Gefitinib Plus Celecoxib in Chemotherapy-Naïve Patients with Stage IIIB/IV Non-small Cell Lung Cancer

A Phase II Study from the Hoosier Oncology Group

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Background: Gefitinib, an inhibitor of the epidermal growth factor receptor (EGFR) pathway, has single agent activity in non-small cell lung cancer (NSCLC). Preclinical studies demonstrate significant interactions between the EGFR and cyclooxygenase 2 (COX-2) pathways and that simultaneous inhibition may have benefits over EGFR inhibitors alone.

Methods: Eligibility criteria: chemotherapy-naive, stage IIIb (with pleural effusion) or IV NSCLC, Eastern Cooperative Oncology Group Performance Status (PS) 0–1. Patients were treated with gefitinib 250 mg po daily plus celecoxib 400 mg po every 12 hours. Cycles consisted of 21-day treatment and continued until unacceptable toxicity or progression of disease. The primary objective was to evaluate the overall response rate; secondary objectives included estimation of progression free survival, overall survival, and to assess the toxicity of this regimen.

Results: From January 2004 to November 2004, 31 patients were enrolled: male/female 13/18; median age 70 years (range, 19–93); 68% had adenocarcinoma; Eastern Cooperative Oncology Group PS 0/1 13/18; stage IIIb/IV 2/29. Two patients died of interstitial lung disease due to treatment. There were three additional deaths during treatment that were not considered treatment related. Two additional patients discontinued treatment due to adverse events (elevated liver enzymes). Select grade 3/4 toxicities included: pneumonitis (3%), hepatic (7%), diarrhea (7%), and skin (3%). Response rate was 16% (95% CI, 5–34%), median progression free survival and overall survival were 3.2 (95% CI, 2.7–5.7 months) and 7.0 months (95% CI, 3.7–14.2 months), respectively. All responders were females with adenocarcinoma, two were remote or never smokers and three were former smokers.

Conclusion: Gefitinib plus celecoxib in an unselected population of chemotherapy naive patients with advanced NSCLC and a PS of 0–1 has a lower response rate and overall efficacy compared with historical controls of combination chemotherapy.

Key Words: Non-small cell lung cancer, Gefitinib, Celecoxib.

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Lung cancer is the leading cause of cancer-related death in both men and women in the United States, with 160,390 projected deaths in the year 2007.[1] Approximately 85% of these patients will have non-small cell lung cancer (NSCLC) type and the majority will present with advanced disease. Modest gains in survival time and quality of life have resulted from the use of chemotherapy in patients with advanced NSCLC.[2–6] A multicentered trial from the United Kingdom randomizing patients to supportive care versus platinum-based chemotherapy demonstrated a small, but statistically significant, survival advantage for the use of chemotherapy.[6] Unfortunately, a plateau in survival times has been reached as comparable survival results are reported with several different regimens.[7] Furthermore, although survival gains are usually modest with chemotherapy, many patients experience grade 3 or 4 toxicities, the extent of which differs based upon the regimen used. Novel strategies and therapeutics with safer side effect profiles are greatly needed for this patient population.

Gefitinib is an inhibitor of the epidermal growth factor receptor (EGFR) intracellular tyrosine kinase. Inhibition of this signal transduction cascade can affect tumor growth, angiogenesis, and survival of lung cancer cell lines. Phase II trials of gefitinib in previously treated patients with advanced NSCLC reported response rates of 11.8% and18.4%, respectively.[8,9] Substantially more patients achieved stable disease for at least 3 months, so that the disease control rate was approximately 40 to 50%, comparable to what is achieved with chemotherapy in this setting. At a dose of 250 mg daily, gefitinib was generally well tolerated with few instances of grade 3 or 4 toxicity.

