# Phase II Study of Celecoxib and Docetaxel in Non-small Cell Lung Cancer (NSCLC) Patients with Progression after Platinum-Based Therapy

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**Introduction:** To evaluate the efficacy and toxicity of the combination of celecoxib and docetaxel in patients with advanced non-small cell lung cancer after failure of platinum-based therapy.

**Methods:** Patients with relapsed non-small cell lung cancer received celecoxib 400 mg orally twice daily beginning 7 days before the first cycle of docetaxel and the celecoxib was continued with no interruption. Docetaxel 75 mg/m$^2$ was administered intravenously on a 21-day cycle. The primary end point of the study was the 6-month survival rate.

**Results:** Twenty-four patients were enrolled and twenty patients were treated (median age 60, M:F 16:8). Most patients had a baseline performance status of 1. The objective response rate was 10% (95% confidence interval [CI], 0–25%) and the 6-month survival rate was 59% (95% CI 37–80%). Median survival time was 6.9 months (95% CI, 2.8–15.2 months) and the 1- and 2-year survival rates were 36% (95% CI, 15–57%) and 1% (95% CI, 0–10%), respectively. The most frequent grade ≥3 adverse events were neutropenia (58%) and neutropenic fever (21%) which resulted in early closure of the trial.

**Conclusions:** The addition of celecoxib to docetaxel did not seem to improve the response rate and survival compared with docetaxel alone. The combination demonstrated considerable neutropenia and complications from febrile neutropenia that suggests celecoxib may enhance the marrow toxicity of docetaxel.

**Key Words:** Non-small cell lung cancer, COX-2, Relapsed, Docetaxel, Celecoxib.

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Each year in the United States over 200,000 new cases of lung cancer are diagnosed, most of which are non-small cell lung carcinoma (NSCLC).[1] Approximately 40% of patients present with metastatic disease and will only be candidates for palliative chemotherapy. Standard initial therapy usually consists of a platinum-based drug regimen sometimes with the addition of bevacizumab.[2,3] However, with a median progression free survival of 3 to 4 months, many patients are candidates for subsequent therapy.

Docetaxel was the first agent approved for the treatment of advanced NSCLC after the failure of initial platinum-based therapy. Unfortunately, the response rate is only around 7% with a 1-year survival rate of 32 to 37%.[4,5] Efforts have been made to use doublet therapy for platinum-refractory or relapsed disease; however, toxicity has outweighed the clinical benefit in this setting.[6–9] More effective and better tolerated therapy is needed for patients who progress after platinum-based treatment.

Cyclooxygenase-2 (COX-2) is an inducible enzyme that facilitates the conversion of arachidonic acid to prostaglandins involved in the regulation of normal growth responses, but has also been implicated in aberrant cellular growth and angiogenesis.[10,11] Prostaglandins derived from COX-2 may stimulate oncogenesis through the inhibition of immune surveillance and apoptosis in addition to the promotion of angiogenesis and tumor invasion.[12–17] Specifically, COX-2 expression facilitates the formation of prostaglandin-$E_2$ ($PGE_2$) which promotes the production and release of vascular endothelial growth factor, an angiogenic growth factor.[18] Overexpression of COX-2 has also been found to increase production of the antiapoptotic proteins Bcl-2 and surviving in lung cancer cell lines.[19,20] Tumoral COX-2 mRNA expression has been associated with decreased survival and early relapses in patients with resected NSCLC.[21]

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Written informed consent was obtained from all patients before initiation of therapy.

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Previous studies have demonstrated that approximately 70% of NSCLCs overexpress COX-2 when compared with normal lung tissue and given the involvement of COX-2 in facilitating tumor angiogenesis and inhibiting apoptosis of malignant cells, it is an attractive target for cancer therapy.[22,23]

Preclinical studies utilizing COX-2 inhibitors have demonstrated a direct antitumor effect in NSCLC models.[24] The addition of a COX-2 inhibitor to taxane chemotherapy might be beneficial as in vitro experiments have demonstrated that taxanes induce COX-2 and subsequent prostaglandin synthesis which may result in reduced effectiveness of the chemotherapy.[25] Indeed, in human NSCLC cell lines, docetaxel plus the COX-2 inhibitor nimesulide demonstrated improved cytotoxicity compared with single-agent taxane therapy.[26] With these considerations, we designed a phase II study to evaluate the effectiveness and tolerability of docetaxel plus celecoxib in patients with NSCLC who progressed after platinum-based chemotherapy.

