Chemotherapy Response in East Asian Non-small Cell Lung Cancer Patients Harboring Wild-Type or Activating Mutation of Epidermal Growth Factor Receptors

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Introduction: Previous exploratory analysis of epidermal growth factor receptor (*EGFR*) mutational status in tumor samples from randomized clinical studies suggested that patients with activating mutation of the *EGFR* had better survival than those harboring wild-type *EGFR*.

Methods: We analyzed the *EGFR* sequence of tumor samples from advanced stage non-small cell lung cancer patients previously participated in treatment clinical trials. Responses to chemotherapy and survival of *EGFR* mutation-positive or -negative patients were compared.

Results: Tumor samples from 122 patients were available for analysis. *EGFR* mutation was present in 58 patients (47.5%). In 105 stage IIIB/IV patients, there was a nonstatistically significant trend toward a higher chemotherapy response rate of patients with mutated *EGFR* than those with wild-type *EGFR* (44.6% versus 30.6%, $p = 0.162$). Female, never-smoking, and adenocarcinoma patients lived longer than male ($p = 0.0139$), smoking ($p = 0.0045$), or nonadenocarcinoma ($p = 0.0151$) patients. There was no difference in the survival of patients with mutated or wild-type *EGFR* ($p = 0.2159$). There was no difference in progression-free survival of first-line chemotherapy between patients with wild-type or mutation in *EGFR* (6.6 months versus 6.1 months).

Conclusion: There is a nonstatistically significant trend toward a higher chemotherapy response rate in patients with mutated *EGFR* than those with wild-type EGFR. *EGFR* gene mutation is not a predictive biomarker for progression-free and overall survival to cytotoxic chemotherapy in East Asians with advanced non-small cell lung cancer.

Key Words: Non-small cell lung cancer, Chemotherapeutic agents, Epidermal growth factor receptor.

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The use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in advanced stage non-small cell lung cancer (NSCLC) has led to the discovery of a group of patients harboring activating mutations of *EGFR*.[1,2] The mutational sites clustered between exons 18 and 21, in the tyrosine kinase-binding domain. Despite the success in the treatment of some advanced stage chemotherapy-treated NSCLC patients,[3,4] gefitinib failed to improve survival compared with placebo in a large randomized trial.[5] Conversely, erlotinib has demonstrated survival advantage when compared with placebo in patients previously treated with combination chemotherapy.[6]

Gefitinib or erlotinib when combined with first-line chemotherapy regimen failed to improve survival compared with chemotherapy alone in four large randomized studies.[7–10] Patients harboring activating mutation of EGFR may preferentially benefit from TKIs treatment.[11] Retrospective studies were performed in these studies testing the tumor samples for *EGFR* mutation in the archived specimen. The results of the analysis were surprising in that gefitinib or erlotinib adding to standard combination chemotherapy failed to improve survival over standard chemotherapy alone even in subsets of patients harboring *EGFR* mutations. However, in these analyses, the survival of EGFR mutation-positive patients was significantly longer than those without *EGFR* mutations in groups of patients who received chemotherapy alone without gefitinib or erlotinib.[12,13] In the Iressa Pan-Asia Survival Study (IPASS) comparing gefitinib with paclitaxel plus carboplatin as the first-line therapy in Asian patients, patients with activating mutation of *EGFR* had a statistically higher response rate (47.3% versus 23.5%) than patients

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without *EGFR* mutations when they received paclitaxel plus carboplatin. The progression-free survivals (PFSs) were not different between patients with and patients without EGFR mutation in the chemotherapy arm.[14] Thus, it is hypothesized that patients with *EGFR* mutations seem to respond better to combination chemotherapy.

To explore whether the different chemotherapy treatment outcomes of advanced stage NSCLC patients with or without *EGFR* mutations in previous biomarker analysis[12,13] can be applied in East Asian NSCLC patients, in whom the *EGFR* mutation rates are highest among the world, we retrospectively collected archived tumor samples from advanced NSCLC patients previously accrued to clinical trials and tested the tumor samples for *EGFR* mutations. The previously recorded clinical data were retrieved and combined. Survival times of these patients were updated. PFS, and overall survival (OS), and responsiveness to chemotherapy were compared by different clinical predictors and *EGFR* mutational status.

