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ORIGINAL ARTICLE

Associations Between Epidermal Growth Factor Receptor Gene Mutation and Serum Tumor Markers in Advanced Lung Adenocarcinomas: A Retrospective Study△

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Key words: advanced lung adenocarcinomas; epidermal growth factor receptor gene; mutation; epidermal growth factor receptor tyrosine kinase inhibitor; carcinoembryonic antigen

Objective To investigate the associations between epidermal growth factor receptor (EGFR) gene mutations and serum tumor markers in advanced lung adenocarcinomas.

Methods We investigated the association between EGFR gene mutations and clinical features, including serum tumor marker levels, in 97 advanced lung adenocarcinomas patients who did not undergo the treatment of EGFR tyrosine kinase inhibitors. EGFR gene mutation was detected by real-time PCR at exons 18, 19, 20, and 21. Serum tumor marker concentrations were analyzed by chemiluminescence assay kit at the same time.

Results EGFR gene mutations were detected in 42 (43%) advanced lung adenocarcinoma patients. Gender (P=0.003), smoking status (P=0.001), and abnormal serum status of carcinoembryonic antigen (CEA, P=0.028) were significantly associated with EGFR gene mutation incidence. Multivariate analysis showed the abnormal CEA level in serum was independently associated with the incidence of EGFR gene mutation (P=0.046) with an odds ratio of 2.613 (95% CI: 1.018-6.710). However, receiver operating characteristic (ROC) curve analysis revealed CEA was not an ideal predictive marker for EGFR gene mutation status in advanced lung adenocarcinoma (the area under the ROC curve was 0.608, P=0.069).

Conclusions EGFR gene mutation status is significantly associated with serum CEA status in advanced lung adenocarcinmoas. However, serum CEA is not an ideal predictor for EGFR mutation.

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LUNG cancer remains the leading cause of cancer-related deaths worldwide and the total 5-year survival rate of lung cancer cases was less than 17%, [1] due to the lack of sensitive screening tests for early detection and ineffective treatment for advanced and metastatic disease. [2] Non-small-cell lung carcinoma (NSCLC) accounts for approximately 80% to 85% of all lung cancers. Epidermal growth factor receptor (EGFR) is a validated target in NSCLC. Two EGFR tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib have been approved for the treatment of advanced NSCLC by the U.S. Food and Drug administration (FDA) and the European Medicines Evaluation Agency (EMEA). [3] Good clinical responses were displayed in Asian, females, nonsmokers, and adenocarcinomas patients, [4] which may related with the higher frequency of EGFR mutations within these subgroups. [5] EGFR-TKIs are known to contribute to the extension of progression-free survival in EGFR-mutant NSCLC considerably and the EGFR mutations are widely accepted as indicators for the clinical efficacy of EGFR-TKIs in advanced adenocarcinomas patients. [6]

The detection of mutations in the EGFR gene of advanced NSCLC patients has some limitations. The best specimen for EGFR gene mutation detection is NSCLC tissues taken by surgery. However, 70%-80% NSCLC patients have difficulties for radical surgery at the time of diagnosis and are unable to obtain tissue samples for EGFR mutation testing. Another way to obtain tissue samples for EGFR mutation testing is tumor biopsy surgery which is also dangerous for the high risk of bleeding in advanced tumors. Meanwhile, the predictive value of peripheral blood for EGFR gene mutation tests is still controversial. [7] So a considerable number of patients can not provide enough NSCLC samples for gene diagnosis.

Thus, we focused on a non-invasive and reliable method to predict the clinical efficiency of EGFR-TKIs for the treatment of advanced adenocarcinomas. Recently, several researches reported the serum level of tumor markers, such as carcinoembryonic antigen (CEA), [8] cytokeratin 19 fragment (CYFRA21-1), [9-11] carbohydrate antigen 19-9 (CA19-9), [12] CA125, [12] polypeptide specific antigen [13], and transforming growth factor-α [14] may predict the treatment efficiency of EGFR-TKIs for NSCLC patients. However, the mechanism was not clear yet. So we proposed these tumor markers may relate with frequency of EGFR gene mutations in advanced lung adenocarcinomas.

In this study, the correlations between mutations of EGFR gene and the serum levels of potential NSCLC biomarkers, CEA, CA125, CA19-9, neuron specific enolase (NSE), and CYFRA21-1 were investigated in advanced lung adenocarcinoma patients retrospectively.

PATIENTS AND METHODS

Patients

From March 2012 to November 2013, 97 primary advanced adenocarcinoma patients who had undergone measurements of EGFR gene mutation and serum CEA, CA125, CA19-9, NSE, and CYFRA21-1 levels in Taizhou Hospital of Zhejiang Province were retrospectively recruited. None of them had received EGFR-TKI therapy before. All patients were pathologically or cytologically diagnosed. Histological diagnosis and tumor grade were in accordance with the World Health Organization International Histological Classification of Lung Tumors criteria. Patients' data were collected including age, gender, smoking history, clinical stage, EGFR gene mutations, and serum levels of CEA, CA125, CA19-9, NSE, and CYFRA21-1.

Detection of EGFR gene mutation

Genomic DNA was extracted from tumors tissue samples or pleural effusion sediment samples using the DNeasy Blood & Tissue kit (Qiagen, Hilden, Germany) according to manufacturer's protocols. Real-time PCR was performed using the AmoyDx™ human EGFR gene mutations fluorescence PCR diagnostic kit (Amoy Diagnostics, Xiamen, China) according to manufacturer's recommendations. A total of 29 mutations in exon 18, 19, 20, and 21 of EGFR gene were analyzed, including G719S/A/C mutations in exon 18, 19, deletion mutations in exon 19, T790M and S768I mutations in exon 20, and L858R/Q and L861Q mutations in exon 21. Positive, negative, and internal controls were included in each real-time PCR run. As defined by the manufacturer's instructions, quantitative real-time PCR assay for EGFR gene mutation was considered positive, if the sample Ct value <29.

Analysis of serum CEA, CA125, CA19-9, NSE, and CYFRA21-1 levels

Serums were obtained from peripheral fasting blood of all cases at the same time of EGFR gene mutation detection. Serum CEA, CA125, CA19-9, NSE, and CYFRA21-1 levels were detected with chemiluminescence assay kit according to the manufacturer's introductions (Roche, Shanghai, China). The normal range of serum NSCLC biomarkers were determined as CEA<5.0 ng/ml, CA125<35 U/ml, CA19-9<37 U/ml, NSE<13.0 ng/ml, and CYFRA21-1<3.3 ng/ml, respectively.