## PATIENTS AND METHODS

### Eligibility

Patients with histologically or cytologically documented NSCLC were entered onto this study between November 2001 and May 2002. Patients were required to have evidence of progressive or relapsed disease during or after treatment with platinum-containing chemotherapy for stage IIIA, IIIB or IV NSCLC. Chemotherapy, radiation therapy, and major surgery were not allowed within 2 weeks of starting celecoxib. In addition, any nonsteroidal antiinflammatory drug therapy must have been discontinued 30 days before the initiation of treatment with the exception of ≤325 mg/d of aspirin for cardiovascular conditions. Other requirements included measurable or evaluable disease, age ≥18, Zubrod performance status (PS) of 0–2, Absolute Neutrophil Count (ANC) ≥1500/mm$^3$, platelet count ≥100,000/mm$^3$, total bilirubin less than or equal to the institutional upper limit of normal, serum glutamic-oxaloacetic transaminase ≤2.5X the upper limit of normal and serum creatinine ≤1.5 mg/dL (132.6 mol/L). Exclusion criteria also included an allergy to sulfa drugs, prior therapy with docetaxel, body weight below 50 kg and symptomatic, uncontrolled brain or leptomeningeal disease. Patients were ineligible if they had peripheral neuropathy of grade ≥2, a thromboembolic event within 4 weeks of study entry, a history of gastrointestinal bleeding within 6 months of study entry or peptic ulcer disease of any duration. The trial was approved by the local Institutional Review Boards and written informed consent was obtained from all patients.

### Treatment

Patients were treated with celecoxib 400 mg administered orally twice daily beginning 7 days before the first cycle of docetaxel. Patients were asked to take each dose with a meal. Docetaxel was administered at a dose of 75 mg/m$^2$ and was repeated every 21 days. Therapy continued until progression or unacceptable toxicity. Patients could be maintained on celecoxib after discontinuation of docetaxel for reasons other than disease progression. Each cycle was of 21 day duration except the first cycle which lasted for 28 days as this cycle included the 7-day induction of celecoxib before the first docetaxel infusion.

### Dose Adjustment for Toxicity

Full dose of docetaxel was delivered if the ANC ≥1500/mm$^3$ and platelets ≤100,000/mm$^3$ and nonhematologic toxicity ≤grade 1; but the dose of docetaxel was reduced by 20% if the nadir ANC was ≤500/mm$^3$ and/or the nadir platelet count was ≤25,000/mm$^3$. Docetaxel was delayed for ANC <1500/mm$^3$ and/or platelets ≤100,000/mm$^3$, or grade ≥3 nonhematologic toxicity for a maximum of 2 weeks. If more than or equal to grade 3 nonhematologic toxicity was observed at any point, then the dose of subsequent cycles of docetaxel was reduced by 20%. Docetaxel could begin when toxicity resolved to les than or equal to grade 1. Patients experiencing more than or equal to grade 3 neurotoxicity resulted in discontinuation of protocol therapy. Grade 2 neurotoxicity resulted in a maximum delay of 2 weeks of docetaxel and a subsequent 20% dose reduction.

Celecoxib was not held or reduced for hematologic toxicity, but was reduced to 300 mg orally twice daily for an increase in serum creatinine between 50 and 100% of the pretherapy value and was held for a serum creatinine >100% of the pretherapy value. If the creatinine level recovered to <100% increase from pretherapy levels within a 2-week period, then the dose was reduced to 300 mg twice daily for all subsequent treatments. Celecoxib was also held for grade ≥3 nonhematologic toxicity and full dose therapy could resume within a 2-week period if the toxicity resolved to grade ≤1.

### Assessment of Response and Toxicity

Patients were considered evaluable for toxicity assessment if treatment with celecoxib was started and were eligible for response if they received at least one dose of celecoxib and docetaxel. Patients underwent appropriate scans to evaluate for response after every two cycles of treatment. Response to therapy was assessed according to the Response Evaluation Criteria in Solid Tumors criteria.[27] Celecoxib and docetaxel were discontinued if a patient developed progressive disease or life-threatening/irreversible toxicity that was not manageable with symptomatic care or dose reduction and/or delay. All toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0 (http://ctep.cancer.gov/reporting/ctc.html).

