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ORIGINAL RESEARCH

EGFR gene-mutation status correlated with therapeutic decision making in lung adenocarcinoma

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Abstract: The purpose of this study was to investigate the correlation between *EGFR*-mutation status and treatment efficacy for advanced lung adenocarcinoma patients. A total of 47 patients receiving erlotinib as first-line therapy were divided into two groups: the *EGFR* gene mutation group included 19 patients with known EGFR-sensitive mutations, and the *EGFR*-mutation status-unknown group comprised 28 patients with unknown *EGFR*-mutation status. Both objective response rate and disease-control rate were significantly higher in the *EGFR*-mutation group compared with the *EGFR*-unknown group (42.1% vs 14.2%, P=0.032; 94.7% vs 57.1%, P=0.005). Age, sex, smoking history, stage of disease, and tissue-sample source were not significantly correlated with the distributions of mutation status. In conclusion, it is important for advanced lung adenocarcinoma patients to undergo gene analysis before being assigned a molecularly targeted drug as first-line treatment.

Keywords: *EGFR*, gene mutation, lung adenocarcinoma

Introduction

Lung cancer is one of the most common cancers and the leading cause of cancer death worldwide. The 5-year survival rate is only 16.8%.[1–3] Approximately 85% of lung cancer is non-small-cell lung cancer (NSCLC), and adenocarcinoma is the most common histological type.[1] Due to the lack of perceivable symptoms at the early stage, the majority of lung adenocarcinoma patients are diagnosed at advanced stages. Therefore, for a long time in the past, traditional chemotherapy was the main treatment option for these patients. However, traditional chemotherapy has a poor prognosis, because of adverse effects. Therefore, it is urgent to develop targeted therapy with more specificity.

More and more evidence has indicated that EGFR plays an important role in NSCLC, especially in adenocarcinoma. EGFR is a membrane-bound tyrosine-kinase receptor that mediates growth and survival signals. Tyrosine-kinase inhibitors (TKIs) can target the EGFR tyrosine-kinase subunit and block its function.[4] Erlotinib is an oral low-molecular-weight agent. Almost 60% of erlotinib can be absorbed after oral administration. The protein-bound rate is 93%. The results from the BR21 and INTEREST clinical trials recommended EGFR TKIs for second- or third-line treatment of advanced NSCLC. Meta-analysis demonstrated that erlotinib had more effectiveness for East Asian patients. Compared with traditional chemotherapy, it has better tolerability and less toxicity.[5] EGFR-sensitive mutations have been proved to be strongly predictive of response to EGFR TKIs in NSCLC.[6,7]

Recently, a number of research results have shown that the effects of first-line TKI treatment are obviously better than traditional platinum-based double-agent chemotherapy

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in EGFR-sensitive mutation patients.[8–11] Surprisingly, newly published molecular epidemiology research of Asian advanced lung adenocarcinoma patients (PIONEER) demonstrated that EGFR-sensitive mutation rates in mainland People's Republic of China (PRC) subgroups were 50.2%.[12] Therefore, detecting such mutations could lead to the identification of subgroups of patients who would benefit substantially from TKIs. In this study, we expected to provide strong clinical research support for understanding of the molecular correlation between *EGFR*-mutation status and treatment efficacy for advanced lung adenocarcinoma patients.

Patients and methods

Eligibility

Patients were required to have histological documentation of primary lung adenocarcinoma, stage IIIB or stage IV, and measurable disease, as defined by RECIST (Response Evaluation Criteria In Solid Tumors). Prior chemotherapy and EGFR TKI treatment were not allowed. Previous surgery and irradiation had to have been completed at least 3 weeks before enrollment. Other eligibility criteria were age ≥18 years and acceptable hepatic, renal, and hematologic function. The institutional review board of the TianJin Medical University General Hospital approved this study, and informed consent was obtained from all the participants.

