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

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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.

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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.

Erlotinib treatment stopping rules were designed to minimize the loss of patients' performance status and to maximize their opportunity to receive conventional chemotherapy subsequently. Therefore, treatment was discontinued for either objective or subjective disease progression. Subjective disease progression was implied by a one-level decline in performance status; development of a new symptom unrelated to therapy; or the doubling or rise of two consecutive tumor markers. If a patient was removed from protocol treatment, the reason (including symptom if appropriate), next planned treatment, response to first-line chemotherapy treatment, and time to progression after chemotherapy was reported. All patients were followed until death.

Response Evaluation

Unidimensional measurements as defined by Response Evaluation Criteria in Solid Tumors (RECIST) were used in this study.[23] Measurable lesions were those that could be accurately quantified in at least one dimension as ≥20 mm with conventional techniques (positron emission tomography, CT, magnetic resonance imaging, radiograph, or physical examination) or as ≥10 mm with spiral CT scan. Liver lesions required a baseline CT scan, with responses documented by follow-up CT scans. All other lesions (or sites of disease), including small lesions, were considered nonmeasurable disease.

All measurements were taken and recorded in metric notation ≤28 days before treatment initiation. Identical techniques and methods of assessment were used to characterize each identified and reported lesion at baseline and during follow-up. Partial responses (PR) or complete responsewere confirmed by repeat assessments performed 4 weeks after the criteria for response were first met. The duration of overall response was measured from the time that measurement criteria were met for complete response or PR (whichever is first recorded) until subjective or objective progression was observed or a new treatment started.

Study records and radiologic images documenting objective response and stable disease were reviewed by the End Point Review Panel, a subcommittee of the Huntsman Cancer Institute's Data, Safety and Monitoring Committee.

Statistical Analysis

The primary end point for this trial was the fraction of patients experiencing progression-free survival after cytotoxic chemotherapy (PFS-CC) at 6 months. PFS-CC was defined as the interval from study initiation until progression of the disease after subsequent cytotoxic chemotherapy, progression of disease on erlotinib if cytotoxic chemotherapy not initiated or death. For the study to be successful, PFS-CC had to meet the historically observed rate of 31% based on Southwest Oncology Group trial.[6] A one-sided binomial test at 5% nominal significance was used to calculate the maximum number of patients whose disease could progress while on chemotherapy by 6 months (≤17/40 patients). For safety reasons, interim monitoring was performed after the first 20 patients and the study would have been terminated if PFS-CC were <25% at 6 months.

Secondary outcomes, overall survival, erlotinib-progression-free survival and chemotherapy-progression-free survival were estimated through Kaplan-Meier methods. Survival was counted from the first dose of erlotinib.

RESULTS

Forty patients were accrued to this trial in two stages from June 1, 2004 to 31 December, 2005. Twenty patients were accrued during the first stage of the study and an additional 20 patients were accrued after the safety threshold for progression-free survival at 6 months was exceeded. The median age was 65 years with a range from 45 to 78. The majority of patients were male ($n = 25$), current or former smokers ($n = 32$), stage IV ($n = 37$), had a performance status of 1 ($n = 35$) and had adenocarcinoma ($n = 22$). Their characteristics are shown in Table 1.

Thirty-one patients received at least two cycles (8 weeks) of therapy. Nine patients stopped before completion of two cycles because of objective or symptomatic progression. Nineteen completed three cycles and 16 received four or more cycles. Four patients remain on active treatment with erlotinib exceeding 2 years from the start of therapy. Reasons for discontinuation of erlotinib were objective progression ($n = 33$), symptomatic progression (two with declining performance status), and acute complications of cancer (pulmonary emboli in one).

Rash and diarrhea were the most commonly observed side effects. Five patients required a dose reduction for rash and one patient for grade 2 bilirubin elevation. No patients required dose reduction for diarrhea. Other toxicities that reached grade 3 included deep vein thrombosis, diarrhea, and mucositis. Grades 1 and 2 toxicities included fatigue, weight

TABLE 1. Patient Characteristics

Age (median and range)	65 (45–78)
Gender	
Male	25
Female	15
Smoking status	
Current	9
Former	23
Never	8
PS	
0	5
1	35
Race	
Asian	3
Caucasian	37
Histology	
Adenocarcinoma	22
Squamous cell	6
NSCLC, not otherwise specified	12

Never smokers were those smoking less than 100 cigarettes lifetime. Current smokers were those using cigarettes within a year of study enrolment, and former smokers were defined as those quitting for more than 1 yr.

PS, performance status; NSCLC, non-small cell lung cancer.