### Statistical Analyses

The primary objective of this study was to assess the 6-month survival rate in patients treated with the combination of docetaxel and celecoxib. To minimize the number of patients required for this study, a two-stage Minimax Simon's design was used.[28] This drug combination would be considered not interesting if the 6-month survival rate is <35%, and it would be of definite clinical interest if the 6-month survival rate is >55%. With 21 patients in stage I and 39 total patients, the 2-stage design used had a 5% type I error and 80% power in testing the hypothesis. The trial was to be terminated at stage I if ≤8 patients survived 6 months. A total of 39

 

evaluable patients were to be accrued unless undue toxicity warranted early termination of accrual.

To be evaluable for efficacy, the patient had to receive at least one dose of celecoxib and one dose of docetaxel. Other endpoints of this study were treatment toxicity, overall survival duration, and time to treatment failure. Overall survival (OS) was defined as the time from the initiation of celecoxib treatment to death from any cause. Time to treatment failure (TTF) was defined as the time from the initiation of celecoxib treatment to the documentation of disease progression, death due to any cause, or early discontinuation of therapy.

Descriptive analyses for baseline characteristics were performed. Six-month survival rate and median survival were conservatively estimated using Kaplan-Meier method with linear interpolation due to the small sample size.[29] Time to event endpoints (OS and TTF) were plotted using Kaplan-Meier curves.[30] The SAS System (Cary, NC) was used for all analyses.

## RESULTS

Twenty-four patients were enrolled onto the study between November 2001 and December 2002. Accrual was stopped after 24 patients since a high rate of neutropenic fever was observed. Data were collected until May 12, 2004 when the last patient on study expired. Patient characteristics are summarized in Table 1. The median age at study entry was 60 years (range, 41–76), 67% were males. All patients had received prior platinum-based chemotherapy and half of the patients were deemed platinum refractory (progression within 3 months of treatment). Eighteen patients had received prior therapy with paclitaxel and 10 patients had received 2 prior regimens. The majority of patients had stage IV disease (79%) and the rest had stage III disease. Sixty-seven percent of the patients had a Zubrod PS of 0 or 1.

**TABLE 1.** Patient Characteristics

| Characteristic | No. | Percentage |
|---|---|---|
| Sex | | |
| Male | 16 | 67 |
| Female | 8 | 33 |
| Age, yr | | |
| Median | 60 | |
| Range | 41–76 | |
| Race | | |
| Caucasian | 15 | 63 |
| African American | 7 | 29 |
| Other | 2 | 8 |
| Performance status | | |
| 0 | 4 | 17 |
| 1 | 12 | 50 |
| 2 | 8 | 33 |
| Stage | | |
| IIIA | 1 | 4 |
| IIIB | 4 | 17 |
| IV | 19 | 79 |
| Number of previous chemo regimens | | |
| 1 | 14 | 58 |
| 2 | 10 | 42 |
| Platinum refractory | 12 | 50 |
| Received prior paclitaxel | 18 | 75 |

**TABLE 2.** Worst Toxicity (≥Grade 3) Experienced per Patient ($n$ = 24) Grade

| Toxicity | 3 | 4 | 5 |
|---|---|---|---|
| Anemia | 2 | 0 | 0 |
| Neutropenia | 6 | 8 | 0 |
| Neutropenic fever | 3 | 2 | 0 |
| Nausea/vomiting | 3 | 0 | 0 |
| Neuropathy | 1 | 0 | 0 |
| Dyspnea | 0 | 1 | 1 |
| Pneumonia | 0 | 0 | 1 |
| Mucositis | 1 | 0 | 0 |
| Fatigue/decline in PS | 2 | 2 | 0 |

PS, performance status.

### Toxicity

A median of 2 cycles were administered (range, 1–14). Four patients (17%) began celecoxib but never received docetaxel. One patient developed pneumonia, was hospitalized and died on day 26. Two patients had a severe decline in PS due to progressive disease and were removed from study. One patient received the celecoxib for 2 days and then requested to be removed from study. Per protocol design, these 4 patients were not evaluable for treatment response, but were included in the toxicity assessment.

Toxicity data are listed in Table 2. The most common grade 3–4 toxicities were neutropenia (58%) and neutropenic fever (21%) and most of these patients required hospitalization. When the 4 patients that had not received docetaxel were excluded, the rates were 70% and 25%, respectively. None developed grade 3–4 thrombocytopenia and only 2 had grade 3 anemia. Six patients (25%) required at least one dose reduction of docetaxel, 5 due to toxicity occurring during the first cycle. Two other patients (8%) had a delay of treatment by 1 week. No patient developed nonhematologic toxicity requiring dose reduction of celecoxib. Twelve patients (50%) required hospitalization during study treatment: 5 for neutropenic fever/sepsis, 4 for progressive dyspnea likely from malignancy, 2 for new onset brain metastases and 1 for nonneutropenic pneumonia.

