Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase II Study of the Efficacy and Safety of Apricoxib in Combination With Either Docetaxel or Pemetrexed in Patients With Biomarker-Selected Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose

Overexpression of COX-2 correlates with advanced stage and worse outcomes in non–small-cell lung cancer (NSCLC), possibly as a result of elevated levels of COX-2–dependent prostaglandin E2 (PGE2). Exploratory analyses of studies that used COX-2 inhibitors have demonstrated potentially superior outcome in patients in whom the urinary metabolite of PGE2 (PGE-M) is suppressed. We hypothesized that patients with disease defined by PGE-M suppression would benefit from the addition of apricoxib to second-line docetaxel or pemetrexed.

Patients and Methods

Patients with NSCLC who had disease progression after one line of platinum-based therapy, performance status of 0 to 2, and normal organ function were potentially eligible. Only patients with a $\geq 50\%$ decrease in urinary PGE-M after 5 days of treatment with apricoxib could enroll. Docetaxel 75 mg/m² or pemetrexed 500 mg/m² once every 21 days per the investigator was administered with apricoxib or placebo 400 mg once per day. The primary end point was progression-free survival (PFS). Exploratory analysis was performed regarding baseline urinary PGE-M and outcomes.

Results

In all, 101 patients completed screening, and 72 of the 80 who demonstrated $\geq 50\%$ suppression were randomly assigned to apricoxib or placebo. Toxicity was similar between the arms. No improvement in PFS was seen with apricoxib versus placebo. The median PFS for the control arm was 97 days (95% CI, 52 to 193 days) versus 85 days (95% CI, 67 to 142 days) for the experimental arm ($P = .91$).

Conclusion

Apricoxib did not improve PFS, despite biomarker-driven patient selection.

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INTRODUCTION

Overexpression of COX-2 has been implicated as a tumor-initiating and tumor-promoting event for several common solid tumors, including lung, breast, and colon cancer. Considerable epidemiologic evidence supports COX-2 inhibition as a method of chemoprevention. In laboratory models, COX-2 inhibition has demonstrated antineoplastic properties in monotherapy and in combination with cytotoxic and targeted agents. Preclinical and clinical data demonstrate that COX-2 is important

in the pathogenesis of non–small-cell lung cancer (NSCLC). COX-2 is overexpressed in 70% to 80% of patients with NSCLC. Selective COX-2 inhibitors have been shown to inhibit the growth of lung cancer cell lines and to enhance the effectiveness of selected chemotherapy against NSCLC cell lines in xenograft models. In early-stage NSCLC, treatment with celecoxib can modulate the increased expression of COX-2–dependent prostaglandin E2 (PGE2) in tumor tissue after neoadjuvant treatment.¹ Several studies have demonstrated that the addition of COX-2 inhibitors to standard

Fig 1. CONSORT diagram.

chemotherapy in patients with evidence of an activated COX-2 pathway (high expression by immunohistochemistry) had superior outcomes.²⁻⁵

One limitation of immunohistochemistry is the need for an adequate tumor specimen. In many cases, a sufficient tumor specimen will require an invasive procedure, and sometimes the tissue was obtained at a substantially earlier time (eg, a specimen obtained at the time of a curative intent resection, which may precede relapse by several years). An alternative approach to evaluating the role of COX-2 in a specific patient's disease is to measure suppression of the urinary prostaglandin E metabolite (PGE-M) of PGE₂. Prostaglandins are derived from the endoperoxide intermediate prostaglandin H₂, which is generated from precursor arachidonic acid by the action of COX enzymes. PGE₂ has been identified as the prostaglandin most involved in the neoplastic process.⁶ Endogenous PGE₂ production can be easily and reproducibly quantified by measurement of PGE-M. Csiki et al⁷ have shown that the greater the decrement of PGE-M after 1 week of celecoxib therapy relative to baseline, the longer the survival. However, baseline urinary PGE-M was not predictive of survival.⁷

We hypothesized that suppression of urinary PGE-M would select for patients with advanced NSCLC who would benefit from selective COX-2 suppression plus chemotherapy in the second-line setting. Apricoxib is a novel, potent, well-tolerated selective inhibitor of COX-2 with the advantage of daily administration and perhaps superior preclinical activity compared with celecoxib.⁸ Analysis of pre- and posturinary PGE-M levels after a 5-day apricoxib run-in allowed for selection of patients on the basis of PGE₂ expression without the need for tumor biopsies.

