Phase II Study of Gefitinib, an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI), and Celecoxib, a Cyclooxygenase-2 (COX-2) Inhibitor, in Patients with Platinum Refractory Non-small Cell Lung Cancer (NSCLC)

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Background: Gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, has demonstrated a response rate of 9%–18% in relapsed non-small cell lung cancer (NSCLC) patients. The probability of response to gefitinib was not influenced by response to previous chemotherapy. Preclinical studies have suggested that celecoxib, a cyclooxygenase-2 inhibitor, has antitumor activity in NSCLC and can enhance the activity of EGFR inhibitors. We conducted a phase II study evaluating the combination of gefitinib and celecoxib in platinum-refractory NSCLC patients, defined as patients whose disease had progressed on platinum-based chemotherapy or within 3 months of completing such therapy.

Methods: Platinum-refractory NSCLC patients with performance status of 0–2 and adequate organ function were included. Patients should not have been on a NSAID for 30 continuous days before study enrollment. Patients were treated with gefitinib 250 mg daily and celecoxib 400 mg twice daily. Disease assessment was performed every 8 weeks.

Results: Twenty-seven patients were enrolled. The response rate was 7% (2/27). The median time to progression was 2.2 months, and the median survival was 4.6 months. One female, nonsmoking patient is progression free more than 3 years after study enrollment. The drug combination was well tolerated, with the most common adverse effects being skin rash and diarrhea.

Conclusion: In unselected platinum-refractory NSCLC patients, the response rate to the combination of celecoxib and gefitinib was similar to that observed with gefitinib alone.

Key Words: Epidermal growth factor receptor, Cyclooxygenase-2, Gefitinib, Celecoxib, Non-small cell lung cancer.

(*J Thorac Oncol.* 2007;2: 299–305)

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Disclosure: Shirish Gadgeel currently has a research grant from AstraZeneca. Antoinette Wozniak has served on an advisory board for AstraZeneca. The other authors declare no conflict of interest.

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ISSN: 1556-0864/07/0204-0299

Lung cancer remains the most common cause of cancer-related mortality in the United States.[1] The high rate of mortality is because most patients have advanced-stage disease at presentation. Platinum-based doublet chemotherapy does improve overall survival and quality of life in advanced non-small cell lung cancer (NSCLC) patients. However, the benefits of such therapy, with median time to progression of 4 months and median survival of 8 months, are modest.[2] Two chemotherapy drugs, docetaxel and pemetrexed, and erlotinib, are currently approved for the management of relapsed NSCLC patients. The response rate with these agents is approximately 9% and the median survival is 7–8 months.[3,4] Tumor progression within 3 months of completing first-line therapy, designated as chemorefractoriness, is a poor prognostic factor in relapsed NSCLC patients. The response rate in these patients, with either docetaxel or pemetrexed, is less than 5%.[3]

Epidermal growth factor receptor (EGFR), a receptor tyrosine kinase, is expressed in many NSCLCs and is involved in many aspects of carcinogenesis.[5] Based on EGFR expression in NSCLC and promising preclinical data, gefitinib was evaluated for the management of relapsed NSCLC patients. In two large phase II studies, gefitinib improved disease-related symptoms in 40% of the patients and demonstrated a response rate of 9% to 18%.[6,7] Time from initial diagnosis, a surrogate for chemorefractoriness, did not influence the possibility of response to gefitinib. Based on the results of these studies, gefitinib was approved for the management of relapsed NSCLC patients.

