A Phase II Study of Erlotinib as Initial Treatment for Patients with Stage IIIB–IV Non-small Cell Lung Cancer

Wallace Akerley, MD,† Kenneth M. Boucher, PhD,* Joel S. Bentz, MD,*‡ Kylee Arbogast, BS,* and Theodore Walters, MD§*

Introduction: Erlotinib improves survival in patients with advanced non-small cell lung cancer who have been previously treated with systemic chemotherapy. The current trial was designed to evaluate erlotinib as a primary therapy before chemotherapy in patients with minimally restricted eligibility criteria.

Methods: Eligibility criteria included stage IIIB/IV or recurrent non-small cell lung cancer, no prior chemotherapy for systemic disease, performance status = 0 to 1, no history of brain metastases, and weight loss less than 10%. Patients received erlotinib 150 mg/d until objective or symptomatic progression when they were offered conventional chemotherapy. The primary end point was progression-free survival.

Results: Forty patients were accrued. The median age was 65 years, 35 had performance status = 1, 8 were never-smoker, and 23 were former smokers. Histologies were adenocarcinoma in 22 and squamous cell in six. The major toxicity was rash (grade 1, 12; grade 2, 16; grade 3, 3). Partial responses were observed in six (15%), stable in 11 (28%), and progressive disease in 23 (58%). The median time on erlotinib was 8 weeks. The median survival was 50 weeks with 1, 2, and 3 years survivals of 44%, 18%, and 16%. Retrospective epidermal growth factor receptor mutational analysis was performed in 18 subjects and four mutations (22%) were identified. Only 25 patients have received subsequent chemotherapy (too early, 4; refused, 9; and unable because of performance status, 2), and, of these, 9 (36%) achieved unconfirmed responses.

Conclusions: Despite a modest response rate, lack of enrichment for never-smokers and absence of conventional chemotherapy in many patients, the median and long-term survivals were comparable with those expected after conventional sequencing of chemotherapy. Erlotinib as initial therapy was well tolerated and warrants randomized evaluation as first-line treatment for advanced lung cancer.

Key Words: Erlotinib, Non-small cell lung cancer, Metastatic.

(*J Thorac Oncol.* 2009;4: 214–219)

*Huntsman Cancer Institute, University of Utah, Utah; †Department of Medicine, University of Utah, Utah; ‡Department of Pathology and ARUP Laboratories, University of Utah, Utah; and §Mountain States Tumor Institute, Boise, Idaho.

Disclosure: The authors declare no conflicts of interest.

Address for correspondence: Wallace Akerley, MD, Huntsman Cancer Institute, 2000 Circle of Hope Rm 2165, Salt Lake City, Utah 84112. E-mail: wallace.akerley@hci.utah.edu

ISSN: 1556-0864/09/0402-0214

Nonsmall cell lung cancer is the most frequent cause of cancer death in the United States with a mortality of approximately 85% for all stages based on population statistics.[1] Systemic chemotherapy for palliative intent with a platinum-based doublet is the mainstay for patients with metastatic or recurrent non-small cell lung cancer (NSCLC). Although these treatments achieve a survival advantage and an improvement in quality of life compared with no treatment or a less effective control,[2–4] many patients will not be treated because of toxicity, poor performance status,[5,6] or patient-physician choice.[7] Alternatives to systemic chemotherapy or new systemic treatment strategies are needed.

Recently, erlotinib and gefitinib, both reversible, oral inhibitors of the epidermal growth factor receptor (EGFR) were approved for the second- or third-line treatment of metastatic or recurrent NSCLC. Although both exhibit antitumor activity demonstrated by symptom relief, antitumor response, and tendency to induce stable disease, erlotinib was also associated with a statistically significant improvement in survival. In BR-21, a placebo-controlled, phase III study of erlotinib in patients with NSCLC previously treated with one or two prior cytotoxic chemotherapy regimens, patients treated with erlotinib achieved an 8.9% response rate and a 43% improvement in median survival from 4.7 to 6.7 months.[8] This incremental benefit in survival is at least comparable with, or perhaps better than, second-line cytotoxic chemotherapy.

Retrospective evaluations to predict which subsets of patients with NSCLC will achieve benefit from erlotinib treatment have not yielded uniform results. Asian race, female gender, adenocarcinoma histology, a never-smoking status, and EGFR gene mutation or amplification have been correlated with greater chances of tumor response, but their association with survival with the exception of never-smoking status was not correlated in BR-21. In multivariate analyses from a subset of these patients with adequate tissue for analyses, adenocarcinoma, never having smoked, and overexpression of EGFR were associated with objective responses, but survival was not influenced by the status of EGFR expression, the number of EGFR copies, or EGFR mutations.[9] A history of never smoking remains the single best clinical predictor of survival benefit associated with erlotinib therapy, but those with a smoking history also showed a survival benefit after erlotinib treatment.[10] Simi-

larly, males and patients with squamous histology also benefited from erlotinib therapy.