TABLE 2. Adverse Events ($n = 40$)

	Grade (*N*)			
Toxicity	**1**	**2**	**3**	**4**
Deep vein thrombosis		1	1	
Fatigue	6	3		
Weight loss	2	2		
Rash	12	16	3	
Dry skin	5	3		
Paronychia			2	
Diarrhea	14	2	2	
Anorexia	8	1		
Mucositis		1	1	
Bilirubin	2	1		

loss, anorexia, and liver toxicity, as assessed by bilirubin. Toxicity results are shown in Table 2.

All patients were included for response assessment for erlotinib including those who received less than 8 weeks of therapy. PR occurred in six patients (15%, 95% CI = 3.9–26.1) with a median duration that will exceed 32 months. Stable disease occurred in 11 patients (28%, 95% CI = 14–41). The majority of patients, 23 (58%, 95% CI = 42–72) had disease progression as best response. Responses occurred in males ($n = 3$), smokers (three former), and nonadenocarcinoma ($n = 2$). Sixteen patients had grade 2 rash and three had grade 3 rash. Of note, there was a trend ($p = 0.06$) for severity of rash exceeding grade 1 to differ by smoking status (never-smokers 63%, former 48%, and current 33%).

Twenty-five patients received subsequent cytotoxic chemotherapy after study therapy with erlotinib. Four patients have not become eligible for secondary chemotherapy because they remain on first-line erlotinib. Eleven patients received erlotinib only as part of the study, but never received subsequent chemotherapy, either because of refusal ($n = 9$), to inadequate performance status ($n = 1$) or death ($n = 1$). Of the patients who received subsequent chemotherapy, all received a carboplatin-based doublet. Nine (36%) had unconfirmed PRs, 11 (44%) had stable disease, and five (11%) progressed after two cycles. Overall, this suggests chemotherapy responsiveness is not diminished after erlotinib treatment.

The median progression-free time on erlotinib was 8.5 (95% CI = 8.3–8.7) weeks. Patients who developed grade 0 to 1 rash discontinued erlotinib sooner than patients who developed grade 2 to 3 rash (7.8 weeks versus 17.7 weeks, respectively $p < 0.05$). There was a trend for smokers (current 7.4 weeks, former 8.0 weeks) to discontinue erlotinib sooner than never-smokers (16 weeks, $p = 0.08$).

The median PFS-CC defined as time on erlotinib until progression on chemotherapy, progression on erlotinib for those who did not receive chemotherapy or death was 27.9 weeks (95% CI = 27.7–28.8). The progression-free rate at 6 months was 56%. Never-smokers had a greater chemotherapy progression-free time than ever-smokers (42.7 versus 23.9 weeks, $p = 0.02$).

The median survival was 50.1 weeks (95% CI = 48.5–51.7) and the 1, 2, and 3-year survivals were 44.2%, 18.2%, and 15.6%, respectively. Five patients are still alive at this time (Figure 1). Never-smokers fared better than ever-smokers with median survivals of 88.9 weeks (95% CI = 88.6–89.3) versus 33.1 (95% CI = 32.9–33.3; $p = 0.04$). Of note, the median survival of patients who did not receive conventional chemotherapy (2, too ill; 9 refused) was 13.7 weeks. Survivals were not affected by performance status, histology, or development of rash.

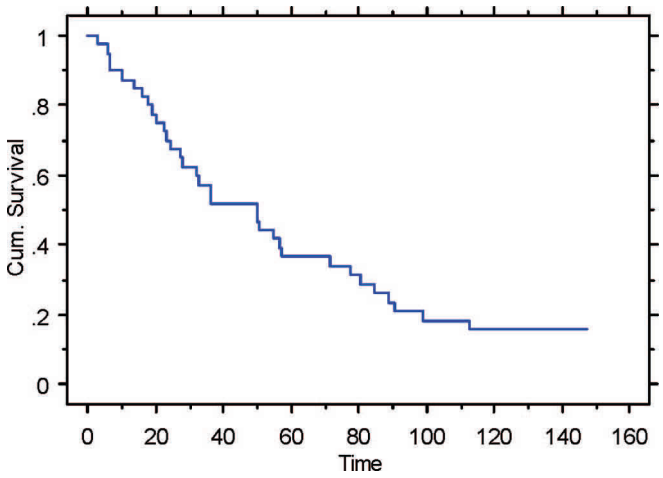

FIGURE 1. Kaplan-Meier cum survival plot for survival (weeks) censor variable: censor sur. Time in weeks.

