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

Bryan J. Schneider, MD, Gregory P. Kalemkerian, MD,* Michael J. Kraut, MD,† Antoinette J. Wozniak, MD,† Francis P. Worden, MD,* Daryn W. Smith, MS,‡ Wei Chen, PhD,‡ and Shirish M. Gadgeel, MD†*

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]

*Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan, Ann Arbor, Michigan; †Thoracic Oncology Program, Karmanos Cancer Institute/Wayne State University, Detroit, Michigan; and ‡Biostatistics Unit, Karmanos Cancer Institute/Wayne State University, Detroit, Michigan.

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Michael J. Kraut is currently at Providence Hospital, Southfield, Michigan, USA.

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

Address for correspondence: Bryan J. Schneider, MD, C361 Med Inn; Box 5848, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5848. E-mail: bryansch@umich.edu

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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

