Efficacy and Safety of Erlotinib Monotherapy for Japanese Patients with Advanced Non-small Cell Lung Cancer

A Phase II Study

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Introduction: The aim of this study was to evaluate the efficacy and safety of Erlotinib in Japanese patients with previously treated non-small cell lung cancer (NSCLC). Available tumor biopsy samples were analyzed to examine relationships between biomarkers and clinical outcome.

Methods: This open-label phase II trial enrolled stage III/IV NSCLC patients who had progressive disease after at least one prior platinum-based chemotherapy regimen. Erlotinib was administered at a dose of 150 mg/d orally until disease progression or intolerable toxicity. Analysis of epidermal growth factor receptor gene mutations in exon 18–21 by direct sequencing was performed in tumor tissue specimens obtained at the first diagnosis.

Results: Sixty-two patients were enrolled and 60 patients were evaluable for efficacy. Objective response rate and disease control rate were 28.3% and 50.0%; median time to progression and overall survival were 77 days and 14.7 months, respectively. In logistic regression analysis, only smoking history was proved to be a statistically significant predictive factor for response (odds ratio: 0.06, $p < 0.001$). Only 7 patients had samples available for mutation analysis. Three patients who had deletion mutations on exon 19 (del E746-A750 or del S752-I759) exhibited objective response. Common toxicities were rash (98%), dry skin (81%), and diarrhea (74%). Discontinuation due to adverse events occurred in 11 patients (18%). Four patients (6%) experienced interstitial lung disease-like events, one of whom died.

Conclusion: Erlotinib is efficacious in Japanese patients with previously treated NSCLC. The toxicity profile was similar to that in Western patients, except for a somewhat higher incidence of skin disorders and interstitial lung disease. Further studies are needed to determine the relationship between epidermal growth factor receptor mutations and outcomes with Erlotinib in Japanese patients.

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Lung cancer affects approximately 1.2 million people annually, and is the leading cause of cancer death in the world.[1] More than 80% of affected patients are diagnosed with non-small cell lung cancer (NSCLC). The standard first-line treatment for metastatic NSCLC is a combination of platinum chemotherapy with a third-generation agent such as docetaxel, paclitaxel, gemcitabine, vinorelbine, and irinotecan.[2,3] Although patients with stage II, IIIA, or IIIB NSCLC receive platinum-based chemotherapy as part of combined modality treatment with thoracic radiotherapy or surgery, many will be candidates for second or third-line chemotherapy. Docetaxel is the only cytotoxic agent with a proven survival advantage over supportive care in patients with disease progression after cisplatin-based chemotherapy for NSCLC.[4] The other agent for which a survival benefit has been demonstrated in this setting is erlotinib,[5] which was approved in Japan for the treatment of relapsed NSCLC in October 2007. Erlotinib is a selective, orally active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). In contrast to the experience with the cytotoxic chemotherapeutic agents, response to treatment with EGFR-TKIs has been reported to be influenced by gender, histological type, race or ethnic origin, and smoking status.[5–8]

Tumor molecular markers, including *EGFR* gene mutations and protein expression, have been widely studied in patients with NSCLC, and there is strong evidence that the presence of *EGFR* gene mutations is a predictor of tumor response and resistance.[9–12] However, few prospective studies have evaluated molecular markers as predictors of outcome, and their clinical usefulness is unproven.

This report presents the results of the first phase II study of erlotinib conducted in Japanese patients with NSCLC. The purpose was to evaluate the efficacy and safety of erlotinib in this population. Where available, tumor biopsy samples were analyzed for EFGR-related markers.

PATIENTS AND METHODS

This phase II, multicenter, open-label study recruited patients at 11 hospitals in Japan. The primary end point was the objective response rate (ORR) to erlotinib treatment (150 mg/d). Secondary endpoints were disease control rate (DCR), response duration, time to progression, overall survival (OS), quality of life (QoL), and safety. The protocol was approved by the ethics review boards of all participating institutions, and conducted in accordance with Japanese Good Clinical Practice guidelines.