### Response and Survival

Two of the 20 evaluable patients had a partial response to treatment (10%, 95% CI, 0–25%). Twelve patients had a partial response or stable disease through 2 cycles of therapy for a tumor control rate of 60% (95% CI 40–80%). The 6-month survival rate was 59% (95% CI 37–80%).

The median time to treatment failure was 1.67 months (95% CI, 1.3–2.9). Median overall survival was 6.9 months (95% CI, 2.8–15.2 months) and the 1- and 2-year survival rates were 36% (95% CI, 15–57%) and 1% (95% CI, 0–10%), respectively. The intent to treat Kaplan-Meier esti-

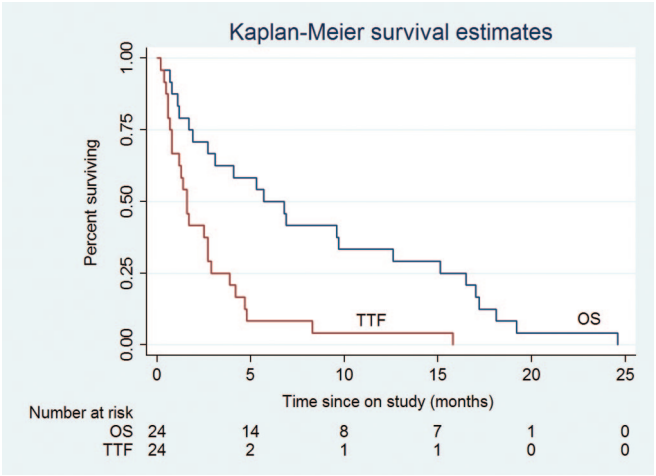


**FIGURE 1.** Intent To Treat Kaplan-Meier estimates for overall and time to treatment failure survival for all patients $n = 24$ (median overall survival, 5.7 months; median time to treatment failure, 1.61 months).

mates of TTF and OS for the 24 patients are presented in Figure 1.

## DISCUSSION

Our study achieved the primary end point of greater than 6-month survival in 59% of the patients enrolled in stage I, although it is underpowered with poor precision due to the early termination. Unacceptable hematologic toxicity resulted in early closure of the trial which included grade 3–4 neutropenia in 70% and neutropenic fever in 25% of patients who received both celecoxib and docetaxel. Although patient selection may have contributed to this (half of the patients were platinum-refractory, one-third had a PS of 2), the response and survival results are, nevertheless, comparable with 2 other trials utilizing docetaxel plus celecoxib in advanced NSCLC. Csiki et al.[31] used the same dose and schedule of docetaxel and celecoxib in 56 patients and reported a response rate of 11%, a median survival of 6 months, and a 1-year survival of 23%. Nugent et al.[32] demonstrated in 39 patients a response rate of 10%, median survival of 11.3 months and 1-year survival of 48%. However, these results are not much different than those observed with single agent docetaxel, suggesting the addition of celecoxib did not improve overall survival.[4,5]

Early clinical data utilizing celecoxib as an antineoplastic agent seemed promising. A study by Altorki et al.[33] demonstrated elevated intratumoral levels of COX-2 and $PGE_2$ after treatment with neoadjuvant carboplatin and paclitaxel, suggesting chemotherapy induced up-regulation of COX-2. Neoadjuvant treatment with celecoxib 400 mg twice daily plus chemotherapy substantially reduced intratumoral $PGE_2$ levels evaluated in the post surgical specimens, however, given the small sample size, these results could not be correlated with survival.

Another study by Altorki et al.[34] confirmed tolerability of the combination of celecoxib, paclitaxel and carboplatin as neoadjuvant therapy for patients with resectable NSCLC. A dramatic reduction in tumoral $PGE_2$ levels was noted compared with control patients and results indicated celecoxib may enhance the response of paclitaxel and carboplatin in patients with NSCLC. Csiki et al. also reported 5 subjects who underwent assessment of intratumoral $PGE_2$ after administration of celecoxib 400 mg twice daily, 4 of whom had significant decreases in $PGE_2$ posttherapy. This trial also evaluated urinary PGE-M levels (the primary urinary metabolite of $PGE_2$) both pre and postadministration of celecoxib. A dramatic reduction in previously elevated urinary PGE-M levels correlated with improvement in survival in patients with advanced NSCLC.