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Cyclooxygenase-2 (COX-2) is also believed to play an important role in the pathogenesis of some malignancies. Investigators at Indiana University characterized the frequency of COX-2 expression by immunoblot analysis in primary lung cancers from frozen tumor tissue and matched normal adjacent tissue.[10] COX-2 protein was expressed more frequently and at higher levels in adenocarcinomas and squamous cell carcinomas of the lung when compared with the normal adjacent tissue. Preclinical data has shown that COX-2 inhibitors inhibit both in vitro and in vivo growth of human cancer lines, demonstrate antiangiogenic activity, increased cellular apoptosis, and decreased cellular proliferation.[11–13] Furthermore, significant intracellular interactions between the EGFR pathway and COX-2 pathway have been reported in preclinical studies, suggesting that simultaneously inhibiting both targets may provide enhanced benefits.[14–17] Therefore, based on the desire to develop more effective and safer regimens for patients with advanced NSCLC, this study was designed to assess the efficacy of gefitinib, an EGFR inhibitor, with celecoxib, a COX-2 inhibitor, in chemotherapy-naive patients with stage IIIb or IV NSCLC.

PATIENTS AND METHODS

Patients were enrolled from participating sites of the Hoosier Oncology Group, a community-based cooperative group. Eligible patients met the following criteria: histologic or cytologic evidence of NSCLC, stage IIIB disease with pleural effusion and/or positive supraclavicular nodes or stage IV disease, chemotherapy-naive, the presence of measurable disease per the RECIST criteria, an Eastern Cooperative Oncology Group Performance Status of 0 or 1 at baseline, adequate baseline hematologic function (absolute neutrophil count $\geq$1500/mm^3, platelet count $\geq$100,000/mm^3, hemoglobin level $\geq$8 g/dl), hepatic function (total bilirubin level $\leq$2 mg/dl, aspartate aminotransferase and alkaline phosphatase $\leq$2.5 $\times$ upper limits of normal), and renal function (serum creatinine level $\leq$2 mg/dl or a calculated creatinine clearance $\geq$50 ml/min). Radiotherapy was allowed, provided the radiated area was not the only site of measurable disease and was completed $>$21 days before study registration. Patients with brain metastases were eligible if the brain metastases were adequately treated, asymptomatic, and clinically stable for at least 2 weeks. Patients were excluded if they had received prior anti-EGFR therapy, had a prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, Gleason $\leq$grade 7 organ confined prostate cancer or other cancers for which the patient has been disease-free for $>$3 years; history of severe or uncontrolled systemic disease (e.g., unstable or uncompensated respiratory, hepatic, or renal disease), active infections, history of neuropathic keratopathy, current treatment for ocular inflammation or corneal ulceration, or evidence of clinically active interstitial lung disease (patients with chronic stable radiographic changes who were asymptomatic were not excluded). Pregnant or lactating women were excluded and women of childbearing potential and sexually active males had to be willing to use contraception during and for 3 months after completion of protocol therapy. All patients gave written informed consent and HIPAA authorization for release of protected health information. The local institutional review boards approved the protocol before enrollment at each site.

All patients were treated with gefitinib 250 mg po daily plus celecoxib 400 mg po every 12 hours. The study was stopped after we failed to meet our endpoints from stage I to go on to stage II. Each cycle consisted of a 21-day time period and treatment continued until disease progression or intolerable toxicities occurred. Physical exams and toxicity evaluations were completed at baseline and before each cycle and disease assessment was undertaken at baseline and prior to every other cycle. Toxicities were graded using the Common Toxicity Criteria version 3.0. Day 1 treatment of a new cycle was administered only when the absolute neutrophil count was $\geq$1000/L and platelets $\geq$100,000/L. Patients who required greater than a 14-day interruption in therapy due to toxicity were taken off study. There were no dose reductions allowed for gefitinib. Patients with grade 3 or 4 skin toxicity, diarrhea, stomatitis and/or any other significant toxicity thought to be related to gefitinib were treated with supportive care and gefitinib could be held up to 14 days. Treatment was restarted when the patient recovered to baseline or $\leq$grade 2. If patients presented with an acute worsening or new onset of respiratory symptoms such as dyspnea, cough, and fever, gefitinib therapy was interrupted and evaluation for interstitial lung disease (ILD) was initiated. If ILD was confirmed, gefitinib was permanently discontinued. If a patient developed any grade 3 or 4 toxicity attributable to celecoxib, treatment with celecoxib was interrupted until symptoms resolved to a grade 2 or less toxicity and then celecoxib was resumed at a 50% dose reduction. Gastrointestinal bleeding attributable to celecoxib would have required the patient be taken off study. A maximum 14-day treatment interruption was allowed with only one dose reduction allowed per patient.