Patient Selection

Patients with histologically or cytologically documented stage IIIB or IV NSCLC at study entry (not curable with surgery or radiotherapy) that was recurrent or refractory to treatment with one or more chemotherapy regimens (including at least one platinum-containing regimen), were enrolled into this study. Additional eligibility criteria included: the presence of measurable lesions by Response Evaluation Criteria in Solid Tumors (RECIST); age $\geq$20, $<$75 years; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, and adequate bone marrow, hepatic, and renal function, i.e., aspartate aminotransferase and alanine aminotransferase (ALT) levels $\leq$2.5 times the upper limit of normal and total bilirubin of $\leq$1.5 times the upper limit of normal. Patients with existing or previous interstitial lung disease (ILD) were excluded, although a history of radiation pneumonitis (limited to the field of radiation treatment) was permitted. Concomitant anticancer treatment and prophylactic medication for adverse events (AEs) were not permitted, nor was prior use of anti-EGFR or anti human epidermal growth factor receptor (HER2) agents (small molecules and monoclonal antibodies). Written informed consent was obtained from all patients.

Treatment Procedure

After completion of the baseline assessments (see below), all patients received erlotinib (150 mg orally) each morning, 1 hour before breakfast, until the occurrence of progressive disease (PD) or unacceptable toxicity (all AEs were graded using the National Cancer Institute Common Toxicity Criteria Version 2.0). In the event of treatment-related toxicity, 2 dose reductions of 50 mg were permitted per patient, and dosing could also be interrupted for up to 14 days. For grade 3 or intolerable grade 2 rash, treatment was withheld until the rash improved to grade 2 or less, when a lower dose of erlotinib was initiated. For grade 3 diarrhea, treatment was withheld until the diarrhea was grade 1 or less, when a lower dose was started. For ILD of any grade, or any grade 4 toxicity, treatment was immediately and permanently discontinued.

Evaluation of Efficacy

Objective tumor response was assessed in accordance with RECIST.[13] Tumor assessments were performed at baseline, then every 4 weeks until week 16, and then every 8 weeks thereafter. Confirmation of complete or partial responses (PR) was required, by means of a second assessment conducted 28 days or more after the initial assessment. Stable disease (SD) was defined as disease control (absence of progression) maintained for at least 6 weeks. An independent response evaluation committee consisting of 2 oncologists and a radiologist reviewed images of patients with complete response, PR, and SD. Individual survival times were determined from the survival status of each patient during the study period and at the post study follow-up survey conducted in June-July 2005 and May-July 2006. OS was defined as the time from first administrated to death.

Quality of Life Evaluation

The Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire (Version 4-A)[14] was used to assess QoL. The full FACT-L questionnaire was administered at baseline and then every 28 days. In addition, the Lung Cancer Subscale (LCS), an independently validated component of FACT-L, was administered weekly during the treatment period. Best responses on the LCS were analyzed for all patients with a baseline LCS score of 24 or less (out of a possible 28 points) and symptomatic improvement was defined as an increase from the baseline score of 2 or more points, sustained for at least 4 weeks.

Evaluation of Safety

Baseline assessment included a full patient history, physical examination, standard laboratory tests, electrocardiography, chest radiography, pregnancy test, and ophthalmologic tests (vision test and slit-lamp examination). Every week until week 8 and every 2 weeks thereafter, vital signs and ECOG PS were monitored and blood samples were taken for hematology and blood chemistry tests. A radiograph examination to assess pulmonary toxicity was conducted weekly until week 4 and every 2 weeks thereafter. Ophthalmologic examinations were repeated at week 8 and at the end of the study. Observation and evaluation of AEs was conducted as appropriate throughout the study period. All AEs were graded using National Cancer Institute Common Toxicity Criteria Version 2.0. For all ILD-like events, the data safety monitoring board (which consisted of oncologists and pneumonologists) reviewed the clinical data and images; the images were also examined by a review committee of radiologists with expertise in drug-induced pulmonary disorders.

Biomarker Analysis

EGFR mutations and EGFR and HER2 protein expression were assessed in patients with suitable tumor tissue specimens at first diagnosis or surgery; these assessments were done only with separate written consent. Tumor samples were obtained from each center as formalin-fixed and paraffin-embedded blocks, or as thinly sliced tissue sections mounted on glass microscope slides. For the mutation analysis, the tissue was microdissected by Targos Molecular Pathology (Kassel, Germany) and direct sequencing was conducted at the Roche Centre of Medical Genomics (Basel, Switzerland), using a nested polymerase chain reaction of exon 18–21. EGFR protein expression was analyzed by Lab Corp (Mechelen, Belgium). EGFR expression analysis was conducted by immunohistochemistry using Dako EGFR PharmDx™ kits (Dako, Carpinteria, CA). A positive test was