, but the overall response rate was still only 48.6%, and it seemed that the overall response rate was not significantly associated with gender, histology and smoking history,which instead show significant difference in DCR. This may be associated with the special mechanisms of molecular targeted therapy and the present efficacy evaluation standard. Currently, the efficacy evaluation criteria of both WHO and RECIST is based on volume change of solid tumors. However, the therapy efficacy of molecular targeted drugs represented by erlotinib more emphasizes the life quality, improvement, survival time elongation, and the long-term effect, but not the tumor volume diminution. The effects of erlotinib appeared later with longer remission. It seems that suppressing tumor cells rather killing tumor cells is the main effect of erlotinib. Therefore, we consider that it is undoubtedly necessary to renew and formulate internationally uniform efficacy evaluation criteria for targeted drugs.

Studies suggest that EGFR and K-ras mutational status is prognostic of survival and predictive of therapeutic efficacy from EGFR-TKIs. Hence, it is usually recommended to test EGFR and K-ras status prior to therapy. EGFR is a transmembrane receptor. Its autocrine pathway contributes to a number of processes important to cancer development and progression, including cell proliferation, apoptosis, angiogenesis, and metastatic spread. A recent publication by Paez et al. [12] showed that about 90% of patients with a tumor response to these drugs had mutations, whereas unresponsive patients did not have mutations. Subsequent a recent prospective study has demonstrated that the overall response rate in North American patients with non-squamous cell histology and EGFR mutations is 55% with a median progression-free survival of 9.2 months [13]. K-ras is a GTP-binding protein and involved in G-protein coupled receptor signaling. In its mutated form, it is constitutively active, able to transform immortalized cells, and promotes cell proliferation and survival. A retrospective study of patients treated with erlotinib as first-line single-agent treatment found that the tumor response rate for patients without mutations was significantly better (20/62, 32%) than tumor response rate for patients with mutations (0/18, $P < 0.01$) [14]. However, interestingly, in our study, we did not carry out EGFR, K-ras gene detection, but the patients show relatively high DCR (77.1%) and CBR (80%). The EGFR, K-ras gene detection failed to show necessity to elderly advanced NSCLC patients, which is similar to the result from Tsao et al. [15, 16]. It is considered necessary to extend the sample size to observe again.

In summary, like Western patients, erlotinib monotherapy was effective and well tolerated as a first-line treatment in Asian elderly patients with advanced NSCLC.

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Conflict of interest The authors declare that no conflict of interest exists for any of the authors.

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