Despite these compelling data that suggest COX-2 is a valid in vivo target, COX-2 inhibition has not consistently demonstrated enhancement of the antitumor activity of cytotoxics in clinical trials. Gridelli et al.[35] used gemcitabine and cisplatin with or without the COX-2 inhibitor rofecoxib in patients with untreated advanced NSCLC and no survival benefit was identified. A recent trial by Lilenbaum et al.[36] evaluated docetaxel plus irinotecan or gemcitabine plus irinotecan with or without the addition of celecoxib for second-line therapy in patients with advanced NSCLC. Survival was actually worse in patients who received chemotherapy plus celecoxib (median survival 6.3 months) compared with the patients who received the chemotherapy alone (median survival 9 months). It was postulated that celecoxib may reduce the level of prostaglandin $I_2$ which has antitumor properties, leading to promotion of tumor growth rather than inhibition.[37]

Unfortunately, efficacy and survival do not seem to have improved with the addition of celecoxib to docetaxel when administered to an unselected population and the marrow toxicity seems to have been enhanced compared with docetaxel alone. The Lilenbaum study reported that 35% of patients who received docetaxel/irinotecan/celecoxib demonstrated grade 3–4 neutropenia compared with 20% who received docetaxel/irinotecan without celecoxib. Similarly, Csiki et al. and Nugent et al. both reported grade 3–4 neutropenia (57% and 26%, respectively) and febrile neutropenia (15% and 9%, respectively) as 2 of the most common toxicities of docetaxel plus celecoxib. This is consistent with our study which suggests a synergistic effect of docetaxel plus celecoxib in the development of neutropenia compared with docetaxel alone.

It is possible that COX-2 is required for marrow recovery after cytotoxic chemotherapy.[38] Preclinical data suggest that chemotherapy-induced bone marrow necrosis requires an inflammatory response to remove dead cells and debris to maintain a proper hematopoetic milieu. Mice deficient in the COX-2 gene demonstrated a slow marrow recovery following administration of 5-fluorouracil compared with wild-type mice given the same agent. Interestingly, when hemolysis was induced in the COX-2 deficient mice, erythropoesis was unhindered compared with the wild-type mice suggesting COX-2 was required for repair of marrow damage, but was not necessary for normal marrow hematopoesis.

Recently, results were presented from the Cancer and Leukemia Group B trial 30203 that evaluated celecoxib and/or zileuton (5-LOX inhibitor) plus standard chemother-

 

apy in advanced NSCLC.[39] Patients received carboplatin and gemcitabine with celecoxib, zileuton, or both and although failure free survival and overall survival did not differ among the three arms (or compared with historic controls), a preplanned analysis of COX-2 expression as a prognostic and predictive marker demonstrated intriguing results. Patients who did not receive celecoxib and demonstrated high intratumoral expression of COX-2 by immunohistochemistry had a worse outcome compared with patients with low expression. This confirmed retrospective studies that suggested overexpression of COX-2 in NSCLC is a negative prognostic factor.[40] Also, patients treated with celecoxib who demonstrated moderate or high COX-2 expression had an improvement in overall survival compared with those with moderate or high COX-2 expression who did not receive celecoxib. Interestingly, patients with low COX-2 expression treated with celecoxib seemed to have a worse overall survival compared with patients who overexpressed COX-2 and received celecoxib. In our trial, patients were not selected based on COX-2 expression and, as Edelman et al. has suggested, a negative effect of celecoxib in patients with low COX-2 expression may have diluted the benefit attained in the patients with moderate to high COX-2 expression.

Nonsmokers seem to have less COX-2 activity compared with active and former smokers, suggesting different dose levels would be required for adequate inhibition based on the smoking status of the patient. With a "one size fits all" dose of celecoxib, previous studies have shown that $PGE_2$ production was inhibited to a greater degree in nonsmokers.[31,41] The preselection of NSCLC patients based on tumor expression of COX-2 may be important to observe an antitumor effect of celecoxib. Immunohistochemical analysis of the tumor or surrogate markers of COX-2 expression such as urinary PGE-M levels could be used prospectively to enhance a clinical trial population most likely to respond to celecoxib.

In conclusion, our study demonstrates that celecoxib added to docetaxel may enhance marrow toxicity and, in unselected patients, there is no clear improvement in survival. Evaluation of celecoxib with or without chemotherapy in appropriately selected patients may be beneficial and warrants further investigation.

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