Cyclooxygenase (COX) is a rate-limiting enzyme involved in the conversion of arachidonic acid to prostaglandins (PGs). There are two isoforms of COX: COX-1, a constitutive enzyme expressed in most cells, and COX-2, an inducible isoform of COX.[8] COX-2 is overexpressed in neoplastic tissues in response to various stimuli[9–11] and through the production of PGs, COX-2 is involved in various processes of cancer formation and progression.[12–15] Many NSCLC tumors express COX-2, and preclinical evidence suggests that the selective COX-2 inhibitor celecoxib can

inhibit NSCLC tumor growth, alone and in conjunction with chemotherapy drugs.[16–18] In a randomized study conducted in patients with familial adenomatous polyposis (FAP), celecoxib 400 mg twice daily demonstrated a statistically significant reduction in the number of colonic polyps, providing the first clinical evidence that COX-2 inhibitors can influence precancerous conditions.[19] A lower dose of 100 mg twice daily failed to demonstrate a statistically significant decline in the number of colonic polyps.

Preclinical data suggest that there is overlap between the EGFR and COX-2 pathways.[20] In colon cancer tumor models, EGFR signaling induces COX-2 expression and increased PG production, whereas COX-2–derived PGE2 can enhance signaling through EGFR.[21–23] In addition, recent studies have shown that COX-2, through the production of PGE2 may sensitize tumor cells to EGFR-TKIs.[24,25] Preclinical studies have also shown that the combination of EGFR inhibitors and COX-2 inhibitors is more effective in inhibiting tumor formation than either agent alone.[26,27]

Based on the activity of gefitinib in NSCLC patients, the preclinical activity of celecoxib in NSCLC cell lines and the possibility of overlap between the EGFR and COX-2 pathways, we conducted a phase II study evaluating the benefits of adding celecoxib to gefitinib in relapsed NSCLC patients. Celecoxib was administered at a dose of 400 mg twice daily based on the results of the study by Steinbach et al.[19] in FAP patients. We restricted the eligibility to NSCLC patients who had progressed on first-line platinum-based doublet chemotherapy or within 3 months of completing such therapy.

MATERIALS AND METHODS

Study Design

The primary objective of this study was to assess the response rate with the combination of gefitinib and celecoxib in NSCLC patients designated as platinum refractory, based on progression of disease on or within 3 months of completing a platinum-based doublet regimen. The secondary end points were overall survival (OS), time to progression (TTP), and toxicity. TTP was defined as the time from the first day of treatment until the date when progressive disease was documented or death from any cause, whichever came first. Surviving patients who did not progress were censored for TTP as of the date of their last tumor assessment. OS was defined as the time from the first day of treatment until the date of death from any cause. Surviving patients were censored for OS as of the date they were last known to be alive.

Patient Selection

Patients aged 18 years and older with histologically or cytologically confirmed platinum-refractory NSCLC were eligible for the study. Patients had to be of performance status (PS) 0–2 and could have received other treatments after the platinum-based therapy. Patients were required to have at least one measurable lesion, adequate hepatic (bilirubin at the upper limit of normal [ULN] or less, aspartate aminotransferase and alanine aminotransferase $\leq$2.5 times the ULN, alkaline phosphatase five times the ULN or less), renal (creatinine $\leq$1.5 times the ULN), and hematologic function (hemoglobin $\geq$8 g/dL, neutrophil count $\geq 1.5 \times 10^9$/liter, platelets $\geq 100{,}000 \times 10^9$/liter). Female patients of reproductive age were required to have a negative pregnancy test, and all patients were advised to use adequate contraception while on therapy.

Patients were required to be at least 2 weeks from previous chemotherapy and 4 weeks after an investigational agent before study enrollment and should have recovered from any adverse effects of previous therapy. Patients were excluded if they were on nonsteroidal anti-inflammatory drugs (NSAIDs) for more than 30 continuous days before enrollment. Patients could not take any other NSAIDs while on study except aspirin at a dose of $\leq$325 mg/day. Patients were excluded if they had allergy to sulfa drugs or a history of gastrointestinal hemorrhage or myocardial infarction, or cerebrovascular event within 6 months. Patients with a history of a venous thromboembolic phenomenon within 4 weeks of study entry were excluded. Patients with brain metastases were allowed as long as the brain metastases had been treated, and the patient had no symptoms from the brain metastases. Any patient with body weight of $<$50 kg was excluded because gefitinib had not been studied in such patients. Patients with any condition that precluded taking the study drugs were not eligible.