PATIENTS AND METHODS

Eligibility Criteria to Select Patients

Advanced stage NSCLC patients accrued to treatment clinical trials between 1994 and 2005 from two Asian medical centers were identified. Patients were eligible for the study if they have archived tissue blocks for analysis of tumor *EGFR* gene. In addition to the informed consent and approval by local ethics committees to participate in prior clinical trials, this retrospective study was further approved by local ethics committees. Clinical parameters such as gender, smoking status, stage, treatments and response to treatments, and progression time point were captured by previous data. Investigators' evaluation of the response was used in this study, despite independent reviews were used in some of the trials (and the results were not available to the sites). The World Health Organization criteria of response were used. In second-line treatment studies, recorded response to first-line chemotherapy in the medical record was used in this study. Additional data such as survival time updates are retrospectively collected from medical records.

EGFR Gene Analysis

Sequence analysis of exons 18 to 21 of *EGFR* genes were described previously.[15] In short, DNA was extracted from paraffin blocks. Fragments of DNA between exons 18 and 21 were amplified by the nested-reverse transcription polymerase chain reaction. The resulted amplified products were subjected to DNA sequence analysis by DNA sequencer.

Statistics Considerations

PFS time of first-line combination chemotherapy was defined as the time from first dose of chemotherapy to documented radiologic progression. OS time was defined as the time from first dose of chemotherapy to death. Response rates to chemotherapy or *EGFR* mutation status in different groups of patients were compared with χ^2 test or Fisher's exact test. Log-rank test was used to compare PFS and OS in patients with different clinical-pathologic or molecular parameters. A significant relationship with survival ($p \leq 0.10$) was used as a criterion for including a variable in the multivariate stepwise modeling procedure. Multivariate analysis was performed using the Cox proportional hazards model with a forward selection procedure to create a final model. The final model was chosen on the basis of those variables for which $p \leq 0.05$. SPSS software version 13.0 (SPSS Inc., Chicago, IL) was used for all analyses.

RESULTS

Demographics of Patients

One hundred twenty-two patients were selected from 14 clinical trials. The baseline characteristics of all patients are listed in Table 1. The first-line chemotherapy regimens used are listed in Table 2. The age and gender distributions were similar to prior reports of the same group of patients in clinical trials in East Asia. The percentages of adenocarcinoma and nonsmokers were higher compared with other trials because of the referral characteristics of these two medical centers. Twenty-one percent of patients had prior surgery and recurred. This rate is higher than the prior surgery rates of other clinical trial population because of the selection effect from the requirement of adequate tumor samples for *EGFR* gene analysis. Seventeen locally advanced stage IIIA/IIIB patients who entered a neoadjuvant chemotherapy trial were not included in response evaluation and survival analysis.

EGFR Mutation in Tumor Samples

Fifty-eight patients (47.5%) were tested positive for activating *EGFR* mutations. The mutation sites of these patients were exon 19 deletions in 27 patients, L858R mutation in 21 patients, and other types of EGFR mutations (K708_E709del and T710N, M825R, I744T, E866G, D855G and L844P, L799R, D761V, and V845M) in 10 patients. The rates of *EGFR* mutation in each subset of patients are listed in Table 1. The rates of EGFR mutation in each chemotherapy regimen are listed in Table 2. The rates of *EGFR* mutation are 44.8, 61.1, and 50.0% in platinum doublets, nonplatinum doublets, and other regimens, respectively. Never smokers and former smokers had statistically higher *EGFR* mutation rate than current smokers. The *EGFR* mutation rate in 17 patients with locally advanced stage was low (11.8%).

Response to Chemotherapy

The responses to first-line combination chemotherapy in stage IIIB/IV patients are listed in Table 3. Forty-four patients (41.9%, 95% confidence interval 32.5–51.3) responded to the first-line chemotherapy treatment. None of the clinical-pathologic factors or *EGFR* mutation status was able to predict for response to initial chemotherapy. Female patients, never or former smokers, and patients with EGFR-mutated tumors had statistically insignificant higher response rates.