PATIENTS AND METHODS

Eligibility

Patients 18 years old or older with Eastern Cooperative Oncology Group performance status of 0 to 2 and stage IIIB or IV NSCLC (by the sixth edition of the American Joint Committee on Cancer staging manual) were eligible (Figure 1). All patients were required to have documented progression after one prior line of platinum-based chemotherapy for metastatic or locally advanced disease. Patients who received adjuvant chemotherapy for completely resected disease and were then treated with the same or another platinum-based regimen at the time of relapse were eligible. If a patient received a platinum-based regimen and an agent substituted for toxicity (as opposed to progression of disease), that patient was considered to have received only one prior regimen. Patients who received erlotinib (before, after, or concurrently with platinum-based therapy) were eligible. Patients who received maintenance chemotherapy (ie, continuing chemotherapy with either the same agent or an agent different from the original platinum-based regimen for stable or responding disease) were eligible, provided that they had not received both docetaxel and pemetrexed. Evaluable or measurable disease assessed by RECIST 1.0 was required. Normal hematologic, renal, and hepatic function were required. For hepatic function, ALT and AST had to be less than 2× the upper limit of normal (ULN); if liver metastases were present, then ALT and AST had to be less than 5× the ULN; total bilirubin needed to be less than or equal to the institutional ULN, and serum albumin had to be more than 2.5 mg/dL. Women of childbearing potential must have had a negative pregnancy test (serum beta human chorionic gonadotropin). Patients were excluded from enrollment if they had known hypersensitivity to apricoxib, docetaxel, other drugs formulated with polysorbate 80, pemetrexed, sulfonamides, aspirin, or other nonsteroidal anti-inflammatory drugs. Also excluded were patients who had undergone radiation therapy within 2 weeks or chemotherapy within 3 weeks of initiating study treatment or patients who had not recovered from therapy-related toxicity to grade ≤ 2 toxicity (except alopecia) as a result of agents administered more than 3 weeks before initiating study treatment. Screening for urinary PGE-M suppression could begin during this time period. Patients were ineligible if they had concurrent severe or uncontrolled medical disease (ie, active systemic infection, diabetes, hypertension, coronary artery disease, or congestive heart failure).

Fig 2. Study schema. NSCLC, non-small-cell lung cancer; PGE-M, urinary metabolite of COX-2-dependent prostaglandin E₂; PS, performance status; Rx, line of therapy.

If patients had symptomatic CNS metastases, then they must have been stable after radiotherapy for ≥ 2 weeks and must have discontinued all steroid or antiepileptic medications for that indication for ≥ 2 weeks. Patients with CNS metastases who were untreated were eligible if there was no evidence of midline shift, no requirement for steroids or antiepileptic medications, and no neurologic symptoms. Patients were excluded if they had a history of upper GI bleeding, ulceration, or perforation within the past 5 years. Concurrent use of COX-2 inhibitors or other nonsteroidal anti-inflammatory drugs for 2 days before the first dose of study treatment and during study, including aspirin for 7 days before the first dose of study treatment and during study, was not permitted.

All patients provided written informed consent before registration. The study was approved by each institution's institutional review board before the enrollment of the first patient at that institution.