Populations and samples

A total of 128 patients with pathology-proven advanced lung adenocarcinoma were enrolled from January 2010 through June 2014 at the Oncology Department of Tianjin Medical University General Hospital. Paraffin-embedded primary and metastatic tumor specimens (surgical, bronchoscopic, or computed tomography-guided needle-biopsy specimens) were collected to perform histological and gene detection. Only 56 patients' samples were available for detection of *EGFR*-gene mutation; the other 72 patients' *EGFR*-mutation status was unknown, because they refused gene detection for economic reasons.

EGFR-mutation detection

EGFR-gene mutations were detected at the SurExam Testing Center using the xTag liquid-chip method. All positive findings were independently verified by sequencing.

Treatment and evaluation

Patients received erlotinib 150 mg orally daily on a continuous basis. One cycle of therapy was defined as 30 days. Treatment was continued until disease progression or unacceptable toxicity. The objective treatment response was assessed according to RECIST criteria prior to every third cycle of treatment.

Statistical analysis

SPSS 13.0 was used to determine the statistical significance of the mean values. A P-value <0.05 was considered to indicate a statistically significant difference.

Results

EGFR-mutation status

A total of 56 patients' specimens were available on which to perform mutation detection; 19 patients (33.9%) had EGFR-sensitive mutations (13 had deletion mutation in exon 19, and six had an L858R mutation in exon 21), and the other 37 patients had wild-type mutations.

Association between *EGFR* mutation and clinical characteristics

The correlation between *EGFR*-mutation status and clinical characteristics was analyzed. There were no significant differences in the distribution of mutation status by age, sex, smoking history, stage of disease, or tissue-sample source (primary tumor vs metastasis). Data are shown in Table 1.

EGFR TKI-treatment response

Patient characteristics

Data collection was terminated in December 2014. Nineteen patients with EGFR-sensitive mutations and 28 patients with unknown *EGFR*-mutation status agreed to take erlotinib as first-line treatment. The clinical characteristics of these patients are displayed in Table 2.

Table 1 Association between *EGFR* mutation and clinical characteristics

Clinical characteristics	*EGFR* mutation	*P*-value
Age, years		
<60	5/16	0.789
≥60	14/40	
Sex		
Female	14/36	0.154
Male	5/20	
Smoking status		
Former smoker	3/18	0.060
Nonsmoker	16/38	
Staging		
IIIB	8/14	0.655
IV	11/42	
Specimen source		
Primary tumor	17/41	0.219
Metastasis	2/15	

Note: *EGFR* mutation data shown as number of patients with that clinical characteristic who have *EGFR* mutation/total number of patients for that clinical characteristic.

Table 2 Patient characteristics in erlotinib treatment

Clinical characteristics	EGFR-M	EGFR-UK
Age, years		
<60	5	8
≥60	14	20
Sex		
Female	14	21
Male	5	7
Smoking status		
Former smokers	3	4
Nonsmokers	16	24
Stage		
IIIB	8	11
IV	11	17

Abbreviations: EGFR-M, *EGFR* mutation; EGFR-UK, *EGFR*-mutation status unknown.

Treatment response

Among 19 patients who had *EGFR*-gene mutation, none of 19 had complete response, eight of 19 (42.1%) had partial response, ten of 19 (52.6%) had stable disease, and one of 19 (5.3%) had progressive disease. Among 28 patients whose gene status was unknown, none of 28 had complete response, four of 28 (14.2%) had partial response, 12 of 28 (42.9%) had stable disease, and 12 of 28 (42.9%) had progressive disease. Both the overall response rate (ORR) and disease-control rate (DCR) were higher in the *EGFR*-mutation group than in the *EGFR*-unknown group (42.1% vs 14.2%, P=0.032; 94.7% vs 57.1%, P=0.005). Details of tumor response rates are shown in Table 3.