Response rates were assessed every 8 weeks according to the Response Evaluation Criteria in Solid Tumors.[28] Toxicity was graded according to the National Cancer Institutte Common Toxicity Criteria, version 2.0.

All patients were required to provide a signed, informed consent before enrollment. The Human Investigation Committee of Wayne State University approved the protocol.

Treatment

Gefitinib was provided by AstraZeneca. Patients were instructed to take gefitinib 250 mg once daily and celecoxib 400 mg twice daily with meals. Each 4-week period was considered a cycle. While on therapy, each patient was assessed every 2 weeks with history and physical examination and laboratory evaluation. After four cycles, if the patient did not have any toxicity higher than grade 2, patients could be evaluated every 4 weeks. Disease assessment was done after every two cycles. Standard measures were to be used to manage skin rash and diarrhea related to gefitinib. The dose of celecoxib was reduced by 25% for increase in serum creatinine of 50%–100% over baseline, and celecoxib was to be held for increase in creatinine $>$100% over baseline. Both drugs were to be held for a maximum of 14 days for any grade 3–4 toxicity not accounted for by disease progression. Patients could restart both drugs at the same dose if the patient recovered to grade 1 toxicity.

Statistical Methods

This phase II trial was planned with a Simon two-stage design.[29] The particular design chosen has Simon-like properties, and results from the Simon algorithm modifications of Green and Dahlberg.[30] The primary end point was complete or partial response (CR+PR). We wished to distinguish these regions of the true, unknown response rate: at most 0.05

versus at least 0.20. The two-stage design called for a maximum of 27 response assessable (R-E) patients, 18 in stage 1 and nine in stage 2. Patients were considered R-E if they completed at least 2 weeks of therapy. The design had power of 0.80, overall type I error of 0.05, and (via the Green and Dahlberg method[30]) a type II (i.e., false negative) error rate of 0.02 for stage 1 of the two-stage design. At least one response among the first 18 R-E patients was needed to justify beginning stage 2 of accrual. In the study results, the response rate is reported based on all 27 registered patients, according to the intent-to-treat principle.

Exact minimum-width 90% confidence intervals (CIs) for response and toxicity rates were calculated using the Casella method[31] as implemented in StatXact software.[32] Standard Kaplan-Meier estimates of the censored TTP and OS distributions were computed. Due to the small sample sizes, survival statistics (e.g., median, 1-year rate) were estimated more conservatively using linear interpolation[33] among successive event times on the Kaplan-Meier curves.

RESULTS

Patient Characteristics

Twenty-seven patients were enrolled from May of 2003 to September of 2004 (Table 1). The median age was 59 years (range, 35–74 years). The majority of the patients were males (63%) and white (70%). All patients but one had stage IV NSCLC at study entry, and 26% of the patients had a PS of 2. One patient with breast cancer 7 years before diagnosis developed a sternal mass, lung lesions, and supraclavicular adenopathy. This patient was diagnosed as NSCLC and was treated with platinum-based doublet chemotherapy. The patient was enrolled in this trial at progression. The patient had stable disease on therapy for 5 months with subsequent mild progression. Due to an unusually prolonged clinical course despite lack of response to any therapy, a review of the pathology from the breast primary (obtained from an outside institution) and the most recent biopsy was conducted, and it suggested similarity. This patient is still alive without any therapy other than zoledronic acid. This patient has been included in all end points for an intent-to-treat analysis.