PGE-M Screening

All patients received apricoxib 400 mg once per day for 5 days. Urine samples were obtained immediately before and after apricoxib. If $\geq 50\%$ PGE-M suppression was demonstrated, then patients were eligible for random assignment. Patients received standard chemotherapy of either docetaxel 75 mg/m² or pemetrexed 500 mg/m² intravenously once every 21 days. Urinary PGE-M analysis was performed at Vanderbilt University by using previously published methods.⁶

Treatment

The choice of regimen was at the discretion of the individual site investigator and was dependent on histology (ie, only patients with nonsquamous histology could receive pemetrexed) and prior therapy. Up to six courses of chemotherapy could be administered. In addition, patients received either apricoxib 400 mg orally once per day or an identical-appearing placebo (Figure 2). Apricoxib or placebo was continued indefinitely until progression. Tragara Pharmaceuticals (San Diego, CA) provided both apricoxib and placebo. Patients who could not receive all six courses of chemotherapy could continue on apricoxib or placebo as long as there was no evidence of progression. Patients were evaluated with patient history and physical examination every 3 weeks and with computed tomography scans of involved areas every 6 weeks.

Statistical Considerations

The primary efficacy end point for this trial was progression-free survival (PFS). PFS was defined as the time from registration to progression or death (if progression was not previously documented). Secondary efficacy end points were overall survival (OS), response rate, and duration of response. The Cancer and Leukemia Group B (CALGB) 30203 trial (Carboplatin and Gemcitabine Combined With Celecoxib and/or Zileuton in Treating Patients With Advanced Non-Small Cell Lung Cancer) demonstrated a marked improvement in failure-free survival (hazard ratio [HR], 0.294) and OS for patients (HR, 0.342) with moderate to high expression of COX-2 who were treated with a COX-2 inhibitor plus chemotherapy. On the basis of the results of that study, we hypothesized that the addition of the selective COX-2 antagonist apricoxib to standard chemotherapy in second-line therapy would result in a comparable level of benefit for patients selected on the basis of PGE-M suppression (a measure of COX-2-dependent disease). In prior studies of unselected patients treated with second-line pemetrexed or docetaxel, the median PFS was approximately 3 months. However, COX-2 expression is a negative prognostic marker; therefore, the median PFS in a population selected for COX-2-dependent disease should be substantially less. The hypothesis of this trial was that there would be an improvement in PFS (the primary end point) at 3 months from approximately 35% (based on the negative prognostic aspects of COX-2-expressing patients who did not receive COX-2 inhibitors in addition to standard chemotherapy) to at least 60%. Assuming 12 months of accrual and a minimum of 3 months of follow-up using the George-Desu method, 35 patients were to be entered onto each arm to have 80% power to detect this difference in PFS with a 0.05 level of significance. With this same number of patients, we would have approximately 77% power to detect a difference in OS, assuming a 25% 1-year survival for a patient who overex-

Table 1. PGE-M Suppression

Variable	All Enrolled Patients	Patients Receiving Apricoxib	Control Patients	P
Baseline PGE-M, creatinine ng/mg				.87
Median	26.67	28.59	24.75	
Range	4.20-166.66	4.20-166.6	5.14-129.53	
Magnitude of suppression, %	79.86	76.02	80.70	.50
Range	50.71-98.07	50.71-94.28	50.78-98.07	

Abbreviation: PGE-M, urinary metabolite of COX-2-dependent prostaglandin E₂.

pressed COX-2 and had a plausible survival benefit of approximately 50%, at a significance level of 5%.

Efficacy analyses were based on an intent-to-treat analysis. Survival analysis was performed by using the Kaplan-Meier approach. Log-rank testing was used to analyze outcome differences between treatment arms and exploratory subsets. The Cox proportional hazards model was used to estimate the HR. A two-sided Fisher's exact test was used to compare tumor response for the experimental arm versus the control arm. Wilcoxon rank sum test was used to compare PGE-M suppression between the different groups. Exploratory analyses included multivariable adjustments to assess PFS and OS by using the Cox model and logistic regression (for response) and for the impact of several baseline factors on the estimates of treatment effect for PFS and OS.

Randomization was stratified on the basis of well-known prognostic factors: sex, performance status 0 to 1 versus 2 and stage IIIB versus stage IV (sixth edition of the American Joint Committee on Cancer staging manual) with a block of size 4. Randomization, study management, and data analysis were performed by the Clinical Trials Office and Biostatistics Core at the University of Maryland Greenebaum Cancer Center.