Of note, a study amendment was made on December 21, 2004, stopping the use of celecoxib after evidence was shown correlating the drug with increased risk of serious cardiovascular events.[18] This amendment was made during the interval between the first and second stages while the data was being analyzed to see if we would proceed with the second stage. This amendment would have only affected those still on study as no further patients were accrued for the study.

Statistical Considerations

The primary objective of this multiinstitutional phase II study was to estimate the overall response rate of the combination of gefitinib plus celecoxib in this patient population. Secondary objectives included estimation of progression free survival, overall survival, and to assess the toxicity of this regimen. Patients were to be entered in two stages. If $\leq$10 of the initial 30 patients achieved an objective response, the study would be terminated. If $>$10 of the initial 30 patients achieved an objective response, accrual would continue to a total 50 patients. A one-sided statistical test was to be carried out at the 10% alpha level. The null hypothesis would be rejected if the lower bound of a one-sided 90% confidence interval constructed around the observed response rate is higher than the historical response rate of 30%. The hypoth-

esis that the response rate is below 30% would be rejected in favor of the alternative that the true response rate is higher than 30% if at least 20 of 50 evaluable patients respond. If the true response rate is 45% or higher, this design was expected to provide better than 80% power to confirm that the true response rate is no less than 30%. For progression-free survival and overall survival, a lower 90% one-sided confidence interval was constructed around the observed median (either median time to progression or death). Therapy was to be considered having exceeded the current therapeutic standard at the 90% confidence level if the lower bound of this confidence interval was higher than 4 and 10 months, respectively.

Response was assessed using the RECIST criteria, and all responses were confirmed a minimum of 4 weeks after the initial response was recorded. Duration of response is defined among responders from earliest date of response to date of progression or death, with those continuing to respond at last data collection as censored. To be assigned a status of stable disease, measurements on imaging could neither have had sufficient shrinkage to qualify for partial response nor sufficient criteria to show progressive disease. This had to have been shown at least once after study entry at a minimum of 6 to 8 weeks. Survival end point is defined as time to death with surviving patients at last data collection as censored. Progression-free survival is defined as time to death or date of progression with surviving patients at last data collection as censored. Follow-up time end point is date of last data collection with censoring at death.

RESULTS

From January 2004 to November 2004, 31 eligible patients were entered onto the study. Two patients were simultaneously consented from separate sites on the same day. Therefore, we elected to allow both patients to enroll. This increased enrollment by 1 patient for the first stage of the study. The study did not meet its predefined criteria of an observation of at least 30% response rate to continue beyond the first stage. Patient demographics and disease characteristics are summarized in Table 1. The majority of patients were female and former smokers; adenocarcinoma was the predominant histologic type. All but two patients had stage IV disease with Eastern Cooperative Oncology Group performance status of 0 for 13 patients and 1 for 18 patients. The median number of completed cycles was 4 (range, 0–19). There were seven patients who stopped celecoxib permanently in December 2004, when the amendment to do so took effect.

TABLE 1. Patient Demographics and Disease Characteristics

	Count	Percent
Sex		
Female	18	58
Male	13	42
Histology		
Adenocarcinoma	21	68
Squamous cell carcinoma	2	6
Other	8	26
ECOG performance		
0	13	42
Status		
1	18	58
Stage		
IIIB	2	6
IV	29	94
Smoking history		
Never smoked	5	16
Former Smoker	20	65
Current Smoker	5	16
Unknown	1	3

ECOG, Eastern Cooperative Oncology Group.