Response and Survival

Among the 27 patients enrolled, two patients (7%, 90% CI: 0.02–0.20) had a PR to the combination of gefitinib and celecoxib. Six other patients had stable disease, for an overall clinical benefit rate of 30% (PR + stable disease, 90% CI: 0.16–0.45). Of the two patients who had a response, one patient continues to be on gefitinib for 36 months. This female nonsmoking patient, who had adenocarcinoma, took the combination for 20 months. However, after the data regarding cardiovascular risks with the use of celecoxib were released, the patient decided to discontinue celecoxib and continue only on gefitinib. This patient continues to have a PR with some mild changes in the pleura persisting. The other patient who had a response was a male who was a former smoker (10 pack-years) with poorly differentiated carcinoma.

TABLE 1. Patient Demographics

No.	27
Age, y	
Range	35–74
Median	59
Gender	N (%)
Males	17 (63)
Females	10 (37)
Race, no. (%)	
White	19 (70)
Black	6 (22)
Asian	2 (8)
PS (ECOG)	
0,1	20 (74)
2	7 (26)
Smoking history	no. (%)
Current	10 (37)
Former	13 (48)
Nonsmokers	4 (15)
Previous chemotherapy regimens	
1	16 (59)
≥2	11 (41)
Stage	
IV	26 (96)
IIIB	1 (4)
Histology*	
Adenocarcinoma	11 (42)
Squamous cell	4 (15)
NOS	8 (31)
Large cell	3 (12)

*One patient had breast cancer and was wrongly enrolled on the study.
PS, performance status; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.

The response rate among nonsmokers was 25% (1/4), although one patient never started on therapy and died within 11 days of study registration from progressive disease. Only one of eight current smokers had stable disease, which lasted for 3 months.

The median time to progression was 2.2 months, and median survival was 4.6 months (Table 2). The 1-year survival rate was 16%, and at 1 year, 8% of the patients had not progressed (Figures 1 and 2).

TABLE 2. Time to Event End Points

Event Statistics	No.	Events	Point Estimate	90% Confidence Interval
Response rate	27	2	7%	2%–20%
Time to progression	27	26		
Median			2.2 mo	1.7 mo–2.9 mo
12-mo rate			8%	0%–17%
Overall survival	27	25		
Median			4.6 mo	2.7 mo–6.2 mo
12-mo rate			16%	4%–27%

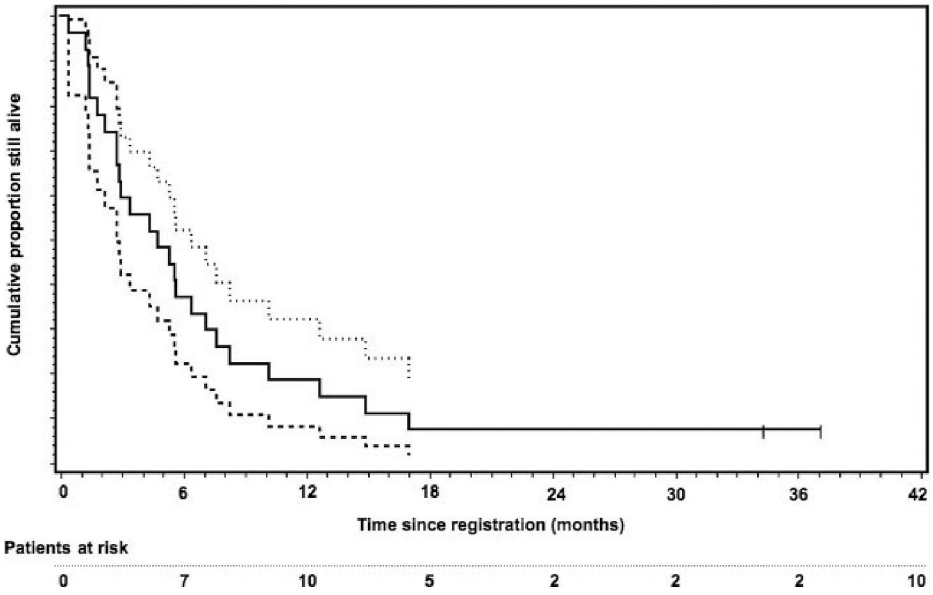

FIGURE 1. The Kaplan-Meier estimate of time to progression in the 27 patients with platinum-refractory non-small cell lung cancer who were treated with gefitinib and celecoxib. The dashed lines represent the 90% confidence limits about each successive estimate of the progression-free rate.