Table 2. Patient Demographic and Clinical Characteristics

Characteristic	Entire Population		Patients Receiving Apricoxib (n = 36)	Control (n = 36)
	No.	%		
Median age, years	64		62	66
Sex				
Male	40	55.6	20	20
Female	32	44.4	16	16
Performance status				
0-1	67	93	33	34
2	5	7	3	2
Race				
White	52	72	27	25
African American	14	19	7	7
Other	6	9	2	4
Histology				
Adenocarcinoma	49	68	24	25
Squamous cell	14	19	8	6
Poorly differentiated/not otherwise specified	9	13	4	5

NOTE. Prior chemotherapy regimens administered (with No. of patients): carboplatin-paclitaxel or docetaxel (30), carboplatin-gemcitabine (8), carboplatin-pemetrexed (26), cisplatin-gemcitabine (1), cisplatin-vincristine (2), bevacizumab administered in conjunction with another regimen (19), erlotinib (7), sunitinib (1), mapatumumab (1), and tecemotide (1).

RESULTS

One hundred nine patients began apricoxib screening and 102 completed screening (Figure 1). Of the 102 patients who completed PGE-M suppression treatment, 80 (79%) were eligible. A total of 72 patients were randomly assigned and received at least cycle 1 day 1 of treatment (Figure 1). The degree of PGE-M suppression was similar between placebo and active arms (Table 1). The demographics of the randomly assigned patients, including the prior chemotherapy regimens administered, are described in Table 2. Demographics by specific chemotherapy regimen (ie, pemetrexed or docetaxel) are provided in Appendix Table A1 (online only). The population was typical for studies of second-line therapy, and there were no significant differences between the arms. Significant (ie, grade ≥ 3) toxicities are detailed in Table 3 and by chemotherapy regimen in Appendix Table A2 (online only) and Appendix Table A3 (online only). Overall, the degree of toxicity is similar to that seen for similar studies that use docetaxel or pemetrexed as single agents in the second-line NSCLC population. The only grade 5 event resulted from a colonic perforation

in a patient in the apricoxib arm. Despite concerns regarding cardiac toxicity and COX-2 inhibitors, there was only one grade 3 event of cardiac ischemia seen in a patient with preexisting cardiac disease.

The median PFS for the control arm was 97 days (95% CI, 52 to 193 days) versus 85 days (95% CI, 67 to 142 days) for the experimental arm (HR, 1.03; $P = .91$; Figure 3A). Patients who received docetaxel plus apricoxib ($n = 17$) had a numerically inferior median PFS of 75 days (95% CI, 47 to 104 days) versus 97 days (95% CI, 48 to 216 days) for docetaxel plus placebo ($n = 20$; HR, 1.62; $P = .18$). Patients who received pemetrexed plus placebo ($n = 16$) had a median PFS of 98 days (95% CI, 37 to 197 days) which was similar to that of patients who received pemetrexed plus apricoxib ($n = 19$) for 103 days (95% CI, 62 to 225 days; HR, 0.782; $P = .49$; Fig 3B).

There was no difference in median OS between the two arms. The OS for the entire population was 245 days (95% CI, 202 to 344 days). For the control arm, OS was 287 days (95% CI, 206 to 384 days) versus 233 days (95% CI, 151 to 365 days; HR, 0.96; $P = .87$) for the experimental arm. Again, there was a nonsignificant inferior outcome for patients who received docetaxel plus apricoxib versus docetaxel plus