TABLE 2. Combined Grade 3 and 4 Toxicities

Toxicity	Count	Percent
ALT, SGPT (serum glutamic pyruvic transaminase)	2	7
Atelectasis	1	3
Cardiac	1	3
Diarrhea	2	7
Dizziness	1	3
Dyspnea	4	13
Fatigue	2	7
Hyperkalemia	1	3
Hypotension	1	3
Mucositus	1	3
Non-neutropenic infection	1	3
Pneumonitis/pulmonary infiltrates	1	3
Pulmonary/upper respiratory	3	10
Renal	1	3
Skin	1	3
Vomiting	1	3
Weight loss	1	3

Toxicity

Toxicity data is summarized in Table 2 for all patients ($n = 31$). Two patients died as a result of toxicity. One female patient, with no prior radiotherapy, developed interstitial lung disease and died 2 to 3 weeks after initiating treatment. Of note, she had pneumonia 4 months before entering the study. The second patient who died due to treatment also died of interstitial lung disease. The patient was a male who had prior radiotherapy to the chest and back completed in September 2004 and started protocol therapy in October 2004. After 6 weeks, he had stable disease but had increasing radiation-markings. He became dyspneic and was given oxygen and steroids for presumed pneumonitis. His symptoms worsened and he died in January 2005, just 2 months after starting protocol therapy. Another patient with known prior history of congestive heart failure developed symptoms of lethargy and respiratory distress with signs of rhonchi and rales on physical examination. Chest radiograph confirmed volume overload and despite diuretic and aerosol treatments the patient died; however, this was not considered treatment related. There were two other patients who died while on treatment, one from Guillain-Barre and another who died suddenly from a presumed pulmonary embolus, not considered to be treat-

TABLE 3. Characteristics of Responding Patients

Sex	Age	Orig.	Description	Pks/yrr	Smoking Status
F	70	Lung	Adenocarcinoma		Never smoked
F	56	Lung	Adenocarcinoma	20	Quit >3 mo ago but <30 yr
F	48	Lung	Adenocarcinoma	20	Quit >3 mo ago but <30 yr
F	58	Lung	Adenocarcinoma	20	Quit >3 mo ago but <30 yr
F	73	Bone	Adenocarcinoma		Hasn't smoked in >30 yr

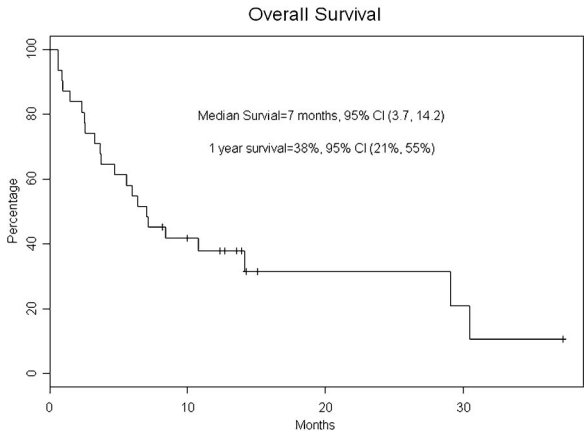

FIGURE 1. Kaplan-Meier curve for overall survival.

ment related. Two patients discontinued treatment before disease progression due to elevated liver enzymes. Twelve patients (39%) had at least one grade 3 or 4 toxicity. Three patients (10%) had grade 3 diarrhea. There were no instances of grade 3 or 4 rash, gastrointestinal bleeds, myocardial infarctions, or cerebrovascular accidents.

Efficacy

All patients ($n = 31$) were considered evaluable for response, progression-free survival, and overall survival. Five patients achieved a partial response (16%, 95% CI, 5–34%), whereas an additional 14 patients (45%, 95% CI, 27–64%) had stable disease; the remaining 12 patients (39%, 95% CI, 22–58%) had progressive disease. The overall disease control rate (partial response plus stable disease) was 61% (95% CI, 42–78%). Median duration of response among five responders was 2.8 months (range of response, 1.5–20.5 months.) Characteristics of the five patients with a partial response are summarized in Table 3. As of this analysis, 9 of 31 patients were alive. The median progression-free survival and overall survival times were 3.2 (95% CI, 2.5–5.7 months) and 7.0 months (95% CI 3.7–14.2 months), respectively (Figure 1 and 2). The 1-year survival estimate is 38% (95% CI, 21–55%).