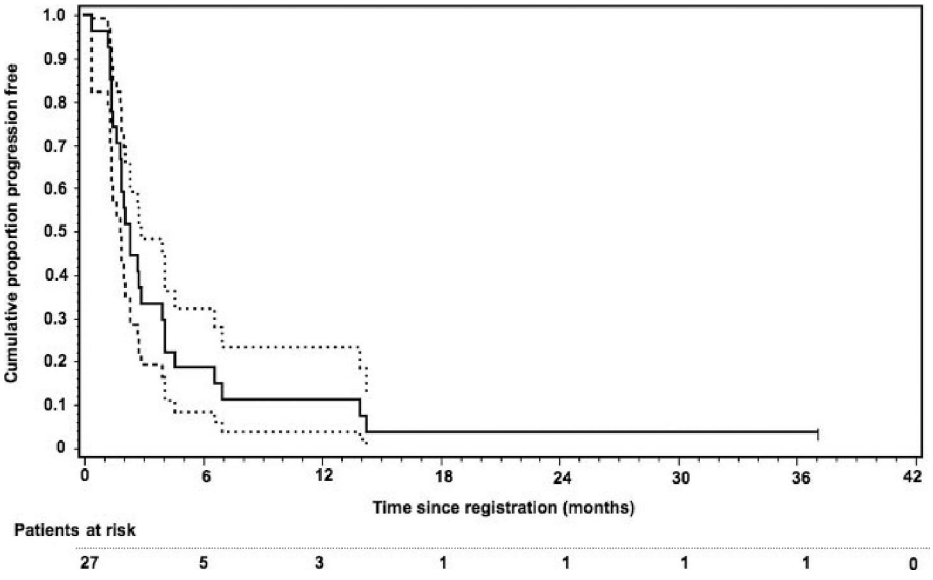

FIGURE 2. The Kaplan-Meier estimate of overall survival in the 27 patients with platinum-refractory non-small cell lung cancer enrolled in the study. The dashed lines represent the 90% confidence limits about each successive estimate of the survival rate.

Toxicity (Table 3)

The combination was well tolerated and the adverse effects attributable to the drugs were very few. Cutaneous adverse effects were observed in seven patients, but none of these were more than grade 2. Diarrhea was observed in five patients, with only one patient developing grade 3 toxicity. Five patients were admitted with respiratory failure and clinical suspicion of pneumonitis. However, all patients had evidence of disease progression. One patient did have radiographic findings suggestive of pneumonitis but also had evidence of disease progression. None of the patients developed a cardiovascular event or episodes of venous thromboembolism. COX-2 inhibitors appear to increase the risk of vascular episodes.[34] It is quite possible that we

TABLE 3. Toxicity

Toxicity Type	Cutaneous	Diarrhea	Edema	Renal	Fatigue	Pulmonary
Grade	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4
No. of patients	4 3	3 1 1	1 2	2 1	3 1	1*

*Five patients were admitted to the hospital with clinical suspicion of pneumonitis. However, only one patient was deemed to have pneumonitis.

did not observe these episodes due to the short duration of therapy with COX-2 inhibitors in most patients in this study. Renal dysfunction was observed in three patients. This was characterized by increase in serum creatinine. In each of these patients, the dose of celecoxib was reduced. The creatinine improved in two patients and in one patient did not change.