Table 3. Toxicity Grade for Apricoxib and Placebo Study Arms

Toxicity	Grade for Apricoxib Arm (n = 36)				Grade for Placebo Arm (n = 36)			
	Any (3, 4, 5)	3	4	5	Any (3, 4, 5)	3	4	5
Hematologic toxicity								
Hemoglobin	2	2			1	1		
Absolute neutrophil count	11	3	8		12	5	7	
Platelets	1	1						
Neutropenic fever							1	
Nonhematologic toxicity								
Allergic reactions					1	1		
Aseptic meningitis	1	1						
Cardiac ischemia (myocardial infarction, angina)	1	1						
Aseptic meningitis	1	1						
Nausea/vomiting	2	2			2	1	1	
Acute renal failure	1	1			1	1		
Confusion	1	1						
Cough					1	1		
Depression	1	1						
Dizziness	1	1						
Deep vein thrombosis or pulmonary embolus	2		2		3	2	1	
GI (other than nausea and vomiting)					2	1	1	
Acute bladder outlet obstruction					1	1		
Decubitus ulcer	1	1						
Dyspnea	3	3						
Fatigue	1	1			2	2		
Generalized edema					2	1		
GI (colon perforation)	1			1				
Glucose								
Increased					2	2		
Decreased	3	3			1	1		
Hypokalemia					1	1		
Hyperkalemia	2	2						
Hyponatremia	2	2						
Hypophosphatemia					1	1		
Subclavian port infection	1		1					
Lymphopenia	1		1		3	3		
Pain	3	3			6	6		
Syncope	1	1						

NOTE. Toxicity is indicated by the number of patients experiencing a toxic event.

Fig 3. Progression-free survival (PFS). (A) PFS for overall study population. PFS by chemotherapy regimen with (B) pemetrexed or (C) docetaxel.

placebo. We analyzed the population for prognostic and predictive factors, including histology, baseline PGE-M, magnitude of PGE-M suppression, and chemotherapy regimen, recognizing the limitations of subset analysis with such small numbers. Data regarding the che-

motherapy regimens is discussed in the preceding paragraph. Baseline PGE-M emerged as a negative prognostic marker for OS ($P = .033$) but not for PFS with a relative risk increase of 1.009 times for each unit increase in PGE-M at baseline (eg, a patient with a baseline urinary PGE-M of creatinine 200 ng/mg had a relative risk of 1.9 compared with a patient with baseline urinary PGE-M of creatinine 100 ng/mL). An adverse interaction between baseline PGE-M and chemotherapeutic agents received (docetaxel v pemetrexed) was seen for PFS ($P = .026$). In patients receiving docetaxel, each unit increase in urinary PGE-M at baseline increased the HR by 1.014 for PFS ($P = .038$) and by 1.015 for OS ($P = .033$), whereas in patients receiving pemetrexed, baseline PGE-M was not significantly associated with PFS or OS ($P > .10$).

DISCUSSION

This study did not achieve the primary end point of improved PFS despite biomarker-driven patient selection. There are several possible reasons for this result. It is possible that COX-2 inhibition is simply not an effective therapeutic approach for solid tumor malignancies such as NSCLC. COX-2 inhibition plus chemotherapy has been evaluated in several tumors, including lung, breast, and colon.⁹ To date, no randomized controlled trial has demonstrated a therapeutic advantage for this approach. For example, in the adjuvant treatment of colorectal cancer, the use of rofecoxib after adjuvant therapy failed to demonstrate a survival advantage.¹⁰ These failures, coupled with increased concern regarding the safety of this approach, which emerged during the evaluation of rofecoxib as a chemopreventive agent, have sharply reduced enthusiasm for COX-2 inhibitors in cancer. However, there are considerable data to support COX-2 inhibition as a valid therapeutic target for NSCLC, but the optimal selection of patients appears to be critical to this targeted approach. As noted previously, COX-2 expression in the tumor may be critical to the selection of patients who may benefit from COX-2 suppression. This method of patient selection is limited by tissue availability and the potential subjectivity of immunohistochemistry evaluation. The suppression of urinary PGE-M is an attractive biomarker, and the level of suppression chosen for this study was based on a prior study combining apricoxib with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib.¹¹ This phase II trial (APRICOT-L [Apricoxib in Combination Oncology Treatment - Lung] A Randomized, Double-Blind, Placebo-Controlled Multicenter Phase 2 Study of the Efficacy and Safety of Apricoxib in Combination With Erlotinib in Non-Small Cell Lung Cancer Patients) used similar biomarker-driven patient selection and evaluated erlotinib plus apricoxib or placebo in advanced, previously treated NSCLC with the primary end point of time to disease progression. APRICOT-L demonstrated a significant improvement in disease control rate, time to progression, and OS for patients younger than 65 years of age.¹²

