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Recurrence patterns in patients with advanced non-small cell lung cancer who have received epidermal growth factor receptor tyrosine kinase inhibitors

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Summary. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), such as gefitinib and erotinib, have shown efficacy in patients with advanced non-small cell lung cancer (NSCLC). However, information on initial failure sites in patients treated with EGFR-TKIs is limited. This retrospective study was undertaken to investigate the recurrence patterns in these patients. We retrospectively reviewed the initial failure sites of 52 EGFR-TKI treated patients with stage III/IV NSCLC and sensitizing EGFR mutation in Shandong Provincial Hospital. The median progression free survival (PFS) was evaluated by the Kaplan-Meier method. The median age of the 52 patients treated with EGFR-TKIs was 57 years (range, 37-80 years). The median PFS was 8 months. The most frequent initial site of progression was the lung (38.46%), which was followed by the central nervous system (CNS) (30.77%), bone (17.31%) and other places (liver, adrenal, skin, etc.). The lung and CNS were two of the most common recurrence sites in EGFR-TKI treated patients with stage IIIB/IV NSCLC harboring somatic EGFR mutation. We should pay more attention to the response of the lung and brain for early detection of disease recurrence.

Key words: NSCLC, EGFR-TKIs, recurrence patterns

Introduction

Lung cancer is the leading cause of cancer death worldwide and non-small cell lung cancer (NSCLC) accounts for almost 80% of all lung cancer occurrences (1). Epidermal growth factor receptor (EGFR) is a kind of receptor tyrosine kinase that contributes to the development and metastasis of tumors by activating its downstream pathways. EGFR- tyrosine kinase inhibitors (TKIs) have been widely used to target EGFR, thus contributing to cancer therapy (2). Compared to standard chemotherapy, EGFR-TKIs could significantly improve the progression-free survival (PFS) of patients with EGFR-activating mutation (3, 4). Furthermore, NSCLC with kinase domain mutations in the EGFR were sensitive to ionizing radiation and EGFR-TKIs could radiosensitize NSCLC cells by suppressing cellular DNA repair capacity (1, 5).

Gefitinib and erlotinib are small-molecule EGFR-TKIs. These two reversible EGFR inhibitors have good efficacy in patients with relapsed NSCLC and can be used as the initial therapy for patients with advanced NSCLC (6, 7). Despite the dramatic responses and substantial PFS of EGFR-TKI treatment observed in various clinical trials, most NSCLC patients with EGFR-activating mutation ultimately de-

veloped local progression or metastases (8). However, our knowledge about the progression patterns in these patients is limited. In this study, we retrospectively investigated the progression patterns of 52 EGFR-TKI treated patients with stage III/IV NSCLC and sensitizing EGFR mutation.

Materials and methods

Patients

The medical records of EGFR-TKI treated NSCLC patients in Shandong Provincial Hospital from January 2010 to December 2013 were retrospectively researched. Fifty-two patients were enrolled in this research based on the following criteria: 18-80 years of age, Eastern Cooperative Oncology Group (ECGO) performance status (PS) of 0-3, histologically and cytologically confirmed NSCLC (sputum cytology alone was not accepted) and clinical stage IIIB or IV with somatic EGFR mutation. Twenty-nine patients received prior chemotherapy and radiotherapy, 18 patients received prior chemotherapy, and 5 patients did not receive any previous therapy. All the 52 patients received oral gefitinib at a dose of 250 mg once a day or erlotinib at a dose of 150 mg once a day until the disease progressed. No patients received any other treatment during the targeted therapy period.

Tumor response was assessed every two months by thoracic computed tomography (CT) scan. Brain imaging was performed if the patients displayed symptoms or signs of CNS involvement. Radionuclide bone scans or positron emission tomography-computed tomography (PET-CT) were performed to evaluate new symptoms related with metastases or to detect any changes in pre-existing disease. The Response Evaluation Criteria in Solid Tumors (RECIST) was used to evaluate tumor progression (9).

Statistical analysis

PFS was calculated from the initiation of EGFR-TKI treatment until the progression of the disease and was obtained using the Kaplan-Meier method.

Results

Patient characteristics

Fifty-two EGFR-TKI treated NSCLC patients with stage IIIB/IV harboring somatic EGFR mutations were enrolled in this study. The baseline characteristics of these patients are shown in Table 1. Twenty-five of the 52 patients were male and 27 were female. The median age of the patients was 57 years (range, 37-80 years). Four of the 52 patients were treated with gefitin-

Table 1. The clinical characteristics of the 52 patients.

Parameter	Number (%)
Gender	
Male	25 (48.08%)
Female	27 (51.92%)
Age (years)	
Median	57
Range	37-80
Smoking history	
Non-smoker	40 (76.92%)
Smoker	12 (23.08%)
ECOG PS	
1	13 (25%)
2	29 (55.77%)
3	10 (19.23%)
Pathology	
Adenocarcinoma	51 (98.08%)
Squamous cell carcinoma	1 (1.92%)
TNM stage	
IIIB	8 (15.38%)
IV	44 (84.62%)
Prior chemotherapy	
Yes	47 (90.38%)
No	5 (9.62%)
Prior radiotherapy	
Yes	29 (55.77%)
No	23 (44.23%)
EGFR-TKI	
Gefitinib	4 (7.69%)
Erlotinib	48 (92.31%)

Note: ECOG, Eastern Cooperation Oncology Group; PS, performance status; TNM, Tumor Node Metastasis

ib, while 48 patients were treated with erlotinib. Before EGFR-TKI treatment, 21 patients had brain metastases, 13 patients had lung metastases, 7 patients had progression in the bone and 3 patients had liver metastases.