Although not part of the original study design, the protocol was amended to seek original biopsy material for EGFR mutation analyses. Block material was available for only two patients, but an additional 16 had material sufficient for analysis from cytology specimens. These were analyzed using polymerase chain reaction with melting amplicon analyses followed by DNA sequencing if a mutation was identified.[24] Of the 18 specimen analyzed, four (22.2%) had mutations in EGFR (exon 19 (del 747) in three and exon 21 (L858R) in one. All four patients with EGFR mutations had adenocarcinoma and three demonstrated objective responses to erlotinib lasting 43, 97, and 100 weeks. Three were never smokers and the fourth was a former smoker who quit 30 years before study. Two remain alive and the median survival for those with mutations will exceed 117 weeks. Of the 14 with wild-type EGFR, there were two with response to erlotinib, five with stable, and seven with progression. Their median survival was 43 weeks. Of the four patients who remained on erlotinib for more than 2 years, two had EGFR mutations and two had wild type.

DISCUSSION

This phase II evaluation of first-line treatment with erlotinib in minimally selected patients yielded a satisfactory outcome with minimal toxicity. Despite a modest 15% response rate, the median survival of 50.1 weeks and the 2-year survival of 18% are quite comparable with studies of initial, multiagent chemotherapy. Nineteen received at least 12 weeks of erlotinib and there was long-term tolerance with four patients (10%) continuing to receive this agent for greater than 2 years. Of note, only two of these latter patients

had EGFR mutations and two had wild type. Furthermore, these survival results were observed in a population of patients where a large fraction did not or chose not to receive conventional chemotherapy. Of the 25 of 40 who did receive chemotherapy, chemosensitivity was maintained as 36% achieved unconfirmed PRs.

It was hypothesized that early institution of erlotinib plus minimally restrictive eligibility criteria including performance status 0 to 1, weight loss less than 10% and absence of brain metastases would enrich for a population that could show greater sensitivity to erlotinib, but the response rate of 15% (95% CI = 4–26) and clinical benefit rate (PR + stable) of 42% are similar to published data for erlotinib administered as second and third-line treatment. Although four (22%) of 18 patients with adequate tissue demonstrated an EGFR mutation and 20% of the patients were never-smokers, which may be slightly greater than expected, it does not seem that the design was successful as an enrichment strategy to select for characteristics that might enhance erlotinib responsiveness.

The favorable results of the current trial are not unique and are supportive of data from other trials of erlotinib as first-line treatment for NSCLC. In one study of unselected patients with NSCLC, 53 untreated patients with advanced NSCLC received erlotinib as primary therapy, which resulted in 23% response rate, median survival of 391 days and 1-year survival of 54%.[25] In another trial of similar design that was limited to patients with age greater than or equal to 70, erlotinib treatment yielded a 10% response rate, median survival of 10.9 months and 2-year survival of 19%.[26] Although smoking history was not an eligibility criterion of these studies, the former trial with the greater response rate enrolled 30% never-smokers and the latter trial included only 10% never-smokers. Even more striking are studies in Asian populations, a prognostic factor for EGFR response,[27] where response rates exceeded 50% in unselected patients,[28] in never-smokers[29] and in those with EGFR mutations.[30] In contrast, a study evaluating the effectiveness of first line therapy for erlotinib for patients with performance status = 2 has shown lesser outcomes with response rates of 2%[31] suggesting that poor performance may define a population of patients who may not benefit from erlotinib as first-line therapy.

One unanticipated finding of this study was the relatively large fraction of patients who agreed to participate in the trial with the understanding that they would receive conventional chemotherapy after erlotinib but subsequently refused after erlotinib progression. Review of these patients versus those who did receive chemotherapy was not substantially different in terms of performance status, erlotinib toxicity, and response to erlotinib. Anecdotally, some stated that they participated in the trial because it offered an alternative to conventional chemotherapy and would have chosen no therapy had this trial not existed. It would be of interest to determine what fraction of "fit" patients with lung cancer and/or their physicians avoid seeking medical oncology consultation because of "antichemotherapy" biases.

In summary, minimally selected patients treated with erlotinib as initial therapy for metastatic NSCLC seem to achieve similar survival with less toxicity than expected with conventional chemotherapy. The strategy of initial treatment with erlotinib followed by subsequent chemotherapy is supported by multiple studies and a randomized trial compared with conventional chemotherapy is warranted to test this hypothesis. This alternative approach may appeal to a broader population of patients than are currently receiving therapy by including those with a fear of chemotherapy. Some minimal patient enrichment criteria such as performance status limited to 0 to 1 would be necessary to ensure that patients are able to withstand ineffective therapy in either arm and allow crossover to second-line treatment. Additional tactics to enhance selection of patients who might derive greater benefit from erlotinib and thus improve the chances of a positive study or reduce the number of patients include EGFR analysis, other biomarkers, prior cigarette exposure, gender, race and/or conditional rash assessment but are not a necessary requirement.

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