Predictive factors associated with gefitinib response in patients with advanced non-small-cell lung cancer (NSCLC)

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Purpose: A number of different clinical characteristics have been reported to singly correlate with therapeutic activity of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in advanced non-small-cell lung cancer (NSCLC). This study aimed to identify predictive factors associated with prognostic benefits of gefitinib.

Patients and methods: EGFR gene typing in 33 advanced NSCLC patients received gefitinib (250 mg/day) were analyzed with mutant-enriched PCR assay. Gefitinib response was evaluated with potential predictive factors retrospectively.

Results: The overall objective response rate (ORR) and median progression-free survival (PFS) in the 33 patients treated by gefitinib were 45.5% and 3.0 (2.0-4.0) months. The ORR and median PFS in EGFR gene mutation patients were significantly higher/longer than those in EGFR gene wild-type patients (P<0.01). Similarly, the ORR and median PFS in non-smoker patients were significantly higher/longer than those in smoker patients (P<0.05, P<0.01, respectively). However, no difference for ORR and median PFS occurred between male and female patients. Logistic multivariate analysis showed that only EGFR mutated gene was significantly associated with the ORR (P<0.01). Both EGFR mutated gene and non-smoker were the major factors that contributed to PFS (P<0.05).

Conclusions: EGFR mutated gene and non-smoker status are potential predictors for gefitinib response in NSCLC patients.

Keywords: Epidermal growth factor receptor inhibitor (EGFR inhibitor); gene mutation; gefitinib; non-small-cell lung cancer (NSCLC); smoking; gender

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Introduction

Gefitinib (Iressa) is an orally active small-molecule compound that inhibits the epidermal growth factor receptor (EGFR) tyrosine kinase (TK) by competing with adenosine triphosphate (ATP) at the ATP-binding site, which played a central role in advancing non-small-cell lung cancer (NSCLC) treatment over the last several years (1). Recent studies have shown that compared with counterparts, female cancer patients have favorable outcomes after gefitinib treatment (2-4) because females are more likely to have EGFR mutations (5-7) and most of females are non-smokers (8,9). However, in our clinical experience we did not observe that there was a gender difference in gefitinib response. This paper aims to identify
the predictive factors that really contribute to gefitinib response in Chinese NSCLC patients including smoking status and gender.

**Patients and methods**

**Patients’ characteristics**

Thirty-three patients with advanced NSCLC patients, who were hospitalized in our hospital, were enrolled in this study. Among them, 21 (63.6%) were men and 12 (36.4%) were women, with a median age of 59 years old (ranging from 29-76 years old). There were 20 (60.6%) non-smokers, 13 (39.4%) former/current smokers. Non-smokers are defined as those who reported smoked less than 100 cigarettes during their lifetime. Former smokers are defined as ever smokers who no longer smoked. Histological and/or cytological type was determined according to the World Health Organization/International Association for the Study of Lung Cancer classifications, with 23 (69.7%) adenocarcinomas, 9 (27.3%) squamous-cell carcinomas and 1 (3.0%) large-cell carcinomas. Current tumor stage was determined according to the TNM classification of malignant tumors. Two (6.1%) patients were classified as at Stage I, 3 (9.1%) at Stage II, 9 (27.3%) at Stage III and 19 (57.6%) at Stage IV. All cases with informed consent were received gefitinib monotherapy (250 mg/day orally) without regard to the gender, smoking history and *EGFR* mutation status. The drug response was evaluated according to the response evaluation criteria in solid tumors guidelines. Objective response is defined as patients with complete response or partial response, meanwhile progression-free survival (PFS) is defined as the time from the initial administration of chemotherapy to the earliest occurrence of disease progression or death from any cause. The protocol was approved by the Institutional Review Board, and fully informed written consent was obtained for all cases.

**EGFR gene analysis**

Before gefitinib monotherapy (250 mg/day), plasma was taken from each patient and *EGFR* gene typing was performed with mutant-enriched PCR assay (10). The majority of *EGFR* gene mutations consist of an in-frame deletion in exon 19 and a point mutation involving the replacement of leucine with arginine at codon 858 (L858R) in exon 21 (11). PCR products were detected with polyacrylamide gel electrophoresis analysis.

**Statistical analysis**

The differences in objective response (complete response + partial response) by each predictive factor (gender, smoking status and mutation status) were examined with the Fisher’s exact test or Pearson’s chi-square test. Multivariate analysis of the predictive factors, including gender (male vs. female), smoking history (smokers vs. non-smokers) and *EGFR* mutation (positive vs. negative) were conducted using the Cox regression model. All analysis was determined to be statistically significant where the P value was <0.05. Analyses were conducted using the SPSS 11.0.