Progression free survival

At the end of follow-up all 52 patients developed local progression or metastases. The median follow-up time was 10 months (range, 5-36 months). The median PFS time was 8 months (range, 2-35 months; 95%CI, 5.644-10.356) (Fig. 1). The PFS of patients with lung metastasis was 6 months (95%CI, 4.546-7.454.

Patterns of disease progression

The progression occurred in pre-existing disease in 19 of the 52 patients, including 12 patients with worsening lung metastases, 6 patients with CNS metastases and 1 patient who had some increase in the size of his liver metastases. The other 33 patients developed new diseases. Fifty-one of the 52 patients had single-site relapse, and 1 patient displayed multi-site relapse. Intrapulmonary progression occurred in 20 patients, extrapulmonary progression occurred in 31 patients and 1 patient displayed both intrapulmonary and extrapulmonary recurrence. The most frequent initial site of progression was the lung (38.46%), which was followed by CNS (30.77%), bone (17.31%) and other places (liver, adrenal, skin, etc.) (Table 2).

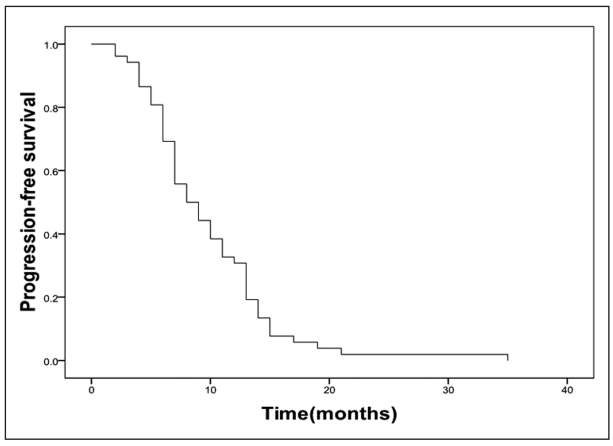

Figure 1. Progression-free survival (PFS). This shows the PFS of all the 52 patients in this study. PFS was calculated from the initiation of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) treatment until the progression of the disease and was obtained using the Kaplan-Meier method.

Discussion

EGFR-TKIs, such as gefitinib and erlotinib, have shown better efficacy in selected subgroups of patients with NSCLC (10-12). However, almost all patients with EGFR-activating mutation eventually develop local relapse or distant metastases (13). In this study, we retrospectively investigated the recurrence patterns in 52 EGFR-TKI treated NSCLC patients with sensitizing EGFR mutation. The median PFS was 8 months. The most frequent initial site of progression was the lung (38.46%), which was followed by CNS (30.77%), bone (17.31%) and other places (liver, adrenal, skin, etc.).

In this study, 19 of the 52 patients (37.04%) had disease progression in pre-existing disease and 33 of the 52 patients (62.96%) developed new diseases. Twelve of the 52 patients (23.07%) had local relapse and 40 of the 52 patients (76.93%) had distant metastasis. Twenty of the 52 patients (38.46%) had intrapulmonary progression, 31 of the 52 patients (59.62%) had extrapulmonary progression and 1 of the 52 patients (1.92%) displayed both intrapulmonary and extrapulmonary recurrence. It seems that EGFR-TKIs were more effective in preventing local relapse and intrapulmonary progression than in preventing distant metastasis.

Table 2. The initial sites of progression.

Sites	Number	Percentage (%)
Lung	20	38.46%
CNS	16	30.77%
brain	9	17.31%
spinal cord	4	7.69%
leptomeninges	3	5.77%
Bone	9	17.31%
Liver	3	5.77%
Adrenal	2	3.85%
Skin	1	1.92%
Multi-sites	1	1.92%

Note: CNS, central nerve system.

The relapse patterns of the patients treated with EGFR-TKIs in this study are similar to the relapse patterns of patients with traditional treatment. For example, 69% of stage III NSCLC patients treated with chemotherapy or radiotherapy relapsed with distant metastases and 31% of stage III NSCLC patients had local-regional tumor progression (14). It seems that CNS metastasis and local recurrence were the main relapse patterns of patients with NSCLC.

In this study, the CNS was one of the most frequent sites of disease recurrence in patients treated with EGFR-TKIs. High rates of CNS progression following initial response to EGFR-TKIs (28%~33%) have also been reported by several other groups (15-17). The high incidence of CNS disease in patients with NSCLC after an initial response to gefitinib was attributed to the possibility of metastatic clones released by active systemic tumors in the cerebrospinal fluid (CSF) and incomplete blood-brain barrier penetration (15). There are reports that the CSF-to-plasma concentration of either gefitinib or erlotinib on the standard daily dose was insufficient for therapeutic concentration (18, 19). Some researchers detected T790M resistance mutation in the CSF of patients with brain metastasis and they confirmed that the mutations were related to TKI resistance in CNS (20, 21). It seems that the CNS may be a susceptible site for progression of NSCLC targeted by EGFR-TKIs. Therefore, CT scan or MRI of the brain should be performed in such patients regularly and the neurological symptoms should be monitored carefully for early detection of CNS recurrence.

In this study, the lung was the most frequent site of disease recurrence in gefitinib or erlotinib treated patients with advanced NSCLC and somatic EGFR mutation. It has been reported that the lung is the most commonly observed initial site of progression (62.4%), especially in patients with such clinical features as a smoking history, non-adenocarcinoma, and chemotherapy (22). Thus we should carefully monitor the response of the lung in patients with the characteristics mentioned above for early detection of disease progression. Individualized treatment should also be given in order to avoid a delay in treatment.

Altogether, these results indicate that the lung and CNS are two of the most common recurrence sites in EGFR-TKI treated NCSLC patients with somatic EGFR mutation. Monitoring of the response by the lung and brain will be helpful in these patients for early detection of lung or CNS failure. Ongoing trials with a larger sample size are needed to support these findings.

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