DISCUSSION

To our knowledge, this is the only published phase II study evaluating the combination of gefitinib plus celecoxib in good performance status patients with advanced NSCLC treated in the first line. Our reported response rate with this combination was similar to the single agent activity of gefitinib alone in a similar patient population, and thus we failed to meet our primary goal and did not continue the study onto its second stage.[19–23] Furthermore, this regimen seems less active than many combination chemotherapy regimens in a similar patient population.[7,24,25] In addition, despite having a performance status of 0 or 1 at study entry, the median survival time of only 7.0 months is substantially lower than historical controls with chemotherapy as first line therapy (9–10 months) for this patient population on most recent studies. Although five patients did achieve a partial response, including some with durable responses, it is unclear what the contribution of celecoxib was for these patients.

Other studies have combined EGFR-tyrosine kinase inhibitors with disappointing results. Gadgeel et al. had a response rate of 7% when combining gefitnib with celecoxib in patients with platinum refractory NSCLC.[26] O'Byrne et al. combined gefitinib with rofecoxib in patients with platinum-pretreated relapsed NSCLC resulting in a 7% response rate.[27] Another study combining erlotinib with celecoxib in patients with relapsed NSCLC resulted in an 8% response rate.[28]

Several studies evaluating single agent gefitinib in a chemonaive patients have been reported. Niho et al. reported a response rate of 30% and median survival of 13.9 months with gefitinib as first-line treatment in advanced NSCLC in an Asian population.[19] Responders on this trial were generally female patients with adenocarcinoma, similar to observations on other studies, including the current study.[10,11] Our data suggests that females who never smoked may be a patient population who would be best treated with an EGFR inhibitor upfront. Whether sequencing of therapy with an EGFR inhibitor as first-line therapy followed by chemotherapy second line would affect overall outcomes compared with the reverse order in this patient population remains unknown. Such a question would be worthy of testing in a randomized trial. Although four randomized trials failed to demonstrate a survival difference when treating patients with chemotherapy alone versus chemotherapy plus an EGFR inhibitor, subset analyses on at least two of these trials suggested that in never smokers a survival advantage may still be realized with combined chemotherapy and EGFR blockade.[29–32] This strategy is being tested in a randomized study by the CALGB in which patients receive erlotinib alone versus chemotherapy plus erlotinib.

In the second-line setting, several studies have combined a chemotherapy agent with a COX-2 inhibitor, suggesting some subsets may benefit from the addition of a COX-2 inhibitor. For example, although Csiki et al. showed no difference in survival by combining celecoxib with docetaxel compared with docetaxel alone as second line therapy, their data suggested that patients with the greatest proportional decline in urinary PGE-M levels experienced survival prolongation when compared with those with no change or an increase in PGE-M (14.8 versus 6.3 versus 5 months).[33] Nugent et al. report in a phase II study of docetaxel and celecoxib in previously treated patients with NSCLC that the

addition of celecoxib may prolong time to disease progression.[34] Gasparini et al. evaluated the combination of celecoxib with weekly paclitaxel and measured circulating vascular endothelial growth factor and reported the subset of patients who responded to the combination of celecoxib and paclitaxel also showed decreased levels of serum vascular endothelial growth factor.[35]

Pulmonary toxicity, in particular ILD, remains a concern for a small percentage of patients treated with EGFR inhibitors. The study by Niho et al. reported a 10% rate of ILD in their studied Japanese population.[19] Other trials suggest much lower rates.[9,36] In the current study, 2 of 31 patients (7%) developed ILD, both of whom died. There were only four patients whom experienced grade 3 and 4 toxicity of dyspnea.

Continued exploration of treating unselected patient populations with targeted agents such as gefitinib or celecoxib are unlikely to significantly improve outcomes. In addition to the potential biomarkers mentioned to determine celecoxib sensitivity, several predictors of gefitinib efficacy have been reported. These include the presence of mutation in the EGFR tyronine kinase domain, increased gene copy number of EGFR band on FISH analysis, lack of Kras mutations, and lack of pTEN loss among others.[37–39]

In conclusion, this study combining gefitinib with celecoxib failed to demonstrate improved outcomes when compared with historical controls of chemotherapy in a similar patient population. As such, we do not recommend pursuit of this combination in an unselected patient population. The value of adding celecoxib to gefitinib remains in doubt, although worthy of further pursuit if a select patient population can be identified.

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