Interestingly, in our study there was a possible adverse interaction (albeit, nonsignificant) with docetaxel plus apricoxib compared with pemetrexed plus apricoxib. Taxanes have been documented to stimulate COX-2 expression.¹ In fact, the use of a COX-2 inhibitor has been suggested as a method to overcome this issue. This hypothesis is supported by several negative studies that have investigated COX-2 suppression plus chemotherapy in NSCLC. Most have used taxanes in the chemotherapy regimen.¹³ Unfortunately the number of patients in

our study was too small to establish whether or not such an interaction exists or whether it is exclusive to taxanes. Manipulations of the eicosanoid pathway, including COX-2 inhibition, remain an interesting, although unproven, approach to the treatment of lung cancer and other malignancies. The use of these agents will require validated, biomarker-driven patient selection because inhibition of this pathway may also be associated with potentially adverse effects.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

Table A1. Characteristics of Baseline Variables by Chemotherapy Regimen

Characteristic	Entire Population (N = 72)		Apricoxib Arm (n = 36)						Control Arm (n = 36)					
			Overall		Pemetrexed		Docetaxel		Overall		Pemetrexed		Docetaxel	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Median age, years	64		62		62		62		66		65		66.5	
Sex														
Male	40	55.6	20	55.6	10	52.6	10	58.8	20	55.6	11	68.9	9	45.0
Female	32	44.4	16	44.4	9	47.4	7	41.2	16	44.4	5	31.3	11	55.0
ECOG PS														
0-1	67	93.1	33	91.7	16	84.2	17	100	34	94.4	14	87.5	20	100
2	5	6.9	3	8.3	3	15.8	—		2	5.6	2	12.5	—	
Race/ethnicity														
White	52	72.2	27	75.0	14	73.7	13	76.5	25	69.4	12	75.0	13	65
African American	14	19.4	7	19.4	4	21.1	3	17.7	7	19.4	2	12.5	5	25.0
Other	6	8.4	2	5.6	1	5.3	1	5.9	4	11.2	2	13.5	2	10.0

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

Table A2. Toxicities by Chemotherapy Regimen: Docetaxel Cohort

Toxicity	Grade for Patients Receiving Apricoxib (n = 17)			Grade for Patients Receiving Placebo (n = 20)		
	3	4	5	3	4	5
Hematologic						
Hemoglobin	1			1		
Absolute neutrophil count		7		3	7	
Platelets	1					
Neutropenic fever					1	
Nonhematologic						
Deep vein thrombosis or pulmonary embolism		2		2	1	
Nausea/vomiting				1		
Allergic reaction				1		
Aseptic meningitis	1					
Confusion	1					
Cough				1		
Depression	1					
Dizziness	1					
Dyspnea	1					
Fatigue	1			2		
GI (colon perforation)			1			
Glucose						
Increased				1		
Decreased	1			1		
Hyperkalemia	1					
Hypokalemia				1		
Hyponatremia	1					
Generalized edema				1		
Lymphopenia		1		1		
Pain	2			5		

Table A3. Toxicities by Chemotherapy Regimen: Pemetrexed Cohort

Toxicity	Grade for Patients Receiving Apricoxib (n = 19)			Grade for Patients Receiving Placebo (n = 16)		
	3	4	5	3	4	5
Hematologic						
Hemoglobin	1					
Absolute neutrophil count	3	1		2		
Platelets						
Neutropenic fever						
Nonhematologic						
Cardiac ischemia (myocardial infarction, angina)	1					
Nausea/vomiting	2				1	
Acute renal failure	1			1		
GI (other than nausea and vomiting)				1	1	
Acute bladder outlet obstruction				1		
Decubitus ulcer	1					
Dyspnea	2					
Glucose						
Increased				1		
Decreased	2					
Hyperkalemia	1					
Hyponatremia	1					
Hypophosphatemia				1		
Subclavian port infection		1				
Lymphopenia				2		
Pain	1			1		
Syncope	1					