DISCUSSION

In this trial, the response rate and survival with the combination of gefitinib and celecoxib were similar to those observed with single-agent gefitinib. We limited the study population to patients whose disease had progressed on platinum-based therapy or within 3 months of completion of such therapy and designated them as platinum-refractory patients. Our objective in restricting the eligibility to these patients was to limit the heterogeneity of patients commonly observed in phase II trials of relapsed NSCLC patients. In addition, the activity of approved chemotherapy drugs in platinum-refractory patients appears to be limited, whereas data from phase II studies of gefitinib suggest that response to the previous chemotherapy regimen did not influence the probability of benefit.

Gefitinib was originally approved based on a response rate of 9% in a large phase II study.[7] However, based on a lack of significant benefit in a randomized phase III study, gefitinib was withdrawn from the U.S. market.[35] In subset analysis of the randomized study, survival advantage with gefitinib was observed in nonsmokers and in patients of Asian ethnicity. The withdrawal was also prompted by results observed with erlotinib, another EGFR-TKI, which did demonstrate significant survival improvement in relapsed NSCLC patients.[4] There has been intense speculation regarding the disparity in results with gefitinib and erlotinib. It appears that one of the possible reasons for the disparity may be differences in drug levels achieved at standard doses with the two drugs.[36,37]

The results of initial phase II studies of EGFR-TKIs suggested that patients with clinical characteristics of nonsmoking status, female gender, Asian ethnicity, and adenocarcinoma histology had a higher likelihood of clinical benefit.[38,39] Retrospective evaluation of tumors of patients with a response identified that the presence of somatic activating mutations in the tyrosine kinase domain of the EGFR gene is predictive of response to EGFR-TKIs.[40,41] It appears that EGFR mutations lead to tumor dependency on the EGFR pathway for survival and blocking of this pathway by gefitinib or erlotinib leads to apoptosis.[42] Subsequently, other investigators have suggested that increased EGFR gene copy number and EGFR expression are more predictive of benefit from EGFR-TKIs.[43] The importance of each of these factors in predicting benefit from EGFR-TKIs remains to be determined in prospective clinical trials. Interestingly, EGFR mutations and increased EGFR gene copy number occur more frequently in tumors of NSCLC patients with clinical characteristics that are predictors of increased likelihood of benefit from EGFR-TKIs, particularly nonsmoking status.[42,43]

Based on preclinical data regarding the role of COX-2 in carcinogenesis, COX-2 inhibitors have been evaluated in cancer prevention and therapy. In prospective, randomized trials, celecoxib reduced the number of colonic polyps in patients with FAP and more recently showed a reduction in the number of colon cancers and precancerous lesions in individuals with a history of colonic polyps.[18,44,45] However, COX-2 inhibitors have not consistently demonstrated benefits in therapeutic trials.[46–48] In a recently reported randomized study conducted by Cancer and Leukemia Group B, addition of celecoxib to platinum-based doublet chemotherapy did not provide any additional benefit in advanced NSCLC patients.[49] This lack of benefit from COX-2 inhibitors in established tumors may be related to greater redundancy of carcinogenic pathways in advanced cancers than in precancerous lesions. A retrospective analysis of the Cancer and Leukemia Group B study suggests that patients with tumors that expressed COX-2 had improved survival with the addition of celecoxib to chemotherapy.

Csiki et al.[46] evaluated docetaxel in combination with celecoxib in patients with previously treated NSCLC. Although the overall results did not suggest an improvement in survival with the addition of celecoxib, the investigators did observe that patients who had the greatest proportional drop in urinary PGE-M levels, a metabolite of PGE2 and a marker of systemic PGE2 levels, had a substantially reduced risk of death compared with patients in whom no change in PGE-M levels were observed. Thus, it is possible that celecoxib is beneficial only in NSCLC patients in whom the urinary PGE-M levels decline and therefore the benefits of adding celecoxib to an EGFR-TKI may also be restricted to these patients. Lilenbaum et al.[50] also did not observe any benefit from the addition of celecoxib to chemotherapy doublets in relapsed NSCLC patients. In an editorial accompanying the Lilenbaum et al. study, Ciski and Johnson[51] suggest that appropriate characterization of the enzymes involved in PGE2 synthesis and metabolism in patient's tumor may be important in selecting patients for treatment with COX-2 inhibitors. They suggest that in certain NSCLC, 15-PG dehydrogenase, an enzyme responsible for PGE2 elimination, may be down-regulated, and in patients with these tumors, celecoxib may actually promote tumor proliferation and therefore may be detrimental. Thus, preselection of NSCLC patients based on tumor expression of COX-2 and the enzymes involved in PG metabolism may be important to observe an antitumor effect of celecoxib. Lack of such preselection may be a reason for the lack of benefit with the addition of celecoxib to gefitinib in our trial.

