Epidermal Growth Factor Receptor Mutations and Their Correlation with Gefitinib Therapy in Patients with Non-small Cell Lung Cancer: A Meta-Analysis Based on Updated Individual Patient Data from Six Medical Centers in Mainland China

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Background: Convincing data on epidermal growth factor receptor (EGFR) mutations in Chinese patients with non-small-cell lung cancer (NSCLC) remain limited. We investigated the relevance of demographic characteristics and EGFR mutations, correlations between the efficacy of gefitinib and EGFR mutations in NSCLC, and to identify individuals who would likely benefit from gefitinib.

Methods: We conducted a meta-analysis based on updated individual patient data from six medical centers in mainland China. Outcome measures included the EGFR mutation status, demographic characteristics, response, and survival.

Results: Among 506 patients with NSCLC who received EGFR mutation analysis, the EGFR mutation rate was 30.04%. Patients with adenocarcinoma had a higher mutation rate than those with non-adenocarcinoma (44.1% vs 9.2%; $p < 0.00001$). The EGFR mutation rate for smokers was 15.1%, lower than that for non-smokers (45.5%) ($p < 0.00001$). Male patients had a lower mutation rate than female patients (23.1% vs 42.9%; $p < 0.0001$). Multivariate analysis showed that "adenocarcinoma" and "non-smoker" were independent predictors of EGFR mutations. In a subgroup of 57 patients with complete treatment data, the response rate to gefitinib in the EGFR mutant group was 60.7%, significantly higher than that in the wild-type EGFR group (17.2%) (odds ratio, 5.78; 95% CI, 1.95–17.13; $p = 0.002$). "EGFR mutation", "adenocarcinoma," and "non-smoker" were independent predictors of response. Overall survival in the EGFR mutant group and the wild-type group did not differ significantly (hazard ratio, 0.60; 95% CI, 0.32–1.12; $p = 0.110$). "Adenocarcinoma status" was an independent prognostic factor for survival.

Conclusions: In mainland China, "adenocarcinoma" and "non-smoker" are independent predictors for EGFR mutations. Response to gefitinib favors patients with EGFR mutations. The clinical selected populations for gefitinib are non-smokers with adenocarcinoma.

Key Words: Protein kinase inhibitors, Receptor, Epidermal growth factor, Carcinoma, Non-small cell lung, Meta-analysis, Chinese.

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Lung cancer is the leading cause of cancer deaths in China and worldwide. It is estimated that, per 100,000 Chinese individuals, approximately 41.8 men and 19.3 women died from lung cancer in 2005.[1] Non-small-cell lung cancer (NSCLC) accounts for approximately 85%.[2] Despite treatment advances, chemotherapy is only marginally effective in most advanced cases.[3,4] For those patients refractory to or intolerant of the current chemotherapy, treatment options are limited. Hence, more effective therapy with fewer side effects is needed.

The epidermal-growth-factor receptor (EGFR) tyrosine-kinase (TK) forms a part of the signaling pathway that regulates tumor-cell proliferation, invasion, angiogenesis, metastasis, and apoptosis.[5] Because EGFR is often over-expressed in NSCLC and the level of EGFR expression correlates with poor prognosis, EGFR inhibitors have been developed as novel therapy for NSCLC.[6,7] Gefitinib, the first molecular targeted agent approved for the treatment of advanced NSCLC, is a highly effective EGFR TK inhibitor (TKI) that selectively blocks the signal transduction pathways implicated in cancer growth.[8,9]

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In 2004, Lynch et al. and Paez et al. reported almost simultaneously that mutations of EGFR may predict the sensitivity of NSCLC to gefitinib,[10,11] which is regarded as a milestone for approaching individualized molecular targeted therapy for NSCLC. Subsequently, many publications have reported data consistent with this finding. Phase II trials with EGFR-TKI in patients with chemorefractory NSCLC have found response rates of 9% to 19% and median survival ranging from 7.6 to 8.4 months.[8,9,12] Furthermore, BR21, a phase III study of erlotinib, showed a significant survival benefit compared with placebo.[13] However, in a similarly designed study, ISEL, gefitinib did not show any survival gain over placebo. Subsets of patients who had never smoked and were of Asian origin seemed to benefit from gefitinib.[14] Whether gefitinib is less efficacious than erlotinib or whether the study design, the patients enrolled, the tumor molecular characteristics, and the dose might have contributed to the different outcome remain unclear.[15] One area of current research focuses on the identification of factors distinguishing those who are more likely to derive benefit from EGFR-TKIs therapy, this information could then aid in patient selection. Based on population, China is the largest country in the world, with a population of approximately 1.3 billion at the end of 2004. However, to date, data on EGFR mutations in mainland China are scarce. Comprehensive review of existing information regarding EGFR mutations is essential for personalized therapy for advanced NSCLC.