Attempts to use these promising agents as first-line treatment of patients with metastatic or relapsed NSCLC were unsuccessful in a series of phase III studies in unselected patients when administered in combination with conventional chemotherapy.[11–14] The reasons for these negative results are unknown, but hypotheses to explain the lack of added benefit between EGFR inhibitors and chemotherapy include both classes benefit the same population of patients with NSCLC; the targeted agent affects such a small fraction of patients that its effect is diluted beyond measurement in unselected patients; or the agents are antagonistic. Antagonism might explain why the progression-free survival curves in some studies separate only during the single agent phase after combined therapy was stopped.[11,13,14] Alternatively, EGFR inhibitors may be less effective in patients with more rapidly growing tumors than in patients with intrinsically more indolent tumors. Kinetic modeling of NSCLC, assuming that those with more rapidly growing tumors die sooner than those with less aggressive tumors, suggests that EGRR inhibitors may be less effective in unselected first-line patients where a mixture of growth rates exist and more effective in patients who survive long enough to enter second- and third-line treatment studies because those with faster growing tumor have expired, enriching for an indolent tumor population.[15]

Clinical indicators of long-term survival, which might imply the presence of indolent tumor kinetics, have been identified in the course of various studies. In the untreated setting, a multivariate analysis for overall survival of patients treated with gefitinib and platinum-based chemotherapy in two large phase III trials (INTACT 1 and 2) revealed worse survival for: performance status 2, weight loss, bone, liver or brain metastases, and gender.[16] In INTACT 2, a trend toward improved survival was observed in patients with adenocarcinoma who had received chemotherapy for >90 days.[13] Good performance status (ECOG 0), no appetite loss, previous surgical resection, number of metastatic sites <4, and no metastases in liver or subcutaneous tissue have also been identified as independent prognostic factors of survival in chemo-naive patients treated with contemporary chemotherapy doublets.[17,18] Another survival model identified O_2 saturation and lung cancer symptom scale parameters (O_2 saturation >90%, number of presenting major symptoms, and scores on the appetite and fatigue subscales) as independent prognostic factors.[19] Still, other multivariate models named brain metastases,[20] inflammatory response measured by C-reactive protein,[21] and pain[22] as independent prognostic factors of lesser survival. Overall, these models predict that best survival can be anticipated from patients with fewer symptoms, better organ function, and optimal functional status.

The current trial was designed to evaluate the effectiveness of erlotinib in patients with untreated advanced NSCLC who were minimally selected based on clinical criteria. EGFR mutations and their association with response were not known at the time of study design. We hypothesized that selection of patients who were likely to survive greater than 90 days based on performance status, weight loss, and absence of brain metastases would enrich for indolent tumor characteristics that may be associated with EGFR inhibitor responsiveness. The goal of this strategy was to provide a less toxic, oral treatment for patients with advanced NSCLC that could delay the time to initiation of chemotherapy and its associated side effects, but not interfere with patients' ability to receive chemotherapy when needed subsequently.

PATIENTS AND METHODS

Patients

Eligible patients were required to be 18 years and older with recurrent or stage IIIB–IV (pathology confirmed) NSCLC, to have received no prior chemotherapy for systemic disease (adjuvant chemotherapy allowed if >6 months from protocol entry) and to have no poor prognostic features defined as brain metastases, weight loss >10% in the preceding 3 months, performance status >1, or dire symptoms necessitating immediate need for chemotherapy. Patients were required to have measurable disease and adequate organ function defined as liver enzymes <2× normal, bilirubin = normal; oxygen saturation >89% on room air unless chronically oxygen dependent (not cancer related); and creatinine <2.0 mg. The protocol was amended subsequently to eliminate oxygen requirement. Women of childbearing potential and sexually active males were strongly advised to use an accepted and effective method of contraception. Pregnant or lactating patients were ineligible. Screening tests including a complete blood count, chemistry panel, and computed tomography (CT) of chest and abdomen were performed before study entry, blood work and visits were repeated monthly and CT scans were repeated every 2 months. The study was approved by the University of Utah, St. Luke's Health System, and Montana Institutional Review Boards. All patients signed informed consent.

Treatment

Erlotinib was administered 150 mg PO daily, repeated every 28 days. Tablets were taken preferably in the morning with up to 200 ml of water, 1 hour before or 2 hours after meals. Patients who were unable to swallow tablets could dissolve tablets in distilled water for administration.

All toxicities were graded according to the Common Toxicity Criteria Version 3.0. For other grade 3 to 4 toxicities, erlotinib was interrupted until toxicity was grade ≤1, then treatment was resumed at 100 mg daily. If grade 3 to 4 toxicity recurred, erlotinib was interrupted until toxicity was grade ≤1, then erlotinib was resumed at 50 mg daily. All dose reductions were permanent.

Supportive measures consistent with optimal patient care were provided throughout the study, including Loperamide to manage erlotinib-associated diarrhea, topical or oral antibiotics, or antihistamines to manage erlotinib-associated skin toxicity. Bisphophonates and hematopoietic factors were allowed.