**Results**

**EGFR gene mutation analysis**

Mutated *EGFR* gene including either *EGFR* gene exon 19 deletion or exon 21 mutation, or both. Plasma samples were collected from 33 patients and *EGFR* gene mutations occurred in 16 patients (48.5%). Seventeen patients (51.5%) were wild type gene type. No difference between the male and female in mutated gene incidence. But there was significant difference between non-smoker and smokers in mutated gene incidence (*Table 1*).

**Gefitinib treatment response**

Fifteen patients had objective response in 33 patients receiving gefitinib chemotherapy. Among them only 1 patient had complete response, 14 patients had partial response. Thirteen patients had stable disease, and 5 patients had progressed disease. The objective response rate

<table>
<thead>
<tr>
<th>Table 1</th>
<th><em>EGFR</em> mutation rate by patient background (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR mutation</strong></td>
<td>No.</td>
</tr>
<tr>
<td>In total</td>
<td>16</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male (n=21)</td>
<td>10</td>
</tr>
<tr>
<td>Female (n=12)</td>
<td>6</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Smokers (n=13)</td>
<td>4</td>
</tr>
<tr>
<td>Non-smoker (n=20)</td>
<td>12</td>
</tr>
</tbody>
</table>

*EGFR*, epidermal growth factor receptor. *, P value represents the difference between the two groups.
(ORR) was 45.5% with PFS 3 (2.0–4.0) months. Among 16 patients with EGFR gene mutations, 1 case had complete response, 11 cases had partial response, while 2 cases had stable disease, 4 cases had no significant change. The ORR was 75.0%. Yet in the rest 17 patients without EGFR gene mutations, the ORR was 17.6% (Table 2). Univariate analysis showed that, for all 33 cases, compared with EGFR wild type gene group or smoker group, EGFR mutated gene group or non-smoker group seemed to be associated with improved gefitinib treatment response. Multivariate regression analysis showed that EGFR mutated gene other than non-smoker is the only independent predictive factor for ORR (Table 2).

PFS in EGFR mutated gene group or non-smoker group was significantly longer than that in EGFR wild type gene group or smoker group (P<0.01). Cox–2 regression model analysis showed that both EGFR mutated gene and non-smoker are independent factors for PFS (Table 3).

**Effect of smoking on gefitinib treatment response in NSCLC patients with EGFR mutated gene or wild-type gene**

All 33 patients treated by gefitinib had been quadripartited into EGFR wild type gene/smoker group, EGFR wild type gene/non-smoker group, EGFR mutated gene/smoker group and EGFR mutated gene/non-smoker group. The ORR was increased from 11.1%, 25%, 50% to 83.3% correspondingly (Table 4). Twelve patients with EGFR...
mutated gene/non-smoker had longest PFS among the four groups (P<0.01) (Table 4).

Discussion

We detected EGFR gene mutations in 33 NSCLC patients with mutant-enriched PCR assay and the positive mutation rate reached 45.5%, which was similar to the result of Scorpion ARMS technique established by Horiike et al. (12). Mutant-enriched PCR assay is a sensitive, specific, and inexpensive clinical well-developed technique (10). We further evaluated the correlation between EGFR gene mutation status and gefitinib response, as well as the predictive factors for gefitinib. In this study EGFR mutated gene patients treated by gefitinib had better ORR (75.0%) and PFS (4 months) than EGFR wild type gene patients (17.6% and 2 months). Multivariate regression analysis confirmed EGFR mutated gene was independent predictive factors for ORR and PFS.

Many retrospective studies have showed that EGFR mutated gene is more common in female than male patients (5-7). However, our study did not find the gender difference of EFGR mutation rate, as well as ORR and PFS. Is there any ethnic variation for gefitinib response? It is worth further studying in future.

Smoking status was an important predictive factor of gefitinib response in NSCLC patients. Our study suggested that, as regards ORR or PFS, NSCLC non-smoker patients have better sensitivity to gefitinib than smoker patients. Multivariate regression analysis confirmed that smoking was an independent predictive factor of PFS in NSCLC patients. Smoking significant shortened PFS in NSCLC EGFR mutated gene patients. However, smoking status did not significantly affect ORR and PFS in NSCLC patients with EGFR wild type gene.

Our results should be interpreted in the context of some limitations. First, our study used gefitinib which is no longer widely available in the United States after lack of survival benefit was reported in previously treated patients with non-selected NSCLC (13). However, some preplanned subgroup analyses revealed survival benefits in Asian and non-smoker patients (3). Gefitinib is still widely used in China. Second, more information on the gefitinib response is needed from the whole country with the highest lung cancer-related deaths rate in China. Third, our samples were just collected from a university hospital, which means that patients’ selection bias cannot be completely ruled out because urban patients may more easily exposed to industrial pollution compared with rural patients. Finally, our sample size was small (total 33 patients).

Conclusions

Despite limitations, our results indicated that EGFR mutation is an important predictive factor of gefitinib response in NSCLC patients, and smoking history will affect gefitinib response. This strategy has great potential to explain the gefitinib resistance but further basic research and clinical trials are urgently needed.

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References