The gold standard for combining evidence from trials is individual patient data meta-analysis (IPD-MA), in which updated data from each relevant trial are centrally collected, processed, and analyzed.[16] In this report, we include all relevant trials from a comprehensive search to provide evidence on the relationship between EGFR mutations and gefitinib therapy for patients with NSCLC from mainland China.

MATERIALS AND METHODS

Selection Criteria

Both published and unpublished trials that match the criteria below were eligible. We included cohort studies on EGFR mutations in NSCLC. Individuals with histologically confirmed NSCLC were study participants. In refractory NSCLC with performance status (PS) of 0 to 2, tissue samples were taken and the EGFR mutation analyses were performed; 250 mg gefitinib was taken once daily uninterrupted until disease progression or intolerable toxicity. The EGFR mutation status, demographic characteristics of pathology, gender, age, smoking history and TNM stage, response, and survival were outcome measures. Any patients that were not from mainland China, patients with small cell lung cancer, and patients who lacked the IPD were excluded.

Search Strategy

Both published and unpublished studies were included. A systematic search was used to identify all relevant trials from January 2000 to June 2006. Computerized bibliographic searches with PubMed, EMBASE, Cochrance Library, Chinese biomedical literature database, and www.clinicaltrials.gov were supplemented with hand searches of conferences abstracts and specialty journals. Articles were identified by use of the related-articles function in PubMed. References of articles identified were also searched manually. All investigators who took part in the meta-analysis were asked to identify trials.[17] We eventually included six clinical trials that explored the role of EGFR mutations in NSCLC in mainland China. Four of these trials, conducted by Guangdong Provincial People's Hospital (GDPPH), Peking Union Medical College Hospital (PKUMCH), Sun Yat-sen University (SYSU), and Shanghai Pulmonary Hospital (SHPH) were reported at the 2005 ASCO annual meeting.[18–21] Fourteen published articles from 11 institutions were detected through electronic searches. Among these, two trials were excluded for lacking the IPD,[22,23] and seven were excluded because the data were generated outside mainland China (Hong Kong, Taiwan, Canada, Spain, and the United States). The remaining two trials[24–28] came from the same studies conducted by PKUMCH and SYSU presented at the 2005 ASCO annual meeting. Finally, 506 individuals from the above four trials and two other unpublished trials directed by Jilin University (JLU) and the Second Shanghai Medical College (SSHMC) through cooperation were included.

Data Collection

The Secretariat decided what data to collect. IPD were obtained directly from the responsible investigator in all eligible trials. Updated information on demographic characteristics, EGFR mutations, and efficacy of therapy were collected, sent to the central coordination center, and reviewed for consistency and completeness before analysis. All data were thoroughly checked and extracted by two reviewers independently; any queries were resolved by discussion to validate the accuracy of extraction.[29] The last follow-up date was February 14, 2006.

EGFR Mutation Analysis

The mutation analysis of the EGFR-TK domain was performed with frozen or paraffin-embedded tumor tissues. Tumor samples were obtained from thoracotomy in early-stage NSCLC, diagnostic procedures such as fiberbrochoscopy and transthoracic needle aspiration biopsy in advanced cases. Genomic DNA was extracted from specimens, and exons 18, 19, 20, and 21 were amplified with four pairs of primers. Uncloned PCR fragments were sequenced and analyzed in both sense and antisense directions. Both forward and reverse sequencing reactions were performed with the respective primers and the ABI (Applied Biosystems, Foster City, CA) company Big Dye Terminator v3.1 Cycle Sequencing Kit. Sequencing products were electrophoresed on an ABI3700 genetic analyzer. All sequence variations were confirmed by multiple independent PCR amplifications and repeated sequencing reactions.[10] EGFR mutations were analyzed using direct sequencing in all the six institutions included.

Assessment of Efficacy

Baseline evaluation included chest and upper abdomen computed tomography including adrenals, brain magnetic resonance imaging, and bone scan within 14 days before