Two other recently reported studies suggest that in unselected patients with advanced NSCLC, the addition of a COX-2 inhibitor to an EGFR-TKI does not improve efficacy. Fidler et al.[52] reported a response rate of 8% (2/26) in relapsed NSCLC patients with the combination of erlotinib and celecoxib. Agarwala et al.[53] reported the results of a study evaluating the combination of gefitinib and celecoxib as frontline therapy and found a response rate of 16% (5/31). These results contrast with the promising response rate of 33% (7/21) observed by Reckamp et al.[54] in a phase I study

seeking an optimal biological dose of celecoxib in combination with a standard dose of erlotinib. In this study, the investigators defined the optimal biological dose of celecoxib, based on reduction in urinary PGE-M levels, to be 600 mg twice daily. It is possible that the superior response rates in this study may be related to the higher dose of celecoxib. However, responses in the study by Reckamp et al. were also observed in patients who received a celecoxib dose lower than 600 mg twice daily. These investigators are planning to conduct a phase II trial evaluating the benefits of adding celecoxib at this dose to erlotinib in advanced NSCLC patients.

The first patient enrolled in this trial is progression free for more than 3 years. This patient is a nonsmoking female with adenocarcinoma, clinical features that predict for higher likelihood of benefit from EGFR-TKIs. We did not have an adequate tumor sample to assess EGFR mutation status or EGFR gene copy number. The impressive clinical outcome of this patient led us to speculate that the combination of EGFR-TKI and COX-2 inhibitor may be most effective in NSCLC with EGFR mutations. We therefore conducted in vitro studies to test this hypothesis. Celecoxib enhanced efficacy of both EGFR-TKIs in two EGFR-mutated cell lines but did not do so in a cell line with wild-type EGFR.[55] It is likely that due to dependency on the EGFR pathway in mutated tumors, the overlap between the EGFR and COX-2 pathways may be more relevant in these tumors and therefore the combination of EGFR-TKI and celecoxib may be most active in these tumors. It is also important to note that urinary PGE-M level, a marker of systemic PGE2 levels, is elevated in smokers than in nonsmokers and that celecoxib reduces the PGE-M levels to a greater extent in former and never smokers. It is therefore possible that celecoxib may have greater antitumor effect on never smokers than on former/current smokers,[46,56] and therefore the addition of celecoxib to EGFR-TKI may be more beneficial in NSCLC patients who have never smoked.

In conclusion, the results of this study show that the addition of celecoxib to gefitinib is not beneficial in unselected platinum-refractory NSCLC patients. Recent studies and observations suggest that EGFR-TKIs and COX-2 inhibitors are likely to be beneficial in NSCLC patients with specific molecular characteristics in their tumors. Based on these data, future studies should evaluate the combination of EGFR-TKI and celecoxib in NSCLC patients with tumors that have molecular characteristics such as EGFR mutations and/or COX-2 expression and also evaluate the combination with celecoxib dosed at 600 mg twice daily to obtain the most optimal COX-2 inhibition.

ACKNOWLEDGMENTS

AstraZeneca provided funds and gefitinib for the conduct of the study. This study was supported in part by Cancer Center Support grant CA-22453 from the National Cancer Institute.

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