Discussion

A recent meta-analysis showed that the overall *EGFR*-mutation rate in NSCLC patients from mainland PRC was 37.5%. The most common mutation types were L858R in exon 21 and del in exon 19, which accounted for 38.3% (741 of 1,935) and 37.0% (716 of 1,935) of all *EGFR*-mutation types, respectively.[13] Zhang et al used mutant-enriched liquid-chip technology to detect *EGFR*-gene mutation for NSCLC patients, and reported a mutation rate of 35.6%.[14] In our study, we used the xTag liquid chip. This is a high-throughput clinical testing platform, the sensitivity of which is 1% and specificity approximately 95%. The results of our study showed that the overall *EGFR*-mutation rate was 33.9%, which was similar to the published data. The distribution of *EGFR* mutations was six in exon 21 (31.6%) and 13 in exon 19 (68.4%); we did not found mutations in exons 18 or 20.

Table 3 EGFR TKI-treatment response

Treatment response	EGFR-M, n (%)	EGFR-UK, n (%)	*P*-value
CR	0	0	
PR	8 (42.1)	4 (14.2)	
SD	10 (52.6)	12 (42.9)	
PD	1 (5.3)	12 (42.9)	
ORR (CR + PR)	8 (42.1)	4 (14.2)	0.032
DCR (CR + PR + SD)	18 (94.7)	16 (57.1)	0.005

Abbreviations: TKI, tyrosine-kinase inhibitor; EGFR-M, *EGFR* mutation; EGFR-UK, *EGFR*-mutation status unknown; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease-control rate.

Past epidemiological research has indicated that most lung adenocarcinoma patients with EGFR-sensitive mutations had special clinical characteristics, such as being Asian, female, and nonsmokers. However, in clinical work, we should not select patients for TKI treatment according to clinical characteristics like ethnicity, sex, or smoking history. In our study, there was no significant difference in the distributions of mutation status by age, sex, smoking history, stage of disease, or tissue-sample source. Due to the limited sample size, ongoing study will enlarge the number of cases and contribute further data for confirmation. In a recent study, the authors detected 14 samples and found that there was no significant difference in the distribution of *EGFR* mutation or EGFR messenger RNA-expression level by sex, age, smoking status, histological type, or stage of disease, which was consistent with this study.[15]

The efficiency of anticancer drugs is not only related to tumor volume or survival time but is also shown by quality of life. EGFR TKIs have relatively tolerable side effects. They have great advantages in improving patients' quality of life compared with traditional platinum-based double-agent chemotherapy. In 2006, two Phase III trials – NEJ002 and WJTOG3405 – which compared gefitinib with standard chemotherapy in first-line treatment for *EGFR*-mutated NSCLC, showed that progression-free survival (PFS) in the gefitinib group was significantly longer than that in the standard chemotherapy group.[16,17] These studies were the first to treat advanced NSCLC patients individually, and they indicated a road to personalized therapy by *EGFR*-mutation status. After that, numerous studies were performed to investigate TKI as first-line treatment. In the Phase II CALGB30406 study, 181 patients who were never- or light former smokers with advanced lung adenocarcinoma were randomly assigned erlotinib alone or with carboplatin and paclitaxel, and the response rate (70% vs 9%), PFS (14.1 vs 2.6 months), and overall survival (31.3 vs 18.1 months) favored *EGFR*-mutant patients.[18] In the EURTAC trial, 174 European patients who had *EGFR* mutations and no previous chemotherapy for metastatic disease were randomized to take either erlotinib or a platinum-based doublet, and the results showed that the median PFS was significantly longer in the erlotinib group (9.7 vs 5.2 months).[11] In the PRC, the OPTIMAL trial used erlotinib to confer a significant PFS

benefit in advanced NSCLC patients with EGFR-sensitive mutations.[10] Our study also showed that patients with EGFR-sensitive mutations had significantly higher ORR and DCR, which is consistent with previous clinical trails.

Conclusion

Our study demonstrated that TKI-treatment efficiency was closely associated with *EGFR*-mutation status, and both ORR and DCR were significantly higher in the EGFR-sensitive mutation group compared with those in the *EGFR*-mutation-unknown group. Therefore, it is important for advanced lung adenocarcinoma patients to receive gene analysis before acceptance of a molecularly targeted drug as first-line treatment. Further studies will enlarge the case numbers to confirm this standpoint.

Disclosure

The authors report no conflicts of interest in this work.

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