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A phase II study of erlotinib monotherapy in pre-treated non-small cell lung cancer without *EGFR* gene mutation who have never/light smoking history: Re-evaluation of EGFR gene status (NEJ006/TCOG0903)

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ABSTRACT

Objectives: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors are particularly effective in non-small cell lung cancer (NSCLC) patients harboring active EGFR mutations. However, some studies have reported survival benefits in NSCLC patients with wild-type EGFR upon erlotinib treatment. This trial was conducted to evaluate the efficacy of erlotinib monotherapy and investigate the predictive values of several biomarkers.

Patients and methods: Patients with previously treated NSCLC but without EGFR gene mutations that had never or light smoked were eligible for this study. Gene status screening was performed using the PNA-LNA PCR clamp method. Erlotinib was administered until disease progression or unacceptable toxicities occurred. EGFR gene status was re-evaluated using the fragment method to detect exon 19 deletions and the Cycleave-PCR method to detect point mutations. Expression of hepatocyte growth factor (HGF), Met, and thymidylate synthase (TS) were evaluated using immunohistochemistry.

Results: Forty-seven patients were enrolled in the study between March 2010 and November 2011. Objective response rate (ORR) and disease control rate (DCR) were 15.2% and 41.3%. Re-evaluations for EGFR gene were performed in 32 tumor samples. EGFR gene mutations were found in eight samples (5:exon 19 deletion, 2:G719X, 1:L858R). Six patients had PR and two had SD among these eight patients. A total of 24 patients were confirmed as wild-type EGFR using different methods. ORR and DCR were 4.2% and 41.7%. The median progression free survival (PFS) and median survival times were 2.0 and 6.0 months, respectively. Patients with tumors expressing HGF showed shorter PFS but not MET or TS.

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Conclusions: Re-examination of EGFR gene status using different detecting method or different sample should be considered to grasp a chance of erlotinib treatment after first line treatment. In confirmed EGFR wild NSCLC, negative HGF staining could be a biomarker for longer PFS by erlotonib treatment.

1. Background

Gefitinib and erlotinib, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), have significant antitumor activities in non-small cell lung cancer (NSCLC) harboring *EGFR* gene mutations [1]. EGFR-TKIs have been widely used as a first- or second-line monotherapy for NSCLC with *EGFR* mutations [2,3].

Although gefitinib failed to demonstrate prolonged overall survival in unselected advanced NSCLC patients compared to best supportive care controls in the Iressa Survival Evaluation in Lung Cancer (ISEL) study [4], erlotinib provided a survival advantage of 6.67 months versus 4.70 months for the placebo in a similar clinical setting study (BR.21) [5]. Furthermore, in molecular and clinical analyses, NSCLC with wild-type *EGFR* gained survival benefits upon erlotinib treatment [6,7]. In another study, erlotinib also demonstrated longer progression survival in NSCLC with wild-type *EGFR* compared to the placebo control, although *EGFR*-mutated NSCLC showed much longer PFS [8]. Therefore, erlotinib is thought to have higher biological activity and distinct clinical outcomes from gefitinib. In NSCLC with wild-type *EGFR*, erlotinib could be a candidate treatment option for pre-treated NSCLC. This fact suggests the possibility of another molecular marker in addition to *EGFR* gene mutation.

However, EGFR-TKIs cause interstitial lung diseases (ILD) in 3-5% of Japanese patients, and one-third of these cases are fatal [9,10]. Smoking history and preexistent ILD are ILD risk factors for EGFR-TKIs [9]. In this context, NSCLC patients with wild-type *EGFR* who may benefit from erlotinib should be selected using other clinical or molecular markers. Although two prospective phase II trials of erlotinib monotherapy were performed in pretreated NSCLC with wild-type *EGFR*, ORRs were varied 3.3% and 17.2% [2,11].

Therefore, we performed this prospective phase II study to investigate the efficacy and safety of erlotinib monotherapy in Japanese NSCLC patients with wild-type *EGFR* after treatment with cytotoxic agents. Patients who had never smoked or only lightly smoked were selected because these patients have lower ILD risks and possibly have molecular markers indicating survival benefits after erlotinib treatment.

2. Patients and methods

2.1. Study design

This was a multicenter phase II study evaluating the effectiveness of erlotinib in previously treated NSCLC patients harboring wild-type *EGFR*. The primary end point was the objective response rate (ORR). Secondary end points included disease control rate (DCR), progression free survival (PFS), overall survival (OS), safety, and biomarker analyses. This study was performed in accordance with the Helsinki Declaration (1964, amended in 2000) of the World Medical Association, and the Institutional Review Board of each participating institution approved the protocol.

2.2. Patients

Patients were required to have the following criteria: histologically or cytologically proven NSCLC, stage IIIB/IV disease or postoperative recurrent tumors without activating *EGFR* gene mutations (exons 18, 19, and 21) based on the PNA-LNA PCR clamp method [13], never smoked or lightly smoked (a total of $\leq$10 pack-years of smoking), age greater than 20 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2, measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [14], no prior history of EGFR-TKI therapy, and adequate organ function. Exclusion criteria were the presence of interstitial pneumonia, pleural, pericardial, or peritoneal effusion requiring drainage, active infection, the presence of T790M mutation, symptomatic brain metastasis, uncontrolled complications, or pregnancy. All enrolled patients provided written informed consent. Patients were registered to the registration center of The Tokyo Cooperative Oncology Group (TCOG).

2.3. Treatment protocol and assessment

Erlotinib was given orally at a dose of 150 mg daily until disease progressed, intolerable toxicity appeared, or the patient withdrew consent. Erlotinib was discontinued when any G4 toxicity occurred, and a dose reduction was considered after interruption if the patient developed G3 toxicities (except rash or diarrhea). Erlotinib was terminated when any grade interstitial lung disease (ILD) developed. During the trial, no other systemic anticancer treatment was permitted. Further therapy after disease progression was at the physician's discretion.

We evaluated objective tumor responses as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) in accordance with the RECIST1.1. Disease control was defined as the best response of CR, PR, or SD, which was confirmed for at least 4 weeks. Baseline assessments were performed within 28 days of treatment commencement. During treatment, tumor response assessments by computed tomography (CT) were performed every 4 weeks for the first 2 months and then every 2 months until disease progression. PFS was defined as the time from enrollment until the date of the first observation of disease progression or death from any cause. OS was defined as the time from enrollment until death of any cause. All adverse events were graded by the National Cancer Institute Common Toxicity Criteria (version 3.0). All data were corrected and managed by TCOG.

2.4. Statistical analyses

The primary end point was the objective response rate. The expected response rate was 20%, and threshold response rate was 4%. Thirty-nine patients were needed for the study to have a statistical power of 90% and a type 1 error of 5%. Finally, we included 43 patients in this study. Patients who were alive without disease progression at the data cutoff point were censored at the last point when the patients were determined to be progression-free. PFS and OS were estimated using the Kaplan-Meier method, and differences between subgroups were analyzed using log-rank tests. *P* values less than 0.05 were considered to indicate significance. The cut-off point for all analyses was December 31, 2012.